GPAT 2016 BOOKLET

PART III

STUDY MATERIAL

MR. AMAR M. RAVAL (M.PHARM)

PHARMAROCKS

THE WAY OF SUCCESS

GPAT STUDY MATERIAL

MR. AMAR M. RAVAL

DRUGS AND THEIR ACTIVE METABOLITES

SR.NO.	DRUG	ACTIVE METABOLITE
1	Allopurinol	Oxipurinol (Alloxanthine)
2	Amytryptylline	Nortryptalline
3	Amphetamine	P-Methoxy Amphetamine
4	Carmapazepine	Carmapazemine-10,11-Eporide
5	Carbimazole	Thiamazole
6	Cephaloglycine	Desacetyl Cephaloglycine
7	Chloral Hydrate	Trichloroethanol
8	Chlordiazepoxide	7-hydroxy Chloropromazine
9	Chlorpromazine	7-hydroxy Chloropromazine
10	Chlorguanidine	Cyclogunal
11	Clofibrate	Free acid metabolite
12	Imipramine	N-oxide metabolite
13	Codeine	Morphine,Norcodeine
14	Diazepam	Oxazepam.N-Me-Oxazepam
15	Fenfluramine	Nor Fenfluramine
16	Guanethadine	N-Oxide
17	Lignocaine	N-Desmethyl metabolite
18	Morphine	Nor morphine
19	Naloxane	6-□-hydroxy Naloxane
20	Phenacetin	Paracetamol
21	Prednisone	Prednisolone
22	Premidone	Phenobarbitone
23	Spironolactone	Canrenone
24	Procainamide	N-Acetyl metabolite
25	Propanolol	N-deisopropyl met
26	Quinidine	3-Hydroxy quinone
27	Rifampicine	Desacetylated metabolite
28	Thioridazine	Mesoridazine

29	Trimethedione	Dimethedione
30	Warfarin	Warfarin alcohol
31	Vit D	1,2 Dihydroxy metabolite
32	Reserpine	Methyl reserpate

PRODUCTS AND ANIMALS USED FOR BIOASSAYS

SR	DRUG PRODUCT	ANIMAL
1	Digitalis	Pigeon
2	Glycogen	Cat
3	Insulin inj,	Rabbit
4	Oxytocin	Chicken
5	Parathyroid	Dog
6	Vasopressin	Rat
7	Posterior pituitary	Chicken
8	Tubocurarine chloride	Rabbit
9	Chorionic gonadotropin	Male rat
10	Cod liver oil	Rachitic rat
11	Heparin sodium	Sheep
12	Iron dextran injection	Microbial cultures
13	Antiseptic and disinfectant	Frog
14	Fungicides and Herbicides	Mouse
15	Diphtheria toxoid	Rat
16	Atropine	Rabbit
17	Insulin inj.	Guinea pig
18	Elastomeric closures Plastic containers	Guinea pig

RECOMENDE NEEDLE SIZE FOR VARIOUS INJECTIONS

INJECTIONS	GUAGE	LENGTH IN INCHES
INTRADERMAL	26G	¼ or 3/8
S.C	26G	½-¾
	25G	½-¾
	22G	1 ½
I.M	24G	¾-1
	23G	1
	22G	1
	20G	1 ½
I.V	22G	1-1/4-1 ½
	20G	1 ½

DRUGS AND THEIR VARIETIES

	DRUG	VARIETY
1	**SENNA**	
	Indian senna	Cassia angustifolia
	Alexandrian senna	Cassia acutifolia
	Dog senna	Cassia obovata
	Palthe senna	Cassia auriculata
2	**ALOE**	
	Cape Aloe	Aloe ferox
	Curcao Aloe	Aloe barbadensis
	Socotriene/ Zangibar aloe	Aloe perryii
3	**RHUBARB**	
	Indian Rhubarb	Rheum emodi
	Chienese Rhubarb	Rheum Webbianum

DRUG AND THEIR SYNONYMS

SR.NO.	DRUG	SYNONYMS
1	Cinchona	Panama bark
2	Lanolin	Wool fat
3	Crowfig seeds	Nuxvomica
4	Deadly night shade	Atropa beladona
5	Digitalis purpuria	Foxglove
6	American podophyllum	May apple
7	Indian tragacanth	Gum karaya
8	Devil's dung	Asafoetida
9	Indian squill	Urgenia
10	Indian tobacco	Lobelia
11	Flax seeds	Linseed
12	Periwinkle	Vinca visea
13	Ashwagandha	Withania somnifera
14	Alexendrian senna	Cassia acutifolia
15	Tinevally senna	Cassia angustifolia
16	Dog senna	Cassia obovata
17	Pathe senna	Cassia auriculata
18	Acasia	Gum arabica
19	Sterculia	Karaya
20	Agar	Japnese is linglass
21	Plantago	Psyllium
22	Starch	Amylum
23	Rhubarb	Rheam.emodi.(IND.Rhubarb)
24	Cascara	Purshiana,sacred barc
25	Discoria	Wild Yam
26	Glycerrhiza	Liquarice
27	Quillalia	Panama bark
28	Quassia	Bitter wool

29	Pale calicher	Gambier catechu
30	Blach caticher	Cutch
31	Castor oil	Ricinus oil
32	Arachis oil	Reauut oil
33	Linseed iol	Flax seed oil
34	Olive oil	Saled oil
35	Hydro carpno oil	Chanlmogra oil
36	Theobrona oil	Cocoa butter
37	Cinnamon	Chinese cassia
38	Saffron	Crocus
39	Colchicum	Autumn Crocus, Meadow saffron seeds
40	Nutmeg	Mygistica
41	Chenopodium	American wore
42	Lipstick tree	Annato tree, Bixin
43.	Clove	Caryo phylum

NAME OF THE DRUG AND SIDE EFFECTS

SR NO	NAME OF THE DRUG	SIDE EFFECTS
1	ACE Inhibitors	Dry Cough
2	Amphotericin-B	Nephrotoxicity
3	Ampicillin	Hypersensitivity
4	Androgen	Virilization
5	Antipsychotics	Sedation, Orthostatic hypotension, Tardive dyskinesia
6	Anti- TB	Hepatotoxicity
7	Aspirin (cox-I Inhibitors)	Hepatotoxicity
8	Atropine	Dryness of mouth, Blurred vision, Constipation

9	Celecoxib, Valdecoxib (cox-II Inhibitors)	Hepatotoxicity
10	Chlorambucil	Alopecia
11	Chloramphenicol	Grey baby syndrome, Bone marrow depression
12	Chloroquine	Phototoxicity
13	Ciprofloxacin	Phototoxicity
14	Clofazimine	Pigmentation of skin, Discoloration of Urine
15	Clozapine	Agranulocytosis
16	Erythromyicin	Cholestatic Juandice
17	Ethambutol	Optic Neuritis, Retrobulbular Neuritis
18	Hydrochlorthiazide	Hypokalamia
19	Isoniazid	Peripheral Neurtis
20	Metronidazole	Disulfiram like reaction
21	Minoxidil	Hirsutism
22	Morphine	Constipation
23	Nimesulide	Hepatotoxicity
24	Nitrogen Mustard	Bone marrow depression
25	Nitroglycerin	Palpitation
26	Penicillin-G	Jarisch Heximer Reaction
27	Phenformin	Lactic acidosis, GI disturbance, Metalic taste
28	Phenytoin	Hirsutism
29	Quinidine	Cinchonism
30	Quinine Sulphate	Black Water Fever
31	Repaglinide	Althralgia
32	Rosaglitazone	Anemia,Weight gain
33	Sitagliptin	Coldness

34	Spironolactone	Hyperkalamia
35	Cimetidine	Gynacomastia
37	Sulfonyl Ureas derivatives	Bone marrow depression
38	Terfenadine	Type-I arrhythmia
39	Tetracyclines	Discoloration of teeth
40	Thalidomide	Phocomelia

CAPSULE NO & THEIR APPROXIMATE CAPACITY IN mg & ml

CAPSULE SIZE	Mg	Ml
000 (Largest)	950	1.37
00	650	0.95
0	450	0.68
1	300	0.50
2	250	0.37
3	200	0.30
4	150	0.21
5 (Smallest)	100	0.13

PROPORTIONS REQUIRED FOR A PRIMARY EMULSION

TYPE OF OIL	OIL: WATER: GUM RATIO
FIXED OILS	4:2:1
VOLATILE OILS	2:2:1
MINERAL OILS	3:2:1
OLEORESINS	1:2:1

CODE: **LPSO** (APPLY THIS FOR TWEENS & SPANS)

For eg. **SPANS 20** MEAN SORBITAN MONO LAURATE

TWEEN 80 MEAN POLYOXYETHYLENE SORBITAN MONOOLEATE

- **L :** LAURATE - 20
- **P :** PALMITATE - 40
- **S :** STEARATE - 60
- **O :** OLEATE - 80

SOLUBILITY

Descriptive Term	Approx. Vol of Solvent in ml/gm of Solute
Very soluble	less than 1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10,000
Practically insoluble	more than 10,000

STORAGE TEMPERATURE

COLD TEMPERATURE	2 to 8 degree centigrade
COOL TEMPERATURE	8 to 25
ROOM TEMPERATURE	Prevailing in the working area
WARM TEMPERATURE	Between 30 to 40
EXCESSIVE HEAT	> 40 degree

SUCROSE BASED DILUANTS

DIPAC	97 % sucrose + 3% moddified dextrose
NUTAB	95 % sucrose + 4 % invert sugar
SUGAR TAB	90 - 93 % sucrose + 7 - 10 % invert sugar

Carr's index

The bulk density was the quotient of weight to the volume of the sample. Tapped density was determined as the quotient of weight of the sample to the volume after tapping a measuring cylinder for 500 times from a height of 2 inch. The Carr's index (percentage compressibility) was calculated as one hundred times the ratio of the difference between tapped density and bulk density to the tapped density

% Carr's Index = (Tapped density – Bulk density) / Tapped density * 100
% Carr's Index = (T_D – B_D) / T_D * 100

Hausner's Ratio

Hausner's ratio is the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density / Bulk density	**H.R = T_D / B_D**

% CI	FLOW CHARACTER	HAUSNER RATIO
< or = 10	Excellent	1 - 1.11
11 – 15	Good	1.12 - 1.18
16 – 20	Fair	1.19 - 1.25
21 – 25	passable	1.26 - 1.34
26 – 31	poor	1.35 - 1.45
32 – 37	very poor	1.46 - 1.59
>38	very very poor	> 1.6

Angle of repose

The angle of repose is a relatively simple technique for estimating the flow properties of a powder. It can easily be determined by allowing a powder to flow through a funnel and fall freely onto a surface. The height and diameter of the resulting cone are measured and the angle of repose calculated from this equation:

Tan Ø = h/r

Where, **'h'** is the height of the powder cone and **'r'** is the radius of the powder cone.

ANGLE OF REPOSE	FLOW CHARACTER
25 – 30	Excellent
31 – 35	Good
36 – 40	Fair
41 – 45	Passable
46 – 55	Poor
56 – 65	Very Poor
>66	Very Very Poor

TYPES OF GLASS USED IN PHARMACEUTICAL INDUSTRIES

Parenteral Use

- **Type I Glass:**

→ Highly Resistant Borosillicate.

→ Used for Buffered and Unbuffered aqueous solution.

- **Type II Glass:**

→ Highly Resistant Sodalime glass.

→ Buffered aqueous solution below pH 7.0

- **Type III Glass:**

→ Moderately Resistant Sodalime glass.

→ Used for dry powder and oily solution.

- **Non-Parenteral Use**

→ Type IV Glass:

→ General Purpose Sodalime glass.

→ Not for parenteral, for tablet, liquid oral and externals.

ANTIDOTES FOR SOME DRUGS

SR NO	DRUG NAME	ANTIDOTE
1	Acetaminophen	NAC (N-acetyl-L-cysteine) dosage
2	Alcohols (ethylene glycol, methanol)	IV ethanol, fomepizol (potent inhibitor of ADH)
3	Heparin	Protamine
4	Warfarin	vitamin k
5	Antidepressants	
	TCA's	benzodiazepines, phenytoin, physiostigmine
	SSRI's	Cycloheptadine
6	6.Benzodiazepines	Flumazenil

7	7.Beta antagonists	glucagon and epinephrine
8	Calcium antagonists	calcium, glucagon, insuline & dextrose combination
9	Cocaine	BZD's for seizuries; labetalol for hypertension; Neuroleptics for psychosis
10	Cyanide	amyl nitrite; sodium nitrite; sodium thio sulphate
11	Digoxin	Digibind
12	12.Electrolytes	
	a.Magnesium	10%CaCl2 temp to antagonize cardiac effects of Mg
	b.Potassium-	10%CaCl2 10%; NaHCO3(causes intracellular shift of pot);
13	Iron	deferoxamine (chelate iron)
14	Isoniazid	pyridoxine (reverses INH induced seizures)
15	Lead	Ca Disodium EDTA ; BAL (dimercaprol)
16	Lithium	no effective treatment
17	Opiates	naloxone; nalmefene
18	Organophosphates	atropine; pralidoxamine
19	Salicylates	activated charcoal
20	Theophylline	charcoal; beta antagonists
21	glucose & Insulin (Intracellular shift of pot.)	sodium polystyrene sulfonate (cationic exchange resin)

SYNONYMS AND THEIR COMMON NAMES

SR NO	SYNONYM	COMMON NAME
1	Rochelle salt	Sodium Potassium Tartarate
2	Dakin's solution	Sodium Hypochloride
3	Glaubers salt	Sodium Sulphate
4	Epsom salt	Magnesium Sulphate

5	China clay	Heavy Kaolin
6	Gypsum	Calcium Sulphate
7	Calomel	Mercurous Chloride
8	Soap clay	Bentonite
9	French chalk	Talc
10	Alum	Potassium Aluminium Sulphate
11	Hypo	Sodium Thiosulphate
12	Precipitated chalk	Calcium Carbonate
13	Slaked lime	Calcium Hydroxide
14	Bleaching powder	Chlorinated Lime
15	Burrows solution	Aluminium Acetate Solution
16	Laughing gas	Nitrous Oxide
17	Tear gas (CS gas)	Chlorobenzylidine Malononitrile
18	Iodine tincture	Weak Iodine Solution
19	knock out drops	Chloral Hydrate
20	Washing soda	Sodium carbonate
21	Baking soda	Sodium bicarbonate
22	Costic soda	Sodium hydroxide
23.	Lugols solution	Aqueous Iodine Solution

VACCINES

LIVE ATTENUATED:	**INACTIVATED**	**RECOMBINANT:**
MEASLES	RABIES	HEPATITIS B
MUMPS	INFLUENZA	
POLIO	TETANUS	**TOXOID:**
RUBELLA	HEPATITS A	DIPTHERIA
TYPHOID		TETANUS
VARICELLA		
TUBERCULOSIS		
YELLOWFEVER		

TEST ORGANISM FOR MICROBIOLOGICAL ASSAY OF ANTIBIOTIC

SR NO	ANTIBIOTIC	TEST ORGANISM
1	Amikacin	*Staphlococcus aureus*
2	Amphotericin B	*Saccharomyces cerevisiae*
3	Bacitracin	*Micrococcus luteus*
4	Bleomycin	*Mycobacterium smegmatis*
5	Carbenicillin	*Pseudomonas aeruginosa*
6	Doxycycline	*Staphlococcus aureus*
7	Erythromycin	*Micrococcus luteus*
8	Framycetin	*Bacillus pumilis , staphylococcus aureus*
9	Gentamycin	*Staphylococcus epidermidis*
10	Kanamycin	*Bacillus pumilis, staphylococcus aureus*
11	kanamycin B	*Bacilus subtilis*
12	Neomycin	*Staphlococcus epidermidis*
13	Novobiocin	*Staphlococcus epidermidis*
14	Nystatin	*Saccharomyces cerevisiae*
15	Oxyteracycline	*Bacillus cereus, staphylococcus aureus*
16	Polymyxin B	*Bordetella bronchiseptica*
17	Rifamycin	*Bacillus subtilis*
18	Streptomycin	*Bacillus subtilis , klebsiella pneumoniae*
19	Tetracycline	*Bacillus cereus, staphylococcus aureus*

DISEASE ASSOCIATED WITH ALTERED NEUROTRANSMITTERS LEVELS IN BRAIN

SR NO	DISEASE	NEUROTRANSMITTERS LEVELS
1	Parkinsonism	Decreased DOPAMINE in striatum
2	Schizophrenia	Increased DOPAMINE levels

3	Depression	Decreased NOREPINEPHRINE & 5-HT
4	Mania	Decreased NOREPINEPHRINE & 5-HT
5	Hallucination	Increased 5-HT
6	Alzheimer's	Decreased ACETYLCHOLINE & Destruction of Cholinergic Neurons
7	Athetosis	Decreased GABA in Putamen
8	Chorea	Decreased GABA in Caudate Nucleus
9	Amyotropic lateral sclerosis	Decreased ACETYLCHOLINE

ENZYMES AND THEIR METAL COFACTORS

FE2+	CYTOCHROMEOXIDASE, CATALASE, PEROXIDASE
CU2+	CYTOCHROME OXIDASE
ZN2 +	DNA POLYMERASE, CARBONIC ANHYDRASE, ALCOHOL DEHYDROGENASE
MG2 +	HEXOKINASE, GLUCOSE 6 PHOSPHATE
MN2+	ARGINASE
K+	PYRUVATE KINASE
NI2+	UREASE
MO	NITRATE REDUCTASE
SE	GLUTATHIONE PEROXIDASE

MICROSOMAL ENZYMES INDUCERS AND INHIBITORS

MICROSOMAL ENZYME INDUCERS
ALCOHOL
CHLORALHYDRATE
CORTISONE

NICOTINE
PREDNISOSLONE
PHENYTOIN
CHLORDIAZEPOXIDE
IMIPRAMINE
PHENOBARBITAL
TESTOSTERONE

MICROSOMAL ENZYME INHIBITORS
ALLOPURINOL
ORAL ANTIDIABETICS
DISULFIRAM
METRONIDAZOLE
ORAL ANTICOAGULANTS
ANABOLIC AGENTS
CHLORAMPHENICOL
ISONIAZID
MONOAMINE OXIDASE INHIBITORS
CEMETIDINE

DISEASE	**DEFECTIVE ENZYME**
ALBINISM -	TYROSINE-3-MONO OXYGENASE
ALKAPTONURIA	- HOMOGENTISATE1,2-DIOXYGENASE
GALACTOSEMIA -	GALACTOSE-1-PHOSPHATE IRIDYLYL TRANSFERASE
HOMOCYSTINURIA -	CYSTATHIONE B- SYNTHASE
PHENYLKETONURIA -	PHENYLALANINE-4-MONO OXYGENASE
TAYSACHS DISEASE	- HEXOSAMINIDASE A
HYPERVALINEMIA	- VALINE TRANSAMINASE
ARGINOSUCCINIC -	ARGINOSUCCINATE LYASE ACIDEMIA
KRABBES DISEASE -	BETA GALACTOSIDASE

FABRYS DISEASE -	ALPHA GALACTOSIDASE
NIEMANN PICK DISEASE -	SPHINGOMYELINASE
FARBERS DISEASE -	CERAMIDASE
GAUCHERS DISEASE -	BETA GLUOSIDASE

DIAGNOSTIC TESTS

NAME OF DISEASE	DIAGNOSTIC TESTS
SYPHILIS	1. VDRL TEST, 2. KAHN TEST, 3. WASSERMAN TEST 4. TREPONEMA IMMOBILIZATION TEST, 5. FLUROESCENT ANTIBODY-ABSORBED SERUM TEST.
DIPTHERIA	1. SCHICK TEST, 2. ELEX TEST
T.B	TUBERCULIN, MANTOUX TEST
LEPROSY	LEPROMIN TSEST
TYPHOID OR ENETRIC FEVER	WIDAL TEST
RHUMETOID ARTHRITIS	ROSE WATER TEST
SMALL POX	OUCHTERLONY
PNEUMONIA	1. COLD HEMAGLUTINATION TEST, 2. STREPTOCOCCUS MG HEMAGLUTINATION TEST
BRUCELLOSIS-	COOMBS TEST(OPSONIZATION TEST)
LYMPHOGRANULOMA VENERUM	FREI TEST
TYPHUS FEVER-	WEIL FELIX TEST

HEMOPHILLIUS-	DUCREY TEST
SCARLET FEVER-	DICK TEST
TO DETECT HUMAN CHORNIC GONADOTROPHIN IN SERUM OF WOMAN	RADIO IMMUNO ASSAY(RIA)

BIOASSAYS OF DRUGS AND ITS EFFECT ON THE ANIMAL

ADRENALINE	BP raising effects in spinal cats
NORADRENALINE	BP raising effects in spinal cats
HISTAMINE	Contraction of isolated guinea pig ileum
INSULIN	Hypoglycemic convulsions in mice
ACETYLCHOLINE	Contraction of isolated frog rectus muscle
D TC	Rabbit head drop due to paralysis of neck muscles
DIGITALIS	Death due to cardiac arrest in guinea pig
OXYTOCIN	Contraction of guinea pig uterine muscles
ANDROGENS	Growth copons comb
ADRENO CORTICO TROPIC HORMONE	Adrenal ascorbic acid estimation in hypophysectomised rats

MICRO ORGANISMS USED AS BIOASSAYS FOR VITAMINS

ASSAY MICRO ORGANISM	VITAMIN
Lactobacillus casei	BIOTIN, FOLICACID, PYRIDOXAL, RIBOFLAVINE

L. Arabinosus	CALCIUM PANTOTHENATE, NICOTINIC ACID
L.leichmanii	CYANOCOBALAMIN
L.viridans	THIAMINE
Saccharomyces urarum	INOSITOL
Acetobacter suboxydans	PANTHOTHENOL
Neurospora crassa (or) s.carlsberginsis	PRIDOXINE

BIOLOGICAL INDICATORS

Moist heat sterilisation (121 degre Centi)	*Bacillus stearo thermophilus*
Dry heat sterilisation (160 degre centi)	*Bacillus subtilis var niger*
Hydrogen peroxide and peracetic acid	*Bacillus stearo thermophilus*
Ethylene oxide , formaldehyde	*Bacillus subtilis var niger*
Ionising radiation	*Bacillus pumilis*

TESTS AND THEIR USES

SR NO	TEST	IDENIFY
1	Watson Schwartz Test	Urobilinogen
2	Schumms Test	Heme
3	Carrprice Test	Vit A
4	Gmelins Test	Bile Pigments
5	Gothlin Test	Scurvy
6	Gofmann Test	Serum Cholesterol
7	Murexide Test	Uric Acid
8	Reinsch Test	Heavy Metals

9	Gordons Test	Spinal Fluid
10	Biuret Test	Peptides
11	Legals Test	For Estimation Of Acetone
12	Ames Test	Carcinogenicity

SHORT CUTS FOR GPAT AND NIPER (EASY TO REMEMBER)

Busulfan feature: ABCDEF

- Alkylating agent
- Bone marrow suppression
- CML Indication
- Dark skin(hyperpigmentation)
- Endocrine insufficiency(adrenal)
- Fibrosis

Drugs causing Torsades de Pointes: APACHE

- Amiodarone
- Procainamide
- Arsenium
- Cisapride
- Haloperidol
- Erythromycin

Morphine side effects: MORPHINE

- Myosis
- Out of It (sedation)
- Respiratory depression
- Pneumonia(aspiration)
- Hypotension
- Infrequency (constipation,urinary retention)
- Nausea
- Emesis

Aspirin side effects: ASPIRIN

- Asthma
- Salicylism

- Peptic ulcer disease/phosphorylation-oxidat
- ion uncoupling/platelet disaggregation
- Intestinal blood loss
- Reye's Syndrome
- Idiosyncracy
- Noise(tinnitus)

SSRIs side effects: SSRI

- Seratonin syndrome
- Stimulate CNS
- Reproductive disfunction in male
- Insomnia

Inhalation anesthetics: SHINE

- Sevoflane
- Halothane
- Isoflurane
- Nitrous oxide
- Enflurane

Teratogenic drugs:"Win Teratogenic

- Warfarin
- Thalidomide

Epileptic drugs:

- Phenytoin,
- Valproate,
- Amazepine
- Retinoid
- ACE inhibitor

Third element: Lithium

Gynaecomastia causing drugs: DISCOS

- Digoxin
- Isoniazid
- Spironolactone
- Cimetidine
- Oestrogens
- Stilboestrol

Methyldopa Side effects: METHYLDOPA

- Mental retardation
- Electrolyte imbalance
- Tolerance
- Headache/ Hepatotoxicity
- Psychological upset
- Lactation in female
- Dry mouth
- Oedema
- Parkinsonism

Antirheumatic agents: CHAMP

- Cyclophosphamide
- Hydroxycloroquine and choloroquinine
- Auranofin and other gold compounds
- Methotrexate
- Penicillamine

Phenytoin: adverse effects PHENYTOIN

- P-450 interactions
- Hirsutism
- Enlarged gums
- Nystagmus
- Yellow-browning of skin
- Teratogenicity
- Osteomalacia
- Interference with B12 metabolism (hence anemia)
- Neuropathies: vertigo, ataxia, and headache

Sodium Valproate side effccts VALPROATE

- Vomiting
- Alopecia
- Liver toxicity
- Pancreatitis/ Pancytopenia

- Retention of fats (weight gain)
- Oedema (peripheral oedema)
- Appetite increase
- Tremor
- Enzyme inducer (liver)

Amiodarone: action, side effects: 6 P's:

- Prolongs action potential duration
- Photosensitivity
- Pigmentation of skin
- Peripheral neuropathy
- Pulmonary alveolitis and fibrosis
- Peripheral conversion of T4 to T3 is inhibited -> hypothyroidism

Antiparkinson Drugs: SALAD

- Selegiline
- Anticholinenergics (trihexyphenidyl, benzhexol, ophenadrine)
- L-Dopa + peripheral decarboxylase inhibitor (carbidopa, benserazide)
- Amantadine
- Dopamine postsynaptic receptor agonists (bromocriptine, lisuride, pergolide)

Therapeutic Index Formula TILE

TI = LD / ED

Anti epeleptic drugs Dr.BHAISAB's New PC.

- Deoxy barbiturates
- Barbiturates
- Hydantoin
- Aliphatic carb acids
- Iminostilbenes
- Succinimides
- BZD's
- Newer drugs

- Phenyltriazines
- Cyclic GABA analogues

Adverse effects of Tetracyclines-KAPIL DEV

- Kidney toxicity
- Antianabolic effect
- Phototoxicity
- Liver toxicity
- Diabetes insipidus

CAPTOPRIL Side effects CAPTOPRIL

- Cough Angioedema
- Agranulocystosis
- Proteinuria/ Potassium excess
- Taste changes
- Orthostatic hypotension
- Pregnancy contraindication/ Pancreatitis/ Pressure drop (first dose hypertension)
- Renal failure (and renal artery stenosis contraindication)/ Rash
- Indomethacin inhibition
- Leukopenia/Liver toxicity

Lithium: side effects LITH

- Leukocytosis
- Insipidus [diabetes insipidus, tied to polyuria]
- Tremor/ Teratogenesis
- Hypothyroidism

Myocardial Infarction (MI): signs and symptoms PULSE

- Persistent chest pains
- Upset stomach
- Lightheadedness
- Shortness of breath
- Excessive sweating

MI: basic management BOOMAR

- Bed rest
- Oxygen
- Opiate
- Monitor
- Anticoagulate
- Reduce clot size

Treatment of Heart Failure: ABCDE

- ACE inhibitors
- Beta-blockers
- Calcium channel blockers
- Diuretics
- Endothelin-converting enzyme inhibitors

Essential Amino acids

My True Love Is Throug Valentine Love Phrases

- Methionine
- Threonine
- Leucine
- Isoleucine
- Tryptophan
- Valine
- Lysine
- Phenyl alanine

BLOOD GROUP AND ITS COLOR OF LABEL MOST IMP

BLOOD GROUP	COLOR OF LABEL
O	BLUE
A	YELLOW
B	PINK
AB	WHITE

ABBREVIATIONS IMP FOR GPAT AS WEL AS IN NIPER

Description of some Important Abbreviations:-

ABBREVIATIONS	FULL FORM
AAAS	American Association of Advancement of Science
AALAS	American Association for Laboratory Animal Science
AIOPI	Association of Information Officers of the Pharmaceutical Industry
ALF	American Liberation Front
ANDA	Abbreviated New Drug Application
BEA	Breeding for Experimental Animals
BINAS	Biosafety Information Network and Advisory Service
BMA	British Medical Association
BMJ	British Medical Journal
BPC	Bulk Pharmaceutical Chemicals
BPI	British Pharmaceutical Index
BrAPP	British Association of Pharmaceutical Physicians
BUAV	British Union for the Abolition of Vivisection
CADD	Computer Aided Drug Design
CDC	Centre for Disease Control
CIOMS	Council for International Organisations of Medical Sciences
CPCSEA	Committee for Purpose of Control & Supervision of Experimental Animals
CPI	Consumer Price Index
CRA	Clinical Research Associate
CRC	Clinical Research Council
CRF	Case Report Form
CRN	Clinical Research Network
CRO	Contract Research Organisation
CSM	Committee on Safety of Medicines
CTA	Clinical Trial Authorisation (formerly the CTX, CTC, DDX)
CTC	Clinical Trial Certificate (Now CTA)
CTC	Clinical Trials Centre

CTD	Common Technical Document
CTD	Common Technical Document
CTX	Clinical Trial Exemption (Now CTA)
DRA	Drug Regulatory Affairs
DUMP	Disposal of Unwanted Medicines and Poisons
EFPIA	European Federation of Pharmaceutical Industries & Associations
EMEA	European Medicine Agency
FDA	Food & Drug Administration
FIP	International Pharmaceutical Federations
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
Gxp	Generic term for good practice requirements in the Pharmaceutical industry
HIS	Indian Health Services
HPLC	High Performance Liquid Chromatography
HRSA	Health Resources & Service Administration
IACUC	Institutional Animal Care and Use Committee
IAES	Institutional Animal Ethics Committee
ICDRA	International Conference for Drug Regulatory Authorities
ICH	International Conference on Harmonization of technical requirement for registration of pharmaceuticals
IIG	Inactive Ingredient Guide
IMP	Investigational Medicinal Products IMP - Investigational Medicinal Products
IMPD	Investigational Medicinal Product Dossier
INDA	Investigational New Drug Application
INN	International non-proprietary names *(for pharmaceutical substances)*
INTDIS	International Drug Information System - the previous WHO adverse reactions database
IPC	Indian Pharmaceutical Congress

IPGA	Indian Pharmacy Graduate Association
ISO	International Organization for Standardization
ISoP	International Society of Pharmacovigilance
ISPE	International Society for Pharmacoepidemiology
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NAFDAC	National Agency for Food and Drug Administration and Control, Nigeria
NCPA	National Community of Pharmacist Association
NCPO	National Conference of Pharmaceutical Organisations
NDA	New Drug Application
NDMS	National Disaster Medical System
NME	New Molecule Entity
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over-The-Counter
PDS	Pharmacoepidemiology and Drug Safety (journal)
PEM	Prescription Event Monitoring
PHRMA	Pharmaceutical Research and Manufacturers Association
PIL	Package Insert Leaflet
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
PMS	Post-Marketing Surveillance
POM	Prescription Only Medicine
PSM	Procurement and Supply Management
PSUR	Periodic Safety Update Report
QA	Quality Assurance
QSM-WHO	Quality Assurance and Safety of Medicines (WHO)
R&D	Research and Development
RAPS	Regulatory Affairs Professionals Society
RCT	Randomised Clinical Trials
RDE	Remote Data Entry
RDS	Research Defence Society
REC	Research Ethics Committee

RGN	Registered General Nurse
RPSGB	Royal Pharmaceutical Society of Great Britain
RSM	Royal Society of Medicine
Rx	Prescription (YOU TAKE)
SARS	Severe Acute Respiratory Syndrome
SCDM	Society for Clinical Data Management
SIDS	Sudden Infant Death Syndrome
SIGAR	Special Interest Group on Adverse Reactions
TGA	Therapeutic Goods Administration, Australia
TMF	Trial Master File
TUFAM	General Directorate of Pharmaceuticals and Pharmacy, Turkey
UDV	Unit Dose Vial
UKECA	United Kingdom Ethics Committee Authority
USP	United States Pharmacopoeia
WIPO	World Intellectual Patent Office

SCHEDULES TO THE RULES

SCHEDULES	THE RULES
A	Perform for application for the licences, issues and renewal of licences, for sending memoranda under the Act.
B	Rates of fee for test or analysis by the Central Drugs Laboratory or the Government analysist.
C	List of biological and other special products whose import, sale, distribution and manufacturing are a governed by special provision.
C1	List of other special products whose import, sale, distribution and manufacturing are governed by special provision.
D	List of drugs exempted from the provisions of import of drugs.
E1	List of poisionous substances under the Ayurvedic (including Sidha) and Unani systems of medicine.

F & F1	Provisions applicable to the production, testing, storage, packing and labeling of biological and other Special products.
F2	Standards for surgical dressings.
F3	Standards for sterilized umbilical tapes.
FF	Standards of ophthalmic preparations.
G	List of substances that are required to be used only under medical supervision and which are to be labeled accordingly.
H	List of prescription drugs.
J	Disease or ailments which a drug may not purport to prevent or cure.
K	Drugs exempted from certain provision relating to manufacture of drugs.
M	GMP requirement of factory premises, plants and equipment.
M1	Requirement of factory premises etc. for manufacture of homoeopathic preparation.
M2	Requirement of factory premises etc. for manufacture of cosmetics.
N	List of minimum equipment for efficient running of a pharmacy.
O	Standard for disinfectant fluid.
P	Life period of drug.
Q	List of coals tar color permitted to be used in cosmetics.
R	Standard for mechanical contraceptive. CONDOMS
S	Standard for cosmetics.
T	Requirement of factory premises and hygienic condition for Ayurvedic (including Sidha) and Unani drugs.
U	Particulars to be shown in manufacturing, raw material and analytical records of drug.
U1	Particulars to be shown in manufacturing, raw material and analytical records of cosmetics.
V	Standard for patent or proprietary medicines.
W	List of drug which is to be marketed under generic names only.

X	List of drugs whose import, manufacture and sale, labeling and packaging are governed by special provision.
Y	Requirement and guideline on clinical trials for import and manufacture of new drug.

BETA BLOCKERS

Comparative information Pharmacological differences

Agents with intrinsic sympathomimetic action (ISA)

- Acebutolol,
- Carteolol,
- Celiprolol
- Mepindolol
- Oxprenolol
- Pindolol

Agents with greater aqueous solubility (hydrophilic beta blockers)

- Atenolol
- Celiprolol
- Nadolol,
- Sotalol

Agents with membrane stabilizing effect

- Acebutolol,
- Betaxolol,
- Pindolol,
- Propranolol

Agents with antioxidant effect

- Carvedilol,
- Nebivolol

INDICATION DIFFERENCES

Agents specifically indicated for cardiac arrhythmia

- Esmolol,
- Sotalol,
- Landiolol

Agents specifically indicated for congestive heart failure

- Bisoprolol,
- Carvedilol,
- Sustained-release metoprolol,
- Nebivolol

Agents specifically indicated for glaucoma

- Betaxolol,
- Carteolol,
- Levobunolol,
- Metipranolol,
- Timolol

Agents specifically indicated for myocardial infarction

- Atenolol,
- Metoprolol,
- Propranolol

Agents specifically indicated for migraine prophylaxis

- Timolol,
- Propranolol

Propranolol is the only agent indicated for control of tremor, portal hypertension, and esophageal variceal bleeding, and used in conjunction with α blocker therapy in phaeochromocytoma.

SOME IMP PH VALUE

Blood:	7.4
Tear	7.2
Skin	7.4
Secretion of Skin:	5.5
Gastric juice:	Infants: 5, Adults: 2
Saliva:	6.3-6.7
Urine:	4.4-8

Stool:	approx. 6
Bile Juice:	8-8.6
Semen:	7.2-8
Vagina:	3.8-4.5

MECHANISM OF ACTION

1-DNA Dependent RNA Polymerase- Rifampcin

2- RNA Dependent DNA Polymerase- Zidovudine

3-Proetin Synthesis Blocker- Erythromycin, Chloramphenicol & Tetracycline

4-ACE Inhibitor- Captopril

5-Ca Channel Blocker- Nifedipine, Diltiazem

6-COX Inhibitor- Asprin

7-GABA Facilitator- Benzodiazepines

8-Antimetabolites- Methotrexate

9-Loop Diuretics- Frusemide

10-High Ceiling Diuretics- Spironolactone

11-Alteration of bacterial DNA- Choloroquine

12-Inhibition of Viral replication- Amantidine, Acyclovir

13-H1 blocking agent- Mepyramine, Loratadine

14-H2 Blocking agent- Rantidine, Cimetidine, Famotidine, Cyprohaptidine

15-Proton Pump inhibitor- Omeprazole

16-DNA Metabolism Inhibitors- Quinacrine (Mepacrine)

17-Spindle Poison- Vinca, Griesofulvin

18-Folic acid synthesis inhibitor- DDS

19-GABA Inhibitor- Sodium Valproate

20-DNA Synthesis Prevention – Nalidixic Acid

21-Prostaglandin Synthesis Inhibition- Oxyphenbutazone, Ibuprofen

22-Mycolic acid synthesis inhibition- INH

23-Folic acid antagonist- MTX, PAS, DDS & Primethamine

24-Desruption of DNA structure- MNZ

25-Inhibition of cell wall synthesis- Beta lactam antibiotics (penicillin)

26-Release of nor epinephrine- Ephedrine

27-Ergosterol Biosnythesis Inhibitors- Clotrimazole, Miconalzole, Ketoconazole

28-Ach esterase inhibitors- Physostigmine, Neostigmine, Edrophonium, Metrifonate

29-Reverse Transcriptase Inhibitors- Stavudine, zidovudine

30-Inhibition of HIV Protease- Amepranavir

31-DNA Gyrase Inhibitor- Cinoxacin

32-Inhibition of DNA Polymerase-Gossypol

33-NMDA Receptor Antagonist- Amantadine, Ketamine, Dextromethorphan, Memantine & Nitrous Oxide

34-DNA intercalating agent- Daunorubicin, Doxorubicin, Ellipticin & Ethidium Bromide

35-Antim mitotic agent- Amphethenile

36-Alkylating agent- Thiotepa

37-Alpha receptor antagonist- Phentolamine

38-Beta receptor antagonist- Propanolol, Aplrenolol

39-Alpha receptor agonist- Norepinehrine

40- Beta receptor agonist- Isoproterenol & Salbutamol

41-DNA Adduct Formation- Procarbazine

42-Carbonic anhydrase inhibitor- Acetazolamide

43-Phosphodiestrase Inhibitor- Theophylline

44-Thrombin action prevention- Heparin

45-Xanthine oxidase inhibitor- Allopurinol

46-Cholinergic Blockade- Ipratropium

47-Adenosine Deaminase inhibitor- Crisnatapase

48-Immunomodulation- Imiquimod

49-Amino acid transfer interference- Econazole

50-Mast Cell Stabilization- Ketosifen

MUST DO THIS TABLE IMP FROM JURI

SR NO	ORGANISATION	LOCATION
1	BCG Vaccine Lab	Chennai
2	Central drug testing lab (CDTL)	Mumbai
3	Central drug Laboratory (CDL)	Kolkata
4	Central Drug Research Institute (CDRI)	Lucknow
5	Central Research Institute (CRI)	Kasauli

6	Indian Drug Manufactures Association (IDMA)	Mumbai
7	Indian Society of Blood Trensfusion & Immunoheamatology	Pune
8	Indian Veterinary Research Institute (IVRI)	Izatnagar
9	Central Indian Pharmacoepia Laboratory (CIPL)	Ghaziabad
10	National Plasma Fractionation Centre (NPFC)	Mumbai
11	National Institute for Communicable Disease (NICD)	New Delhi
12	Indian Institute for Virology (IIV)	Pune
13	Organization of Pharmaceutical Procedures	Mumbai
14	Dabur Research foundaion	Ghaziabad
15	Institute of applied man power research	New Delhi
16	CD Testing Lab	Mumbai
17	Synthetic Drug Plant	Hyderabad
18	National Institute of Nutrition (NIN)	Hyderabad
19	National Brain Research Institute (NBRI)	Manesar (Gurgaon)

IMPORTANT PHARMACOLOGICAL TERMS:

•Antagonism

–The opposition between 2 or more medications ex. narcotics and Naloxone

•Bolus

–A single, often large dose of a drug. Often the initial dose

•Cumulative action

–An increased effect caused by multiple doses of the same drug. Caused by buildup in the blood.

•Hypersensitivity

–A reaction to a drug that is more profound than expected and which often results in an exaggerated immune response

•Idiosyncrasy

–A reaction to a drug that is significantly different from what is expected

•Indication

–The medical condition for which the drug has proven therapeutic value.

•**Parenteral**

–Any route of administration other than the digestive tract

•**Pharmacodynamics**

–Study of the mechanisms by which drugs act to produce biochemical or physiological changes in the body

•**Pharmacokinetics**

–Study of how drugs enter the body, reach their site of action and are eliminated from the body.

•**Potentiation**

–The enhancement of a drug's effect by another drug

–Eg. Promethazine may enhance the effect of morphine; also alcohol and barbiturates

•**Refractory**

–The failure of a patient to respond as expected to a certain medication

•**Synergism**

–The combined action of 2 or more drugs that is greater than the sum of the 2 drugs acting independently.

•**Therapeutic Action**

–The intended action of a drug given in an appropriate medical setting

•**Therapeutic Threshold**

–The minimum amount of a drug that is required to cause the desired response

•**Therapeutic Index**

–The difference between the therapeutic threshold and the amount of the drug considered to be toxic

–Often referred to as Safe and Effective range.

•**Tolerance**

–The decreased sensitivity or response to a drug that occurs after repeated doses

–Increased doses are required to achieve the desired effect

• **Untoward Effect**

–A side effect of a drug that is harmful to the patient

STERILIZATION OF MEDIA

In almost all cases, once a medium is made, it must be treated to eliminate any microorganisms contaminating containers, media ingredients, weighing papers, or other

surfaces that come in contact with the medium. If this is not performed correctly, contaminates arise during incubation, making microbiological investigations impossible. Sterilization is defined as the inactivation (or removal) of all life forms (including the pseudo-life forms, viruses) in a specific area. Culture media must be made sterile without inactivating nutrients necessary for growth of the microorganism. Equipment and media used in the microbiology laboratory are most often sterilized using one of the methods outlined below.

Autoclaving - moist heat (121°C) under pressure (15-17 lb/in2)

Mode of action - coagulates proteins

Materials - heat stable items such as most culture media, glass and metal, but not plastics

Oven - dry heat (160°C for several hours)

Mode of action - coagulates proteins

Materials - glass and metals but not liquids nor plastics

Filtration - 0.22 to 0.45 µm pore size

Mode of action - prevents organisms from passing through the filter, but does allow viruses to pass so therefore not sterilization in true sense.

Materials - Solutions of heat sensitive compounds such as some amino acids, vitamins, sugars etc.

Radiation - ultraviolet light or gamma rays

Mode of action - damages nucleic acids

Materials - heat sensitive solids such as plastics, however effective on surfaces only

Gas - ethylene oxide

Mode of action - inactivates enzymes

Materials - heat sensitive solids such as some plastics.

Temperature Relationships

Microorganisms as a whole, are able to grow at a tremendous range of temperatures. Bacteria have been discovered growing near the Galopagos trench (a marine ocean vent) at temperatures of 110°C and in super-cooled foods as low as -12°C. The temperature range that a specific microorganism is able to grow at is thought to be limited by the activity of its enzymes and the fluidity of the membrane. Extreme temperatures either prevent enzymes from carrying out their reactions quickly enough (at low temperatures) or denature (inactivate) enzymes (at high temp and sometimes low temperatures). It is also possible that temperature has its effect by interfering with the fluidity of membranes, too fluid at high

temperatures, frozen at low temperatures. Overly fluid membranes cannot maintain their intergrety and leak, frozen membrane cannot perform vital functions such as electron transport.

Microbes can be classified by their **optimum** temperature for growth.

Organisms having an optimum of **<20°C** are termed **Psychrophiles.**
Those that grow optimally from **20 to 45°C** are called **Mesophiles**.
Microorganisms that have temperature optima of **>45°C** are termed **Thermophiles**.

It is possible for an organisms to have an optimum temperature in one classification, but be capable of growing at temperatures much above or below the optimum. For example, *Bacillus coagulans* is capable of growth at mesophillic temperatures, but will also grow at temperatures of 55-60°C. These organisms are termed facultative thermophiles.

Microorganisms will cease to grow below their optimum temperature, but frequently will survive in an inert state. In fact refrigeration or freezing of bacteria can have a preservative effect. Most microorganisms are killed above the optimum temperature

SOME IMPORTANT NOTES FOR GPAT AND NIPER EXAM

Partition Coefficient:

OCTANOL: water partition coefficient often used in formulation development.

Q10 Method of Shelf Life Estimation:

Shelf life estimation

Q10 = e {(Ea/R) [(1/T + 10) – (1/T)]}

Arrhenius Equation: log = k2\k1 = Ea (T2 – T1)\ 2.3 RT1T2

Shelf Life Estimates:

Q10 = [K (T+10)]/KT =e [(Ea /R) ({1/T+10} {1/T}]

Q10 = 2 Lower limit

Q10 = 3 Average, best estimate

Q10 = 4 Upper limit

t90 Equation for Shelf Life Estimates:

t90 (T2) = t90 (T1)/Q10 (Delta T/10).

Note: A "+" Delta T decreases shelf life and a "-" Delta T increases shelf life.

Sweetening Agents:

- Dextrose
- Mannitol
- Saccharin
- Sorbitol
- Sucrose

Preservative Utilization:

- •Benzoic acid/sodium benzoate
- •Alcohol
- •Phenylmercuric nitrate/acetate
- •Phenol
- •Cresol
- •Chlorobutanol
- •Benzalkonium chloride
- •Methyl paraben/propyl paraben
- •Others

Preservatives may be used alone or in combination to prevent the growth of microorganisms.

Alcohols

Ethanol is useful as a preservative when it is used as a solvent. It needs a relatively high concentration (> 10%) to be effective.

Propylene glycol also used as a solvent in oral solutions and topical preparations. It can function as a preservative in the range of 15 to 30%. It is not volatile like ethanol.

Acids

- → **Benzoic acid** and **sorbic acid** have low solubility in water.
- → They are used in a concentration range from **0.1 % to 0.5%.**
- → Only the non-ionized form is effective and therefore its use is restricted to preparations with a pH below 4.5.

Esters

Parabens are esters (methyl, ethyl, propyl and butyl) of p-hydroxybenzoic acid.

- → They are used widely in pharmaceutical products
- → They are effective and stable over a pH range of **4 to 8.**
- → They are employed at concentrations up to about **0.2%.**
- → Frequently 2 esters are used in combination in the same preparation.
- → To achieve a higher total concentration
- → To be active against a wider range of microorganisms.

Quaternary Ammonium Compounds

- ❖ **Benzalkonium chloride** is used at a relatively low concentration **0.002 to 0.02%.**
- ❖ This class of compounds has an optimal activity over the pH range of 4 to 10 and is quite stable at most temperatures.
- ❖ Because of the cationic nature of this type of preservative it is incompatible with many anionic compounds.

Antioxidants

Vitamins, essential oils & almost all fats and oils can be oxidized.

Oxidation reaction can be initiated by:

1. Heat: maintain oxidizable drugs in a cool place

2. Light: use of light- resistant container

3. Heavy metals (e.g. Fe, Cu): effect of trace metals can be minimized by using citric acid or ethylenediamine tetraacetic acid (EDTA) i.e. sequestering agent.

Antioxidants as propyl & octyl esters of gallic acid, tocopherols or vitamin E, sodium sulfite, ascorbic acid (vit. C) Can be used.

•SWEETENING AGENTS

Sucrose is the most widely used sweetening agent.

Advantages: Colourless, highly water soluble, stable over a wide pH range (4-8), increase the viscosity, masks both salty and bitter taste, has soothing effect on throat.

Polyhydric alcohols (sorbitol, mannitol and glycerol) possess sweetening power and can be used for diabetic preparations.

Humectants: such as glycerin and sorbitol (5-20% in MW)

- ❖ Increase the viscosity of the preparation
- ❖ Enhance the sweetness of the product
- ❖ Improve the preservative qualities of the product.

Surfactants: Non-ionic and anionic surfactants aid in the solubilization of flavors and in the removal of debris by providing foaming action. **Cationic surfactants such as cetylpyridinium chloride** are used for their antimicrobial properties, but these tend to impart a bitter taste.

Flavours: are used in conjunction with alcohol and humectants to overcome disagreeable tastes. The principle flavoring agents are **peppermint, cinnamon, menthol or methyl salicylate.**

Otic Solutions:

The main classes of drugs used for topical administration to the ear include local anesthetics, **e.g.:** benzocaine; antibiotics e.g.; neomycin; and anti-inflammatory agents, e.g.; cortisone.

Polyols (e.g. glycerin or sorbitol) may be added to

- retard crystallization of sucrose or increase the solubility of added ingredients.

Invert sugar

D is more readily fermentable than sucrose

D tend to darken in color

C retard the oxidation of other substances.

The levulose formed during inversion is sweeter than sucrose; therefore the resulting syrup is sweeter than the original syrup.

When syrup is overheated it caramelizes.

The sucrose in the **66.7% w/w solution** must be at least **95% inverted.**

MUCILAGES

The official mucilages are thick viscid, adhesive liquids, produced by dispersing gum (acacia or tragacanth) in water.

Mucilages are used as suspending agents for insoluble substances in liquids; their colloidal character and viscosity prevent immediate sedimentation.

Synthetic agents e.g. carboxymethylcellulose (CMC) or polyvinyl alcohol are nonglycogenetic and may be used for diabetic patients.

ELIXIRS

Are clear, pleasantly flavored, sweetened hydroalcoholic liquids intended for oral use.

They are used as flavors and vehicles

E.g. Dexamethasone Elixir USP and Phenobarbital Elixir USP.

COLLODIONS:

Are liquid preparations containing pyroxylin (a nitrocellulose) in a mixture of ethyl ether and ethanol

Rubefacient

A substance for external application that produces redness of the skin e.g. by causing dilation of the capillaries and an increase in blood circulation.

Counterirritant

A medicine applied locally to produce superficial inflammation in order to reduce deeper inflammation.

Effervescent tablet:

contain acid substances **(citric and tartaric acids) and carbonates or bicarbonates** and which react rapidly in the presence of water by releasing carbon dioxide.

Oxymels: These are preparations in which the vehicle is a mixture of acetic acid and honey.

Magnesium sulphate: Magnesium cause smooth muscle relaxation secondary to inhibition of calcium uptake.

Atopy is strongest predisposing factor for developing asthma.

Asthma is a **chronic inflammatory disorder of the airways** in which many **cells & cellular elements play a role**

(Mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, & epithelial cells).

Child-onset asthma

–Associated with **Atopy**

–**IgE** directed against common **environmental antigens**

(House-dust mites, animal proteins, fungi

–**Viral wheezing** Infants/children, allergy/allergy history associated with **continuing asthma** through childhood.

Leukotriene modifiers:

- Zafirlukast - leukotriene receptor antagonist
- Zileuton - 5-lipoxygenase inhibitor is alternative therapy to low doses of inhaled steroids/nedocromil/cromolyn. 5-lipoxygenase inhibitor

Long-acting beta2-agonists (LABA)

Beta2-receptors are the predominant receptors in bronchial smooth muscle Stimulate ATP-cAMP which leads to relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity Inhibits release of mast cell mediators such as histamine, leukotrienes, and prostaglandin-D2. Beta1-receptors are predominant receptors in heart, but up to 10-50% can be beta2-receptors.

Long-acting beta2-agonists (LABA)

- Salmeterol (Serevent)
- Salmeterol with fluticasone (Advair).
- Albuterol

DRUGS AND SCHEDULE

Schedule I

Drugs in this schedule have a high abuse potential (narcotic and hallucination effects). Examples are **heroin, marijuana.**

Schedule II

Drugs in this schedule have a high abuse potential with severe psychic or physical dependence liability. Included are certain narcotic analgesics, stimulants, and depressant drugs. Examples are opium, morphine, codeine, hydromorphone, methadone, meperidine, oxycodone, anileridine, cocaine, amphetamine, methamphetamine, phenmetrazine, methylphenidate, amobarbital, pentobarbital, secobarbital, methaqualone, and phencyclidine.

Schedule III

Drugs in this schedule have an abuse potential less than those in Schedules I and II and include compounds containing limited quantities of certain narcotic analgesic drugs, and other drugs such as barbiturates, glutethimide, methyprylon, and chlorphentemine. Any suppository dosage form containing amobarbital, secobarbital, or pentobarbital is in this schedule.

Schedule IV

Drugs in this schedule have an abuse potential less than those listed in Schedule III and include such drugs as barbital, phenobarbital, chloral hydrate, ethchlorvynol, meprobabmate, chlordizepoxide, diazepam, oxazepam, chloroazepate, flurazepam, etc.

Schedule V

Drugs in this schedule have an abuse potential less than those listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotic analgesic drugs used for **antitussive and antidiarrheal** purposes.

SOME IMP PONTS FROM PHARMACEUTICS

Creams – semisolid emulsion systems (o/w, w/o) containing **more than 10% of water.**

Pastes – semisolid dispersion system, where a **solid particles (> 25%, e.g. ZnO)** are dispersed in ointments – mostly oleaginous (Petrolatum).

Antioxidants which act by providing electrons and easily available hydrogen atoms that acceptable more readily by the **free radicals** (atoms containing one or more unpaired electrons as molecular oxygen O-O or free hydroxyl group (OH)

Examples of Antioxidants: Na2SO3, NaHSO3, H3PO2 and Ascorbic

In oligeanous preparation –

- ✓ Alpha tocopherol,
- ✓ BHA (butylhydroxyanisole),
- ✓ BHT (butyl hydroxytoluene)
- ✓ Ascorbic palmitate.

EXAMPLES:

Epinephrine preparations - Adrenergic - do not use the if it is brown or contains precipitate

Nitroglycerin Tablets - Antianginal - to prevent loss of potency, keep these tablets in the original container

Paraldehyde - Hypnotic - subject to oxidation to form acetic acid.

POLYMORPHISM:

Important factor on formulation is the crystal or amorphous from of the drug substance.

The amorphous form of a compound is always **more soluble** than a corresponding **crystal form**.

The most widely used methods are hot stage microscopy, thermal analysis, **infrared spectroscopy, and x-ray diffraction.**

PROBABLE MODES OF ACTION OF SOME PRESERVATIVES

1. **Benzoic acid, boric acid, p-hydroxybenzoates:** Denaturation of proteins.
2. **Phenols, chlorinated phenolic cmpds:** lytic, denaturation action on cytoplasmic membranes and for chlorinated preservatives, also by oxidation of enzymes
3. **Alcohols:** lytic and denaturation action on membranes.

Quaternary compounds: Lytic action on membranes.

4. **Mercurials:** Denaturation of enzymes by combining with **thiol (-SH) groups.**

Flavoring Agents

******* To mask effectively the unwanted or disagreeable taste of drugs

In general, **low molecular weight are salty, like NaCl, KCl, NH4Cl, NaBr** and higher molecular salts are **bitter** except some lead salts.

Examples: Anise oil, Cinnamon, Peppermint, and Orange.

With organic compounds, an increase in the number of OH group seems to increase the sweetness of the compound. **Sucrose** which has **8 OH group**s is sweeter than **glycerin** which has **3 OH groups.**

SWEETENING PHARMACEUTICALS

SACCHARIN = metabolized and excreted by the kidneys virtually unchanged.

CYCLAMATE = metabolized or processed in digestive tract and it's by product are excreted by the kidneys.

ASPARTAME = breaks down in the body into three basic components: the amino acids **phenylalanine and aspartic acid, and methanol**.

Because of its metabolism to phenylalanine, the use of aspartame by persons with phenylketonuria (PKU) is discourages, and diet foods and drinks must bear appropriate label warning.

Saccharin and cyclamate were "Generally Recognized as Safe" or what is known as **GRAS.**

ACESULFAME = is more stable than aspartame at elevated temperature;

It is use in candy, chewing gum, confectionery, and instant coffees and teas.

STEVIA POWDER = Stevia *Rebaudiana bertoni*.

It is natural, nontoxic, safe, and about **30 times** as sweet as cane sugar, or sucrose.

AESTHETIC VALUE

Liquid preparations - the amount is ranging from **0.0005 to 0.001%** depending upon the colorant and intensity desired **Solid or powdered, Compressed Tablets** - generally larger proportion is required **(0.1% Ointments, suppositories, opthalmic and parenteral** -no color additives)

DISSOLUTION APPRATUS IP AND USP

APPRATUS	IP	USP
Apparatus 1	Paddle (37º)	Basket (37º)
Apparatus 2	Basket (37º)	Paddle (37º)
Apparatus 3	Reciprocating Cylinder (37º)	Reciprocating Cylinder (37º)
Apparatus 4	Flow-Through Cell (37 º)	Flow-Through Cell (37 º)
Apparatus 5	Paddle over Disk (32º),	Paddle over Disk (32º),
Apparatus 6	Cylinder (32º)	Cylinder (32º)
Apparatus 7	Reciprocating Holder	Reciprocating Holder

SOME IMP DRUG INTREACTION

S.N	DRUG INTERACTION	EFFECT
1	Aluminium Hydroxide Gel + Pseudoephedrine	Decrease effect of that drug due to increases pH of gastric fluid
2	Ciprofloxacin + Theophyline	Increases plasma level of Theophyline
3	Aminoglycoside + beta- Lactam antibiotics	synergestic effect but if given in same syring it‘s become inactive due to complex formation
4	Cortisone + Ampicillin=	Antagonist

5	Erythromycin /Clarithromycin/ Telrithromycin + Carmazepam/ Phenytoin =	Increases level of Carbamazapine and Phenytoin
6	Methotrexate + Sulfamethoxazole	Displace from binding site and increases free plasma concentration of drug
7	Amphotericin B + Flucytosine	Synergestic effect
8	Ketoconazole + Amphotericin B	Antagonized effect due to decreases ergosterol level
9	Azoles (including All) + Terbinafine	Contraindicated
10	Posconazole + Ergot alkaloid	Contraindicate
11	Cimetidine + Terbinafine	increases plasma concentration of Terbinafine
12	Gresiofulvin + Alcohol	Potentiate toxicity of alcohol
13	Miconazole+ Warfarin	inhibit metabolism of warfarin
14	MAO inhibitors + Pethidine	Hyperpyrexia
15	TCA + SSRIs	TCA toxicity

GOLD NUMBER & PROTECTION OF COLLOIDS

• Lyophilic sols are more stable than lyophobic sols.

• Lyophobic sols can be easily coagulated by the addition of small quantity of an electrolyte.

• When a lyophilic sol is added to any lyophobic sol, it becomes less sensitive towards electrolytes. Thus, lyophilic colloids can prevent the coagulation of any lyophobic sol.

"The phenomenon of preventing the coagulation of a lyophobic sol due to the addition of some lyophilic colloid is called sol protection or protection of colloids."

• The protecting power of different protective (lyophilic) colloids is different. The efficiency of any protective colloid is expressed in terms of gold number.

GOLD NUMBER

Zsigmondy introduced a term called gold number to describe the protective power of different colloids.

This is defined as, "weight of the dried protective agent in milligrams, which when added to 10 ml of a standard gold sol (0.0053 to 0.0058%) is just sufficient to prevent a colour change from red to blue on the addition of 1 ml of 10 % sodium chloride solution, is equal to the gold number of that protective colloid."

Thus, smaller is the gold number, higher is the protective action of the protective agent.

Protective power ∝ 1/Gold number

HYDROPHILIC SUBSTANCE	GOLD NUMBER
Gelatin	0.005 - 0.01
Sodium oleate	0.4 – 1.0
Sodium caseinate	0.01
Gum tragacanth	2
Hamoglobin	0.03 – 0.07
Potato starch	25
Gum arabic	0.15 – 0.25

IMP YEARS LIST: USEFUL FOR GPAT & NIPER JEE

1935	RBI established
1949	RBI Nationalized
2005	RTI ACT
2005	Product Patent In India
1956	Companies Act
1932	Partnership Act
1993	End of GATT era
1997	National Pharmaceutical Pricing Authority (NPPA)
1994	Dolly sheep – First clone
1950	First Planning Commission
1984	Hatch-Waxman Act
1955	SBI nationalized

2005	IPC constituted
1896	First Olympics
2000 (26 Jan.)	Human Genome Revealed
1970	Indian Patents Act
1919	Poison Act
1948	Pharmacy Act
1940	Drug and Cosmetic Act
1930	Dangerous Drug Act
1857	Opium Act
1954	Drug and Magic Remedies Act
1971	Medical Termination of Pregnancy Act (MTP)
1989	First ICH Indian pharmacopoeias:
1955	1st Edition IP
1966	2nd Edition IP
1985	3rd Edition IP
1996	4th Edition IP
2007	5th Edition IP
2010	6th Edition IP
2014	7th Edition IP

LIST OF WELL KNOWN POISONS & ANTIDOTES

POISONING	**ANTIDOTE USED**
Paracetamol	N-acetylcysteine
Anticoagulants (warfarin)	Vitamin K
Opioids	Naloxone
Iron (&other heavy metals)	Desferrioxamine, Deferasirox or Deferiprone
Benzodiazepines	Flumazenil
Ethylene glycol	Ethanol or fomepizole, and thiamine, methanol - ethanol or fomepizole, and folinic acid
Cyanide	Amyl nitrite, Sodium nitrite and Sodium thiosulfate
Organophosphates	Atropine and Pralidoxime

Magnesium	Calcium Gluconate
Ca++ Cha. Blockers Vera, Dilti. CCB	Calcium Gluconate
Beta-Blockers (Propranolol, Sotalol)	Calcium Gluconate and/or Glucagon
Isoniazid	Pyridoxine
Atropine	Physostigmine
Thallium	Prussian blue
Hydrofluoric acid	Calcium Gluconate
Anticholinergics	Cholinergics (&vice-versa)

SOME IMPORTANT FACTS GPAT NOTES

1. Lipid insoluble and water insoluble drugs are not absorbed from gut.
2. Most of the drugs are weakly acidic are weakly basic because stronger forms has high ability to form corresponding ions.
3. Most (90%) of drugs absorbed through passive diffusion(non-ionic diffusion)
4. 0% protein binding – Lisinopril
5. 99% protein binding - oxyphenbutazone (metabolite of phenylbutazone)
6. To show an efficient drug action protien binding should be moderate, insufficient protein binding shows less Vd & high protein binding lessens amount of drug at active site.
7. Extent of binding ----- albumin > acid glycoprotein > lipoprotein > globulins.
8. Drug having less Vd means its not bioavailable.(i.e decresed rate & amount of drug)
9. Bioavailability of Higher to Lower ------- parenteral > oral > rectal > topical.
10. Short acting barbiturates are due its rapid rate of distribution from brain.
11. Only unbounded drug (free form) undergoes metabolism.
12. The unbound drug 1st reaches liver from where it goes to other parts like kidneys
13. Only lipid soluble and non-ionic drugs can enters brain.
14. All orally administerd drugs undergo first pass metabolism.
15. Propanolol & Ca++ channel blockers have extensive first pass metabolism.
16. Mainly metabolism occurs to excrete the drug.
17. Acidic drugs are exerted at basic pH & vice-versa.
18. Absorption, Distribution, Elimination follows 1st order kinetics.
19. Drugs showing 0 order elimination kinetics are asprin, ethanol, phenytoin, Theophyline, Tolbutamide, phenylbutazone, Warfarin, Heparin, salicylates etc.

20. Metabolism, Protein binding, carrier mediated transport at saturated conditions, IV infusion IM implants, osmatic pumps undergo 0 order kinetics i.e rate or process directly proportional to concentration or amount of reactants.

COUNTRY – CAPITAL – CURRENCY IMP FOR GPAT & NIPER JEE EXAM

COUNTRY – CAPITAL – CURRENCY

1. France – Paris – France
2. Germany – Berlin – Deutsche Mar
3. Greece – Athens – Drachma
4. Hong Kong - Victoria – Dollar
5. India - New Delhi – Rupee
6. Indonesia - Jakarta – Rupiah
7. Iran - Teheran – Rial
8. Iraq - Baghdad – Dinar
9. Ireland – Dublin – Pound
10. Italy - Rome – Lira
11. Japan – Tokyo – Yen
12. Kenya - Nairobi – Shilling
13. Malaysia - Kuala Lumpur – Ringgit
14. Nepal – Kathmandu – Rupee
15. New Zealand - Wellington – Dollar
16. Oman - Muscat – Rial
17. Pakistan – Islamabad – Rupee
18. Qatar – Doha – Riyal
19. Russia - Moscow – Ruble
20. Saudi Arabia – Riyadh – Rial
21. Singapore – Singapore City – Dollar
22. South Africa - Madrid – Rand
23. Spain – Madrid – Peseta
24. Sri Lanka - Colombo – Rupee
25. Sweden - Stockholm – Krona
26. Switzerland – Berne – France
27. Russia – Moscow – Ruble
28. Ukraine – Kiev – Hyrvnia

29. Azerbaijan – Baku – Ruble
30. Thailand – Bangkok – Baht
31. United Arab Emirates (UAE) – Abu Dhabi – Dirham
32. United Kingdom (UK)-London – Pound Sterling
33. United States of America (US) -Washington – Dollar
34. Yemen – Sana – Rial
35. Zimbabwe -Harare – Dollar

DRUGS BANNED IN INDIA

- Tetracycline liquid oral suspension
- Penicillin skin/eye ointement
- Methaquinone
- Oxytetracycline liquid oral preperations
- Demeclocycline liquid oral preperations
- Rosiglitazone
- Astemizole
- Terfinadine

DIFFERENT TESTS FOR CARBOHYDRATES

Name of test	Use
Molisch test	reducing sugars
Iodine test	Starches
Benedicts reagent test	Reducing sugars
Barfords Test	Same like Molisch test but reduction carried in mild acidic medium .to distinguish monosaccharide from disaccharides. - reducing sugars.
Seliwanoffs Test	Ketohexoses
Foulgers Test	Ketohexoses
Rapid furfural test	Ketohexoses
Osazone Test	-
Sucrose hydrolysis test	Sucrose

DIFFERENT TESTS FOR AMINO ACIDS AND PROTEINS

NAME OF TEST	USE
Biuret reaction	Two peptide linkage
Ninhydrin reaction	Alfa amino acids
Xanthoproteic reaction	Aromatic amino acids like, Phenylalanine, tyrosine, tryptophan
Milons reaction	Phenolic amino acids (tyrosine)
Hopkins kole reaction	Indole ring (tryptophan)
Sakaguchi reaction	Guanidino group (arginine)
Nitroprusside reaction	Sulfahydryl group (cysteine)
Sulfer test	Sulfahydryl group (cysteine)
Pauly's test	Imidazole ring (histidine)
Folin coicateau's test	Phenolic group (tyrosine)

DIFFERENT TESTS FOR BIOCHEMICAL CONSTITUENTS OF BODY

NAME OF TEST	USE/ DETECTION
Sodium hypobromide test	Urea
Specific urease test	Urea
Benedicts uric acid test	Uric acid
Mureoxide test	Uric acid (caffine, Theophyline etc.)
Jaffe's test	Creatinine
Benzatidine test	Blood in urine etc.
Rothera test	Ketone bodies
Hay's rest	Bile salt
Petterkofer's test	Bile salt
Gmelin test	Bile pigments
Fouchets test	Bile pigments

Folin wu method	Blood glucose estimation
O-toulidine method	Blood glucose estimation
Glucose –oxidase peroxidase (GOD-POD)	Blood glucose estimation
Van den Bergh reaction	Serum bilirubin
Henry-Caraways method	Serum uric acid
Western blot TEST	confirmatory test for AIDS

MECHANISM OF ACTION

1- DNA Dependent RNA Polymerase- Rifampcin

2- RNA Dependent DNA Polymerase- Zidovudine

3-Proetin Synthesis Blocker- Erythromycin, Chloramphenicol & Tetracycline

4-ACE Inhibitor- Captopril

5-Ca Channel Blocker- Nifedipine, Diltiazem

6-COX Inhibitor- Asprin

7-GABA Facilitator- Benzodiazepines

8-Antimetabolites- Methotrexate

9-Loop Diuretics- Frusemide

10-High Ceiling Diuretics- Spironolactone

11-Alteration of bacterial DNA- Choloroquine

12-Inhibition of Viral replication- Amantidine, Acyclovir

13-H1 blocking agent- Mepyramine, Loratadine

14-H2 Blocking agent- Rantidine, Cimetidine, Famotidine, Cyprohaptidine

15-Proton Pump inhibitor- Omeprazole, ALL PRAZOLE

16-DNA Metabolism Inhibitors- Quinacrine (Mepacrine)

17-Spindle Poison- Vinca, Griesofulvin

18-Folic acid synthesis inhibitor- DDS

19-GABA Inhibitor- Sodium Valproate

20-DNA Synthesis Prevention – Nalidixic Acid

21-Prostaglandin Synthesis Inhibition- Oxyphenbutazone, Ibuprofen

22-Mycolic acid synthesis inhibition- INH

23-Folic acid antagonist- MTX, PAS, DDS & Primethamine

24-Desruption of DNA structure- MNZ

25-Inhibition of cell wall synthesis- Beta lactam antibiotics (Penicillin)

26-Release of nor epinephrine- Ephedrine

27-Ergosterol Biosnythesis Inhibitors- Clotrimazole, Miconalzole, Ketoconazole

28-Ach esterase inhibitors- Physostigmine, Neostigmine, Edrophonium, Metrifonate

29-Reverse Transcriptase Inhibitors- Stavudine, zidovudine

30-Inhibition of HIV Protease- Amepranavir

31-DNA Gyrase Inhibitor- Cinoxacin

32-Inhibition of DNA Polymerase-Gossypol

33-NMDA Receptor Antagonist-Amantadine, Ketamine, Dextromethorphan, Memantine & Nitrous Oxide

34-DNA intercalating agent- Daunorubicin, Doxorubicin, Ellipticin & Ethidium Bromide

35-Antim mitotic agent- Amphethenile

36-Alkylating agent- Thiotepa

37-Alpha receptor antagonist- Phentolamine

38-Beta receptor antagonist- Propanolol, Aplrenolol

39-Alpha receptor agonist-Norepinehrine

40- Beta receptor agonist- Isoproterenol & Salbutamol

41-DNA Adduct Formation- Procarbazine

42-Carbonic anhydrase inhibitor- Acetazolamide

43-Phosphodiestrase Inhibitor- Theophylline

44-Thrombin action prevention- Heparin

45-Xanthine oxidase inhibitor- Allopurinol

46-Cholinergic Blockade- Ipratropium

47-Adenosine Deaminase inhibitor- Crisnatapase

48-Immunomodulation- Imiquimod

49-Amino acid transfer interference- Econazole

50-Mast Cell Stabilization- Ketosifen

DRUG & THEIR IMORTANT SIDE EFFECT

1. Grey Baby Syndrome- Chloramphenicol
2. Pin Point Pupil, Straubb's syndrome-Morphine
3. Reyes Syndrome- Asprin
4. Urine Coloration- Rifampcin
5. Frontal Headache- Indomethacin
6. Captopril- Persistant dry cough
7. Bleomycin-Pulmonary fibrosis
8. Vancomycin- Red man syndrome
9. Nicotinic acid- Flush
10. Steven Johnsons syndrome- Allopurinol, Sulphonamides, Itraconazole
11. sulphonamides-kernicterus
12. aminoglycosides-ototoxicity
13. Discolouration of teeth-tetracyclines
14. Doxorubucin & duanorubucin- cardiomyopathy.
15. Chloroquine- Cardiotixicity, retinopathy, discolouration of hair
16. Doxycycline- esophageal ulceration
17. Vincristin & Vinblastin- Neuropathy

18).cyclophosphamide- Alopecia, Pancretitis

19. Cimetidine & Spironolactone- Gynaecomastia
20. Jaurisch hexheimer reaction- Penicillin
21. Blue baby syndrome- Amiodarone
22. Nephrotoxicity- Cisplatin
23. Shake and bake syndrome-Amphotericin B
24. S-Thallidomide-Phocomelia
25. Phenytoin-Gingival hyperplasia
26. Valproic acid-curling of hair
27. Carbamazepine-Aplastic anaemia
28. Anticholinergics-Atropine fever

MICROSCOPY OF SOME IMPOTANT DRUGS

1-Liquorice- Ulignified Septate fibre

2-Solanacoeus Plants- Anisocytic stomata

3-Rhubarb- Star spots

4-Squill- Ca oxide raphides

5-Cardamom- Clothing of glandular trichome

6-Quillaria- Thin membrane arillus

7-Digitalis- Rhytidomes & Glandular Trichomes

8-Atropa Belladona- Anisocytic Stomata

9-Verbascus Thapsus- Clusters of Ca Oxalate

10-Artemisia- T-Shaped Trichomes

11-Stromanium- Phloem Fibres

12-Nuxvomica – Lignified trichomes

13-Fennel- Reticulate lignified trichomes

14-Coriander- Wavy sclerenchyma

15-Indian Dill- Lateral ridges with vascular bundle

16-Anise- Branched & unbranched vittae

17-Cinnamon- Absence of cork & cortex

18-Ginger- Non Lignified vessels & starch grains, Endodermis with no starch

19-Collapsed Endodermis

20-Caraway-Collapsed Parenchyma

21-Chenopodium-Epidermis with no trichomes

22-Chirata- Stomata on lower surface only with no trichomes

23-Cinchona - Large sclerenchymatous bast cells with medullary ray.

24-Cinnamon- Parenchyma cells with starch.

25-Colchicum- Spiral Ducts, Parenchyma with starch

26- Coriander- Prismatic and aggregate crystals of calcium oxalate

27-Saffron- Trichome of stigma

28-Turmeric- Parenchyma with pasty starch

29-Digitalis- Glandular trichomes

30-Euclyptus- Crystal bearing fiber

31-Gentian- Large reticulate ducts

32-Liquorice- Parenchyma with crystals and starch

33-Hycyamus- Endosperm tissue with proteid granules and oil.

34-Ipecac- Parenchyma with raphides

35-Mentha- Trichomes, simple, showing cuticular markings (a medium sized trichome).

36-Pilocarpus- Aggregate crystals of calcium oxalate.

37-Podophyllum- Reticulate ducts and tracheids, Spiral duct,

Aggregate crystals of calcium oxalate, Cork

38-Quassia- Medullary ray with starch, large porous duct

39-Rheum- Parenchyma with starch, resin and crystals, reticulate ducts.

40-Senega- Parenchyma with fat, Cork & Porous duct.

41-Senna- Bast of vascular bundles, Crystal bearing fibers from vascular tissue

42-Stromanium- Parenchyma cells of petiole

43-Strophanthus- Endosperm tissue, showing oil and crystals, Outer tissue with granular proteid matter and starch

44-Tobbaco- Parenchyma (collenchymatous) from midrib, Leaf parenchyma with chlorophyll.

45-Ginger- Parenchyma with starch and one cell with resin

46-Belladona- Tracheids and spiral duct, Leaf parenchyma cells with crystals, Bast Cells, Porous ducts & Crystal Sand

DRUG OF CHOISE IMP FOR GPAT

1. Paracetamol poisoning - acetyl cysteine
2. Acute bronchial asthma - salbutamol
3. Acute gout - NSAIDS
4. Acute Hyperkalemia - calcium gluconate
5. Severe DIGITALIS toxicity - DIGIBIND
6. Acute migraine - sumatriptan
7. Cheese reaction - Phentolamine
8. Atropine poisoning - physostigmine
9. Cyanide poisoning - Amyl nitrite
10. Benzodiazepine poisoning - flumazenil
11. Cholera - tetracycline
12. KALA-AZAR - Lipozomal amphotericin- B
13. Iron poisoning - Desferrioxamine
14. MRSA - vancomycin
15. VRSA - LINEZOLID

16. Warfarin Overdose - vitamin-K
17. OCD - fluoxetine
18. Alcohol Poisoning - fomepizole
19. Epilepsy in pregnency - Phenobarbitone
20. Anaphylactic shock - Adrenaline

CANIZZARO REACTION

THE ALDEHIDE DO NO HAVE ALFA HIDROGEN GIVES CANIZARO REACTION IN PRESENCE OF CONCE. NaOH

2 Molecule of Aldehide + conc. NaOH => ALCOHOL + CARBOXILIC ACID

ONE MOLECULE OF ALDEHIDE GET REDCTION REACTION & PRODUCE ALCOHOL, OTHER GOT OXIDATION PRODUCE CARBOXILIC ACID

SOME IMPORTANT TOPICS FOR GPAT FROM TABLET AND CAPSULE

➢ PICKING AND STICKING

This is when the coating removes a piece of the tablet from the core. Overwetting or examples or excessive film tackiness causes tablets to stick to each other or to the coating pan. On drying, at the point of contact, a piece of the film may remain adhered to the pan or to another tablet, giving a **"picked"** appearance to the tablet surface and resulting in a small exposed area of the core. It is caused by over-wetting the tablets, by under-drying, or by poor tablet quality.

REMEDY: A reduction in the liquid application rate or increase in the drying air temperature and air volume usually solves this problem. Excessive tackiness may be an indication of a poor formulation.

➢ TWINNING

This is the term for two tablets that stick together, and it's a common problem with capsule shaped tablets.

REMEDY - Assuming you don't wish to change the tablet shape, you can solve this problem by balancing the pan speed and spray rate. Try reducing the spray rate or increasing the pan speed. In some cases, it is necessary to modify the design of the tooling by very slightly changing the radius. The change is almost impossible to see, but it prevents the twinning problem.

➢ COLOR VARIATION

This problem can be caused by processing conditions or the formulation. Improper mixing, uneven spray pattern and insufficient coating may result in color variation. The migration of soluble dyes, plasticizers and other additives during drying may give the coating a mottled or spotted appearance.

REMEDY:

1. The use of lake dyes eliminates dye migration.
2. A reformulation with different plasticizers and additives is the best way to solve film instabilities caused by the ingredients.

- **ORANGE PEEL EFFECT**

This refers to a coating texture that resembles the surface of an orange. Inadequate spreading of the coating solution before drying causes a bumpy or "*orange-peel*" effect on the coating. It is usually the result of high atomization pressure in combination with spray rates that are too high. This also indicates that spreading is impeded by too rapid drying or by high solution viscosity.

REMEDY: Thinning the solution with additional solvent may correct this problem.

- **MOTTLED COLOR**

This can happen when the coating solution is improperly prepared, the actual *spray rate differs from the target rate*, the tablet cores are cold, or the drying rate is out of specification.

- **CAPPING AND LAMINATION**

This is when the tablet separates in laminar fashion. Capping is partial or complete separation of top or bottom crowns of tablet main body. Lamination is separation of a tablet into two or more distinct layers. Friability test can be used to reveal these problems

The problem stems from improper tablet compression, but it may not reveal itself until you start coating. How you operate the coating system, however, can exacerbate the problem.

REMEDY: Be careful not to over-dry the tablets in the preheating stage. That can make the tablets brittle and promote capping.

- **ROUGHNESS**

A rough or gritty surface is a defect often observed when coating is applied by a spray. Some of the droplets may dry too rapidly before reaching the tablet bed, resulting in the deposits on the tablet surface of "spray dried" particles instead of finely divided droplets of coating solution. Surface roughness also increases with pigment concentration and polymer concentration in the coating solution.

REMEDY: Moving the nozzle closer to the tablet bed and reducing the degree of atomization can decrease the roughness due to "spray drying".

- **HAZING / DULL FILM**

This is sometimes called Bloom. It can occur when too high a processing temperature is used for a particular formulation. Dulling is particularly evident when cellulosic polymers are applied out of aqueous media at high processing temperatures. It can also occur if the coated tablets are exposed to high humidity conditions and partial salvation of film results.

- **BRIDGING**

This occurs when the coating fills in the lettering or logo on the tablet and is typically caused by improper application of the solution, poor design of the tablet embossing, high coating viscosity, high percentage of solids in the solution, or improper atomization pressure. During drying, the film may shrink and pull away from the sharp corners of an intagliation or bisect, resulting in a "bridging" of the surface. This defect can be so severe that the monogram or bisect is completely obscured.

REMEDY: Increasing the plasticizer content or changing the plasticizer can decrease the incidence of bridging.

- **FILLING**

Filling is caused by applying too much solution, resulting in a thick film that fills and narrows the monogram or bisect. In addition, if the solution is applied too fast, Overwetting may cause the liquid to quickly fill and be retained in the monogram.

REMEDY: Judicious monitoring of the fluid application rate and thorough mixing of the tablets in the pan can prevent filling.

- **EROSION**

This can be the result of soft or friable tablets (and the pan turning too fast), an over-wetted tablet surface, inadequate drying, or lack of tablet surface strength.

- **PEELING AND FROSTING**

This is a defect where the coating peels away from the tablet surface in a sheet. Peeling indicates that the coating solution did not lock into the tablet surface. This could be due to a defect in the coating solution, over-wetting, or high moisture content in the tablet core which prevented the coating to adhering.

- **CHIPPING**

This is the result of high pan speed, a friable tablet core, or a coating solution that lacks a good plasticizer

- **BLISTERING**

When coated tablets require further drying in ovens, too rapid evaporation of the solvent from the core and the effect of high temperature on the strength, elasticity and adhesion of the film may result in blistering.

REMEDY: Milder drying conditions are warranted in this case.

- **CRACKING**

It occurs if internal stresses in the film exceed the tensile strength of the film.

REMEDY: tensile strength of the film can be increased by Using higher molecular weight polymers or polymer blends.

TABLET AND CAPSULE MACHINES

1. Rotosort- for filled/unfilled capsule sorting machine and for de-dusting.
2. Rotofill- to fill pellets in hard gelatin capsule
3. Rotoweigh- A high speed capsule weighing machine.
4. Accogel- filling of dry powder in soft gelatin capsule.
5. Accofill- fill exact powder dose in hard gelatin capsule
6. Wurster- for coating.
7. Osaka- capsule filling machine (powder, granules)
8. Zanasi- capsule filling (powder, pellets, tablets)
9. Lily/parke-davis: capsule filling (powder)
10. Farmatic, holfiger & kary-liquid filling in HGC.
11. Erweka- De-dusting and polishing capsule machine.
12. Seidender- Uses a Belt for visual inspection.
13. Vericap 1200- capsule weighing machine.

PHYTOCHEMICAL SCREENING OF DIFFERENT CLASSES OF DRUGS IN PHARMACOGNOSY NOTES FOR GPAT

Phytochemical screening is done to identify the nature and type of constituents present in a drug. This technique is of extreme help when a new drug is being investigated for the chemical constituents. In phytochemical screening there are both general and specific tests for finding the nature of chemical constituents in the drug. This topic is very simple and short but contains due weightage in the GPAT due to its importance in the pharmacognosy. Here I am discussing the topic in detail stressing on the regions important from the perspective of GPAT.

❖ GENERAL CHEMICAL TESTS FOR ALKALOIDS:

Alkaloids are tested by the following reagents. Each reagent or test has accuracy and specificity.

i) Dragendroff's reagent- This reagent is constituted of Potassium Bismuth Iodide (PBI). Alkaloids give reddish brown color with the dragendroff's reagent.

ii) Mayer's reagent- This reagent is constituted of Potassium Mercuric Iodide (PMI). Alkaloids give cream color with the Mayer's reagent. Remember M for Mayer M for Mercuric

iii) Wagner's reagent- This reagent is constituted of Iodine Potassium Iodide (IPI). Alkaloids give reddish brown precipitate with the Wagner's reagent.

iv) Hager's reagent- This reagent is constitutes of Picric Acid. Alkaloids give yellow precipitate with the Hager's reagent.

v) Tannic acid- With tannic acid alkaloids give buff colored precipitate.

vi) Picrolinic acid- Yellow colored precipitate are produced with picrolinic acid.

❖ CHEMICAL TESTS FOR GLYCOSIDES:

❖ General test for glycosides- The general test for glycoside is as follows-

Test A- Dissolve the 200 mg drug with sulphuric acid. Then, add 5% NaOH solution for neutralization. Add Fehling solution A & B to the above mixture. Red color is produced.

Test B- Dissolve the 200 mg drug with sufficient amount of water. Add further water to dilute the solution. This solution is tested with Fehling solution A & B. Red color is produced from the reducing sugar present in the drug.

→ Compare the red color from the two tests of the drug.

→ If the color of test A is more intense than test B; glycoside presence confirmed.

❖ CHEMICAL TEST FOR ANTHRAQUINONE GLYCOSIDES-

Brontrager's test- This test is performed for the O-glycosides. Drug is dissolved in 1ml H_2SO_4 and mixture is boiled. Filter the solution, filterate is then mixed with chloroform. Chloroform layer mixed with ammonia gives rose pink color if O-glycosides are present.

Modified brontrager's test- This test is performed for the investigation of C-glycosides. Drug is mixed with H_2SO_4 and $FeCl_3$. The next procedure is same as for the O-glycosides in brontrager's test.

Hydroxy anthraquinones- Drug is mixed with Potassium Hydroxide. If hydroxy anthraquinones are present red color is present.

❖ CHEMICAL TEST FOR CARDIAC GLYCOSIDES-

Kedde's test- Extract the drug with $CHCl_3$. 90% alcohol with 2% 3, 5-dinitrobenzoic acid is added to the extract. To this mixture 20% NaOH is added. Purple color confirms the presence of cardiac glycoside.

Keller-killiani test- This test is performed only for the digitoxose sugar moiety. Drug is extracted with chloroform first. 0.4 ml acetic acid is added then along with $FeCl_3$. After adding H_2SO_4 if purple color is produced in the acid layer then presence of digitoxose sugar confirmed.

Raymond's test- Reagent used in this test is Methanolic alkali. Violet color confirms the presence of cardiac glycosides.

Legal's test- This test is performed by using pyridine and alkaline sodium nitroprusside is used. Red color is produced if cardiac glycoside is present.

Baljet test- Reagent used in this test is picric acid and sodium picrate. Orange color is produced in the presence of cardiac glycoside.

❖ CHEMICAL TEST OF CYANOGENETIC GLYCOSIDE-

Sodium picrate test- Drug is mixed with dilute H2SO4. After the addition of sodium picrate red color is produced in the presence of cyanogenetic glycoside.

Mercuric acetate test- After mixing the mercuric acetate with drug. Drug acetate is formed and mercury is separated out which confirms the presence of cyanogenetic glycoside.

❖ CHEMICAL TEST FOR STEROIDS & TERPENOIDS:

i) Liberman-Burchard test- Drug is mixed with acetic anhydride. To this mixture con. Sulfuric acid is added. There forms two layers with browning at the junction. Upper layer with green color represents steroids whereas lower layer represents terpenoids red color.

ii) Salwoski test- Drug is mixed with con. Sulfuric acid. Upper layer is of steroids which are red in color and lower yellow colored layer represents trirepenes.

iii) Sulphur powder test- If sulfur is added to the mixture of drug, sulfur sinks down the mixture.

❖ CHEMICAL TEST FOR FLAVONOIDS:

i) Shinoda test- Shinoda test is performed by adding magnesium along with the HCl in the drug mixture. Red/pink/green to blue color confirms the presence of flavonoids.

ii) Alkaline reagent test- As the name suggests, an alkaline reagent is used for this test. Sodium hydroxide is added to the drug. Yellow color is produced; if on addition of dilute acid this color disappears then it confirms the presence of flavonoids.

iii) ZnHCl test- Flavonoids give red color with the Zinc hydrochloride.

❖ E) CHEMICAL TESTS FOR TANNINS:

i) Gold beater's skin test- This is most common test for tannins. This test is performed on the membrane of OX. Goldbeater's skin is first treated with HCl and rinsed with distilled water. After this, this skin is paced in the solution of drug and rinsed with water. After addition of 1% FeSO4, brown or black color is produced in the skin due to the presence of tannins.

ii) FeCl3 test- Yellow color is produced with FeCl3 in the case of hydrolysable tannins whereas condensed tannins give green color.

iii) Phenazone test- Sodium phosphate is mixed with drug and filtered. To the filtrate phenazone is added which produce precipitate if tannins are present.

iv) Gelatin test- Precipitate is produced with gelatin which confirms the presence of tannins.

F) CHEMICAL TESTS FOR VOLATILE OILS:

i) Volatile containing drugs when mixed with alcoholic solution of Sudan III gives red color.
ii) Volatile oil containing crude drugs also produces red color with tincture alkane.

TABLET DOSAGE FORM

Tablet is the most common solid dosage forms prescribed and accepted worldwide. Although there are various types of tablets available in the market depending upon the size, use and formulation but the basic excipients used in the formulation of tablet are same everywhere.

- **What is tablet?**

In simple language, tablet is a solid dosage from comprised of active pharmaceutical ingredient along with several excipients for attaining the desirable biological and pharmaceutical properties. From an estimate, two-third of the prescribed medicines in the world is tablet. Most of the tablets are given through oral route but depending on the need and patient's concition it can also be given rectally, vaginally, buccally and sub-lingually.
Size and shape of the tablet also vary according to the formulation and need of the patient. Some tablets are just of few millimeters while other go up to 1 centimeter. Also, shape of the tablet can also be either oval, round, capsule shaped etc.
Formulation of the tablet: Different excipients used in the tablet

Beside from the active ingredient, tablet contains various other ingredients like diluents, binder, disintegrant, glidant and lubricant. Chief role of the excilients in the tablet formulation is to impart desirable pharmaceutical and biological properties to the tablet. Here is the detail of the different excipients used in the formulation of the tablet.

- **DILUENT**

The main role of the diluents in the tablet formulation is to impart bulk to the tablet. Generally, the active ingredient required in a single tablet ranges from 1 mg to 1000 mg. So,

it is not possible to make a tablet with such small weight therefore diluent is mixed with the active compound. Major diluents used in the tablet formulation include-

a) CaCO3- Insoluble in water

b) α-Lactose- Most common, inexpensive and inert

c) Mannitol- Used for chewable tablets

d) Microcrystalline cellulose- Increase disintegrant property also

- **DISINTEGRANTS**

Disintegrants are used for the purpose of breaking the tablet when introduced in the biological system. Mainly water and pH of the system are responsible for the disintegration of the tablet. Tablet after disintegration releases its active constituent into the system which exerts its pharmacological action. Disintegrants used in the tablet are-

a) Alginic acid/Na Alginate – Used concentration is 2-10% w/v

b) Na carboxy methyl cellulose (Nymcel) - Used concentration is 1-20% w/v

c) Microcrystalline cellulose (Avicel) - Used concentration is 10% w/v

d) Starch - Used concentration is 2-10% w/v

- **BINDERS (GRANULATING AGENT)**

Binders are used to increase the cohesive forces between the ingredients of the tablet so that tablet can be compressed easily. The concentration of the binder should be used carefully as it can greatly influence the properties of the tablet. Binders used in the tablet formulation are:

a) Acacia mucilage (20%) - It gives very hard granules.

b) Gelatin (5-20%)

c) PVP (2-10%) – Used for Non-aqueous granulation

d) Starch (5-10%) - Common binder

e) Tragacanth (20%) – Gives hard granules

- **GLIDANTS/FILLER**

Glidants are used to enhance the flow properties of the granules or powders so that granules do not stick with each other. Mainly at present there are only two types of glidants used in the tablet formulation:

a) Colloidal Silica (0.1-0.5%) – Most common and excellent glidant properties

b) Talc (1-2%)

➢ LUBRICANTS

Lubricants are used for the comfortable ejection of the tablet from punching machine without sticking to the die walls. Lubricants used in the tablet formulation include-

a) Stearic acid

b) Liquid Paraffin (5%)

c) Na Benzoate (5%)

d) Na Lauryl sulphate (0.5-5%)

(For tablet and capsule chapter LACHMAN is the best book for GPAT so also refer the LACHMAN once along with this study material)

MICROBIOLOGY

❖ Control of microorganisms

Reduction in numbers and / or activity of the total Achieved by

• Physical agents

• Chemical agents

• Chemotherapeutic agents

❖ Antimicrobial action is influenced by some factors:

• Environment: Effectiveness of heat is greater in presence of water, acid than in alkali, consistency of the material (aqueous or viscous), and presence of organic matter.

• Kinds of microorganisms: Growing vegetative cells more susceptible than spore forms, bacterial spores most resistant of all living organisms.

• Physiological state of cells: Young actively metabolizing cells more susceptible than old, dormant cells.

❖ Mode of action of antimicrobial agents:

• Damage to the cell wall or inhibition of cell wall synthesis

• Alteration of the permeability of the cytoplasmic membrane

• Alteration of the physical or chemical state of proteins and nucleic acids

• Inhibition of enzyme action

• Inhibition of protein or nucleic acid synthesis

❖ Control by Physical agents:

• High temperature

• Low temperature

• Desication : Time of survival of microorganisms after desiccation depends upon factors – kind of microorganisms, material on which the organisms are dried, completeness of drying process, physical conditions to which the dried organisms are exposed – light, temperature, humidity..

• Osmotic pressure

• Radiations – Ionising radiations: knock out electrons from molecules and ionize them forming hydrogen radicals, hydroxyl radicals, peroxides.

• Non-ionising radiations: less energetic, absorbed specifically by different compounds causing excitation of their electrons and raise them to higher energy levels.

• UV radiations are absorbed most specifically by nucleic acids – pyrimidine dimers thus inhibiting DNA replication and resulting mutations.

• Filters – HEPA (high efficiency particulate air) filters.

Control by Chemical agents

General terms for use with various chemical agents of control:

• Sterilization: is a process in which all viable life forms are either killed or removed.

• Disinfectant: kills growing forms not necessarily the spores of disease producing organisms

• Disinfection: Process of killing infectious agents

• Antiseptic: that opposes sepsis. Usually associated with substances applied to the body

• Sanitizer: that reduces the microbial population to safe levels. Applied to equipment and utensils used in food industries, restaurants etc.

• Germicide (microbicide): that kills vegetative forms but not necessarily the spores of germs/microorganisms.

• Bactericide: that kills bacteria

• Bacteriostatic: A condition in which the growth of bacteria is prevented.

• Chemotherapeutic agents: used to treat infections.

Major groups of chemical antimicrobial agents:

Phenols and phenolic compounds:

Phenol was the first disinfectant used in 1880 by Joseph Lister to reduce the infection of surgical incisions. Used as a standard against which other disinfectants are compared to determine their antimicrobial activity. Cresol, phenyl phenol etc. are very effective disinfectants. A 5% solution of phenol rapidly kills the vegetative cells of microorganisms.

• Mode of action:

Precipitation of proteins, inactivation of enzymes, leakage of amino acids from cells.

Phenol coefficient technique: Test organisms are *Salmonella typhi* or *Staphylococcus aureus.* It is calculated by dividing the greatest dilution of the disinfectant killing the test organism in 10 min but not in 5 min with the greatest dilution of the phenol showing the same result.

Alcohols: Ethyl alcohol in concentrations between 50 and 90% is effective against vegetative or non-spore forming cells. Methyl alcohol is less bactericidal, higher alcohols – propyl, butyl, amyl are more germicidal than ethyl alcohol but since the alcohols higher than propyl are not miscible with water, they are not commonly used in disinfectants.

• **Mode of action:** Protein denaturants, also damage the lipid complex in cell membrane.

Halogens:

Iodine is one of the oldest and most effective germicidal agents.

Tincture of iodine. Also used in the form of substances – iodophores –

Mixtures of iodine with surface-active agents – polyvinylpyrrolidone (PVP).

• **Mode of action:** Oxidises and inactivates essential metabolic compounds – Proteins with sulfhydryl groups.

• Chlorine and chlorine compounds: Chlorine gas, hypochlorites, chloramines.

• **Mode of action:** when chlorine is added in water it forms hypochlorous acid which is further decomposed to form nascent oxygen. Nascent oxygen being a strong oxidizing agent denatures major cellular constituents. Chlorine can also combine directly with proteins of cell membranes and enzymes.

$$Cl2 + H2O = HCl + HClO \text{ (hypochlorous acid)}$$

$$HClO = HCl + O$$

❖ **Heavy metals and their compounds:**

Mercury, silver, copper. By combining with cellular proteins especially containing sulfhydryl groups and inactivating them.

❖ **Dyes:**

• Triphenylmethane dyes - malachite green, brilliant green, crystal violet.

Gram +ve bacteria more susceptible than gram –ve. Interfere with cellular oxidation processes.

• Acridine dyes – acriflavine, tryptoflavine. Selective inhibition against staphylococci and gonococci.

Synthetic detergents:

Detergents are wetting agents, surface tension depressants.

• **Anionic detergents** – those with detergent property resident in the anion

Soap, Sodium lauryl sulphate (SLS).

• **Cationic detergents** – those with detergent property resident in cation

Cetylpyridinium chloride. Cationic detergents are more germicidal than anionic compounds.

• **Quaternary ammonium compounds**: Most of germicidal cationic-detergent

→ Compounds are quaternary ammonium salts in which R1, R2, R3 and R4 groups are

→ Carbon groups linked to the nitrogen atom.

→ The bactericidal power is high againt Gram+ve bacteria.

Mode of action: denaturation of proteins, interference with glycolysis and Membrane damage.

Aldehydes:

Most effective are formaldehyde and gluteraldehyde. Highly reactive chemicals – combine readily with vital nitrogen compounds – proteins, nucleic acids.

Gaseous agents:

Ethylene oxide – powerful sterilizing agent – liquid at <10.8oC – highly flammable.

• **Mode of action** – Alkylation reactions with organic compounds – enzymes and proteins.

Antibiotics and other chemotherapeutic agents:

• Inhibition of cell wall synthesis

• Damage to cytoplasmic membrane

• Inhibition of nucleic acid and protein synthesis

• Inhibition of specific enzyme systems

• **Inhibition of cell wall synthesis:** Penicillins, ampicillin, cephalosporins – interfere with final stages of Peptidoglycan synthesis – inhibit transpeptidase reaction – cross-linking of the two linear polymers.

Cycloserine, vancomycin - inhibits the enzymes involved in the synthesis of pentapeptide side chains.

• Damage to cytoplasmic membrane: Polymyxins, Gramicidins, Tyrocidines – act on membrane having sterols – fungi and animal cells but not bacteria.

• Inhibition of nucleic acid and protein synthesis: Streptomycin, tetracycline – interfere with binding of 30S ribosomes, chloramphenicol, erythromycin - binds with 50s ribosome.

• Inhibition of specific enzyme systems – Sulfonamides

Antifungal antibiotics – Nystatin, Griseofulvin

Synthetic chemotherapeutic agents: Nitrofurans – both g+ve and g-ve bacteria,

Nalidixic acid – Inhibition of DNA synthesis in g-ve bacteria.

❖ CONTROL OF MICROORGANISMS IN FOODS

Aseptic handling

High Temperature – Boiling, Steam under pressure, Pasteurization, Sterilization,

Aseptic processing

Low Temperature – Refrigeration, Freezing,

Dehydration

Osmotic pressure – In concentrated sugar, brine

Chemicals – Organic acids, SO2, substances developing during food processing, substances contributed by microbial activity (acids)

Radiations – Ionizing radiations, non-ionizing radiations

High Temperature: One of the safest and most reliable methods. Steam under pressure cooker, most effective as it destroys all vegetative cells and spores.

Canning – 100°C for high acid foods, 121°C for low acid foods.

Pasteurization: LTH T– 145°F (62.8°C) for 30 min, HTST – 161°F (71.7°C) for 15 sec.
This destroys all yeasts, Molds, gm-ve bacteria and most gram+ve bacteria.
Most heat resistant pathogen Coxiella Burnetti is also killed.
Sterilization: UHT -140-150°C for few seconds.
To understand thermal destruction of microorganisms for use in Food Preservation it is necessary to understand certain basic concepts:
Thermal Death Time (TDT): Time necessary to destroy a given population of microorganisms at a specified time.
Thermal Death Point (TDP): Temperature necessary to destroy a given population of microorganisms in a fixed time, usually 10 min.
Decimal reduction Time (D Value): Time necessary to destroy 90% of the organisms at a particular temperature.
Z Value: Temperature in °F required to vary D value by 90%.
D Value: Indicates resistance of microorganisms of to a specified temperature.
Z Value Indicates relative resistance to different temperatures.
Z value is used to construct equivalent thermal processes.
At 220°F, D value = 113 min
At 203.5°F, D value = 1130 min (If Z value is 17.5 °F)
At 237.5°F, D value = 11.3 min (If Z value is 17.5 °F)

Aseptic Packaging: In traditional canning methods non-sterile food is placed in a non-sterile metal/glass container followed by container closure and sterilization.
In aseptic packaging sterile food is placed in a sterile container under aseptic conditions and sealed under aseptic conditions.

Low temperature: Activities of spoilage organisms are lowered or stopped.

Dehydration: Drying reduces the a_w and thus prevents the growth of microorganisms.

Osmotic pressure: NaCl and sugars exert drying effect – Plasmolysis – death.

Halodurics, halophiles, Osmophiles tolerate the high osmotic pressure.

Direct antimicrobials:

Benzoic acid and parabens:

C_6H_5COOH and its sodium salt –

$C_7H_5NaO_2$ along with esters of p-Hydroxybenzoic acid (Parabens).

Antimicrobial activity of benzoate is affected by pH – Greatest activity at low pH – Ineffective at neutral pH.

ANTIMICROBIAL ACTIVITY RESIDES IN UN-DISSOCIATED MOLECULE

- → At pH 4.0 60% compound is un-dissociated.
- → At pH 6.0 only 1.5% compound is un-dissociated.

Effective against yeasts and molds.

Generally employed in high acid foods – Apple juice, Soft drinks, Tomato ketchup and Salads.

Max permissible limit is 0.1%

Common permissible parabens are heptyl-. Methyl-, propyl-, butyl-, ethyl-,

Parabens less sensitive to pH than benzoate – effective upto pH 8.0

Both benzoate, and parabens block oxidation of glucose to pyruvic acid.

Also inhibit uptake of substrate molecules.

SORBIC ACID:

$CH_3CH=CHCH+CHCOOH$ – usually employed as Ca, Na or K salt. Permissible limit is 0.2%

Like benzoate also active in acid foods than neutral foods

Generally in-effective at pH >6.5.

- → At pH 4.0, 86% un-dissociated
- → At pH 6.0, 6% compound is un-dissociated

Generally effective against molds and yeasts but also to certain bacteria.

Generally used in bakery products, cheese, fruit juices, beverages, salad dressings.

Inhibits dehydrogenase enzyme system.

Also inhibition of cellular uptake of substrate molecules – amino acids, phosphate, organic acids.

PROPIONIC ACID:

CH_3CH_2COOH as Ca and Na salts.

Mainly a mold inhibitor – used in breads, cakes, cheese.

At pH 4.0 88% is un-dissociated

At pH 6.0 6.7% is un-dissociated

Inhibits cellular uptake of substrate molecules

SULPHUR DIOXIDE AND SULPHITES:

SO2, Na or K salts of SO3 (sulphite), HSO3 (Bisulphite), S2O5 (metabisulphite).

Generally effective againt bacteria

Aerobes more sensitive than anaerobes

More active at acidic pH

SO2 < pH 3.0. HSO3 at pH 3.0-5.0, SO3 > pH 6.0.

At higher concentration yeasts and molds are also inhibited.

Permissible limit is 100-200 ppm

Effect is due to reducing power – reduces the O2 tension to a point at which aerobes are not able to grow. Also act on enzyme systems – enzyme poison – generally act on disulphide bonds.

Also used in dried foods to prevent enzymatic browning.

NITRITES AND NITRATES:

Many bacteria are capable of utilizing nitrate as electron acceptor which is reduced to nitrite highly reactive and capable of serving both reducing and oxidizing agent.

Under acidic conditions it ionizes to form nitrous acid (HONO) – further decomposes to give nitric oxide (NO) – capable of reacting with catalase, peroxidases, and cytochromes thus inhibiting aerobic bacteria.

1. What is Regulatory Affairs?

Ans-Regulatory Affairs in a Pharmaceutical industry, is a profession which acts as the interface between the pharmaceutical industry and Drug Regulatory authorities across the world. It is mainly involved in the registration of the drug products in respective countries prior to their marketing.

2. What are the goals of Regulatory Affairs Professionals?

Ans- Protection of human health Ensuring safety, efficacy and quality of drugs Ensuring appropriateness and accuracy of product information

3. What are the Roles of Regulatory Affairs professionals?

Ans- Act as a liaison with regulatory agencies Preparation of organized and scientifically valid NDA, ANDA,INDA ,MAA,DMF submissions Ensure adherence and compliance with all the applicable cGMP, ICH, GCP, GLP guidelines, regulations and laws Providing expertise and regulatory intelligence in translating regulatory requirements into practical workable plans Advising the companies on regulatory aspects and climate that would affect their proposed activities Apart from the above main roles, there are various other roles which Regulatory Affairs professionals play.

4. What is an Investigational New Drug (IND) application?

Ans- It is an application which is filed with FDA to get approval for legally testing an experimental drug on human subjects in the USA

5. What is a New Drug Application?

Ans- the NDA is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational new drug become part of the NDA In simple words, “It is an application which is filed with FDA to market a new Pharmaceutical for sale in USA”

6. What is an Abbreviated New Drug Application (ANDA)?

Ans- It is an application filed with FDA, for a U.S. generic drug approval for an existing licensed medication or approved drug. In simple words, “It is an application for the approval of Generic Drugs “

7. What is a Generic Drug Product?

Ans- A generic drug product is the one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use.

8. What is a DMF?

Ans- A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.Important facts regarding DMFs It is submitted to FDA to provide confidential informationIts submission is not required by law or regulationsIt is neither approved nor disapprovedIt is filed with FDA to support NDA, IND, ANDA another DMF or amendments and supplements to any of theseIt is provided for in the 21 CFR (Code of Federal Regulations) 314. 420It is not required when applicant references its own information

9. What are the types of DMF's?

Ans-Type I: Manufacturing Site, Facilities, Operating Procedures, and Personnel (No longer accepted by FDA) Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product Type III: Packaging Material Type IV: Excipient, Colorant, Flavour, Essence, or Material Used in Their Preparation Type V: FDA Accepted Reference Information (FDA discourages its use)

10. What is a 505 (b) (2) application?

Ans- 505 (b)(2) application is a type of NDA for which one or more investigations relied on by applicant for approval were not conducted by/for applicant and for which applicant has not obtained a right of reference.

11. What kind of application can be submitted as a 505(b) (2) application?

Ans- New chemical entity (NCE)/new molecular entity (NME) Changes to previously approved drugs

12. What are the examples of changes to approved drug products for which 505(b) (2) application should be submitted?

- Ans- Change in dosage form.

- Change in strength
- Change in route of administration Substitution of an active ingredient in a formulation product
- Change in formulation
- Change in dosing regimen
- Change in active ingredient new combination Product
- New indication
- Change from prescription indication to OTC indication
- Naturally derived or recombinant active ingredient
- Bioequivalence

13. What are the chemical classification codes for NDA?

- Number Meaning
- New molecular entity (NME)
- New ester, new salt, or other monovalent derivative
- New formulation
- New combination
- New manufacturer
- New indication
- Drug already marketed, but without an approved NDA
- OTC (over-the-counter) switch

14. What are the differences between NDA and 505 (b) (2) application?

Ans- S.No.New Drug Application (NDA) 505 (b) (2) Application

- All investigations relied on by applicant for approval were conducted by/for applicant and for which applicant has right of reference One or more investigation relied on by applicant for approval were not conducted by/for applicant and for which applicant has not obtained a right of reference
- Generally, filed for newly invented pharmaceuticals. Generally, filed for new dosage form, new route of administration, new indication etc for all already approved pharmaceutical. Note: 505 (b) (2) application is a type of NDA.

15. What is a Marketing Authorization Application?

Ans- It is an application filed with the relevant authority in the Europe (typically, the UK's MHRA or the EMA's Committee for Medicinal Products for Human Use (CHMP)) to market a drug or medicine. As per UK's MHRA-Applications for new active substances are described as 'full applications'. Applications for medicines containing existing active substances are described as 'abbreviated' or 'abridged applications'.

16. What is an ASMF?

Ans-Active substance master file is a submission which is made to EMA, MHRA or any other Drug Regulatory Authority in Europe to provide confidential intellectual property or 'know-how' of the manufacturer of the active substance. In simple words, "It is a submission made to European Drug regulatory agencies on the confidential information of Active Substance or Active pharmaceutical Ingredient (API)".

17. What are the types of active substances for which ASMFs are submitted?

Ans-New active substances existing active substances not included in the European Pharmacopoeia (Ph. Eur.) or the pharmacopoeia of an EU Member StatePharmacopeial active substances included in the Ph. Eur. or in the pharmacopoeia of an EU Member State

18. What is the difference between DMF and ASMF (with respect to submission)?

Ans-ASMF is submitted as Applicant's Part (Open Part) and Restricted Part (Closed Part) there isn't any differentiation of DMF's into parts

19. What is ICH?

Ans-International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.

20. What is CTD?

Ans-The Common Technical Document (CTD) is a set of specification for application dossier, for the registration of Medicines and designed to be used across Europe, Japan and the United States. Quality, Safety and Efficacy information is assembled in a common format

through CTD .The CTD is maintained by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).CTD format for submission of drug registration applications/dossiers is widely accepted by regulatory authorities of other countries too like Canada, Australia etc.

21. What are the ICH guidelines to be referred for preparation of registration dossiers/applications of medicines (With respect to format and contents in each module)?

- M4 Guideline
- M4Q Guideline
- M4S Guideline
- M4E Guideline

22. What are the modules in CTD?

Ans- the Common Technical Document is divided into five modules:

- Module 1. Administrative information and prescribing information
- Module 2. Common Technical Document summaries
  (Overview and summary of modules 3 to 5)
- Module 3. Quality
- Module 4. Nonclinical Study Reports (toxicology studies)
- Module 5. Clinical Study Reports (clinical studies)

22. What is Orange Book?

Ans-It is the commonly used name for the book "Approved Drug Products Equivalence Evaluations", which is published by USFDA.It contains the list of drug products, approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act.

23. What is Hatch-Waxman act?

Ans-It is the popular name for Drug Price Competition and Patent Term Restoration Act, 1984. It is considered as the landmark legislation which established the modern system of generic drugs in USA. Hatch-Waxman amendment of the federal food, drug and cosmetics act established the process by which, would be marketers of generic drugs can file

Abbreviated New Drug Application (ANDA) to seek FDA approval of generic drugs. Paragraph IV of the act, allows 180 day exclusivity to companies that are the "first-to-file" an ANDA against holders of patents for branded counterparts.In simple words “Hatch-Waxman act is the amendment to Federal, Food, Drug and Cosmetics act which established the modern system of approval of generics ”

24. What are the patent certifications under Hatch-Waxman act?

Ans-As per the Hatch and Waxman act, generic drug and 505 (b) (2) applicants should include certifications in their applications for each patent listed in the “Orange Book” for the innovator drug. This certification must state one of the following:(I) that the required patent information relating to such patent has not been filed (Para I certification);(II) that such patent has expired (Para II certification);(III) that the patent will expire on a particular date (Para III certification); or(IV) that such patent is invalid or will not be infringed by the drug, for which approval is being sought(Para IV certification).A certification under paragraph I or II permits the ANDA to be approved immediately, if it is otherwise eligible. A certification under paragraph III indicates that the ANDA may be approved when the patent expires.

25. What is meant by 180 day exclusivity?

Ans-The Hatch-Waxman Amendments provide an incentive of 180 days of market exclusivity to the “first” generic applicant who challenges a listed patent by filing a paragraph IV certification and thereby runs the risk of having to defend a patent infringement suit.180 Day Exclusivity could be granted to more than one applicant.

The recent example is- 180 day exclusivity was granted to Ranbaxy and Watson Laboratories for marketing generic version of Lipitor (Atorvastatin calcium).

26. What are the procedures for Approval of Drug in EU?

- Centralised Procedure (CP)
- Decentralised Procedure (DCP)
- Mutual Recognition Procedure (MRP)
- National Procedure (NP)

27. What is the Full form of abbreviation, CEP?

Certificate of Suitability to the monographs of the European Pharmacopoeia (or) Certificate of suitability of monographs of the European Pharmacopoeia (or) Certification of suitability of European Pharmacopoeia monographs

It is also informally referred to as Certificate of Suitability (COS)

28. What is a CEP?

Ans. It is the certificate which is issued by Certification of Substances Division of European Directorate for the Quality of Medicines (EDQM), when the manufacturer of a substance provides proof that the quality of the substance is suitably controlled by the relevant monographs of the European Pharmacopoeia.

29. What are the recently approved new Drugs by FDA (Under NDA Chemical Type 1)?

AS. NO. NDA	NAME OF DRUG NAME OF ACTIVE INGREDIENT COMPANY
1203188	KALYDECOIVACAFT OR VERTEX PHARMS
2203388	ERIVEDGE VISMODEGIBGENEN TECH
3202324	INLYTA AXITINIBPFIZER
4202833	PICATOINGENOL MEBUTATELEO PHARMA AS
5202514	ZIOPTAN TAFLUPROSTMERCK SHARP DOHME
6021746	SURFAXINLUCINACTANT DISCOVERY LABORATORIES INC30.

FULL FORM

NDA	New Drug Application
ANDA	Abbreviated New Drug application
IND	Investigational New Drug Application
DMF	Drug Master File
ASMF	Active Substance Master File
MAA	Marketing Authorisation Application
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia

ICH	The International Conference on Harmonisation of technical requirements for registration of Pharmaceuticals for human use.
CTD	Common technical document for the registration of pharmaceuticals for human use.
AP	Applicant's Part
RP	Restricted Part
OP	Open Part
CP	Closed Part
NME	New Molecular Entity
NCE	New Chemical Entity
SmPC	Summary of Product Characteristics
PL	Packaging Leaflet
RMS	Reference Member State
CMS	Concerned Member State
CHMP	The Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CVMP	Committee for Medicinal Products for Veterinary Use
SUPAC	Scale-up and post approval changes
BACPAC	Bulk Active Chemicals Post approval Changes
cGMP	Current good Manufacturing Practice
GCP	Good clinical Practice
GLP	Good Laboratory Practice

31. Well known Drug Regulatory Agencies across the world-

NAME OF COUNTRY	REGULATORY AGENCIES
United States of America	United States Food and Drug Administration (USFDA)
United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)

European Union	European Medicines Agency (EMA)
European Union	European Directorate for the Quality of Medicines (EDQM)
Australia	Therapeutic Goods Administration (TGA)
Canada	Therapeutic Products Directorate (TPD) in Health Product and food branch (HPFB) of Health Canada (HC)
Japan	Pharmaceutical and Medical Devices Agency (PMDA)
France	Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS)Translated into English as- French Agency for the Safety of Health Products
Germany	Bundesinstitut für Arzneimittel und Medizinprodukte, (BfArM) Tanslated into English as- Federal Institute for Drugs and Medical Devices
Brazil	Agência Nacional de Vigilância Sanitária (ANVISA) Tanslated into English as- The National Health Surveillance Agency
India	Drugs Controller General of India (DCGI) who heads Central Drugs Standard Control Organisation (CDSCO)
Switzerland	Swiss Agency for Therapeutic Products (SWISSMEDIC)
Singapore	Health Sciences Authority (HSA)

D & C ACT (1940) LIST OF AMENDING ACTS AND ADAPTATION ORDER

1. The Repealing and Amending Act, 1949 (40 of 1949).
2. The Adaptation of Laws Order, 1950.
3. The Part B States (Laws) Act, 1951 (3 of 1951)
4. The Drugs (Amendment) Act, 1955 (11 of 1955)
5. The Drugs (Amendment) Act, 1960 (35 of 1960)
6. The Drugs (Amendment) Act, 1962 (21 of 1962)
7. The Drugs and Cosmetics (Amendment) Act, 1964 (13 of 1964)
8. The Drugs and Cosmetics (Amendment) Act, 1972 (19 of 1972).
9. The Drugs and Cosmetics (Amendment) Act, 1982 (68 of 1982)
10. The Drugs and Cosmetics (Amendment) Act, 1986 (71 of 1986)
11. The Drugs and Cosmetics (Amendment) Act, 1995 (22 of 1995)

THE DRUGS AND COSMETICS ACT, 1940

ARRANGEMENT OF SECTIONS

CHAPTER I

INTRODUCTORY

SECTIONS

CHAPTER II

THE DRUGS TECHNICAL ADVISORY BOARD, THE CENTRAL DRUGS LABORTORY AND THE DRUGS CONSULTATIVE COMMITTEE

CHAPTER III

IMPORT OF DRUGS AND COSMETICS

8. Standards of quality
9. Misbranded drugs
9A. Adulterated drugs
9B. Spurious drugs.
9C. Misbranded cosmetics.
9D. Spurious cosmetics
10 Prohibition of import of certain drugs or cosmetics.
10A. Power of Central Government to prohibit import of drugs and cosmetics in public interest.
11. Application of law relating to sea customs and powers of Customs officers.
12 Power of Central Government to make rules.
13 Offences.
14 Confiscation
15. Jurisdiction

CHAPTER IV

MANUFACTURE, SALE AND DISTRIBUTION OF DRUGS AND COSMETICS

SECTIONS

16. Standards of quality.
17. Misbranded drugs.
17A. Adulterated drugs.
17B. Spurious drugs.
17C. Misbranded cosmetics.
17D. Spurious cosmetics.
18. Prohibition of manufacture and sale of certain drugs and cosmetics.
18A. Disclosure of the name of the manufacturer, etc.
18B. Maintenance of records and furnishing of information.
19. Pleas .
20. Government Analysts.
21. Inspectors.
22. Powers of Inspectors.
23. Procedure of Inspectors.
24. Persons bound to disclose place where drugs or cosmetics are manufactured or kept.

25. Reports of Government Analysts.

26. Purchaser of drug or cosmetic enabled to obtain test or analysis.

26A. Power of Central Government to prohibit manufacture etc. of drug and cosmetic in public interest.

27. Penalty for manufacture, sale, etc., of drugs in contravention of this Chapter.

27A. Penalty for manufacture, sale, etc., of cosmetics in contravention of this Chapter.

28. Penalty for non-disclosure of the name of the manufacturer, etc.

28A. Penalty for not keeping documents, etc., and for non-disclosure of information.

28B Penalty for manufacture, etc. of drugs or cosmetics in contravention of section 26A.

29. Penalty for use of Government Analyst's report for advertising.

30. Penalty for subsequent offences.

31. Confiscation.

31A. Application of provisions to Government departments.

32. Cognizance of offences.

32A. Power of Court to implead the manufacturer, etc.

33. Power of Central Government to make rules .

33A. Chapter not to apply to Ayurvedic, Siddha or Unani drugs.

CHAPTER IVA

PROVISIONS RELATING TO AYURVEDIC SIDDHA AND UNANI DRUGS

SECTIONS

33B. Application of Chapter IVA.

33C. Ayurvedic, Siddha and Unani Drugs Technical Advisory Board.

33D. The Ayurvedic, Siddha and Unani Drugs Consultative Committee.

33E. Misbranded drugs.

33EE. Adulterated drugs.

33EEA. Spurious drugs.

33EEB. Regulation of manufacture for sale of Ayurvedic, Siddha and Unani drugs.

33EEC. Prohibition of manufacture and sale of certain Ayurvedic, Siddha and Unani drugs.

33EED. Power of Central Government to prohibit manufacture etc., of Ayurvedic, Siddha or Unani drugs in public interest.

33F. Government Analysts.

33G. Inspectors .

33H. Application of provisions of sections 22, 23, 24 and 25.

33I. Penalty for manufacture, sale, etc., of Ayurvedic, Siddha or Unani drugs in contravention of this Chapter.

33J. Penalty for subsequent offences.

33K. Confiscation.

33L. Application of provisions to Government departments.

33M. Cognizance of offences.

33N. Power of Central Government to make rules.

33O. Power to amend First Schedule.

CHAPTER V MISCELLANEOUS

33P. Power to give directions.

34. Offences by companies.

34A. Offences by Government departments.

34AA. Penalty vexatious search or seizure.

35. Publication of sentences passed under this Act.

36. Magistrate's power to impose enhanced penalties.

36A. Certain offences to be tried summarily.

37. Protection of action taken in good faith.

38. Rules to be laid before Parliament.

YEAR AND ACT

1970	Indian Patents Act
1919	Poison Act
1948	Pharmacy Act
1940	Drug and Cosmetic Act
1930	Dangerous Drug Act
1857	Opium Act
1954	Drug and Magic Remedies Act
1971	Medical Termination of Pregnancy Act (MTP)
1989	First ICH Indian pharmacopoeias:
1955	1st Edition IP
1966	2nd Edition IP

1985	3rd Edition IP
1996	4th Edition IP
2007	5th Edition IP
2010	6th Edition IP
2014	7th Edition IP

TECHNIQUE FOR NANOPARTICLE PREPARATION:

- → Desolvation, denaturation
- → Emulsion & interfecial polymerization
- → Emulsification diiffusion
- → Salting out.

STRENGTHS

- → HCl (IP)-36
- → H2SO4-12 N

IMP CHARACTERS:

- → Nutmeg-Aril
- → Stropanthus- Arista (Awn)
- → Cardamon- Arilode
- → Colchicum- Strophiole
- → Castor- Caruncle

WHITEFIELD OINTMENT

- → 6%benzoic acid
- → 3%salicylic acid.
- → Used as keratolytic.

SMART POLYMER:

- → Polylactic acid
- → Polyglycolic acid
- → Poly-lactide co-glycolide
- → Poly (dl-lactide-co-caprolactone)
- → N-isopropylacrylamide

Difference between Aldol condensation & Cannizaro reaction:

- → If aldehyde & ketone have alpha proton than Aldol condensation occur.
- → If not, than cannizaro reaction occurs.

➢ SOME IMPORTANT NOTES FOR GPAT EXAM

- Betonite - derivative of monmorillonite.
- Hydrocaprolic acid-cyclic unsat fatty acid.
- Glucose-No UV abs.
- Vitamin B6 deficiency- sideroblastic anemia
- Smell of acetophenone when lobelia leaves burn.
- Rauwolfia tetraphylla devoid of recinnamine.
- Bromhexin- semisynthetic from vasaka.
- All electron withdrawing functional group are generally Meta directing except halogen group
- Stability order of carbocation is 3>2>1...
- Herceptin is Antineoplastic agent which cause CHF.
- Rasagaline is free from amphetamine prop due 2 aminoindane metabolite
- Rheumatoid factor is usually Ig M.
- Ca. sandoz is product of NOVARTIS.
- Phosphate is salt of Codeine.
- Seed of Indrajav is kurchi
- Transferosome are liposome used to increase Transdermal Permeation, in this deformability achieved by using surfactant in proper ratio.
- Abacavir, a nucleoside reverse transcriptse inhibitor NRTI is converted to which active metabolite?? Ans is Carbovir triphosphate.
- Cholesterol used in liposomes because it fills gaps created by imperfect packing of lipids when protein are embeded in membrane.
- Clenbutrol - anabolic drug uesd illicitly by athletes 2 improve performance
- For chest infection in asthma-clarithromycin used.
- Lotaustralin- isoleucin
- Squill, Manna, Psyllium Contain Trisaccharide.
- Diluents can be used in ratio 5-10% in tablet.
- In MRI max of 1.5 tesla magnetic field strength can be used.
- Lutrol is known as intelligent polymer.
- Chemical shift-independent of magnetic field
- Secondary structure of protein-alfa-beta helix
- 1960-prevention of cruelty to animals act.
- 1963-CPCSEA came into existence.
- 1998-breeding of and experimentation on animals act.

- Hydrolysis of ethyl acetate is pseudo first order reaction
- Suspensions follow pseudo zero order reaction
- Cis form gives 5-12 delta value and trans form gives 12-18 delta value in NMR
- Polystyrene and water are both used as standard for calibration of IR
- B-cyclodextrin has max Solubility
- H-bond can detected by IR & NMR
- Free radicals are identified by E.S.R (electron spin resonance)
- TRIPS-trade related aspects of intellectual property rights
- TRIMS-trade related investment measures
- WIPO-world intellectual property organisation.
- Seliwanoffs reagent contain resorcinol + glacial acetic acid.
- Lucas reagent HCl+ZnCl2.
- Ames test to detect carcinogenicity
- Nitrocellulose is used as base in nail lacquers.
- Nucleosome contain DNA with histone protein in ratio 30:1
- Neumanns test is used for the identification of Casein.
- Gaultheria con. Methyl salicylate.
- PULSED FLOW IS THE disadvantage of reciprocating pump in HPLC.
- *P.bracteatum* do not contain morphine.
- **BENTING & BEST** founded insulin.
- H1N1-'N' stands for Neuramidase.
- Fiehls test is used for determination of sucrose
- Shinoda test for identification of flavanoids.
- Murexide test for caffeine.
- Bacteria need 0.5%NaCl for maintaining isotonicity not 0.9% NaCl.
- RITONAVIR IS also known as pharmacokinetic enhancer. Because it increases bioavailability of antiviral drugs.
- Banana bond is the characteristic of cyclopropane.
- Caffine is Pseudo tannin.
- Rivastigmine is used in Alzheimer's disease and it is a pseudo irreversible inhibitor of cholinesterase enzyme.
- Carvedilol-a mixed adrenoceptor antagonist has antioxidant effect also.
- Minoxidil-K channel opener + release NO.
- Liquid Nitrogen temperature is -197 degree Celcius.

- Caco2, a cell line model is used to classify drug for its BCS
- Classification bleomycin & nitrosourea coming under cycle nonspecific anticancer Agent
- All xanthophylline act on Adenosine receptor except enrophylline.
- Omalizumab used in asthma, it is anti IgE antibody.

BIOCHEMISTRY IMPORTANT PINPOINTS

- A living cell is true representative of life with its own organization & specialized Functions.
- Accumulation of lipofuscin, a pigment rich in lipids and proteins, in the cell has been Implicated in ageing process.
- Leakage of lysosomal enzymes into the cell degrades several functional macromolecules and this may lead to certain disorders (e.g. arthritis).
- Zellweger syndrome is rare disease characterized by the absence of functional peroxisome.
- Lysosomes are the digestive bodies of the cell, actively involved in the degradation of Cellular compounds. Peroxisomes contain the enzyme cataloes that protects the cell from the toxic effects of H2O2.
- The cellular ground matrix is referred to as cytosol which, in fact, is composed of a network of protein filaments, the cytoskeleton.

- **Mutarotation:** The α and β Anomers of glucose have different optical rotations. The specific optical rotation of a freshly prepared glucose (α anomer) solution in water is +112.2^{o} which gradually changes and attains an equilibrium with a constant value of +52.7^{o}. ln the presence of alkali, the decrease in optical rotation is rapid. The optical rotation of p-glucose is **+18.7^{o} (19^{o})**
- **Mutarotation of fructose:** Fructose also exhibits Mutarotation. Ln case of fructose, the pyranose ring (six-membered) is converted to furanose (five-membered) ring, till an equilibrium is attained. And fructose has a specific optical rotation of **-92^{o}** at equilibrium
- **von Gierke's disease (type ii)**: The incidence of type I glycogen storage disease is 1 per 200,000 persons. It is transmitted by autosomal recessive trait. This disorder results in various biochemical manifestation
- **Anderson's disease (amylopectinosis):** A rare disease, glycogen with only few branches accumulate; cinhosis of liver, impairment in liver function.

- **Pompe's disease:** Glycogen accumulates in lysosomes in almost all the tissues; heart is mostly involved; enlarged liver and heart, nervous system is also affected; death occurs at an early age due to heart failure.
- **Cori's disease:** Branched chain glycogen accumulates; liver enlarged; clinical manifestations are similar but milder compared to von Gierke's disease.

Distinct deficiency conditions of certain b-complex vitamins are known

VITAMIN	DEFICIENCY
Thiamine	Beriberi
Niacin	Pellagra
Riboflavin	Cheilosis, glossitis
Pyridoxine	Peripheral neuropathy
Folic acid	Macrocytic anemia
Cobalomin	Pernicious anemia

- B-complex vitamin deficiencies are usually multiple rather than individual with overlapping symptoms.
- A combined therapy of vitamin B12 and folic acid is commonly employed to treat the patients of megaloblostic anaemias.
- Megodoses of niacin are useful in the treatment of hyperlipidemia.
- Long term use of isoniazid for the treatment of tuberculosis causes 86 deficiency.
- Folic acid supplementation reduces elevated plasma homocysteine level which is Associated with atherosclerosis and thrombosis.
- Sulfonamides serve as antibacterial drugs by inhibiting the incorporation of PABA to produce folic acid.
- Aminopterin and amethopterin, the structural analogues of folic acid, are employed in the treatment of cancers.
- Lipoic acid is therapeutically useful as an antioxidant to present stroke, myocardial infarction, etc.

Colour reactions of proteins/amino acids Reaction Specific group or amino acid

REACTION	SPECIFIC GROUP OR AMINO ACID
Biuret reaction	Two peptide linkages
Ninhydrin reaction	α-Amino acids
Xanthoproteic Reaction	Benzene ring of aromatic amino acids (Phe, Tyr, Trp)
Millons reaction	Phenolic group(Tyr)
Hopkins-Cole Reaction	lndole ring (Trp)
Sakaguchi reaction	Guanidino group (Arg)
Nitroprusside reaction	Sulfhydryl groups (Cys)
Sulfur test	Sulfhydryl groups (Cys)
Pauly's test	Imidazole ring (His)
Folin coicalteau's test	Phenolic groups (Tyr)

DRUGS OF CHOICE

1. Paracetamol poisoning- acetyl cysteine
2. Acute bronchial asthma: - salbutamol
3. Acute gout: - NSAIDS
4. Acute hyperkalemia: - calcium gluconate
5. Severe DIGITALIS toxicity: - DIGIBIND
6. Acute migraine: - sumatriptan
7. Cheese reaction: - phentolamine
8. Atropine poisoning: - physostigmine
9. Cyanide poisoning: - amyl nitrite
10. Benzodiazepine poisoning: - flumazenil
11. Cholera: - tetracycline
12. KALA-AZAR:- lipozomal amphotericin- B
13. Iron poisoning: - desferrioxamine -
14. MRSA: - vancomycin
15. VRSA: - LINEZOLID

16. Warfarin overdose: - vitamin-K (NIPER- 2009)
17. OCD: - fluoxetine
18. Alcohol poisoning: - fomepizole
19. Epilepsy in pregnency: - Phenobarbitone
20. Anaphylactic shock: - Adrenaline
21. MRSA Infection-Vancomycin
22. Malaria in Pregnancy-Chloroquine
23. Whooping Cough or Pertussis- Erythromycin
24. Kawasaki disease-IV Ig
25. Warfarin Overdose-Vit-K
26. Heparin Overdose-Protamine
27. Hairy Cell Leukemia-Cladirabine
28. Multiple Myeloma- Melphalan
29. CML-Imatinib
30. Wegner's granulomatosis-Cyclophosphamide
31. HOCM- Propranolol
32. Delirium Tremens-Diazepam
33. Drug Induced Parkinsonism-Benzhexol
34. Diacumarol Poisoning-Vit-K
35. Type-1 Lepra Reaction-Steroids
36. Type- 2 Lepra Reaction-Thalidomide
37. Allergic Contect Dermatitis-Steroids
38. PSVT- 1st-Adenosine, 2nd-Verapamil, 3rd-Digoxin
39. Z-E Syndrome- Proton Pump Inhibitor
40. Chancroid-Cotrimoxazole
41. Dermatitis Herpetiformis-Dapsone
42. Spastic Type of Cerebral Palsy-Diazepam
43. Herpis Simplex Keratitis-Trifluridine
44. Herpes Simplex Orolabialis-Pancyclovir
45. Neonatal Herpes Simplex-Acyclovir
46. Pneumocystis carinii Pneumonia- Cotrimoxazole for Nodulo
47. Cystic Acne- Retinoic acid
48. Trigeminal Neuralgia-Carbamezapine
49. Actinomycosis-Penicillin

50. Plague- Streptomycin
51. Opioid Withdrawal- Methadone 2nd-Clonidine
52. Alcohol Withdrawal- Chlordiazepoxide 2nd-Diazepam
53. Post Herpetic Neuralgia- Fluphenazine
54. WEST Syndrome-ACTH
55. Diabetic Diarrhoea- Clonidine
56. Lithium Induced Neuropathy-Amiloride Communicable Disease:
57. Tetanus: PEN G Na; TETRACYCLINE; (DIAZEPAM
58. Diphteria: PEN G K; ERYTHROMYCIN
59. Pertusis: ERYTHROMYCIN; AMPICILLIN
60. Meningitis: MANNITOL (osmotic diuretic); DEXAMETHASONE (anti-inflammatory); DILANTIN/PHENYTOIN (anti-convulsive); PYRETINOL/ENCEPHABOL (CNS stimulant)
61. Cholera: TETRACYCLINE
62. Amoebic Dysentery: METRONIDAZOLE
63. Shigellosis: CO-TRIMOXAZOLE
64. Typhoid: CHORAMPHENICOL
65. Rabies: LYSSAVAC, VERORAB
66. Immunoglobulins: ERIG or HRIg
67. Malaria: CHLOROQUINE
68. Schistosomiasis: PRAZIQUANTEL
69. Felariasis: DIETHYLCARBAMAZINE CITRATE
70. Scabies: EURAX/ CROTAMITON
71. Chicken pox: ACYCLOVIR/ZOVIRAX
72. Leptospirosis: PENICILLIN; TETRACYCLINE; ERYTHROMYCIN
73. Leprosy: DAPSONE, RIFAMPICIN
74. Anthrax: PENICILLIN
75. Tuberculosis: R.I.P.E.S.
76. Pneumonia: COTRIMOXAZOLE; Procaine, Penicillin
77. Helminths: MEBENDAZOLE; PYRANTEL, PAMOATE
78. Meningitis: MANNITOL (dec. ICP); DEXAMETHASONE (relieve cerebral edema); DIAZEPAM (anticonvulsant); PENICILLIN
79. Syphilis: PENICILLIN
80. Gonorrhoea: PENICILLIN

Classification of antimicrobial agents: On the basis of their mechanism of action

Antimicrobial agents are used for the treatment of the microbial infections in the body and the treatment is termed as chemotherapy. Paul Ehlrich is known as the father of Chemotherapy who used Arsphenamine for the treatment of Syphilis. Chemotherapy is an important perspective for the student's GPAT preparation as lots of questions are asked from this section. Here, we are introducing the classification of antimicrobial agents on the basis of their mechanism of action.

Classification of antimicrobial agents

1. Antibiotics that inhibits Bacterial Cell Wall synthesis

- **Pencillins,**
- **Cephalosporins**
- **Carbepenam**
- **Monobactam**

Mechanism:

These drugs inhibit the transpeptidase enzyme used in the bacterial cell wall synthesis.

- **Vancomycin**

Mechanism:

This drug makes complex with C-terminal D-alanine residues of peptidoglycan precursors.

- **Cycloserine**

Mechanism:

It inhibits alanine racemase and D-alanyl-D-alanine synthetase.

2. Antibiotics that inhibit Ribosome function and prevent protein synthesis

a) Aminoglycosides: It causes misreading in mRNA

b) Tetracyclines: This class of drug binds with 30S ribosomes and inhibits the binding of aminoacyl-tRNA into the A site of the bacterial ribosome.

c) Chloramphenicol: It binds with the peptidyl transferase enzyme on the 50S ribosome and inhibits protein synthesis.

d) Spectinomycin

e) Azithromycin and Clarithromycin: Inhibits translocation which leads the protein synthesis inhibition.

3. Antibiotics that affect the function of cytoplasmic membranes

a) Antifungal drugs:

- Amphotericin B
- Ketoconazole
- Clotrimazole
- Fluconazole
- Miconazole
- Nystatin.

b) Bacitracin & Polymyxin B & E:

They cause the leaking of nuclear material which leads to the cell death.

c) Gramicidin: It produces aqueous pores in the cell membrane.

4. Antibiotics that inhibit Nucleic acid synthesis

a) Agents that interfere with Nucleotide synthesis:

- Zidovudine: DNA polymerase inhibition.
- Acyclovir: Thymidine kinase and DNA polymerase inhibition of Herpes virus.
- Flucytosine: Thymidylate synthetase inhibition.

b) Agents that interfere with DNA replication:

- Metronidazole: DNA strand breakage by the reduced Nitro group.
- Quinolones: DNA gyrase inhibition

c) Agents that inhibit RNA polymerase:

- Rifamycin

d) Agents that interfere with the precursor synthesis:

Sulfonamides: Inhibit the conversion of Pteridine & p-Amino Benzoic acid (PABA) into dihydrofolic acid.

Trimethoprim: Inhibits the conversion dihydrofolic acid into tetrahydrofolic acid.

e) Agents that interfere with the Template function of DNA:

ALL THE BEST

DO THIS FIST MATERIAL WELL ALL IMP POINTS ARE INCLUDED

REVISE THEM DAILY: AMAR RAVAL

PHARMACOLOGY GPAT NOTES PHARMAROCKS

Pharmacodynamics : - What drug does to body.

Pharmacokinetics : - What body does to the drug.

Pharmacotherapeutics : - Use of drugs in prevention & treatment of disease.

Clinical pharmacology : - Scientific study of drugs in man.

Toxicology : - Aspect of pharmacology deals with adverse effects of Drugs.

Pharmacodynamic agents : - Designed to have pharmacodynamic effects in the recipient.

Chemotherapeutic agents : - Designed to inhibit/kill parasites/malignant cells & does not have or with minimal pharmacodynamic effects in recipient.

Orphan drugs : - Drugs or Biological Products for diagnosis/treatment/ Prevention of a rare disease.

E.g.:- Liothyronine (T3), Desmopressin, Baclofen, Digoxin Antibody.

Routes of drug Administration

1) Oral 2) Parentral

Injections:-

A) Intradermal: - given in to layers of skin. E.g.:- BCG vaccine, for testing drug sensitivity.

B) S.C:- Only non-irritant drug are given absorption can be enhanced by enzyme Hyalurinase S.C.drug implants can act as depot therapy. E.g.:- steroid hormones. In children saline is injected in large quantities – Hypodermalysis.

C) I.M:- Mild irritants, suspensions & colloids can be injected by this route.

D) I.V:- Directly to vein.

E) Intra arterial: - Only used for diagnostic studies. E.g.:- Angiograms, embolism therapy.

F) Intrathecal: - Spinal anaesthetics in to subarachinoid space.

G) Intra medullary: - Drug introduced to Bone marrow.

H) Intra articular & Intra tensional: - Drug administered into joints. E.g.:- Hydrocortisone acetate in rheumatoid arthritis.

PHARMACOKINETICS

Absorption of Drugs:-

A) **Simple diffusion:** - Bidirectional process rate of transfer across the membrane is proportional to concn gradient. E.g.:- H_20 soluble drugs with low mol-wt, lipid soluble drugs.
B) **Active transport:** - requires energy – independent of physical properties of membrane. E.g.:- H_20 soluble drugs with high mol-wt.
Carrier mediated transport: - E.g.:- Intestinal absorption of Ca^{2+}.
C) **Pinocytosis:** - Important in unicellular organisms like Amoeba.

Bioavailability: - Amount of drug reaches systemic circulation following a non-vascular drug administration.

$$F = \frac{\text{AUC Oral}}{\text{AUC IV}}$$

Barriers:-
B.B.B:- made up of choroid cells (strong Barrier).
Testis Barrier: - made up of seroid cells.
Placental Barrier: - made up of sertoli cells (weak Barrier).
Endothelial Barrier: - in all blood cells (very weak).
For absorption of vitB_{12}, **IF** factor is required which is synthesized by parietal cells?

Solubility of drugs:-
Ionized form – soluble
Unionized form – more absorbed

Distribution of drugs:-
Plasma protein binding: - many drugs have affinity towards plasma proteins, Acidic drugs towards Albumin, Basic drugs towards acid Glycoprotein, Prothrombin, and Thromboplastin.
Radioligand binding: - is used to determine drug in protein complex.

$$\text{PPB} \quad \frac{1}{V_d}$$

Tissue storage of drugs:-
Skeletal muscle, Heart: - Digoxin, emetine
Liver: - Chloroquine, tetracycline's, digoxin
Kidney: - Chloroquine, digoxin, emetine
Thyroid: - Iodine
Brain: - CPZ, Acetazolamide, Isoniazid
Retina: - Chloroquine
Iris: - Ephedrine, Atropine
Bone & Teeth: - Heavymetals, Tetracycline's
Adipose tissue: - Phenoxy Benzamine, Minocycline, ether, Thiopentane.

Metabolism of drugs :- (Biotransformation / Detoxification)
Chemical alteration of drug in physiological system

1. Inactive form
2. Active metabolite, E.g.:- Codeine to morphine
3. Prodrug to active drug, E.g.:- L-Dopa to Dopamine

Phase I metabolism: - Nonsynthetic

Reaction	Enzyme	Examples
Oxdn	Monooxygenases cytp450 in lives	Drugs with "OH" & "COOH"groups
Redn	Reductases	Halothane, trichloroethand
Hydrolysis	Esterases	Lidocaine procainide Benzocaine
Cyclisation		Proguanil to cycloguanil
Decyclisation		Phenobarbitone & Phenytoin

Phase II Metabolism: - Synthetic or Conjugation

Conjugation	Endogenous substrate	Examples
1. Glucouronide	Glucouronic acid (glucose)	"Oh" & "COOH" group drugs
2. Acetylation	Acetyl co-A (Citric acid cycle)	"NH_2" & Hydrazine group drugs
3. Methylation	Methionine	"NH_2" & Phenol group drugs
4. Sulphate	Sulfokinases	Phenolic compds & Steroids
5. Glycine(rarely occur)	Glycine	Salicylates & "COOH" group drugs
6. Glutathione		Paracetamol
7. Ribonucleotide		Purine & Pyrimidine antimetabolites

Prodrug	Active form	Active drug	Active Metabolite
Levodopa	Dopamine	Chloralhydrate	Trichloroethanol
Enalpril	Enalaprilat	Phenacetin	Paracetamol
L-Methyldopa	L-Methylnorepinephrine	Primidone	Phenobarbitone
Dipivefrine	Epinephrine	Digitoxin	Digoxin
Benorylate	Aspirin+Paracetamal	Codeine	Morphine
Proguanil	Proguanil triazine	Spironolactone	Canrenone
Prednisone	Prednisolone	Amitryptiline	Nor-tryptiline
Becampicillion	Ampicillin	Diazepam	Desmethyl diazepam, oxazepam
Sulphasalazine	5-amino salicylic acid	Trimethadione	Dimethadione

Microsomal enzymes: - These are inducible by drugs, diet E.g.:- cytP_{450}, Monooxygenases, Glucouronyl transferase etc.
Catalyses many oxdn, redn, Hydrolysis & glucouronide conjugations.

Non Microsomal enzymes: - E.g.:- Flavoprotein oxidases, esterases, amidases & conjugases. Catalyses some oxdn & redn, many hydrolytic reactions & all conjugations except glucouronidation.

Hofmann elimination: - Inactivation of drug in body fluids by spontaneous molecular rearrangement without enzymes. E.g.:- Atracurium.
Enzyme inducers: - Phenytoin, Barbiturates, Rifampicin, Carbamazepine.

Enzyme Inhibitors: - Cimetidine, erythromycin, chloramphenicol, ciprofloxacin, MAO inhibitors, sulfonamides, verapamil, INH, Disulfiram etc.

Excretion of drugs: - elimination of drug in inactive form,
Urine – H_20 soluble drugs, Feces – Unabsorbed drugs (complex drugs insoluble drugs),
Swets – salts & heavy metals,
Saliva – Hm, Lead, SCN, Lithium, & Tetracycline's,
Lungs – gaseous drugs, Alcohol paraldehyde etc.,
Lacrimal – drugs applied to eye.

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{plasma concn of drug}}$$

PHARMACODYNAMICS

Drug produces action by stimulation, depression, irritation, replacements cytotoxic action.
Mechanism of drug action:-

	Properties	Drugs
Physical	Mass of drug Adsorptive property Osmotic activity Radioactivity Radio opacity	Bulk laxatives, protectives charcoal, kaolin $mgso_4$, mannitol I^{131} & other isotope $Baso_4$, urografin
Chemical	Neutralizing germicidal chelating	Antacids $Knmo_4$, I_2 EDTA, Penicillamine

Through enzymes: - Drugs may also increase or decrease rate of enzymatically mediated reactions.
Stimulation: - e.g.:- Adrenaline stimulates Adenyl cyclase pyridoxine increases decarboxylase activity.

a) Inhibition :-
   1) Non specific inhibition: - Many drugs act by denaturing proteins. E.g.:- Hm, Acid & Alkalies, Alcohol, Formaldehyde, Phenol etc.

2) **Specific inhibition :-**

i) Competitive: - Physostigmine & neostigmine with Ach for sulfonamides with PABA for folatesynthetase Allopurinol with Hypoxanthine for xanthine oxidase carbidopa & methyldopa with L – Dopa for dopa decorboxylase.

ii) Non-competitive:- Ach & Papaverine on smooth muscles Ach & Decamethionine on NmJ.

Through receptors:-

1) Clark-Arheneous theory (occupation theory):- The effect of drug is proportional to fraction of receptors occupied by drug & maximum effect results when all receptors are occupied.
2) Raton's theory (Rate theory):- The effect of drug is a function of receptor occupation & the rate of drug receptor combination. Here response depends on rate of Association between drug molecule & receptor.

G proteins are Heterotrimeric proteins involved in receptor transduction it has 3 subunits.

PAx = - log (A) $_x$,
PA2 = - log (A) $_2$,
PD2 = - log (a) $_2$,
Where (A) = molar concn of antagonist, where (a) = molar concn of against.

Eudismic ratio: - ratio of the activities of active enantiomer (eutomer) and inactive enantiomer (distomer) in chiral pharmocodynamics.

AUTONOMIC NERVOUS SYSTEM

Sympathetic or Adrenergic system enables the individual to adjust to stress & prepares the body for '**Fight or Flight'** response.
Parasympathetic or Cholinergic mainly participate in tissue building reactions.
Both sympathetic & parasympathetic nervous system consists of myelinated preganglionic fibre which forms a synapse with the cell body of non-myelinated post ganglionic fibre.

Synapse: - It is the structure formed by the close opposition of a neuron either with another neuron or with effector cells.
The synapse b/w preganglionic & postganglionic fibres is termed as Ganglion
The synapse b/w postganglionic &receptors is termed as Neuroeffector junction.

Neurohumoral transmission: - The transmission of an impulse across the synapse in central & peripheral nervous system occurs as a result of release of a neurohumoral transmitter substance in to the synaptic cleft.

Junctional transmission: - The arrival of an action potential at the axonal terminals initiates the series of events that put in to effect neurohumoral transmission of an excitatory/inhibitory impulse across the synapse / neuroeffector junction.

ADRENERGIC RECEPTORS:-

Receptor	Agonist	Antagonist	Tissue	Response	Molecular mechanism
a_1	Methoxamine	Quinazoline derivatives (Prazosin)	Blood vessel Smooth muscle Liver	Vasoconstriction Contraction Increased blood glucose level	Stimulation of phospholipase-C & formation of IP_3 /DAG
a_2	Clonidine	Yohimbine. Raulosine	Islet cells Platelets Vascular smooth muscles	Decreased insulin Aggregation Contraction	Inhibition of Adenylcyclase & neuronal ca^{2+} channels
b_1	Dobutamine	Atenolol, Acebutolol, Bisoprolol, Metoprolol	Heart Juxta glomerular cells	$+^{ve}$ Inotropic actions Increased rennin release	Activation of Adenylcyclase
b_2	Terbutaline, salbutamol	Butoxamine Methyl Propranalol	Smooth muscles	Relaxation	Activation of Adenylcyclase
b_3	Sibutramine (Antiobesity)	----------	Adipose tissue	Lipolysis	Activation of Adenylcyclase

Adrenergic receptors are membrane bound G- Protein coupled receptors which function primarily by increasing/decreasing the intracellular production of secondary messengers' cAMP/IP_3- DAG. In some cases the activated G-Protein itself operates K^+/Ca^{2+} channels or increases prostaglandin production.

Classification of Adrenergic drugs:-

A. Therapeutic classification-

1. Pressor drugs: - Adrenaline, NA, Metarminol
2. Inotropic agents: - Dopamine, Dobutamine, Isoprenaline& Xamoterol
3. CNS Stimulants:-Amphetamine
4. Smooth muscle relaxants:-Adrenaline, Isoprenaline, Isoxsuprine& b_2 stimulants (Salbutamol)
5. Drugs used in allergy: - Adrenaline & ephedrine
6. Local vasoconstrictor effect:-Adrenaline, Naphozoline, Phenylephrine
7. Nasal decongestants: - Oxymetazoline, Tuaminoheptanesulfate
8. Anorectics: - Fenfluramine, dexfenfluramine&Phenteramine
9. Antiobesity: - Sibutramine

B.Chemical classification:-

1. Catecholamines – Adrenaline, NA, Dopamine, 5-HT & Isoprenaline
2. Non-Catecholamines – Amphetamine, Ephedrine, Isoxsuprine, Mephentamine

Pharmacological Actions:-

1. **Heart**: - Due to its stimulant action on $\mathbf{b_1}$ receptors causes $+^{ve}$ inotropic actions. This is associated with increased metabolism of myocardium & increased O_2 consumption, thus decreasing cardiac efficiency.

2. **Blood vessels**: - Raises systolic B.P. by its cardiac actions lowers diastolic B.P. by its peripheral actions & hence not suitable in Hypotensive shock

- In moderate doses rise in B.P. is followed by a fall as it activates both the receptors. This is called as 'Biphasic response'.
- By prior administration of **a** blockers (ergot) leads to stimulation of only $\mathbf{b_2}$ receptors & thus causes a fall in B.p. This phenomenon is called as 'Dale's vasomotor reversal'

Compared to Adrenaline, the NA has feeble actions on b_2 receptors.

3. **Smooth muscles**: - relaxes bronchial muscles

Produce contraction of spleemic capsule producing a release of erythrocytes in to the Peripheral circulation. This serves as protective mechanism during stress such as hypoxia & Hemorrhage

4. **Eye**: - Mydriasis due to contraction of radial muscle fibres of IRIS. On topical application do not produce Mydriasis but cause reduction in intraocular tension.
5. **Respiration**: - Bronchodilator & weak stimulant
6. **Metabolic effects**: - Increases Blood glucose, Blood lactate, free fatty acids. Inhibits insulin release.
7. **CNS**: - Catecholamines cannot cross BBB

8. **Miscellaneous**: - Skeletal muscle contraction, Accelerates Blood coagulation, Platelet aggregation, Leucocytosis& Eosonopenia. Inhibit cellular anaphylactic mechanism& prevent release of allergic mediators (Histamine from mast cells)
Major excretory products are Vanillin mandelic acid

Therapeutic Uses:-

1. Na in elevating B.P. in shock
2. In glaucoma. To control hemorrhage
3. Cardiac resuscitation
4. Bronchial asthma
5. First line drug in Hypersensitivity
6. Along with Local anaesthetics to prolong their action.

Note: - Metyltyrosine/Metyrosine/2-methyl p-tyrosine inhibits Tyrosine hydroxylase in synthesis of catecholamines & used in treatment of Pheocytochroma.

Catecholamines	Non-catecholamines
Not effective orally Do not cross BBB Susceptible to MAO	Orally effective Crosses BBB Relatively resistant to MAO

Nasal decongestants: - Most of the Sympathetic amines on topical application produce Local vasoconstriction & used as Decongestants
E.g. Oxymetazoline, Zylometazoline, Naphozoline.tuaminoheptanesulfate

Potency of agonists at a&b receptors are-
a - Adrenaline > NA > Isoprenaline
b - Isoprenaline > Adrenaline > NA

b_2 selective receptor stimulants: -
- Isoprenaline used in Asthma will cause adverse cardiac effects due to action on **b_1**
- Therefore selective **b_2** stimulants are used in Asthma & as Tocolytics
- E.g.Nylidrin.Isoxsuprine

Drugs used in CCF:-
- Dopamine& Dopexamine acts on **a & b** receptors as well as D_1&D_2 receptor.
- Dobutamine acts only on **a** &**b** receptor
- Xamoterol has selective **b_1** agonist action.

ADRENERGIC BLOCKING AGENTS:-

Classification:-

α-Blockers:-

1. β- Haloalkylamines- Dibenamine& Phenoxybenzamine
2. Imidazoline derivatives- Tolazoline& Phentolamine
3. Quinazolines- Prazosin, terazosin, tremazosin
4. Natural & dehydrogenated ergot alkaloids
5. Miscellaneous- yohimbine, Indoramine, Cpz

The receptor blockade produced by Dibenamine& Phenoxybenzamine is ir-reversible type. Phenoxybenzamine is 6-10 times more potent than Dibenamine but has be converted to active metabolite.

Therapeutics Uses: - In pheocytochroma, Hypertension, Secondary shock, CHF, BHP, Male sexual dysfunction, Scorpion Bite.

β-Blockers:-

1. Specific **b**- Blockers- Timolol, Nadolol
2. Blockers with membrane stabilizing action: - Propranalol, Oxyprenolol, Pindolol
3. Blockers with cardioselective action: - Atenolol, Acebutolol, Metoprolol&Esmolol
4. Both **a** &**b** blockers: - Labetolol, Carvedilol, Dilevilol&Medroxolol

Atenolol with poor lipid solubility does not cross BBB at all.

- Propranolol, Alprenolol&Metoprolol are metabolized by liver, Practolol is largely excreted unchanged by kidneys.
- Pindolol, Atenolol, Acebutolol& Timolol by both the routes.
- They are contraindicated in the myocardial insufficiency, Bradycardia, Asthma, Heartblock& Insulin dependent diabetes.

T.Uses:-Anginapectoris, MI, Cardiac arrhythmia, Hypertension, Thyrotoxicosis, Pheocytochroma, to decrease cardiac symptoms prior to important speech/meetings.
Propranalol is useful in prevention of Migrane & treatment of Essential tumor.

CHOLINERGIC DRUGS

Ach produces its dual actions as Muscarinic actions on Muscarinic & Nicotinic actions on nicotinic receptors.
Muscarinic receptors (mol, wt-80,000) belong to g-Protein coupled receptors. Nicotinic receptors are Pentameric proteins.

Receptors	Agonist	Antagonist	Tissue	Response	Molecular Mechanism
N_m	Phenyl trimethyl ammonia	D-Tc **a**- Bangarotoxin	NMJ	End plate depolarization	Opening of cation channels
N_n	Dimethyl phenyl piperazinum	Trimethophan Hexamethonium Succinylcholine	Autonomic Ganglia Adrenal medulla	Depolarization& firing of Post ganglionic neurons. Secretion of catecholamines	Opening of cation channels
M_1	Oxytremonium	Pirenzepine Telenzepine Atropine	Autonomic Ganglia Gastric Glands	Depolarisation & Late EPSP. Histamine release	Stimulation of phospholipase-C & formation of IP_3 /DAG
M_2	Methacholine	Methocrotamine Atropine	Heart	Negative Inotropic effect	Inhibition of Adenylcyclase
M_3	Bethnecol	Atropine Hexahydrosiledenifol	Smooth Muscles Secretory Glands	Contraction Increased secretion	Stimulation of phospholipase-C & formation of IP_3 /DAG

CLASSIFICATION:-

1. Esters of Choline – Ach, Methacholine, Carbachol& Bethnechol
2. Cholinomimetic Alkaloids – Pilocarpine, Muscarine&Arecholine
3. Cholinesterase inhibitors –

a) Reversible: - Physostigmine (Natural), Neostigmine.Pyridostigmine, demecarium Tacrine (Acridine) used in Alzhmeir's disease.

b) Ir-reversible: - Di-isopropylflurophosphate (therapeutically useful), OMPP, Malathion, Parathion, Nerve gases (Tabun, sarin& Soman) Propoxur (carbamates)

Pharmacological actions:- Undergoes Hydrolysis in Neutral or Alkaline medium & hence preserved in Acidic medium.
On oral administration gets destroyed by GIT & hence given by I.v.
There is no circulating Ach in the Blood.

Muscarinic actions –
1. **CVS**: - Negative Inotropic actions, Dilates Blood vessels, Coronary arteries&veins. Increases tone & rhythmic activity of smooth muscles of GIT & enhance Peristalsis.

2. **Secretions**: - Increases Nasal, Bronchial, Gastric, salivary, Pancreatic & Intestinal secretions.

3. **Eye**: - on instillation no effect. But on injection to carotid arteries produces-
Constriction of Pupil (Miosis) – By contracting circular fibres of sphincter pupillae
Spasm of accommodation – Due to contraction of ciliary muscle, resulting in relaxation of suspensory ligament of lens.

Nicotinic actions –
1. Increases output of Ach&NA from Post ganglionic sympathetic & Parasympathetic nerve endings & increases B.p.

2. Produce paralysis of skeletal muscles at NMJ

Contraindications of choline esters: - Hyperthyroidism, Bronchial asthma, Peptic ulcer& MI

T.Uses: - Glaucoma, Post operative paralytic ileus & abdominal distension

Anticholinesterases: - they act by inhibiting true & Pseudo cholinesterases, thus causing accumulation of Ach at various sites.

MOA: - **Ach is inactivated by combination of 2 sites on enzyme Cholinesterase.**
Anionic site bearing $-^{ve}$ charge attracts Quaternary nitrogen atom of Ach
Esteratic site which attracts carboxylic acid group of Ach. As a result of union of Ach with cholinesterase the esteratic site of enzyme is acetylated & this results in splitting of choline. The acetyl group in combination with esteratic site is However immediately removed as a result of combination with water forming Acetic acid.
This sets esteratic site of enzyme free for further inactivation of Ach.

Reversible Anticholinesterases: - These are structurally similar to Ach & combine with Anionic & esteratic sites of cholinesterase as well as with Ach receptor. However the complex with esteratic site is much readily hydrolysed compared to Ach. This produces temporary inhibition of the enzyme.
Uses – Glaucoma, Myasthenia gravis, Snake venomPoisonimg, Curare Poisoning& Alzhmeir's disease.

Ir-reversible: - These organophosphorous compounds combine only with esteratic site of cholinesterase & consequently esteratic site is phosphorylated. The hydrolysis of esteratic site is extremely slow /does not occur at all.
This will lead to Morbidity & Mortality, to overcome this we use cholinesterase reactivators like Pralidoxime, Diacetylmonoxime&Obidoxime chloride.

Note: - Edrophonium forms reversible complex only with Anionic site & Hence shorter duration of action.

Echothiopate forms complex with both Anionic & esteratic sites & hence is much more potent than other compounds.

ANTI-CHOLINERGIC DRUGS

They Block only Muscarinic actions but not the Ganglionic & skeletal neuromuscular actions of Ach.

Classification:-

1. Natural alkaloids – Atropine, Scopalamine
2. Semisynthetic derivatives – Homatropine, Ipatropium
3. Synthetic compounds – a) Mydriatics: - Cyclopentolate, Tropicamide
   B) Antisecretory: - Propantheine, Pirenzepine

MOA: - Belladonna alkaloids block muscarinic effects of Ach. The antagonism is of competitive type which is reversed by an increase in Ach concentration at the cholinergic nerve endings

P.actions:- Atropine & scopolamine have qualitatively similar actions except that Atropine is CNS stimulant While Scopalamine is CNS Depressant.

1. **Secretions** – Decreases gastric secretions including total acidity & enzymes, leading to decreased motility
   Decreases Nasal, Bronchial & other secretions

2. **Smooth muscles** – Relaxation,
   Causes Urinary retention

3. **Eye** - Mydriatic (1%), ciliary smooth muscle is paralyzed& produces tightening of suspensory ligament resulting in flattening of lens with consequent increase in focal length. Thus individual is able to see only at long distance (paralysis of accommodation/cycloplegia) Because of sphincter paralysis he cannot constrict the pupils for viewing near objects clearly in response to Bright light (Photophobia).

4. **CNS** – Atropine due to stimulation of medullary vagal nuclei & higher cerebral centers produces bradycardia, increase rate & depth of respiration produced by Anticholinesterases. Scopolamine by S.C.depresses RAS & Produces euphoria, Amnesia & dreamless sleep.

Therapeutic uses:-

- ♣ To control hypermotility, Colicky pain
- ♣ Organophosphorous compound poisoning
- ♣ As Antisecretory in Pre anaesthetic medication, Peptic ulcer& pulmonary embolism
- ♣ Motion sickness (scopolamine)
- ♣ Parkinsonism
- ♣ As Mydriatic& cycloplegic
- ♣ As Antispasmodic in drug induced diarrhoea, Spastic constipation, Gastritis&Dysmenorrhoea.

Contraindications:-

- ♣ May cause Congestive glaucoma in patients over 40yrs
- ♣ CCF with tachycardia
- ♣ Pyloric obstruction, pylorospasm&Cardiospasm

Ganglionic Stimulants: -

1. Nicotine, lobeline
2. Synthetic compounds (TMA, DMPP)

Activation of Nicotinic receptors facilitate the release of Ach, NA, dopamine, 5-HT & **b** Endorphin

- ♣ Nicotine releases GH, Prolactin & ACTH
- ♣ Increases muscle twitching followed by paralysis of myoneuronal transmission
- ♣ Induces Hepatic microsomal enzymes
- ♣ Increases BMR, reduces body weight & Appetite
- ♣ Causes lipolysis & releases free fatty acids Excessive release of cortisol affect mood & contribute to Osteoporosis
- ♣ Vomitting due to action on CTZ, releases ADH by stimulating Supraoptic nuclei of Hypothalamus
- ♣ Acidic urine Increases excretion of free nicotine, TMA & DMPP are excreted unchanged
- ♣ A.R:- Bronchitis, Emphysema, Tobacco Amlobia

Cigarette contains – Nicotine, Pyridine.CO, Furfural, Volatile acids& polycyclic hydrocarbons
Antidepressant like Bupropion is used to quit smoking in some individuals.

Note: - Mydriatics – Homatropine, Eucatropine & cyclopentolate
Other Antimuscarinics – Atropine methanitrate, Methoscopalmine bromide/Nitrates
Propantheline (probanthine) – used in peptic ulcer
Methantheline (Banthine), Dicyclomine
Pirenzepine (Gastrozepin) – in duodenal ulcer
Flavoxate (Uripas) & Oxybutynine (Ditropan) – In Dysurea,
In urinary frequencies Tolteridine – M_3 antagonist in Urinary incontinence.

Ganglionic Blocking agents: - Blocks transmission across Autonomic ganglia (Both sympathetic & Parasympathetic)
E.g.Hexamethonium, trimethomine&Hexamylamine

Skeletal muscle relaxants: - Used to treat spasm/spasicity

- ➢ Spasm – Involuntary contraction of muscle or group of muscles usually accompanied by pain & limited function.
- ➢ Spasticity – due to increased skeletal muscle tone associated with decrease in skeletal muscle power due to damage to the corticonotoneuronic pathways as in CNS injury, cerebral palsy, stroke or Multiple sclerosis.

Classification:-

1. Drugs acting centrally – diazepam, Baclofen& Mephenesin
2. Drugs acting peripherally at NMJ –
a) Competitive Blockers: - D-TC,
b) Depolarization blockers: - Succinyl choline
c) Inhibitors of release of Ach from the motor nerve terminals: - Botulinum Toxin – A & Antibiotics (Tetracycline& Aminoglycosides)
3. Drugs directly acting on Skeletal muscles: - Dantrolene

PHYSIOLOGY OF SKELETAL MUSCLE CONTRACTION:-

1. Due to nerve action potential releases Ach from synaptic vesicles of motor nerve in to synaptic cleft in large quantities, While in absence of NAP Ach is released due to miniature end plate potential (MEPP) in small quantities.

2. The released Ach binds to nicotinic receptors on the motor endplate resulting in Localised depolarization & development of End plate polarization (EPP). Depolarization is due to influx of Na^+ & Efflux of K^+ ions from motor endplate.

3. When EPP is achieved the surround area of muscle fibre gets excited resulting in development of muscle action potential (MAP) which initiates contraction of a muscle as a result of release of ca^{2+} in to the Sarcoplasm.

4. Ach is metabolized enabling repolarisation of motor endplate& muscle fibre membrane. This is achieved by reversal of ionic fluxes. The polarized muscle is now capable of responding to fresh nerve impulse.

Skeletal muscle contraction can be blocked as follows –

1. Blocking transmission of impulse across the motor nerve – local anaesthetics
2. Inhibit the synthesis of Ach in motor nerve – Hemicholinum
3. Inhibit the release of Ach – Botulinum Toxin-A & antibiotics (tetracyclines& Aminoglycosides)
4. Modifying the motor endplate so that it does not respond to Ach – dantrolene

D-Tc: - dextrorotatory, quaternary ammonium alkaloid from Chondrodendron Tomentosum
Relaxes smooth muscles, Releases Histamine
On repeated Administration produces cumulative toxicity. Do not cross BBB & Placental Barrier.
Di-Methyl Tubocurarine has slightly longer duration of action

Other drugs: - Alcuranium Chloride- Similar to D-Tc
Pancuranium & Atracuranium – 5 times more potent than D-Tc
Vercuranium Similar to Pancuranium but duration of action is less.
Gallamine – Similar to D-TC, less potent completely excreted by Kidneys in Unchanged form.

DRUGS USED IN PARKINSONISM

Extra pyramidal motor disorder characterized by Rigidity, tremor & Akinesia.
Here Dopamine level decreases (responsible for Akinesia) & Ach level increases (Rigidity, Tremor).

Pathology: - There is a degeneration of neurons in substantial nigra & Nigrostatial (Dopaminergic) Tract. The cause for this degeneration is due to the formation of free radical (Metabolism of Dopamine by MAO-B). In normal Protective mechanisms Free radical are quenched by glutathione & other protective mechanisms. If this fails the free radical will cause DNA damage.
A synthetic toxin n-methyl 4-phenyl tetrahydropyridine is responsible for damage to Nigrostatial tract.

CLASSIFICATION:-

A. Drugs acting on dopaminergic system:-

1. Precursors of dopamine – L-Dopa
2. Drugs inhibit Dopamine Metabolism – A) Mao inhibitors: - Selelegine
   B) Comt inhibitors:-Tolcapone& Entacapone
3. Drugs that release dopamine – Amantidine
4. Dopamine agonists – Bromocryptine, Lysuride, ropinrole, Pergolide, Pirebedil

B. Anticholinergics: - Trihexyphenidyl, Benzohexol, Benzatropine

C. Antihistaminics: - Promethazine

L-Dopa:-

- Pharmacologically inert, while its metabolite is active.
- Only 1% enters CNS, Most of the drugs get decarboxylated in GIT& liver
- It is excreted in urine partly unchanged& partly as Homovanilic acid.
- Gives Positive Comb's test even though hemolytic anemia is not reported.
- Blood urea nitrogen & SGOT show a transient rise.

Contraindications:-

- Pyridoxine accelerates Peripheral decarboxylation of L-DOPA.
- Reserpine & Phenothiazines block the effects of dopamine to which L-Dopa is converted.
- Methyldopa intensifies the adverse effects of L-Dopa.
- Anticholinergics increase the stay of L-dopa in stomach & increase its degradation & hence if needed must be taken 2hrs before taking L-Dopa.

Dopa decarboxylase inhibitors (DCI):-

- Pharmacologically inactive but on combined administration with L-Dopa they do not enter BBB But decreases peripheral decarboxylation Of L-Dopa

E.g. Carbidopa, Benserazide

L-dopa – Carbidopa combination results in control of symptoms smoother, dose of L-dopa Can be reduced up to 75%, Pyridoxine does not antagonize the actions of L- Dopa.

Selelegine (Deprenyl):- Inhibits MAO-B (responsible for dopamine metabolism)
L-dopa – Carbidopa – Selelegine combination must be avoided.
Note – MAO-A is responsible for Oxidative deamination of NA & 5-HT.

Amantidine: - Liberate dopamine from residual intact nerve endings & produces rapid response than L-Dopa.

Dopamine Agonists: - Crosses BBB & need not to be converted to active metabolite.
Causes nausea& severe neuropsychatric adverse effects.

CENTRAL NERVOUS SYSTEM

Drugs act on CNS in following ways:-

1. They may act directly on neurons & modify neuronal functions.
2. They may act reflexly by sending afferent impulses to the CNS via chemoreceptors, Baroreceptors & peripheral nerves.
3. They may affect the nutrition & oxygen supply of the CNS by altering its Blood supply or affecting its metabolism.

Neurotransmitters: - Which stimulate/Inhibit the post synaptic neurons after a brief latency & have short duration of action.
Amines – Ach, NA, 5-HT, Histamine& Dopamine
Aminoacids – l-Glutamic acid, Aspartic acid, GABA &Glycine
Peptides – Substance-P, Cholecytokinin

Note: - Glutamate & Aspartate are excitatory amino acids. While GABA is inhibitory aminoacid.

Neuromodulators: - which act on the post synaptic neurons with a longer latency, have a longer duration of action & modify the responsiveness of the target neurons to the action of the neurotransmitters.

Aliphatic Alcohols:-

- Ethanol in 70% acts as antiseptic, in 40-50% as rubifacient & mild irritant action
- By dissolving in the lipid membrane of the neurons & altering the functions of ion channels & other proteins. It increases GABA-mediated synaptic inhibition. It also inhibits NMDA glutamate receptors. & depress CNS in descending order.
- Impairs Gluconeogenesis, Reduces synthesis of Albumin & Transferrin, Increases synthesis of VLDL with consequent Hypertriglyceredemia&Diminishes fatty acid oxidation.
- Alcohol causes liver damage & cause Cirrhosis. Elevated Gamma glutamyl transpeptidase (GGTP) is the most sensitive indication of Alcohol liver disease.
- Uses: - Appetizer, in methanol poisoning.

Treatment of Acute alcohol poisoning: - I.v glucose 50%,
I.v. Thiamine 100mg (Bolus), I.v. $MgSo_4$ 2-4gm

Treatment of Chronic alcoholism: - Disulfiram (Antabuse) & Citrated calcium cyanamide (Carbimide)

Disulfiram – It interferes with the oxidation of acetaldehyde formed during the metabolism of alcohol. It also inhibits dopamine-**b** Oxidase & thus interferes with the synthesis of NA. This causes depletion of catecholamines.
4-Methyl pyrazole (inhibitor of alcohol dehydrogenase) used in treatment of methanol & ethylene glycol poisoning.

GENERAL ANAESTHETICS

They bring about loss of all Modalities of sensation in particularly pain along with a reversible loss of consciousness.
Minimum Alveolar concentration: - It is the minimum amount of the anaesthetic in pulmonary alveoli required to produce immobility in response to a painful stimuli, used in dose fixation& Capacity of anaesthetic is measured.

Classification:-
A.Inhalational Anaesthetics –
1. Volatile liquids:-Chloroform, Diethyl ether, Trichloroethylene, Halothane, Enflurane & Isoflurane
2. Gases: - Cyclopropane, Nitrous oxide, chloroform & Cyclopropane

B. Non – volatile (I.v.) Anaesthetics –
1. Inducing agents: - Thiopentone sodium, Propafol, Etomidate
2. Slower acting drugs: - a) Benzodiazepines – Diazepam, Lorazepam&Midazolam
b) Dissociative Anaesthetics: - Ketamine
c) Neurolept Analgesia: - Fentanyl + Droperdiol
(Analgesic) (Butyrophenone)

M.O.A.:- Most of the general anaesthetics acts by blocking synaptic transmission but some act by blocking excitatory transmission but some act by prolonging the synaptic inhibition (Potentiaion of GABA-A) thus depressing all the functional elements of CNS.
Inhalational anaesthetics, Barbiturates & Benzodiazepines act by potentiating the action of the inhibitory neurotransmitter GABA at $GABA_A$ receptor.
Ketamine selectively inhibits the excitatory NMDA type of glutamate receptor.

Stages of Analgesia:-
1. Stage of analgesia – Minor surgical procedures such as incision of Abcess, dental extraction
Are carried successfully in this stage.
2. Stage of delirium – must be avoided.
3. Stage of surgical anaesthesia – Includes 4 Planes.
4. Stage of respiratory Paralysis –

Pre-Anaesthetic medication: - Term applied to the use of drugs prior to the administration of an anaesthetic agent, with the objective of making anaesthesia safer & more agreeable to the patient.
1. Opoid analgesics – Morphine, Pethidine, Buprenorphine to reduce anxiety & apprehension of the patient.
2. Sedative & Tranquilizers – Benzodiazepines& Barbiturates
3. Anticholinergics – Atropine or Scopalamine
4. Antiemetics – Phenothiazines(Promethazine & trimeprazine), Metoclopramide
5. H_2 Blockers – Ranitidine & famotidine to avoid gastric regurgitation & aspiration pneumonia
6. Neuroleptics – Cpz, triflupromazine

Alphaxolone is a steroidal drug having anaesthetic property.

SEDATIVE & HYPNOTICS

Sedative reduces excitement & is commonly used as an Anxiolytic
Hypnotic produces sleep resembling natural sleep.

CLASSIFICATION:-

1. Barbiturates – Long acting (Phenobarbitone & mephobarbitone)
Short acting (Butobarbitone, Secobarbitone, and Pentobarbitone)
Ultra short acting (Thiopentone, Methohexitone& Hexobarbitone)
2. Benzodiazepines – Anticonvulsant (Diazepam, Clonazepam& Clobazepam)
Antianxiety (Diazepam, oxazepam, lorazepam, alprazolam, Chlordiazepoxide)
Hypnotics (Diazepam, nitrazepam, flurazepam, temazepam, midazolam)
3. Alcohols – chloralhydrate, Ethchlorvynol
4. Aldehydes – Paraldehyde
5. Acetylated carbinols – Ethinamate, Meprobamate
6. Imidazopyridine – zolpidem
7. Cyclopyralone – Zopiclone
8. Oxazolidine Diones – Paramethadione & Trimethadione
9. Miscellaneous – Methaqualone, antihistaminics & scopolamine

M.O.A.:-

Barbiturates – They act primarily at the GABA: BZD receptor – Cl^- channel complex & they potentiate GABAergic inhibition by inducing the opening of the chloride channel.

Benzodiazepines – They act by enhancing presynaptic/postsynaptic inhibition through a specific BZD receptor, which is an integral part of the $GABA_A$ receptor – Cl^- channel complex. The binding site for GABA is located in the **b** subunit while the **a** subunit contains the BZD binding site. The modulatory BZD receptor increases the frequency of cl^- channel opening.

DRUGS AFFECTING $GABA_A$ RECEPTOR- CL^- CHANNEL COMPLEX ARE

	$GABA_A$	**$GABA_B$**	**BZD site(a site)**
Endogenous agonist	GABA	GABA	
Agonist	Muscimol	Baclofen	BZD
Competitive antagonist	Bicculine	Saclofen	Flumenazil
Inverse agonist			**b** carboline

ANTI – CONVULSANTS

These are the agents used to treat convulsions
Agents that produce convulsions are Bicculine, Pentylene tetrazole, Strychnine& Picrotoxin

CLASSIFICATION:-

1. Hydantoin derivatives – Phenytoin,Methatoin & ethatoin
2. Barbiturates – Phenobarbitone & Primidone
3. Iminostilbines – Carbamazepine
4. Succinimides – Ethosuximide & Methsuximide
5. GABA Transaminase inhibitors – Sodium Valproate, Vigabatrin
6. GABA reuptake inhibitors – Tiagabin
7. GABA Agonists – Gabapentin
8. Benzodiazepines – Diazepam,Clonazepam&Clobazepam
9. Miscellaneous– Lamotrigine,Acetazolamide,Sultiame(Sulphonamide), Amphetamine

1. Hydantoin derivatives:-

M.O.A. – It acts by inhibiting the spread of seizure discharges in the Brain & Shortens the duration of after discharge. The drug causes dose-dependent block of sodium channels, thus reducing the neuronal sodium concentration leading to a reduction in Post titanic potentiation (PTP) & to increase the neuronal Potassium concentration.
AR – Hyperplasia, Hypertropy of gums, Osteomalacia, Hyperosmolar&non-Ketotic Coma.
Uses – Grandmal, Focal cortical epilepsy. Psychomotor seizures & Neuralgia

2. Barbiturates;-

M.O.A. – Potentiates GABAergic inhibition
AR – Vit-K depletion, Megaloblastic Anaemia & osteomalacia
USE: They are used in the treatment of resistant grandmal, cortical seizures.

Primidone is a Deoxy Barbiturate converted in the liver to 2 active metabolites Phenobarbitone & Phenyl ethyl malonamide.

3. Iminostilbines: - It increases threshold to PTZ & Electroshock convulsions
AR – Peripheral neuritis, Agranulocytosis, Obstructive jaundice, Aplastic anaemia & Thrombocytosis, Diplopia, Vertiga, Ataxia & Lupus like Syndrome.
Uses – Temporal lobe & Grandmal epilepsy, Trigeminal neuralgia, Diabetes insipidus & Alternative to Lithium CO_3 in Mania.

4. Succinimides: - It acts by suppressing T-Current
AR – Blood dyscrasiasis, SLE, Psychic disturbances & GIT disturbances.
Used in Temporal lobe epilepsy

5. GABA transaminase Inhibitors: - Potentiates Post synaptic GABA activity & decrease brain levels of EAA.

6. Oxazolidine Diones: - Raises threshold to Seizures
AR – Hemeralopia, Kidney damage **Used** in Petitmal epilepsy

7. Miscellaneous:-

Lamotrigine – blocks voltage sensitive sodium channel
Acetazolamide – Inhibits CA & acts by increasing CO_2 levels in the Brain or by decreasing sodium there by increasing Seizure threshold.

ANTIPSYCHOTICS

Antipsychotics/ Tranquilizers/ Ataractics are the drugs reduce Apomorphine induced Sterotype & Amphetamine induced Hyperactivity & also inhibit conditional avoidance response and cause some Ataxia.

CLASSIFICATION:-

1. Phenothiazine derivatives –

a) Aliphatic side chain: - CPZ, triflupromazine
b) Piperidine side chain: - Thioridazine & Mesoridazine
c) Piperazine side chain: - trifluperazine, Fluphenazine&thioproperazine

2. Butyrophenones – Haloperidol, Trifluperidol, Droperdiol&Penfluridol
3. Rauwolfia Alkaloids – Reserpine
4. Thioxanthines – Chlorprethixene, Thiothixene& Flupenthixol
5. Indole derivatives – Molindone
6. Substituted Benzamides – Sulpiride
7. Atypical neuroleptics – Clozapine (Dibenzodiazepines), Reserpidone
8. Miscellaneous – Oxypertine, Loxapine, Pimozide

M.O.A:-

Most of them act by following 3 ways-

1. Cause Blockade mainly of post synaptic Dopaminergic (D_2) receptors & to a small extent 5-HT receptors.
2. Modify functions of Mesolimbic system.
3. Reduce incoming sensory stimuli by acting on the brain stem reticular formation.

All Antipsychotics except clozapine have potent Dopamine (D_2) blocking action.
Dopamine acts as an excitatory neurotransmitter at D_1 & D_5 while Dopamine acts as an inhibitory neurotransmitter at D_2 , D_3& D_4 receptors.
Clozapine acts by 5-HT_2 as well as $\mathbf{a}_1$ Blockade.
Reserpidone acts by 5-HT_2 as well as D_2 Blockade.

AR- Anticholinergic effect, Extrapyrimidal effects, Weight gain

ANTI-ANXIETY AGENTS

Elevated plus Maze test is used to evaluate Anti-anxiety agents.

Class	Drugs	M.O.A.
Benzodiazepines	Diazepam,Alprozolam,Oxazepam, Lorazepam,Chlordiazepoxide	Potentiates GABAergic Inhibition.
Azapirone	Buspirone,Gepirone,Ipsapirone	Stimulates Presynaptic 5-HT_{1A} Autoreceptors.
Others	Meprobamate,Hydroxyzine	Antihistaminic with sedative, antimuscarinic & Spasmolytic actions.
b- blockers	Propranolol	By reducing B.p. tremor & palpitation.

AFFECTIVE DISORDERS

Refers to pathological change in mood state. The 2 Extremes are Mania & Depression.
Drugs like Antidepressants & Antimanics (Mood stabilizers) are used.

Anti-Depressants:-

A.MAO Inhibitors

1. Non-selective

a) Hydrazines: - Phenelzine, Isocarboxazid& iproniazid
B) Non-Hydrazine:- Tranylcypromine

} Irreversible

c) Reversible: - Moclobemide

2. Isoenzyme Selective

a) MAO-A Inhibitor: - Clorgiline, Moclobemide
b) MAO-B Inhibitor: - Selelegine (Deprenyl)

B. Tricyclic Antidepressants

1. Nor-Adrenaline & 5-HT reuptake Inhibitors

Imipramine, Amitryptiline, Trimipramine, Doxepin, Clomipramine, Dothiepin & Venlaflexin

2. Nor-Adrenaline reuptake Inhibitors

Nortryptyline, Desipramine, Protryptiline, Amoxapine

3. Selective 5-HT reuptake Inhibitors

Fluoxetine, Fluvoxamine, Paroxetine, sertraline & Alpacrolate

4. Atypical Antidepressants

Trazodone, Bupropion, Mianserin, Tianeptine

M.O.A:-

MAO Inhibitors act by inhibiting MAO (Enzyme responsible for degradation of Catecholamines). Tricyclic Antidepressants Inhibit active uptake of Biogenic amines NA & 5-HT in to their respective neurons & thus potentiate them.

ANTIMANICS/ MOOD STABILIZING DRUGS:-

Lithium carbonate – They act by replacing Na^+ by Li^+ this affects ionic fluxes across Brain cells or modify the property of cellular membranes.

They decrease the release of NA & dopamine in the Brain with out affecting 5-HT release.
They inhibit action of ADH on distal tubules & causes diabetes insipidus like state.

Alternatives used as Antimanics – Carbamazepine, Sodium valproate.

Hallucinogens: - (Psychomimetics/ Psychedelics/ Psychodysleptics/ Psychotogens)

These drugs alter mood, behavior, thought & perception in a manner similar to that seen in Psychosis.

Classification:-

1. Indole amines: - LSD, Psilocybin, Harmine, Bufotenine & dimethyltyrptamine
2. Phenyl alkylamines: - Mescaline
3. ArylcycloHexylamines: - Phencyclidine
4. Cannabinoids: - Tetrahydro Cannabinol

Phencyclidine is a Hallucinogen structurally similar to Ketamine.

Psychomotor stimulants: -
Caffeine, Amphetamine & Piperidyl derivatives (Pipradrol & Methyl phenidate).
Used in Narcolepsy, Catoplexy & Attention deficit Hyperactivity disorder (ADHD).

OPIOID ANALGESICS

- ♣ The opioid drugs produce their effects by combining with opioid receptors which are widely distributed in CNS & other tissues.
- ♣ Opiods & their Antagonists act at Mu receptors.
- ♣ The side effects such as vomiting, Sweating & Hallucinations are due to action of drugs on subtype of Kappa receptors.

	m	**j**	**k**
Endogenous agonists	Endomorphin 1&2 **b**-Endorphin (31a.a)	Leu/Meth Enkephalein (5a.a)	Dynorphin A
Exogenous agonists	Morphine	Morphine	Ketocyclazocine
Selective agonists	**b**-Funaltrexamine $\mathbf{m_1}$-naloxanazine		Norbinaltorphimine

B-Endorphin is a pain modulator in the CNS derived from Pro-opio-Melanocortin

Opium alkaloids are divided as
1. Phenanthrene group
2. Benzyl isoquinoline – Papaverine, Noscapine
Devoid of analgesic activity, Intracarvenosal injection of papaverine causes penile errection. Noscapine is a potent releaser of Histamine. & large doses cause Hypotension.

Morphine – Used as sulfate/HCl salt
Produces Analgesia, Euphoria, sedation& Hypnosis.
Causes direct depressant action on Brain stem respiratory centre & reduce the sensitivity of medullary respiratory centre to increased plasma CO_2 concentration. With toxic doses breathing is entirely maintained by 'Hypoxic Drive' mediated through the carotid & aortic body chemoreceptors & results in **'Cheyne Stokes Respiration'**.
Causes Miosis, Nausea Cough suppression, Stimulates Vagus nuclei, Excites spinal cord & raises CSF.It also releases ADH.
GIT: - spasms followed by increase in intrabiliary pressure.

T.uses – Powerful analgesic, sedative, Pre-anaesthetic medication, general anaesthetic
Contraindications- In, hypopitutarism, Addison's disease, Head injuries, impaired kidney & liver functions.

Codeine – Devoid of respiratory depression, enhances analgesic effect in combination with Aspirin.
Note: - All the 3 types of receptors are antagonized by Opioid antagonists such as Naloxone & Naltrexone.
The drugs which act as partial agonist-antagonists at the opioid receptors are Nalorphine, Levallorphan, and Pentazocine&Nalbuphine.

NSAIDS: - Extensively protein bound drugs.
Classification –
1. Salicylates:-
2. p-Aminophenol derivatives: - Phenacetin, Paracetamol, & Acetanilide
3. Pyrazolone derivatives: - Phenyl Butazone
4. Indole & related drugs: - Indomethacin, Sulindac
5. Heterocyclic Aryl acetic acid derivatives: - Diclofenac, Tolmetin&Keterolac
6. Propionic acid derivatives: - Ibuprofen, fenoprofen, Naproxen, Ketoprofen
7. Fenamates: - Flufenamic acid, & Mefenamic acid
8. Oxicams: - piroxicam
9. Sulfonanilides: - Nimesulide

M.O.A:- Cox-1 is present in Stomach, Kidney& Blood vessels. Where as Cox-2 in inflammatory cells& activated leucocytes.NSAIDS act by inhibiting COX, responsible for the conversion of arachidonic acid to Prostaglandins.

Salicylates: - prevent the release of Histamine, Lowers ESR (erythrocyte sedimentation rate) Inhibits platelet aggregation. In small doses elevate plasma urate levels while in large doses causes uricosuria. Induces release of adrenaline from adrenal medulla.
In case of salicylate poisoning supplement of Vit-k is given along with other formalities.
Trusses – Antirheumatic,

Antiplatelet, Analgesic, Antipyretic, Counterirritant, Keratolytic, fungistatic, Antiseptic, Antiinflammatory.
Selective Cox-2 inhibitors: - Nimesulide, celecoxib, rofecoxib, meloxicam

GASTROINTESTINAL DRUGS

Achlorhydria: - Absence in production of HCL leading to improper digestion. It can be treated by 10ml of 10% HCL diluted 100ml H_20.

Hypochlorhydria: - decreased production of HCL.

Sialorrhoea: - increased salivary production

ORS: - Oral rehydration solution. Glucose – 20g, Nacl – 3.5g, Kcl – 1.5g, $NaHCo_3$ (2.5g) or tri sodium citrate (2.9g) – distilled water (1-L).

Mumps: - infectious, inflammatory swelling of paratoid & other salivary glands.

Hydragogue: - Drug which produces watery stools.

Dyspepsia: - disorder of abdomen or chest with flatulence, nausea etc.

Achyliagestrica: - Absence of HCL.

Bitters: - They increase appetite by promoting gastric acid secretion. E.g.:- gentian, chirata, picrorrhiza Alcohol & 2 other Antihistaminics (cyproheptidine, Buclizine) also acts as appetite stimulants.

Anorexia nervosa: - Chronic disease characterized by loss of appetite, weight loss, physiological & psychological alterations.

Digestants: - which aid in digestion in GIT.
E.g.:- Diastase & Taka diastase – Amylolytic,
Papain – Proteolytic,
Pancreatin – Amylolytic & Proteolytic,
Bromelain – Amylolytic, lipolytic & proteolytic,
Lipase – Lipolytic.
Carminatives: - expels gas with relaxation of sphincters. E.g.:- Volatile oils & Spices.

Gall stone dissolving drugs: - Ursodiol & chenodiol
Bile salts are essential for digestion of cholesterol, when the amount of cholesterol in body increases, they form gall stones, and thereby bile acids are used for dissolving gall stones.

Bile acids: - Chenodiol (cholic acid) & Ursodiol (taurocholic acid) both inhibit absorption of cholesterol.

Bile salts: - Sodium glycocholate & sodium taurocholate.

Bile pigments: - Bilurubin, Biliverdin, Stercobilin & Stercobilinogen.

Peptic ulcer: - due to imbalance between aggressive factors (acid, pepsin & H-pylori) & defensive factors (gastric mucus & bicarbonate secretions, PG'S innate resistance of the mucosal cells).

METHODS OF TREATING PEPTIC ULCER:-

1. **By reducing gastric acid secretion :-**

Class	Drugs	M.O.A	A.R.
H2 Blockers	Cimetidine ranitidine Roxatidine famotidine	Blacks H2 receptors	Cimetidine causes gynacomastia & inhibiting cytp450
Proton pump inhibitors	Omeprazole Lansoprazole Pantoprazole	H+K+ inhibits Atpase present in parietal cells	Nausea headache loose stools
Anticholinergies	pirenzepine Propantheline	Decreases cholinergic secretions	Intolerable side effects
PG Analogues	Misoprostol Rioprostil Enprostil	Inhibit acid secretion & promote mucus & bicarbonate secretion Inhibit gastrin production	Contraindicated in pregnancy

Cimetidine Produces Anti Androgen Effect by displacing the Dihydro testosterone from the cytoplasmic receptors, Increases plasma prolactin level & inhibits the metabolism of Estrogens.

2. **Neutralization of gastric acid: -** Systemic antacids – NaHco3, Non Systemic antacids – Al $(oH)_3$, Mg $(oH)_2$.

MAGALDRATE – Hydrated complex of Hydroxy Magnesium Aluminate.

Acid neutralizing capacity: - Number of milli equivalents of 1N HCL that is brought to PH 3.5 in 15 mins by unit dose of the preparation.

3. **Ulcer protectives :-**

Sucralfate – Aluminium salt of sulfated sucrose at pH – 4 it polymerizes to form a gel & gets deposited on the wall of stomach.
Colloidal Bismuth Sub citrate – increases Pg synthesis. They also destroy H.Pylori

4. **Ulcer healing drugs: -** Carbenoxolone sodium, Deglycyrrhizinised licorice.

5. **Anti.H.Pylori:-** Metronidazole, Tinidazole.

Combination therapy = Clarithromycin + Amoxycillin + Omeprazole.

Polymethyl siloxane: - Collapes froth, improves dispersion of Antacid, reduces gastro esophageal reflux & thus relieves Heart Burn.

Drug contraindicated in peptic ulcer: Caffeine, reserpine, Aminophylline, glucocorticoids, NSAIDS

EMETICS

Emetine, Apomorphine, Hypertonic saline solution, mustard (sinigrin)
Anti emetics:-
Anticholinergies – Hyoscine, Dicyclomine
H_1 Antihistaminics – Promethazine, Diphenhydramine, Cyclizine, Cinnarazine
Neuroleptics – CPZ, Haloperidol, Prochlorperazine
Prokinetic drugs – Metoclopramide, Domperidone,
$5HT_3$ antagonists – Ondansetron, granisetron

DRUGS ACTING ON RESPIRATORY SYSTEM

Respiratory quotient: - ratio of oxygen consumed to the carbondioxide evolved.

1. **Pharyngeal demulcents: -** sooth the throat directly as well as by promoting salivation E.g.:- Lozenges, Glycerine, Liquorice.
2. **Expectorants (mucokinetics):-**
   Directly acting:- eucalyptus & lemon oil, Guainaphenesin, Vasaka.
3. **Reflexly acting: -** saline expectorants (NH4cl, KI, K-citrate)
4. **Antitussives :-**
   - ♣ Opioids – Codeine, morphine.
   - ♣ Non-Opioids – Noscapine, Dextrometrorphan, Clophedianol, Carbetopentane & Oxeladin

5. **Antihistaminics –** Chlorpheniramine, diphenhydramine,Promethazine
6. **Mucolytic agents: -** decreases viscosity of sputum. E.g.:- Acetylcysteine, bromohexine, Ambroxol pancreatic dornase.
7. **Nasal decongestants: -** ephedrine, phenyl ephrine Naphazoline & Oxymetazoline.

Bronchodilators:-

1. **Sympathominetics** – ephedrine, adrenaline, salmeterol
2. **Methyl xanthines** – Theophylline
3. **Anticholinergics** – Ipratropium bromide Atropine methonitrate.

- ♣ Cromolyn sodium is a prophylactic agent that stabilizes most cells in asthma.
- ♣ Prednisolone is life saving in serve status asthamaticus & inhibitor of phospholipase A_2.
- ♣ Ipratropium is bronchodilator in chronic obstructive pulmonary disease with least cardiac effects.
- ♣ Ketotifen – Orally active, Prophylactic agent in Bronchial Asthma & Allergic disorders.
- ♣ Inhalational Steroids – Beclomethasone, dipropionate& Budesonide.

Catarrh: - state of irritation of mucous membranes associated with a copious secretion of mucus.

DRUGS ACTING ON C.V.S

Cardiac glycosides: - These glycosides have cardiac inotropic activity. They increase myocardial contractility & output without proportionate increase in O_2 consumption. E.g.:- Digitoxin, Digoxin, Lanatoside – C, quabain

M.O.A:- Cardiac glycosides selectively bind to membrane bound Na^+/K^+ ATPase pump. This results in accumulation of Na^+ intracellularly and this indirectly results in intracellular accumulation of $Ca2^+$, this leads to increased myocardial contractility.
Therapeutic index = 1.5 – 3.0 (Digitalis)

Properties	Digitoxin	Digoxin	Lanatoride – c	Quabain
Oral absorption	Excellent	Good	Low	Low
PPB	95 %	25%	25%	Poor
2plasma t1/2	7 days	2 days	2 days	1 day
Potency	Less	Intermediate	Intermediate	High
Elimination	Hepatic	Renal	Renal	Renal

Uses: - CCF, cardiac arrhytmias such as atrial flutter & atrial fibrillation.

Cardiac arrhythmias: - refers to changes in Cardiac rhythm.

Antiarrhythmic drugs:-

I – Sodium channel Blockers

Class	M.O.A	Examples
IA	Prolongs repolarisation	Quinidine, Procainamide Disopyramide.
IB	Shortens repolarisation	Lidocaine, Phenytoin tocainide.
IC	Slows conduction	Encainide, Flecainide Propafenone.

Affinity towards Na+channel = class IC > class IA > class IB

II – B Blockers E.g.:- propranalol
M.O.A:- slows conduction & suppresses automaticity.

III – K+ channel blocker E.g.:- Amiadarone, Bretylium, Sotalol
M.O.A:- prolongs refraction

IV – ca2+ channel blocker E.g.:- verpamil, Diltiazem blocks inward ca2+ current.

V – Digitalis.

Cardiac arrhythmic disorders	**First line drugs/ Drug of choise**
PSVT	Adenosine/Verpamil
Av Block	Atropine
Atrial extra systole	Quinidine
Atrial flutter/Atrial fibrillation	Verapamil
Ventricular extra systole/ventricular tachycardia	Lidocaine
Wolf Parkinson white syndrome	Amiodarone/Flecainide

ANTI-ANGINAL DRUGS

Used to treat Angina pectoris

Angina pectoris: - where the O_2 demand of the myocardium exceeds that of the supply.

Stable angina: - generally caused due to stress

Unstable angina: - due to occlusion of coronary arteries by plague.

Variant / Prinzmetal angina: - It occurs at rest due to recurrent localized coronary vasospasms.

Classification:-

A. **Organic nitrates: -** i) short acting: - glyceryl trinitrate.
ii) Long acting: - ISDN, ISMN.
B. **B – Blockers: -** Propranalol.
C. **$Ca2^+$ channel Blockers: -** Verapamil, Nifedepine, Diltiazem.
D. **K^+ channel openers: -** Nicorandil, minoxidil.
E. **Antiplatelet drugs: -** Aspirin, Dipyridamole.
F. **Cytoprotectives: -** Trimetazidine.

Nitric oxide (EDRF) is synthesized in body from L-arginine as follows –

- L-arginine N.O.synthetase N.O. +citrulline

- Organic nitrates are rapidly denitrated in the smooth muscle cell to release the reactive free radical N.O. that activates guanyl cyclase, which causes the formation of CGMP from GTP. CGMP causes desphorphorylation of MLCK through CGMP dependent proteinkinase. Reduced availability of phosphorylated MLCK interferes with activation of myosin & it fails to interact with actin & this leads to relaxation.

- Nitrates are also used to treat cyanide poisoning as nitrates form methemoglobin with Hb. So that cyanide cannot act on methemoglobin.

Potassium channel openers: - since intracellular concn of K^+ is much higher compared to extra cellular region, K+ channel opening results in outflow of K^+ ions & hyperpolarisation.
Uses: - Angina pectoris, Hypertension, CHF.
AR: - Hirsutism.

Desferrioxamine: - A high affinity iron cheater used as a protective in ischemic myocardial injury through its anti-free radical effect.

Vasodilators: - They are used in Hypertension, myocardial infarction, angina attacks etc.
1) Arteriolar vasodilators: - Hydralazine, minoxidil, nifedepine, diazoxide, nicorandil.
2) Venous vasodilators: - Glyceryl trinitrate, ISDN.
3) Mixed vasodilators: - Losartan, sodium nitroprusside, prazosin.

Selective phosphodiesterase inhibitor: - Amrinone is an inotropic agent. It is a bipyridine derivative & inhibits PDE – III.
Milrinone (derivative of Amrinone) & 10 times more potent than Amrinone.
Drotavarin inhibits PDE – V.

Non-selective PD inhibitor: - Cilastazole & Theophylline dithiothreol is used to stop the action of nitrates by removing nitrate groups attached to 'SH'.

ANTIHYPERTENSIVE DRUGS:

- These are drugs used to lower BP in Hypertension.
- Blood pressure is the product of cardiac output and peripheral resistance.
- Cardiac output is the amount of blood pumped by the heart in one minute and is therefore the product of stroke volume and the heart rate. Stroke volume refers to the volume of blood pumped during each contraction.
- **B.P = C.O * T.P.R, C.O = stroke volume * Heart rate.**
- Thus it can be observed that most of the antihypertensive drugs act by either decreasing peripheral resistance or by decreasing cardiac output.

CLASS	DRUGS	MECHANISM OF ACTION MOA	ADVERSE EFFECTS
ACE inhibitor	Enalpril, (prodrug) Lisinorpril, (prodrug) Ramipril (prodrug) Captopril (nonprodrug) Saralasin	They inhibit ACE essential for the conversion of AT-I to AT-II, which is a potent vasoconstrictor	Dry cough, angioedema, Urticaria and taste disturbance.
Angiotensin receptor antagonist	Losartan, irbesatran valsartan, telmisatran candesartan (Peptide analogue).	They antagonize the action of AT-II at the angiotensin receptor.	Usually well tolerated.
Calcium channel blockers	Verapamil, nifedepine, amlodipine	They lower b.p by decreasing peripheral resistance	Agents such as diltiazem/verapamil have negative inotropic action.
Diuretics	Chlorthiazide, furosemide, spironolactone.	They induce diuresis that reduces plasma volume which in turn reduces C.O leading to a drop in b.p.	Thiazide diuretics cause hypokalemia and also hyperglycemia in diabetics.
β Blockers	Metoprolol, propranolol	They decrease sinus rhythm, which leads to a decrease in heart rate, which leads to a drop in b.p.	Myocardial insufficiency Bradycardia Asthma Heart block. Insulin dependent diabetics.

α Adrenergic blockers	Prazosin, terazosin	They block the action of adrenaline at the a receptor present in blood vessels thereby leading to vasodilatation	Impotence postural hypo tension
Central sympatholytics	Methyldopa clonidine (h2 agonist)	The-nor methyl adrenaline formed from methyldopa acts as false neuro transmitter on a2 and decreases efferent sympathetic activity.	Sedation, lethargy and reduced mental capacity.
Neurotransmitter depletors	Guanethedine reserpine	Displaces N.T. from synapse increases N.T.metabolism	
Vasodilators	Hydralazine, minoxidil	Vasodilatation leads to a decrease in peripheral resistance, which in turn leads to fall in b.p.	Hydralazine on prolonged use causes SLE (Systematic lupus erythrematosus), hirsustism, peripheral pooling of blood.

Ethacyranic acid is contraindicated in Angina in Asthma B2 blockers is avoided.

ANTIHYPERLIPIDEMIC DRUGS:

These drugs lower the levels of lipoproteins and lipids in blood. The different types of hyperlipoproteinemia are:

Type	Disorder	Elevated plasma lipoprotein	Elevated plasma lipids
I	Lipoprotein lipase deficiency	Chylomicron	Cholesterol & triglycerides
IIa	Familial hypercholesterolemia	LDL	Cholesterol
IIb	Polygenic hypercholesterolemia	LDL (B-lipoprotein)	Cholesterol (moderate increase)
III	Familial Dysbetalipoproteinemia	IDL, chylomicron remnants	Cholesterol & triglycerides
IV	Hypertriglycereridemia	VLDL (pre-B lipoprotein)	Triglycerides
V	Hyperlipedemia	VLDL, LDL	Cholesterol & triglycerides

THE CLASSIFICATION OF HYPOLIPEDEMIC DRUG IS AS FOLLOWS:

Class	Drugs	Mechanism of action	Adverse effects
HMG-CoA Reductase inhibitors	Lovastatin, atorvastatin, simvastatin	They inhibit the enzyme HMG-CoA Reductase essential for the conversion of HMG-CoA to mevalonate and thus inhibit synthesis of cholesterol.	Headache, rise in serum transaminase, rise in CPK levels.
Bile acid sequestrants	Cholestyramine, colestipol	These are ion exchange resins that bind bile acids in the intestine inhibit their enterohepatic circulation. Cholesterol is absorbed with the help of bile acids and in their absence, it is excreted.	Unpalatable and may cause nausea, flatulence, heartburn, constipation.
Fibric acid derivatives	Clofibrate, Gemfibrozil, fenofibrate	They activate lipoprotein lipase which is essential for the degradation VLDL resulting in lowering of TG's.	Increased appetite and weight gain, myalgia and increased incidence of gallstones.
Others	Neomycin, gugulipid probucol	Neomycin lowers LDL-CH by complexing with bile acids in the intestine. Guggul lipid probucol acts as Antioxidant	Neomycin may however damage intestinal mucosa. Loose stools.

- ***Comniphora molmol*** – myrh (antiseptic),
- ***Comniphora mukul*** – guggul (antihyperlipedemic).
- **Dromotropic** – Drug affects conductivity of impulses in neuronal cells.

HORMONES

- They are mediator molecules act as chemical messengers.
- They are released in one part of the body & regulates activity of cells in other ports of Body.
- Hormones are secreted by endocrine or ductless glands.
- Most hormones enter interstitial fluid & then the Bloodstream.

M.O.A:- Hormones like, neurotransmitters, influence their target cells by chemically binding to specific protein or glycoprotein receptors.

SITE OF ACTION:-

At cell membrane receptors – E.g.:- Adrenaline, glucagons, FSH, LH, TSH, ACTH calcitonin, vasopressin, oxytocin, insulin etc.

At cytoplasmic receptors – E.g.:- steroidal Hormones.

At nuclear receptors – Thyroid Hormones.

Down regulation: - when hormone is present in excess, the no. of target cells receptors decreases. This makes target cells less responsive to the hormone.
Up regulation:- when there is a deficiency in hormone is the no. of receptors may increase. This makes target cells more sensitive to hormone

Classification of hormones: - The endocrine glands include pituitary, Thyroid, Parathyroid, Adrenal and pineal glands.
Water soluble hormones: - protein eicosanoid hormones.
Lipid soluble hormones: - Steroid, Thyroid & gaseous hormone (Nitric oxide).
Placental hormones: - Chronic gonadotropin – Prolactin, Estrogens – Progesterone, **Placental lactogen** – Chorionic thyrotropin.

Hormones of the Anterior & Posterior Pituitary:-

Hormone	Secreted by	Releasing Hormone (stimulates secretion)	Inhibiting hormone (suppresses secretion)
Human growth hormone (hGH) or somatotropin (191aminoacid)	Somatotrophs	Growth hormone-releasing hormone (GHRH) or somatocrinin (44A.A)	Growth harmone-inhibiting hormone (GHIH) or somatostain (14AA)
Thyroid-stimulating hormone (TSH) or thyrotropin	Thyrotrophs	Thyrotropin releasing hormone(tripeptide)	Growth hormone-inhibiting hormone somatostatin
Follicle-stimulating harmone (FSH)	Gonadotrophs	Gonadotrophic releasing harmone(decapeptide)	---------
Luteinizing harmone (LH)	Gonadotrophs	Gonadotrophic releasing harmone	---------
Prolactin (PRL) (198aminoacid)	Lactotrophs	Prolactin releasing harmone	Prolactin inhibiting harmone or dopamine
Adrenocorticotropic harmone (ACTH) or corticotrophin	Corticotrophs	Corticotropin releasing harmone(41aminoacids)	----------
Mealanocyte-stimulating harmone (191aminoacid)	Corticotrophs	Corticotropin releasing harmone	Dopamine

- ♣ Leuprolide is a synthetic non-peptide of GTRH.
- ♣ Dropamine antagonist not given in lactating women because it inhibits prolactin.
- ♣ Enuresis – Bed wetting (Desmopressin)
- ♣ Melatonin – (responsible for normal sleep)
- ♣ Posterior pituitary or neurohypophysis does not synthesize harmones; it stores and releases two harmones oxytocin and antidiuretic harmones (vasopressin).

HORMONE	PRINCIPAL ACTIONS
Human growth harmone (hGH) or somatotropin	Stimulates liver, muscle, cartilage, bone, and other tissues to synthesize and secrete insulin like growth factors. (IGF's); IGFs promote growth of body cells, protein synthesis, tissue repair, lipolysis, and elevation of blood glucose concentration.
Thyroid-stimulating harmone (TSH) or thyrotropin	Stimulates synthesis and secretion of thyroid harmones by thyroid gland
Follicle-stimulating harmone (FSH)	In females, initiates development of oocytes and induces ovarian secretion of estrogens. In males stimulates testes to produce sperm.
Luteinizing harmone (LH)	In females, stimulates secretion of estrogens and progesterone, ovulation and formulation of corpus luteum. In males, stimulates interstitial cells in testes to develop and produce testosterone.
Prolactin (PRL) more active in presence of oxytocin	Together with other harmones, promotes milk secretion by the mammary glands.
Adrenocorticotropic harmone (ACTH) or corticotrophin	Stimulates secretion of glucocorticoids (mainly coritsol) by adrenal cortex.
Melanocyte-stimulating harmone	Exact role in humans is unknown but may influence brain activity, when present in excess, can cause darkening of skin.
Oxytocin (OT)	Stimulates contraction of smooth muscle cells of uterus during childbirth; stimulates contraction of myoepithelial cells in mammary glands to cause milk ejection.
Antidiuretic harmone (ADH) or vasopressin	Conserves body water by decreasing urine volume; decreases water loss through perspiration; raises blood pressure by constricting arterioles.

Pitutary harmone derivates:-

	ANALOGUE	USES
Bromocriptine	Prolactin inhibitor	Cancer therapy
Desmopressin	ADH	Diabetes insipidus
Gasrelin, coryntropin, Leuprolide	ACTH	Infantile spasms
Menotropins, urofollitin	FSH, LH	Infertility
Naferelin	GNRH	Cancer, Infertility
Ocreolide	Somatostatin	Inhibits glandular

GONADAL HARMONES	USES
Tamoxifen	Breast cancer
Diethylstilbesterol	After contraception
Estrogen & progesterone	Oral contraception
Norgesterol & medroxyprogesterone	chronic contraception
Mifepristone	Abortifacient
Oxandralone	Anabolic

THYROID GLAND

The follicular cells produce two harmones; thyroxine (tetraiodothyronine) and tri-iodothyronine, which are known as thyroid harmones.

Synthesis and secretion of T3 and T4 occurs as follows:

a. **Iodine trapping:** Follicular cells trap iodine ions by an active transport mechanism.
b. **Synthesis of thyroglobulin:** While the follicular cells are trapping iodide ions, they are also producing thyroglobulin (TGB).
c. **Oxidation of iodide:** Iodine ions are oxidized by peroxidase to form iodine (I2).
d. **Iodination of tyrosine:** as iodine molecules form, they react with tyrosines that are part of thyroglobulin molecules. Binding of one iodine atom with tyrosine yields mono-iodotyrosine (T1), while two iodine atoms yields di-iodotyrosine (T2),
e. **Coupling of T1 and T2**: two T2 molecules combine to form T4 while one T1 and one T2 combine to form T3 in the presence of peroxidase.

Calcitonin: - It is a harmone produced by the parafollicular cells of the thyroid gland. It decreases the level of calcium in blood by inhibiting the action of osteoclasts, the cells that break down bone matrix.

Parathormone: - It is secreted by the parathyroid glands and it increases blood calcium and magnesium levels, while it decreases phosphate levels.

The harmones produced by the adrenal cortex are of three types:

a. Mineral corticoids : Aldosterone
b. Glucocorticoids: Cortisol, Coorticosterone & Cortisone.
c. Androgens: Dehydroepidandrosterone.

The harmones produced by the chromaffin cell of the adrenal medulla are Epinephrine and nor epinephrine.

The four types of pancreatic islets that produce harmones are:-

1. A cells secrete glucagons.
2. B cells secrete insulin.
3. D cells secrete somatostatin.
4. F cells secrete pancreatic polypeptide.

Hormone	Control of secretion	Principal actions
Thyroid harmone	Secretion is increased by thyrotopin-releasing harmone and high thyroid iodine levels suppresses secretion.	Increase basal metabolic rate, stimulate synthesis of proteins, and increase use of glucose.
Calcitonin	High blood calcium levels stimulates secretion, low levels suppresses secretion.	Lowers blood levels of ionic calcium and phosphate.
Parathyroid hormone	Low blood calcium levels stimulate secretion; High blood calcium levels inhibit secretion.	Increases blood calcium and magnesium levels and decreases phosphate levels.
Mineral corticoids	Increased blood K+ level and angiotensin II stimulates secretion.	Increases blood levels of Na+ and water and decrease blood level of K+.
Glucocorticoids	ACTH stimulates release.	Increase protein breakdown stimulate gluconeogenesis.
Androgens	ACTH stimulates release.	Assist in early growth of axillary and public hair.
Epinephrine and Nor epinephrine	Sympathetic preganglionic neurons release acetylcholine, which stimulates secretion.	Produce effects that enhance those of the sympathetic division of the automatic nervous system during stress.
Glucagon	Decreased blood level of glucose, exercise and mainly protein meals stimulate secretion.	Raises blood glucose level by accelerating breakdown of glycogen into glucose in liver.
Insulin	Increased blood level of glucose, acetylcholine, arginine and leucine, glucagon, GIP, hGH, and ACTH stimulate secretion.	Lowers blood glucose level by accelerating transport of glucose into cells, converting glucose into glycogen and stimulates protein synthesis.
Somatostatin	Pancreatic polypeptide inhibits secretion.	Inhibits secretion of insulin and glucagon and slows absorption of nutrients from the gastrointestinal tract.
Pancreatic polypeptide	Meals containing protein, fasting, exercise, and acute hypoglycemia stimulate secretion.	Inhibits somatostatin secretion, gallbladder contraction, and secretion of pancreatic digestive enzyme.

Hormones affecting calcium homeostasis:-

- Calciferol (25 Hydroxy Vit-D3)
- Calcitrol (1, 25 dihydroxy Vit-D3)
- Cholecalciferol (Vit-D3)
- Secalcifediol (24, 25 dihydroxy vitD3)
- Ergocalciferol (VitD2)
- **Androgens: -** Testosterone, Oxandrolone, Stanozolol.
- **Antiandrogens: -** Finasteride (synthetic inhibitors).
- **Antiprogestins: -** Mifepristone.

USEFUL TIPS

- ✓ **WELCOME TO PHARMAROCKS**
- ✓ **THESE ARE THE MOST IMPORTANT NOTES OF PHARMACOLOGY**
- ✓ **IT COVER GENERAL PHARMACOLOGY, ANS, CNS AND CVS**
- ✓ **REVISE THIS DAILY FOR THE PROPER PREPARATION**
- ✓ **DRUG CLASIFICATION, MOA, SIDE EFFECTS, USE , COVER UNDER THIS**
- ✓ **THIS NOTES ALWAYS HELPS U IN GPAT AS WELL AS DURING YOUR SEMESTER EXAMS U CAN PREPARE FROM THIS.**
- ✓ **IF POSSIBLE TAKE THE PRINT OUT THIS AND REVISE REGULARLY TO IMPROVE YOUR KNOWLEDGE FOR PHARMACOLOGY**

CHEMOTHERAPY MASTER GPAT NOTES

It deals with the use of chemical agent to arrest the progress of infectious diseases by destroying infective parasites or microbes without damaging the host tissues.

M.O.A:-

1. INHIBITING PROTEIN SYNTHESIS BY BINDING TO RIBOSOMAL SUBUNIT & DESTROYING THE BACTERIAL CELL.

E.g.:- Gentamycin & streptomycin.

2. REVERSIBLE INHIBITION OF PROTEIN SYNTHESIS BY ACTION ON RIBOSOME.

E.g.:- Broad spectrum Antibiotics.

3. BY DETERGENT ACTION (LEAKAGE OF CELL CONSTITUENTS)

A. Direct cell membrane. E.g.:- Colistin, Polymyxin

B. Drug binding to cell wall sterols. E.g.:- Nystatin, Amphotercin.

4. INHIBITION OF CELL WALL SYNTHESIS: -

E.g.:- Penicillins, Cephalosporins, sulphonamides.

5. DRUGS AFFECTING NUCLEICACID METABOLISM:-

A. Inhibition of DNA dependent RNA polymerase. E.g.:- Refampicin.

B. Inhibition of DNA supercoiling & DNA synthesis. E.g.:- Quinolones & Fluoroquinolones.

DRUG RESISTANCE:-

1. **Natural: -** Organisms do not have target sit for drugs to act. E.g.:- Antifungals in Bacterial infections.
2. **Acquired: -** Organisms are exposed to the drug in such a manner that it develops resistance.

Cross resistance: -

Development of resistance to one substance may also show resistance to another substance to which the organism has not been exposed.

E.g.:- resistance between Sulphonamides, resistance between Tetracycline's, resistance between Tetracycline's & Chloramphenicol.

There is no cross resistance between Animoglycosides.

Super infection/Supra infection: -

- It is due to the use of Broad spectrum antibiotics.
- There is no. of microorganisms inhabiting GIT & these organisms constitute the microbial flora. They are called as "commensals" under normal conditions; these organisms compete with another for nutrients. & therefore they are unable to proliferate rapidly.
- When a Broad spectrum antibiotic such as chloramphenical / tetracycline is administered, it might kill most of the microbial flora barring a few organisms. Now these few microbes are free to proliferate rapidly in the absence of competition & they multiply, spread all over the body & cause infections called super infections.

Antimicrobial agent: - An agent which kills M.O. or suppresses their growth. The susceptibility of AMA is determined by

1. Radiometric method
2. Resistance ratio method (Traditional).

Sulfonamides & Sulfones

These are derived from prontosil red (dye) & are effective against pyogenic Bacterial Infections.

CLASSIFICATION:-

1. Short acting: - Sulfadiazine, Sulfisoxazole.
2. Intermediate: - Sulfamethoxazole.
3. Long acting: - Sulfadoxine, Sulfamethopyrazine.
4. In intestinal infections: - Sulfasalazine.
5. In Burn therapy: - Silver sulfadiazine, mafenide.
6. In ophthalmic infection: - Sulfacetamide.

M.O.A:-

Guanosine……> PABA _____> Dihydropteroic acid

Several steps (-) Sulfonamides (-) Trimethoprim <……_____Dihydrofolic acid folate reductase folic acid

DIHYDRO FOLATE REDUCTASE

- Tetrahydrofolic acid ----------N5, N10 methylene FAH4
- N5formylFaH4 -------- N10 formyl FAH4
- N5formylFAH4, N5N10 methylene FAH4, N10formyl FAH4 is very essential for several Biosynthetic pathways in humans & Bacteria.
- The growth and cell division in bacteria can be stopped if any drug blocks Biosynthesis of folate co-enzymes.
- Folate co-enzymes are biosynthesized from dietary folic acid in humans & other animals.
- Sulfonamides act as competitive inhibitors for the incorporation of PABA to form Dihydropteroic acid.
- Trimethoprim is an inhibitor of dihydrofolate reductase required for the conversion of dihydrofolic acid in to tetrahydrofolic acid in bacteria.

Mechanism of resistance: - It may be due to

1. Increased production of PABA by resistant bacteria
2. Decrease the affinity of folate synthetase enzyme for sulfonamides.
3. Adopts an alternative pathway in folate metabolism. E.g.:- gonococci, pneumococci, E.coli, S.aureus etc

Cotrimoxazole: - fixed dose combination of trimethoprim and sulfamethoxazole in a ratio of (1:5). As this inhibits 2 different steps in pathway, the development of resistance is reduced.

Adverse reactions:-

1. Stevens Johnson's syndrome
2. Hemolytic anemia
3. Kernicterus (neonatal Hyperbilirubinemia)
4. Skinrash, Urticaria
5. Crystalluria is due to crystals of sulfanilamide, This can be presented by
    i) Alkalanizing the urine
    ii) By increasing the urine flow
    iii) By reducing PKa of drug.

Metabolism: - It occurs by acetylation at N4 they are excreted as mixtures of unmetabolised drugs, N4 acetates & glucouronides.

Sulfones: - less active than sulfonamides

M.O.A:- similar to sulfonamides. E.g.:- Dapsone

QUINOLONES

E.g.:- Nalidixic acid

Fluoroquinolones: - These are more potent than quinolones.

First generation: Norfloxacin, Ofloxacin, Ciprofloxacin, Perfloxacin.

Second generation: Sparfloxacin, Lomefloxacin.

M.O.A:- They inhibit Bacterial DNA gyrase (An enzyme responsible for introducing negative supercoiling in to circular duplex DNA.) Negative super coiling relieves the tortional stress of unwinding helical DNA & thereby allows transcription & replication to occur. Humans have Topoisamerase II in place of gyrase & this accounts for the low toxicity of FQ's to the host cells.

Resistance: - Due to chromosomal mutation producing a DNA gyrase with reduced affinity for FQ's.

AR: - Hypersensitivity reactions, Hemolytic anemia GI disturbances.

Uses: - Typhoid, soft tissue infection, UTI.

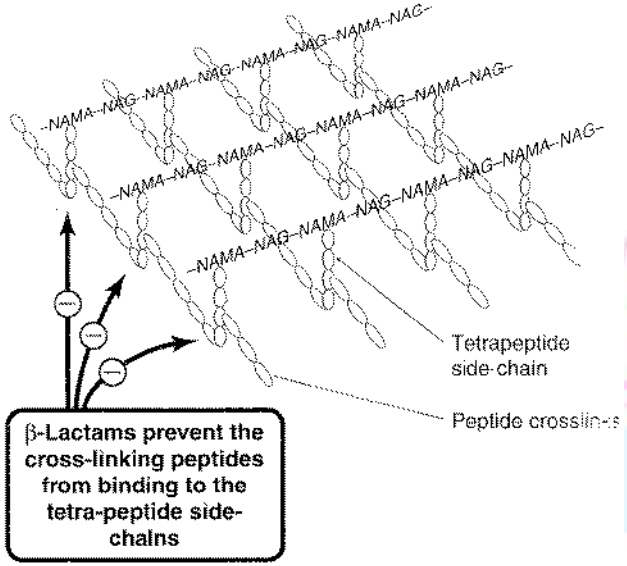
B Lactam Antibiotics

E.g.:- Pencillins & Cephalosporins

M.O.A:- microorganism synthesize two pentapeptides –

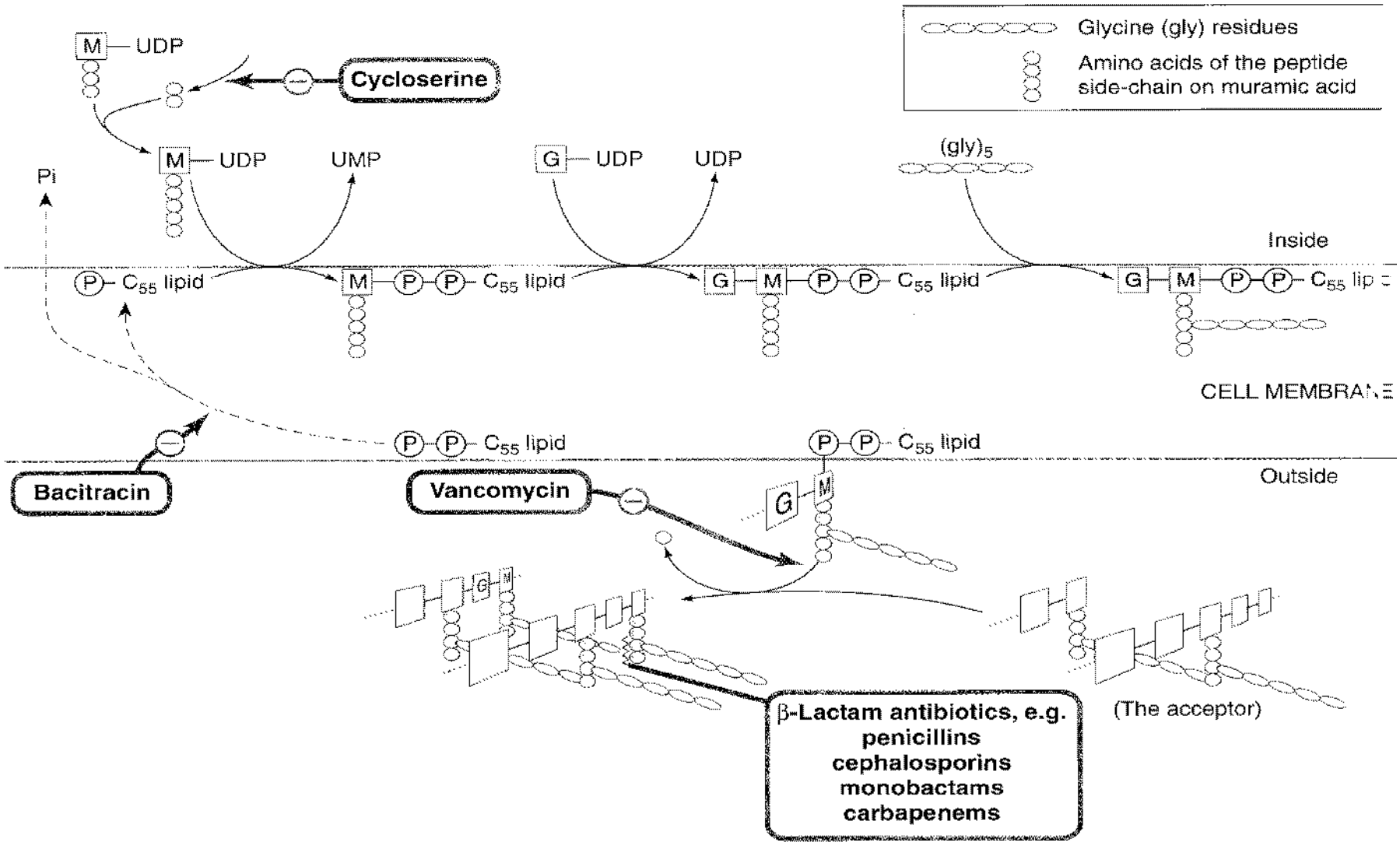
1. UDP-N-acetyl muramic acid (NAMA)
2. UDP-N-acetyl glucosamine (NAGA)

These peptidoglycon residues are linked together in forming long strands & the UDP is split off. The final step is cleavage of the terminal D-Alanine by 'transpeptidase'. The energy released is utilized for establishment of crosslinkages between peptide chains of the neighbouring strands.



Beta lactam Antibiotics inhibit the enzyme 'transpeptidase' so that crosslinking does not take place. These enzymes constitute the pencillin binding proteins which are located in the bacterial cell membrane. When Bacteria divide in presence of a B-lactam antibiotic cell wall deficient forms are produced & these forms burst resulting in cell lysis.

Blood, pus & tissues fluids do not interfere with the antibacterial action of B-lactam Antibiotics.


Glycine (gly) residues
Amino acids of the peptide side-chain on muramic acid
M UDP
Cycloserine
M UDP
UMP
G UDP
UDP
(gly)5
Pi
Inside
P C55 lipid
M P P C55 lipid
G M P P C55 lipid
G M P P C55 lipid
CELL MEMBRANE
P P C55 lipid
P P C55 lipid
Outside
Bacitracin
Vancomycin
β-Lactam antibiotics, e.g.
penicillins
cephalosporins
monobactams
carbapenems
(The acceptor)

CLASSIFICATION OF PENICILLIN'S:-

- ♣ Natural: - Penicillin-G, procaine penicillinG
- ♣ Acid resistant: - Penicillin V (phenoxymethyl penicillin)
- ♣ Broad spectrum: - Ampicillin, Amoxicillin, Piperacillin Methicillin
- ♣ B lactamase inhibitors: - clavulonic acid, sulbactam
- ♣ Monobactams: - Aztreonam
- ♣ Carbapenems: - Imipenam, Thienamycin

BACTERIAL RESISTANCE: -

Gram positive organisms develop resistance by producing B-lactamases. (Opens B lactam ring & inactivates) In methicillin resistant S.aureus the penicillin Binding proteins has been mutated. So that it does not binds methicillin efficiently.

AR: - penicillin allergy due to formation of Antigenic penicilloyl proteins.

Jarisch-Herxhemier reaction is Syphilis patient.

Degradation of penicillin can be controlled by adjusting the PH of aq-solutions between 6.0 – 6.8.

USES: -

Gonorrhea, Syphilis, Diphtheria & coccal infections.

Augmentin = Clavulanic acid + Amoxicillin

Unasyn = Sulbactam + Ampicillin

CLASSIFICATION OF CEPHALASPORINS:-

Cephalosporin = B lactam ring + dihydrothiazine ring

Penicillin = B lactam ring + thiazolidine ring.

	I	II	III	IV
Oral	Cephalexin	Axetal Cefaclor Cefuroxime	Cefixime Cefpodoxime	---
Parentral	Cephadroxil	Cefomandole Cefonacid	Cefotoxime Ceftriaxone	Cefepime

Antipseudomonal Cephalosporins: -

Cefoperazone, Moxalactam, Cefotaxime, Ceftizoxime & Ceftriaxone.

Disulfiram effect: -

Cefomandole, cefoperazone, cefometazone, cefotetan & moxolactam due to tetrazole group produce Disulfiram effect when taken with alcohol.

Aztreonam is used to treat hospital acquired infections (Nosocomical infections).

Tetracyclines, Chloramphenicol, Aminoglycoside and Macrolide antibiotics

In order to understand the mechanism of the above antibiotics it is essential to understand the process of protein synthesis:

- On a specific signal from the cytoplasm, the DNA in the nucleus unwinds itself with the help of the enzyme DNA gyrate or topoisomerase (humans).

- One of the strands of the DNA acts a template for the synthesis of a complimentary strand of mRNA in the presence of RNA polymerase. The synthesis of mRNA from DNA is called transcription.
- The mRNA which now contains the code for protein synthesis comes out of the nucleus and attaches itself to the 30's ribosomal subunit.
- This is followed by the attachment of the 50's ribosomal subunit to the mRNA-ribosomal complex.
- There are two sites present on the 50's ribosomal subunit, the acceptor site and the peptidyl site.
- Protein synthesis does not begin until the mRNA has the initiator codon AUG (codes for formylmethionine) on it.
- Once the mRNA exposes the initiator codon AUG, a specific tRNA carrying the amino acid formylmethionine will arrive at the acceptor site of 50's subunit.
- The tRNA carrying the amino acid is now transferred to the peptidyl site where the tRNA dissociates leaving the amino acid at the peptidyl site.
- The ribosome now moves along the mRNA to expose the next coon.
- Depending upon the codon the corresponding amino acid is brought to the acceptor site by a specific tRNA.
- The tRNA carrying the amino acid is now transferred to the peptidyl site where the tRNA dissociates leaving the amino acid at the peptidyl site.
- Again, the ribosome now moves along the mRNA to expose the next codon and this process continues until the mRNA shows one of the terminatory codons UAA or UAG or UGA. These terminatory codons are called non-sense codons, as they do not code for any particular amino acid.
- The transfer of data contained in the mRNA to form proteins is called translation.
- When only one ribosome is attached to the mRNA it is called monosome when there are more than one ribosome attached to the mRNA it is called polysome.

Antibiotic	**Tetracycline**	**Chloramphenicol**	**Aminoglycoside**	**Macrolide**
Source	Soil actinomycetes S.aureofaciens	Streptomyces Venezuelae	Streptomycin- S.griseus	Erythromycin- S.erythreus
Spectrum of activity	Broad spectrum	Broad Spectrum	Active only against aerobes. Bactericidal	Active against mainly gram + organisms.
Mechanism of action	Binds to the 30's ribosomal subunit and inhibits the attachment of aminoacid-tRNA complex to the mRNA-ribosomal complex.	It acts by interfering with the transfer of the elongating peptide chain to the newly attached amino acid at the ribosome mRNA complex. Therefore, it inhibits peptide bond formation. It specifically attaches to 50's ribosome.	It binds to the 30's subunit, the 50's subunit as well to the 30s-50s interface. They freeze initiation of protein synthesis, prevent polysome formation. Binding to the 30s-50s interface causes distortion of the mRNA codon resulting in wrong amino acids entering the peptide chain and these defective proteins affect the integrity of the cell membrane resulting in cell death.	It combines with 50s ribosomal subunit and interferes with translocation of the elongated peptide chain back to the peptidyl site. The ribosome fails to move along the mRNA to expose the next codon and thus protein synthesis is terminated prematurely.

Mechanism of Resistance	Due to plasma mediated synthesis of a protection protein that protects the ribosomal binding site from TC's. Posess cross resistance with chloramphenicol.	Resistant organisms produce Chloramphenicol acetyl transferase, which inactivates the drug.	A. Inactivating enzymes that adenylate/acetylate or phosphorylate the antibiotic. B. Decrease in the affinity of the ribosomal protein that binds the antibiotic. C. Porins become less permeable to the drug.	Resistant organisms produce erythromycin esterase that inactivates the drug or the organisms become less permeable to the drug.
Pharmacokinetics	TC's have chelating property- form insoluble and unabsorbable complexes with calcium and other metals.	Oral form is Chloramphenicol palmitate. Parenteral form is Chloramphenicol Succinate.	All ionize in solution and are not absorbed orally. Excreted unchanged in urine.	Erythromycin is acid labile. To protect it from the gastric acid it is given an enteric coat.
Adverse Effects Fanchony syndrome.	a. Liver damage b. Kidney damage c. Photo toxicity d. Deposition of	a. Gray baby syndrome: seen in infants because they lack the glucoronic acid required for conjugation with	a. Ototoxicity ♣ Cochlear damage ♣ Vestibular damage b. Nephrotoxicity	a.Gastrointestinal distress a. Hepatitis.

Shown by only doxycycline	calcium tetracycline chelate in bones and teeth. e. Vestibular toxicity-Ataxia, vertigo and nystagmus (involuntary eye ball moment). f. Diabetes insipidus-Demeclocyclin	Chloramphenicol. b. Super infections c. Bonemarrow depression-aplasticanemia, agranulocytosis, thrombocytopenia.	c. Neuromuscular blockade	
Uses	a. Used to treat infections, when the causative organism is unknown. b. venereal diseases c. Cholera, plague, Brucellosis, etc.	a. Typhoid (enteric fever) b. H.influenzae meningitis c. Anaerobic infections D.Intraocular infections.	a. Tuberculosis b. SABE c. Plague d. Tularemia sub acute Bacterial endocarditis (sabe)	a. Atypical pneumonia caused by mycoplasma pneumoniae b. Diphtheria, tetanus, Syphilis, etc...

Tetracyclines:-

More stable & long acting ------ 6-deoxy tetracycline, methacycline, doxycline minocycline.

Miscellaneous Antibiotics:-

1) **Lincosamide antibiotics:** - clindamycin M.O.A & spectrum of activity is similar to erythromycin & also exhibits partial cross resistance.
2) **Glycopeptide Antibiotics:** - E.g.:- Vancomycin acts by inhibiting cell wall synthesis. It binds to the terminal dipeptide sequence of peptidoglycon units at the cell membrane & their cross linking to form the cell wall does not take place.

   Uses: - In MRSA infections.

3. **Polypeptide Antibiotics:** - Bactericidal agents have detergent like action on cell membrane. They have high affinity for phospholipids & thus they orient between phospholipid & the protein layers in gram negative organisms, resulting in formation of pseudopore. As a result aminoacids leak out leading to cell death. E.g.:- Polymyxin B, Bacitracin, Colistin, Thyrotricin, Capreomycin, Nespirocin.

Urinary Antiseptics: - Nitrofurantoin, Hexamine

Urinary Analgesic: - Phenazopyridine HCL.

ANTITUBERCULAR AGENTS

Tuberculosis is caused by mycobacterium tuberculosis.

First line drugs: - INH, Rifampicin, Pyrazinamide, Ethambutol.

Second line drugs: - Ciprofloxacin, Azithromycin.

DRUG	M.O.A	PHARMACOKINETICS	A.R
P-amino salicylic acid	Prevents incorporation of PABA	It undergoes Acetylation At lowPH-decarboxylation At highPH-oxidation	Hypersensitivity reactions
I N H	Inhibits the synthesis of mycolic acid (imp component of mycobacterial cell wall)	Acetylated by liver.	Peripheral neuritis due to renal excretion of vit B_6 ,Hepatitis
Rifampicin	Inhibits DNA dependent RNA polymerase	Metabolized in liver to an active deacteylated metabolite.	Hepatitis respiratory syndrome, Cutaneous syndrome, Flu syndrome, Abdominal syndrome.
Pyrazinamide	Not known penetrates inflamed meninges in treatment of tuberculosis meningitis.	Penetrates CSF & metabolised in liver.	Hepatatoxicity, Hyperuricaemia (due to inhibition of uric acid tubular secretion)
Ethambutol (d isomer is more patent)	Interferes with mycolic acid incorporation in cell wall & inhibits RNA synthesis.	75% of oral dose is absorbed & temporarily stored in R.B.C.	Loss of visual acuity, field effects due to optic neuritis.

Antitubercular Antibiotics: - Cycloserine, Capreomycin, Viomycin, Rifampicin.

Effective treatment :- (Sterilization period).

INH 300mg, Rifampicin 600mg, Pyrazinamide 25mg/kg (for 8 weeks)

(Maintainance period) INH & Rifampicin (for 16 weeks)

ANTILEPROTIC AGENTS

Leprosy is called by *Mycobacterium leprae*.

Drug	M.O.A	Pharmacokinetics	A.R
Dapsone	Inhibits incorporation of PABA in to folic acid	Completely absorbed orally, gets concentrated in skin, liver & kidney.	Mild Hemolytic anemia, gastric intolerance.
Cycloserine	Inhibits bacterial cell wall synthesis by inhibiting the enzyme that racemises h-alanine and links two D-Alanine residues.		
Clofazimine (dye)	Binds with nucleic acids & concentrate in reticuloendothelial tissue & interfere with template function of DNA.	Gets accumulated in tissues especially in crystalline form.	Well tolerated reddish Block discolouration of skin

ANTIFUNGAL AGENTS

Classification:-

1. **Azoles: -** Clotrimazole, Ketaconazole, Miconazole.
2. **Allylamine & related compounds: -** Tolnafate, Terbinafine.
3. **Fatty acids: -** Propionic acid, Triacetin, Salicylic acid.
4. **Phenol & their derivatives: -** Haloprogin, Cyclopirox.
5. **Nucleosides: -** Flucytosine.
6. **Antibiotics: -** Nystatin, Amphotericin, Candidicin.
7. **Heterocyclic Benzofuran: -** Griseofulvum.

Drug	Amphotericin B	Griseofulvin	Imidazoles & triazoles.	Flucytosine	Tolnafate
Mechanism of action	Has high affinity for ergosterol present in fungal cell membrane. Binds to it forming a micropore, through which amino acids leak out leading to cell death.	It interferes with mitosis and causes abnormal metaphase configurations. The daughter nuclei fail to move apart and thus cell division is arrested at metaphase.	They inhibit the fungal cytochrome P_{450} enzyme lanosterol 14-demethylase required for conversion of lanosterol to ergosterol. This results in membrane abnormalities in the fungus.	It is taken up by fungal cells and then converted into 5-FU and then to 5-fluorodeoxyuridylic acid which is an inhibitor of thymidylate synthetase required for the synthesis of thymidylic acid, which is a component of DNA.	Interfere with fungal ergosterol Biosynthesis by epoxidation of squalene by the enzyme squalene epoxidase.

Spectrum of activity	Candida albicans, Histoplasma capsulatum, etc.	Dermatophytes such as Epidermophyton, Trichophyton, microsporum, etc.	Dermatophytes, candida albicans, nocardia, leishmania, etc.	Cryptococcus neoformans, candida, torula, aspergilllus, chromoblastomyces.	Dermatophytes candida.
Pharmacokinetics	Administered both orally and prarenterally.	Gets deposited in the Keratin forming cells of skin, hair and nails. Absorption is enhanced by micronisation.		Administered orally	
Adverse effects	Nephrotoxicity-azotemia, reduced g.f.r acidosis.	Peripheral neuritis, transient leukopenia, albuminuria.	Inhibits CYP3A4, thereby raising the blood levels of drugs like warfarin, terfenadine.	Leucopenia, thrombocytopenia.	
Uses	Systemic mycoses and Leishmaniasis.	Dermatophytosis.	Systematic and topical infections.	Chromoblastomycosis.	Athlete's foot ringworm.

Antiviral agents: Infectious virus particle is called virion. **DNA containing virus**

Adenovirus	Many types	Respiratory tract & eye infections
Herpes virus	H.simplex I & II vercilla zoster Herpes zoster	Encephalitis chicken pox shingles
Papora virus	Human wart virus polyoma virus	Human wart salivary gland infection
Pox virus	Vaccine	Small pox, chicken pox, cow pox, eczema.

RNA CONTAINING VIRUS:-

Orthomyxovirus	Influenza A,B,D	Influenza A,B,D
Picornovirus	Rhinovirus	Respiratory disease poliomyletis
Retrovirus	Type C Type B Type D HIV	Leukemia Mammary tumor Monkey Aids AIDS
Rhabdovirus	Rabies virus	Rabies
Togavirus	Rubella virus	Rubella
Unclassified virus	Hepatitis A,B,&C viruses	Hepatitis

CLASSIFICATION:-

A. Anti-herpes virus. Most of the antiviral drugs of this class act by inhibiting DNA polymerase. E.g.:- Idoxuridine, acyclovir, Ganciclovir, Foscarnet.

B. Anti-retro virus. Non-nucleoside reverse transcriptase inhibitors. E.g.:- Zidovudine (AZT), Didanosine, and Zalcitabine. Nevirapine, Delaviridine.

   Protease inhibitors. E.g.:- Saquinavir, Indinavir.

C. Anti-influenza virus. E.g.:- amantadine.

D. Others. E.g.:- interferons, ribavirin.

Drug	Mechanism of action	Mechanism of resistance	Adverse effects	Uses
Idoxuridine	It is phosphorylated by viral thymidylate kinase to monophosphate, then to triphosphate. The triphosphate is an inhibitor of viral DNA polymerase, causing inhibition of viral DNA synthesis and it is also incorporated in the DNA resulting in faulty DNA, which code for wrong proteins.	Resistant viruses decrease the amount of thymidylate kinase required for the activation of the drug. Decrease in the affinity of DNA polymerase for the drug.		1. H.simplex keratoconjuctivities. (Cytomegalblasto virus)
Foscarnet	A phosphonoformate derivative binds to the pyrophosphate binding sites of viral DNA polymerase and reverse transcriptase to prevent the incorporation of nucleotides into DNA.		Hypokalemia, hypomagnesia, renal toxicity.	CMV retinitis, varicella zoster infections.
Zidovudine, Stavudine	On phosphorylation in the body into zidovudine triphosphate, it inhibits the enzyme viral reverse transcriptase which is required for the synthesis of DNA from viral RNA.	Decrease in the affinity of reverse transcriptase for the drug.	Anaemia, neutropenia, myopathy.	AIDS

Saquinavir	An aspartic enzyme protease encoded by HIV is involved in the production of structural protein and enzymes of the virus. Inhibition of the aspartic enzyme by Saquinavir will deprive the virus of the essential proteins.		G.i.t intolerance, asthenia, paresthesia and exacerbation of diabetes.	Used to treat later stages of AIDS infections.
Amantadine	It acts on an ion channel M2 and interferes with the step of uncoating.		Insomnia, dizziness, hallucination.	influenzaA2, Parkinson's.
Ribavirn	Its mono and triphosphate derivatives inhibit GTP and viral RNA synthesis.			InfluenzaA & B, measles.
Acylclovir	Converted to monophosphate by viral thymidine kinase.			Herpes infections.

Interferons: - are the cytokines produced by the body in response to viral infections. They bind to cell specific receptors and interfere with various stages of viral replication such as uncoating, penetration of virus into the host cell, synthesis of viral protein. Interferon's bind to receptors and induce production of Interferon induced protein that has antiviral effects. They are active against both DNA & RNA viruses. They are host specific. They are indicated for:-

- ♣ Chronic hepatitis B & C
- ♣ AIDS related Kaposi sarcoma (cancer & aids)
- ♣ Hairy cell leukemia.
- ♣ Rhinoviral cold.

Adverse effects include myelosupression, neurotoxicity, etc.

ANTIMALARIAL AGENTS

Malaria is caused by four species namely

1. plasmodium vivax,
2. P.falciparum,
3. P.malariae and P.ovale.
4. P.falciparum does not have secondary Schizontic stage.

CLASSIFICATION:-

1. Cinchona Alkaloids: - Quinine
2. 4 Amino quinoline: - Chloroquine, Amodiaquine
3. 8 Amino quinoline: - Primaquine, pamaquine
4. 9 Amino Acridines: - Quinacrine
5. Biguanides & dihydrotriazines: - Chlorguanide
6. Pyrimidines: - Pyrimethamine
7. Sulfonamides: - Sulfadoxine, Dapsone, Sulfamethopyrazine
8. Quinoline methanol: - Mefloquine
9. Phenanthrene methanol: - Halofantrine
10. Miscellaneous: - Qinghaosu, tetracycline's.

DRUG	CHLOROQUINE	MEFLOQUINE	QUININE	CHLOROGUANIDE PROGUANIL
Mechanism of action	It moves into acidic vesicles of the parasite, raises pH and inhibits the degradation of Hemoglobin by Iysosomal products. It inhibits the enzyme haempolymerase that polymerizes toxic free haem to nontoxic haemzoin.	Inhibits the enzyme haem polymerase.	Inhibits the enzyme haempolymerase.	It is cyclised in the body to a triazine derivative, which inhibits plasmodial dihydrofolate reductase, which is essential for the synthesis of folate coenzymes.
Resistance	It occurs due to the increased efflux of the drug from the parasitic vesicles.	Increased expression of an efflux transporter similar to human transporter, P-glycoprotein.	Increased expression of an efflux transporter similar to human transporter, P-glycoprotein.	It occurs by mutation resulting in decrease in the affinity of the DHFRase for drug.
Spectrum of activity	Erythrocytic stages of all the four plasmodial species.	Blood Schizonticide Against P.Falciparum & P.vivax.	Blood schizonticide on all the four plasmodial species.	Slow acting Erythrocytic Schizonticide.
Adverse effects	Liver damage.	Gastrointestinal disturbance, giddiness, insomnia. Prolongation of QT intervals leading to arrhythmias.	Cinchonism-tinnitus, paraplegia, metallic taste. Cardiac arrhytmias, blood dyscriasis can also occur.(bone marrow depression)	Mild abdominal upset, hematuria.
Uses	Also active Entamoeba histolytica & Giardia lamblia.	Treatment of an acute attack.	Resistant falciparum malaria, cerebral malaria.	Prophlaxis of malaria.

- Pyrimethamine also acts by inhibiting plasmodial dihydrofolate reductase and it is a more potent than chlorguanide.
- Primaquine acts on the exoerythrocytic stages and is highly active against the gametocytes and hypnozoites.
- It causes hemolytic anemia in patients with G6-PD deficiency.
- Halofantrine, a blood schizonticidal agent is active against multiresistant.
- P.falciparum. Cross-resistance is seen between Halofantrine and mefloquine.
- Artemesinin, a sesquiterpine lactone is active against multiresistant.
- P.falciparum. It acts by interacting with haem and generated free radicals that binds to the membrane proteins and damages the parasite.

ANTIAMOEBIC DRUGS

Ameobiasis is a protozoal disease caused by Entamoeba Histolytica.

Intestinal amoebiasis: - Here E.Histolytica invade the intestinal wall of the colon.

Extra intestinal amoebiasis: - It affects liver, lungs & Brain.

E.Histolytica exists in two forms

1. Cysts: - inactive form
2. Trophozite: - active form

CLASSIFICATION:-

A. Tissue amoebicides

- For both intestinal and extra intestinal amoebiasis. Nitroimidazoles. E.g.: Metronidazole, tinidozole rhimostrozole. Alkaloids. E.g. : emetine
- For extra intestinal amoebiasis only. E.g. : chloroquine

B. Luminal amoebicides

- ♣ Amide. E.g. : Diloxanide furoate
- ♣ 8-Hydroxyquinolines. E.g.: Quiniodochlor, Diiodohydroxyquin clioquinol.
- ♣ Antibiotics. E.g.: Tetracycline's.

Drug	**Metronidazole, tinidozole**	**Emetine**	**Diloxanide furoate**	**Quiniodochlor, Diiodohydroxyquin**
Mechanism of action	The nitro group of the compound is reduced to intermediate compounds that cause cytotoxicity by damaging DNA.	It inhibits protein by arresting the intraribosomal translocation of peptidyl tRNA aminoacid complex.	It prevents the formation of cysts. From trophozoites. Interferes with protein synthesis.	Kill the cyst forming trophozoites in the intestinal tract by chelating ferrous ions which are essential for protozoal metabolism.
Spectrum of activity	Anaerobic organisms.	Kills trophozoites but has no action on cysts.	Kills trophozoites responsible for cyst formation.	Active against entamoeba, Giardia trichomonas and some fungi.
Adverse effects	G.i.t disturbances, CNS symptoms.	Hypo tension, tachycardia, ECG changes and myocarditis.	Flatulence, itching is occasional.	Iodism. Prolonged use caused 'sub acute myelopatic neuropathy' (SMON).
Uses	Amoebiasis, Giardiasis, Ulcerative gingivitis, H.Pylori infections.	Liver fluke infestation	Asymptomatic amoebiasis.	Amoebiasis, Giardiasis, monolial vaginitis, fungal infections.

Suramin sodium: - anionic in nature & binds with cationic sites in proteins & enzymes in glycolytic pathway.

Sodium stilbogluconate: - These pentavalent antimonials get converted to trivalent antimonials, which inhibit phosphofructokinase, an enzyme catalyses a limiting step in glycolysis.

Leishmaniasis is caused by Leishmania donovani and the drugs used to treat are Sodium Stilbogluconate, Meglumine, pentamidine, Amphotericin B, Ketoconazole and allopurinol. Severe form of leishmaniasis is Kala-azar.

ANTHELMINTICS

These agents destroy or eliminate parasitic worms (helmints) from GIT/body tissues.

Anthelmintic may act as:-

1) Vermifuge :- expels worms by paralyzing them
2) Vermicide :- kill worms in the body
3) Some may also impair the egg production process in worms.

Drug	Mebendazole/Albendazole	Pyrantel pamoate	Piperazine	Diethyl carbamazine
Mechanism of action	Inhibit glucose uptake, thereby depleting glycogen stores. Bind with affinity to micro tubular protein B-tubulin and inhibit its polymerization.	It causes activation of nicotinic cholinergic receptors in the worm resulting in persistent depolarization, which leads to paralysis. Worms are then expelled.	It causes neuromuscular blockade by antagonizing Ach action and causes hyperpolarisation, which leads to paralysis. Worms are then expelled.	Alteration of the Microfilariae (MF) membrane so that they are readily phagocytosed by tissue fixed monocytes.
Spectrum of activity	Round worm, hook worm, tirichuriasis, pinworm & guinea worm.	Hook worm Round worm, thread worm.	Round worm,	Mf of Wuchereria bancrofti, Brugia malayi, o.volvulus.

Drug	Levamisole	Niclosamide	Praziquantel	Ivermectin
Mechanism of action	It is an immunomodulator-restores T-cell function	It inhibits oxidative phosphorylationin mitochondria and thereby interferes with anaerobic generation of ATP.	Causes leakage of intracellular calcium from the membranes leading to paralysis. The lose grip of the intestine and are expelled.	Potentiation of GABAergic transmission in worms leading to paralysis.
Spectrum of activity	Ascaris & stronglyloides larvae.	Taenia saginata, T. solium, hymenlepsis nana.	Tape worms schistosomiasis.	Onchocerca volvulus, which causes river blindness.

Thiabendazole acts by inhibiting fumarate reductase. In T.C.A. cycle useful in strongylodias.

ANTICANCER AGENTS

These are cytotoxic drugs either kill cancer cells or modify their growth cell cycle:

G_1 (pre-synthetic phase)

↓

S – Synthesis of DNA

↓

G_2 – Post synthetic phase

↓

M - Mitosis phase

↙ ↘

G_1 G_1 (daughter cells)

↓

G_0 – Resting phase

- The cells in resting stage are those that are non-proliferating.
- These remain quiescent, but they can be recruited in the cell cycle when stimulated later.
- Cytotoxic drugs are either cell cycle specific or cell cycle non-specific (they kill both resting as well as dividing cells).
  - Cytotoxic drugs that are cell cycle specific include drugs like Methotrexate, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Mitomycin, Doxorubicin act on the S phase, drugs like Daunorubicin, Bleomycin, etoposide that act on the G_2, drugs like vincristine, Vinblastine and paclitaxel that act on the M phase.
  - Cytotoxic drugs that are cell cycle nonspecific include nitrogen mustards, cyclophosphomide, Chlorambucil, 5-FU, L-asparginine, Cisplatin, Procarbazine, Dacarbazine, etc.

CLASSIFICATION:

A. Alkylating agents: These can be further classified into:

a. Nitrogen mustards. E.g.: Mustine, Cyclophosphamide, Ifosfamide, chlorambucil

b. Ethyleneimine. E.g.: Thiotepa

c. Alkylsulfonate. E.g.: Busulphan

d. Nitrosourea. E.g.: Carmustine, Lomustine (they cross B.B.B & used in Brain tumors)

e. Triazine. E.g.: Dacarbazine.

f. Hydrazine. E.g.: Procarbazine

B. Antimetabolites

a. Folate antagonist. E.g.: Methotrexate (amethopterin)

b. Purine antagonist. E.g.: 6-Mercaptopurine, Azathiopurine, 6-Thioguanine

c. Pyrimidine antagonist. E.g.: 5-Fluorouracil, Cytarabine.

C. Vinca alkaloids. E.g.: Vincristine (oncovin), Vinblastine.

D. Taxanes. E.g.: paclitaxel, Taxotere.

E. Epipodophyllotoxin. E.g.: etoposide, Teniposide Daunorubicin.

F. Antibiotics. E.g.: Actinomycin D (Dactinomycin), Doxorubicin Bleomycins, Mitomycin.

G.Miscellaneous. E.g.: cisplatin, L-asparaginase.

TOXICITY OF ANTICANCER DRUGS:-

They have a profound effect on rapidly proliferating cells, the most important target of action are the nucleic acids and their precursors; rapid nucleic acid synthesis occurs during cell division. The different Toxicities that arise from Anticancer agents are:-

1. Bone marrow depression (Myelo suppression / Blood dyscriasis) resulting in granulocytopenia, agranulocytosis, thrombocytopenia, Aplastic anemia
2. Lymphocytopenia and the suppression of Humoral & Cell mediated immunity.
3. Stomatitis, diaarohea, shedding of mucosa, hemmorages
4. Skin: Alopecia
5. Inhibition of gonadal cells causes oligozoospermia& impotence in males.
6. Teratogenic in nature.
7. Hyperuricaemia

Virus: - Epstein barr virus is responsible for production of cancer

Genes: - Oncogene is responsible for production of cancer

ALKYLATING AGENTS: -

- → These compounds produce highly reactive carbonium intermediates, which transfer alkyl groups to cellular macromolecules by forming covalent bonds. The position 7 of guanine residues in DNA is highly susceptible because it is highly nucleophilic.
- → This results in cross linking / abnormal base pairing / scission of DNA strand.
- → Crosslinking of nucleic acids can also take place.
- → In case of Meclorethamine (mustine), Aziridinium is the intermediate formed.
- → In case of Cyclophosphamide, Phosphoramide & Acrolein are the intermediates formed.

- → Phosphoramide is the active metabolite; While Acrolein is toxic to the Urinary bladder.
- → (Mercapto sulphonic acid is given to avoid damage of urinary bladder due to Acrolein)
- → Ifosfamide is the congener of Cyclophosphamide.
- → Thiotepa produces Aziridinium as an intermediate.
- → Alkyl sulfonates undergo a process known as "Sulphur Stripping" to react with cellular macromolecules & is used in Myeloid Leukemia.
- → Carmustine & Lomustine crosses B.B.B. and hence used in treatment of Brain Tumors

ANTIMETABOLITES: - These compounds prevent biosynthesis or utilization of normal cellular macromolecules.

FOLATE ANTAGONISTS: -

- → Methotrexate (Amethopterine) / Aminopterine act by inhibiting dihydrofolate reductase (DHFR), which is essential for the conversion of Dihydrofolic acid to Tetrahydrofolic acid, & step which has to occur if synthesis of folate co-enzymes has to proceed.
- → Thus, they inhibit the synthesis of thymidilic acid, which is a component of the DNA.
- → Administration of Folinic acid counteracts toxicity of Methotrexate.
- → Methotrexate acts on S phase of the cell division.

PURINE ANTAGONISTS: -

- → 6-mercaptopurine, 6-thioguanine are converted to monoribonucleotide by Hypoxanthine guanine phosphoribosyl transferase (HGPRT).
- → Tumor cells lack the enzyme HGPRT develop resistance to the above drugs.Monoribonucleotides inhibit the conversion of 5-Phosphoribosylpyrophosphate to 5-phosphoribosylamine, which is required for the synthesis of purines.

PYRIMIDINE ANTAGONISTS: -

- 5-fluorouracil is converted in the body to the corresponding nucleotide.
- **5**-fluro-2-deoxyuridine monophosphate, which inhibits thymidilate synthetase & blocks the conversion of deoxyuridilic acid to deoxy thymidilic acid. Thus, it inhibits the synthesis of DNA.
- Fluorouracil itself gets incorporated in to nucleic acids and this may contribute to its toxicity.

Cytarabine: -

- It is phosphorylated in the body to the corresponding nucleotide, which inhibits DNA synthesis.
- The triphosphate of cytarabine is an inhibitor of DNA polymerase & blocks the generation of cytidilic acid.

Vinca alkaloids: -

- These are mitotic inhibitors that bind to the micro tubular protein **"tubulin",** prevent its polymerization & assembly of microtubules & thus cause disruption of mitotic spindle &interfere with cytoskeletal function.
- Therefore the chromosomes fail to move apart during mitosis.
- They are cell cycle specific and they act in metaphase phase. E.g.: vincristine & vinblastine

Taxanes: -

- Paclitaxel enhances polymerization of tubulin. As a result, the microtubules are stabilized & their depolymerisation is prevented.
- This stability results IU inhibition of normal dynamic reorganization of the microtubule network that is essential for vital interphase & mitotic functions. Abnormal arrays or bundles of microtubules are produced throughout the cell cycle.
- The major adverse effects seen are "stocking & glove" neuropathy.
- Epipodophyllotoxins such as etoposide arrest cells in the G_2 Phase & causes DNA breaks by stimulating DNA topoisomerase-2

DRUG	MECHANISM OF ACTION
Actinomycin D (Dactinomycin)	It inhibits DNA topoisomerase-2 & also interrelates in DNA, causing DNA breaks
Daunorubicin(Rubidomycin),Doxorubicin	It inhibits DNA topoisomerase-2& generates quinone type free radicals.
Mitomycin	It is converted in the body to act as an alkylating agent.
Hydroxyurea	It blocks the conversion of ribonucleotides to deoxy ribonucleotides by inhibiting the enzyme ribonucleoside diphosphate reductase & thus interferes with DNA synthesis.
Procarbazine	After metabolic activation, it depolymerises DNA & causes chromosomal damage. Inhibition of DNA synthesis occurs.
L-asparginase	The enzyme L-Asparginase degrades l-asparginase to L- aspartic acid, depriving leukemic cells of an essential metabolite & this may cause cell death.
Cisplatin	A platinum co-ordination complex is hydrolysed intracellularly to produce a highly reactive moiety that causes cross-linking of DNA.

DIAGNOSTIC TESTS OF DISEASES:-

Diseases	Test
1.Diptheria	Shick test
2.Haemophilus	Ducrey test
3.Leprosy	Lepromin test
4.Scarlet fever	Dick test
5.Syphilus	VDRL & Widal test
6.Tuberculosis	Tuberculin test
7.Typhoid	Widal test

Deficiency disorder	Drug given
1.Hypocalcaemia	Calcium gluconate i.v.
2.Addisons disease	Corticosteroid
3.Anaemia	Ferrous sulphate

Toxicity	Drugs
1.Paracetamol, Chloroform	Acetyl cysteine
2.Copper,Gold	Penicillamine
3.Arsenic	Dimercaprol
4.Lead	Calcium EDTA
5.Iron	Desferroxamine
6.Benzodiazepines	Flumenazil
7.CO,CO_2	Oxygen
8.Caffeine, Theophylline	Esmolol

PHARMAROCKS

GPAT STUDY MATERIAL

ANTIBIOTICS & CHEMOTHERAPY

PHARMACOLOGY

PHARMAROCKS GPAT SUCCESS TEST SERIES

ORGANISE BY MR. AMAR RAVAL

ANTIBIOTICS BY CLASS				
GENERIC NAME	**BRAND NAMES**	**COMMON USE**	**POSSIBLE SIDE EFFECT**	**MECHANISM OF ACTION**
AMINOGLYCOSIDES				
Amikacin	Amikin	Infections caused by Gram-negative bacteria, such as *Escherichia coli* and *Klebsiella* particularly *Pseudomonas aeruginosa*. Effective against Aerobic bacteria (not obligate/ facultative anaerobes) andtularemia.	Hearing loss Vertigo Kidney damage	Binding to the bacterial 30S ribosomal subunit (some work by binding to the 50S subunit), inhibiting the translocation of the peptidyl-tRNA from the A-site to the P-site and also causing misreading of mRNA, leaving the bacterium unable to synthesize proteins vital to its growth.
Gentamicin	Garamycin			
Kanamycin	Kantrex			
Neomycin	Neo-Fradin			
Netilmicin	Netromycin			
Tobramycin	Nebcin			
Paromomycin	Humatin			
ANSAMYCINS				
Geldanamycin		Experimental, As antitumor antibiotics		
Herbimycin				
CARBACEPHEM				
Loracarbef	Lorabid	Discontinued		Prevents bacterial cell division by inhibiting cell wall synthesis.

CARBAPENEMS				
Ertapenem	Invanz	Bactericidal for both Gram-positive and Gram-negative organisms and therefore useful for empiric broad-spectrum antibacterial coverage. (Note MRSA resistance to this class.)	Gastrointestinal upset and diarrhea Nausea Seizures Headache Rash and allergic reactions	Inhibition of cell wall synthesis
Doripenem	Doribax			
Imipenem Cilastatin	Primaxin			
Meropenem	Merrem			
CEPHALOSPORINS (FIRST GENERATION)				
Cefadroxil	Duricef	Good coverage against Gram positive infections.	Gastrointestinal upset and diarrhea Nausea (if alcohol taken concurrently) Allergic reactions	Same mode of action as other beta-lactam antibiotics: disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
Cefazolin	Ancef (discontinued)			
Cefalotin or Cefal othin	Keflin (discontinued)			
Cefalexin	Keflex			
CEPHALOSPORINS (SECOND GENERATION)				
Cefaclor	Distaclor	Less gram positive cover, improved gram negative cover.	Gastrointestinal upset and diarrhea, Nausea (if alcohol taken concurrently) Allergic reactions	Same mode of action as other beta-lactam antibiotics: disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
Cefamandole	Mandol (discontinued)			
Cefoxitin	Mefoxin (discontinued)			

Cefprozil	Cefzil			
Cefuroxime	Ceftin, Zinnat (UK)			
CEPHALOSPORINS (THIRD GENERATION)				
Cefixime	Suprax	Improved coverage of Gram negative organisms, except Pseudomonas. Reduced Gram positive cover.	Gastrointestinal upset and diarrhea Nausea (if alcohol taken concurrently) Allergic reactions	Same mode of action as other beta-lactam antibiotics: Disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
Cefdinir	Omnicef, Cefdiel			
Cefditoren	Spectracef			
Cefoperazone	Cefobid (discontinued)			
Cefotaxime	Claforan			
Cefpodoxime	Vantin			
Ceftazidime	Fortaz			
Ceftibuten	Cedax			
Ceftizoxime	Cefizox (discontinued)			
Ceftriaxone	Rocephin			

CEPHALOSPORINS (FOURTH GENERATION)				
Cefepime	Maxipime	Covers pseudomonal infections.	Gastrointestinal upset and diarrhea Nausea (if alcohol taken concurrently) Allergic reactions	Same mode of action as other beta-lactam antibiotics: disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
CEPHALOSPORINS (FIFTH GENERATION)				
Ceftaroline fosamil	Teflaro	Used to treat MRSA	Gastrointestinal upset and diarrhea Allergic reaction	Same mode of action as other beta-lactam antibiotics: Disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
Ceftobiprole	Zeftera	Used to treat MRSA	Gastrointestinal upset and diarrhea Nausea (if alcohol taken concurrently) Allergic reactions	Same mode of action as other beta-lactam antibiotics: Disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.

GLYCOPEPTIDES				
Teicoplanin	Targocid (UK)	Active agaist aerobic and anaerobic Gram positive bacteria including MRSA; Vancomycin is used orally for the treatment of C. difficile		Inhibiting peptidoglycan synthesis
Vancomycin	Vancocin			
Telavancin	Vibativ			
LINCOSAMIDES				
Clindamycin	Cleocin	Serious staph-, pneumo-, and streptococcal infections in penicillin-allergic patients, also anaerobic infections; clindamycin topically for acne	Possible C. difficile-related pseudomembranous enterocolitis	Bind to 50S subunit of bacterial ribosomal RNAthereby inhibiting protein synthesis
Lincomycin	Lincocin			
LIPOPEPTIDE				
Daptomycin	Cubicin	Gram-positive organisms		Bind to the membrane and cause rapid depolarization, resulting in a loss of membrane potential leading to inhibition of protein, DNA and RNA synthesis

MACROLIDES				
Azithromycin	Zithromax, Sumamed, Xithrone	Streptococcal infections, syphilis, upper respiratory tract infections, lower respiratory tract infections, mycoplasmal infections, Lyme disease	Nausea, vomiting diarrhea (especially at high doses) Prolonged QT interval (especially erythromycin) Jaundice	Inhibition of bacterial protein biosynthesis by binding reversibly to the subunit 50S of the bacterial ribosome, There by inhibiting translocation of peptidyl tRNA.
Clarithromycin	Biaxin			
Dirithromycin	Dynabac (discontinued)			
Erythromycin	Erythocin,Erythroped			
Roxithromycin				
Troleandomycin	Tao (discontinued)			
Telithromycin	Ketek	Pneumonia	Visual Disturbance, Liver Toxicity.[4]	
Spectinomycin	Trobicin	Gonorrhea		
Spiramycin	Rovamycine	Mouth infections		
MONOBACTAMS				
Aztreonam	Azactam			Same mode of action as other beta-lactam antibiotics: Disrupt the synthesis of

				thepeptidoglycan layer of bacterial cell walls.
Nitrofurans				
Furazolidone	Furoxone	Bacterial or protozoal diarrhea orenteritis		
Nitrofurantoin	Macrodantin, Macrobid	Urinary tract infections		
PENICILLINS				
Amoxicillin	Novamox, Amoxil	Wide range of infections; penicillin used for streptococcal infections, syphilis, Lyme disease	Gastrointestinal upset and diarrhea Allergy with seriousanaphylactic reactions Brain and kidney damage (rare)	Same mode of action as other beta-lactam antibiotics: Disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
Ampicillin	Principen (discontinued)			
Azlocillin				
Carbenicillin	Geocillin (discontinued)			
Cloxacillin	Tegopen (discontinued)			
Dicloxacillin	Dynapen (discontinued)			
Flucloxacillin	Floxapen(Sold to European			

	generics Actavis Group)			
Mezlocillin	Mezlin (discontinued)			
Methicillin	Staphcillin (discontinued)			
Nafcillin	Unipen (discontinued)			
Oxacillin	Prostaphlin (discontinued)			
Penicillin G	Pentids (discontinued)			
Penicillin V	Veetids (Pen-Vee-K) (discontinued)			
Piperacillin	Pipracil (discontinued)			
Penicillin G	Pfizerpen			
Temocillin	Negaban (UK) (discontinued)			

Ticarcillin	Ticar (discontinued)			
PENICILLIN COMBINATIONS				
Amoxicillin clavulanate	Augmentin			The second component prevents bacterialresistance to the first component
Ampicillin sulbactam	Unasyn			
Piperacillin tazobactam	Zosyn			
Ticarcillin clavulanate	Timentin			
POLYPEPTIDES				
Bacitracin		Eye, ear or bladder infections; usually applied directly to the eye or inhaled into the lungs; rarely given by injection, although the use of intravenous colistin is experiencing a resurgence due to the emergence of multi drug resistant organisms.	Kidney and nerve damage (when given by injection)	Inhibits isoprenyl pyrophosphate, a molecule that carries the building blocks of the peptidoglycanbacterial cell wall outside of the inner membrane
Colistin	Coly-Mycin-S			Interact with the gram

Polymyxin B				negative bacterial outer membrane and cytoplasmic membrane. It displaces bacterial counter ions, which destabilizes the outer membrane. They act like a detergent against the cytoplasmic membrane, which alters its permeability. Polymyxin B and E are bactericidal even in an isosmotic solution.
QUINOLONES				
Ciprofloxacin	Cipro,Ciproxin, Ciprobay	Urinary tract infections, bacterial prostatitis, community-acquiredpneumonia, bacterial diarrhea, mycoplasmal infections, gonorrhea	Nausea (rare), irreversible damage to central nervous system(uncommon), tendinosis (rare)	Inhibit the bacterial DNA gyrase or thetopoisomerase IV enzyme, There by inhibiting DNA replication and transcription.
Enoxacin	Penetrex			
Gatifloxacin	Tequin			
Levofloxacin	Levaquin			
Lomefloxacin	Maxaquin			

Moxifloxacin	Avelox			
Nalidixic acid	NegGram			
Norfloxacin	Noroxin			
Ofloxacin	Floxin, Ocuflox			
Trovafloxacin	Trovan	Withdrawn		
Grepafloxacin	Raxar	Withdrawn		
Sparfloxacin	Zagam	Withdrawn		
Temafloxacin	Omniflox	Withdrawn		
SULFONAMIDES				
Mafenide	Sulfamylon	Urinary tract infections (except sulfacetamide, used for eye infections, and mafenide and silver sulfadiazine, used topically forburns)	Nausea, vomiting, and diarrhea Allergy(including skin rashes) Crystals in urine Kidney failure Decrease inwhite blood cellcount Sensitivity to sunlight	Folate synthesis inhibition. They are competitive inhibitors of the enzyme dihydropteroate synthetase, DHPS. DHPS catalyses the conversion of PABA (*para*-aminobenzoate) to dihydropteroate, a key step in folate synthesis. Folate is necessary for the cell to
Sulfonamidochrysoidine(archaic)	Prontosil			
Sulfacetamide	Sulamyd, Bleph-10			
Sulfadiazine	Micro-Sulfon			
Silver sulfadiazine	Silvadene			
Sulfamethizole	Thiosulfil Forte			
Sulfamethoxazole	Gantanol			
Sulfanilimide (archaic)				

Sulfasalazine	Azulfidine			synthesize nucleic acids (nucleic acids are essential building blocks of DNA andRNA), and in its absence cells will be unable to divide.
Sulfisoxazole	Gantrisin			
Trimethoprim-Sulfamethoxazole (Co-trimoxazole) (TMP-SMX)	Bactrim, Septra			
TETRACYCLINES				
Demeclocycline	Declomycin	Syphilis, chlamydial infections, Lyme disease, Mycoplasmal infections, Acne rickettsialinfections, * malaria * Note: Malaria is caused by a protist and not a bacterium.	Gastrointestinal upset Sensitivity to sunlight Potential toxicity to mother and fetus during pregnancy Enamel hypoplasia (staining of teeth; potentially permanent) transient depression of bone growth	Inhibiting the binding of aminoacyl-tRNA to them RNA-ribosome complex. They do so mainly by binding to the 30S ribosomal subunit in the mRNA translation complex.
Doxycycline	Vibramycin			
Minocycline	Minocin			
Oxytetracycline	Terramycin			
Tetracycline	Sumycin,Achromycin V,Steclin			
DRUGS AGAINST MYCOBACTERIA				
Clofazimine	Lamprene	Antileprotic		
Dapsone	Avlosulfon	Antileprotic		

Capreomycin	Capastat	Antituberculosis		
Cycloserine	Seromycin	Antituberculosis, urinary tract infections		
Ethambutol	Myambutol	Antituberculosis		
Ethionamide	Trecator	Antituberculosis		Inhibits peptide synthesis
Isoniazid	I.N.H.	Antituberculosis		
Pyrazinamide	Aldinamide	Antituberculosis		
Rifampicin (Rifampin in US)	Rifadin, Rimactane	mostly Gram-positive andmycobacteria	Reddish-orange sweat, tears, and urine	Binds to the β subunit of RNA polymerase to inhibit transcription
Rifabutin	Mycobutin	Mycobacterium avium complex	rash, discolored urine, GI symptoms	
Rifapentine	Priftin	Antituberculosis		
Streptomycin		Antituberculosis	Neurotoxicity,ototoxicity	As other aminoglycosides
OTHERS				
Arsphenamine	Salvarsan	Spirochaetal infections (obsolete)		
Chloramphenicol	Chloromycetin	Meningitis, MRSA, topical use, or for low cost internal treatment. Historic: typhus, cholera. gram negative, gram positive, anaerobes	Rarely: aplastic anemia.	Inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome

Fosfomycin	Monurol	Acute cystitis in women		Inactivates enolpyruvyl transferase, thereby blocking cell wall synthesis
Fusidic acid	Fucidin			
Linezolid	Zyvox	VRSA	Thrombocytopenia	
Metronidazole	Flagyl	Infections caused by anaerobic bacteria; also amoebiasis, trichomoniasis, Giardiasis	Discolored urine,headache, metallic taste, nausea ; alcohol is contraindicated	Produces toxic free radicals which disrupt DNA and proteins. This non-specific mechanism is responsible for its activity against a variety of bacteria, Amoebae, and protozoa.
Mupirocin	Bactroban	Ointment for impetigo, cream for infected cuts		Inhibits isoleucine t-RNA synthetase (IleRS) causing inhibition of protein synthesis
Platensimycin				
Quinupristin/Dalfopristin	Synercid			
Rifaximin	Xifaxan	Traveler's diarrhea caused by E. coli		

Thiamphenicol		Gram-negative, Gram-positive, anaerobes. Widely used in veterinary medicine.	Lacks known anemic side-effects.	A chloramphenicol analog. May inhibit bacterial protein synthesis by binding to the 50S subunit of the ribosome
Tigecycline	Tigacyl			
Tinidazole	Tindamax Fasigyn	protozoan infections	upset stomach, bitter taste, and itchiness	
Trimethoprim	Proloprim, Trimpex	Urinary Tract Infections		

- HI FRIENDS HERE ALL THE DRUGS ARE COVER FROM ANTIBIOTIC SECTION OF PHARMACOLOGY
- MUST PREPARE THIS ALL TABLES
- THEY HELS DURING YOUR GPAT EXAM AS WELL AS IN THE FINAL YEAR OF B.PHARM
- PREPARE WELL ABOUT DRUG AND THEIR SIDE EFFECTS AND MOA.
- ALL THE BEST
- KEEP ROCKING WITH PHARMAROCKS

AMAR M. RAVAL

OWNER: PHARMAROCKS

SOLID DOSAGE FORMS – TABLETS

Syllabus:

Types of tablets

Tablet ingredients: Diluents, binders, disintegrating agents, lubricants, colorants, flavoring and sweeteners.

Principles, materials and equipment involved in drying and mixing of powders, granulation and compression of tablets.

Layout of a tableting section. Principles of refrigeration-air conditioning, humidification and dehumidification and fluidization as applied to the manufacturing of tablets.

Principles, processes, materials and equipment involved in coating of dosage forms with sugar, enteric coating materials and film-formers.

Quality control and standards of coated dosage forms.

Questions:

1. *Short note on tablet coatings.*
2. *Explain the advantages of tablet dosage forms*
3. *Describe the different methods of preparation of tablets*
4. *Write a brief note on tablet additives with examples*
5. *Discuss the different classes of pharmaceutical excipients that go into tablet formulation giving examples to each class.*
6. *Draw a sketch of the layout of a tablet manufacturing unit.*
7. *Differentiate between capsule unit and this. Short note on proper drying of granules.*
8. *Write an account on the phenomena, processing and importance of enteric coating.*
9. *Discuss the details of manufacturing of ascorbic acid tablets, explaining each step in the manufacture.*

DEFINITION

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or moulding methods.

This dosage form is intended to be administered through oral route.

Definition according to Indian Pharmacopoeia

"Pharmaceutical tablets are flat or bi-convex discs prepared by compressing a drug or a mixture of drugs with or without suitable diluents."

Advantages of tablet dosage form over other oral drug delivery systems:

From patients stand point?

1. They are easy to carry.
2. They are easy to swallow.
3. They are attractive in appearance.
4. Unpleasant taste can be masked by sugar coating.
5. They do not require any measurement of dose. The strip or blister packing has further facilitated the process of taking the dose by the patient. Moreover, it provides a sealed covering which protects the tablets from atmospheric conditions like air, moisture and light etc.
6. Some of the tablets are divided into halves and quarters by drawing lines during manufacturing to facilitate breakage whenever a fractional dose is required.

From the standpoint of manufacturer:

7. An accurate amount of medicament, even if very small, can be incorporated.
8. Tablets provide prolonged stability to medicament. They have the best combined properties of chemical, mechanical and microbiological stability of all the oral dosage forms.
9. The incompatibilities of medicaments and their deterioration due to environmental factors are less in tablet forms.
10. Since they are generally produced on a large scale, therefore, their cost of production is relatively low, hence economical.
11. They are in general the easiest and cheapest to package and ship among all oral dosage forms.

12. Some specialized tablets like enteric coated tablet, sustained release tablets may be prepared for modified release profile of the drug.
13. Product identification is potentially the simplest and cheapest requiring no additional processing steps when employing an embossed or monogrammed punch face.

Disadvantages of tablet dosage forms:

(i) Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.
(ii) Drugs with poor wetting, slow dissolution properties, intermediate to large dose, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate bioavailability.
(iii) Bitter tasting drugs, drugs with objectionable odour, or drugs sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression (if feasible of practical) or the tablets may require coating.

TYPES OF TABLETS

Tablets are classified according to their route of administration or function. The following are the four main classification groups:

(A) Tablets ingested orally:
(i) Compressed tablets
(ii) Multiple compressed tablets
(iii) Enteric coated tablets
(iv) Sugar coated tablets
(v) Film coated tablets
(vi) Chewable tablets

(B) Tablets used in the oral cavities:
(i) Buccal cavities
(ii) Sublingual tablets
(iii) Lozenges
(iv) Dental cone

(C) Tablets administered by other routes:
(i) Implantation tablets
(ii) Vaginal tablets

(D) Tablets used to prepare solutions:
(i) Effervescent tablets
(ii) Dispensing tablets
(iii) Hypodermic tablets
(iv) Tablet triturates

(A) TABLETS INGESTED ORALLY

These tablets are designed to be swallowed except the chewable tablets. The tablets covered in this category are:

Compressed tablets (C.T.)

These tablets are formed by compression and contain no special coating. They are made from powdered, crystalline or granular materials, alone or in combination with diluent, binders, disintegrants, lubricants, antiadherants and in many cases colorants.

These tablets contain water soluble drugs which after swallowing get disintegrated in the stomach and its drug contents are absorbed in the gastrointestinal tract and distributed in the whole body. E.g. Aspirin (, Dispirin) paracetamol tablets (Crocin)

Multiple compressed tablets:

These are compressed tablets made by more than one compression cycle:

Layered tablets

Such tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or three layers. Special tablet presses are required to make layered tablets such as *Versa press*. (Stokes/Pennwalt)

These tablets are prepared to separate physically or chemically incompatible ingredients or to produce repeat action or prolonged action products.

To avoid incompatibility, the ingredients of the formulation except the incompatible material are compressed into a tablet and then incompatible substance along with necessary excipients are compressed over the previously compressed tablet.

Sustained action tablets:

These are the tablets which after oral administration release the drug at a desired time and prolong the effect of the medicament. These tablets when taken orally release the medicament in a sufficient quantity as and when required to maintain the maximum effective concentration of the drug in the blood throughout the period of treatment.

E.g. Diclofenac SR tablets.

Enteric coated tablets:

These are compressed tablet meant for administration by swallowing and are designed to by-pass the stomach and get disintegrated in the intestine only.

These tablets are coated with materials resistant to acidic pH (like cellulose acetate phthalate, CAP) of the gastric fluid but get disintegrated in the alkaline pH of the intestine. These tablets are made to release the drug undiluted and in the highest concentration possible within the intestine, e.g. tablets containing anthelmintic and amoebicides.

Sugar coated tablets:

These are compressed tablets containing a sugar coating. Such coatings are done to mask the bitter and unpleasant odour and the taste of the medicament. The sugar coating makes the tablet elegant and it also safeguard the drug from atmospheric effects.

Film coated tablets:

The compressed tablets having a film coating of some polymer substance, such as hydroxy propyl cellulose, hydroxy propyl methyl cellulose and ethyl cellulose. The film coating protects the medicament from atmospheric effects. Film coated tablets are generally tasteless, having little increase in the tablet weight and have less elegance than that of sugar coated tablets.

Chewable tablets:

These are the tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing.

A number of antacid tablets and multivitamin tablets are prepared as chewable tablets.

For the preparation of chewable tablets mannitol is used as a sweetening base. Since mannitol is expensive other substances like sorbitol, lactose, chocolate powder, dextrose and glycerin can be substituted in place of mannitol. These tablets do not require any disintegrating agents to be present in the formulation.

These tablets should have very acceptable taste and flavour.

E.g. antacid tablets

Vitamin C chewable tablets e.g. CELIN - (Glaxo)

(B) TABLETS USED IN ORAL CAVITY

Buccal tablets:

These tablets are to be placed in the side of the cheek (buccal pouch) where they dissolve or erode slowly and are absorbed directly in the buccal cavity without passing into the alimentary canal.

Therefore, they are formulated and compressed with sufficient pressure to give a hard tablet e.g. Progesterone tablets.

Sublingual tablets:

These tablets are to be placed under the tongue where they dissolve or disintegrate quickly and are absorbed directly without passing into GIT e.g. tablets of nitroglycerin, isoproterenol hydrochloride or erythrityl tetranitrate.

Lozenges tablets:

These tablets are designed to exert a local effect in the mouth or throat. These tablets are commonly used to treat sore throat to control coughing in common cold. They may contain local anaesthetics, antiseptics, antibacterial agents, astringents and antitussives.

These are prepared by compression at a high pressure by the moulding process and generally contain a sweetening agent, flavouring agent (e.g. peppermint, clove oil) and a substance which produces a cooling effect (e.g. mentha). E.g. Vicks lozenges.

Dental cones:
These are compressed tablets meant for placement in the empty sockets after tooth extraction. They prevent the multiplication of bacteria in the socket following such extraction by using slow-releasing antibacterial compounds or to reduce bleeding by containing the astringent.
These tablets contain an excipient like lactose, sodium bicarbonate and sodium chloride.
These cones generally get dissolved in 20 to 40 minutes time.

(C) TABLETS ADMINISTERED BY OTHER ROUTES
Implantation tablets:
These tablets are placed under the skin or inserted subcutaneously by means of minor surgical operation and are slowly absorbed. These may be made by heavy compression but are normally made by fusion. The implants must be sterile and should be packed individually in sterile condition. Implants are mainly used for the administration of hormones such as testosterone steroids for contraception. These tablets are very usefully exploited for birth control purpose in human beings.
The disadvantages of implant tablets are their administration changing rate of release with change of surface area and possibility of tissue reactions.
Vaginal tablets:
These tablets are meant to dissolve slowly in the vaginal cavity. The tablets are typically ovoid or pear shaped for the ease of insertion. These tablets are used to release steroids or antimicrobial agents. The tablets are often buffered to promote a pH favorable to the action of a specified antimicrobial agent. The contains easily soluble components like lactose or sodium bicarbonate.

(D) TABLETS USED TO PREPARE SOLUTIONS
Effervescent tablets:
These tablets along with the active medicament contain ingredients like sodium bicarbonate, citric acid and tartaric acid which react in the presence of water liberating carbon dioxide and producing effervescence leading to disintegration of the tablet, thus hastens solution formation and increase the palatability.
Dispensing tablets:
These tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as dosage form.
E.g. the drugs commonly incorporated are mild silver potentiate, bichloride of mercury merbromin a quarternary ammonium compounds.
Hypodermic tablets:
Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. These tablets are dissolved in sterile water or water for injection and administered by parenteral route. These tablets are not preferred now-a-days because the resulting solution is not always sterile.
Tablet triturates (Moulded tablets):
These are powders moulded into tablets. They are flat, circular discs, usually containing a potent substance mixed with lactose, lactose and sucrose, dextrose, or other suitable diluent.
Since they are intended to disintegrate very quickly in contact with moisture, water insoluble adjuncts are avoided. The name 'tablet triturate' is appropriate because they usually contain triturations (*trituration = dilution with an inert substance*).

TABLET INGREDIENTS

In addition to the active or therapeutic ingredient(s), tablets contain a number of inert materials. The latter are known as **additives** or **excipients**.

They may be classified according to the part they play in the finished tablet.

Group-I: Contains those which help to impart satisfactory processing and compression characteristics to the formulation. This includes: *diluents*, *binders*, *glidants* and *lubricants*.

Group-II: Helps to give additional desirable physical characteristics to the finished tablet. This includes: *disintegrants*, *colours*, and in the case of chewable tablets, *flavors* and *sweetening agents*.

Group-III: In the case of controlled-release tablets, polymers or waxes or other solubility-retarding materials.

DILUENTS

Objectives of incorporating diluents:

(i) Frequently, the single dose of the active ingredient is small and an inert substance is added to increase the bulk in order to make the tablet a practical size for compression.

Compressed tablets of dexamethasone contains 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible.

The dose of some drugs is sufficiently high that no filler is required (e.g. aspirin and certain antibiotics).

Diluents used for this purpose include *dicalcium phosphate* (DCP), *calcium sulfate, lactose, cellulose, kaolin, mannitol, dry starch* and *powdered sugar*.

(ii) Certain diluents, such as *mannitol, lactose, sorbitol, sucrose* and *inositol*, when present in sufficient quantity, can impart properties that will help in disintegration of the tablet in the mouth by chewing. Such tablets are commonly called **chewable tablets**.

(iii) Diluents used for direct compression formulas give the powder mixture necessary flowability and compressibility.

(iv) To delay or control the rate of release of drug from the tablet.

Characteristics of an ideal diluents:

1. They must be nontoxic and acceptable to the regulatory agencies in all countries where the product is to be marketed.
2. They must be commercially available in an acceptable grade in all countries where the product is to be manufactured.
3. They must be cheap compared to the active ingredients.
4. They must be physiologically inert.
5. They must be chemically stable alone and/or in combination with the drug(s) and/or other tablet components.
6. They must be free of any unacceptable "microbiological load".
7. They must be color-compatible (should not produce any off-color appearance).
8. They must have no negative effects on the bioavailability of the drug(s) in the product.

[N.B. e.g. Calcium phosphate as diluent, reduces the bioavailability of some antibiotics like tetracycline.]

Classification of diluents:

DILUENTS

Sugars	Polysaccharides	Inorganic compounds	Miscellaneous compounds
Dextrose	Starches	Calcium phosphate dihydrate	Bentonite
Lactose	Modified starch	Calcium sulfate dihydrate	Polyvinyl pyrrolidone
Sucrose	E.g. Sta-RX 1500, Celutab etc.	Calcium lactate trihydrate	Kaolin
Amylose	Cellulose	Calcium carbonate	Silicone derivatives
Mannitol	Cellulose derivatives	Magnesium carbonate	
Sorbitol	Microcrystalline cellulose	Magnesium oxide	
Inositol	(MCC)		

CALCIUM SALTS

Example: Dibasic calcium phosphate dihydrate (or dicalcium orthophosphate) (DCP) [$CaHPO_4$, 2 H_2O], Calcium sulfate dihydrate ($CaSO_4$, $2H_2O$).

Advantages:

- Diluents that exist in their common salt form as hydrates, containing appreciable bound water as water of crystallization. This bound water of calcium sulfate is not released below 80^0C. They possess very low concentration of unbound moisture. Hence, these salts are excellent diluents for water-sensitive drugs. It is superior to anhydrous diluent, which has a moderate to high moisture demand.

Disadvantages:

- Tetracycline products made with calcium phosphate diluent had less than half the bioavailability of the standard product. Divalent cation (Ca^{++}) form insoluble complexes and salts with number of amphoteric or acidic functionality antibiotics, which generally reduces their absorption (*which is also why milk should not be co-administered with these drug*).

LACTOSE

Lactose is the most widely used diluent for tablet formulation.

- It is obtained in hydrous and anhydrous form. The anhydrous form, picks up moisture when exposed to elevated humidity. Such tablets should be packed in moisture proof packets or containers. When a wet granulation method is employed, the hydrous form of lactose should generally be used.
- Two grades of lactoses are commercially available:
  (i) A 60 to 80 mesh – coarse
  (ii) A 80 to 100 mesh – regular grade

Advantages:

1. Lactose has no reaction with most of the drugs, whether in hydrous or anhydrous form.
2. Lactose formulations show good release rates
3. Their granulations are readily dried, and the tablet disintegration times of lactose tablets are not strongly sensitive to variations in tablet hardness.
4. It is a low cost diluent.

Disadvantages:

1. Lactose reacts with amine drug bases in presence of alkaline lubricants e.g. metal stearates (e.g. magnesium stearate) and gradually discolours (dark brown) with time due to the formation of furaldehyde. This reaction is called Maillard reaction.

SPRAY DRIED LACTOSE

Advantages:

1. It is used for direct compression (containing drug + diluent + disintegrant + lubricant)
2. In addition to the direct compression properties, spray dried lactose also has good flow characteristics. It can usually be combined with as much as 20 to 25% of active ingredients without losing these advantageous features.

Disadvantages:

1. If spray dried lactose is allowed to dry out and the moisture content falls below the usual 3% level, the material loses some of its direct compressional characteristics.
2. Spray-dried lactose is especially prone to darkening in the presence of excess moisture, amines, and other compounds owing to Maillard reactions. Hence, a neutral or acid lubricant should be used.

STARCH

Starch may be obtained from corn, wheat or potatoes. It is occasionally used as a tablet diluent

- USP grade of starch is usually possesses moisture content between 11 to 14%.
- Specially dried types of starch that have a standard moisture level of 2-4% are available, but are costly. Use of such starches in wet granulation is wasteful since their moisture level increase to 6-8% following moisture exposure.

DIRECTLY COMPRESSIBLE STARCHES

Sta–Rx 1500 – free flowing, directly compressible starch
– used as diluent, binder, disintegrant

Emdex and Celutab – are two hydrolyzed starches
– contains dextrose 90–92%
Maltose 3–5%
– free flowing and directly compressible
– may be used in place or mannitol in chewable tablets because of their sweetness and smooth feeling in the mouth.

DEXTROSE (D–Glucose)

Available in two forms: as hydrates and anhydrous forms.

Dextrose may sometimes be combined in formulation to replace some of the spray-dried lactose, which may reduce the tendency of the resulting tablets to darken.

MANNITOL

Advantages

- Because of the negative heat of solution (cooling sensation in the mouth) its slow solubility, and its pleasant feeling in the mouth, it is widely used in chewable tablets.
- It is relatively non-hygroscopic and can be used in vitamin formulations.
- Low calorie content and non-carcinogenic.

Disadvantages

- Costly
- Mannitol has poor flow characteristics and usually require fairly high lubricant level.

SORBITOL

It is an optical isomer of mannitol and is sometimes combined with mannitol formulations to reduce the diluent cost.

Disadvantages: It is hygroscopic at humidities above 65%.

SUCROSE

Some sucrose based diluents are:

Sugar tab – 90 to 93% sucrose + 7 to 10% invert sugar
Di Pac – 97% sucrose + 3% modified dextrins
Nu Tab – 95% sucrose + 4% invert sugar + small amount of corn starch + Mg-stearate

Advantages: They are all used for direct compression.

Disadvantages: All are hygroscopic when exposed to elevated humidity.

MICROCRYSTALLINE CELLULOSE (MCC)

Trade Name: Avicel – is a directly compression material

Two grades are available PH 101 → powder
PH 102 → granules

Advantages: It acts as diluent and disintegrating agents.

BINDERS

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators.

Objective of incorporating binders

1. They impart a cohesiveness to the tablet formulation (both direct compression and wet–granulation method) which insures the tablet remaining intact after compression.
2. They improves the free-flowing qualities by the formation of granules of desired size and hardness.

Characteristics of binder

Method-I

Binders are used in dry form in the powder and then moistened with a solvent (of the binder) to form wet lumps.

Method-II

Binders are often added in solution form. It requires lower concentration of binder.

By Method-I the binder is not as effective in reaching and wetting each of the particles within the mass of the powder. Each of the particle in a powder blend has a coating of adsorbed air on its surface, and it is this film of air which must be penetrated before the powder can be wetted by the binder solution.

Method-III

In direct compression method MCC, microcrystalline dextrose, amylose and PVP are used – those have good flow property and cohesiveness as well.

It has been postulated that MCC is a special form of cellulose fibril in which individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking intercrystallite bonds by the disintegrating medium.

STARCH PASTE

Corn starch is often used in the concentration of 10–20%.

Method of preparation

Corn starch is dispersed in cold purified water to make a 5 to 10% w/w suspension and then warming in water both with continuous stirring until a translucent paste is formed... (Actually hydrolysis of starch takes place.)

LIQUID GLUCOSE

50% solution in water is fairly common binding agent.

SUCROSE SOLUTION

50% to 74% sugar solution is used as binder. They produce hard but brittle granules. Their cost is low.

GELATIN SOLUTION

Concentration 10–20% aqueous solution

Should be prepared freshly and added in warm condition other wise it will become solid.

Method of preparation

The gelatin is dispersed in cold water and allowed to stand until hydrated. The hydrated mass is warmed in water bath to dissolve.

CELLULOSIC SOLUTIONS

HPMC (Hydroxy propyl methyl cellulose) Soluble in cold water.

Method of preparation: HPMC is dispersed in hot water, under agitation. The mixture is cooled as quickly as possible and as low as possible

HEC (Hydroxy ethyl cellulose), HPC (Hydroxy propyl cellulose) are other successful binders.

PVP (Polyvinylpyrollidone) Used as an aqueous or alcoholic solution. Concentration 2% and may vary.

LUBRICANTS

Objectives:

1. Prevents adhesion of the tablet material to the surface of dies and punches.
2. Reduce inter-particular friction, improve the rate of flow of tablet granulation.
3. Facilitate ejection of the tablets from the die cavity.

Examples:

Talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and polyethylene glycols (PEG).

Method of addition of lubricants:

1. The lubricant is divided finely by passing it through a 60 to 100 mesh nylon cloth on to the granulation. In production this is called 'bolting the lubricant'.
2. After addition the granulation is tumbled or mixed gently to distribute the lubricant without coating all the particles too well.
   * Complete coating will produce dissolution problem.
   * Prolonged mixing will produce excessive fines by breaking the granules.

Soluble lubricants

Examples: Sodium benzoate – includes a mixture of sodium benzoate and sodium acetate
Sodium chloride, leucine and carbowax 4000.

Magnesium stearate

Though it is a widely used lubricant it retards disintegration and dissolution. To overcome this some time surfactants like sodium lauryl sulfate are included.

Lubricants are included to reduce the friction during tablet ejection between the walls of the tablet and the wall of the die in which the tablet was formed.
Antiadherents are used for the purpose of reducing the sticking or adhesion of any of the tablet ingredients or powder to the faces of the punches or to the die wall.
Glidants are intended to promote flow of the tablet granulation or powder materials by reducing the friction between the particles.

An ingredient used for lubrication purpose may possess other two properties as well.
Relative properties of some tablet lubricants:

Material	Usual percent	Glidant properties	Antiadherent properties	Lubricant properties
1. Calcium or Magnesium stearate	1 or less	Poor	Good	Excellent
2. Talc	1 – 5	Good	Excellent	Poor
3. Stearic acid	1 – 5	None	Poor	Good
4. High melting waxes	3 – 5	None	Poor	Excellent
5. Corn starch	5 – 10	Excellent	Excellent	Poor

Water soluble tablet lubricants

Lubricant	Percentage
Boric acid	1
Sodium chloride	5
Sodium benzoate	5
Sodium acetate	5
Sodium oleate	5
PEG 4000, 600	1 – 4
dl-leucine	1 – 5

DISINTEGRANTS

Definition

A disintegrant is a substance to a mixture of substances, added to tablet to facilitate its breakup or disintegration after administration in the GIT.

The active ingredients must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution.

Disintegrants can be classified chemically as:

Starches, clays, celluloses, alginates, gums and cross-linked polymers.

Starch

Corn starch, potato starch

For their disintegrating effect starches are added to the powder blends in dry state.

Mode of action:

Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix.

Others have suggested that the spherical shape of the starch grains increases the porosity of the tablet, thus promoting capillary action.

Normally 5% w/w is suggested.

For rapid disintegration 10 – 15% w/w may be taken.

Super disintegrants

Croscarmelose - cross linked cellulose
Crospovidone - cross linked polyvinyl pyrrolidone
Sodium starch glycolate - cross linked starch

Mode of action

Croscarmelose swells 4 to 8 fold in less than 10 seconds
Crospovidone acts by wicking or capillary action.
Sodium starch glycolate swells 7 to 12 folds in less than 30 seconds.

Other materials

Veegum HV, Methyl cellulose, Agar, Bentonite, Cellulose, Alginic acid, Guargum, and Carboxymethyl cellulose.

- Sodium lauryl sulfate is a surfactant. It increases the rate of wetting of the tablet, thus decreases the disintegrating time.

Method of blending with powder

The disintegrants are usually mixed with active ingredients and diluents prior to granulation.

Starch may be divided into two portions:

One part – added prior to granulation
Remainder – added prior to compression.

While disintegration the portion of the starch added prior to compression rapidly breaks down the tablet to granules, and the starch mixed prior to granulation disintegrates the granules into smaller particles.

COLOURING AGENT

Objectives of using colors

(i) It makes the tablet more esthetic in appearance.

(ii) Colour helps the manufacturer to identify the product during its preparation.

All colorants used in pharmaceuticals *must be approved and certified by the FDA (food & Drug Administration*). Dyes are generally listed as FD&C (food, Drug & Cosmetic Dyes) dyes and D&C (Drug & Cosmetic Dyes).

Colour	Other Names	Color Index (CI, 1971)
D&C Red 22	Eosin Y	45380
FD&C Yellow 5	Tartrazine	15985
FD&C Yellow 6	Sunset Yellow FCF Yellow Orange 5	19140
FD&C Blue 1	Brilliant Blue FCF	42090
FD&C Blue 2	Indigocarmine	73015
FD&C Green 3	Fast Green FCF	42035
Caramel	Burnt sugar	
Titanium dioxide	–	77891

Colorants are obtained in two forms **dyes** and **lakes**.

- Dyes are dissolved in the binding solution prior to the granulating process. However, during drying their color may migrate to the surface and may produce mottling of the tablet.
- So another approach is to adsorb the dye on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with other ingredients.
- Color lakes are dyes which are adsorbed onto a hydrous oxide of a heavy metal (like aluminium) resulting in an insoluble form of the dye.

FLAVOURS AND SWEETENERS

Flavours are usually limited to chewable tablets or other tablets intended to dissolve in the mouth.

Flavor oils are added to tablet granulations in solvents, are dispersed on clays and other adsorbents or are emulsified in aqueous granulating agents (i.e. binder).

N.B. Usually, the maximum amount of oil that can be incorporated to a granulation without influencing its tableting characteristics is 0.5 to 0.75% w/v.

The use of sweeteners is primarily limited to chewable tablets.

E.g. Sugar
Mannitol – 72% as sweet as sugar, cooling & mouth filling effect
Saccharin – Artificial sweetener
500 times sweeter than sucrose
Disadvantages (i) it has a bitter after taste
(ii) Carcinogenic
Cyclamate – either alone or with saccharin
– It is banned
Aspartame (Searle) – widely replacing saccharin
– *Disadvantage* – lack of stability in presence of moisture

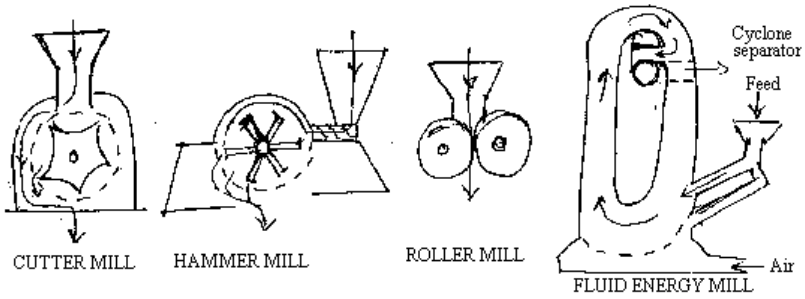
MANUFACTURE OF TABLETS

Manufacture of tablets involves certain well defined *steps*: namely,

Pulverization and mixing Granulation Compression Coating (if required)

PULVERIZATION AND MIXING

In this step the different solid / powder ingredients are reduced to the same particle size since particles of different sizes will segregate while mixing.



Instruments used for milling or size reduction:

General characteristics of various types of mills

Types of Mill	Action	used for	Not used for
Cutter	Cutting	fibrous, crude animal and vegetable drugs	friable material
Revolving	Action and impact	fine grinding of abrasive materials	soft material
Hammer	Impact	almost all drugs	abrasive materials
Roller	Pressure	soft material	abrasive material
Attrition	Attrition	soft and fibrous material	abrasive material
Fluid energy mill	attrition and impact	moderately hard and friable material	soft and sticky material

For mixing dry powders following mixers are used:

Twin shell blender Cubic blender Cylindric blender

GRANULATION

Objectives:

Simple powder may not have the desired flow property because there are may types of forces acting between solid particles:

1. Frictional forces,
2. surface tension forces,
3. mechanical forces caused by interlocking of particles of irregular shapes
4. electrostatic forces and
5. Cohesive or van der Waals forces.

Though bulk density and shape of the particles are important but two of the most common experiments done to get some idea about the flow property are

(i) Angle of repose and (ii) hopper flow rate measurement.

Values for angle of repose $\leq 30^0$ usually indicate a free-flowing material and

Values of angle of repose $\geq 40^0$ suggests a poorly flowing material.

Hopper flow rates have been used as a method to assess flowability of the powder mass. In this method the flow of powder from a conical hopper is continually monitored by the flow of material out of the hopper on to a recording balance device.

Question: "Mostly the materials, intended for compression into tablets are converted into granules" – Why?

Ans: Materials intended for compaction into tablets must possess two characteristics:

(1) Fluidity and (2) compressibility.

Good flow properties are essential for the transport of the material through the hopper, into and through the feed frame into the dies. Tablet materials should therefore be in a physical form that flows uniformly and smoothly. The ideal physical form is sphere, since spheres offers minimum contact surface between themselves and with the walls of the machine parts.

Unfortunately, most materials do not easily form spheres; however shapes approaching spheres improve flowability. Hence flow properties of powder materials are improved by forming sphere like regular shaped aggregates called granules.

WET GRANULATION

Step-I Milling of the drug and excipients

- Milling of the active ingredients, excipients etc. are milled to obtain a homogeneity in the final granulation.
- If the drug is given in solution then during drying it will come up to the surface. To avoid this problem drug is mixed with other excipients in fine state.

Step-II Weighing

- Weighing should be done in clean area with provision of air flow system.
- In the weighing area all the ingredients must not be brought at a time to avoid cross-contamination.

Step-III Mixing

Commonly used blenders are:
(a) Double cone blender
(b) V – blender
(c) Ribbon blender
(d) Planetary mixer

Any one of the blender may be used to mix dry powder mass.

Step-IV Wet Massing

Wet granulation forms the granules by binding the powders together with an adhesive.
Binder solutions can be added in two methods:

Method-I	Method-II
Drug + Diluent	Drug + Diluent
↓	↓
Dry binder is added	Binder Solution is added
↓	↓
Blended uniformly	↓
↓	↓
Suitable solvent is added to activate the dry binder	↓
↓	↓
Blended in a Sigma - mixer or Planetary mixer till properly wet mass is formed	

- The powder must be moist and not paste.
- Blending may take 30 mins to 1 hour.

N.B.

- To determine the proper moistening, the moist mass is balled in a palm, pressed by two fingers, if fragments of granules are formed and not powder then the blending is stopped.
- Since, in general, the mass should be moist rather than wet or paste, there is a limit to the amount of solvent that may be incorporated.

Therefore, when
(i) A small quantity of solvent is permissible, method-I is adopted and
(ii) A large quantity of solvent is required method-II is adopted.

- However, method-II will give more cohesiveness than method-I if the amount of binder remains constant.
- If granulation is over-wetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance.
- If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

Step-V Wet Screening

Wet screening process involves converting the moist mass into coarse, granular aggregates by
(i) Passage through a hand screen (in small scale production) or,
(ii) Passage through an oscillatory granulator of hammer mill equipped with screens having large perforations (# 6 – 8 mesh screen).

Purpose (i) Increase particle contact point
(ii) Increase surface area to facilitate drying.

Step-VI Drying

- Drying is usually carried out at **60^0C.** Depending on the thermolabile nature of the drug the temperature can be optimized.
- Drying is required in all wet granulation procedures to remove the solvent, but is not dried absolutely because it will pose problems later on. Hence, certain amount of moisture (1 – 4 %) is left within the granules – known as the *residual moisture*.

Methods: Drying can be carried out

1. *Tray dryers* – it may take 24 hrs of drying
2. *Truck dryers* – the whole cabinet can be taken out of the dryer
3. *Fluid-bed dryer* – dried for 30 mins.

The total surface of the granules are dried uniformly but in tray dryer the lower surface of the granules may not be dried uniformly. *Case hardening* may some time occur in tray dried products.

N.B. In case hardening the outer surface of the lumps of the wet powder will be dried quickly and become hard (forming a hard crust), while the inner part will remain wet. This phenomenon is called case hardening.

Step-VII Dry Screening

After drying, the granule size is reduced by passing through smaller mesh screen.

- For drying granules the screen size to be selected depends on the diameters of the punch. The following sizes are suggested:

Tablet diameter upto	Mesh Size
3/16 ”	# 20
3.5 / 16 – 5/16”	# 16
5.5/16 – 6.5/16”	# 14
7.0/16 or larger	# 12

Step-VIII Lubrication of granules

- After dry granulation, the lubricant is added as a fine powder. It usually, is screened onto the granulation through 60 or 100 mesh nylon cloth to eliminate small lumps as well as increase the covering capacity of the lubricant.
- The lubricant is blended very gently using tumbling action to maintain the uniform granule size.
- Too much fine powder is not desirable because fine powder may not feed into the die uniformly causing variation in weight and density.
- Since, the very nature of lubricant produce hydrophobic surface on the particle hence over blending prevents the inter granule bonding that takes place during compression.

Example of wet granulation formulae:-

Ferrous sulfate tablets

Ingredients	Quantity / tablet	Remarks
Ferrous sulfate (dried)	300 mg	Active ingredient
Corn Starch	60 mg	Diluent
20% sugar solution	q.s.	Binder
Explotab	45 mg	Disintegrant
Talc	30 mg	Glidant & Antiadherent
Magnesium stearate	4 mg	Lubricant

Method of preparation

FeSO4 + Corn Starch
↓ *Mix*
↓ *Moistened with sugar solution*
↓ *Passed through #12*
Wet granules
↓ *Dried on tray dryer (Temp: 60 – 65^{0}C, over night)*
↓ *Dry Screened through #18*
Dry granules ← Explotab + talc + Mg-stearate
↓ *Compression*
TABLET

DRY GRANULATION

Dry granulation is followed in situations where
(i) The effective dose of a drug is too high for direct compaction,
(ii) If the drug is sensitive to heat, moisture or both, which precludes wet granulation.
E.g. many aspirin and vitamin formulations are prepared for tableting by compression granulation.

Steps of granulations

Milling → Weighing → Screening → Blending → Slugging → Granulation (Dry) → Lubrication
↓
Compaction

Slug:

Slug may described as poorly formed tablets or, may be described as compacted mass of powdered material.
Purpose: To impart cohesiveness to the ingredients, so as to form tablets of desired properties.
Method: It is done either by (i) by high capacity heavy duty tablet press
(ii) Of by Chilsonator roller compactor.

(i) By *high capacity tablet press* large tablets are made because

(a) Fine powders flow better into large cavities, and
(b) Large slugs reduces production time

- The punches are flat faced
- Sufficient pressure should be applied.
- Powdered materials contains a considerable amount of air; under pressure this air is expelled and fairly dense piece is formed. More time is allowed for this air to escape.
- The compressed slugs are comminuted in desired mesh screen.
- Lubricant is added twice : i.e.
  1. During blending with other powders and
  2. Added to the granulations
- The lubricant is blended gently with the granulation and is compressed into tablets

(ii) *Chilsonator roller compactor*

- Chilsonator consists of two grooved rollers. Powder is flowed into the grooves and compressed mass is produced as the rollers rotates.
- Distance between two rollers can be adjusted.
- By the impeller always the air is removed from the powder mass.
- By using oscillatory granulator granules are prepared and lubricant is blended with the granules and compressed into tablets.

Advantages of chilsonator over tablet press

1. Very high production rate
2. Pressure can be controlled
3. Lubrication is not required in the primary stage.

Using a tablet press	Using a chilsonator
Powder + Lubricant	Powders
↓	↓
Slugs	Slugs
↓	↓
Granules	Granules
↓	↓
Lubricated	Lubricated
↓	↓
Compressed	Compressed

Hence, in a chilsonator only once lubricant is used. Since lubricants, such as talc, magnesium stearate etc. are hydrophobic in nature they will

(i) Impart problem in in-vitro disintegration

(ii) Compaction will not be efficient due to the decrease in inter-particular cohesive force.

Advantages of dry granulation over wet granulation

1. No application of moisture (required in wet granulation) and heat (for drying). So the drugs susceptible to either moisture or heat or both can be made by dry granulation. E.g. calcium lactate cannot be used by wet granulation. (Aspirin, Vitamin C)
2. Dry granulation involves less steps and hence less time is required than that of wet granulation.
3. Less steps requires less working space and energy.

Since popularity of wet granulation is more that dry granulation because former will meet all the physical requirement for the compression of good tablets.

Example of dry granulation

Preparation of Aspirin tablets

Ingredients	Quantity required per tablet	Remarks
Aspirin (#20 mesh)	325.0 mg	Active ingredient
Starch (dried)	32.5 mg	Diluent / Disintegrant
Cab-o-sil	0.1 mg	Lubricant

Method:

Aspirin + Starch + Cab-o-sil

10 mins ↓ mixed in twin-shell blender for 10 mins

Powder blend

↓ Compressed into slugs of 1 inch diameter flat-face punch

Slugs

↓ Size reduction by Oscillatory granulator

Granulation (# 16 mesh)

↓

Compressed

N.B. All operations are carried out in a dehumidified area at a relative humidity less than 30% at 70^0F (21.1^0C).

DIRECT COMPRESSION

Steps:

Milling
↓
Weighing
↓
Sieving
↓
Blending
↓
Compression

Advantages: (i) It is much quicker than any of the previous process
(ii) Minimum number of steps are required.

Modified diluents, binders etc. are available in the market which assure spherical shape of the granules to modify flow property. However, they are not used extensively.

1. If active medicament is less in amount then there will be no problem but in case of high dose large amount of active ingredient is to be replaced by specially treated vehicles to improve flow property or compressibility.
2. These specially treated materials are costly.

Example **Vitamin B1 tablets**

Ingredients	Quantity for each tablet	Remarks
Thiamine hydrochloride	100 mg	Active ingredient
Avicel PH 102	83.35 mg	Glidant
Lactose (anhydrous)	141.65 mg	Diluent
Mg-stearate	6.65 mg	Lubricant
Cab-o-sil	1.65 mg	Lubricant

Method:

Vitamin B1 + Avicel + Lactose + Cab-o-sil
↓
Mg-stearate + Mixture
↓ Mixed for 5 minutes
Compressed

N.B. Anhydrous lactose can be replaced with Fast Flo lactose which will reduce the requirement of glidant (Avicel).

PROBLEMS FACED IN TABLETING

1. CAPPING AND LAMINATION

Capping is the partial or complete separation of the top or bottom crowns of a tablet from the main body of the tablet.

Lamination is the separation of tablet into two or more distinct layers.

Usually these problems are apparent immediately after compression, or even hour or days later.

Detection: Subjecting tablets to the friability test is the quickest way to reveal such problems.

(a) **Reason:** Entrapment of excess air in the granules during compression. If the granules are light and fluffy this type of problems are encountered frequently.

Remedies: Increasing the density of granules by adding more binder or changing the solvent of binder.

(b) **Reason:** New set of punches and dies are very tightly fitted; i.e. the clearance is very negligible hence air cannot come out.

Remedy: In that case punch diameter should be reduced by 0.005" (i.e. 5 thou)

(c) **Reason:** Granules should not be completely dried. If over dried or under dried then capping may take place.

Remedy: So moisture content should be kept within 1 – 2%.

(d) **Reason:** Concave punches, used for longer period of time will form claw-shaped curve – this forms capping.

Remedy: Punches are changed.

2. PICKING AND STICKING

Picking and sticking are the removal of surface materials from a tablet by sticking to the punch faces.

Picking: When some portion of the surface of the tablet is removed – it is termed as picking.

Cause: When punch tips have engraving or embossing, usually of letters B, A, O are difficult to manufacture cleanly. These may produce picking.

Remedy: (i) Lettering should be designed as large as possible, particularly on punches of small diameter.

(ii) Plating of the punch faces with chromium produces smooth, non-adherent face.

(iii) Colloidal Silica (Cab-o-sil) is added as polishing agent that makes the punch faces smooth; so that material does not cling to them.

Sticking: Sticking refers to tablet materials adhering to the die wall.

***Disadvantages*:**

1. When sticking occurs, additional force is required to overcome the friction between tablet and the die wall during ejection.
2. Serious sticking at ejection can cause chipping of a tablet's edges and can produce a rough edge.
3. Also, a sticking problem does not allow the lower punches free movement and therefore can place unusual stresses on the cam tracks and punch heads, resulting in their damage.
4. Sticking can also cause build-up of material on punch faces.

***Causes*:**

1. Excessive moisture may be responsible for sticking.

Remedy: Further drying of the granulation is then required.

2. During compression heat is generated and

(a) Low m.p. lubricants e.g. stearic acid may produce sticking.

Remedy: Low melting point lubricant are replaced with high melting point lubricants (e.g. Poly ethylene glycol)

(b) Low m.p. substances, either active ingredients or additives may soften sufficiently form the heat of compression to cause sticking.

Remedies:

- Dilution of active ingredient with additional high m.p. diluents.
- Increase in the size of tablet.
- If a low m.p. medicament is present in high concentration then refrigeration of the granules and then compressing may be the order.

3. MOTTLING

Mottling is an unequal distribution of color on a tablet, with light or dark patches in an otherwise uniform surface.

Cause: Migration of water soluble dyes to the surface while drying.

Remedies:

- Change the solvent system.
- Change the binder system
- Reduce the drying temperature
- Grind to a smaller particle size.
- *** Use lakes instead of water soluble dyes.

QUALITY CONTROL OF COMPRESSED TABLET

Quality control of compressed tablet can be done by

(i) Official methods and

(ii) Unofficial methods.

1. WEIGHT VARIATION (Official)

This test is based on the fact that, if the weight variation is not much then it can be said that *the amount of medicament will not vary considerably*. Conversely, if the weight variation is larger then it can be concluded that the active medicament will also vary considerably.

Sources of weight variation

Weight variation is solely dependent on the poor flow property of granules and filling of die cavity.

Poor flow properties arise from: (a) improper lubrication

(b) Size of granules

(c) Adjustment of lower punch.

Weight variation test

The U.S.P. weight variation test is run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if

"Not more than 2 tablets are outside the percentage limit and if No tablet differs by more than 2 times the percentage limit."

N.B.

Say 20 tablets weighed separately

Percentage limit is ± 10%.

Say the average weight was 100 mg.

Then the sample of tablets will pass the USP weight variation test if

18 tablets remain within 90 mg to 110 mg and

2 tablets remain within 80 mg to 120 mg.

The weight variation tolerance for uncoated tablets differ on average tablet weight.

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	± 10
130 to 324	± 7.5
More than 324	± 5

N.B. Weight of tablets: $w_1, w_2, w_3, wn.., w20$.

Average weight of the tablets = $\overline{w}$

So the weight variation of n^{th} tablet = $\frac{\left(\left|\overline{w} - w_n\right|\right)}{\overline{w}}$ x 100%

2. CONTENT UNIFORMITY TEST

N.B. Weight variation test is applicable when the amount of medicament in the tablet is high. In potent drug the medicament is less in amount in comparison to the other excipients. The weight variation may meet the Pharmacopoeial limitation but this will not ensure the correct variation of potency. Hence, in this case the weight variation test is followed by content uniformity test.

Content uniformity test

In this test 30 tablets are randomly selected for sample, and at least 10 of them are assayed individually according to the official assay method.

Nine of the 10 tablets must have potency within ± 15 % of the labeled drug content. Only one tablet may be within ± 25%.

If this conditions are not met then the tablets remaining from the 30 must be assayed individually and none may fall outside ± 15% of the labeled content.

N.B. For example:

30 tablets are taken at random
10 tablets are assayed individually
In which 8 tablets remained within ± 15%
And 2 tablets remained within ± 15 % and ± 25 %.
So the test has to be carried out with rest of the 20 tablets.
And those 20 tablets must remain within ± 15%.
Conclusion: Out of the 30 tablets the potency of only 2 tablets may remain within 15 to 25 % rest of all the tablets should remain within ±15%.

3. TABLET HARDNESS

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness.

Method:

A tablet is taken between the 2nd and 3rd finger and pressing it with the thumb as fulcrum. If the tablet breaks with a "sharp snap", yet, it does not break when it falls on the floor – is said to possess proper hardness.

Instruments used:

1. Monsanto Hardness Tester
2. Strong Cobb Hardness Tester — Manual mode of operation are more or less similar
3. Pfizer Hardness Tester
4. Schleuniger Apparatus – Operates without manual involvement.

Hardness of a tablet:

The hardness at which the tablet crushes is the hardness of the tablet.

Unit of hardness: Kg/sq.in. Or lb/ sq.in

Limit: Generally maximum 5 kg/sq.in. Hardness is required.

N.B.

- If the tablets are too hard then it may not meet tablet disintegration test.
- If the tablets are too soft then it may not with stand the handling, packaging and shipping operations.

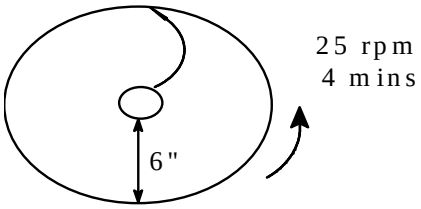
4. FRIABILITY

Tablet hardness is not an absolute indicator of strength since some formulations, when compressed into very hard tablets may produce chipping, capping and lamination problems. Therefore another measure of tablet strength i.e. friability is often measured, i.e. the friability.

Instrument: ROCHE FRIABILATOR

Objective of friability test:

This apparatus is designed to evaluate the ability of the tablet to withstand abrasion, in handling, packaging and shipping operation.



Roche Friabilator

Method:

Few tablets, previously weighed are taken in the plastic chamber of the laboratory friability tester. In the plastic chamber the tablets are subjected to abrasion and shock by rotating the plastic chamber at 25 rpm for 4 mins (i.e. total 100 revolutions). The tablets are dusted and reweighed.

Limit

For conventional compressed tablet the weight loss should be within 0.5 to 1.0 %.

5. DISINTEGRATION TEST OF TABLETS (Official)

For most tablets, the first important step toward solution is breakdown of the tablet into smaller particles or granules – this process is known as disintegration.

- The time a tablet takes to disintegrate is the disintegration time.

USP disintegration test apparatus

The USP device to test disintegration uses glass tubes with the following dimensions:

Number of tubes = 6
Length = 3 inches
Upper end open, lower end closed with #10 mesh screen.

To test the disintegration time one tablet is placed in each tube, and the basket rack assembly is positioned in a 1-litre beaker of water, simulated gastric fluid or simulated intestinal fluid, at $37^0C \pm 2^0C$, such that the tablet remain 2.5 cm from the bottom of the beaker.

A standard motor moves the basket up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cpm (cycles per minute).

Perforated plastic discs may also be placed on top of the tablets to impart an abrasive action to the tablets. They are useful for tablets that float.

- USP disintegration test will be passed if all the tablets disintegrate and the particles passed through the #10 mesh screen within the specified time. If any residue remains, it must have a soft mass with no palpable firm core.
- Disintegration time is suggested for 5 minutes for uncoated Aspirin tablets. Majority of the uncoated tablets have maximum disintegration time (DT) of 30 minutes.
- Enteric coated tablets shows no evidence of disintegration after 1 hr in simulated gastric fluid. The same tablets are then tested in simulated intestinal fluid and are to disintegrate in 2 hrs plus the time specified in the monograph.

6. DISSOLUTION TEST

Why is it required?

1. Disintegration test simply identifies the time required for the tablet to break up under the condition of the test but it does not ensure the drug release in the bulk of the fluid.
2. Rate of dissolution is directly related to the efficacy of the drug.
3. Rate of dissolution is a good index for comparing the bioavailability of two tablet products of the same drug.

USP XX / NF XV, Supplement 3 specifies two apparatus for dissolution test.

1. Apparatus - I

In general, a single tablet is placed in a small wire mesh basket and immersed in the dissolution medium (as specified in the monograph) contained in a 1000 ml flask at $37^0 \pm 0.5^0C$. Generally it is rotated at 50 rpm unless otherwise specified.

2. Apparatus 2

The same equipment is used. Instead of basket a paddle is introduced as the stirring element. The tablet is allowed to sink at the bottom of the flask before stirring.

Limit: A value of $t_{90\%}$ (i.e 90% drug release) within 30 minutes is often considered satisfactory and is an excellent goal since a common dissolution tolerance in the USP/NF is not less than 75% dissolved in 45 minutes.

TABLET COATING

Reasons behind coating of tablets:

The reasons behind coating of tablets are as follows:

1. To mask the taste, odour or colour of the drug. Improving the product appearance, particularly where there are visible differences in tablet core ingredients from batch to batch.
2. Provide physical protection, facilitates handling, particularly in high speed packaging / filling lines.
3. To provide chemical protection from its surrounding environment (particularly air, moisture and light).
4. To control the release of drug from the tablet e.g. sustained release tablets, repeat action tablets.
5. To protect the drug from the gastric environment of the stomach with an acid resistant enteric coating.

Tablet properties (or Core properties)

Tablets that are to be coated are called core. This core must possess the proper physical characteristics.

1. In pan coating process the core tablets roll in the pan or cascade in the air stream in air suspension coating. To endure the intense attrition between tablets or wall of the pan the tablets must have enough hardness.
2. Sugar coating can mask the imperfection on the surface but film coating cannot, hence, for film coating the core surface must be smooth.
3. The tablets must be in constant motion during the early drying phase or tablet agglomeration may occur. The ideal shape for coating is a sphere; the worst shape is a square flat-faced tablet and in practice rounded, convex shaped tablet cores are taken.
4. For coating materials to adhere to the tablet the coating composition must wet the surface of the core. E.g. hydrophobic tablet surfaces are difficult to coat with aqueous-based coating.

TABLET COATING PROCESSES

Two types of tablet coating are popular –
(i) Sugar coating and (ii) film coating.

SUGAR COATING OF COMPRESSED TABLETS

The sugar coating process can be subdivided into six main steps:

1. Sealing
2. Subcoating
3. Smoothing (Syruping)
4. Color coating
5. Polishing and
6. Printing

1. Sealing

Objectives	(i) To prevent moisture penetration into the tablet core, a seal coat is applied. (ii) To strengthen the tablet core without a seal coat, the over wetted tablets would absorb excess moisture, leading to tablet softening, and may affect the physical and chemical stability.

Ingredients	• Alcoholic solutions of Shellac (10 – 30% solid) or • alcoholic solution of zein, • alcoholic solution of cellulose acetate phthalate (CAP) or • Alcoholic solution of polyvinyl acetate phthalate. N.B. • With aging the disintegration and dissolution time is found to increase with shellac due to polymerization • Zein is an alcohol soluble protein derivative obtained from corn (maize).

2. Subcoating

Objectives	To round the edges and build up the tablet size. Sugar coating can increase the tablet weight by 50 to 100% at this step.
Method	The subcoating step consists of alternately applying a sticky binder solution to the tablets followed by a dusting of subcoating powders and then drying. Subsequent coatings are applied in the same manner until the tablet edges have been covered and the desired thickness is achieved.
Ingredients	• Binder solution formulations for subcoating:- Gelatin 3.3%(w/w) Gum acacia (powder) 8.7%(w/w) Sucrose 55.3%(w/w) Water to 100%(w/w) • Dusting powder formulation Calcium carbonate 40.0%(w/w) Titanium dioxide 5.0%(w/w) Talc (asbestos free) 25.0%(w/w) Sucrose powder 28.0%(w/w) Gum acacia powder 2.0%(w/w)

3. Smoothing or syruping

Objectives	To cover and fill in the imperfections in the tablet surface caused by the subcoating step.
Ingredients	Simple syrup solution (approximately 60 – 70 %(w/w)). Often the smoothing syrups contain a low percentage of titanium dioxide (1 – 5%) as an opacifier. This gives a very bright and reflective background for the subsequent coloring step.

4. Colour coating

Objective	To impart an elegant and uniform colour.
Ingredient	Syrup (60 – 70% sucrose) containing the desired color.
Method	Syrup solutions containing the dyes are coated upto 60 individual applications until the desired color is achieved. After each application of color the coatings are dried. In the finishing step a few clear coats of syrup may be applied.

5. Polishing

Objective	To produce the desired luster on the surface of the tablet.
Ingredients	Mixtures of waxes (like beeswax, carnauba wax, candella wax or hard paraffin).
Method	Either this mixtures of waxes are applied as powder or as dispersions in various organic solvents in a polishing pan (canvas line pan).

6. Printing

In order to identify sugar-coated tablets often it is necessary to print them, using pharmaceutical grade ink, by means of a process of offset rotogravure.

FILM COATING

Film coating adds 2 to 5% to the tablet weight.

Film coating can be done by the following three methods.

(i) **Pan-pour method:**

Viscous coating materials are directly added from some container into the rotating pan moving with the tablet bed. Tablets are subjected to alternate solution application, mixing and then drying.

Disadvantages:

- The method is relatively slow.
- It relies heavily on the skill of the operator.
- Tablets always require additional drying to remove the latent solvent.
- Aqueous film coating are not suitable for this method because localized over wetting will produce physicochemical instability.

(ii) **Pan-spray method:**

Coating material is sprayed over the tablet bed from nozzles and hot air is passed through the tablet bed to dry it.

The variables to be controlled is pan-spray film coating process are:

(a) Pan variables:

Uniform mixing is essential to deposit the same quantity of film on each tablet.

1. *Pan design or baffling*:

Some tablet shapes mixes freely while other shapes may require a specific baffling arrangement to ensure adequate mixing.

Disadvantages: Baffles may produce chipping and breakage if not selected properly.

(b) Pan speed

Pan speed affects mixing and the velocity at which the tablet pass under the spray.

- Too slow speed cause localized over-wetting resulting in tablets sticking to each other or to the pan.
- Too high speeds may not allow enough time for drying before the same tablets are reintroduced to the spray. This results in a rough coating appearance on the tablets.
- Optimum pan speed: 10 – 15 rpm for nonaqueous film coating
  3 – 10 rpm for aqueous film coating.

(c) Spray variables

1. Rate of liquid application
2. Spray pattern
3. Degree of atomization

These three spray variables are interdependent.

For spraying two types of systems are there:

(a) High-pressure, airless system and

(b) Low-pressure, air atomization system.

- The proper rate of liquid application depends on the mixing and drying efficiency of the system and the coating formula.
- A band of spray should be spread evenly over the tablet mass. In larger pans, more nozzles must be added to cover the tablet bed width.

A spray pattern that is too wide will apply coating on the pan.

A spray pattern that is too narrow will produce localized over-wetting.

Spray width can be adjusted by moving the nozzles closer or further away from the tablet bed.

- Atomization is the process where by the liquid stream is finely subdivided into droplets. The degree of atomization (i.e. the size and size-distribution of the droplets). Too fine atomization causes some droplets to dry before reaching the tablet surface, resulting in roughness on the tablet surface and

excess dust in the pan. Too large atomization causes localized over-wetting – leads to sticking, picking or a rough "**orange peel**" effect.

(d) Process air variables (temperature, volume, and rate) are required for optimum drying of the coating by evaporation of the solvent.

The balance between the supply and exhaust air flow should be such that all the dust and solvent are confined within the coating system.

(iii) **Fluidized bed process** (air suspension coating)

This process have been successfully used for rapid coating of tablets, granules and capsules. Process variables are as follows:

(a) Chamber design and air flow rate controls the fluidization pattern.
(b) Tablet shape, size and density.
(c) Volume and rate of air flow
– Too high rate produce attrition and breakage of tablets
– Too low rate → mass does not move fast enough through the spray region → over-wetting occurs.
(d) Inlet and exhaust air temperature.

DEVELOPMENT OF FILM COATING

Before coating a tablet the coating formula is first cast on either a glass, Teflon or aluminium foil surface. Glass is preferred for cast films. The coating is done by spreading with a glass rod. After drying, the cast films are assessed for the following properties:

(i) Physical appearance – potential colorant or opaquant separation is noted.
(ii) Lack of color uniformity
(iii) Insoluble additives have been properly suspended or not.
(iv) Water vapor permeability
(v) Film tensile strength

MATERIAL USED FOR FILM COATING

Film formers

Nonenteric materials : e.g.	Hydroxypropyl methylcellulose (HPMC) Methylhydroxy ethyl cellulose (MHEC) Ethylcellulose (EC) Hydroxypropyl cellulose (HPC) Polyvinyl pyrrolidone (PVP) Sodium carboxymethyl cellulose (Sod. CMC) Polyethylene glycols (PEG) Acrylate polymers e.g. Eudragit E
Enteric materials: e.g.	Cellulose acetate phthalate (CAP) Acrylate polymers (Eudragit L, S) Hydroxypropyl methylcellulose phthalate (HPMCP) Polyvinyl acetate phthalate (PVAP)

Solvents

Criteria

1. It should either dissolve or disperse the polymer system.
2. It should easily disperse other coating solution components into the solvent system.
3. Small concentration of polymers (2 to 10%) should not result in an extremely viscous solution system (> 300 cps), creating process problems.

4. It should be colorless, tasteless, odourless, inexpensive, non-toxic, inert and non-inflammable.
5. It should have no environmental impact.

Colorants: Same as tablet.

Opaquant extenders:

Very fine inorganic powders e.g.

		Titanium dioxide (TiO_2)
Silicates	like	talc, aluminium silicate
Carbonates	like	magnesium carbonate
Sulfates	like	calcium sulfate
Oxides	like	magnesium oxide and
Hydroxides	like	aluminium hydroxides.

Miscellaneous coating solution components

Flavors and sweeteners
Surfactants are used to solubilize immiscible or insoluble ingredients
Antioxidants
Antimicrobial agents.

FILM DEFECTS

Variations in formulation and processing conditions may result in unacceptable quality in the film coating. Some of the problems are as follows:

Picking

Overwetting or excessive film tackiness or when the drying system is inefficient – tablets stick to each other or to the coating pan. On drying, at the point of contact, a piece of the film may remain adhered to the pan or to another tablet, giving a "**picked**" appearance to the tablet surface and resulting in a small exposed area of the core tablet.

Remedy:

- A reduction in the liquid application rate or,
- Increase in the drying air temperature and air volume usually solve this problem.
- If excessive tackiness is there then the formulation is changed.

Roughness

A rough or gritty surface is a defect often observed when the coating is applied by spray. Some of the droplets may dry too rapidly before reaching the tablet bed, resulting in droplets on the tablet of "spray dried" particles instead of finely divided droplets of coating solution.
Roughness also increases with pigment concentration and polymer concentration.

Remedy

- Moving the nozzle closer to the tablet bed
- Reducing the viscosity of coating solution.

Bridging and filling

During drying, the film may shrink and pull away from the sharp corners of a bisect, resulting in "bridging" of the surface depression.

This defect may be so severe that the monogram or the bisect is completely obscured.

This is a problem in the formulation.

Remedy

- Increasing the plasticizer amount in the formulation
- Changing the plasticizer can decrease the incidence of bridging.

Filling: If the solution is applied too fast, over-wetting may cause the liquid to quickly fill and be retained in the monogram – this is called filling.

Remedy

- Judicious monitoring of the fluid application rate, and
- Thorough mixing of the tablets in the pan prevent filling.

Blistering

When coated tablets require further drying in ovens, too rapid evaporation of the solvent from the core and the effect of high temperature on the strength, elasticity and adhesion of the film may result in blistering.

Remedy Milder drying conditions are adopted.

Hazing / Dull film (Bloom)

It can occur when too high a processing temperature is used for a particular formulation. It is particularly evident when cellulosic polymers are applied out of aqueous media at high processing temperatures.
It can also occur if the coated tablets are exposed to high humidity conditions and solution of film results.

Color variation

- Improper mixing, uneven spray pattern.
- Insufficient coating may result in color variation.
- The migration of soluble dyes, plasticizers, and other additives during drying may give the coating a mottled or spotted appearance.

Remedy

- Use of lake instead of dye.
- Changing the plasticizer and additives.

Cracking

Cracking occurs if the internal stresses in the film exceed the tensile strength of the film. The tensile strength of the film can be increased by using higher molecular weight polymers or polymer blends.

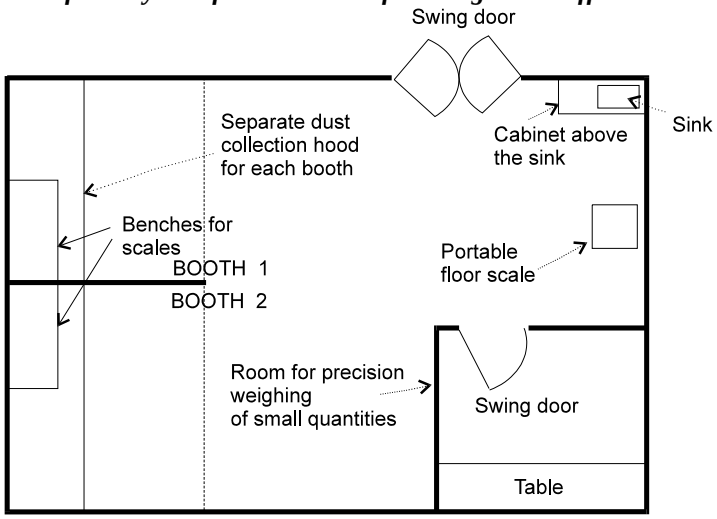
Internal stresses in the film can be minimized by adjusting the plasticizer type and concentration, and the pigment type and concentration.

Plasticizers

These are used to impart flexibility to the film.

e.g. Castor oil, propylene glycol, glycerin,
Polyethyleneglycol (PEG) 200 and 400,
Surfactants e.g. polysorbates (Tweens), Sorbitan esters (Spans) and organic esters.

1. **Ques:** ***Draw a sketch of the layout of a tablet manufacturing unit. Differentiate between capsule unit and this.***



Chemical Weighing Room
(Schematic)

TABLETS DOSAGE FORM IMPORTANT POINTS FOR GPAT EXAM

- 90% of drugs are in oral dosage form.
- Tablet is unit dosage form.
- Liquid dosage forms r given in dose of medication 5-30%.
- Tablet should have 2-4% of moisture.

EVALUATION

GENERAL APPEARANCE

- Size and shape – compressed tablets shape and dimensions are determined by the tooling during the compression process.

  Rem-when compression force is constant, tablet thickness varies with changes in die fill, with particle size distribution, packing of particle mix and tab. Weight.

  When die fill is constant, thickness varies with variation in compressive load.

* Crown thickness of tablet measured by Micrometer.
* Total crown thickness is measured by Vernier calliper.
* Tablet thickness should be controlled with ±5% of std. Value.
* The more the convex the tablet surface more is the capping problem so one has to use slower tablet machine or one with pre compression capabilities.
* Unique identification markings-given in Physicians' Desk Reference (PDR).
* Product code is given from National Drug Code (NDC).
* Mottling-non uniformity of colour over tablet surface.
* For colour quantification 3 methods-reflectance spectrophotometry, tristimulus colorimetry and micro-reflectance photometry.

Hardness and Friability

- Hardness of tablet directly effects dissolution behaviour.
- It is the force req. to break the tablet in diametric compression test.
- Hardness also called crushing strength.

➢ **Devices used**

* Monsento tester (stockes tester)-easy to handle. Manually operated, gives strength in kgs.
* Strong-cobb tester-force applied by hydraulic pressure and later air pressure not manually. It gives value 1.6 times higher than the original strength.
* It gives strength in kgs.
* Pfizer tester-same principle as pair of pliers.(kgs)
* **Two testers to eliminate operation variations:-**

  1. Erweka tester-gives strength in Kgs.

  2. Schleuniger tester-operates in horizontal position-gives strength in KGs and Strong Cobb units.

- Hardness and thickness of tablet is a function of die fill and compression force.
- At constant compression force, hardness increase with increasing die fill.
- At constant die fill, hardness increase and thickness decrease when compression force is applied.
- Roche friabilator machine is used for measuring friability of tablet.
  Tablets fall from-6 inch distance
  Total RPM -25, Total revolutions – 100, Time - 4 minutes
  Limits- ***0.5-1.0% (USP), not more than 1% (IP).***
- Effervescent tablets and chewable tablets show higher friability value than above so stack packaging for them.
- Vickers test is used to measure the surface hardness.
- 'Whiskering' phenomenon is related with tablets with deeply concave surfaces or punches used were in poor condition and such tablets have higher than normal friability values.

HARDNESS LIMITS

TABLET	HARDNESS LIMIT
SOFT	2 KG
SUSTAINED RELEASE	8 KG
GENERAL	4 KG
HARD	6 KG
EFFERVESCENT	1.3 KG

STANDARD HARDNESS SHOULD BE MIN. 4 KG

Webster and Van Abbe tester-indicate edge damage during handling.

➢ WEIGHT VARIATION

- Total tablets taken-**10.**
- Limits -Tablets meet USP if not more than 2 tablets are outside the limit and no tablet should differ by more than 2 times the original limit.
- This test is used if the tablet contains 90-95% API. It is not appropriate for low dose containing tablets. API should be more than 50mg. (i.e-potency).
- For these content uniformity test is used.

USP LIMITS

AVERAGE WT OF TABLETS(MG)	MAX. % DIFF. ALLOWED
130 or less	10
130-324	7.5
More than 324	5

I.P LIMITS

AVERAGE WT OF TABLETS (MG)	MAX. % DIFF. ALLOWED
80 or less	10
80-250	7.5
More than 250	5

➢ CONTENT UNIFORMITY TEST:

- It should be between **95-105%.**
- Tablet potency for this test should be less than **50mg.**
- For digitoxin it is **90-110%.**
- If larger wt. Variation, no good content uniformity.

Test:

→ Total tablets-30

→ Total assayed-at least 10

→ 9 of the tablets should contain 85-115% API.

→ 10^{th} tablet may contain 75-125% API. Test passed

→ If above conditions not met other 20 tablets should be assayed, and no one should fall outside **85-115%** range.

➢ DISINTEGRATION

APPARATUS

- → **6 test tubes**
- → Mesh size: 10 mesh i.e 1.7mm (USP), 8 mesh i.e 2mm (IP)
- → Glass tubes are **3 inches** long
- → Beaker contains 1L of water, simulated gastric fluid or simulated intestinal fluid.
- → Temperature: **37±2 degree** Celsius. (Remember with reference to difference with dissolution)
- → Tablets remain 2.5 cm below surface of liquid on upward movement and vice versa.
- → No. of cycles per minute: 28-32

IP LIMITS

Tablet/Capsule	Liquid	Disintegration time(min)
Uncoated tablet	Water	15 min (USP-30 min)
Sugar coated	Water	60 min
Enteric coated	0.1N HCl with phosphate buffer	2 hr in gastric fluid media and 1 hr in intestinal fluid(USP it is reverse)
Film coated	Water or 0.1N HCl	30 min
Vaginal tablets	Water	30 min
Soluble, dispersible and effervescent tablets	Water (19-21 deg. Celcius)	3 min
Hard gelatin capsules	Water	15 min
Soft gelatin capsules	Water	60 min

➢ DISSOLUTION

USP

Apparatus 1-Basket type

Mesh screen-10 mesh (USP)

Temperature: **37±0.5** degree Celsius. **900** ml flask.

Apparatus 2-paddle type

900 ml. Flask.

Contains wire helix to prevent tablet from floating.

Limits (USP)

→ Not less than 75% should be dissolved in 45 min.

→ 90% of the drug should be dissolved in 30 min.(this is not USP limit, it is industrial limit)

→ Above both values are Q values.

→ Dissolution acceptance criteria(IP)

Stage	No. Of dosage units tested	Acceptance criteria
S1	6	No dosage unit is less than Q+5%.
S2	6	Average of 12 dosage units is equal to or not more than Q% and no unit is less than Q-15%.
S3	12	Average of 24 dosage units is equal to greater than Q% and not more than 2 dosage units are less than Q-15% and no dosage unit is less than Q-25%.

TABLET COMPRESSION APPARATUS

- Dies define shape and size of tablet.
- Cam tracks guide the movement of punches.
- Multi-station presses are called rotary presses.
- Turrets-the portion of the head that hold the upper and lower punches.
- Fette machines-they chill the compression components to allow compression of low melting solids such as waxes use (in case of suppositories0.

TOOLING

- BB tooling-most commonly used.length-5.25 inch,
- Nominal barrel diameter-0.75 inch, 1 inch head diameter.
- B tooling-5.25 inch, nominal barrel diameter-3 $^{9/16}$ inch, 1 inch head diameter.
- D tooling-used for larger tablets. 5.25 inch,
- Nominal barrel diameter-1 inch, 1.25 inch head diameter.
- Dwell time-time for which tablet remains under compression.
- Remember-Devices which measure compression force at each compression station.
  - → Pharmakontroll,
  - → Killiani Control System,
  - → Thomas Tablet Sentine

➢ PROCESSING PROBLEMS IN TABLET

1) Capping and lamination-capping is partial or complete separation of top or bottom parts of tablet from main body of tablet.

Lamination is separation of tablet into 2 or more distinct layers. It is due to:-

- → Deformational properties of formulation i.e plastic deformation
- → Deep concave punches.
- → Absence of adequate moisture.
- → Tablet tooling
- → Incorrect setting of press.

2) Picking and sticking- Picking occurs due to engraving and embossing.

In sticking tablet material sticks to die wall.

3) Mottling- uneven distribution of color on tablet.

4) Weight Variation

5) Poor flow- Talc or colloidal silica helps in improving the flow.

Poor flow can result in bridging, arching and rat holling.

6) Poor mixing

7) Punch variation

8) Hardness variation

9) Double impression

➢ TABLET GRANULATION

- → It improves flow properties of tablet.
- → Shape factor of granule should be 6 just like sphere for good flow.
- → The method used for measurement of surface area solid granules or particles are air permeability method and gas-adsorption method (He gas is used).
- → Dense granules require higher compression force to form cohesive compact and they are less friable.
- → For determining granule density-Mercury displacement method is used.
- → Other method uses benzene as organic solvent.
- → As granule size increase bulk density decreases.
- → As particle becomes more spherical bulk density increases.
- → The strength of tablet is mainly due to surface tension of liquid and capillary forces.
- → For measuring granule strength and friability ASTM (American Society for Testing Materials) specification is taken into account and compression strength are taken into account.

➢ **TYPES OF GRANULATION**

➢ **DRY GRANULATION**

- Also called compression granulation.
- Used when drug is sensitive to moisture.
- Slugs are formed in this.so process also called slugging.
- Roller compactor instrument is used. Can produce 500 kg of slugs.
- Main advantage is that no need to use excess lubricants.

❖ **WET GRANULATION**

* Granules formed by adhesive forces.
* Surface tension forces and capillary pressure are initially responsible for wet granulation.
* Solvents are used considering EPA (Environmental Protection Agency) regulations.

EQUIPMENTS FOR WET GRANULATION

1. **Littleford Lodige mixer**- ***Capable of both wet massing and blending.***
   → Time taken-30-60 sec.
   → Horizontal in operation.
   → Temperature rise of 10-15 deg. is expected.
2. **Diosna mixer or granulator**- ***contains bowl in vertical position.***
   → Total time 11-12 min.
3. **Littleford MGT mixer**- ***vertical in operation***.
4. **Gral mixer**- ***Modification of planetary mixer (IMP).***

- **DIRECT COMPRESSION**

* Eg. NaCl, KCl can be directly compressed.
* Uses directly compressible diluents like spray dried lactose.
* They have good flow and compressibility.
* Maximum of 30% of API is used in direct compression tablet.

➢ **TABLET INGREDIENTS**

- **DILUENTS:**
  * Used to increase bulk of tablet.
  * 5-80% can be used.

* All the sugar containing diluents have tendency to undergo reaction with drugs containing –NH2 group. This is called ***Maillard reaction*** which only changes color not content.

STARCH

→ 11-14% moisture present

→ Dried starch has 2-4% moisture.

→ Their moisture level increase to 6-8% following moisture exposure.

→ Two types:

1) **Directly compressible starch (Sta-Rx 1500)-**used as diluents, binder and disintegrant. Contains 10% of moisture.
2) **Hydrolysed starch** (Emdex, Cellutab: contain 90-92% dextrose and 3-5% maltose)- directly compressible. Used in chewing tablets and have 8-10% of moisture.

LACTOSE

Three types of lactose.

1) **Alfa-lactose monohydrate -** Crystalline nature, has 5% moisture, poor flow and compressibility and used in wet granulation. ***It gives Maillard reaction.***
2) **Spray dried lactose -** <3% moisture. Good flow and compressibility. Used in direct compression.it gives Maillard reaction. (In Maillard reaction furfuraldehyde is formed).
3) **B-lactose (anhydrous) -** hygroscopic. Used in direct compression and does not gives Maillard reaction.

DEXTROSE

→ Also called cerelose.

→ Can be used instead of lactose.

MANNITOL

→ Used in chewable tablet due to negative heat of solution.

→ Non-hygroscopic.

→ Non-cariogenic.

→ Used in vitamin formulations.

SORBITOL

→ Optical isomer of mannitol.

→ Hygroscopic.

SUCROSE

Available as co-processed form such as

SUGARTAB (90-95% sucrose + 7-10% invert sugar),

DIPAC (97%sucrose + 3% modified dextrin)

NUTAB (95%sucrose + 4% invert sugar + Mg. stearate + corn starch).

Used in direct compression.

Hygsroscopic

Important point-Kaolin and bentonite, diluents, is not used with cardiac glycoside, synthetic estrogens and alkaloids.

MICROCRYSTALLINE CELLULOSE (MCC)

- Trade name- **AVICEL**
- DIRECTLY COMPRESSIBLE
- Two grades: **PH 101(powder) and PH 102(granules)**
- Also act as disintegrating agent.
- Hygroscopic in nature.
- May delay the release of drug.

DICALCIUM PHOSPHATE (DCP)

- Non-hygroscopic (Just like mannitol)
- Moisture sensitive drugs can be used with it
- ***Not used with tetracycline due to complex formation.***

CLASSIFICATION IN OTHER WAY

- **Wet granulating diluents-** alfa lactose, kaolin, bentonite, dicalcium sulphate
- **Direct compression-** Spray dried lactose, colloidal silica, NaCl and NaHCO3 for dental cones, direct com. starch.
- **Binders and adhesives**

Used to provide cohesive qualities.

More the binder, harder is the tablet.

NATURAL GUM

- *Acacia and tragacanth* are examples
- Used in 10-25%

GELATIN

- Natural protein
- 10-20% in solution form.
- Upon storage disintegration time will increase with the use of such binders Starch
- 10-20%solution.
- Give translucent paste.
- It undergoes hydrolysis to dextrin and glucose.
- Liquid glucose is 50%solution in water.

Modified natural polymers

- Methylcellulose (alcohol soluble, more soluble in cold water than hot water)
- Hydroxy propylcellulose HPC (alcohol sol.)
- Hydroxy propyl methylcellulose HPMC (water soluble)
- Ethylcellulose EC (alcohol soluble, retard D.T)
- PVP (polyvinyl pyrrolidone) used in 2%.used in aqueous and alcoholic solution.
- IPA (isopropyl alcohol)-widely used binder.

➢ **ANOTHER CLASSIFICATION**

→ **Solution binders-** Starch, Sucrose, Gelatine, Acacia, Tragacanth.

→ **Dry binders-** HPMC. Cross linked PVP.

➢ **LUBRICANTS**

→ Decrease friction between diewall and tablet surface

→ Can be used intragranularly (PEG, Vegetable oils) and extragranularly (talc, stearates).

→ They are hydrophobic in nature.

→ Fluid lubricant-liq. Paraffin

→ Boundary lubricant-stearic acid

➢ **What is bolting of lubricant?**

Lubricant is passed through 60-100 mesh nylon cloth in order to get fine particles this is called bolting of lubricant.

→ Hydrocarbon/mineral oil

→ Applied as fine spray.

→ Mostly used for aspirin tablets

→ Calcium and Mg. Stearate

→ used in 1%

→ may cause delay release

→ Mg.stearate is used with SLS due to its hydrophobic property.

→ It is not used with acidic drugs

➢ **COMPRITOL 888**

→ It is glyceryl monoester of behenic acid.

→ Water soluble lubricants

→ Sodium Benzoate, sodium acetate, NaCl, leucine, PEG etc.

➢ **GLIDANTS**

1) TALC

→ Used in 5%.

→ Can also be used as anti-adherent.

→ Contains traces of iron so may act as catalyst for the drugs which are degraded by Fe.

→ Also contain calcium so not used with tetracycline.

2) COLLOIDAL SILICA

Available in 3 forms

1. Cab-o-sil (<1%)
2. Aerosil (0.25-3%)
3. Syloid.

3) CORN STARCH

→ Use in 5-10%

DISINTEGRANTS

➢ Facilitate breaking up of tablet Act by 3 mechanism

1. **By swelling -** Alginate, starch dye, PVP
2. **By wetting -** SLS, Clay, Bentonite
3. **Effervescent -** NaHCO3 and citric acid

EXAMPLES

STARCH

- → 5-20%
- → Modified starches are used which are: Primogel and Explotab.
- → they are low substituted carboxymethyl starches.(1-8% used, but 4%is optimum)

➢ **CLAYS**

- → Veegum (Mg. Aluminium silicate) (10%)
- → Bentonite (10%)
- → both are used only for colored tablets
- → They are most effective in sulfathiazole tablets.

➢ **SUPER DISINTEGRANTS**

- → They are used in lower concentration. of **2 % to 6 %,**
- → while traditional disintegrants such as starches often require concentrations of about 20 %.

VIVASTAR® Sodium Starch Glycolate		EXPLOTAB® Sodium Carboxymethyl Starch
VIVASOL® Croscarmellose Sodium		EMCOSOY® Soy Polysaccharides

- → Primojel®, sodium starch glycolate, and Primellose®, croscarmellose sodium, which show outstanding disintegration characteristics for tablets prepared by direct compression, wet granulation and for capsule formulations.

COLORING AGENTS

- → Lake are the dyes that have absorbed on hydrous oxide
- → As coloring concentration increases, mottling increases.
- → To improve photosensitivity of dye use of UV absorbing chemical such as benzophenone can be used.

❖ **DI-PACLINE is a commercially available directly compressible sugar.**

SWEETENERS

- → Used in (0.5-0.75%)
- → Cyclamates can be used.
- → *Cyclamates is 70 times sweeter than sugar. But are carcinogenic*
- → Aspartate (phenyl ester of methylacetic acid).
- → *Aspartam180-200 times sweeter than sugar and non-carcinogenic.*
- → Saccharin is carcinogenic and 500 times sweeter than sugar.
- → *Mannitol is used in chewable tablets and 72 times sweeter than sugar.*

SOME INSTRUMENTS

MIXING

- ➢ **For large qt. Of powder-twin-**
  - → Shell blender
  - → Double-cone blender,
  - → Planetary mixer.
- ➢ **For continuous production**
  - → Ribbon blender
  - → Rotocabe-blender
- ➢ **Mass mixer**
  - → Sigma blade mixer
- ➢ **High speed granulators**
  - → Diosna mixer,
  - → Littleford MGT,
  - → Gral mixer
- ➢ For continuous production extruders are used E.g. *Reitz extruders*
- ➢ *Topo granulators* to prepare granules under high vaccum.
- ➢ Spheronization refers to formation of spherical particle from wet granulation.
- ➢ *Marumerizer and CF-granlator* are used for Spheronization.

- ➢ **SPRAY CONGEALING/SPRAY CHILLING**
- → *It is the process consist of melting solid and reducing them to beads or powders by spraying molten feed into stream of colder air or gases.*
- → Monoglycerides are spray congealed at **50 deg F**
- → Carbohydrates are spray congealed at **167 deg F**

- **IMPORTANT INFORMATION**

→ Versa press is used for the preparation of layered tablets.

→ Manestey dry cota instrument is used.

→ Implantation tablets should have size of less than 8mm.

→ *Kern-injector-contain hollow needle and plunger.*

→ *It is used for administration of rod shaped tablet.*

→ For sub-lingual and vaginl tablets, lactose is used as diluent.

CAPSULES

Syllabus:

Principles, materials and equipment involved in the formulation and filling of hard gelatin capsules and their quality requirements, layout of capsule section. Account of soft gelatin capsules.

DEFINITION

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin.

Advantages of capsule dosage forms

1. They obscure the taste and odour of unpleasant drugs.
2. They are attractive in appearance.
3. They are slippery when moist and, hence, easy to swallow with a draught of water.
4. If properly stored, the shells contain **12-15% of moisture** which gives flexibility and, consequently very considerable resistance to mechanical stresses (cf. cachets).
5. Less adjuncts are necessary than tablets.
6. The contents are usually in fine powder which combined with adjuncts, provides rapid and uniform release of medicament in the GIT.
7. The shells can be opacified with TiO_2 or coloured to give protection from light.
8. The shells are physiologically inert and easily and quickly digested in the GIT.
9. Presentation of a drug in capsules, rather than in tablets, allows quicker submission of a new drug for clinical trials, because fewer development problems are involved. Also it is easier to vary the dose.

Disadvantages of capsule dosage forms

1. Capsules are not used for administering extremely soluble materials such as potassium chloride, potassium bromide, or ammonium chloride since sudden release of such compounds in the stomach could result in irritation.
2. Capsules should not be used for highly efflorescent or deliquescent materials.
   - Efflorescent materials may cause the capsules to soften.
   - Deliquescent materials may dry the capsule shell to excessive brittleness.

MATERIALS

Capsules are made principally of gelatin blends and may contain small amounts of certified dyes, opaquing agents, plasticizers and preservatives.

To modify the solubility of the capsules (e.g. to impart enteric property) methyl cellulose, polyvinyl alcohols and denatured gelatin are used.

GELATIN

- Gelatin is a heterogeneous product derived by irreversible hydrolytic extraction of treated animal collagen (obtained from animal skin and bone).
- Common sources of collagen are animal bones, hide portions, and frozen pork skin.
- There are mainly two types of gelatin commercially available:

Type A: Gelatin is derived mainly from pork skin by acid treatment. This gelatin has an isoelectric point in the region of pH 9.

Type B: Gelatin is derived from bones and animal skins by alkaline processing (pH 4 – 5).

B Dry bone → 5% HCl → Lime 10% → Lime → pH
10 - 15 days 4-8 weeks removal adjustment

B Calf skin → wash → Lime 10% → Water wash
6-12 weeks

A Pork skin → wash → Acid 1-5% HCL Acid removal
10-30hrs

Hot water → Filter → Vacuum → Cool to → Air dry → Mill
Extraction concentration solidify to size.

Blends of Gelatin A and Gelatin B are used.

- Bone gelatin produces a tough, firm film, but tends to be hazy and brittle.
- Pork skin gelatin contributes plasticity and clarity to the blend, hence bone gelatin and pork skin gelatin are generally used in blends.

Method of production of empty hard gelatin capsule shells

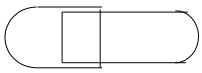
1. Hundred and fifty (150) pairs of stainless mold pins (on which capsule is formed) are dipped into a gelatin sol (melted gelatin) of carefully controlled viscosity to form the caps and bodies simultaneously.
2. The pins are usually rotated to distribute the gelatin uniformly during which time the gelatin may be set or gelled by a blast of cool air.
3. The pins are moved through a series of controlled air drying kilns for the gradually and precontrolled removal of water.
4. The capsules are stripped from the pins by bronze jaws and trimmed to length by stationary knives while the capsule halves are being spun in chucks or collets.
5. After being trimmed to exact length, the cap and body sections are joined and ejected from the machine.

The entire cycle of the machine lasts approximately 45 minutes.

CAPSULE SHAPE

1. Simple telescoping hard gelatin capsules Body moves easily inside the cap

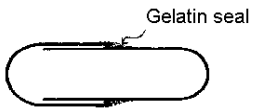
Disadvantages



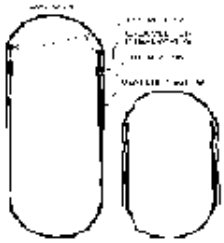
(a) Body can come out of the cap easily spilling over the powder inside.

(b) In high speed capsule filling machines capsules may split and/or denting of the capsule shell may occur.

2. Gelatin seal fuses the two capsule halves to create a one-piece capsule that is tamper proof.



3. in the body:-



(a) Tapered rim is provided to prevent splitting / denting.

(b) Grooves which interlock the two halves together once the capsule has been filled.

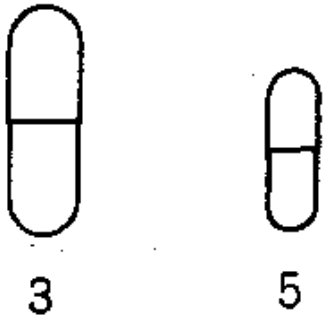
(c) Indentations to prevent premature opening.

CAPSULE SIZE

Empty gelatin capsules are manufactured in various sizes, varying in length, in diameter, and capacity.

Their capacities vary with the bulk-density of the contents and the pressure applied during filling.

For human use, empty capsules ranging in size from 000, the largest, to 5, the smallest are commercially available.



CAPSULE NUMBER AND VOLUME FILL IN IT

Capsule No.	000	00	0	1	2	3	4	5
Approx. Vol (ml)	1.50	0.90	0.75	0.55	0.40	0.30	0.25	0.15

CAPSULE FILLING EQUIPMENT

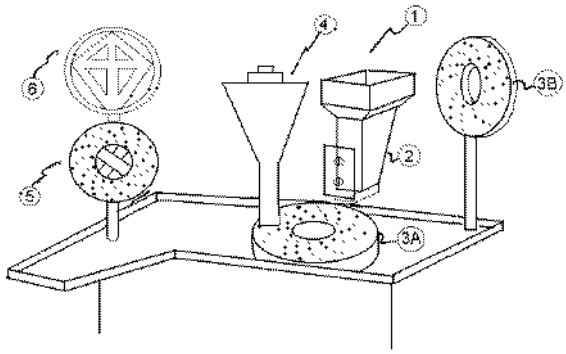
There are several equipment available in the market but they may be classified into two classes depending on the mode of operation.

- **Lily**, Parke-Davis, Höfliger and Karg, Osaka and Perry
- **Zanasi**, Macofar, Farmatic and mG2 equipment

LILY TYPE CAPSULE FILLING EQUIPMENT

Number of operators required = 1

Number of capsule output = 200,000 capsules / day



(a) The empty capsules are fed from the storage hopper (1) and through the rectifying unit (2), into the two-piece filling ring (3A and 3B). Rectification is based on dimensional differences between the outside diameters of the cap and body portions of the capsule.

(b) As the ring (3A and 3B) is rotated, a vacuum is applied on its underside. The vacuum sucks the bodies into the lower half of the ring, while the caps are retained in the upper portion. The two pieces of the ring are separated, and the cap-containing portion is placed aside.

(c) The body containing portion of the ring is placed on a variable speed turntable and is mechanically rotated under the powder hopper (4), which contains an auger for the forced delivery of the powder.

(d) After one (or more) complete rotations of the rings, the powder hopper (4) is removed, and the two segments of the ring (3A and 3B) are rejoined.

(e) The intact ring is positioned in front of the peg ring (5) and the closing plate (6) is pivoted to a positioned approximately 180^0 from the position showed in the figure. Pneumatic pressure is applied to the peg ring (5), which forces the caps in position.

(f) After opening the closing plate 96) the capsules are ejected through the portion of the ring by giving slight hand pressure against the peg ring.

(g) The filled capsules are collected through the chute (7) into a collection chamber.

- Highest turntable speed: minimum total fill weights
  Maximum weight variation
- Lowest turntable speed: maximum total fill weights
  Minimum weight variation

ZANASI CAPSULE FILLING MACHINE

- No. of operators required = 0 (automatic)
- No. of capsules output = 4000 to 150,000 capsules / hr.
- In this type of equipment the empty capsule shells come down from hopper through individual tubes and rectified. The capsule shells are seated in a holder with the body downward. Vacuum assists its placement.
- Another vacuum is applied over the top of the holder to separate the cap from the body of the capsule.
- The cap containing half is moved aside. The lower part of the holder is exposed for filling.
- The powder is continuously mixed within the powder hopper and is maintained at a constant level prior to change.
- A set of volumetric dosing nozzles, each of which picks up the product from the constant level container, first compressing and then ejecting the powder into the capsule bodies.
- The cap holder half is repositioned over the block and closing is accompanied by both upper and lower closing pins.
- Ejection is accomplished by compressed air.

PREPARATION OF FILLED HARD GELATIN CAPSULES

The preparation of filled hard gelatin capsules may be divided into the following steps.

1. Developing and preparing the formulation and selecting the size of the capsule.
2. Filling the capsules shells.
3. Cleaning and polishing the filled capsules.

CAPSULE FORMULATION

In developing a capsule formulation, the goal is to prepare a formulation that results in accurate dosage, good bioavailability characteristics, and ease of capsule filling during production.

(a) To achieve uniform drug distribution throughout the powder mix the density and particle size of the drug and excipients should be similar.

If required the particle size may be reduced by milling.

Then the drug and excipients are blended thoroughly to get a uniform powder mix.

(b) The powder mix must provide the type of flow characteristics required by the equipment.

- In case of **Lily** type equipment powder must be *free flowing* e.g. with acetyl salicylic acid flowable *corn starch* is used.
- In case of **Zanasi** type equipment powder must have sufficient cohesiveness to retain its slug form during delivery to the capsules. E.g. with acetyl salicylic acid compactible excipients such microcrystalline cellulose are required.
- Lubricant such as, magnesium stearate can be used in Lily type and binders like mineral oil can be used in Zanasi type capsule filling equipments.

(c) Selection of capsule size.

(i) When the dose of the drug is large and the diluent is not required or negligible in quantity, the size may be selected after the development and preparation of the formulation.

(ii) When the capsule is meant for young or elderly patients the capsule size (smaller size) is selected first and then formulation is prepared. If required the dose may be divided into two capsules.

(iii) A properly filled capsule should have its body filled with the drug mixture and its cap fully extended down the body – a capsule size should be selected to meet this requirement.

FILLING THE CAPSULE SHELLS

(a) Manual punch method

For filling a small number of capsules in a dispensary pharmacists generally use punch method.

- Precise number of empty hard gelatin capsule shells are taken.
- The powder is taken on a clean sheet of paper or glass or porcelain plate. With a spatula a cake is formed with the powder having a height of approximately 1/4 to 1/3 the length of the capsule body.
- Then the empty capsule body is held between thumb and forefinger and "punched" vertically into the powder cake repeatedly until filled. The capsule bodies are capped.
- After capping the capsules are weighed to ensure accurate filling.

(b) Filling can be done by hand-operated capsule filling machine, Lily and Zanasi type capsule filling machines.

Lily is semi-automatic and Zanasi is fully automatic.

[For details see the equipment - how they are filled]

CAPSULE SEALING

To make the capsules "tamper evident" (previously the term was "tamper resistant") two types of sealing processes are there

(i) *Banding*: The two capsule parts are sealed with a gelatin or polymer band at the seam of the cap and body.

(ii) The contact areas of the cap and body are wetted with a mixture of water and ethanol and then thermally bonded at 40 to 45^0C.

Capsule sealing equipment may be linked with capsule filling equipment to maintain production levels of upto 150,000 capsules per hour per unit.

CLEANING AND POLISHING

After filling some powder formulation may adhere to the outside of the capsules. This powder

- may be bitter or unpalatable,
- May reduce the appearance of the capsule.

Methods of cleaning

1. *Pan polishing*: The Accela-Cota tablet coating pan may be used to clean and polish capsules. A *polyurethane* or *cheese cloth* liner is placed in the pan, and the liner is used to trap the removed dust as well as to impart a gloss to the capsules.

2. *Cloth dusting*: In this method, the bulk filled capsules are rubbed with a cloth that may not be impregnated with an inert oil. Though it is a hand operation but by this method

(a) large volume of capsules can be polished,

(b) Powders too resistant to remove by other methods can be removed easily by this method.

(c) It imparts a somewhat improved gloss to the capsules.

3. *Brushing*: In this procedure, capsules are fed under rotating soft brushes, which serve to remove the dust from the capsule shell. This operation is accompanied by a vacuum for dust removal.

e.g. **ROTOSORT**– it removes loose powder,
Removes unfilled joined capsules
Removes capsules with loose caps

Erweka KEA – dedusting and polishing

Scidenader PM60 – for cleaning and polishing

SOFT GELATIN CAPSULES

Advantages of soft gelatin capsules:

(i) Soft gelatin capsules are useful when it is desirable to seal the medication within the capsule.

(ii) The capsules are especially important to contain liquid drugs or drug solutions.

(iii) Also, volatile drug substances or drug materials especially susceptible to deterioration in the presence of air may be better suited to a soft gelatin capsule than hard gelatin capsules.

(iv) Soft gelatin capsules are elegant and are easily swallowed by the patients.

CAPSULE SIZES AND SHAPES

Shape	Diagram	Size range (number represents the nominal capacity in minims (1 cc = 16.23 minim)
Round		1,2,3,4,5,6,7,9,28,40,90,
		40T,80T
Oval		1,2,3,4,5,6,7.5,10,.12,16,20,30,40,60,80,85,110.
Oblong		3,4,5,6,8,9.5,11,14,16,20,90,360
Tube		55,65,90,160,250,320,480

MATERIALS

The capsule shell is basically composed of gelatin, a plasticizer and water. It may contain additional ingredients such as preservatives, coloring and opacifying agents, flavours, sugars, acids and medicaments to achieve desired effects.

GELATIN

The gelatin should be of USP grade and it should have some additional specifications, namely, bloom strength, viscosity and iron content of the gelatin used.

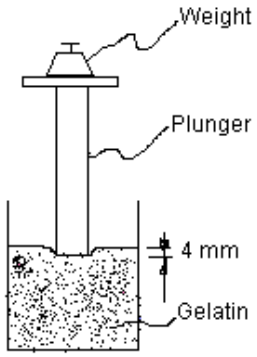
Bloom or gel strength

It is a measure of the cohesive strength of the cross-linking that occurs between gelatin molecules and is proportional to the molecular weight of the gelatin.

Determination

6 2/3 % gelatin gel kept at 10^0C for 17 hours

A plastic plunger having diameter 0.5 inch.



Bloom strength = the weight (in gram) required to move the plastic plunger in the Gelatin mass upto 4 mm.

- Normally for soft-gelatin capsules the bloom strength of gelatin required ranges from 150 to 250 g.

In general with all the other factors being equal, the higher the Bloom strength of the gelatin used, the more physically stable is the capsule shell.

- Cost is, in general, proportional to Bloom strength; hence, higher Bloom strength gelatins are only used when necessary to improve the physical stability of the product or large capsules (over 50 minims).

Viscosity of gelatin

Viscosity of a 6 2/3 % gelatin in water solution at 60^0C is a measure of the molecular chain length and determines the manufacturing characteristics of the gelatin film.

General range of viscosity 25 to 45 mill poise, it may be within narrow range 38 ± 2 millipoise.

Iron content

Iron is always present in new gelatin, and its concentration usually depends on the iron content of the large quantities of water used in its manufacture.

Limit: Gelatin used for soft gelatin capsules should not contain more than 15 ppm of iron.

Disadvantages:

(i) Iron may react with the certified dyes.

(ii) It may react with organic compounds to produce color (e.g. with phenolic compounds).

PLASTICISERS

Very few plasticisers are used for soft gelatin capsules

(i) Glycerin USP

(ii) Sorbitol USP or

(iii) A combination of glycerin and sorbitol

The ration by weight of dry plasticiser: dry gelatin determines the 'hardness' of the gelatin shell.

TYPICAL SHELL HARDNESS AND THEIR USES.

Hardness	Ratio of Dry glycerin / Dry gelatin	Usage
Hard	0.4 / 1	Oral, oil-based, or shell-softening products and those destined primarily for hot humid areas. Oral, tube, vaginal
Medium	0.6 / 1	Oil-base, water-miscible-base, or shell hardening products and those destined for temperate areas (hot & humid areas) Tube, vaginal
Soft	0.8 / 1	Water-miscible base or shell hardening products and those destined primarily for cold, dry areas.

ADDITIONAL COMPONENTS OF THE GELATIN MASS

Ingredients	Concentration	Purpose
Category-I		
Methyl paraben	0.2 %	Preservative
Propyl paraben (4 : 1)	q.s.	
FD&C and D&C water-soluble dyes, certified lakes, pigments, vegetable colours	0.2 to 1.2 % 0.1 %	Colorants
Titanium di-oxide	2 %	Opacifier
Ethyl vanillin, Essential oils		Flavor
Category-II		To produce chewable shell and taste
Sugar (sucrose)	to 5 %	Aids solubility reduces aldehydic
Fumaric acid	to 1 %	tanning of gelatin

NATURE OF THE CAPSULE CONTENT

Soft gelatin capsules can be used to dispense a variety of liquids, Solids, Combination of miscible liquids, Suspension of solids in liquids.

Selection of capsule size

The maximum capsules size and shape for convenient oral use in humans is the **20 minims oblong, 16 minims oval** or **9 minims round**

Types of liquids for encapsulation in soft gelatin capsules

1. Water, ethanol, and emulsion – these are water miscible or volatile components and they cannot be included as major constituents of capsule since they can migrate into the hydrophilic gelatin shell and volatile from the surface.
2. Gelatin plasticizers like glycerin, propylene glycol cannot be major constituents of capsules owing to their softening effect on the gelatin shell.
3. Upto 10% glycerin and / or propylene glycol can be used as co-solvents with PEG or other liquids that have a shell-hardening effect when capsulated alone.

Most widely used liquids for human comsumptions are

- Oil active ingredients e.g. clofibrate
- Vegetable oils e.g. soybean oil
- Mineral oil, non-ionic surfactants e.g. polysorbate 80 and PEG (400 and 600) either alone or in combination
- Fish oils in vitamin capsules.

Other conditions for manufacturing soft gelatin capsules

1. The suspension products must be homogeneous, air free and preferably should flow by gravity at room temperature but not a temperature above 35^0C because the sealing temperature of gelatin films is usually 37 to 40^0C.
2. pH should be in between 2.5 and 7.5, since preparations that are more acidic can cause hydrolysis and leakage of the gelatin shell, and preparations those are more alkaline can tan the gelatin and thus affect the solubility of the shell.

CAPSULE MANUFACTURING

***Plate process*:** It is the oldest process, contains sets of plates containing die packets.

Rotary die process

Reciprocating die process

Accogel machine is unique in that it is the only equipment that accurately fills **powdered dry solids** into soft gelatin capsules.

PROCESS

Gelatin preparation department

(i) Weighing of gelatin ┐
Weighing of other liquids → chilled at 7^0C ┘ → Mixed in Pony mixer

(ii) The resultant fluffy mixture transferred to melting tanks and melted under vacuum at 93^0C

(iii) A sample of the resulting fluid mass is visually compared with a color standard, and additional colorants are added if required.

(iv) The mass is then maintained at 57 to 60^0C before and during capsulation process.

Material preparation department

(i) *Blending* → milling or homogenization

Equipments: Homoloid mill
Stone mill
Hopper mill
Urschel comitrol

(ii) *Deaeration* →all mixtures are subjected to deaeration by

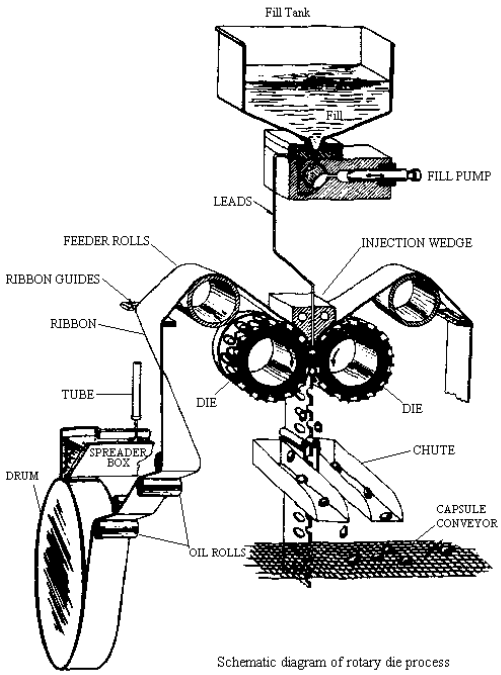
To achieve uniform capsule fill weight
And it reduces oxidation of the product.

Most liquids and suspensions may be deaerated by means of equipment designed to expose thin layers of the material continuously to a vacuum (29.5 mm Hg).

(iii) After deaeration the volatile ingredients are added and blended.

Material filling by rotary die process

- The gelatin mass is fed by gravity to a metering device (spreader box), which control the flow of the mass onto air cooled (13 to 14^{0}C) rotating drums. Gelatin ribbons of controlled thickness are formed. The wet film thickness may vary from 0.022 to 0.045 inch.
- The ribbons are fed through mineral oil lubricating bath, over guide rolls, and then down between the wedge and the die rolls.
- The materials to be encapsulated flows by gravity into a positive displacement pump. The pump accurately meters the material through the leads and wedges and into the gelatin ribbons between the die rolls. The bottom of the wedge contains small orifices lined up with the die pockets of the die rolls.



Schematic diagram of rotary die process

- The capsule is about half sealed when the pressure of the pumped material forces the gelatin into the die pockets, where the capsules are simultaneously filled, shaped, hermetically sealed, and cut from the gelatin ribbon. The sealing of the capsule is achieved by mechanical pressure on the die rolls and the heating (37 to 40^{0}C) of the ribbons by the wedge.
- Immediately after the manufacture, the capsules are automatically conveyed through a naphtha wash unit to remove the mineral lubricating oil.
- The washed capsules may be automatically subjected to a preliminary infrared drying step which removes 60 to 70% of the water that is to be lost, or may be manually spread directly on trays. All the capsules are allowed to come to equilibrium with forced air conditions of 20 to 30 % relative humidity at 21 to 24^{0}C.

PREFORMULATION

Definition:

Preformulation may be described as a phase of the research and development process where the preformulation scientist characterizes the physical, chemical and mechanical properties of a new drug substance, in order to develop stable, safe and effective dosage form.

Objectives:

The preformulation investigations confirm that there are no significant barriers to the compound's development as a marketed drug. The formulation scientist uses these informations to develop dosage forms.

Preformulation is a multidisciplinary development of a drug candidate. See TABLE-1

Principal areas of preformulation

1. **Bulk characterization**
   - (i) Crystallinity and polymorphism
   - (ii) Hygroscopicity
   - (iii) Fine particle characterization
   - (iv) Powder flow
2. **Solubility analysis**
   - (i) Ionization constant – pKa
   - (ii) pH solubility profile
   - (iii) Common ion effect – K_{SP}.
   - (iv) Thermal effects
   - (v) Solubilization
   - (vi) Partition coefficient
   - (vii) Dissolution
3. **Stability Analysis**
   - (i) Stability in toxicology formulation
   - (ii) Solution stability
     – pH stability profile
   - (iii) Solid state stability
     – Bulk stability
     – Compatibility

1. Bulk characterization

When a drug molecule is discovered all the solid-forms are hardly identified. So during bulk characterization the following characteristics are studied.

(i) Crystallinity and polymorphism

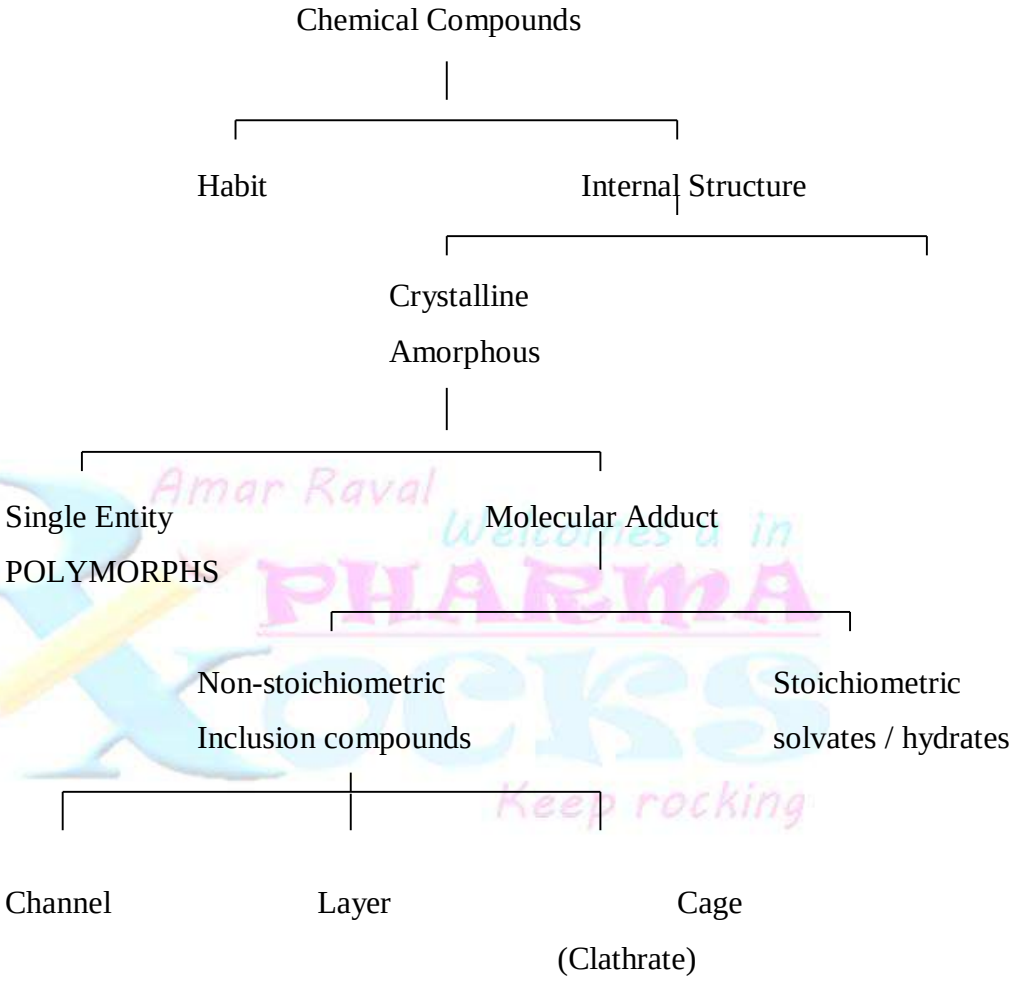
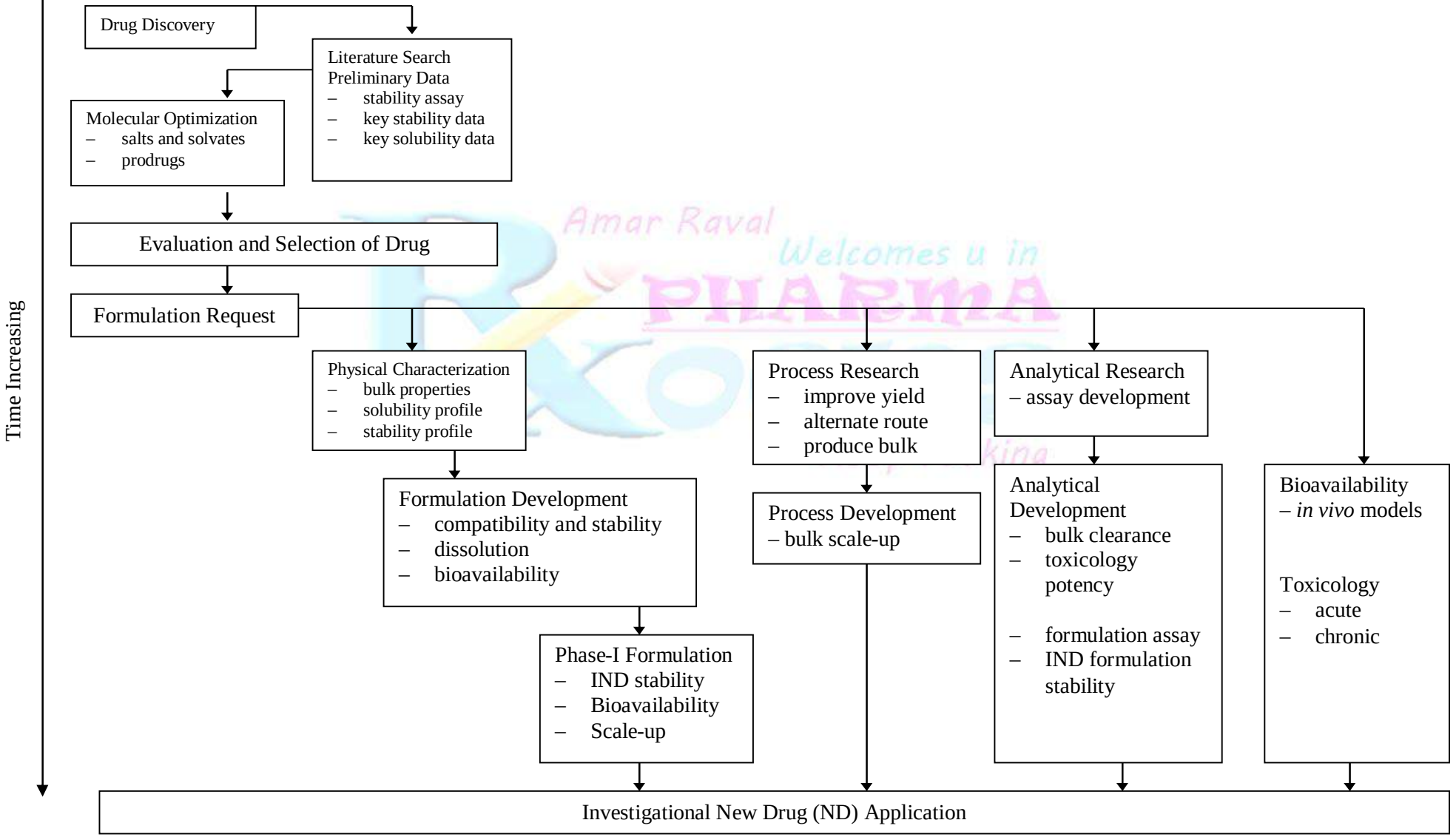


TABLE –1

Medicinal Chemistry And Pharmacology	Preformulation Research	Formulation Development	Process Research And Development	Analytical Research And Development	Toxicology and Drug Metabolism



- **Flowability of powder and chemical stability depends on the habit and internal structure of a drug.**

Habit is the description of the outer appearance of a crystal. A single internal-structure for a compound can have several different habits, depending on the environment for growing crystals. Different habits of crystals are given below.

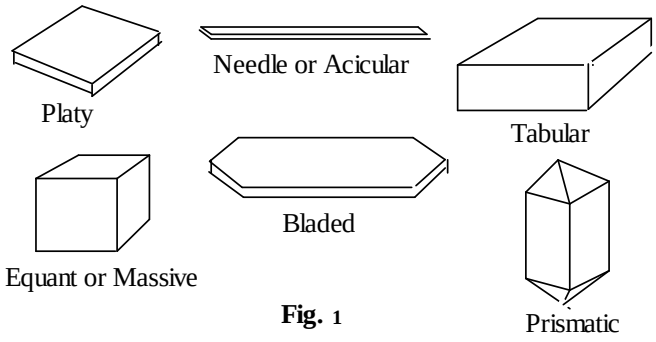


Fig. 1

Internal Structure

Crystalline state

In this state of matter atoms or molecules are arranged in highly ordered form and is associated with three-dimensional periodicity.

[N.B. Atoms or molecules tend to organize themselves into their most favorable thermodynamic state, which under certain conditions results in their appearance as crystals.
N.B. The repeating three-dimensional patterns are called crystal lattices. The crystal lattice can be analyzed from its X-ray diffraction pattern.]

Amorphous forms

In this forms the solids do not have any fixed internal structure. They have atoms or molecules randomly placed as in a liquid.
e.g. Amorphous Novobiocin
[N.B. Amorphous forms are prepared by rapid precipitation, lyophillization or rapid cooling of molten liquids e.g. glass]

DIFFERENCE BETWEEN CRYSTALLINE AND AMORPHOUS FORM

Crystalline forms	Amorphous forms
(i) Crystalline forms have fixed internal structure (ii) Crystalline forms are more stable than its amorphous forms. (iii) Crystalline forms are more stable than its amorphous forms. (iv) Crystalline form has lesser solubility than its amorphous form. (v) Crystalline form has lesser tendency to change its form during storage.	(i) Amorphous forms do not have any fixed internal structure (ii) Amorphous form has higher thermodynamic energy than its crystalline form. (iii) Amorphous forms are less stable than its crystalline forms. (iv) Amorphous forms have greater solubility than its crystalline forms. (v) Amorphous tend to revert to more stable forms during storage.

Polymorphs

When a substance exists in more than one crystalline form, the various forms are called Polymorphs and the phenomenon as polymorphism.

E.g. Chloramphenicol palmitate has three polymorphs A, B and C.

[N.B. various polymorphs can be prepared by crystallizing the drug from different drugs under diverse conditions. Depending on their relative stability, one of the several polymorphic forms will be physically more stable than the others. Such a stable polymorph represents the lowest energy state, has highest melting point and least solubility. The representing polymorphs are called metastable forms which represents higher energy state, the metastable forms have a thermodynamic tendency to convert to the stable form. A metastable form cannot be called unstable because if it is kept dry, it will remain stable for years.]

Molecular Adducts

During the process of crystallization, some compounds have a tendency to trap the solvent molecules.

1. Non-Stoichiometric inclusion compounds (or adducts)

In these crystals solvent molecules are entrapped within the crystal lattice and the number of solvent molecules are not included in stoichiometric number. Depending on the shape they are of three types:-

(1) ***Channel***

When the crystal contains continuous channels in which the solvent molecule can be included. E.g. Urea forms channel.

(2) ***Layers***: - Here solvent molecules are entrapped in between layers of crystals.

(3) ***Clathrates*** (**Cage**):- Solvent molecules are entrapped within the cavity of the crystal from all sides.

2. Stoichiometric inclusion compounds (or stoichiometric adducts)

This molecular complex has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice and has stoichiometric number of solvent molecules complexed.

When the incorporated solvent is water, the complex is called hydrates and when the solvent is other than water, the complex is called solvates. Depending on the ratio of water molecules within a complex the following nomenclature is followed.

(i) *Anhydrous* : 1 mole compound + 0 mole water

(ii) *Hemihydrate*: 1 mole compound + ½ mole water

(iii) *Monohydrate:* 1 mole compound + 1 mole water

(iv) *Dihydrate* : 1 mole compound + 2 moles water

Properties of solvates / hydrates

(i) Generally, the anhydrous form of a drug has greater aqueous solubility than its hydrates. This is because the hydrates are already in equilibrium with water and therefore have less demand for water. E.g. anhydrous forms of Theophyline and ampicillin have higher aqueous solubility than the hydrates.

(ii) Non aqueous solvates have greater aqueous solubility than the non-solvates. E.g. chloroform solvates of Griseofulvin are more water soluble than their nonsolvate forms.

ANALYTICAL METHODS FOR CHARACTERIZATION OF SOLID FORMS

Methods of studying solid forms are listed as below:

Method	Material required per sample
Microscopy	1 mg
Hot stage microscopy	1 mg
Differential Scanning Calorimetry (DSC)	2 – 5 mg
Differential Thermal Analysis (DTA)	2 – 5 mg
Thermogravimetric Analysis	10 mg
Infrared Spectroscopy	2 – 20 mg
X-ray Powder Diffraction	500 mg
Scanning Electron Microscopy	2 mg
Dissolution / Solubility Analysis	mg to gm

Microscopy

In this type of microscope light passes through cross-polarizing filters.

Amorphous substances (e.g. super-cooled glass and non-crystalline organic compounds or substances with cubic crystal lattices e.g. NaCl) have single refractive index. Through this type of microscope the amorphous substances do not transmit light, and they appear black. They are called isotropic substances.

Hot-stage microscopy

In this case, the polarizing microscope is fitted with a hot stage to investigate polymorphism, melting points, transition temperatures and rates of transition at controlled rates. It facilitates in explaining the thermal behavior of a substance from the DSC and TGA curves.

[N.B. A problem often encountered during thermal microscopy is that organic molecules can degrade during the melting process, and recrystallization of the melt may not occur, because of the presence of contaminant degradation products.]

Thermal Analysis

Differential Thermal Analysis

In DTA instrument a record is produced where temperature difference (ΔT) (between the sample and reference material) is plotted against temperature (T) when two specimens are subjected to an identically controlled temperature regime. The reference material is alumina, keiselguhr.

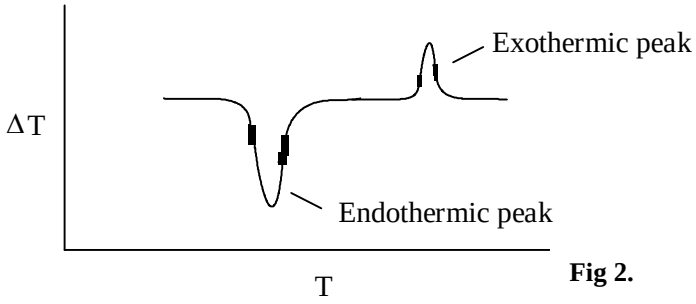


Fig 2.

Differential Scanning Calorimetry

In DSC method the difference in energy inputs (ΔH) into a sample and reference material is measured as a function of temperature as the specimens are subjected to a identically controlled temperature programme.

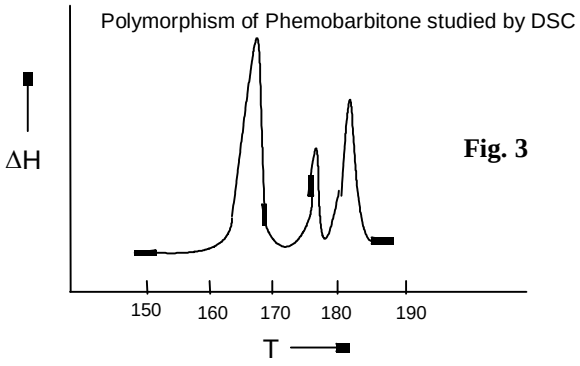


Fig. 3

Samples that may be studied by DSC or DTA are:

Powders, fibres, single crystals, polymer films, semi-solids or liquids.

Applications of DTA / DSC in preformulation studies

1. To determine the purity of a sample
2. To determine the number of polymorphs and to determine the ratio of each polymorph.
3. To determine the heat of solvation
4. To determine the thermal degradation of a drug or excipients.
5. To determine the glass-transition temperature (t_g) of a polymer.

Thermogravimetric Analysis (TGA)

TGA measures the changes in sample weight as a function of time (isothermal changes) or temperature.

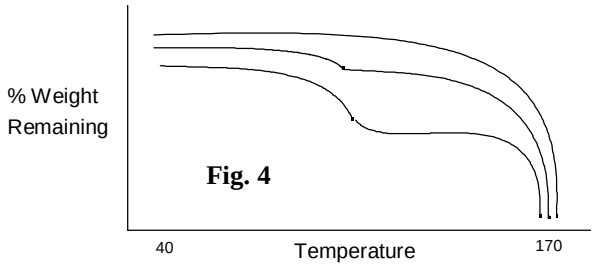


Fig. 4

Application of TGA in preformulation study

1. Desolvation and decomposition processes are monitored.
2. Comparing TGA and DSC data recorded under identical conditions can greatly help in the explanation of the thermal process.

TGA and DSC analysis of an acetate salt of an organic amine that has two crystalline forms, anhydrous and dihydrate are shown above. Anhydrous / dihydrate (10:1) mixture was prepared by dry blending. Heating rate was 5^0C/min.

From DSC curve, it is evident that the dihydrate form loses two molecules of water via an endothermic transition between 70^0C and 90^0C. The second endotherm at 155^0C corresponds to melting process.

From TA curve, it is evident that at 70 – 90^0C weight-loss was due to the loss two molecules of water and the weight loss at 155^0C was due to vaporization of acetic acid and decomposition.

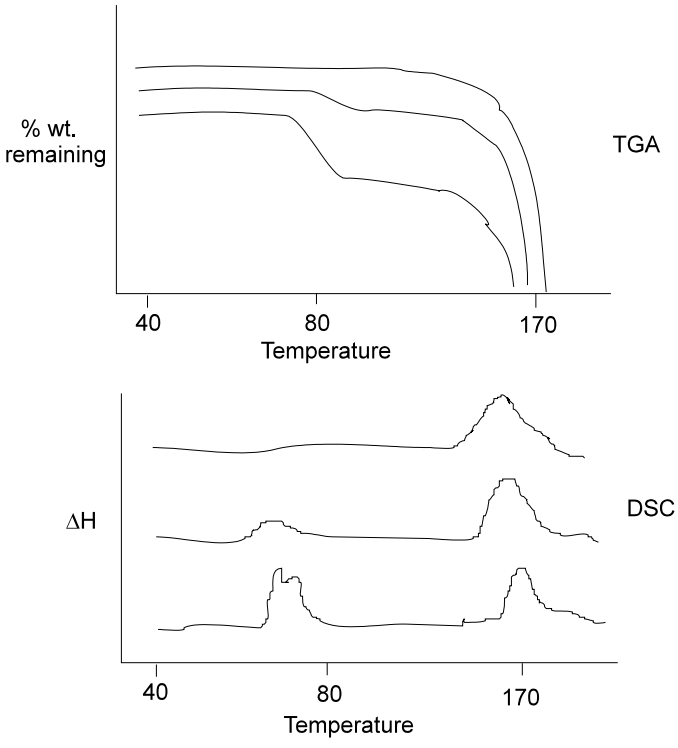


Fig. 5

X-RAY POWDER DIFFRACTION

When a X-ray beam falls on a powder the beam is diffracted. This diffraction in found only in case of crystalline powder. Amorphous forms do not show X-ray diffraction.

Uses:

(i) Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound. So in a mixture different crystalline forms can be analyzed using normalized intensities at specific angles.

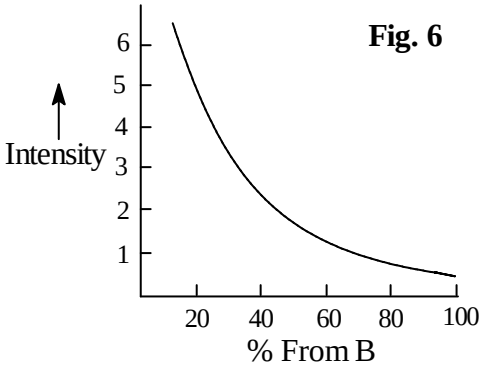


Fig. 6

(ii) Identification of crystalline materials by using their diffraction pattern as a 'finger print'. First, the powder diffraction photograph or diffractometer trace are taken and matched with a standard photograph. All the lines and peaks must match in position and relative intensity.

HYGROSCOPICITY

***Definition*:** Many pharmaceutical materials have a tendency to adsorb atmospheric moisture (especially water-soluble salt forms). They are called hygroscopic materials and this phenomenon is known as hygroscopicity.

Equilibrium moisture content depends upon:

(i) The atmospheric humidity
(ii) Temperature
(iii) Surface area
(iv) Exposure time
(v) Mechanism of moisture uptake.

***Deliquescent materials*:**

They absorb sufficient amount of moisture and dissolve completely in it.
(e.g. anhydrous calcium chloride).

Tests of hygroscopicity

Procedure

Bulk drug samples are placed in open containers with thin powder bed to assure maximum atmospheric exposure. These samples are then exposed to a range of controlled relative humidity (RH) environments prepared with saturated aqueous salt solutions.

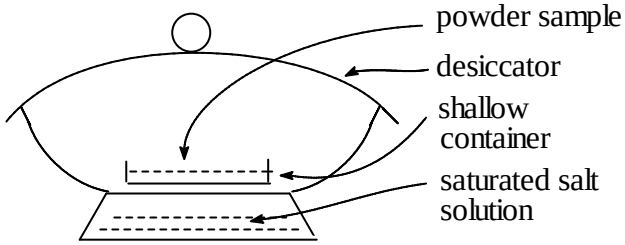


Fig. 7

The amount of moisture adsorbed can be determined by the following methods:

(i) Gravimetry

(ii) Thermogravimetric analysis (TGA)

(iii) Karl-Fischer titration (KF-titration)

(iv) Gas chromatography (GC)

Time of monitoring depends on the purpose:

(i) For the purpose of '*handling*' data points from 0 to 24 hours are taken

(ii) For the purpose of '*storage*' data points from 0 to 12 weeks are taken.

Significance of hygroscopicity test

(a)

Fig. 8

To decide special handling procedure (with respect to time).

(b)

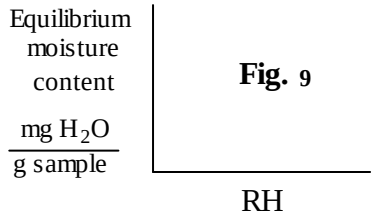


Fig. 9

To decide

(i) the storage condition i.e. at low humidity environment.

(ii) special packaging – e.g. with desiccant.

(c) Moisture level in a powder sample may affect the flowability and compactibility which, are important factors during tableting and capsule filling.

(d) After adsorption of moisture, if hydrates are formed then solubility of that powder may change affecting the dissolution characteristics of the material.

(e) Moisture may degrade some materials. So humidity of a material must be controlled.

FINE PARTICLE CHARACTERIZATION

Parameters those are measured:

(i) particle size and size-distribution

(ii) shape of the particle

(iii)surface morphology of the particles

Instrumental methods of particle size characterization

(i) Light microscope

First a standard graticule (BS 3625) is standardized with a stage micrometer. Then small number of particles are spread over a glass slide and placed on the stage of the microscope. Particles are focussed and the particle diameters are measured. Several hundred particles are measured and reported as a histogram.

Disadvantage: The procedure is time consuming.

(ii) Stream counting devices

Examples: (a) Coulter counter – electrical sensing zone method

(b) HIAC – counter – optical sensing zone

(c) Malvern particle & droplet sizer – Laser diffraction method.

***Procedure*:**

Samples prepared for analysis are dispersed in a conducting medium (e.g. saline) with the help of ultrasound and a few drops of surfactant (to disperse the particles uniformly). A known volume (0.5 to 2 ml) of this suspension is then drawn into a tube through a small aperture (0.4 to 800 μm diameter) across which a voltage is applied.

As each particle passes through the hole, it is counted and sized according to the resistance generated by displacing that particle's volume of conducting medium.

Size distribution is reported as histogram.

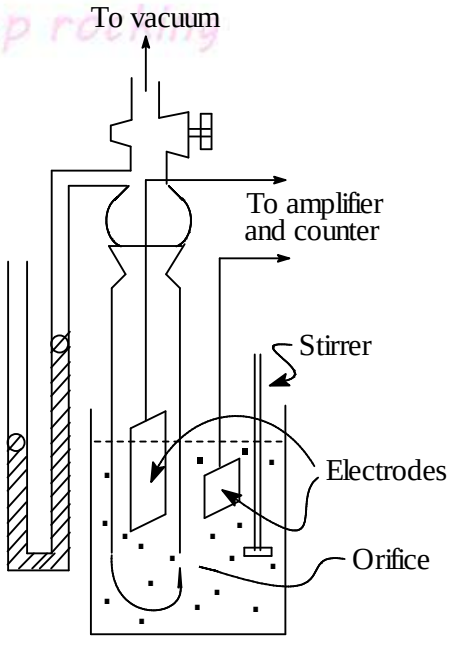


Fig. 10 Coulter counter

(iii) Sieve analysis

A powder sample is passed through a standard sieve set. The particle size is plotted against % weight retained on each sieve.

Use: This method is used generally for large samples.

Instrumental method for determination of specific surface area

Brunauer, Emmett and Teller (BET) nitrogen adsorption method:

A layer of nitrogen molecules is adsorbed to the sample surface at -196^0C. Once the surface is saturated, the sample is heated to room temperature, the nitrogen gas is desorbed, and its volume is measured and converted to the number of adsorbed molecules via the gas law. Since each N_2 molecule occupies an ara of 16 A^2, one may readily compute the surface area per gram of each pre-weighed sample.

Instrumental method for characterization of surface morphology

The scanning electron microscope creates the magnified images by using electrons instead of light waves. The images are black and white.

Procedure

- Biological materials are dried in a special way that prevents them from shrinking.
- Since SEM illuminates them with electrons, they are made conductive by coating with a very thin layer of gold by a machine called *sputter-coater*.
- The sample is placed inside the microscope's vacuum column through an airtight door.
- After the air is pumped out of the column, an electron gun emits a beam of high-energy electrons. This beam travels downward through a series of magnetic lenses designed to focus the electrons to a very fine spot.
- Near the bottom, a set of scanning coils moves the focussed beam back and forth across the specimen, row by row.
- As the electron beam hits each spot on the sample, secondary electrons are knocked loose from its surface.

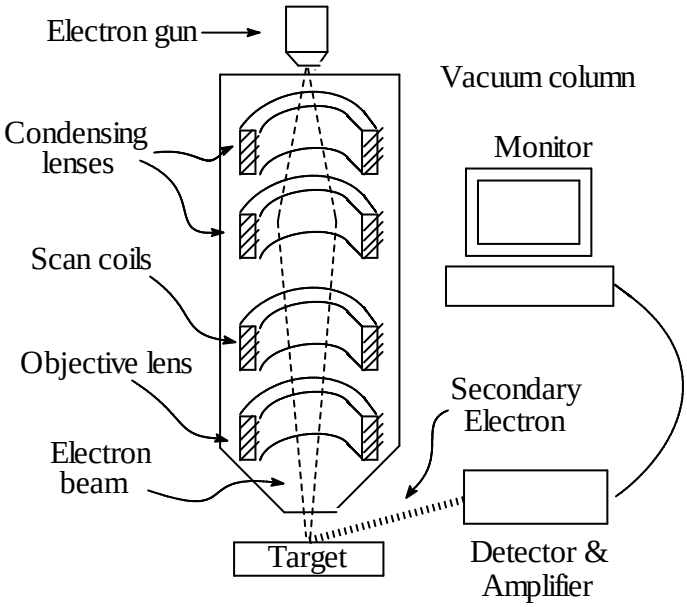


Fig. 11 Scanning Electron Microscope

- A detector counts these electrons and sends the signals to an amplifier.
- The final image is built up from the number of electrons emitted from each spot on the sample.

BULK DENSITY

Apparent Bulk Density (g/cm^3)

Bulk drug powder is sieved through 40 mesh screen. Weight is taken and poured into a graduated cylinder via a large funnel. The volume is called *bulk volume*.

$$Apparent\ Bulk\ \ Density = \frac{Weight\ of\ \ the\ powder}{Bulk\ Volume}$$

Tapped density (g/cm^3)

Bulk powder is sieved through 40 mesh screen. Weight is taken and poured into a graduated cylinder. The cylinder is tapped 1000 times on a mechanical tapper apparatus. The volume reached a minimum – called *tapped volume*.

$$Tapped\ density = \frac{Weight\ \ of\ \ the\ \ powder}{Tapped\ \ volume}$$

True density (g/cm^3)

Solvents of varying densities are selected in which the powder sample is insoluble. Small quantity of surfactant may be mixed with the solvent mixture to enhance wetting and pore penetration. After vigorous agitation, the samples are centrifuged briefly and then left to stand undisturbed until floatation or settling has reached equilibrium.

The samples that remains suspended (i.e. neither suspended not floated) is taken. So the true density of the powder are equal. So the true density of the powder is the density of that solvent. The density of that solvent is determined accurately with a pycnometer.

Source of variation of bulk density

Method of crystallization, milling, formulation.

Methods of correction

By milling, slugging or formulation.

Significance

(i) Bulk density

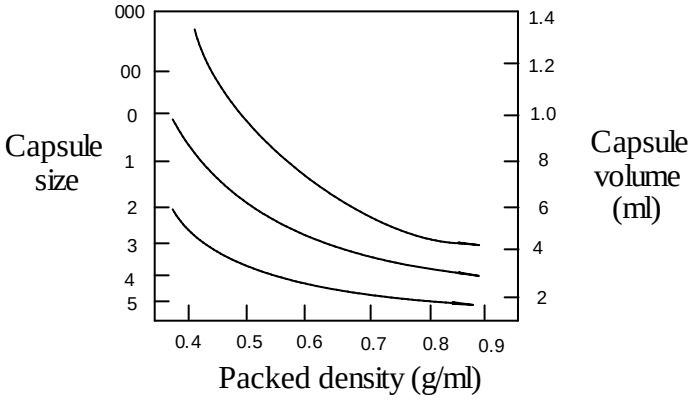
Bulk density is required during the selection of capsule size for a high dose drug.

In case of low dose drug mixing with excipients is a problem if the bulk densities of the drug and excipients have large difference.

(ii) Tapped density

Knowing the dose and tapped density of the formulation, the capsule size can be determined.

Fig. 12



(iii) True density

From bulk density and true density of powder, the void volume or porosity can be measured.

$$Void\ volume = \left(\frac{m}{\rho_{bulk}} - \frac{m}{\rho_{ture}}\right) = m\left(\frac{1}{\rho_{bulk}} - \frac{1}{\rho_{true}}\right)$$

$$Porosity = \frac{Void\ volume}{Bulk\ volume} = \frac{m\left(\frac{1}{\rho_{bulk}} - \frac{1}{\rho_{true}}\right)}{\frac{m}{\rho_{bulk}}} = 1 - \frac{\rho_{bulk}}{\rho_{true}}$$

Powder flow properties

Powder flow properties depends on

(i) particle size

(ii) density

(iii)shape

(iv)electrostatic charge and adsorbed moisture

That may arise from processing or formulation.

A free-flowing powder may become cohesive during development. This problem may be solved by any of the following ways.

(i) by granulation

(ii) by densification via slugging

(iii)by filling special auger feed equipment (in case of powder)

(iv)by changing the formulation.

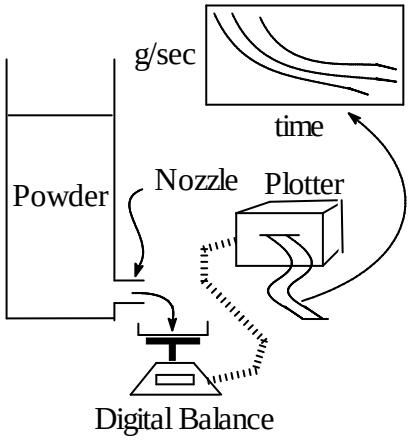
Procedure

For free flowing powder

A simple flow rate apparatus consisting of a grounded metal tube from which drug flows through an orifice onto an electronic balance, which is connected to a strip chart recorder. Several flow rate (g/sec) determinations at various orifice sizes (1/8 to ½ inch) should be carried out.

The grater the standard deviation between multiple flow rate measurements, the greater will be the weight variation of the product (tablets or capsules).

Fig. 13



Compressibility :-

$$\%\,compressibility = \frac{\rho_t - \rho_0}{\rho_t} x100$$

ρ_t = tapped bulk density

ρ_0 = Initial bulk density

Solubility Analysis

Determination of equilibrium solubility of a drug

The drug is dispersed in a solvent. The suspension is agitated at a constant temperature. Samples of the suspension are withdrawn as a function of time, clarified by centrifugation, and assayed to establish a plateau concentration.

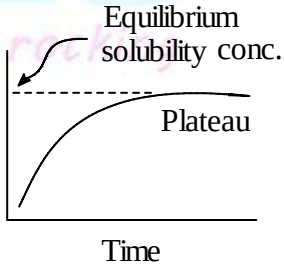


Fig. 14

Solvents taken

(i) 0.9% NaCl at room temperature

(ii) 0.01 M HCl at RT

(iii) 0.1 M HCl at RT

(iv) 0.1 M NaOH at RT

(v) At pH 7.4 buffer at 37^0C

Drug concentration is determined by the following analytical methods

(i) HPLC

(ii) UV –Spectroscopy

(iii) Fluorescence Spectroscopy

(iv) Gas Chromatography

Solubility depends on

(i) pH

(ii) Temperature

(iii) Ionic strength

(iv) Buffer concentration

Significance

(i) A drug for oral administrative should be examined for solubility in an isotonic saline solution and acidic pH. This solubility data may provide the dissolution profile invivo.

(ii) Solubility in various mediums is useful in developing suspension or solution toxicologic and pharmacologic studies.

(iii) Solubility studies identify those drugs with a potential for bioavailability problems. E.g. Drug having limited solubility (7 %) in the fluids of GIT often exhibit poor or erratic absorption unless dosage forms are tailored for the drug.

pK_a Determination

When a weakly acidic or basic drug partially ionizes in GI fluid, generally, the unionized molecules are absorbed quickly.

Handerson-Hasselbalch equation provides an estimate of the ionized and unionized drug concentration at a particular pH.

For acidic Drug:

e.g. $HA + H_2O \rightleftharpoons H_3O^+ + A^-$

Weak acid — Strong base

$$pH = pKa + \log\frac{[ionized]}{[unionized]} = pKa + \log\frac{[A^-]}{[HA]} = pKa + \log\frac{[base]}{[acid]}$$

For basic compounds e.g.

$$\underset{\text{Weak base}}{B} + H_3O^+ \rightleftharpoons \underset{\text{Strong acid}}{BH^+} + H_2O$$

$$pH = pKb + \log\frac{[unionized]}{[ionized]} = pKa + \log\frac{[B]}{[BH^+]} = pKa + \log\frac{[base]}{[acid]}$$

Drug	Stomach PH 1.5	Plasma PH = 7.4	Duodenum PH = 5.0
Weak acid e.g. Ibuprofen pKa = 4.4	[HA] = 100 ⇌ [HA] = 100 ⇌ [HA] = 100 ⇅ ⇅ ⇅ $[A^-]$ = 0.13 $[A^-]$ = 100,000 $[A^-]$ = 398.1 [Total] = 100.13 [Total] = 100,100 [Total] = 498.1		
Weak base e.g. Nitrazepam pKa = 3.2	[B] = 100 ⇌ [B] = 100 ⇌ [B] = 100 ⇅ ⇅ ⇅ $[BH^+]$ = 5012 $[BH^+]$ = 0.006 $[BH^+]$ = 1.6 [Total] = 5112 [Total] = 100.006 [Total] = 101.6		

Method of determination of pKa of a drug

(i) Detection of spectral shifts by UV or visible spectroscopy at various pH.

Advantage: Dilute aqueous solutions can be analyzed by this method.

(ii) Potentiometric titration

Advantage: Maximum sensitivity for compounds with pKa in the range of 3 to 10.

Disadvantage: This method is unsuccessful for candidates where precipitation of the unionized forms occurs during titration. To prevent precipitation a co-solvent e.g. methanol or dimethylsulfoxide (DMSO) can be incorporated.

(iii) Variation of solubility at various pH.

Effect of temperature on stability

Heat of solution, ΔH_S represents the heat released or absorbed when a mole of solute is dissolved in a large quantity of solvent.

Significance

- Most commonly, the solubility process is endothermic, e.g. non-electrolytes, unionized forms of weak acids and bases $\Rightarrow \Delta H$ is positive $\Rightarrow$ Solubility increases if temperature increases.
- Solutes that are ionized when dissolved releases heat

$\Rightarrow$ the process is exothermic $\Rightarrow \Delta H_S$ is negative $\Rightarrow$ Solubility increases at lower temperature.

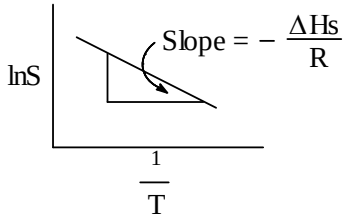
Determination of ΔH_S.

The working equation $\ln S = -\frac{\Delta H_S}{R}\left(\frac{1}{T}\right) + C$ where, S = molar solubility of the drug at T^0K

and R = gas constant

S is detemined at 5^0C, 25^0C, 37^0C and 50^0C.

ΔH_S = – Slope x R



Solubilization

For drug candidates with poor water solubility, preformulation studies should include limited experiments to identify the possible mechanisms for solubilization.

Means of increasing the solubility are:

(i) Addition of a cosolvent to the aqueous system e.g. ethanol, propylene glycol and glycerin.

MOA: These co-solvents disrupt the hydrophobic interactions of water at the non-polar solute / water interfaces.

(ii) Solubilization in micellar solutions such as 0.01 M Tween 20 solution.

(iii) Solubilization by forming molecular complexes e.g. benzoic acid forms complex with caffeine.

Partition coefficient

Partition coefficient is defined, as the ratio of un-ionized drug concentrations between the organic and aqueous phases, at equilibrium.

$$K_{O/W} = \left[\frac{C_{oil}}{C_{water}} \right] \; at\; equilibrium$$

Generally, ***Octanol and chloroform are taken as the oil phase. IMP***

Significance: Drug molecules having higher $K_{O/W}$ will cross the lipid cell membrane.

Dissolution

The dissolution rate of a drug substance in which surface area is constant during disintegration is described by the modified Noyes-Whitney equation.

$$\frac{dc}{dt} = \frac{DA}{hV}(C_S - C)$$

Where, D = diffusion coefficient of the drug in the dissolution medium

h = thickness of the diffusion layer at the solid/liquid interface

A = surface area of drug exposed to dissolution medium.

V = volume of the medium

C_S = Concentration of saturated solution of the solute in the dissolution medium at the experimental temperature.

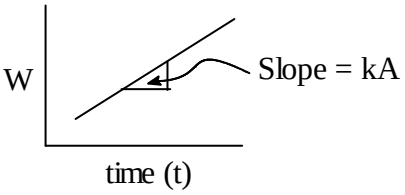
C = Concentration of drug in solution at time t.

When A = constant and $C_S >> C$ the equation can be rearranged to

$$\frac{dC}{dt} = \frac{DA}{hV} C_S \quad or, \frac{V\,dC}{dt} = \frac{DA}{h} C_S \quad or, W = k\,At \qquad \text{Where, } k = \frac{D}{h}$$

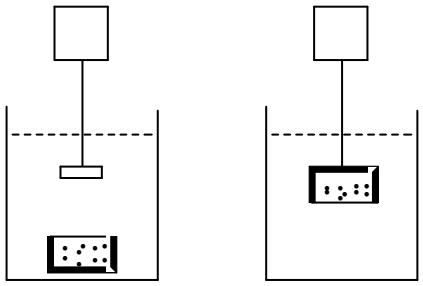
where, W = weight (mg) of drug dissolved at time t

k = intrinsic dissolution rate constant $\left(\frac{mg}{\min\, cm^2} \right)$



Determination of k

- Pure drug powder is punched in a die and punch apparatus to give a uniform cylindrical shape. The tablet is covered with wax in all sides. One circular face is exposed to the dissolution medium. Thus, as dissolution proceeds, the area, A, remains constant.
- Time to time dissolution medium is taken out and fresh medium added to the chamber.
- With two types of assembly, the experiments can be carried out.



Static disc dissolution apparatus

Rotating disc dissolution apparatus

Stability analysis

Preformulation stability studies are the first quantitative assessment of chemical stability of a new drug. This may involve

1. Stability study in toxicology formulation
2. Stability study in solution state
3. Stability study in solid state.

Stability study in toxicology formulation

A new drug is administered to animals through oral route either by

(i) mixing the drug in the feed

(ii) in the form of solution

(iii)in the form of suspension in aqueous vehicle

- Feed may contain water, vitamin, minerals (metal ions), enzymes and different functional groups that may severely reduce the stability of the new drug. So stability study is should be carried out in the feed and at laboratory temperature.
- For solution and suspension, the chemical stability at different temperature and pH should be checked.
- For suspension-state the drug suspension is occasionally shaken to check dispersibility.

Solution stability

Objective: Identification of conditions necessary to form a stable solution.

Stability of a new drug may depend on:

(i) pH (ii) ionic strength (iii) co-solvent

(iv) light (v) temperature (vi) oxygen.

pH stability study

(i) Experiiments to confirm decay at the extremes of pH and temperature. Three stability studies are carried out at the following conditions

(a) 0.1N HCl solution at 90^0C

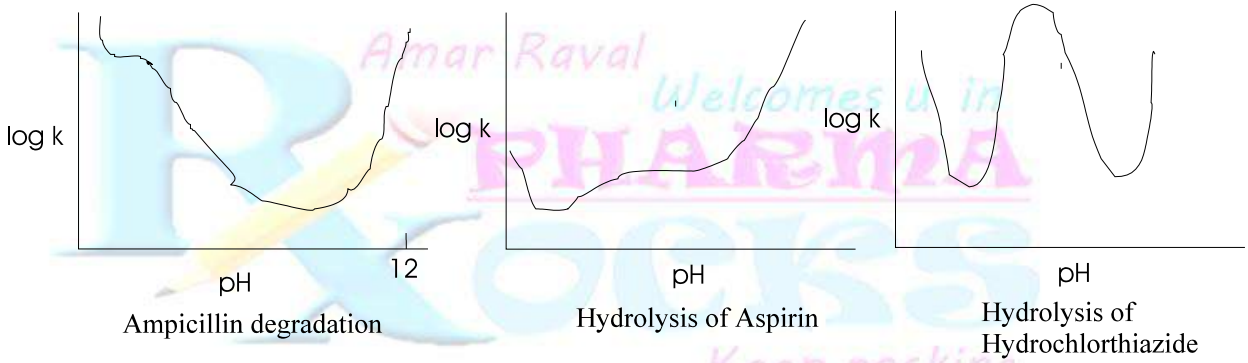
(b) Solution in water at 90^0C

(c) 0.1 N NaOH solution at 90^0C

These experiments are intentionally done to confirm the assay specificity and for maximum rates of degradation.

(ii) Now aqueous buffers are used to produce solutions with wide range of pH values but with constant levels of drug concentration, co-solvent and ionic strength.

All the rate constants (k) at a single temperature are then plotted as a function of pH.



Ampicillin degradation | Hydrolysis of Aspirin | Hydrolysis of Hydrochlorthiazide

(ii) ***Ionic strength***

Since most pharmaceutical solutions are intended for parenteral routes of administration, the pH-stability studies should be carried out at a constant ionic strength that is compatible with body fluids. The ionic strength (μ) of an isotonic 0.9%w/v sodium chloride solution is 0.15.

Ionic strength for any buffer solution can be calculated by

$$\mu = \frac{1}{2}\sum m_i Z_i^{\,2}$$

where, m_i = molar concentration of the ion

Zi = valency of that ion

For computing, μ all the ionic species of the buffer solution and drugs are also taken into calculation.

(iii) *Co-solvents*

Some drugs are not sufficiently soluble to give concentrations of analytical sensitivity. In those cases co-solvents may be used. However, presence of co-solvents will influence the rate constant. Hence, k values at different co-solvent concentrations are determined and plotted against % of co-solvent. Finally, the line is extrapolated to 0% co-solvent to produce the actual k value (i.e. in pure solvent).

(iv) *Light*

Drug solutions are kept in

(a) clear glass ampoules

(b) amber color glass container

(c) yellow-green color glass container

(d) container stored in card-board package or wrapped in aluminium foil – this one acts as the control.

Now the stability studies are carried out in the above containers.

(v) *Temperature*

The rate constant (k) of degradation reaction of a drug varies with temperature according to ***Arrhenius equation.***

$$k = Ae^{-\frac{E_a}{RT}} \qquad \text{or , } \ln = \ln A - \frac{E_a}{R}\left(\frac{1}{T}\right)$$

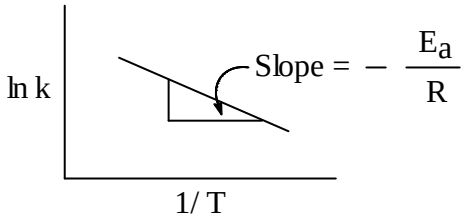
where, k = rate constant

A = frequency factor

E_a = energy of activation

R = gas constant

T = absolute temperature



Procedure

Buffer solutions were prepared and kept at different temperatures. Rate constants are determined at each temperature and the ln k value is plotted against (1/T)).

Inference

- The relationship is linear ⇒ a constant decay mechanism over the temperature range has occurred.

- A broken or non-linear relationship ⇒ a change in the rate-limiting step of the reaction or change in decay mechanism.

Uses

Shelf life of the drug may be calculated.

e.g. Time Concentration of drug remaining

0 100 %

$t_{10\%}$ 90%

Therefore, $\ln C = \ln C_0 - k_1 t$

$\text{Ln } C/C_0 = -k_1 t$

or, $\ln \frac{90}{100} = -k_1 t_{10\%}$ or, $t_{10\%} = \frac{\ln 0.90}{-k_1} = \frac{0.105}{k_1}$

where, $t_{10\%}$ = time for 10% decay to occur if the reaction follows 1st order kinetics

Conclusion

If the drug is sufficiently stable, liquid formulation development may be started at once.

If the drug is unstable, further investigations may be necessary.

Solid state stability

Objectives

Identification of stable storage conditions for drug in the solid state and identification of compatible excipients for a formulation.

Characteristics

Solid state reactions are much slower, so the rate of appearance of decay product is measured (not the amount of drug remaining unchanged).

- To determine the mechanism of degradation thin layer chromatography (TLC), fluorescence or UV / Visible spectroscopy may be required.
- To study polymorphic changes DSC or IR-spectroscopy is required.
- In case of surface discoloration due to oxidation or reaction with excipients, surface reflectance equipment may be used.

***A sample scheme for determining the bulk stability profile of a new drug*:**

Storage condition	***4 weeks***	***8 weeks***	***12 weeks***

5^0C – Refrigerator

22^0C – Room Temperature

37^0C – Ambient humidity

37^0C / 75% RH (Relative Humidity)

Light box

Clear box

Amber glass

Yellow-Green glass

No exposure (Control:- Card-board box or wrapped with aluminium foil)

50^0C – Ambient Humidity

– O_2 Head Space

– N_2 Head Space

70^0C – Ambient Humidity

90^0C – Ambient Humidity

Procedure

1. Weighed samples are placed in open screw-capped vials are exposed to a variety of temperatures, humidities and light intnesities. After the desired time samples are taken out and measured by HPLC (5 – 10 mg), DSC (10 to 50mg), IR (2 to 20mg).
2. To test for surface oxidation samples are stored in large (25ml) vials for injection capped with Teflon-lined rubber stopper. The stoppers are penetrated with needles and the headspace is flooded with the desired gas. The resulting needle holes are sealed with wax to prevent degassing.
3. After fixed time those samples are removed and analyzed.

Drug-excipient stability profile

Hypothetical dosage forms are prepared with various excipients and are exposed to various conditions to study the interactions of drug and excipients.

EMULSION

Syllabus:

Definitions, general formulation of an emulsion and the components used in the formulation of emulsions with examples: Emulsifying agents, oil phase ingredients, aqueous phase ingredients, preservatives, stabilizers, coloring and flavouring agents and such other components processing and equipments on industrial scale. An account of lotions, creams, collodions with the processing and equipment.

Questions:

Q.1 What are emulsions and emulsifying agents? Give examples. [8]
Q.2. Give any one method of formulation of emulsion and production on large scale with different additives. (98) [8]
Q.3. Explain the different mechanical equipments those are at present available for emulsification. (96) [8]
Q.4. Discuss problems that may arise in production of emulsions. (96) [8]
Q.5. Write notes on auxiliary emulsifiers.

DEFINITION

An emulsion is a thermodynamically unstable dispersed system consisting of at least two immiscible liquid phase, one of which is dispersed as globules in the other liquid phase.

The system is stabilized by the presence of an *emulsifying agent*.

Emulsified systems range from lotions of relatively low viscosity to ointments and creams, which are semisolid in nature.

The particle diameter of the dispersed phase generally extends from about 0.1 to 10 μm and as 100 μm are not uncommon in some preparations.

TYPES OF EMULSIONS

(I) Ordinary emulsion systems / Primary emulsion systems / Simple emulsion systems

(i) o/w type – oil dispersed in water
oil → dispersed phase
water → continuous phase

(ii) w/o type – water dispersed in oil
water → dispersed phase
oil → continuous phase

(II) Special emulsion systems

(i) Multiple emulsions → w/o/w – type
o/w/o – type

(ii) Micro emulsion

Simple emulsion type:

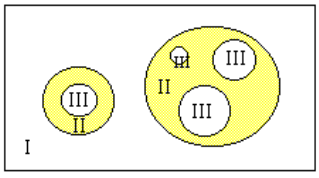
o/w- type of emulsion is a system in which the oil is dispersed as droplet throughout the aqueous phase. Most pharmaceutical emulsions designed for oral administration are of the o/w type; emulsified lotions and creams either of o/w or w/o type depending on their use.

Certain foods such as butter and some salad creams are w/o type emulsions.

Multiple emulsion type

These multiple emulsions have been developed with a view to delay the release of an active ingredient. In this type of emulsions three phases are present, i.e. the emulsion has the form w/o/w or o/w/o. In these "emulsions within emulsions", any drug present in the innermost phase now has to cross two phase-boundaries to reach the external continuous phase.

I : Continuous phase (External aqueous phase)
II: Middle oil phase
III: Inner aqueous phase



Photomicrograph of w/o/w emulsion system

Advantages of multiple emulsions

(i) Prolongation of drug action

(ii) Location of drug in the body.

Micro emulsions

Microemulsions are liquid dispersion of water and oil that are made homogeneous, transparent and stable by the addition of relatively large amount of a surfactant and a co-surfactant. They appear to represent a state intermediate between thermodynamically unstable emulsions and solubilized systems.

Unlike emulsions, they appear as clear transparent solution, but unlike solubilized systems micro-emulsions may not be thermodynamically stable.

Microemulsions containing droplets (w/o or o/w types) with the globule size 10 to 200nm and the volume fraction of the dispersed phase varies from 0.2 to 0.8.

DETERMINATION OF EMULSION TYPE

Several methods are commonly used to determine the type of emulsion. The types of emulsion determined by one method should always be confirmed by means of second method.

(1) Dye solubility test

A small amount of a water soluble dye (e.g. methylene blue or brilliant blue) may be dusted on the surface of the emulsion.

If water is the external phase (i.e. o/w type) then the dye will be dissolved uniformly throughout the media.

If the emulsion is of the w/o -type then particles of dye will lie in clumps on the surface.

(2) Dilution test

This method involves dilution of the emulsion with water. If the emulsion mixes freely with the water, it is of o/w -type. Generally, addition of disperse phase will crack an emulsion.

(3) Conductivity test

This test employs a pair of electrodes connected to an external electric source and immersed in the emulsion. If the external phase is water, a current will pass through the emulsion and can be made to deflect a volt-meter needle or cause a light in the circuit to glow. if the oil is the continuous phase then the emulsion will fail to carry the current.

Methods for determination of emulsion type:

Test	Observation	Comments
1. Dilution test	Emulsion can be diluted only with external phase.	Useful for liquid emulsions only.
2. Dye test	Water-soluble solid dye tints only o/w emulsion and reverse. Microscopic observation usually is helpful.	May fail if ionic emulsifiers are present.
3. Conductivity test	Electric current is conducted by o/w emulsions, owing to the presence of ionic species in water.	Fails in nonionic o/w emulsions.
4. Fluorescence test	Since oils fluoresce under UV-light, o/w emulsions exhibit dot pattern, w/o emulsions fluoresce throughout.	Not always applicable
5. $CoCl_2$ / filter paper test	Filter paper impregnated with $CoCl_2$ and dried (blue) changes to pink when (o/w) emulsion is added.	May fail if emulsion is unstable or breaks in presence of electrolyte.

FORMULATION OF EMULSION

In developing the formula of an emulsion the crucial decisions are related to the choice of the aqueous and oil phases and of the emulgents and their relative proportions. There can be no general guideline in this respect and the choice of phases and emulgents should be related to the qualities desired for the final product. Usually, ingredient selection is made on the basis of the experience and personal tastes of the formulator and by trial and error.

CHEMICAL PARAMETERS

Chemical stability

All the ingredients of an emulsion should be chemically compatible.

e.g. a soap cannot be used as an emulsifier in a system having a final pH of less than 5.

e.g. some lipids are subjected to chemical changes due to oxidation (rancidity); so in general it is simpler to avoid their use than to depend on antioxidants

Safety

All the ingredients should pass the toxicological tests. It is essential, therefore, for the formulator to depend heavily on toxicologic information from suppliers or in the scientific literature, and on regulatory activities by governmental agencies.

Choice of lipid phase

The choice of lipid phase depends on the ultimate use of the product.

(i) If the oily phase is the active-ingredient itself (e.g. liquid paraffin emulsion) the formulator has nothing to choose from.

(ii) The drug in a pharmaceutical preparation should not be too soluble in lipid phase then it will reduce the rate of transfer of the drug molecule to other phases.

(iii) Emulsions prepared for topical purpose (e.g. cosmetics and pharmaceutical emulsions) should possess a good "feel". Emulsions normally leave a residue of the oily components on the skin after the water has evaporated. Therefore, the tactile characteristics of the combined oil phase are of great importance in determining consumer acceptance of an emulsion

Phase - volume ratio

The ratio of the internal phase to the external phase is frequently determined by the **solubility** of the active ingredients, which must provide the required dose.

If this is not the primary criteria, the phase ratio is normally determined by the desired **consistency** of the product. For liquid emulsions the limits of internal phase vary from 40 to 60%, since with such amounts a stable and acceptable emulsion can be prepared. Lower amounts of internal phase (i.e. disperse phase) gives a product of low viscosity with pronounced degree of *creaming* while higher percentage may produce highly viscous emulsions with tendency of *phase inversion*.

TABLE 1: *Ingredients for oil-phase of emulsions*

Class	Identity	Consistency
Hydrocarbon	Mineral oils	Fluids of varying viscosity
Hydrocarbon	Petrolatum	Semisolid
Hydrocarbon	Polyethylene waxes	Solids
Hydrocarbon	Microcrystalline waxes	Solids
Ester	Vegetable oils	Fluids of varying viscosity
Ester	Animal fats	Fluids or solids
Ester	Lanolin	Semisolid
Ester	Synthetic (e.g. isopropyl myristate)	Fluids
Alcohols	Long chain (natural & synthetic)	Fluids or solids
Fatty acids	Long chain (natural & synthetic)	Fluids or solids
Ethers	Polyoxypropylene	Fluids of varying viscosity
Silicones	Substituted silicones	Fluids of varying viscosity
Mixed	Plant waxes (e.g. Candellia)	Solid
Mixed	Animal waxes (e.g. Beeswax)	Solid

Choice of emulsifying agents / Emulsifiers / Emulgents

Emulsifying agents are broadly classified into three classes:

(i) Synthetic emulsifying agent / Surface active agents (SAA) / Surfactants

(ii) Hydrophilic colloid

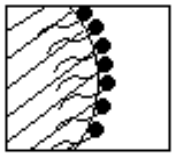
(iii) Finely divided solids

When an emulsifier is used alone to stabilize an emulsion – it is called ***primary emulsifier***. Some times a second emulsifier is used to help the primary emulsifier in stabilizing the system – the second emulsifier is known as ***auxiliary emulsifier.*** Generally emulsifiers from (ii) and (iii) category are used both as primary and auxiliary emulsifier.

A successful emulsifier must possess some or all of the following characteristics:

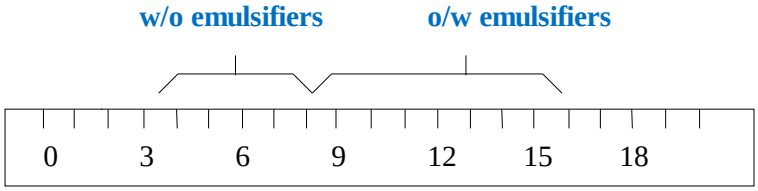
(a) The surface tension should be reduced to a value less than 10 dynes/cm^2.
(b) A complete and coherent film should be formed around the dispersed globules so as to prevent their coalescence.
(c) Should assist in building up the zeta potential and viscosity since both of these phenomena contribute to the stability.

Choice of synthetic surface active agents / Surfactants:



Molecules and ions that are absorbed at interfaces are termed surface-active-agents or surfactants. An alternative expression is *amphiphile*, which suggests that the molecule or ion has a certain affinity for both polar and nonpolar solvents. Due to the amphiphilic nature of surfactants they absorb at the oil-water interface.

Griffin devised an arbitrary scale of values to serve as a measure of the hydrophilic-lipophilic balance (HLB) of surface-active -agents.



Griffin's HLB Scale

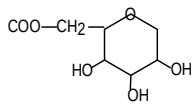
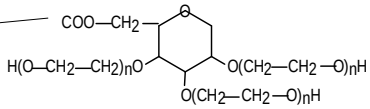
Mode of action of synthetic surfactants

This group of emulsifiers form a flexible film on the oil-water interface. They lower interfacial tension markedly and this contribute to the stability of emulsion. In case of ionic surfactants surface charge is developed, increasing the zeta-potential, which will cause repulsion between two adjacent globules.

e.g. Sodium lauryl sulphate
Polyoxyethylene sorbitan mono oleate (Polysorbate 80).

Classification of synthetic Surface Active Agents

			Chemical formula (in aqs. soln.)	
Class	Surface Active Agent	Lipophilic group	Hydrophilic group	Surface inactive ion
1. *Anionic*				
(a) Alkali soap	Potassium stearate	$C_{17}H_{35}$	COO^-	K^+
(b) Organic sulphates	Sodium lauryl sulphate (Sod. dodecyl sulphate)	$C_{12}H_{25}$	OSO^{3-}	Na^+
(c) Organic sulphonates	Sodium cetyl sulphonate (Sod. hexadecane sulfonate)	$C_{16}H_{33}$	SO^{3-}	Na^+
2. *Cationic*				
(a) Quaternary ammonium compounds	Cetyl trimethyl ammonium bromide (or cetrimide)	$C_{16}H_{33}$	$N^+(CH_3)_3$	Br^-
(b) Pyridinium compounds	Dodecyl pyridinium chloride	$C_{12}H_{25}$	$N^+C_5H_5$	Cl^-
3. *Ampholytic*				
Amino acids	N-dodecyl alanine	$C_{12}H_{25}$	In alkaline soln.– anionic $NH - CH_2 - CH_2 - COO^-$	Na^+
		$C_{12}H_{25}$	In acid solution – cationic $N^+H_2 - CH_2 - CH_2 - COOH$	Cl^-
		$C_{12}H_{25}$	At isoelectric point – zwitterion $N^+H_2 - CH_2 - CH_2 - COO^-$	none
			Chemical formula (in aqs. soln.)	

Class	Surface Active Agent	Lipophilic group	Hydrophilic group	Surface inactive ion
4. *Non-ionic*				
(a) Alcohol-polyethylene glycol ethers	Polyethylene glycol 1000 monocetyl ether (cetomacrogol 1000)	$CH_2–(CH_2)n$ (n= 15 to 17)	$(O–CH_2–CH_2)m–COO^-$ (m = 20 to 24)	none
(b) Fatty acid-polyethylene glycol ethers	Polyethylene glycol 40 monostearate	$C_{17}H_{33}$	$CO–(O–CH_2–CH_2)_{40}–OH$	none
(c) Fatty acid-polyhydric alcohol esters	Sorbitan mono-oleate (TWEEN)	$C_{17}H_{33}$		none
	Polyoxyethylene sorbitan mono-oleate	$C_{17}H_{33}$		none

The HLB number of surfactants may vary from 40 (sodium lauryl sulfate) to 1 (oleic acid). Emulsifying agents, sometimes used singly, are preferably a combination of two emulsifying agents, which will give a weighted HLB of 8 to 16 which is satisfactory for o/w emulsions and an HLB 3 to 8 for w/o emulsions.

NOTE: The HLB required for emulsifying a particular oil in water can be determined by trial and error method; i.e. by preparing appropriate emulsions with emulsifiers having a range of HLB values and then determining that HLB values that yields the "best emulsion". That HLB value is named as Required HLB or RHLB".

TABLE : REQUIRED HLB VALUE FOR SOME OIL PHASE INGREDIENTS

Oil	RHLB for o/w	RHLB for w/o
Cottonseed oil	6-7	–
Petrolatum	8	–
Beeswax	9-11	5
Paraffin wax	10	4
Mineral oil	10-12	5-6
Methyl silicone	11	–
Lanolin, anhydrous	12-14	8
Carnauba wax	12-14	–
Lauryl alcohol	14	–
Castor oil	14	–
Kerosene	12-14	–
Cetyl alcohol	13-16	–
Stearyl alcohol	15-16	–
Carbon tetrachloride	16	–
Lauric acid	16	–
Oleic acid	17	–
Stearic acid	17	

Example: **Formula of an emulsion is as follows:**

Ingredient	Amount	RHLB (o/w)
1. Beeswax	15g	9
2. Lanolin	10g	12
3. Hard paraffin wax	20g	10
4. Cetyl alcohol	5g	15
5. Emulsifier	2g	
6. Preservative	0.2g	
7. Color	q.s.	
8. Water, purified q.s.	100g	

To calculate the overall RHLB of the emulsion the following calculation is carried out:

Oil Phase	Amount	(Amount/Total)xRHLB
1. Beeswax	15g	(15/50)x9 = 2.7
2. Lanolin	10g	(10/50)x12 = 2.4
3. Paraffin	20g	(20/50)x10 = 4.0
4. Cetyl alcohol	5g	(5/50)x15 = 1.5
Total	**50g**	**10.6**

Next, a blend of two emulsifiers is chosen, one with an HLB above 10.6 and the other below 10.6. Let these two surfactants be Tween80 (HLB = 15) and Span 80 (HLB = 4.3). These two surfactants should be mixed in such a ratio that the mixture will have a HLB of 10.6. By aligation method:

HLB of Tween80 → RHLB → Parts of Tween80 : 15 → 6.3 → 10.6

HLB of Span80 → RHLB → Parts of Span80 : 4.3 → 5.6 → 10.6

Required amount of Tween80 = {6.3/(6.3+5.6)}x Total amount of emulsifier
= 0.53x2 g
= 1.06 g

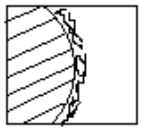
Required amount of Span80 = {5.6/(6.3+5.6)}x Total amount of emulsifier
= 0.47x2 g
= 0.94 g

Therefore, using 1.06 g Tween80 and 0.94 g of Span 80 we can stabilize the above formula of an emulsion.

Choice of hydrophilic colloids

The naturally occurring gums and synthetic hydrophilic polymers are used as either primarily or (mainly) auxiliary emulsifiers.

Mode of action



(i) They do not reduce the surface tension but forms a rigid film on the oil droplets and form a stable o/w emulsion – thus inhibits coalescence of droplets.
(ii) As an auxiliary emulsifier they increase the viscosity of the continuous phase so that movement of dispersed phase is reduced.

Examples:

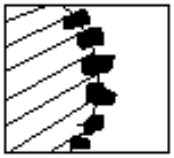
(i) Plant origin: Acacia, tragacanth, alginates, chondrus and pectin.
(ii) Animal source: Gelatin, egg yolk, casein, woolfat, cholesterol and lecithin.
(iii) Synthetic: Methyl cellulose, Hydroxyethyl cellulose, Polyoxyethylene polymer and Carboxyvinyl polymer.

The natural gums exhibit some type of incompatibility or instability depending on the presence of various cations, on pH, or on a second hydrophilic polymer.

Choice of finely divided solid particles

The compounds most frequently used in pharmacy are the colloidal clays: bentonite (aluminium silicate) and veegum (magnesium aluminium silicate). They act as good emulsifiers, especially in combination with surfactants or viscosity building agents.

Mode of action



(i) They tend to absorb at the oil-water-interface and form thick impenetrable films.
(ii) Sometimes increases the viscosity of water (as continuous phase).

Generally finely divided solids are used in conjunction with a surfactant to prepare o/w emulsions but both o/w and w/o preparations can be prepared by **adding the clay to the external phase first**.

They are used frequently for external purposes such as lotion or cream.

Specific formulation consideration: Consistency

Once the desired emulsion and emulsifiers have been chosen, a consistency that provides the desired stability and yet has the appropriate flow characteristics must be attained.

The sedimentation or creaming rate of suspended spherical particles is inversely proportional to the viscosity in accordance with Stoke's law.

Since emulsions should flow or spread easily and since higher viscosity favors stability – so Thixotropy in an emulsion is desirable (Thixotropy = phenomenon in which the viscosity of a preparation is reduced by agitation but increases after agitation has been stopped.

Viscosity of emulsions responds to the following changes:

1. When the viscosity of the continuous phase is increased the viscosity of emulsion is also increased.
   o/w emulsion: Viscosity of water is increased by using gums, clays and viscosity building agents.
   w/o emulsion: Viscosity of oil is increased by addition of polyvalent metal soaps or the use of high melting waxes and resins.
2. The greater the volume of internal phase, (i.e. greater phase volume ratio) the greater is the apparent viscosity.
3. The viscosity and stability of an emulsion is increased by reducing the size of droplets and by formation of floccules or clumps.
4. It is routinely observed that viscosity of emulsions increases upon aging. Hence, it is recommended that a newly formulated emulsion be allowed to rest undisturbed for 24 hours before checking its viscosity.

Choice of an antimicrobial preservative

Sources of contamination:

(i) Contaminated raw materials
(ii) Poor sanitation during preparation
(iii) Contamination by the end users

Substrates of contamination:

(i) Mainly the water phase is a good medium for microbial growth.
(ii) Some ingredients, such as carbohydrates, pectin, proteins, sterols, and phosphates readily supports the growth of a variety of microorganisms.

Remedies:

(i) Use of uncontaminated raw materials
(ii) Careful and through cleaning of equipment with steam.
(iii) Addition of preservatives

Preservatives commonly used:

Chlorocresol, chlorobutanol, mercurials [e.g. phenyl mercuric nitrate (PMN), phenyl mercuric acetate (PMA), esters of parahydroxy benzoate (methyl, propyl, butyl, benzyl paraben), sodium benzoate, sorbic acid etc.

[*For more details see Lieberman & Lachman, Industrial Pharmacy, 3rd Edn. pp 521.*]

Since microorganisms can reside in the water or the lipid phase or both, the preservative should be available at an effective level in both phases. So it is advisable to add an oil soluble and an water soluble preservative simultaneously.

A good example is methyl and propyl paraben. In this case methyl paraben is soluble in water while propyl and higher esters are almost water-insoluble.

Preservatives sometimes *interact* with some ingredients. e.g. phenolic preservatives are especially susceptible to interaction with compounds containing polyoxyethylene groups. Sometimes preservatives are solubilized by the surfactants. The bound or complexed or solubilized preservative can not act as preservative.

Choice of antioxidants

The inclusion of an antioxidant in an emulsion formulation may be necessary to protect, not only an active ingredient but also formulation components (e.g. unsaturated lipids) which are oxygen labile.

Oxidation occurs spontaneously under mild conditions generally involved some free radical reactions.

Kinetic measurements of fat oxidation in o/w emulsions indicate that the rate of oxidation is dependent on

(i) the rate of oxygen diffusion in the system,
(ii) oxygen pressure (i.e. oxygen content)

(iii) trace element of metal such as Cu, Mn, or Fe or their ions may catalyze the oxidative reactions. Thus the use of chelating agents, in a formulation may markedly improve product stability.
(iv) Some oxidative degradation is pH dependent. So the pH stability profile of the drug and of protective formulation should be established during product development.

List of selected antioxidants for emulsion system:

1. *Chelating agents* e.g. Citric acid
EDTA (Ethylene diamine tetraacetic acid)
Phenyl alanine
Phosphoric acid (H_3PO_4)
Tartaric acid

2. *Preferentially oxidized compounds (Reducing agents)*
e.g. Ascorbic acid
Sodium sulphite (Na_2SO_3)
Sodium bisulfite ($NaHSO_3$)
Sodium metabisulfite ($Na_2S_2O_5$)

3. *Chain terminators*
Water soluble compounds e.g. Cystine hydrochloride
Thioglycerol
Thioglycollic acid
Thiosorbitol
Lipid soluble compounds e.g. Alkyl gallates (octyl, propyl, dodecyl)
Butylated hydroxy toluene (BHT)
Butylated hydroxy anisole (BHA)
α-tocopherol (Vit-E)
Hydroquinone

Deaeration
The formulator may wish to deaerate the system by :
(i) bubbling N_2 gas through the liquids to remove dissolved O_2.
(ii) boiled before use
(iii) exposure to vacuum during ultrasonic agitation
(iv) the end space above the container can be flushed with N_2 just before sealing.

Reducing agents: e.g. Ascorbic acid (Vit-C)
Sulphites etc.
They preferentially get oxidized before the oxidation of oil takes place.

Uses:
(i) BHA, BHT, Vit-E and the alkyl gallates are particularly popular in pharmaceuticals and cosmetics.
(ii) BHA and BHT have a pronounced odour and should be added at low concentration.
(iii) Alkyl gallates have a better taste.
(iv) L-tocopherol (Vit-E) is well suited for edible or oral preparations, such as those containing Vitamin A.
(v) Some trace metals like copper, iron, manganese ions catalyze the auto-oxidation reaction; therefore, a small amount of sequestering agents like citric acid, EDTA, tartaric or phosphoric acid reduce the reaction rate.

PREPARATION

- After the purpose of the emulsions has been determined, i.e oral or topical use,
- and the type of emulsions, o/w or w/o,
- and appropriate ingredients selected
- and the theory of emulsification considered

Experimental formulations may be prepared by a method suggested by Griffin.

Experimental method
1. Group the ingredients on the basis of their solubilities in the aqueous and nonaqueous phase.

2. Determine the type of emulsion required and calculate an approximate HLB value
3. Blend a low HLB emulsifier and a high HLB emulsifier to the calculated value
   [N.B. For experimental formulations, use a higher concentration of emulsifier (e.g. 10 to 30% of the oil phase) than that required to produce a satisfactory product.
4. Dissolve the oil-soluble ingredients and the emulsifiers in the oil. Heat, if necessary, to approximately 5 to 10^0C over the melting point of the highest melting ingredient of to a maximum temperature of 70 to 80^0C.
5. Dissolve the water-soluble ingredients (except acids and salts) in a sufficient quantity of water. Heat the aqueous phase to a temperature which is 3 to 5^0C higher than that of the oil phase.
6. Add the aqueous phase to the oily phase with suitable agitation.
7. If acids or salts are employed, dissolve them in water and add the solution to the cold emulsion.
8. Examine the emulsion and make adjustments in the formulation if the product is unstable.

Large scale industrial method

The preparation of an emulsion requires work to reduce the internal phase into small droplets and disperse them throughout the external phase. This can be accomplished by a mortar and pestle or a high speed emulsifier. The addition of emulsifying agents not only reduces this work but also stabilizes the final emulsion. Emulsions may be prepared by four principle methods:

1. Addition of internal phase to external phase

Let us take a model of o/w emulsion.

(i) The water soluble substances are dissolved in water and the oil soluble substances are dissolved in oil.

(ii) The oil mixture is added in portions to the aqueous preparation with agitation (in a colloid mill or homogenizer).

N.B. Sometimes, in order to give a better shearing action during the preparation, all of the water is not mixed with the emulsifying agent until the primary emulsion with oil is formed; subsequently, the remainder of the water is added.

e.g. *Emulsion using Gelatin-type A as the emulsifier.*

Gelatin (Type A)	8g
Tartaric acid	0.6g
Flavour as desired	
Alcohol	60ml
Oil	500ml
Purified water, to make	1000ml

Procedure

(i) The gelatin & tartaric acid are added to approximately 300ml water, allowed to stand for few minutes, heated until gelatin is dissolve, then temperature is raised to 98^0C and this temperature is maintained for about 20 minutes. Cooled to 50^0C, flavor and alcohol are added and more water was added to make 500 ml.

(ii) The oil is added to the aqueous phase (i.e. external phase), and the mixture is agitated thoroughly and passed it through a homogenizer or colloid mill.

2. Addition of the external phase to the internal phase

Let us take a model of o/w emulsion.

In this method water (external phase) is first added slowly to the oil (internal phase) to promote the formation of a more w/o emulsion due to the presence of more oil than water. After further addition of water phase inversion to an o/w emulsion should take place.

This method is especially successful when hydrophilic agents such as acacia, tragacanth or methyl cellulose are first mixed with oil, effecting dispersion without wetting. Water is added and, eventually, an o/w emulsion is formed.

e.g. *Mineral oil emulsion*

Mineral oil	500ml
Acacia, in very fine water	125g
Syrup	100ml
Vanillin	40mg
Alcohol	60ml
Purified water, upto	1000ml

(i) The mineral oil and acacia are mixed in a dry mortar. Purified water, 250 ml (Phase volume ratio o/w = 2: 1) is added and the mixture triturated vigorously until an emulsion is formed.

(ii) A mixture of the syrup, 50 ml of purified water and the vanillin dissolved in alcohol are added in divided portions with trituration
(iii) Sufficient purified water is then added to the proper volume, the mixture well and homogenized.

3. Mixing both phases after warming each

This method is use when waxes or other substances which require melting are used. The oil-soluble emulsifying agents, oils and waxes are melted and mixed thoroughly. The water-soluble ingredients dissolved in the water and warmed to a temperature slightly higher than the oil phase.

The oil phases are then mixed and stirred until cold. For convenience, but not necessity, the aqueous solution is added to the oil mixture.

This method frequently is used in the preparation of ointments and creams.

e.g. ***An oral emulsion (o/w) containing an insoluble drug***

1.	Cotton seed oil	460g
2.	Sulphadiazine	200g
3.	Sorbitan monostearate	84g
4.	Polyoxyethylene 20 sorbitan mono stearate	36g
5.	Sodium benzoate	2g
6.	Sweetener	q.s.
7.	Purified water	1000g
8.	Flavor oil	q.s.

Procedure

(i) Heat the first three ingredients to 50^0C and pass through colloid mill.
(ii) Add the next four ingredients at 50^0C to the first three ingredients at 65^0C and stirred while cooling to 45^0C.
(iii) Add the flavor oil and continue stirring until room temperature is reached.

4. Alternate addition of the two phases to the emulsifying agent

Model: Let us prepare an o/w type of emulsion.
(i) A portion of the oil is added to all of the oil-soluble emulsifying agents with mixing.
(ii) Equal quantity of water is added to all of the water-soluble emulsifying agents with mixing.
(iii) Aqueous solution is mixed with oil phase stirred until the emulsion is formed.
(iv) Further portions of water and oil are added alternately until the final product is formed.

N.B. The high concentration of the emulsifying agent in the original emulsions makes the initial emulsification more likely and the high viscosity provides effective shearing actin leading to small droplets in the emulsion. This method is often used successfully with soaps.

EQUIPMENTS

- The preparation of emulsion requires certain amount of energy to form the interface between the two phases, and additional work must be done to stir the system to overcome the resistance to flow.
- In addition, heat often is supplied to the system to melt waxy solids and /or reduce the viscosity of the oil phase.

Because of the variety of oils used, emulsifying agents, phase-volume ratio and the desired physical properties of the product, a wide selection of equipment is available for preparing emulsions.

1. Mortar and pestle

It consists of a glass or porcelain mortar and a pestle.

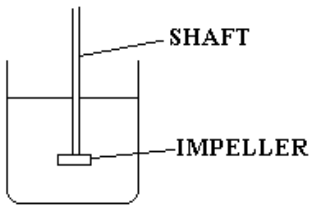
Advantages:

(i) Small quantity emulsions can be prepared in the laboratory.
(ii) Low cost
(iii) Simplest operation among all other instruments.

Disadvantages

(i) Generally, the final particle size is considerable larger then in other equipments.
(ii) It is necessary for the ingredients to have a certain viscosity prior to trituration in order to achieve a satisfactory shear.

2. Agitators / Mechanical stirrers



An emulsion may be stirred by means of various impellers (propellers: produce axial movements; turbines produce radial and tangential movements) mounted on shafts, which are placed directly into the system to be emulsified.
For low viscosity emulsions propeller type can be used but for higher viscosity turbine type is used.

The degree of agitation is controlled by the rotational speed of impeller, by the patterns of the liquid flow and the resultant efficiency of mixing are controlled by the type of impeller, its position in the container, the presence of baffles, and the general shape of the container.

***Advantages*:**

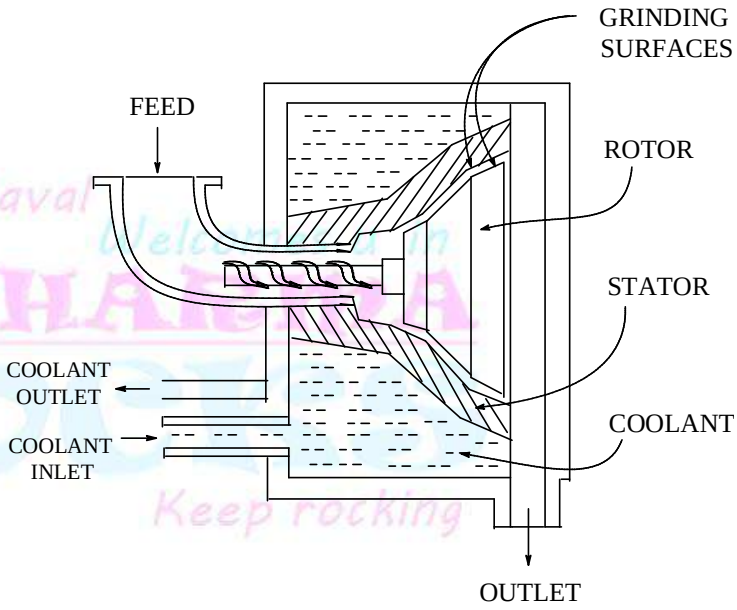
(i) Agitators are used particularly for the emulsification of easily dispersed, low-viscosity oils.
(ii) Can be used for small-scale production and laboratory purpose.

Disadvantages:

Continuous shaking tends to break up not only the phase to be dispersed but also the dispersion medium, in this way, impairs the ease of emulsification.

3. Colloid mill

The principle of operation of the colloid mill is the passage of the mixed phases of an emulsion formula between a stator and a high speed rotor revolving at speeds of 2000 to 18,000 rpm.
The clearance between the rotor and the stator is adjustable, usually from 0.001 inch upward. The emulsion mixture, while passing between the rotor and the stator, is subjected to a tremendous shearing action which effects a fine dispersion of uniform size.
The shearing forces applied in the colloid mill usually raises the temperature within the emulsion. Hence, a coolant is used to absorb the excess heat.



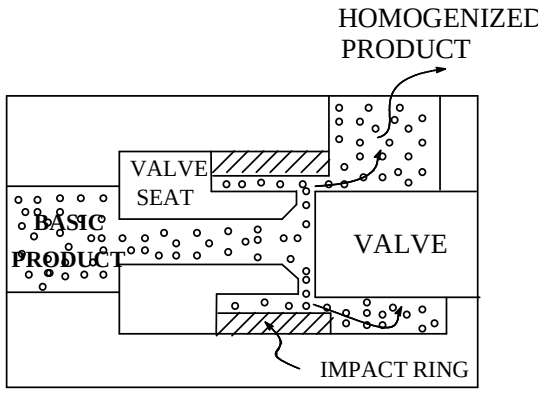
Advantage

(i) Very high shearing force can be generated.
(ii) Very fine particles can be prepared.
(iii) Particularly useful in preparing suspensions containing poorly wetted solids.
(iv) Useful for the preparation of relatively viscous emulsions.

4. Homogenizers

Impeller type of equipment frequently produce a satisfactory emulsion; however, for further reduction in particle size, homogenizers may be employed.
Homogenizers may be used in one of two ways:

(i) The ingredients in the emulsion are mixed and then passed through the homogenizer to produce the final product.
(ii) A coarse emulsion is prepared in some other way and then passed through a homogenizer for the purpose of decreasing the particle size and obtaining a greater degree of uniformity and stability.



The coarse emulsion (basic product) enters the valve seat at high pressure (1000 to 5000 psi), flows through the region between the valve and the seat at high velocity with a rapid pressure drop, causing cavitation; subsequently the mixture hits the impact ring causing further disruption and then is discharged as a homogenized product. It is postulated that circulation and turbulence are responsible mainly for the homogenization that takes place.

Sometimes a single homogenization may produce an emulsion which, although its particle size is small, has a tendency to clump of form clusters. Emulsions of this type exhibit increased creaming tendencies. This is corrected by passing the emulsion through the first stage of homogenization at a high pressure (e.g. 3000 to 5000 psi) and then through the second stage at a greatly reduced pressure (e.g. 1000 psi). This breaks down any clusters formed in the first step (it is a two stage homogenizer).

5. Ultrasonic devices

The preparation of emulsions by the use of ultrasonic vibrations also is possible. An oscillator of high frequency (100 to 500 kHz) is connected to two electrodes between which placed a piezoelectric quartz plate. The quartz plate and electrodes are immersed in an oil bath and, when the oscillator is operating, high-frequency waves flow through the fluid. Emulsification is accomplished by simply immersing a tube containing the emulsion ingredients into this oil bath.

Advantages

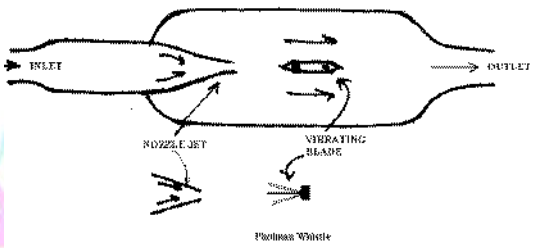
Can be used for low viscosity and extremely low particle size.

Disadvantages

Only in laboratory scale it is possible. Large scale production is not possible.

Example: Pohlman Whistle

Commercial products may be prepared using ultrasonics based upon the device known as the Pohlman whistle. In this apparatus, the premixed liquids are forced through a thin orifice and are allowed to impinge upon the free end of a knife-edge bar which is made to vibrate.



Ultrasonic waves are produced and areas of compression and rarefaction are formed. Shock waves are produced by the collapse of bubbles which produced a shear effect, thereby producing fine particle sizes.

STABILITY OF EMULSION

The stability of an emulsion must be considered in terms of physical stability of emulsion system and the physical and chemical stability of the emulsion component including pharmacologically active ingredients, if any.

Definition: A physically stable emulsion component may be defined as a system in which the globules retain their initial character and remain uniformly distributed throughout the continuous phase.

Symptoms of instability

As soon as an emulsion has been prepared, time and temperature dependent processes occur to effect its separation. During storage, an emulsion's stability is evidenced by (i) creaming, (ii) flocculation and / or (iii) coalescence.

CREAMING

Creaming is the upward or downward movement of dispersed droplets related to the continuous phase due to the difference of density between two phases.

N.B. The downward creaming is also called sedimentation. Generally the term "sedimentation" is associated with the downward movement of solid particles in suspension.

Creaming is undesirable in a pharmaceutical product where homogeneity is essential for the administration of correct and uniform dose. It may still be pharmaceutically acceptable as long as it can be reconstituted by a modest amount of shaking. However, in case of cosmetic products creaming is usually unacceptable because it makes the product inelegant.

Creaming or sedimentation brings the particle closer together and may facilitate a serious problem of coalescence. The rate at which a spherical droplet or particle sediments in a liquid is governed by Stoke's equation.

$$v = \frac{d^2(\rho_1 - \rho_2)g}{18\eta}$$

where v = velocity of creaming
d = diameter of globule
ρ_1 , ρ_2 = densities of dispersed phase and continuous phase respectively
η = viscosity of the continuous medium

A consideration of this equation shows that the rate of creaming will be decreased by:

(i) reduction of droplet size
(ii) a decrease in the density difference between the two phases
(iii) increase in the viscosity of the continuous phase

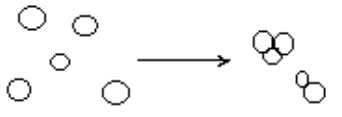
- *Reduction in droplet size* is done by using an efficient homogeniser or colloid mill. There are, however, technical difficulties in reducing the diameter of droplets to below about 0.1 μm.
- Stoke's equation predicts that no creaming is possible if the specific gravities of the two phases are equal. A few successful attempts have been made to equalize the densities of the oil and aqueous phase. This method is of little use in pharmaceutical practice because, it usually involves the addition of substances those are unacceptable in pharmaceutical preparations.
- The most frequently used approach is to raise the viscosity of the continuous phase although this can be done to the extent that the emulsion still can be removed readily from its container and spread on the body surface conveniently.

FLOCCULATION

Flocculation of the dispersed phase may take place before, during or after creaming.

Flocculation is reversible aggregation of droplets of the internal phase in the form of three- dimensional clusters.

In the floccules the droplets remain aggregated but intact. The droplets can remain intact when the mechanical or electrical barrier is sfficient to prevent droplet coalescence.



Flocculation

e.g. if an insufficient amount of emulsifier is present, emulsion droplets aggregate and coalesce.

The reversibility of this type of aggregation depends on the strength of the interaction between particles, as determined by:

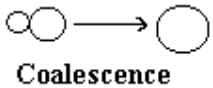
(i) the chemical nature of the emulsifier,
(ii) the phase-volume ratio, and
(iii) the concentration of dissolved substances, especially electrolytes.

The viscosity of an emulsion depends to a large extent on flocculation, which restricts the movement of particles and can produce a fairly rigid network. Agitation of an emulsion breaks the particle-particle interactions with a resulting drop of viscosity; i.e. shear thinning.

COALESCENCE

Coalescence is a growth process during which the emulsified particles join to form larger particles.

Any evidence for the formation of larger droplets by merger of smaller droplets suggests that the emulsion will eventually separate completely.


Coalescence

The major factor which prevents coalescence in flocculated and deflocculated emulsions is the mechanical strength of the interfacial barrier. Thus macromolecules and particulate solids forms thick interfacial film – and hence natural gums and proteins are useful as auxiliary emulsifiers when used at low level, but can even be used as primary emulsifiers at higher concentrations.

Any agent that will destroy the interfacial film will crack the emulsion. Some factors are:

(i) the *addition of a chemical* that is incompatible with the emulsifying agent. Examples include surfactants of opposite ionic charges, addition of large ions of opposite charge, addition of electrolytes such as Ca and Mg salts to emulsions stabilized with anionic surfactants.
(ii) *Bacterial growth*: Protein materials and non-ionic surfactants are excellent media for bacterial growth.
(iii) *Temperature change*: Protein emulsifying agent may be denatured and the solubility characteristics of non-ionic emulsifying agents change with a rise in temperature. Heating above 70^0C destroys almost all emulsions. Freezing will crack an emulsion; this may be due to the ice-crystals disrupting the interfacial film around the droplet.

EVALUATION OF EMULSION

SHELF LIFE

The final acceptance of an emulsion depends on stability, appearance, and functionality of the packaged product. There is no quick and sensitive methods for determining potential instability in an emulsion are available to the formulator. To speed up the stability test program the emulsion is subjected to various stress conditions.

The stress conditions normally employed include:

(i) aging and temperature

(ii) centrifugation, and
(iii) agitation

Aging and temperature

It is routine to determine the shelf life of all types of preparations by storing them for varying periods of time at temperatures that are higher than those normally encountered. A particularly useful means of evaluating shelf life is cycling between two temperatures preferably between 4^0 and 45^0C.

The normal effect of aging an emulsion at elevated temperature is acceleration of the rate of coalescence or creaming, and this is usually coupled with changes in viscosity.

Centrifugation

Stoke's law shows that creaming is a function of gravity (g), and an increase in gravity therefore accelerates separation. Centrifugation at 3750 rpm in a 10-cm radius centrifuge for a period of 5 hours is equivalent to the effect of gravity for about one year. Thus shelf-life under normal storage conditions can be predicted rapidly by observing the separation of the dispersed phase due to either creaming or coalescence when the emulsion is exposed to centrifugation.

Agitation

Droplets in an emulsion exhibit Brownian movement. Coalescence takes place when droplets impinge upon each other. Simple mechanical agitation contributes to the energy with which two droplets impinge upon each other.

Thus agitation can also break emulsion. A typical case is the manufacture of butter from milk.

Conventional emulsions may deteriorate from gentle rocking on a reciprocating shaker. This works in two ways:

(i) increases the rate of impingement of droplets, and
(ii) Reduction of viscosity of a normally thixotrophic system.

PHYSICAL PARAMETERS

The most useful parameters commonly are measured to assess the effect of stress conditions on emulsions include

1. phase separation,
2. viscosity,
3. electrophoretic properties, and
4. Particle size analysis and particle count.

PHASE SEPARATION

The rate and extent of phase separation after aging of an emulsion may be observed visually or by measuring the volume of separated phase.

A simple means of determining phase separation due to creaming or coalescence involves withdrawing a samples of the emulsion from the top and the bottom of the preparation after some period of storage and comparing the composition of the two samples by appropriate analysis of water content, oil content, or any suitable constituent.

VISCOSITY

The viscosity of an emulsion for the use of shelf studies is not concerned with absolute values of viscosity, but with changes in viscosity during aging. Since emulsions are generally non-Newtonian systems and the viscosity is measured by viscometer of the cone-plate type are particularly useful for emulsions, but instruments utilizing co-axial cylinders (e.g. cup and bob viscometer) are the easiest to use. The use of a penetrometer is often helpful in detecting changes of viscosity with age.

In case of w/o emulsions flocculation is quite rapid. After flocculation viscosity drops quickly and continues to drop for some time (5 to 15 days at room temperature).

In case of o/w emulsions globule flocculation causes an immediate increase in viscosity. After this initial change, almost all emulsions show changes in viscosity with time which follow a linear relationship when plotted on a log-log scale.

A practical approach for the detection of creaming or sedimentation, before it becomes visibly apparent, utilizes the Helipath attachment of the Brookfield viscometer

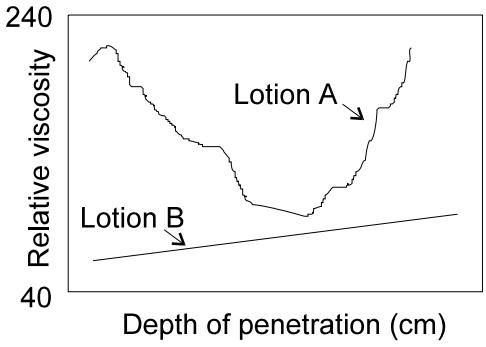
N.B. The Brookfield viscometer determines the resistance encountered by rotating spindle or cylinder immersed in a viscous material. The Helipath attachment slowly lowers the rotating spindle into the medium so that the resistance measured is always that of previously undisturbed test substances.

As a result of emulsion separation, the descending rotating spindle meet varying resistance at different levels and registers fluctuations in viscosity.

Example

Lotion A in the figure contains solids suspended in an emulsion, and the high viscosity near the top is due to non-wetted solid and creamed emulsion; the high viscosity at the lower level is due to sedimented particles.

The addition of polyoxyethylene monooleate (SAA) and methyl cellulose (viscosity enhancer) in lotion B yields a much more uniform viscosity pattern after eight weeks storage.



ELECTROPHORETIC PROPERTIES

If the instability of the emulsion is due to flocculation only (and not due to coalescence) then the zeta potential will have to be measured.

Zeta potential can be determined with

(i) the aid of the moving boundary method or

(ii) more quickly and directly, by observing the movement of particles under the influence of electric current.

The zeta potential is especially useful for assessing flocculation since electrical charges on particles influence the rate of flocculation.

The measurement of electrical conductivity has been claimed to be a powerful tool for the evaluation of emulsion shortly after preparation.

PARTICLE SIZE NUMBER ANALYSIS

Changes of the average particle size or of the size distribution of droplets are important parameters for evaluating emulsions.

Particle size determination can be carried out by microscopic method pr by electronic counting machines. (e.g. Coulter counter). Light scattering and related reflectance relationships have been used for particle size determination.

The utility of particle size for predicting or interpreting emulsion shelf-life is somewhat doubtful.

Practical recommendation for shelf-life prediction in temperate (hot and humid) zone

A typical test program for an "acceptable: emulsion (in temperate zone) may be as follows:

The emulsion should be stable with no visible signs of separation for at least:

(i) 60 to 90 days at 45 or 50^0C,

(ii) 5 to 6 months at 37^0C and

(iii) 12 to 18 months at room temperature.

(iv) After 1 month storage at 4^0C

(v) After 2 to 3 freeze-thaw cycles between –20 and $+25^0$C.

(vi) After 6 to 8 freeze-thaw cycles between 4 and 45^0C with storage at each temperature for not less than 48 hours.

(vii) No deterioration by centrifuging at 2000 to 3000 rpm at room temperature.

(viii) No deterioration by agitation for 24 to 48 hours on a reciprocating shaker (≈ 60 cycles per minute) at room temperature and at 45^0C.

SUSPENSION

Syllabus:

Definition, general formulation with example, suspending agents, preservatives, vehicles, stabilizers, colorants, flavoring agents and such other components, processing and equipment.

Questions:

1. Define and differentiate between solution and suspension
2. Give the importance of suspending agents in pharmaceutical dosage forms. Discuss the different methods of formation of suspensions
3. How do you evaluate the stability of a suspension? What are structured vehicles? How do they help in increasing the stability of a suspension? Mention any two materials which help in improving the stability of suspension with a brief explanation.
4. Write an account of an ideal suspending agent and stabilizer used in suspension.
5. Define suspensions. Describe the formulation of a suspension.

DEFINITION

A suspension is a two phase system composed of a solid material dispersed in a liquid. The liquid can be oily or aqueous. However, most suspensions of pharmaceutical interest are aqueous.

ADVANTAGES

Suspensions offer distinct advantages _ they are as follows:

1. **Stability**: Some drugs are not stable in solution form. In such cases it is necessary to prepare an insoluble form of that drug. Therefore drugs are administered in the form of suspension. e.g. Procaine Penicillin G.
2. **Choice of solvent**: If the drug is not soluble in water and solvents other than water are not acceptable, suspension is the only choice. e.g. Parenteral corticosteroid.

3. **Mask the taste;** In some cases drugs are made insoluble and dispensed in the form of suspension to mask the objectionable taste. e.g. Chloramphenicol base is very bitter in taste, hence the insoluble chloramphenicol palmitate is used which does not have the bitter taste
4. **Prolonged action:** Suspension has a sustaining effect, because, before absorption the solid particles should be dissolved. This takes some time. e.g. Protamine Zinc Insulin and procaine penicillin G.
5. **Bioavailability:** Drugs in suspension exhibit a higher bioavailability compared to other dosage forms (except solution) due to its large surface area, higher dissolution rate. e.g. Antacid suspensions provides immediate relief from hyperacidity than its tablet chewable tablet form.

TYPES OF SUSPENSIONS

The pharmaceutical suspension preparations are differentiated into suspensions, mixtures, magmas, gels and lotions.

Suspensions

Simple suspension is the insoluble solid dispersed in a liquid. The stability considerations suggest that the manufacture of drugs in dry form is ideal. They are reconstituted as suspensions using a suitable vehicle before administration.

Few examples are:

i) Dispersible tablets of antibiotic, amoxycillin (e.g. PRESSMOX)

ii) Procaine penicillin G powder (E.G. PENIDURE)

Gels

Gels are semisolid systems consisting of small inorganic particles suspended in a liquid medium. It consists of a network of small discrete particles. It is a two-phase system. e.g. Aluminum hydroxide gel.

Lotions

Lotions are suspensions which are intended to be applied to the unbroken skin without friction. e.g. Calamine lotion, hydrocortisone lotion.

Magmas and Milks

Magmas and milk are aqueous suspensions of insoluble, inorganic drugs and differ from gels mainly in that the suspended particles are larger. when prepared they are thick and viscous and because of this, there is no need to add a suspending agent. e.g. Bentonite magma, milk of magnesia.

Mixtures

Mixtures are oral liquids containing one or more active ingredients, dissolved, suspended or dispersed in a suitable vehicle. Suspended solids may separate slowly on standing, but are easily redispersed on shaking. e.g. Kaolin mixture with pectin.

CLASSIFICATION OF SUSPENSIONS

Based on the proportion of solids, suspensions are empirically classified as dilute or concentrated systems.

i) **Dilute suspensions** : Solid content 2 - 10 % e.g. Cortisone acetate and prednisolone acetate suspension.

ii) **Concentrated suspensions**: Solid content 10 - 50 % e.g. Zinc oxide suspension for external use, Procaine penicillin G injection, Antacid suspension etc.

Depending on the nature and behavior of solids suspensions are classified as flocculated and deflocculated.

DEFLOCCULATED SUSPENSION

In this system, solids are present as individual particles.

FLOCCULATED SUSPENSION

In this system, particles aggregate themselves by physical bridging. These flocs are light, fluffy conglomerate which are held together by weak van der Waal's forces of attraction.

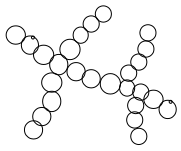


Fig. floccule

If the aggregate is an open network it is called **floccule**. They are fibrous, fluffy, open network of particles. It is loosely packed after sedimentation.

If the aggregate is a closed one - it is called **coagule**. They are tightly packed, produced by surface film bonding.

Fig. Coagule

TABLE: COMPARISON BETWEEN DEFLOCCULATED AND FLOCCULATED SYSTEM

DEFLOCCULATED SYSTEM	FLOCCULATED SYSTEM
i) Pleasant appearance, because of uniform dispersion of particles.	i) Somewhat unsightly sediment.
ii) Supernatant remains cloudy.	ii) Supernatant is clear
iii) Particles exist as separate entities	iii) Particles form loose aggregates.
iv) Rate of sedimentation is slow, as the size of particles are small.	iv) Rate is high, as flocs are the collection of smaller particles having a larger size.
v) Particles settle independently and separately	v) Particles settle as flocs.
vi) The sedimentation is closely packed and form a hard cake.	vi) Sediment is a loosely packed network and hard cake cannot form.
vii) The hard cake cannot be redispersed.	vii) The sediment is easy to redisperse.
viii) Bioavailability is higher due to large specific surface area.	viii) Bioavailability is comparatively less due to small specific surface area.

FACTORS AFFECTING THE STABILITY OF A SUSPENSION

SETTLING IN SUSPENSIONS

Brownian movement

Brownian movement of particles prevents sedimentation. In general, particles are not in a state of Brownian motion in pharmaceutical suspensions, due to

i) larger particle size (Brownian movement is seen in particles having diameter of about 2 to 5 μm (depending on the density of the particles and the viscosity and the density of the suspending medium.
ii) and higher viscosity of the medium.

Sedimentation

The rate of sedimentation of particles can be expressed by the Stoke's law, using the following formula:

$$Sedimentationrate = \frac{d^2(\rho_s - \rho_l)g}{18\eta}$$

Where d is the particle diameter

ρ_s, ρ_l are densities of a particle and liquid respectively.

g is the acceleration of gravity.

η is the viscosity of the medium.

Stock's law is applicable if:

i) Particles are spherical; but particles in the suspension are largely irregular.

ii) Particles settle freely and independently.

In suspensions containing 0.5 - 2 % (w/v) solid, the particles do not interfere with each other during sedimentation - hence free settling occurs.

Most pharmaceutical suspensions contain 5 - 10 % or higher percentages of solid. in this cases particles interfere with one another as they fall - hence hindered settling occurs and Stoke's law no longer applies.

Stoke's law is applicable to deflocculated systems, because particles settle independently. However, this law is useful in a qualitative manner in fixing factors which can be utilized in formulation of suspensions.

1. Particle size

Rate of sedimentation $\propto$ (diameter of particle)^2

So smaller the particle size more stable the suspension. The particle-particle interaction results in the formation of floccules or coagules where the sedimentation rate increases. The particles are made fine either by **dry milling** prior to suspension or **wet-milling** of the final suspension in a colloid mill or a homogenizer.

2. Viscosity of the medium

According to Stoke's law:

Rate of sedimentation $\propto$ 1 / (viscosity of the medium)

The viscosity of suspension should be optimum. Viscosity can be increased by adding suspending agents or thickening agents. selection of high viscosity have both advantages and disadvantages.

Advantages

i) Sedimentation rate is retarded, hence enhances the physical stability of the suspension.

ii) Inhibits crystal growth, because movement of particles is diminished.

iii) Prevents the transformation of metastable crystals to stable crystals.

Disadvantages

i) Redispersibility of the suspension on shaking is difficult.

ii) Pouring out of the suspension from the container may be difficult.

iii) Creates problems in the handling of materials during manufacture.

iv) May retard absorption of drugs from the suspension.

3. Density

Rate of sedimentation ∞ (density of solid – density of liquid medium)

Lesser the difference between the densities of solid particles and liquid medium slower is the rate of sedimentation. Since it is very difficult to change the absolute density of the solid particles so the density of the liquid medium can be manipulated by changing the composition of the medium. The addition of nonionic substances such as sorbitol, polyvinylpyrrolidone (PVP), glycerin, sugar, or one of the polyethyleneglycols or combination of these may be helpful in the manipulation.

If the density of the particles is greater than the continuous medium the particles will settle downwards, the phenomenon is known as sedimentation. If the density of particle is lesser than that of the liquid medium then the particles will move upward - the phenomenon is known as creaming.

FORMULATION OF SUSPENSIONS

The product must

1) Flow readily from the container
2) Possesses a uniform distribution of particles in each dose.

Two approaches are commonly employed to secure the two requirements,

(i) the use of structured vehicle t maintain deflocculated particles in suspension. Structured vehicles are pseudoplastic and plastic in nature; it is frequently desirable that thixotropy be associated with these two type of flow. Structured vehicles act by entrapping the particles so that, ideally no settling occurs. In reality some degree of sedimentation will usually take place. The *shear thinning* property of these vehicle does however facilitate the redispersion when shear is applied.

(ii) and the application of the principles of flocculation to produce flocs that, although, they settle rapidly are easily redispersed with a minimum of agitation.

WETTING OF PARTICLES

The initial dispersion of an insoluble powder in a vehicle is an important step in the manufacturing process. Powders sometimes are added to the vehicle, particularly in large scale operations, by dusting on the surface of the liquid. It is frequently difficult to disperse the powder owing to an adsorbed layer of air, minute quantity of grease and other contaminants. Powders those are not easily wetted by water and accordingly show a large contact angle, such as sulfur, charcoal and magnesium stearate are said to be *hydrophobic*. Powders those are readily wetted by water when free of adsorbed contaminants are called *hydrophilic*. e.g. zinc oxide, talc, magnesium carbonate etc. belong to this category.

When a strong affinity exists between a liquid and a solid, the liquid easily forms a film over the surface of the solid. When this affinity is non-existent or weak, the liquid faces difficulty in displacing the air or other substances surrounding the solid.

Hydrophilic solids usually can be incorporated into suspensions without the use of a wetting agent, but hydrophobic materials are extremely difficult to disperse and frequently float on the surface of the fluid owing to poor wetting of the particles or the presence of tiny air pockets on the surface of the solid particles.

To reduce the **contact angle** between solid and liquid (i.e. increase the wettability) the following agents can be tried out:

1. **Surfactants** Solid-liquid interfacial tension is reduced by incorporating a surfactant with a HLB value between 7 to 9. These are employed to allow the displacement of air from hydrophobic material and permit the liquid, to surround the particles and provide a proper dispersion. The surfactant is mixed with the solid particles if required by shearing. The hydrocarbon chain is preferentially adsorbed to the hydrophobic surface, with the polar part of the surfactant being directed towards the aqueous phase.
2. **Hydrophilic polymers** such as sodium carboxymethyl cellulose, certain water-insoluble hydrophilic material such as bentonite, aluminum-magnesium silicates, and colloidal silica, either alone or in combination can be incorporated in desired concentration. These materials are also used as suspending agents and may produce a deflocculated system particularly if used at low concentration.
3. **Solvents** such as alcohol, glycerol and glycols which are water miscible will reduce the liquid / air interfacial tension. The solvent will penetrate the loose agglomerates of powder

displacing the air from the pores of the individual particles thus enabling wetting by dispersion medium.

Method of selection of a suitable wetting agent

In order to select a suitable wetting agent Heistand has used a narrow trough, several inches long and made of a hydrophobic material, such as Teflon, or coated with paraffin wax. At one end of the trough is placed the powder and the other end the solution of the wetting agent. The rate of penetration of the wetting agent solution into the powder can then be observed directly. Greater the rate of penetration of the solution into the powder better is the wetting property of the solution.

RHEOLOGIC CONSIDERATIONS

Rheologic consideration are important in

(i) the viscosity of a suspension as it affects the settling of particles. As viscosity increases rate of sedimentation of the particles reduces.

(ii) the change in flow properties of the suspension when the container is shaken and when the product is poured out off the bottle.

(iii) the spreading quality of the lotion when applied to the affected area.

(iv) during the manufacture of the suspensions.

Importance of suspending agents

- The particles in a suspensions are experiencing bombardment constantly with each other owing to the Brownian movement.
- During this type of inter-particular interaction the particles may circumvent the repulsive force between them and form larger particles which will then settle rapidly.
- Suspending agents reduce this movement of the particles by increasing the viscosity of the medium.
- According to Stoke's law rate of sedimentation is inversely proportional to the viscosity of medium. So the settling of the particles, either in flocculated or deflocculated system, can be slowed down by increasing the drag force on the moving particles by increasing the viscosity of the medium.
- Hydrophilic polymers such as sodium carboxymethyl cellulose, certain water-insoluble hydrophilic material such as bentonite, aluminum-magnesium silicates, and colloidal

silica, either alone or in combination can be incorporated in low concentration as **wetting agent.**

- Hydrophilic polymers also acts as **protective colloids** and particles coated in this manner are less prone to cake than are uncoated particles.

Cellulose polymers

- Sodium carboxymethyl cellulose SCMC
- Methylcellulose MC
- Hydroxy propyl methylcellulose. HPMC

Proteins e.g. gelatin.

Synthetic polymer e.g. Polyacrylic acid (Carbopol)

Clays essentially hydrated aluminum and/or magnesium silicates are also useful in suspension formulation.

Characteristics of ideal suspending agent

(i) An ideal suspending agent should have a high viscosity at negligible shear; i.e. during shelf storage; and it should have a low viscosity at high shear rates, i.e. it should be free flowing during agitation, pouring and spreading on the skin.

(ii) Suspending agents should coat the particles which will be less prone to caking than the uncoated particles.

- Pseudoplastic substances e.g. tragacanth, sodium alginate and sodium carboxymethylcellulose show these desirable qualities.
- It is a shear thinning system, i.e. when this type of system is shaken or agitated the viscosity diminishes.
- A suspending agent that is thixotropic as well as pseudoplastic should prove to be useful since it forms gel on standing and becomes fluid when disturbed.

E.g. Bentonite - Carboxymethylcellulose has both pseudoplastic and thixotropic behavior.

Suspending agent	Concentration in which generally used
Sodium carboxymethyl cellulose (SCMC)	0.5 – 2.5 %
Tragacanth	1.25 %
Guargum	0.5 %
Carbopol 934	0.3 %

CONTROLLED FLOCCULATION

Assuming that the powder is properly wetted and dispersed attention may now be given to the various means by which controlled flocculation may be produced so as to *prevent compact sediment which is difficult to redisperse.*

Controlled flocculation can be described in terms of the materials used to produce flocculation I suspensions, namely, (i) electrolytes, (ii) surfactants, and (iii) polymers.

(i) Electrolytes act as flocculating agents by reducing the electric barrier between the particles, as evidenced by a decrease in the zeta-potential and formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.

Example:

- When bismuth subnitrate is suspended in water it has been found (by electrophoretic studies) that they possess a large positive charge, or zeta potential. Because of the strong forces of repulsion between adjacent particles, the system remains in deflocculated (peptized) state.
- The addition of monobasic potassium phosphate (KH_2PO_4) to the suspension causes the positive zeta-potential to decrease owing to the adsorption of the negatively charged phosphate anion. The particles then can come closer to form aggregates.
- On further addition of KH_2PO_4 the zeta potential eventually falls to zero and then increases in a negative direction.
- Microscopic examination of the various suspensions shows that at a certain positive zeta potential, maximum flocculation occurs and will persist until the zeta potential has become sufficiently negative for deflocculation to occur once again.
- The onset of flocculation coincides with the maximum sedimentation volume determined. F remains reasonably constant while flocculation persists, and only when the zeta potential becomes sufficiently negative to effect deflocculation.

(ii) Surfactants both ionic and nonionic, have been used to bring about flocculation of suspended particles. The concentration necessary to achieve this effect would appear to be critical since these compounds may also act as wetting agents to achieve dispersion.

(iii) Polymers are long chain, high molecular weight compounds containing active groups spaced along their length. These agents act as flocculating agents because part of the chain is adsorbed on the particle surface, with the remaining parts projecting out into the dispersion medium. Bridging between these latter portions leads to the formation of flocs.

Hydrophilic polymers also acts as protective colloids and particles coated in this manner are less prone to cake than are uncoated particles.

FLOCCULATION IN STRUCTURED VEHICLE

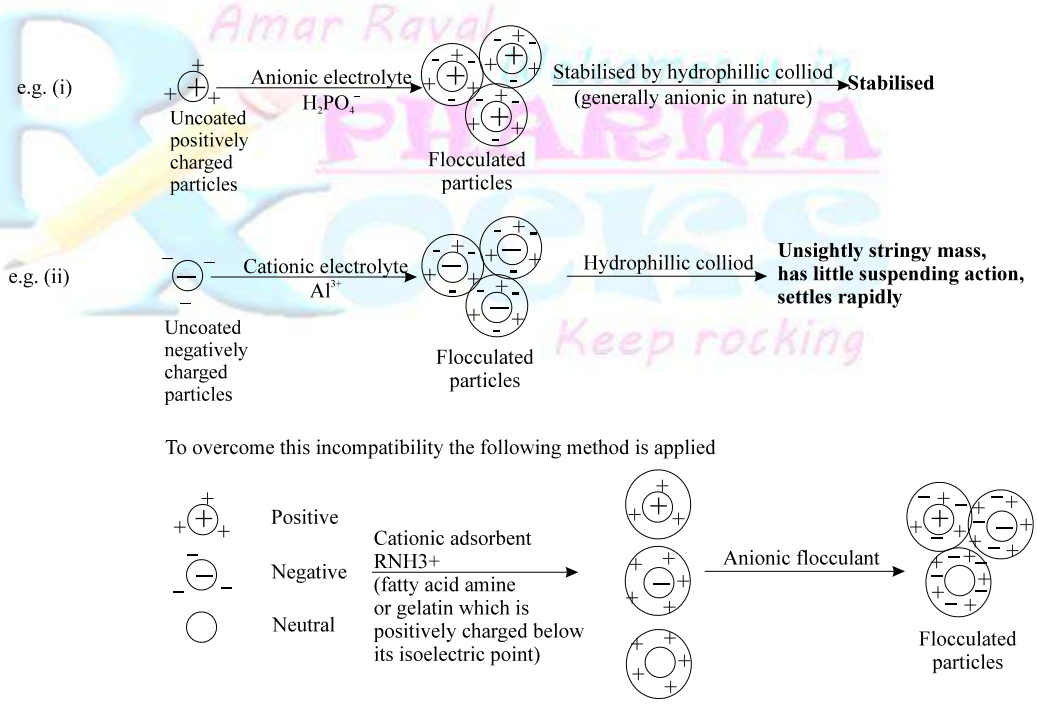
Although the controlled flocculation approach is capable of fulfilling the desired physical chemical requisites of a pharmaceutical suspension, the product can look unsightly if F, the sedimentation volume, is not close to or equal to 1.

So a suspending agent is added to retard sedimentation of the flocs. Such agents as carboxymethylcellulose (CMC), Carbopol 934, Veegum, tragacanth or bentonite have been employed, either alone or in combination.

These may lead to incompatibilities, depending on

(i) the initial particle charge

(ii) the charge carried by flocculating agent and



(iii) the charge carried by suspending agent.

PREPARATION OF SUSPENSIONS

Method of preparations can be subdivided into two broad categories:

Precipitation method

There are three methods

1. organic solvent precipitation

2. precipitation effected by changing the pH of the medium and
3. double decomposition

(i) Organic solvent precipitation

Water insoluble drugs can be precipitated by dissolving them in water-miscible organic solvents (e.g. alcohol, acetone, propylene glycol and polyethylene glycol) and then adding the organic phase to distilled water under standard conditions produces a suspension having a particle size in the 1 to 5 μm range.

Example: Prednisolone is precipitated from a methanolic solution to produce a suspension in water.

Disadvantage: Harmful organic solvents may be difficult to remove.

Advantage: In case of parenteral or inhalation therapy very fine particles are required, which can be prepared by this method.

(ii) Precipitation effected by changing the pH of the medium

A drug may be readily soluble at a certain pH and precipitate at another pH. This type of drug is first dissolved in the favorable pH and then the solution is poured in another buffer system to change the pH of the medium and the drug will form a suspension in the medium of the second pH.

***Example 1*:** Estradiol suspensions can be prepared by changing the pH of its aqueous solution; estradiol is readily soluble in alkali as potassium or sodium hydroxide solutions.

If a concentrated solution of estradiol is thus prepared and added to a weakly acidic solution of hydrochloric, citric or acetic acids, under proper conditions of agitation, the estradiol is precipitated in a fine state of subdivision.

***Example 2*:** Insulin suspension may also be prepared by pH change method.

Insulin has an isoelectric point of approximately pH5.

When it is mixed with a basic protein, such as protamine, it is readily precipitated when pH is between the isoelectric points of the two components, i.e. pH 6.9 to 7.3. Protamine-Zinc-Insulin (PZI) contains an excessive quantity of zinc to retard the rate of absorption.

According to the British Pharmacopoeia phosphate buffer is added to an acidified solution of PZI so that the pH is between 6.9 to 7.3 to form the suspension.

(iii) Double decomposition method

In this method two water soluble reagent forms a water insoluble product.

Example: White Lotion NF is prepared by slowly adding zinc sulfate solution in a solution of sulphurated potash to form a precipitate of zinc polysulphide.

Dispersion method

In this cases the powder form of the drug is directly dispersed in the liquid medium. The liquid medium should have good power of wetting the powder.

1. Small scale preparation method

A suspension is prepared on the small scale by grinding or levigating the insoluble material in the mortar to a smooth paste with a vehicle containing the dispersion stabilizer and gradually adding the remainder of the liquid phase in which any soluble drugs may be dissolved. The slurry is transferred to a graduate, the mortar is rinsed with successive portions of the dispersion medium is finally brought to the final volume.

2. Large scale preparation method

On large scale dispersion method the solid particles are suspended using ball, pebble and colloid mills. Dough mixers, pony mixers and similar apparatus are also employed.

EVALUATION OF SUSPENSION STABILITY

Sedimentation volume

Since redispersibility is one of the major considerations in assessing the acceptability of a suspension, and since the sediment formed should be easily dispersed by moderate shaking to yield a homogeneous system, measurement of the sedimentation volume and its ease of redispersion are the two common evaluative procedures.

Definition:

The sedimentation volume, F, is defined as the ratio of the final, or ultimate volume of the sediment (Vu), to the original volume of the suspension (Vo), before settling. Thus

$$F = Vu / Vo$$

The sedimentation volume can have values less than 1 to greater than 1.

If the volume of sediment in a flocculated system equals the original volume of suspension, then F = 1. Such a product is said to be in **'flocculation equilibrium'.**

Procedure: The suspension is taken in a measuring cylinder upto a certain height and left undisturbed. The particles will settle gradually. The value of F is determined from the ratio of the volume of the sediment at that instant of time (Vu) and the original volume of the suspension (Vo). The value of F is plotted against time (t). The plot will, will start at 1.0. at time zero. The curve will either run horizontally or gradually sloping downward to the right as time goes on.

One can compare different formulations and choose the best by observing the line, the better formulation obviously producing lines that are more horizontal and/or less steep.

If the suspension is highly concentrated then the suspension is diluted with the continuous medium (liquid phase) and then the sedimentation volume is determined.

Degree of flocculation

A more useful parameter is the degree of flocculation, β.

Definition: ***degree of flocculation is the ratio of ultimate sediment volume of flocculated suspension to that of a deflocculated suspension.***

$$\beta = \frac{\text{sedimentation volume of } \textit{flocculated} \text{ suspension (F)}}{\text{sedimentation volume of } \textit{deflocculated} \text{ suspension (F}\infty\text{)}}$$

$F\infty = V\infty / Vo$ $F\infty$ = sedimentation volume of *deflocculated* suspension

$V\infty$ = ultimate sediment volume of *deflocculated* suspension

Vo = original volume of suspension

$F = Vu / Vo$ F = sedimentation volume of *flocculated* suspension

Vu = ultimate sediment volume of *flocculated* suspension

Therefore, $\beta = F / F\infty$

$= (V\infty / Vo) / (Vu / Vo)$

$= (V\infty / Vu)$

$$\beta = \frac{\text{ultimate sediment volume of } \textit{flocculated} \text{ suspension (Vu)}}{\text{ultimate sediment volume of } \textit{deflocculated} \text{ suspension (V}\infty\text{)}}$$

Redispersibility

The evaluation of redispersibility is also important. To quantitate this parameter to some extent, a mechanical shaking device may be used. It simulates human arm motion during the shaking process and can give reproducible result when used under controlled conditions.

Rheologic methods

Rheologic behavior can also be used to help determine the settling behavior and the arrangement of the vehicle and particle structural features for purposes of comparison. The structure of the suspension changes during storage period. This structural changes can be evaluated by rheologic method.

A practical rheologic method involves the use of a Brookfield viscometer mounted on a helipath stand. The T-bar spindle is made to descend slowly into the suspension, and the dial reading on the viscometer is then a measure of the resistance the spindle meets at various level in the sediment. In this technique, the T-bar is continually changing position and measures undisturbed samples as it advances down in the suspension This technique also indicates in which level of the suspension the structure is greater, owing to the particle agglomeration, because the T-bar descends as it rotates, and the bar is continually entering new and essentially undisturbed material.

Thus using the T-bar spindle and the helipath, the dial reading can be plotted against the number of turns of the spindle. The result indicates how the particles are setting with time. In a screening study the better suspensions show a lesser rate of increase of dial reading with spindle turns, i.e. the curve is horizontal for a longer period.

Electrokinetic techniques

***Instrument* : Microelectrophoresis apparatus.**

- Such instrument permit measurement of the migration velocity of the particles with respect to the surface electric charge or the zeta potential.
- Zeta potential correlated well with the visually observed caking and certain zeta potential produced more stable suspensions because aggregation was controlled and optimized.

Particle Size Changes

- During storage or transport the product may experience a fluctuation of temperature which may lead to crystal growth or physical incompatibilities.
- Normally it may take time to check the stability regarding crystal growth.
- So to accelerate this effect ***freeze-thaw cycling*** technique is particularly applicable.

- The product is put into refrigerator and again brought into room temperature
- This type of temperature cycling promotes the growth of particle size.
- The growth of particle and size distribution are estimated by microscopic means.

Example(i) The crystal growth of sulfathiazole in suspensions is found to accelerate after temperature cycling

Example(ii) the preservative and protective colloid, may have a profound effect on the physical performance of a suspension under freeze-thaw conditions. Two low solid content steroid injectable preparations of following compositions underwent freeze-thaw condition the first preparation showed intense caking while the latter was unaffected.

Preparation	Protective colloid	Preservative	Result after freeze-thaw
I	sodium carboxy methylcellulose	benzyl alcohol	Caked badly
II	carboxy methyl cellulose	methyl paraben, propyl paraben	No caking

Example (iii) Gelatin solidifies at low temperature and methyl cellulose is precipitates in hot water.

SEMISOLID DOSAGE FORMS

Syllabus Topics

Ointment bases: oleaginous bases, hydrocarbon and silicon containing bases.

Absorption bases, emulsion bases, water soluble bases.

Preparation and preservation of these ointments with industrial equipment used for processing.

***Questions*:**

1. Define and differentiate between Ointment and creams, lotion and liniment. (98) [4+4]
2. Give different ointment bases with examples. (98)[8]
3. Discuss various methods for manufacturing of ointments. [8]
4. Write a note on different types of raw materials that are used in the manufacture of semisolid dosage forms. What are the factors that affect skin penetration of drugs from semisolids (96)[16]
5. Preservative in ointment. (95) [4]
6. How do you select the ointment base for a water soluble and insoluble drug to be incorporated for a medicinal preparation? Discuss on the selection of ointment base (94) [16]
7. Discuss on the importance of packing materials for ointments. What is the influence of packing materials for ointment storage? (94) [16]
8. Write in brief the factors governing the selection of ointment bases. (93) [6]
9. Give the characteristics and examples of oleaginous bases. (93)[6]
10. Discuss the different methods of ointment preparations. (93) [4]

INTRODUCTION

DEFINITION

- Semi solids are the topical dosage form used for the therapeutic, protective or cosmetic function. They may be applied to the skin, or used nasally, vaginally, or rectally.
- Pharmaceutical semisolid dosage preparations include ointments, pastes, cream, emulsions, gels and rigid foams.

Ointments are soft semisolid preparations meant for external application to the skin or mucous membrane. They usually contain medicament, which is either dissolved or suspended in the base.
They have emollient and protective action.

Creams are semisolid emulsions for external application and are generally of softer consistency and lighter than ointments. They are less greasy and are easy to apply.

Pastes are semisolid preparations for external application that differs from similar products in containing a high proportion of finely powdered medicaments. They are stiffer and are usually employed for their protective action and for their ability to absorb serous discharges from skin lesions. Thus when protective, rather than therapeutic action is desired, the formulation pharmacists will favor a paste, but when therapeutic action is required, he will prefer ointments and creams.

Jellies are transparent or translucent, non-greasy, semisolid preparation mainly used externally.
In these systems the liquid phase is entrapped within a three-dimensional polymeric matrix in which a high degree of physical cross-linking has been introduced.
The polymers (gelling agents) used include:

NATURAL POLYMERS:

- Tragacanth,
- pectin,
- carageenan,
- agar,
- alginic acid
- Gelatin.

SYNTHETIC AND SEMISYNTHETIC POLYMERS:

- Methyl cellulose,
- hydroxymethyl cellulose,
- Carboxymethyl cellulose and Carbopols.

STRUCTURE OF SKIN

The skin has three main layers: the epidermis, dermis and hypodermis.

Epidermis is the outermost layer. It consists of:

(a) The *basal layer* (innermost) is one cell thick layer. Its cells divide constantly and the daughter cells are steadily pushed towards the surface.

(b) The *prickle cell layer*: The cells in this region are linked by tiny bridges or prickles.

(c) The *granular layer*: When they reach this region, the upwardly moving cells become granules and begin to synthesize the inert protein keratin.

(d) The *horny layer* (stratum corneum). This is the outermost layer and the cells are heavily keratinized and dead. The dead cells sloughs off gradually.

Dermis is the middle and the main part of the skin. The dermis is made up of protein collagen and elastin. The collagen is in the form of gel that is reinforced by a framework of elastin.

Dermis contains the following structures:

(a) Blood vessels, lymphatics and nerves.

(b) Epidermal appendages e.g. hair follicles, sebaceous glands and sweat glands.

Hypodermis, the innermost layer, consists of adipose tissues. It gives physical protection and thermal insulation to underlying structures.

- Epidermis is non-granular but is penetrated by hair follicles, sebaceous glands and sweat glands.
- Sebum is the secretion of sebaceous glands. Sebum is a mixture of fatty substances and emulsifiers; it mixes with water producing a fluid of pH 5.5 that covers the skin surface and permeates the upper layer of keratinized cells – this is called the "*acid-mantle*" of skin.
- Keratin is hydrophillic, the stratum corneum normally contains about 20% w/w of water, the amount varying with atmospheric humidity. This moisture keeps the skin supple and if its level falls below about 12% the cells becomes dry and brittle and then shrink and curl at the edges, making the skin feel rough.
- Cracking may follow, causing discomfort. Loss of water may be the result of excessive evaporation, over-usage of detergents (which removes sebum) and cold weather (which inhibits sebum production).

PERMEABILITY OF DRUG THROUGH EPIDERMIS

Most dermatological preparations belong to one of two classes:

1. *Preparation intended to remain on the surface*

E.g. products for penetration or for emollient action.

2. *Preparations intended to penetrate the skin but will not enter into blood stream*

Drugs penetrate the epidermis by two man routes:

(a) Through the keratinized cells of the stratum corneum.

The keratinized cells are fused together so drug molecules directly diffuse through them. These cells contains keratin which is hydrophilic and phospholipids which is hydrophobic, so drug molecules having solubility in both water and oil have good permeability through this route.

(b) Via hair follicles

Although the hair follicles occupy only a small area of the total epidermis, they provide a very important route of penetration. The fat soluble drugs dissolve in sebum, diffuses in to the sebum-filled follicles and passes to dermis.

FACTOR AFFECTING PERMEABILITY OF A DRUG THROUGH SKIN

A. **Factor associated with the skin**

(a) *Hydration of the horny layer*

The hydration of keratinized cells is raised by covering the area with a moisture-proof plastic film to prevent evaporation of perspiration. Hydration increases the drug penetration.

(b) *Thickness of the horny layer*

The horny layer is thickest on palms and soles and thinnest on the face; penetration rate increases with decreased thickness of horny layer.

(c) *Skin condition*

The permeability of the skin is affected by age, disease, climate and injury. For example, absorption occurs rapidly in children and if the dermis is exposed by a wound or burn.

B. Factors associated with the medicament

(a) *Solubility of the drug*

Highly lipid soluble molecules enters through hair follicles. Moderately lipid soluble molecules penetrates directly across the horny layer.

(b) *Dissociation constant (pKa)*

If a drug is ionized in the surrounding pH of the dermis then the penetration of the ionic species are restricted by electrostatic interactions. Degree of ionization depends on the pKa of the drug.

E.g. Methyl salicylate and methyl nicotinate penetrate much faster than salicylic acid and nicotinic acid respectively.

(c) *Particle size*

Reducing the particle size increases the dissolution of a poorly soluble drug in suspension and thus increases the release rate from the vehicle.

(d) *Crystal structure*

The metastable polymorph is much more soluble than its stable form, so the release of drug in metastable state is much faster than stable form.

C. **Factors associated with vehicles**

The rate of release of a drug from a vehicle to stratum corneum is governed by *vehicle-to-stratum corneum partition coefficient*. The thermodynamic activity of the drug in the vehicle is the product of the concentration of the drug and the activity coefficient (γ) of the drug in the vehicle. Drugs held firmly by the vehicle exhibit low activity coefficient, hence slow rate of release from that drug-vehicle combination. Drug held loosely by the vehicle shows higher activity coefficient, hence shows faster rate of release.

The vehicles may enhance the penetration of a drug in one or more of the following ways:-

a) By ensuring good contact with the surface of the body
b) By increasing the degree of hydration of the stratum corneum
c) By penetrating the epidermis
d) By directly altering the permeability of the skin

(a) Contact with body surface

Sticky bases such as soft paraffin, Paraffin ointment B.P.C., Simple ointment B.P. etc. adheres well to the skin but are difficult to apply evenly and remove completely.

Creams are easier to apply and remove. Oil in water (o/w) creams mix with sebum and are more suitable for weeping or wounded surface.

(b) Hydration of stratum corneum

An occlusive layer reduces evaporation of water from skin, increasing hydration of the horny layer and, therefore, promotes penetration of medicament.

E.g. hydrocarbons, wool fat and isopropyl myristate containing ointments produce occlusive films on the skin. Water in oil (o/w) type creams have some occlusive effects.

Humectants like glycerols are not good for retaining water because at low atmospheric humidities, because they tend to increase loss of water by absorbing it from the skin.

(c) Penetration of the epidermis

Bases miscible with the sebum penetrate into the regions of the skin in which sebum is found.

E.g. Woolfat (originating from sebaceous glands of sheep) penetrates into the skin.

Vegetable oils penetrate more slowly and liquid paraffin does not penetrate at all.

(d) Alteration of skin permeability

Penetration can be improved by dissolving the medicament in an organic liquid such as ethanol, dimethylformamide (DMF), dimethyl acetamide, dimethylsulfoxide (DMSO) and propylene glycol. They increases the hydration of skin.

OINTMENT

Definition: Ointments are semisolid preparations for application to the skin or mucosae. The ointment bases are almost always anhydrous and generally contains one or more medicaments in suspension or solution.

***Characteristics of an ideal ointment*:**

1. It should be chemically and physically stable.
2. It should be smooth and free from grittiness.
3. It should melt or soften at body temperature and be easily applied.
4. The base should be non-irritant and should have no therapeutic action.
5. The medicament should be finely divided and uniformly distributed throughout the base.

Classification of ointments

According to their therapeutic properties based on penetration of skin.

(a) Epidermic,

(b) Endodermic,

(c) Diadermic

(a) Epidermic ointments

- These ointments are intended to produce their action on the surface of the skin and produce local effect.
- They are not absorbed.
- They acts as protectives, antiseptics and parasiticides.

(b) Endodermic ointments

- These ointments are intended to release the medicaments that penetrate into the skin.
- They are partially absorbed and acts as emollients, stimulants and local irritants.

(c) Diadermic ointments

- These ointments are intended to release the medicaments that pass through the skin and produce systemic effects.

OINTMENT BASES

The ointment base is that substance or part of an ointment preparation which serves as carrier or vehicle for the medicament.

An ideal ointment base should be inert, stable, smooth, compatible with the skin, non-irritating and should release the incorporated medicaments readily.

Classification of ointment bases:

1. Oleaginous bases
2. Absorption bases
3. Water-miscible bases
4. Water soluble bases

OLEAGINOUS BASES

These bases consists of oils and fats. The most important are the

Hydrocarbons i.e. petrolatum, paraffins and mineral oils.

The *animal fat* includes lard.

The combination of these materials can produce a product of desired melting point and viscosity.

(a) Petrolatum (Soft paraffin)

- This is a purified mixture of semi-solid hydrocarbons obtained from petroleum or heavy lubricating oil.

Yellow soft paraffin (Petrolatum; Petroleum jelly)

- This a purified mixture of semisolid hydrocarbons obtained from petroleum. It may contain suitable stabilizers like, antioxidants e.g. α-tocopherol (Vitamin E), butylated hydroxy toluene (BHT) etc.
- Melting range: 38 to 56^0C.

White soft paraffin (White petroleum jelly, White petrolatum)

- This a purified mixture of semisolid hydrocarbons obtained from petroleum, and wholly or partially decolorized by percolating the yellow soft paraffin through freshly burned bone black or adsorptive clays.
- Melting Range: 38 to 56^0C.
- *Use:* The white form is used when the medicament is colourless, white or a pastel shade.
- This base is used in

  Dithranol ointment B.P.

  Ammoniated Mercury and Coal tar ointment B.P.C. Zinc ointment B.P.C.

(b) Hard paraffin (Paraffin)

This is a mixture of solid hydrocarbons obtained from petroleum.

It is colourless or white, odorless, translucent, wax-like substance. It solidifies between 50 and 57^0C and is used to stiffen ointment bases.

(c) Liquid paraffin (Liquid petrolatum, White mineral oil)

It is a mixture of liquid, hydrocarbons obtained from petroleum. It is transparent, colourless, odourless, viscous liquid.

On long storage it may oxidize to produce peroxides and therefore, it may contain tocopherol or BHT as antioxidants.

It is used along with hard paraffin and soft paraffin to get a desired consistency of the ointment. Tubes for eye, rectal and nasal ointments have nozzles with narrow orifices through which it is difficult to expel very viscous ointments without the risk of bursting the tube. To facilitate the extrusion upto 25% of the base may be replaced by liquid paraffins.

Advantages of hydrocarbons bases:

(i) They are not absorbed by the skin. They remain on the surface as an occlusive layer that restricts the loss of moisture hence, keeps the skin soft.

(ii) They are sticky hence ensures prolonged contact between skin and medicament.

(iii) They are almost inert. They consist largely of saturated hydrocarbons, therefore, very few incompatibilities and little tendency of rancidity are there.

(iv) They can withstand heat sterilization, hence, sterile ophthalmic ointments can be prepared with it.

(v) They are readily available and cheap.

Disadvantages of hydrocarbon bases;

(i) It may lead to water logging followed by maceration of the skin if applied for a prolonged period.

(ii) It retains body heat, which may produce an uncomfortable feeling of warmth.

(iii) They are immiscible with water; as a result rubbing onto the surface and removal after treatment both are difficult.

(iv) They are sticky, hence makes application unpleasant and leads to contamination of clothes.

(v) Water absorption capacity is very low, hence, these bases are poor in absorbing exudate from moist lesions.

ABSORPTION BASE

- The term absorption base is used to denote the water absorbing or emulsifying property of these bases and not to describe their action on the skin.
- These bases (some times called *emulsifiable ointment bases*) are generally anhydrous substances which have the property of absorbing (emulsifying) considerable quantity of water yet retaining its ointment-like consistency.
- Preparations of this type do not contain water as a component of their basic formula but if water is incorporated a W/O emulsion results.

Wool Fat (anhydrous lanolin)

It is the purified anhydrous fat like substance obtained from the wool of sheep.

- It is practically insoluble in water but can absorb water upto 50% of its own weight. Therefore it is used in ointments the proportion of water or aqueous liquids to be incorporated in hydrocarbon base is too large.
- Due to its sticky nature it is not used alone but is used along with other bases in the preparation of a number of ointments.

E.g. Simple ointment B.P. contains 5% and the B.P. eye ointment base contains 10% Woolfat.

Hydrous Wool Fat (Lanolin)

- It is a mixture of 70 % w/w wool fat and 30 % w/w purified water. It is a w/o emulsion. Aqueous liquids can be emulsified with it.
- It is used alone as an emollient.
- Example: - Hydrous Wool Fat Ointment B.P.C., Calamine Coal Tar Ointment.

Wool Alcohol

It is the emulsifying fraction of wool fat. Wool alcohol is obtained from wool fat by treating it with alkali and separating the fraction containing cholesterol and other alcohols. It contains not less than 30% of cholesterol.

Use:-

- It is used as an emulsifying agent for the preparation of w/o emulsions and is used to absorb water in ointment bases.
- It is also used to improve the texture, stability and emollient properties of o/w emulsions.

Examples: - Wool alcohol ointment B.P. contains 6% wool alcohol and hard, liquid and soft paraffin.

Beeswax

It is purified wax, obtained from honey comb of bees.

It contains small amount of cholesterol. It is of two types: (a) yellow beeswax and (b) white beeswax.

Use:-

Beeswax is used as a stiffening agent in ointment preparations.

Examples:-Paraffin ointment B.P.C. contains beeswax.

Cholesterol

It is widely distributed in animal organisms. Wool fat is also used as a source of cholesterol.

Use: - It is used to increase the water absorbing power of an ointment base.

Example: - Hydrophilic petroleum U.S.P. contains:

Cholesterol	3%
Stearyl alcohol	3%
White beeswax	8%
White soft paraffin	86%

Advantages of absorption bases:

(i) They are less occlusive nevertheless, are good emollient.

(ii) They assist oil soluble medicaments to penetrate the skin.

(iii)They are easier to spread.

(iv)They are compatible with majority of the medicaments.

(v) They are relatively heat stable.

(vi)The base may be used in their anhydrous form or in emulsified form.

(vii)They can absorb a large quantity of water or aqueous substances.

Disadvantages: Inspite of their hydrophilic nature, absorption bases are difficult to wash.

WATER MISCIBLE BASES

- They are miscible with an excess of water. Ointments made from water-miscible bases are easily removed after use.
- There are three official anhydrous water-miscible ointment bases:-

Example:-

- Emulsifying ointment B.P. – Contains anionic emulsifier.
- Cetrimide emulsifying ointment B.P. – contains cationic emulsifier
- Cetomacrogol emulsifying ointment B.P. – contains non-ionic emulsifier

Uses: they are used to prepare o/w creams and are easily removable ointment bases

E.g. Compound Benzoic Acid Ointment (Whitfield's Ointment) – used as antifungal ointment.

Advantages of water miscible bases:

(i) Readily miscible with the exudates from lesions.

(ii) Reduced interference with normal skin function.

(iii) Good contact with the skin, because of their surfactant content.

(iv) High cosmetic acceptability, hence there is less likelihood of the patients discontinuing treatment.

(v) Easy removal from the hair.

WATER SOLUBLE BASES

Water soluble bases contain only the water soluble ingredients and not the fats or other greasy substances, hence, they are known as grease-less bases.

Water soluble bases consists of water soluble ingredients such as polyethylene glycol polymers (PEG) which are popularly known as "carbowaxes" and commercially known as "macrogols".

They are a range of compounds with the general formula:

$$CH_2OH.\ (CH_2OCH_2)_n\ CH_2OH$$

The PEGs are mixtures of polycondensation products of ethylene and water and they are described by numbers representing their average molecular weights. Like the paraffin hydrocarbons they vary in consistency from viscous liquids to waxy solids.

Example:-

Macrogols 200, 300, 400	– viscous liquids
Macrogols 1500	– greasy semi-solids
Macrogols 1540, 3000, 4000, 6000	– waxy solids.

Different PEGs are mixed to get an ointment of desired consistency.

Advantages of PEGs as ointment base:

(a) They are water soluble; hence, very easily can be removed from the skin and readily miscible with tissue exudates.

(b) Helps in good absorption by the skin.

(c) Good solvent properties. Some water-soluble dermatological drugs, such as salicylic acid, sulfonamides, sulfur etc. are soluble in this bases.

(d) Non-greasy.

(e) They do not hydrolyze, rancidity or support microbial growth.

(f) Compatibility with many dermatological medicaments.

Disadvantages:

(a) Limited uptake of water. Macrogols dissolve when the proportion of water reaches about 5%.

(b) Reduction in activity of certain antibacterial agents, e.g. phenols, hydroxybenzoates and quaternary compounds.

(c) Solvent action on polyethylene and Bakelite containers and closures.

Certain other substances which are used as water soluble ointment bases include tragacanth, gelatin, pectin, silica gel, sodium alginate, cellulose derivatives, etc.

FACTORS GOVERNING SELECTION OF AN IDEAL OINTMENT BASE

1. Dermatological factors
2. Pharmaceutical factors

1. Dermatological factors

(a) Absorption and Penetration:

'Penetration' means passage of the drug across the skin i.e. cutaneous penetration, and 'absorption' means passage of the drug into blood stream.

- Medicaments which are both soluble in oil and water are most readily absorbed though the skin.
- Whereas animal and vegetable fats and oils normally penetrate the skin.
- Animals fats, e.g. lard and wool fat when combined with water, penetrates the skin.
- O/w emulsion bases release the medicament more readily than greasy bases or w/o emulsion bases.

(b) Effect on the skin

- Greasy bases interfere with normal skin functions i.e. heat radiation and sweating.
- They are irritant to the skin.
- O/w emulsion bases and other water miscible bases produce a cooling effect due to the evaporation of water.

(c) Miscibility with skin secretion and sebum

Skin secretions are more readily miscible with emulsion bases than with greasy bases.

Due to this the drug is more rapidly and completely released to the skin.

(d) Compatibility with skin secretions:

The bases used should be compatible with skin secretions and should have pH about 5.5 because the average skin pH is around 5.5. Generally neutral ointment bases are preferred.

(e) Non-irritant

All bases should be highly pure and bases especially for eye ointments should be non-irritant and free from foreign particle.

(f) Emollient properties

Dryness and brittleness of the skin causes discomfort to the skin therefore, the bases should keep the skin moist. For this purpose water and humectants such as glycerin, propylene glycol are used. Ointments should prevent rapid loss of moisture from the skin.

(g) Ease of application and removal

The ointment bases should be easily applicable as well as easily removable from the skin by simple washing with water. Stiff and sticky ointment bases require much force to spread on the skin and during rubbing newly formed tissues on the skin may be damaged.

2. PHARMACEUTICAL FACTORS

(a) Stability

Fats and oils obtained from animal and plant sources are prone to oxidation unless they are suitably preserved. Due to oxidation odour comes out. This type of reactions are called *rancidification*. Lard, from animal origin, rancidify rapidly. Soft paraffin, simple ointment and paraffin ointment are inert and stable. Liquid paraffin is also stable but after prolonged storage it gets oxidized. Therefore, an antioxidant like *tocopherol* (Vit -E) may be incorporated. Other antioxidants those may be used are *butylated hydroxy toluene* (BHT) or *butylated hydroxy anisole* (BHA).

(b) Solvent properties

Most of the medicaments used in the preparation of ointments are insoluble in the ointment bases therefore, they are finely powdered and are distributed uniformly throughout the base.

(c) Emulsifying properties

Hydrocarbon bases absorbs very small amount of water.

Wool fat can take about 50% of water and when mixed with other fats can take up several times its own weight of aqueous solution.

Emulsifying ointment, cetrimide emulsifying ointment and cetomacrogol emulsifying ointment are capable of absorbing considerable amount of water, forming w/o creams.

(d) Consistency

The ointments produced should be of suitable consistency. They should neither be hard nor too soft. They should withstand climatic conditions. Thus in summer they should not become too soft and in winter not too hard to be difficult to remove from the container and spread on the skin.

The consistency of an ointment base can be controlled by varying the ratio of hard and liquid paraffin.

PREPARATION OF OINTMENTS

A well-made ointment is –

(a) ***Uniform throughout*** i.e. it contains no lumps of separated high melting point ingredients of the base, there is no tendency for liquid constituents to separate and insoluble powders are evenly dispersed.

(b) ***Free from grittiness,*** i.e. insoluble powders are finely subdivided and large lumps of particles are absent. Methods of preparation must satisfy this criteria.

Two mixing techniques are frequently used in making ointments:

1. **Fusion**, in which ingredients are melted together and stirred to ensure homogeneity.

2. **Trituration**, in which finely-subdivided insoluble medicaments are evenly distributed by grinding with a small amount of the base or one of its ingredients followed by dilution with gradually increasing amounts of the base.

1. OINTMENTS PREPARED BY FUSION METHOD:

When an ointment base contain a number of solid ingredients such as white beeswax, cetyl alcohol, stearyl alcohol, stearic acid, hard paraffin, etc. as components of the base, it is required to melt them. The melting can be done in two methods:

Method-I

The components are melted in the decreasing order of their melting point i.e. the higher m.p. substance should be melted first, the substances with next melting point and so on. The medicament is added slowly in the melted ingredients and stirred thoroughly until the mass cools down and homogeneous product is formed.

Advantages:

This will avoid over-heating of substances having low melting point.

Method-II

All the components are taken in subdivided state and melted together.

Advantages:

The maximum temperature reached is lower than Method-I, and less time was taken possibly due to the solvent action of the lower melting point substances on the rest of the ingredients.

Cautions:

(i) Melting time is shortened by grating waxy components (i.e. beeswax, wool alcohols, hard-paraffin, higher fatty alcohols and emulsifying waxes) by stirring during melting and by lowering the dish as far as possible into the water bath so that the maximum surface area is heated.

(ii) The surface of some ingredients discolors due to oxidation e.g. wool fats and wool alcohols and this discolored layers should be removed before use.

(iii) After melting, the ingredients should be stirred until the ointment is cool, taking care not to cause localized cooling, e.g. by using a cold spatula or stirrer, placing the dish on a cold surface (e.g. a plastic bench top) or transferring to a cold container before the ointment has fully set. If these precautions are ignored, hard lumps may separate.

(iv) Vigorous-stirring, after the ointment has begun to thicken, causes excessive aeration and should be avoided.

(v) Because of their greasy nature, many constituents of ointment bases pickup dirt during storage, which can be seen after melting. This is removed from the melt by allowing it to sediment and decanting the supernatant, or by passage through muslin supported by a warm strainer. In both instances the clarified liquid is collected in another hot basin.

(vi) If the product is granular after cooling, due to separation of high m.p. constituents, it should be remelted, using the minimum of heat, and again stirred and cooled.

Example:

(i) **Simple ointment B.P. contains**

Wool fat	50g
Hard paraffin	50g
Cetostearyl alcohol	50g
White soft paraffin	850g

Type of preparation: Absorption ointment base

Procedure:

Hard paraffin and cetostearyl alcohol on water-bath. Wool fat and white soft paraffin are mixed and stirred until all the ingredients are melted. If required decanted or strained and stirred until cold and packed in suitable container.

(ii) Paraffin ointment base

Type of preparation: Hydrocarbon ointment base

(iii) Wool alcohols ointment B.P.

Type of preparation: Absorption base

(iv) Emulsifying ointment B.P.

Type of preparation: Water-miscible ointment base.

(v) Macrogol ointment B.P.C

Type of preparation: Water soluble ointment base

Formula: Macrogol 4000

Liquid Macrogol 300

Method:

- Macrogol 4000 is melted and previously warmed liquid macrogol 300 is added.
- Stirred until cool.

2. OINTMENT PREPARED BY TRITURATION

This method is applicable in the base or a liquid present in small amount.

(i) Solids are finely powdered are passed through a sieve (# 250, # 180, #125).

(ii) The powder is taken on an ointment-slab and triturated with a small amount of the base. A steel spatula with long, broad blade is used. To this additional quantities of the base are incorporated and triturated until the medicament is mixed with the base.

(iii)Finally liquid ingredients are incorporated. To avoid loss from splashing, a small volume of liquid is poured into a depression in the ointment a thoroughly incorporated before more is added in the same way. Splashing is more easily controlled in a mortar than on a tile.

Example:

(i) Whitfield ointment (Compound benzoic acid ointment B.P.C.)

Formula: Benzoic acid, in fine powder 6gm

Salicylic acid, in fine powder 3gm

Emulsifying ointment 91gm

Method: Benzoic acid and salicylic acid are sieved through No. 180 sieves. They are mixed on the tile with small amount of base and levigated until smooth and dilute gradually.

(ii) Salicylic acid sulphur ointment B.P.C.

3. OINTMENT PREPARATION BY CHEMICAL REACTION

Chemical reactions were involved in the preparation of several famous ointments of the past, e.g. Strong Mercuric Nitrate Ointment, of the 1959 B.P.C.

(a) Ointment containing free iodine

Iodine is only slightly soluble in most fats and oils but readily soluble.

Iodine is readily soluble in concentrated solution of potassium iodide due to the formation of molecular complexes $KI.I_2$, $KI.2I_2$, $KI.3I_2$ etc.

These solutions may be incorporated in absorption-type ointment bases.

E.g. *Strong Iodine Ointment B.Vet.C* (British Veterinary Pharmacopoeia) is used to treat ringworm in cattle. It contains free iodine. At one time this type of ointments were used as counter-irritants in the treatment of human rheumatic diseases but they were not popular because:

They stain the skin a deep red color.

(i) Due to improper storage the water dries up and the iodine crystals irritate the skin, hence glycerol was some times added to dissolve the iodine-potassium iodide complex instead of water.

- *Example:*
  - Strong Iodine Ointment B. Vitamin C.
    - Iodine
    - Woolfat
    - Yellow soft paraffin
    - Potassium iodide
    - Water

Procedure:

(i) KI is dissolved in water. I_2 is dissolved in it.

(ii) Woolfat and yellow soft paraffin are melted together over water bath. Melted mass is cooled to about 40^0C.

(iii) I_2 solution is added to the melted mass in small quantities at a time with continuos stirring until a uniform mass is obtained.

(iv) It is cooled to room temperature and packed.

Use: - Ringworm in cattle.

(b) Ointment containing combined iodine

Fixed oils and many vegetable and animal fats absorb iodine which combines with the double bonds of the unsaturated constituents, e.g.

$$\underset{\text{Oleic acid}}{CH_3.(CH_2)_2.CH=CH.(CH_2)_7.COOH} + I_2 \rightarrow \underset{\text{di-iodostearic acid}}{CH_3.(CH_2)_2.CHI.CHI.(CH_2)_7.COOH}$$

Example: **Non-staining Iodine Ointment B.P.C. 1968**

Iodine

Arachis Oil

Yellow Soft Paraffin

Method:

(a) Iodine is finely powdered in a glass mortar and required amount is added to the oil in a glass-stoppered conical flask and stirred well.

(b) The oil is heated at 50^0C in a water-bath and stirred continually. Heating is continued until the brown color is changed to greenish-black; this may take several hours.

(c) From 0.1g of the preparation the amount of iodine is determined by B.P.C. method and the amount of soft paraffin base is calculated to give the product the required strength.

(d) Soft paraffin is warmed to 40^0C. The iodized oil is added and mixed well. No more heat is applied because this causes deposition of a resinous substance.

(e) The preparation is packed in a warm, wide-mouthed, amber color, glass bottle. It is allowed to cool without further stirring.

4. PREPARATION OF OINTMENTS BY EMULSIFICATION

An emulsion system contain an oil phase, an aqueous phase and an emulsifying agent.

For o/w emulsion systems the following emulsifying agents are used:

(i) Water soluble soap

(ii) cetyl alcohol

(iii) Glyceryl monostearate

(iv) Combination of emulsifiers: triethanolamine stearate + cetyl alcohol

(v) Non-ionic emulsifiers: glyceryl monostearate, glyceryl monooelate, propylene glycol stearate

For w/o emulsion creams the following emulsifiers are used:

(i) Polyvalent ions e.g magnesium, *calcium and aluminium* are used.

(ii) Combination of emulsifiers: *beeswax + divalent calcium ion*

- The viscosity of this type of creams prevent coalescence of the emulsified phases and helps in stabilizing the emulsion.

Example:

COLD CREAM:

Procedure:

(i) Water immiscible components e.g. oils, fats, waxes are melted together over water bath (70^0C).

(ii) Aqueous solution of all heat stable, water soluble components are heated (70^0C).

(iii) Aqueous solution is slowly added to the melted bases with continuous stirring until the product cools down and a semi-solid mass is obtained.

N.B. The aqueous phase is heated otherwise high melting point fats and waxes will immediately solidify on addition of cold aqueous solution.

MANUFACTURE OF OINTMENTS / CREAMS IN INDUSTRIAL SCALE

1. Preparation of oil and aqueous phase

Oils + Fats

↓ *Equipment*: Steam jacketed kettle

Melted and mixed

↓

Strained through several layers of cheese Cloths to remove foreign matter

Water soluble ingredients + Purified water

↓ *Equipment*: Mechanical stirrer

Dissolved

↓

Filtered

↓

Heated to the melting point of oil phase

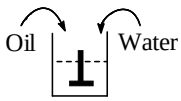
- Cakes, flakes or powdered waxes are directly weighed in a physical balance.
- Semisolid petrolatum is melted in the container supplied by an immersion heater, the liquid petrolatum is then transferred by a *metering pump* through *metal reinforced inert plastic hoses and insulated pipes*.

2. Mixing of oil and water phases

Mixing temperature is 70–72^{0}C for proper mixing.

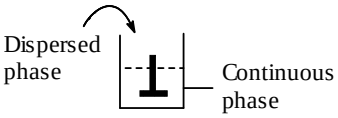
Three methods of mixing are there:

(A) Simultaneous blending



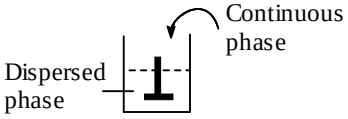
- For continuous or large batch operation
- *Equipments*
  Proportioning pump
  Continuous mixer

(B) Addition of disperse phase to continuous phase



- For an emulsion having low volume of dispersed phase.
- *Equipment*:
  Simple metering pump

(C) Addition of continuous phase to disperse phase



- For an emulsion formed by phase inversion method.
- *Equipment*:
  Simple metering pump.

- Batch sizes are on weight basis. For weighing a *hydraulic load cell* is fitted under one of the leg of the mixing kettle.

3. Cooling the semisolid

- Cooling should be slow to prevent crystallization of high m.p. waxes.
- Perfumes are added at 43 to 45^0C.
- *Equipments*: Kettle fitted with heating / cooling arrangements, agitator and sweep blades (For scrapping the wall).

Cooled to 43 to 45^0C

↓ Kettle with agitator and sweep blades

Addition of perfume

↓

Addition of drug powder

↓

Dispersed or dissolved

4. Homogenization

Creams or ointments

↓ *Equipment*: Low-shear gear pump and

Roller mill / colloid mill / valve type homogenizer

Homogenization

5. Storage of semisolids

Stored before packaging. In the mean time Q.C. report comes. Stored in a tight-fitting stainless steel (SS#316) container.

6. Transfer of materials for packaging

Equipment: Ointment filling machine

Washing of the equipments with high-pressure (up to 1000psi), low-volume pumps and hot water and detergents should be done.

To sterilize the equipments, containers, pumps and other accessories are flushed with chlorinated water or formalin – followed by rinsing them with bacteria free water.

STABILITY OF OINTMENTS

The ointments should remain stable from the time of preparation to the time when the whole of it is consumed by the user.

(i) To stop microbial growth preservatives are added. Preservatives for ointment includes: p-hydroxy benzoates, phenol, benzoic acid, sorbic acid, methyl paraben, propyl paraben, quaternary ammonium compounds, mercury compounds etc.

(ii) The preservatives should not react with any of the component of the formulation. Plastic containers may absorb the preservative and thereby decreasing the concentration of preservative available for killing the bacteria.

(iii) Some ingredients like wool fat and wool alcohols are susceptible to oxidation. Therefore, a suitable antioxidant may be incorporated to protect the active ingredients from oxidation.

(iv) Incompatible drugs, emulsifying agents and preservatives must be avoided. The drugs which are likely to hydrolyze must be dispensed in an anhydrous base.

(v) Humectants such as, glycerin, propylene glycol and sorbitol may be added to prevent the loss of moisture from the preparation.

(vi) Ointment must be stored at an optimum temperature otherwise separation of phases may take place in the emulsified products which may be very difficult to remix to get a uniform product.

PRESERVATIVE:

PRESERVATIVE some base, although, resist microbial attack but because of their high water content, it require an antimicrobial preservative.

Commonly used preservatives include

- Methyl hydroxybenzoate
- Propyl hydroxybenzoate Chlorocresol
- Benzoic acid Phenyl mercuric nitrate

ANTIOXIDANTS:

ANTIOXIDANTS Oxygen is a highly reactive atom that is capable of becoming part of potentially damaging molecules commonly called “free radicals.” Free radicals are capable of attacking the healthy cells of the body, causing them to lose their structure and function. To prevent this an antioxidants are added.

E.g. Butylated hydroxy anisole, Butylated hydroxy toluene.

CLASSIFICATION OF ANTIOXIDANTS:

CLASSIFICATION OF ANTIOXIDANTS ANTIOXIGENS REDUCING AGENT ANTIOXIDANT SYNERGISTS Acts by reacting with free radical.

E.g. butylated hydroxyanisole (BHA)

Butylated hydroxytoluene (BHT)

Tocopherlos (used for oil system)

Have lower redox potential than drug, hence gets oxidised first.

E.g. Ascorbic acid Potassium and sodium metabisulfite Thiosulfite (used for aqueous system)

Chelating or sequestering agent, enhacne the effects of antioxidants.

E.g. Citric acid Tartaric acid lecithin 26

GELLING AGENTS:

GELLING AGENTS gelling agents, forms a gel, dissolving in the liquid phase as a colloid mixture that forms a weakly cohesive internal structure. These are organic hydrocolloids or hydrophilic inorganic substances.

E.g. **Tragacanth, Sodium Alginate, Pectin, Starch, Gelatin, Cellulose Derivatives, Carbomer, and Poly Vinyl Alcohol Clays.**

PERMEATION ENHANCERS:

Skin can act as a barrier. With the introduction of various penetration enhancers, penetration of the drug through the skin can be improved. Sr. no Permeation enhancer Drugs used

1. Menthol, carvacrol, linalool Propranolol hydrochloride
2. Limonene Indomethacin, ketoprofen
3. Geraniol, nerolidol Diclofenac sodium
4. Oleic acid Piroxicam

EMULSIFIER:

EMULSIFIER An emulsifier (emulgent) is a substance that stabilizes an emulsion by increasing its kinetic stability. One class of emulsifiers is known as surface active substances, or surfactants. Ideal properties of emulsifier includes,

a) Must reduce surface tension for proper emulsification.

b) Prevents coalescence and should quickly absorb around the dispersed phase.

c) Ability to increase the viscosity at low concentration.

d) Effective at low concentration

PHARMAROCKS: AMAR RAVAL
SIZE REDUCTION AND SIZE SEPARATION

Syllabus:
Definition, objectives of size reduction and size separation, factors affecting size reduction, laws governing energy and power requirements of mills including ball mill, hammer mill, fluid energy mill etc., sieve analysis, standards of sieves, size separation equipment shaking and vibrating screens, gyratory screens, cyclone separator, air separator, bag filters, cottrell precipitator, scrubbers, size separators basing on sedimentation theory.

Definition

Size reduction (or Comminution)
Size reduction or *comminution* is the process of reducing substances to smaller particles.

Size separation (or Classification)
Size separation (or classification) is a process in which particles of desired size are separated from other fractions.

Objectives
Objectives of size reduction
1. Size reduction leads to increase of surface area.
   Example-I: The rate of dissolution of solid drug particles increases many folds after size reduction. Griseofulvin, an antifungal drug, when administered in its micronized form shows around five times better absorption.
   Example-II: The absorptive power of charcoal and kaolin increases after size reduction due to increase in surface area.
2. Size reduction produces particles in narrow size range. Mixing of powders with narrow size range is easier.
3. Pharmaceutical suspensions require finer particle size. It reduces rate of sedimentation.
4. Pharmaceutical capsules, insufflations (i.e. powders inhaled directly into the lungs), suppositories and ointments require particles size to be below 60μm size.

Objectives of size separation
1. Any solid materials, after size reduction, never gives particles of the same size but contains particles of varying sizes. The size-reduced particles are then passed through sieves to get fractions of narrow size range.
2. During tablet granulation the granules should be within narrow size range, otherwise, weight variation will take place during tablet punching.

Factors affecting size-reduction

The pharmaceutical industry uses a great variety of materials, including chemical substances, animal tissues and vegetable drugs.

A. Factors related to the nature of raw materials
Hard materials: Hard materials like pumice and iodine are most difficult to comminute. During size reduction these types of materials will produce abrasive wear of milling surfaces, which will then contaminate the material.
Fibrous materials: Crude drugs obtained from plants like glycyrrhiza, rauwolfia, ginger etc. are fibrous in nature and cannot be crushed by pressure. So they may be size-reduced by cutter mill.
Friable materials: Sucrose and dried filter cakes are friable (i.e. brittle) hence they are easy to comminute by hammer mill or fluid energy mill.
Plastic materials: Synthetic gums, waxes and resins become soft and plastic during milling. These low melting substances should be chilled (made cold) before milling. These types of materials are milled by using hammer mill and fluid energy mill.
Hygroscopic materials: Hygroscopic materials absorbs moisture rapidly hence they must be comminuted inside a closed equipment like ball-mill.
Thermolabile materials: Thermolabile materials like vitamins and antibiotics are milled inside chilled equipment.
Inflammable materials: Fine dust, such as dextrin, starch and sulphur, is a potential explosive mixture under certain conditions. All electrical switches should be explosive proof and the mill should be earthed properly.
Particle size of the feed: For a mill to operate satisfactorily, the feed should be of proper size.
Moisture content: Presence of more than 5% moisture hinders the milling process and produces a sticky mass.

B. Factors related to the nature of the finished product

Particle size: Moderately coarse powders may be obtained from various impact mill. If very fine particles like micronized particles of griseofulvin may be obtained from fluid energy mill.
Ease of sterilization: When preparations are intended for parenteral (injection) purpose and ophthalmic uses, size reduction must be conducted in a sterile environment. Mills should be sterilized by steam before use.
Contamination of milled materials: In case of potent drugs and low dose products, contamination of the products should be avoided. Equipment free from wearing (e.g. fluid energy mill) may be used in this case.

Laws governing energy and power requirements of mills

During size reduction energy is supplied to the equipment (mill). Very small amount of energy (less than 2%) actually produce size reduction. Rest of the energy is dissipated (wasted) in:

(i) Elastic deformation of particles
(ii) Transport of material within the milling chamber
(iii) Friction between the particles
(iv) Friction between the particles and mill
(v) Generation of heat
(vi) Vibration and noise.
(vii) Inefficiency of transmission and motor.

Theories of milling

A number of theories have been proposed to establish a relationship between energy input and the degree of size reduction produced.

Rittinger's theory
Rittinger's theory suggests that energy required in a size reduction process is proportional to the new surface area produced.

$$E = K_R (S_n - S_i)$$

where, E = energy required for size reduction
K_R = Rittinger's constant
S_i = initial specific surface area
S_n = final specific surface area
Application: It is most applicable in size reducing brittle materials undergoing fine milling.

Bond's theory
Bond's theory states that the energy used in crack propagation is proportional to the new crack length produced

$$E = 2K_B \left(\frac{1}{\sqrt{d_n}} - \frac{1}{\sqrt{d_i}} \right)$$

where, E = energy required for size reduction
K_B = Bond's work index
d_i = initial diameter of particles
d_n = final diameter of particles
Application: This law is useful in rough mill sizing. The work index is useful in comparing the efficiency of milling operations.

Kick's theory
Kick's theory states that the energy used in deforming (or fracturing) a set of particles of equivalent shape is proportional to the ratio of change of size, or:

$$E = K_K \log \frac{d_i}{d_n}$$

where, E = energy required for size reduction
K_K = Kick's constant
d_i = initial diameter of particles
d_n = final diameter of particles
Application: For crushing of large particles Kick's theory most useful.

Walker's theory

Walker proposed a generalized differential form of the energy-size relationship:

$$dE = -K\frac{dD}{D^n}$$

where E = amount of energy (work done) required to produce a change
D = size of unit mass
K = Constant
n = constant

For n =1.0 Walker equation becomes Kick's theory used for coarse particles > 1 μm.

For n =1.5 Walker equation becomes Bond's theory. This theory is used when neither Kick's nor Rittinger's law is applicable.

For n =2.0 Walker equation becomes Rittinger's theory used for fine particles < 1 μm size.

Methods of size reduction

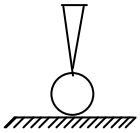
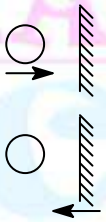
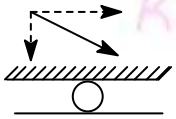
	Method	Diagram	Common Examples
Approximate increase in fineness of product	Cutting		Scissors Cutter mill
	Compression		Roller mill Crusher mill
	Impact		Hammer mill
	Attirtion (Pressure and friction)		File Fluid energy mill

Table: Uses of size reduction methods

Degree of size reduction	*Typical methods*	*Examples*
Large pieces	Cutter or compression mills	Rhubarb
Coarse powders	Impact mills	Liquorice, cascara
Fine powders	Combined impact and attrition mills	Rhubarb , belladonna
Very fine powders	Fluid energy mills	Vitamins and antibiotics

CUTTER MILL

Method of size reduction: Cutting

Construction and working principle:
The equipment has two parts – one is rotor and another part is the casing. Stationary knives are fitted on the casing and rotating knives are fitted on the rotor. Feed enters through the top hopper. The rotor rotates and both stationary and rotating knives cut the material into pieces. The lower part consists of a screen, so that material is retained in the mill until sufficient degree of size reduction has been effected.

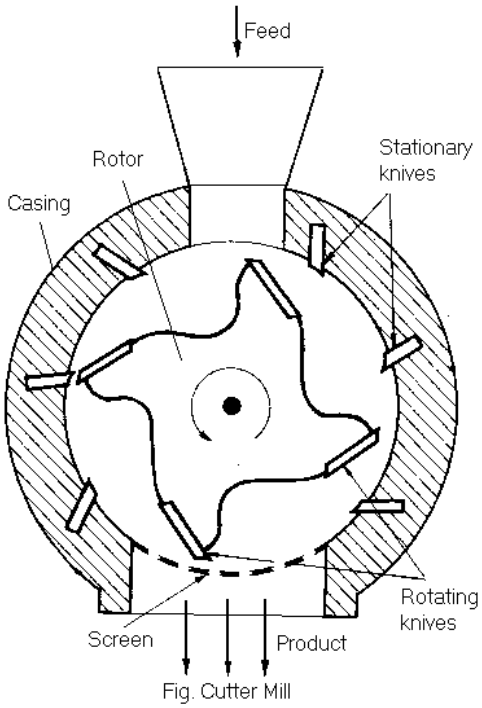


Fig. Cutter Mill

Applications:
This method is used to obtain coarse degree of size reduction of soft materials. Applied in size reduction of roots, peels or woods, prior to extraction.

ROLLER MILL

Method of size reduction: Compression

Construction and working principle:
The roller mill has two cylindrical rolls of stone or metal, mounted horizontally, which are capable of rotating on their longitudinal axes. One roll is rotated directly and the other rotates freely. When material is placed above the rolls it is drawn in through the nip and the second roll is rotated b y friction.
Diameter of the rolls: Few centimeter up to several meters
The gap between the roll may be adjusted to control the degree of size reduction.

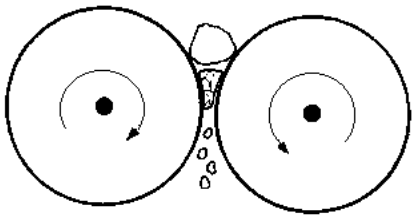


Fig. Roller mill

Applications:
Used for crushing or cracking seeds prior to extraction of fixed oils or bruising soft tissues (often after cutting) to aid solvent penetration.

HAMMER MILL

Method of size reduction: Impact

Construction and working principle:
Hammer mill consists of a stout metal casing, enclosing a central shaft to which four or more *hammers* are attached. These are mounted with *swivel* joints, so that the hammers swing out to a radial position when the shaft is rotated. The lower part of the casing consists of screen through which materials can escape, when sufficiently size reduced. The material is collected in a container placed below the screen.

- The screen can be changed according to the particle size required.
- According to the purpose of operation the hammers may be square-faced, tapered to a cutting form or have a stepped-form.
- The interior of the casing may be undulating in shape, instead of smooth circular form for better impact.
- The rotor operates at a speed of 80cycles per second.

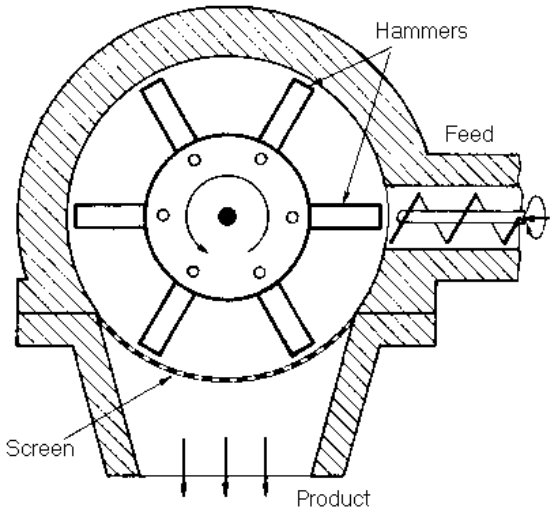


Fig. Hammer Mill

Advantages:
(a) It is rapid in action, and is capable of grinding many different types of materials.
(b) The product can be controlled by variation of rotor speed, hammer type and size and shape of mesh.
(c) Operation is continuous.
(d) No surface moves against each other so very little problem of contamination of mill materials.

Disadvantages:
(a) High speed of operation generates heat that may affect thermolabile materials or drugs containing gum, fat or resin.
(b) The rate of feed should be controlled otherwise the mill may be choked.
(c) Because of high speed of operation, the hammer mill may be damaged if some foreign materials like stone, metal pieces etc. are present in the feed.

Applications: Powdering of crystals and filter cakes.

BALL MILL

Construction
The ball mill consists of a hollow cylinder rotated on its horizontal axis. Inside the cylinder balls or pebbles are placed.

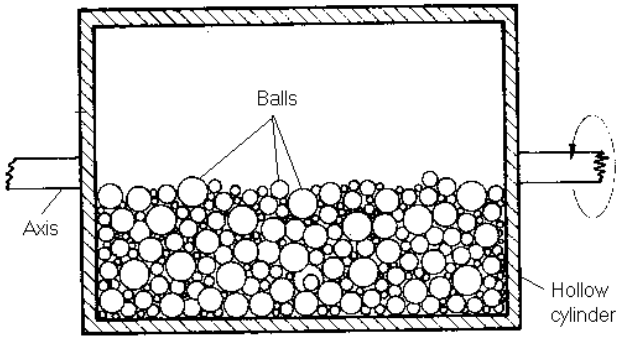


Fig. Ball mill

Cylinder:
- Cylinder may be made up of metal, porcelain or rubber.
- Rubber reduces the abrasion. Diameter of the cylinder ranges from 1 to 3m in pharmaceutical practice.

Balls:
- Balls occupy about 30 to 50% of the volume of the cylinder.
- Diameter of the balls depends on the feed size and diameter of the cylinder. The diameter of balls ranges from 2cm to 15cm.
- Balls may be of metal, porcelain or pebbles.

Working Principle:
Larger particles are fed through an opening of the cylinder. The opening is closed. The cylinder is rotated at the critical speed of ball mill. The optimum size reduction in a ball mill depends o the following factors:

Feed quantity:
Too much feed will produce cushioning effect and too little feed will produce loss of efficiency of the mill.

Speed of rotation of the cylinder:
- At low speed the mass of balls will slide or roll over each other and only a negligible amount of size reduction will take place.
- At high speeds, balls will be thrown out to the wall of the cylinder due to centrifugal force and no grinding will occur.
- At 2/3rd speed at which centrifugation just occurs is called the critical speed of the ball mill. At this speed the balls are carried almost to the top of the mill and then fall in a cascade across the diameter of the mill. By this means the maximum size reduction is obtained by impact of the particles between the balls and by attrition between the balls. Generally it is 0.5 cycles per seconds (cps).

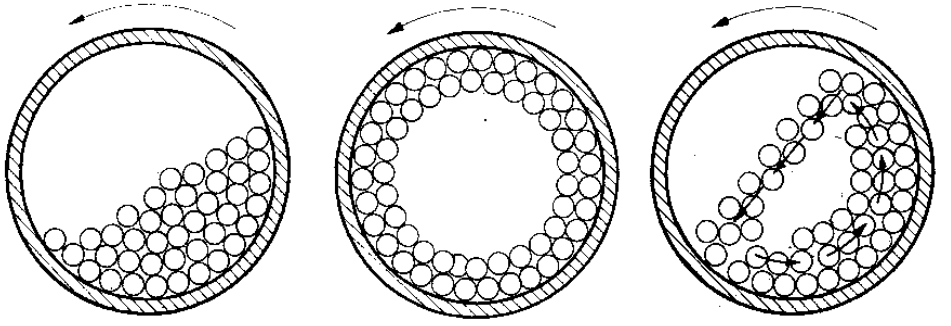

(a) Low speed with sliding (b) High speed with centrifuging (c) Correct speed with cascading

Fig. Ball mill operation

Advantages
1. It is capable of grinding a wide variety of materials of differing hardness.
2. It can be used in completely enclosed form, which makes it suitable for use with toxic materials.
3. It can produce very fine powders.
4. It is suitable both for dry and wet milling. Wet milling is required for preparation of pharmaceutical suspensions.

Disadvantages
1. Wear occurs from the balls and the inside surface of the cylinder hence there is possibility of contamination of product with mill material. Abrasive materials increase wear.
2. Soft or sticky materials may cause problems by caking on the sides of the mill or by holding the balls in aggregates.
3. The ball mill is a very noisy machine, particularly if the cylinder is made of metal.

Applications:
Large ball mills are used to grinding ores prior to manufacture of pharmaceutical chemicals. Smaller ball mills are used for grinding of drugs or excipients or for grinding suspensions.

Various types of ball mills:
Hardinge mill: In this type of ball mills the cylinder has a conical end towards a discharge point. In this mill the larger balls remain within the cylinder and the smaller balls are collected in the conical portion. As a result, coarser grinding takes place in the cylinder portion and finer grinding takes place in the apex of the conical portion. The product is more finer and uniform than general cylindrical ball mill.

Tube mill: They consist of long cylinder and can grind to a finer product than the conventional ball mill.

Rod mill: Instead of balls they contains rods, which extends the length of the mill. This rods are useful with sticky materials since rods do not form aggregates like balls.

Vibration mill: In this type of mills vibratory movements are given instead of rotation. The cylinder is mounted on springs which sets up vibration. The cylinder moves through a circular path with an amplitude of vibration up to abut 20mm and a rotational frequency of 15 to 50 per second.

FLUID ENERGY MILL

Construction:
It consists of a loop of pipe, which has a diameter of 2 to 20cm. The height of the loop may be up to 2m. Several nozzles are fitted at the bottom of the pipe. A classifier is fitted at the product collection point.

Working principle
A fluid usually air, is injected at very high pressure through nozzles at the bottom of the loop. This gives rise to a high velocity of circulation that produce turbulence. Solids are introduced into the stream through the feed inlet. As a result of high degree of turbulence, impacts and attrition occur between the particles. A *classifier* is fitted in the system so that only finer size particles are collected as products and the larger size particles are again sent to the stream of air for further size reduction.
The feed to the mill is previously size reduced and passed through a 100mesh screen.
The size of the product may be 5μm or below.

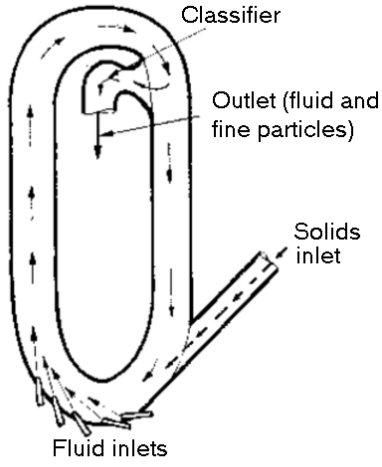


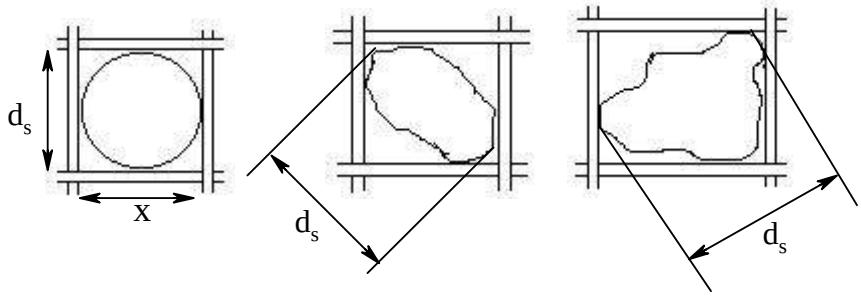
Fig. Fluid energy mill

Advantages:
1. The particle size of the product is smaller than that produced by any other method of size reduction.
2. Expansion of gases at the nozzles lead to cooling, counteracting the usual frictional heat that can affect heat-sensitive (thermolabile) materials.
3. Since the size reduction is by inter-particulate attrition there is little or no abrasion of the mill and no contamination of the product.
4. For oxygen or moisture sensitive materials inert gases like nitrogen can be used instead of normal air.
5. This method is used where fine powders are required like micronization of griseofulvin (an antifungal drug), antibiotics etc.

SIEVE ANALYSIS

Equivalent diameter

Sieve diameter, d_s, is the particle dimension that passes through a square aperture (length = x).



Sieve diameter, d_s for various particle shapes

Range of analysis

The International Standards Organization (ISO) sets lowest sieve diameter of 45μm. Powders are usually defined as particles having a maximum diameter of 1000μm, so this is the upper limit. In practice sieve analysis can be done over a range of 5 to 125000μm.

ISO Range : 45 to 1000 μm
Range available in practice: 5 to 125000 μm

Sample preparation

- Powders in dry state is usually used.
- Powders in liquid suspension can also be analyzed by sieve.

Principle of measurement with sieve

Sieve analysis utilizes a set of sieves. Each sieve is a woven, punched or electroformed mesh, often in brass or stainless steel, with known aperture diameter which form a physical barrier to particles. In sieve analysis a set of sieves (known as 'stack' or 'nest' of sieves) are arranged in such a way that the smallest aperture will be at the bottom and the largest aperture will be at the top.

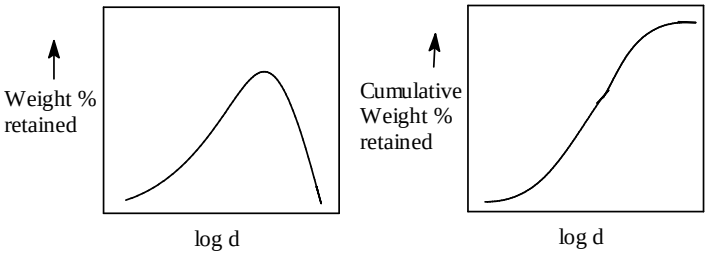
1. A sieve-nest usually comprises 6 to 8 sieves with an aperture progression based on $\sqrt{2}$ or $2\sqrt{2}$ change in diameter between adjacent sieves.
2. Initial weight (W_0) of powder sample was taken on the first sieve (i.e. topmost sieve). The sieve-set was closed and shaking was started. After shaking for a stipulated time, the sieve-set was taken out. All the sieves were disassembled.
3. The powder retained on each sieve was collected on a paper (bearing the mesh number) and weighed.

TABLE - 1

Sieve number (Passed/ Retained)	Size of opening (Passed / Retained)	Arithmetic mean Size of openings d (μm)	Weight Retained on smaller sieve (gm)	% Retained on smaller sieve	Cumulative % oversize
M1/M2	d1/d2	½(d1 + d2)	W1	p1=100w1/W	p1
M2/M3	d2/d3	½(d2 + d3)	W2	p2=100w2/W	p1+p2
M3/M4	d3/d4	½(d3 + d4)	W3	p3=100w3/W	p1+p2+p3
--	--	--	--	--	--
--	--	--	--	--	--
--	--	--	--	--	--
			Total = W	Total = 100	

TABLE – 2: Plot

log d	Weight % retained	Cumulative % oversize



STANDARDS OF SIEVES

It is required that wire-mesh sieves will be made from wire of uniform, circular cross-section and for each sieve the following particulars are stated:

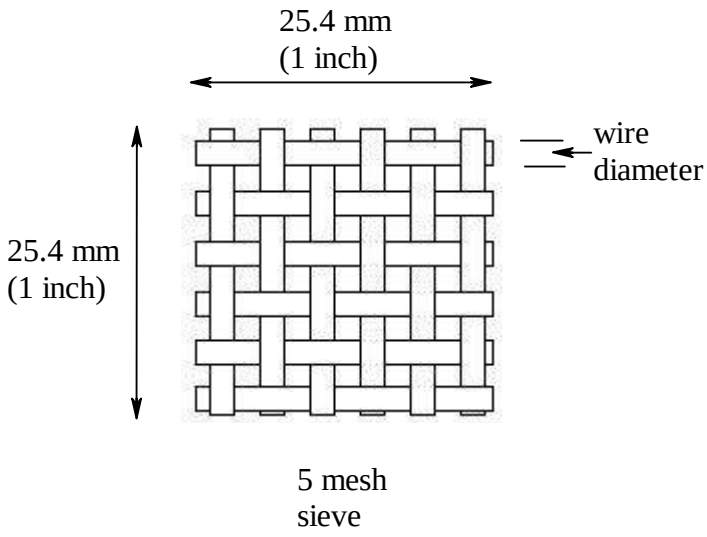
Number of sieve

This is the number of meshes in a length of 25.4mm (i.e. 1 inch), in each direction.

Nominal size aperture

This is the distance between the wires, so that it represents the length of the side of the square aperture.

N.B. While it is the diameter of the largest sphere that would pass the mesh, it is not necessarily the maximum dimension of the particle, plate like particles will pass through diagonally and long fibrous particles require only suitable orientation.

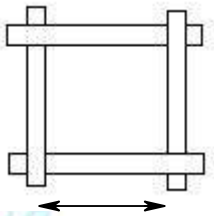


5 mesh sieve

Nominal diameter of the wire

The wire diameter is selected to give a suitable aperture size. It is also required to give the necessary strength to avoid distortion.

The diameter of the wire is represented by Standard Wire Gauge.



Nominal aperture

Approximate screen area

This standard expresses the area of the meshes as a percentage of the total area of the sieve. It is governed by the diameter of the wire. It is generally kept within 35 to 45% of the total area of the sieve.

This represents the useful area of a sieve. Greater screen area is preferred.

$$\text{Approximate Screen Area} = \frac{\text{Total sieve area - Area occupied by the wire}}{\text{Total area of the screen}} \times 100\%$$

Aperture tolerance average

Some variation in the aperture size is unavoidable and this variation is expressed as a percentage, known as aperture tolerance average. It is the maximum limit within which the dimension of meshes can be allowed to vary and still be acceptable for sieving.

Finer wires are likely to be subject to a greater proportional variation in diameter than coarse mesh. Hence, the aperture tolerance average is smaller for sieves of 5 to 10 mesh than in case of 300mesh.

Tyler Standard Screen Scale

Mesh	Clear Opening, mm	Wire Diameter, mm
3	6.680	1.778
4	4.699	1.651
6	3.327	0.914
8	2.362	0.813
10	1.651	0.889
14	1.168	0.635
20	0.833	0.437
28	0.589	0.318
35	0.417	0.310
48	0.295	0.234
65	0.208	0.183
100	0.147	0.107
150	0.104	0.066
200	0.074	0.053

SIZE SEPARATION EQUIPMENTS

SHAKING SCREEN

Principle:

Particles of different sizes are separated by passing them through a sieve, which oscillates to-and-fro continuously.

Construction:

Shaking screen consists of metal frame to which a screen is fixed at the bottom. The screen cloth may be riveted directly or fitted by using a removable bolted frame. The metal frame is suspended by hanger rods, so that it can move freely. The metal frame may be suspended either horizontally or in inclined position. One side of the frame is attached with an ordinary eccentric on a rotating shaft. The entire frame experiences a reciprocating (to-and-fro) motion.

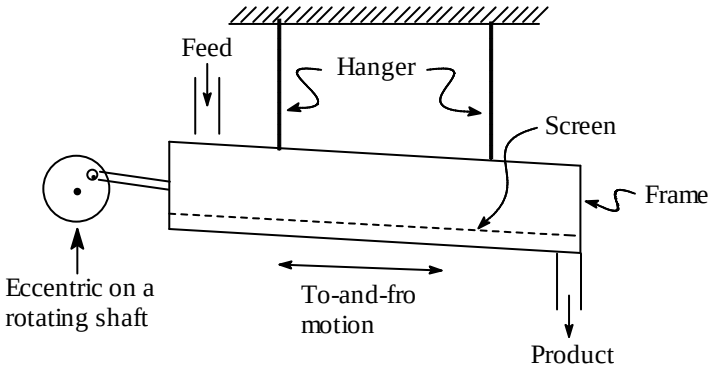


Fig. Shaking screen

Working:

The screen is allowed to shake in a reciprocating motion. The feed (material to be screened) is introduced on to the screen from a side. . Fine particles are screened off initially. The remaining materials moves forward and the over-sized particles are collected at the other end.

Advantages:

It requires low-head room and low power requirement.

Disadvantages:

High cost of maintenance of screens and supporting structures.

Its capacity is low.

SHAKING AND VIBRATING SCREENS (ROTEX SCREEN)

Principle: Rotex screen works on oscillating agitation (to-and-fro motion) by means of an eccentric mechanism. Further vibrations are caused by rubber balls.

Construction:

This equipment consists of a set of screens, which are slightly inclined at 5 degrees with horizontal axis. Each screen set is double layered. The upper screen is of a fixed size and the lower one is coarser screen, which is a supporting sieve. Between these two screens, wooden blocks are placed at different intervals. Between the wooden blocks rubber balls are placed. This two-sieve system represents one unit. Several such units are arranged in the descending order, i.e. sieve or larger size opening remains at the top and finer size opening remains at the bottom. The overall assembly of screens is supported on sliding contacts at the lower end. The upper end of the screen system is connected to an eccentric pin on a flywheel.

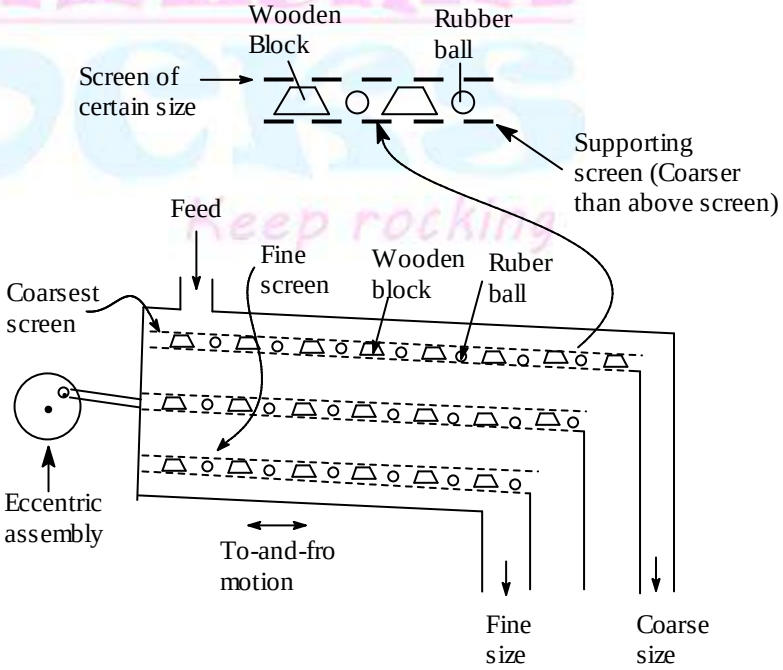


Fig. Rotex Screen

Working:

The screen system is allowed to agitate with the help of eccentric. The shaking motion of the screen causes the balls to fly between the screens. As they strikes the inclined surface of the wooden blocks, the balls deflect upward and strike the screen cloth and thus prevents blocking of the mesh. The feed is introduced at the higher end of the screen. The material passes through the upper screen and reaches the next screen. This process continues until all the materials are separated into fractions. The fractions are collected separately at the outlet point.

Uses: Rotec screen is used for handling a variety of dry powders, granules and dry foods.

GYRATORY SCREENS (FINEX)

Principle:

The Finex shifting machine consists of a horizontal screen to which a gyratory movement of great intensity and small amplitude is imparted by eccentric mechanism. Every particle is given a rotary movement on one axis and a second rotary movement on an axis at right angles to the first.

Construction:

Screens are fitted horizontally. The topmost has the largest opening and the bottom one will have finer opening. The overall assembly is given a gyratory motion by eccentric mechanism. Clearing gates are fitted at one side of the periphery.

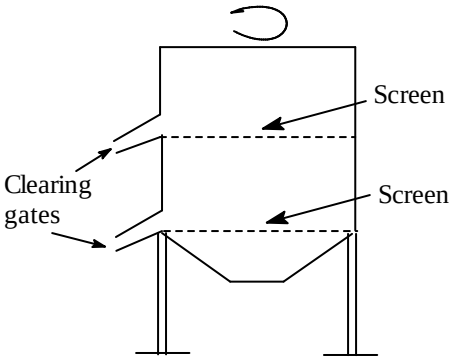


Fig. Gyratory Screens

Working:

The feed is introduced at the center of the screen and the gyratory motion drives the larger sizes to the periphery of the screen where it is discharged through a clearing gate set in upright side of the sieve. In some devices a spiral strip of metal is welded to the screen. The larger size passes progressively from the center to the periphery.

CYCLONE SEPARATOR

Principle

In cyclone separator centrifugal force is used to separate solid from fluids. The separation process depends on particle size and particle density. It is also possible to allow fine particles to be carried with the fluid.

Construction

It consists of a short vertical, cylindrical vessel with a conical base. The upper part of the vessel is fitted with a tangential inlet. The solid outlet is at the base. Fluid outlet is provided at the center of the top portion, which extends inwardly into the separator. Such an arrangement prevents the air short-circuiting directly from the inlet to the outlet of the fluid.

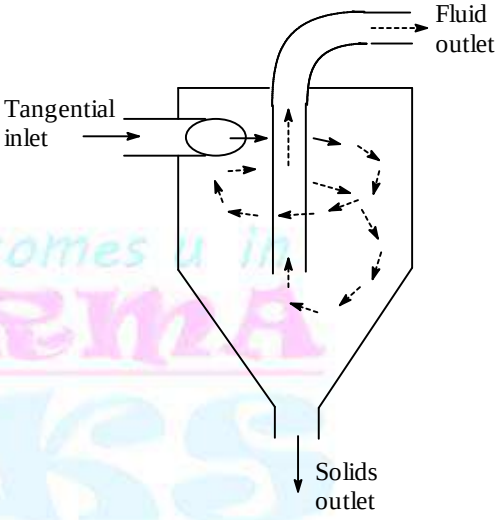


Fig. Cyclone separator

Working

The solids to be separated are suspended in a stream of fluid (usually air or water). Such feed is introduced tangentially at a very high velocity, so that rotary movement takes place within the vessel. The centrifugal force throws the particles to the wall of the vessel. As the speed of the fluid (air) diminishes, the particles fall to the base and collected at the solid outlet. The fluid (air) can escape from the central outlet at the top.

Uses

1. Cyclone separators are used to separate solid particles from gases.
2. It is also used for size separation of solids in liquids.
3. It is used to separate the heavy and coarse fraction from fine dust.

AIR SEPARATOR

Principle

The cyclone separator alone cannot carry out size separation on fine materials. For such separations a current of air combined with centrifugal force is used. The finer particles are carried away by air and the coarser particles are thrown by centrifugal force, which fall at the bottom.

Construction

It consists of a cylindrical vessel with a conical base. A rotating plate is fitted on a shaft placed at the center of the vessel. A set of fan blades are also fitted with the same shaft. At the base of the vessel two outlets are provided: one for the finer particles and the other for coarse particles.

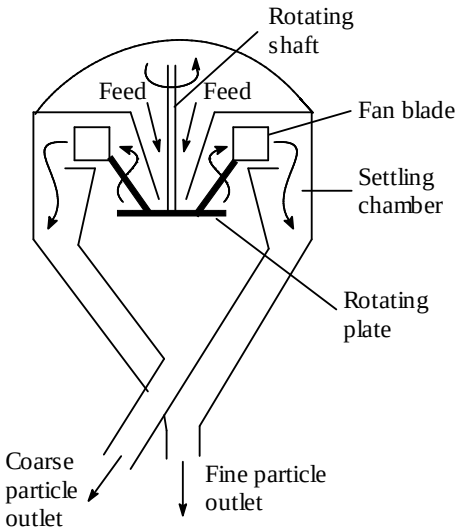


Fig. Air separator

Working

The disc and the fan are rotated by means of a motor. The feed (powder) enters at the center of the vessel and falls of the rotating plate. The rotating fan blades produce a draft (flow) of air in the direction as shown in the diagram. The fine particles are picked up by the draft of air and carried into space of settling chamber, where the air velocity is sufficiently reduced so that the fine particles are dropped and removed through the fine particle outlet.

Particles too heavy to be picked up by the air stream are removed at the coarse particle outlet.

Uses

Air separators are often attached to the ball mill or hammer mill to separate and return over sized particles for further size reduction.

BAG FILTER

Principle

In a bag filter, size separation of fines (or dust) from the milled powder is achieved in two steps. In the first step, the milled powder is passed through a bag (made from cloth) by applying suction on the opposite side of the feed entry. This facilitates the separation. In the next step, pressure is applied in order to shake the bags so that powder adhering to the bag falls off, which is collected from the conical base.

Construction

It consists of a number of bags made of cotton or wool fabric. These are suspended in a metal container. A hopper is arranged at the bottom of the filter to receive the feed. At the top of the metal container, a provision is made for vacuum fan and exhaust through discharge manifold. At the top of the vessel a bell-crank lever arrangement is made to change the action from filtering to shaking.

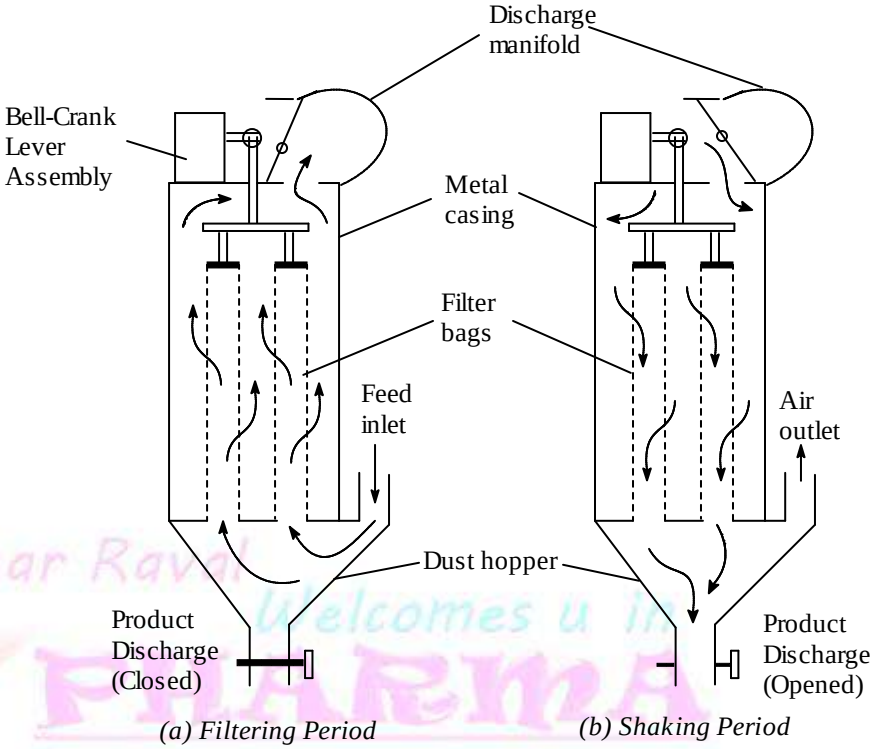


Fig. Bag filter

Working

(a) *Filtering period*: During this period the vacuum fan produce a pressure lower than the atmospheric pressure within the vessel. Gas to be filtered enters the hopper, passes through the bags, and out of the top of the apparatus. The particles are retained within the bags.

(b) *Shaking period*: During this period the bell-crank lever first close the discharge manifold and air enters through the top so the vacuum is broken. At the same time it gives a violent jerking action to the bags so that they are freed from the dust. The fine particles are collected at the conical base.

Uses

1. Bag filters are used along with other size separation equipment, e.g. a cyclone separator.
2. They are use on the top of fluidized bed dryer for drying to separate the dusts.
3. They are used to clean the air of a room.
4. Household vacuum cleaner is a simple version of bag filter.

COTTRELL PRECIPITATOR

Principle

If a gas is subjected to a strong unidirectional electrostatic field, the gas become ionized and drifts toward one electrode. If a finely divided solid particle (or liquid droplet) is suspended in the gas, the particle (or droplet) will become charged and will drift toward the same electrode as the ionized gas.

Construction

There will be two electrodes: (i) Discharge electrode and (ii) Collecting electrode.

- The discharge electrode is usually a wire, chain, wire screen or other arrangement with a large surface.
- The collecting (or smooth) electrode may be parallel plate or pipe.
- In case of parallel plate design the gas flows parallel to plates.
  Plate dimensions: Length = 10 to 18 ft Width = 3 to 6 ft.
- In case of pipe design the pipes are placed vertically and a wire (discharge electrode) is fitted at the center of the pipe. Gas flows from the bottom to the top of the pipe. At the bottom of the pipe a hopper is given to collect the particles. *Pipe dimensions*: Height 6 to 15 ft.

Working

AC current is first stepped up with a step up transformer to raise the potential difference to 50,000 to 60,000 volts. Then the voltage is made unidirectional by a motor-disc assembly where the motor is rotating at a speed similar to the frequency (i.e. cycles per second or Hz) of the AC current. This results in a pulsating but unidirectional electrostatic field.

The particles will be charged and precipitated on the smooth plate or pipe, which is then collected through the hopper.

Use

The Cottrell process is successfully used for the removal of fine dusts from all kind of waste gases.

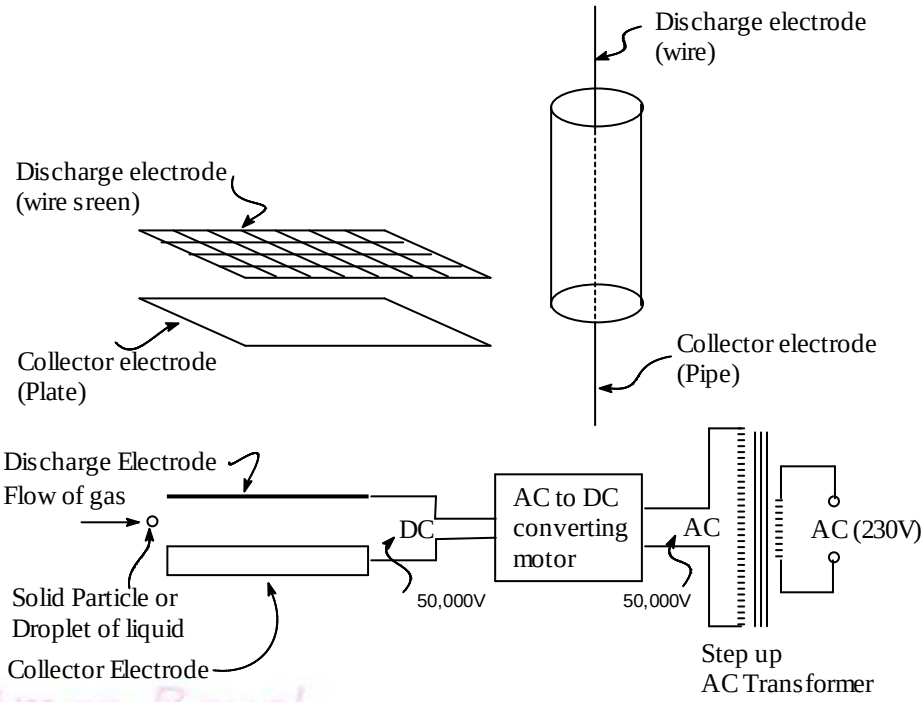


Fig. Cottrell Precipitator

SCRUBBERS

Principle

Solid and liquid particles suspended in gas can be removed (or scrubbed) by introducing water from the top of the equipment and gas through the bottom of the equipment, i.e. water and gas flow in counter-current flow.

Construction

This equipment consists of a cylindrical *shell* with conical bottom. The gas containing the suspended particles enters through a tangential inlet at the bottom. *Deflector cones* are placed on *stationary vanes*. These vanes are placed on *annular shelves*. One deflector cone, vanes and the annular ring as a whole called a *contact*. There are several such contacts placed inside the shell. The *liquid inlet* is placed at the second top contact. The topmost contact is called *entrainment separator*. Dust collector outlet is placed at the bottom of the equipment. The gas is taken out through the gas outlet placed at the top of the separator.

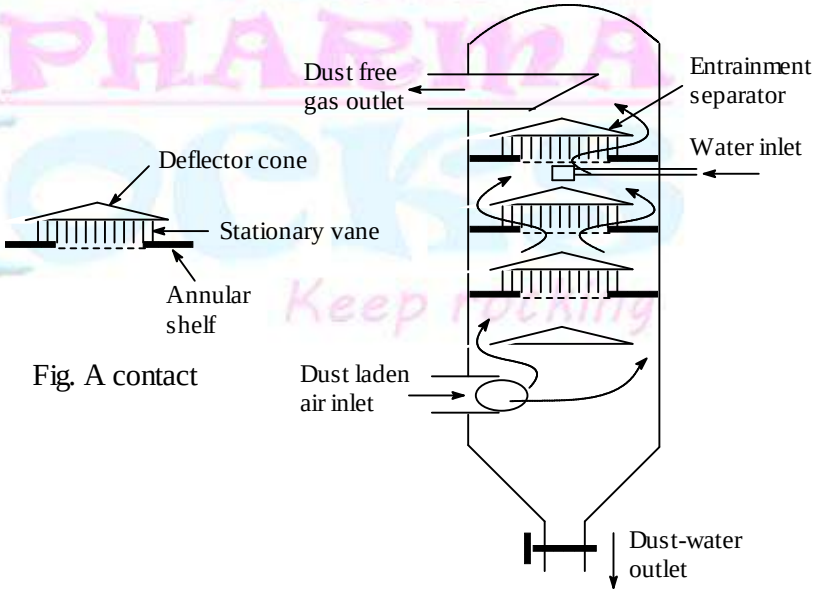


Fig. A contact

Fig. Scrubber

Working

The gas carrying the particles (or droplets) are introduced through the gas inlet at the bottom and passes upward through the vanes under deflector cones. Liquid (e.g. water) is introduced from the top. It falls on the conical deflector and flows over the vanes to produce a curtain of liquid. The gas passes through these curtains. Particles or droplets are retained in the liquid and gas passes to the next contact. After passing through several such contacts the gas passes through the entrainment separator where small droplets of water (known as entrainment) are separated and the gas leaves the separator through the gas outlet. The discharged gas goes to a cyclone separator where the entrained water (if any) are finally removed from the gas.

Use

To clean the dust of air before entering inside a room or before discharging a gas in the environment from an industry.

SIZE SEPARATORS BASING ON SEDIMENTATION THEORY

Size separation by sedimentation utilizes the differences in settling velocities of the particles with different diameter (d) and these can be related to Stoke's law.

Stoke's law

When a solid particle is suspended in a liquid the particle settles downward at a velocity, V. This velocity is called sedimentation rate. It is found that this rate of sedimentation depends on the diameter of the particle, density of the liquid and particle, viscosity of the liquid and the acceleration due to gravity. All this parameters can be combined in the form of Stoke's equation:

$$V = \frac{d^2(\rho_1 - \rho_2)g}{18\eta}$$

Where d = diameter of the particle
ρ_1 = density of the particle
ρ_2 = density of the liquid
g = acceleration due to gravity
η = viscosity of the liquid.

CONTINUOUS SEDIMENTATION TANK

A shallow tank is arranged with inlet and outlet pipes as shown in the figure. Particles entering the tank will be acted upon by a force that can be divided into two components:

(i) a horizontal component due to the flow of liquid carrying the particles forward and
(ii) a vertical component due to gravity, which causes the particles to fall towards the bottom of the tank. This component is governed by Stoke's law so that the velocity of sedimentation is proportional to the square of the diameter of the particles.

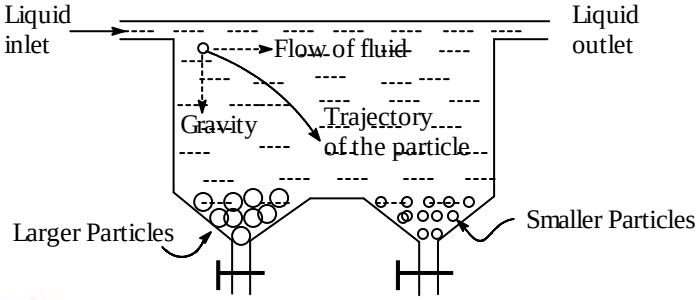


Fig. Sedimentation Tank

Thus the particles will settle at the bottom of the tank in such a way that the coarsest (largest) particles will settle near to the inlet of liquid and the finest particles near to the outlet of the liquid. Partitions are arranged at the floor of the tank to enable collection of different size fraction particles.

DOUBLE CONE CLASSIFIER

Principle

The separation takes place by elutriation principle.

N.B. In sedimentation method the fluid is stationary and the separation is taking place by the velocity of the particles. In elutriation method the liquid is flowing to the opposite direction of the sedimentation of the particle.

In elutriation method the fluid flows in opposite direction to the sedimentation movement. In this equipment the liquid moves upward. If the sedimentation velocity of a particle is less than the velocity of the liquid then the particle will move upward. If the sedimentation velocity of the particle is more than the velocity of the liquid then the particle will move downward. So if the velocity of the liquid is kept within the sedimentation velocities of the coarse and fine particles then the finer particles (has lesser sedimentation velocity) will move upward and the coarser particles (have greater sedimentation velocity) will move downward.

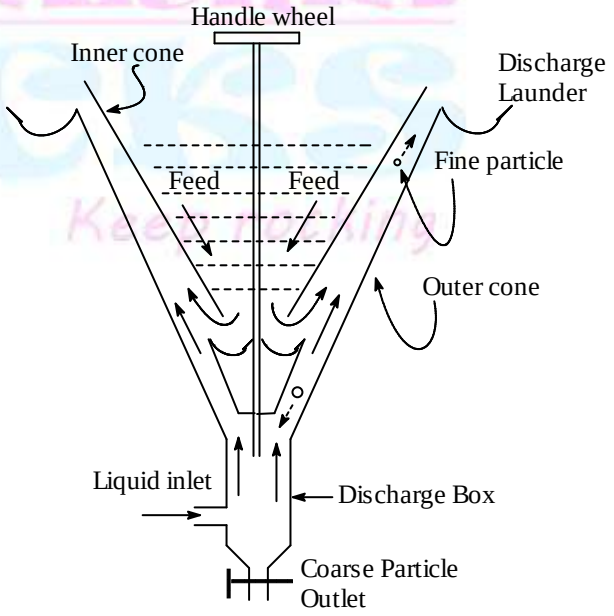


Fig. Double cone classifier

Construction

Two cones of different sizes are placed one in another. At the top of the outer cone a *discharge launder* is fitted at the outside surface of the outer cone. Water inlet is provided at the bottom of the equipment. The inner cone is shorter than the outer cone. The inner cone can be moved along its vertical axis with the help of a hand wheel. At the bottom a collecting box is provided to collect the coarse particles.

Working

The feed enters the inner cone and water is introduced through the water inlet at the bottom. The particles settle from the inner cone meet a rising stream of water at lower end of inner cone. The fine particles pass upward and are collected in the discharge launder. The coarse particles settle into the collecting box for coarse material and are drawn off at intervals.

The degree of separation is regulated by the velocity of water supply and the height of the inner cone regulated by the hand-wheel.

FORMULATION AND EVALUATION OF VARIOUS COSMETIC AND DENTAL PRODUCT

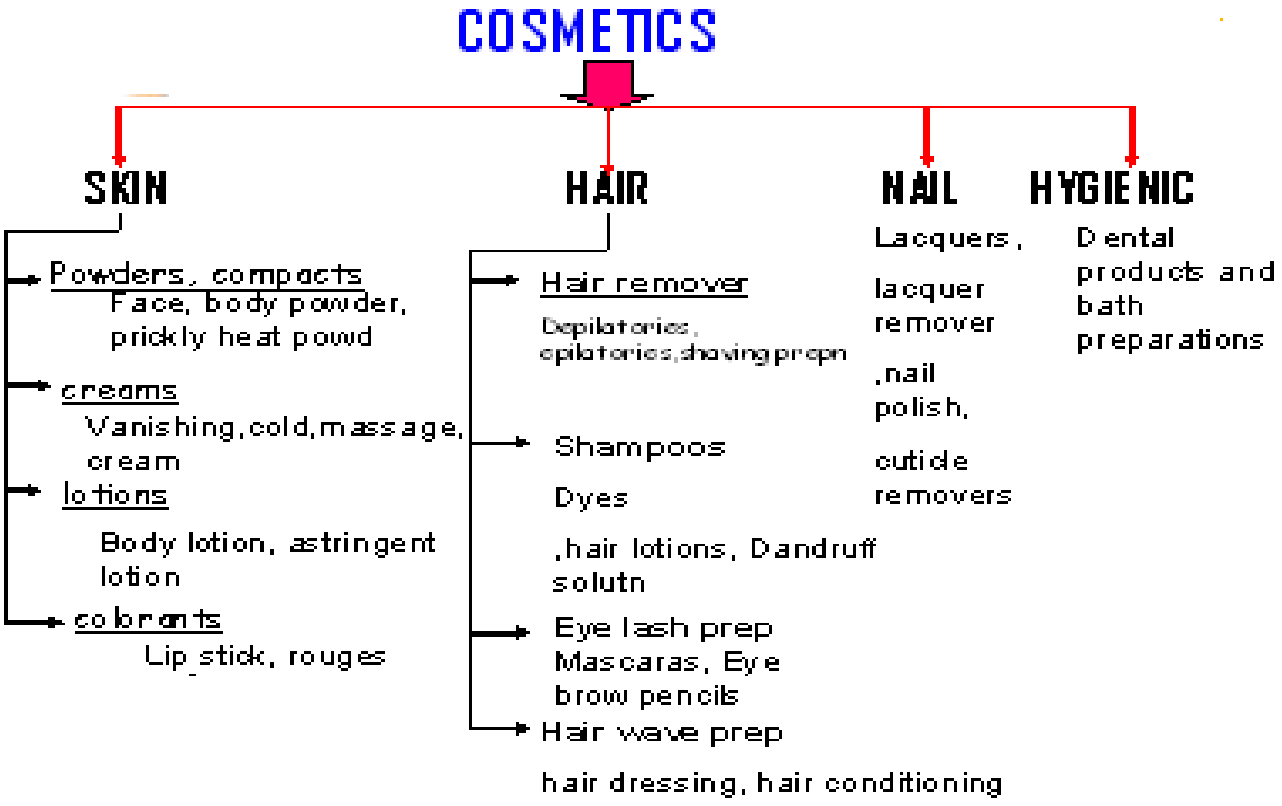
1) DEFINITION:-

The term cosmetics have been derived from the term "**COSMETIKOS**" which means the skill to decorate. Thus cosmetics is the art of decorating yourself to look beautiful.

According to D & C Act:-

Cosmetics mean any articles meant to be **rubbed, poured, sprinkled or sprayed on** or **introduced into** or otherwise applied to any part of the human body for **cleansing, beautifying, promoting attractiveness or altering appearance** and include any article intended for use as a component of cosmetic. Soap is not covered under cosmetic product.

2) CLASSIFICATION OF COSMETICS:-



3) INGREDIENTS OF COSMETICS:-

1. Water
2. Oils, Fats, Waxes
3. Humectants

4. Surfactants
5. Preservatives
6. Perfumes And Colors
7. Herbal Or Plant Material
8. Functional Raw Materials

1. WATER:-

It is the main ingredient of cosmetics formulation. Thus stability and quality of final product is dependent on the purity of water used so pure water should be used in manufacturing of cosmetics. Pure water on large scale can be manufactured by any of the methods mentioned below.

- Ion exchange system
- Distillation
- Reverse osmosis

2. OIL, FATS and WAXES:-

These are used in preparation of creams, lotions, brilliantine, hair oil, lipsticks etc. The source of oil, fat & wax can be mineral source & animal source. The source and example is given below.

Source:-1) Mineral source
-mineral oil
-paraffin and petroleum jelly
2) Animal source
-wool fat
-bees wax, Spermaceti

OILS:-

Name of oil (Vegetable)	Use in cosmetics
Almond	Creams (emollient)
Arachis	Hair oil, Brilliantines
Castor	Lip stick, hair oil cream ,lotion
Olive	Bath oils ,creams lotions
Type of mineral oil	**Use in cosmetics product**
Light liquid paraffin	In bath oil, hair oil,lotions,creams,brilliantine
Heavy liquid paraffin	In bath oil, hair oil,lotions,creams,brilliantine (emollient)

- ***waxes*:-** The commonly used waxes in preparation of cosmetics Include bees wax, spermaceti,ceresin,ozokerite wax

3. HUMECTANTS:-

This is added to prevent drying out of cosmetics

(e.g. o/w creams)

Type of Humectant	Examples
1.Inorganic	Calcium chloride (not used now due to compatibility problems)
2.Metal organic	Sodium lactate (used in sunscreen lotions)
3.Organic	Polyethylene glycol, Propylene glycol, glycerol, sorbitol, mannitol, glucose

4. SURFACTANTS:

Surfactants lower one or more boundary tensions at interface in the system. one common feature of surfactant is that they all are amphipathic molecules containing a hydrophobic part & a hydrophilic part. Used in cosmetics to impart following functions:.
DETERGENCY, WETTING, FOAMING, EMULSIFICATION, SOLUBILIZATION

Surfactants on basis of their ionic behavior can be divided into following 4 types:-

Type of surfactant	Examples
1.Anionic	Fatty acid soaps, alkyl sulphates, alkyl sulphonates, polyethylene glycol ester,alkyl ether sulphates taurines,sarcosinates etc.
2.Cationic	Alkyl trimethyl ammonium salts, Dialkyl dimethyl ammonium salts alkyl pyridinium salts, quaternised diamine salts.
3. Non ionic	Alkanolamides,alkyl polyglycol ether, thioethers, alkyl polyethyleneimine amides.
4.Ampholytic	Betains, alkylimidazolines, acyl peptides,etc.

5. PRESERVATIVES:-

Used to prevent spoilage which occurs due to
1) Oxidation of oils 2) Microbial growth

- Unused cosmetics are usually contaminated wit PSEUDOMONAS but used cosmetics are contaminated with STAPHYLOCOCCI,FUNGI,YEAST
- Types of preservatives :-
    1) Anti microbial agents:- e.g. .Benzoic acid, formaldehyde, cresol, phenol, thiomersol,phenyl mercuric salts. Etc.
    2) Antioxidants :- Gallic acid, methyl gallate,BHA,BHT,Tocopherol, citric acid,Ethanolamine,lecithin,ascorbic acid, sodium sulphite, Sodium metabisulphite
    3) Antioxidant synergists: - Enhance the efficacy of antioxidants. examples include:-ascorbic acid, citric acid, phosphoric acid
    4) UV absorbers:-These are mainly used in products which are vulnerable to visible or UV light. By incorporating UV absorbers colorless containers can be used if deterioration is due to UV light only.

6. PERFUMES:-

The word perfume has been derived from “per” means through and “fumum” means smoke. It suggests that early perfumes were pleasant smells obtained by burning wood and grass etc.

Source of perfume	Example
Natural (Animal source)	Musk ,civet, Ambergris, Castroreum etc.
Natural (Plant source)	Rose ,jasmine, lemon, lavender etc.
Aroma chemical	Eugenol, Farnesal, Rose oxide, Citral ,Limonene
Floral base	Rose base, Jasmine base
Woody base	Citrus base(in colognes),spice base, oriental base, fruity base ,etc

7. COLORS:-

It defined as visual sensation caused by a definite wavelength by an object by one/more phenomenon of emission, reflection, refraction, transmission.

Colors can be classified into three classes:-

a) Natural colors:- Plant source :- e.g. Saffron, turmeric
Animal source:-e.g. Cochineal (red)

b) Inorganic colors:- e.g. Iron oxides, chromium oxides, carbon black, titanium dioxide, zinc oxide etc.

c) Coal tar colors:-Tartrazine, amaranth, Erythrosine, Indigocarmine. etc.

8.HERBAL OR PLANT MATERIAL:-

These herbal or plant materials are used in different cosmetics preparations.

NAME	USE IN COSMETICS
Almond	Facial and body scrubs
Azadiracta	Tooth paste and skin care
Comfrey	Creams and lotions
Tulsi	Skin cream and lotions
Cucumber	Masks, toner, cleanser
Henna	Dyeing of hair
Amla	Shampoo
Jasmine	Hair oil
Lemon	Skin tonic, cleansers

Apricot	Facial and body scrubs

9. FUNCTIONAL RAW MATERIALS:-

These agents contribute towards some functional property .

TYPE	EXAMPLE & USE
VITAMINS	Vit C (antioxidant in emulsion),vit A, Vit E (skin beautification)
AMINO ACIDS	AV HILL MP TT (all essential amino acids)
ANTI INFLAMMATORY AGENTS	Allantoin (hand cream & lotion) Cade oil(eczema& psoriasis),Calamine
SUNSCREEN AGENTS	PABA, Vitamin C, Quinine salts Coumarin derivatives
ANTIDANDRUFF	Selenium, cadmium sulphide, ZPTO

(4) FORMULATION

❖ COSMETICS FOR SKIN

Function:-

1) To provide decoration
2) To supplement natural functions of skin

Type of cosmetics used for skin:-

1. Skin cream
2. Lotion
3. Face powder & Compacts
4. Skin colorants
5. Body powder
6. Face pack & Masks
7. Bath Preparations (bath salt,oil,powder,foam)
8. Astringents &Skin tonics (antiperspirants, astringent lotion, preshave & after shave lotion, colognes)

1. CREAMS: - These are the solid or semisolid preparation which is either a o/w or w/o type emulsion.

- **TYPES OF CREAMS:**
  A. Cleansing cream
  B. Massage creams
  C. Night creams
  D. Moisturizing creams

E. Foundation creams
F. Vanishing creams
G. All purpose creams

A) CLEANSING CREAM:- Cleansing cream is required for removal of facial make up, surface grime, oil, water and oil soluble soil efficiently mainly from the face & throat.

Characteristic of a good cleansing cream:-

1) Be able to effectively remove oil soluble & water soluble soil, surface oil from skin.
2) Should be stable &have good appearance.
3) Should melt or soften on application to the skin
4) Should spread easily without too much of drag.
5) Its physical action on skin & pore openings should be that of flushing rather than absorption

Type of cleansing cream:-

I.**) Anhydrous type:-** It contains mixture of hydrocarbon, oils and waxes. It also contains cetyl alcohol, spermaceti, cocoa butter, fatty acid esters etc. Not popular.

Mineral oil-80 gm, Petroleum jelly– 15gm
Ozokerite wax -5 gm Preservative and perfumes –q.s

Note :- Formation crusty surface is avoided by adding Ozokerite & petrolatum (prevent bleeding of mineral oils.)
Opaque character obtained by adding Zno, mg.stearate, Tio2

II.**) Emulsified type:-** They can be either o/w or w/o type.
Common Ingredients:-
Oil phase……..Spread easily
Waxes……..Give appropriate thixotropy
Emollient material……likes cetyl alcohol, spermaceti, lanolin
Water phase with preservative

Different types:-

(1) Cold Cream:- Cooling effect is produced due to slow evaporation of the water contained in the formulation. These are w/o type.

(2) Beeswax Borax type:- These contain high percentage of mineral oil. These are o/w type. This cream contains high amount of mineral oil for cleansing action. Basically these are o/w type emulsion. After the cream is being rubbed into the skin sufficient quantity of water evaporates to impart a phase inversion to the w/o type. The solvent action of the oil as external phase imparts cleansing property. In this type of cream borax reacts with free fatty acids present in the bees wax and produces soft soap which acts as the emulsifying agent and emulsifies the oil phase .

A typical formulation:-
Bees wax -2 gm Borax-2 gm
Almond oil -50 gm Rose water 35.5 gm
Lanolin– 0.5gm preservative and perfume –q.s

B) NIGHT & MASSAGE CREAM:-

These are generally applied on the skin and left for several hours say overnight and assist in the repair of skin which has been damaged by exposure to various elements or exposure to detergent solution or soap. The mostly have a moisturizing & a nourishing effect of affected skin. These also contain vitamins and hormones basing on the application. This cream give better look to the skin and prevent dryness.

A typical formulation

- Mineral oil-38gm Borax 1gm
  Petroleum jelly-8gm Water 35gm
  White bees wax-15gm Perfume & preservative q.s
  Paraffin wax – 1.0gm
  Lanolin 2gm

C) VANISHING CREAM:-

These are named so as they seem to vanish when applied to the skin. High quantity of stearic acid as oil phase used.This provides an oil phase which melts above body temp, and crystsllises in a suitable form, so as to invisible in use and give a non greasy film.

- Main component is emollient esters ,stearic acids
- Part of stearic acid is saponified with an alkali & rest of stearic acid is emulsified this soap in large quantity of water.
- The quality of cream depends on the amount of acid saponified & nature of alkali used.
- NaoH makes harder cream than koH.
- Borax makes cream very white but product has tendency to grain.
- Pearliness can be attained using liq.paraffin, cocoa butter, starch, castor oil, almond oil.
- Ammonia solution has a tendency to discolor creams made with it after some time.
- Cetyl alcohol improves texture and stability at low temperature without affecting sheen.

A typical formulation

Stearic acid 15gm Glycerin 5gm
KOH 0.5 gm water 75.82 gm
NaOH 0.18 gm preservative &perfume q.s
Cetyl alcohol 0.50 gm
Propylene glycol 3.0gm

Stearic acid has whiteness like snow so some times the preparation is called as SNOW.

D) FOUNDATION CREAM:-

- Applied to skin to provide a smooth emollient base or foundation for the application of face powder & other make up preparations. They help the powder to adhere to skin. They are almost o/w type.

Types:

1) Pigmented
2) Unpigmented

A typical formulation

- Lanolin 2 gm Propylene glycol 8gm

- Cetyl alcohol 0.50 gm water 79.10 gm
- Stearic acid 10gm Perfume &preservative q.s
- KoH 0.40 gm

E) HAND & BODY CREAM:-

- The repeated or constant contact with soap and detergent damages & removes film of sebum thus this cream is used to impart following functions to the skin.
- The function of these creams are
  - Replace/reduce water loss.
  - Provide oily film to protect the skin.
  - Keep the skin soft, smooth but not greasy.

Type:-

a) Liquid cream:-consistency is of liquid nature
b) Solid creams:- Consistency is higher
c) Nonaqueous type:-Not containing any aqueous medium.

A typical formulation

a.) Isopropyl myristate - 4 gm
Mineral oil -- 2 gm
Stearic acid – 3.gm
Emulsifying wax - .275 gm
Lanolin - 2.5 gm

b.) Glycerin -3.0 gm
Triethanolamine **–** 1 gm
Water -84.225 gm
Perfume and Preservative -q.s

(F) ALL PURPOSE CREAMS:-

All purpose means it is suitable for hands, face and body. They are w/o types.

Formula:- Oil phase	**Water phase**
Mineral oil 18%	Water 61.3%
Lanolin 2%	Glycerol 5%
Petroleum jelly 2%	Magnesium sulphate 0.2%
Ozokerite 7 %	Perfume, preservative q.s
Paraffin wax 3%	

2) LOTIONS:-

(I) Cleansing lotion

A typical formulation

Mineral oil 38%,
Bees wax 2%,
Triethanolamine stearate 8%,
Water to make 100%
Preservative & Perfumes –q.s

Note: - Triethanolamine discolors on standing so it should be made in situ using calculated amount of stearic acid and Triethanolamine. O/W lotion have tendency to increase in viscosity with ageing (this is prevented by using ethoxylated cholesterol)

(II) Sunscreen lotions:-

These lotions have property of protecting the skin from sun burning.

An ideal sunscreen agent should have following properties.

- Absorb light over the range of 200-400 nm.
- Be stable to heat, light & perspiration
- Be nontoxic & nonirritant
- Not be rapidly absorbed
- Be neutral
- Be readily soluble in suitable vehicles.

US dept of health has recommended following ingredients to be used as sunscreen agents. They absorb U.V radiation.

- CYCLOFORM
- MONOGLYCERYL PARA AMINO BENZOATE
- DIGALLOYL TRIOLEATE
- BENZYL SALICYLATE
- BENZYL CINNAMATE

And few others are PABA, cinnamic acid derivatives, coumarin derivatives, Quinine salts, uric acid derivatives.

A typical formulation

Glyceryl p-amino benzoate	3.0 %
Glycerin	5.0 %
Alcohol	10 %
Methyl cellulose	0.5 %
Perfume	q.s
Water to make 100 %	

3. POWDERS:-

These are categorized as face powder, body powder, and Compacts.

The powders should have following properties:-

- Must have good covering power so can hide skin blemishes.
- Should adhere perfectly to the skin & not blow off easily.
- Must have absorbent property.
- Must have sufficient slip to enable the powder to spread on the skin by the puff .
- The finish given to the skin must be preferably of a matt or peach like character.

The raw materials used to manufacture of various powders are classified with example as follows:-

RAW MATERIAL FOR POWDER IMPARTING	EXAMPLE
Covering prop	Titanium dioxide,zno,kaolin,zn stearate
Adhesion prop	Mg.stearate,talc,mg & ca salt of myristic acid

Slip & Softness	Zn/mg undecanate,aluminium hydrosilicate
Absorbency prop	Starch, colloidal kaolin,bentonite,pptd chalk
Peach like finish	Rice starch,silica,powdered silk
Frosted look	Guanine, bismuth oxychloride,mica,Zn,Al
Color & perfumes	Iron oxides

FACE POWDER:-

Types of Face Powders:-

- **A.** Loose face powder
- **B.** Compact face powder
- **C.** Talcum powder
- **D.** Baby powder

A) LOOSE FACE POWDER :-

The essential feature of a good face powder includes Covering power, slip, Adhesiveness, Absorbency, Bloom, Coloring, Perfuming.

Type:-

b) Light type
c) Medium type
d) Heavy type

Type of face powder	purpose & composition
LIGHT	Dry skin, contains large amount of talc
MEDIUM	Normal or moderately oily skins, lesser talc & zinc oxide
HEAVY	Extremely oily skins ,low talc but higher amount of Zinc oxide

TYPICAL FORMULATION OF FACE POWDERS:-

LIGHT POWDER	MEDIUM POWDER	HEAVY POWDER
Talc ---------63gm	**Talc---------39.7gm**	**Talc---------20.0gm**
Kaolin --------20 gm	Kaolin-------39.5 gm	Kaolin(light)-20 0gm
Cal. carbonate(l) 5 gm	Cal. carbonate(l) 5 gm	. Cal. carbonate(l) 39 g
Zinc oxide ---5.0gm	**Zinc oxide ---7.0gm**	**Zinc oxide ---15.0gm**
Zinc stearate-5.0gm	Zinc stearate-7.0gm	Mg.stearate—5.0gm
Mg.carbonate—1.0gm	Mg.carbonate—1.0gm	Color ------0.5gm

Color ------0.5gm	Color ------0.2gm	Perfume------0.5gm
Perfume------0.5gm	Perfume------0.6gm	

B) COMPACT FACE POWDER:-

It is a dry powder which has been compressed into a cake. The pressure for compaction is very important. The powder must come off easily when rubbed with puff.

Type of binder	Examples
1) Dry binder	Zn/Mg.stearate
2) Oil binder (water repellant)	Mineral oil, isopropyl myristate, Lanolin derivative
3) Water soluble binder	PVP, CMC, Cellulose, Acacia, Tragacanth
5) Emulsion binder	Triethanolamine stearate, Glycerol monostearate

(C) TALCUM POWDER:- It is used as an adsorbent for making the skin from the excess moisture. Light magnesium carbonate added to mix perfume.

Formula:- Zinc oxide …….. .. 50
Zinc stearate …… 50
Chlorhexidine diacetate ……3
Light magnesium carbonate.100
Talc ……797
Perfume……0.2

D) BODY POWDER:-

It consists of mainly talc, with small portion of a metallic stearate, precipitated chalk, magnesium carbonate(light). Talcum/body powders containing antiseptic substances are also used for prickly heat, and fungus infections. Boric acid act as antiseptic.

A typical formulation

Talc - 75 gm Aluminum stearate – 4 gm
Colloidal Kaolin –10 gm Boric acid – 0.3 gm
Colloidal silica--- 5 gm Perfume --- 0.7 gm
Magnesium Carbonate- 5 gm

3. SKIN COLORANTS:-

It includes a) Lipsticks
b) Rouge

a) LIPSTICK:-These are basically dispersions of coloring matter in a base consisting of a suitable blend of oils, fats, and waxes suitably perfumed and flavored molded in the form of a stick.

Ideal character of lipstick includes:-

- Should cover the lips adequately with some gloss and last for long time.
- It should make the lips soft.
- The film must adhere firmly to the lips without being brittle.& tachy.

- Should have high retention of color intensity without any change in shade.
- Should be completely free from grittiness & free from drying.
- Nonirritating to the lips.
- Desirable degree of plasticity & have a pleasant odor and flavor.

- **Classification of raw materials:-**

1) Wax mixtures (bees, candeilla, carnauba, ceresin, Ozokerite wax)
2) Oil mixtures (castor, paraffin, THFA, isopropyl myristate)
3) Bromo mixture
4) Colors
5) Preservatives

Types of lipsticks

1) Transparent lipstick
2) Liquid lipstick
3) Lip rouge
4) Lip jelly
5) Lip salve
6) Lip glosses

A typical formulation of lipstick.

Castor oil	54 gm
Lanolin (anhydrous)	11 gm
Candeilla wax	9 gm
Isopropyl myristate	8 gm
White beeswax	5 gm
Carnauba wax	3 gm
Ozokerite wax	3 gm
Eosin	2 gm
Lakes	5 gm
Rose flavor	q.s
Antioxidant	q.s
Preservative	q.s

b) SKIN ROUGE: - These are the cosmetics preparations used to apply a color to the cheeks. The color may vary from the palest of pinks to the deep blue reds .The tint or color may be achieved using water insoluble colors such as iron oxides and certain organic pigments or by using water soluble organic colors which actually stain the skin.

Types :-

- Powder rouges
- Wax based rouges (Stick rouge)
- Emulsion cream rouges
- Liquid rouges
-

Powder Rouges	**Stick rouge**
Talc……40 Zinc oxide……..10	Carnauba wax……3 Candelilla……6

Magnesium carbonate…….20 Pigment……..14 Lanolin……..30 Perfume……..2	Ozokerite……1.5 Bees wax……1.5 Hexadecyl stearate……10 Isopropyl myristate……..8 Castor oil……65 BHA……0.02 Color……5

Emulsion cream rouge (vanishing type)	Liquid rouge
Stearic acid……15 Potassium hydroxide……0.5 Sod. Hydroxide……..0.18 Glycerin……..8 Water……..76 Pigment, Perfume & Preserative……q.s	(A) Iso stearic acid……..0.02 Mineral oil……..30 Iso propyl myristate……5 Colloidal silica……..1 Color……..3 (B) Water……48.3 Triethanolamine……4 Perfume……0.2

(4) ANTIPERSPIRANTS & DEODORANTS:-

Anti perspirants:- Aluminium chlorhydrate used which has antibacterial and astringent action. Aluminium chloride and Zirconium compounds are also used as antiperspirants.

Deodorants:--11 (Hexachlorophene)

- TMTD (Tetra methyl triuram disulphide)
- Bithionol
- Bromosalicylanilide
- Diaphene
- Neomycin (Antibiotic)
- Ion-exchange resin used like Amberlite
- Metal chelates like 1,3 Diketones used which chelate copper, aluminium, Mg compounds.

❖ COSMETICS FOR HAIR:-

Includes following type of preparations:-

1. Shampoo
2. Hair tonics & Conditioners
3. Hair colorants and hair color remover
4. Hair grooming preparations
5. Depilatory & Epilatory
6. Shaving soaps & creams
7. Hair wave sets & lacquers ,rinses

1. SHAMPOO

Ideal characters of a shampoo:-

- Should effectively and completely remove the dust, excessive sebum.
- Should effectively wash hair.

- Should produce a good amount of foam
- The shampoo should be easily removed by rinsing with water.
- Should leave the hair non dry ,soft, lustrous with good, manageability.
- Should impart a pleasant fragrance to the hair,.
- Should not make the hand rough and chapped.
- Should not have any side effects or cause irritation to skin or eye.

Composition of shampoo:-

1) Principal surfactant (anionic type)
   Non ionic surfactant has sufficient cleansing property but have low foaming power. Cationic are toxic. So anionic are preferred.
2) Secondary surfactant (anionic or ampholytic detergent)
   They modify detergent and surfactant properties of principal surfactant.
3) Antidandruff agents (selenium, cadmium sulfide, ZPTO)
4) Conditioning agent (lanolin, oil, herbal extract, egg, amino acids)
5) Pearlescent agents (substituted 4 methyl coumarins)
6) Sequestrants (EDTA)
   Added because Ca, Mg salts are present in hard water. Soaps cause dullness by deposition of Ca, Mg soaps on hair shaft. This prevented by EDTA.
7) Thickening agents (alginates, PVA, MC)
8) Colors, perfumes and preservatives

Types of shampoo:-

1) Liquid cream shampoo
2) Solid cream and gel shampoo
3) Powder shampoo
4) Antidandruff shampoo
5) Aerosol foam shampoo

Formulation of shampoo:-

Liquid Cream shampoo	**Solid cream and Gel Shampoo**
SLS 30% PEG 400 Distearate Mag. Stearate Dist. Water Ninol AB 21 Oleyl alcohol Perfume PEG 400 distearate and Mg stearate used to convert clear liquid shampoo to liquid cream shampoo. Ninol AB 21- Thickening agent Oleyl alcohol- Conditioning agent	SLS……20% Coconut monoethanolamide….1% Propylene glycol monostearate..2% Stearic acid……5% Sodium hydroxide……0.75% Water, perfume, Colour…….100

1**) Powder shampoo**	2) **Antidandruff shampoo**
Henna powder …… 5 gm Borax ……15 gm	Selenium disulphide…… 2.5 gm Bentonite ..... 5 gm

Sod. carbonate …… 25 gm Pot. Carbonate …….. 5 gm Soap powder…….. 50 gm Perfume …….. q.s.	Sod. Lauryl Sulphates ... 40 g Water …….. 52.5 gm Perfume…….. q.s.

Aerosol Shampoo:- SLS……30%
Triethanolamine lauryl stearate……..5%
Polyethylene glycol stearate……3%
Perfume……..0.3%
Water……100

90 parts of above packed with 2 parts of propellant 12 and 8 parts of propellant 14.

2) CONDITIONERS:- These are the preparations used after shampooing to render the hair more lustrous, easy to comb, and free from static electricity when dry. Conditioners are usually based on cationic detergents and fatty materials like lanolin, or mineral oil.

3) HAIR COLORANTS:-These are used either to hide gray hair or to change the color of the hair .

An ideal hair dye should have following properties:-

- Should be nontoxic to the skin or hair, should not impair natural gloss and texture.
- Should not be a dermatitic sensitizer.
- The color imparted must be stable to air, light, water, shampoo.
- Should be easy to apply.

Hair dyes are divided into

1) Vegetable
Example is Henna

2) Metallic
Example:- Lead dyes, Bismuth dyes, Silver dyes, Copper, nickel, cobalt salts
Formula:- (Lead dyes)
Precipitated sulphur……1.3%
Lead acetate……..1.6%
Glycerine……9.6%
Rose water……87.5%

3) Synthetic organic dyes
They are of two types.
a) Semipermanent dye. b) Permanent dyes
Thyoglycolic acid……50% Paraphenylene diamne dye
NH_3 solution(P^H 9.2)…100%

HAIR DYE REMOVER:-
Formula:- Formamidine sulfinic acid……1.5%
PVP……5%
Ethylene glycol monobutyl ether……..5%
Ammonium carbonate……1%
Ammonia……..0.5%
CMC……2.5%
Water up to ……1oo
Formamidine sulfinic acid is acting as hair dye remover.

4) HAIR GROOMING AIDS :-These are important group of cosmetics which are used both by men and women to keep their hair in order for good looking, &enhance overall appearance.

Types:-

1. Brilliantines & Hair oils
2. Hair setting lotions
3. Hair creams
4. Hair lacquers or sprays

5) DEPILATORIES:-

- These are the preparations that remove superfluous hair by chemical breakdown. This removes hair at the neck of the hair follicle and thus has advantage over razor shaver which removes hair on a level with the surface of epidermis.
- **Desirable Characters of an ideal depilatory preparation are**:-
  - Selective in action
  - Efficient and rapid action in few minutes.
  - Non toxic and non allergic to the skin.
  - Odorless
  - Easy to apply
  - Stable
  - Non staining

- **INGREDIENTS** :-

1. Inorganic sulphates (Sod,calcium,barium sulphide,Strontium sulphide)
2. Thioglycollates: - (Calcium.thioglycollate & Lithium thioglycollate)
3. Stannites: - sodium stannite
4. Enzymes:-Keratinase (3-4%)
5. Humectant: - Glycerol,Sorbitol ,Propylene glycol

FORMULATION

Name of ingredient	Amount
1.Strontium sulphide	20.0 gm
2.Talc	20.0gm
3.Methyl cellulose	3.0 gm
4.Glycerin	15.0 gm
5.Water	42.0 gm
6.Perfume	q.s
7. Preservative	q.s

6) EPILATORIES:-

Epilation is longer lasting or even can be of permanent nature. This is achieved by plucking the hair out and removing the root either by tweezers, threading,or by waxing.

- it is a permanent or long lasting effect (done by plucking the hair out, removing the root)
- Camphor-impart cooling effect to reduce discomfort of hair pulling.
- Local Anaesthetics:- overcomes discomfort and pain

FORMULATION

Rosin	70 gm
Bees wax	20 gm
Ozokerite	10 gm
Perfume	q.s

7) <u>SHAVING PREPARATIONS</u>: - These are preparations used to carryout shaving.

Types:-

a) Ued before shaving
b) Used after shaving

<u>Preparations before shaving includes</u>

1) Lather shaving creams
2) Brushless shaving cream
3) Shaving soaps (solid, cream)
4) Aerosol preparation

Aftershave lotion

SOAP BAR **SOAP CREAM**

I Ingredients	***A amount***	***I Ingredients***	***A Amount***
Stearic acid	49 gm	A. **A.**	鼾
Coconut oil	1 13 gm	1. Stearic acid	30 gm
Caustic potash	22 gm	2. Coconut oil	10 gm
Caustic soda	12 gm	3. Palm kernel oil	05 gm
Water	1.25 gm	B**. B.**	
Sodium dioxy stStearate (50%)	o.75 gm	1. Pot. hydroxide	07 gm
Sorbital liquid	1.25 gm	2. Sod. hydroxide	1.5 gm
Glycerol	0.75 gm	3. Water	36.5 gm
Perfume	q.s	4. Perfume	q.s
Preservative	q.s	5. Preservative	q.s

1) BRUSHLESS SHAVING CREAM –

Here Lathering with shaving brush is avoided.

Formulation of brushless shaving cream

INGREDIENTS	***AMOUNT***
1. Stearic acid	16 gm
2. Mineral oil	14 gm
3. Spermaceti	2 gm
4. Glycerin	6 gm
5. Dil .ammonia solution	2 gm
6. Water	6 gm
7. Perfume	q.s
8. Preservative	q.s

2) LATHER SHAVING CREAM:-

Lathering with shaving brush is required.

INGREDIENTS	A AMOUNT (%)
Stearic acid	28
Coconut oil	12
Palm oil	5
Pot. hydroxide	6.5
Sod. hydroxide	1.5
Glycerin	10
Perfume	q.s
Preservative	q.s
Water to make	100

AFTER SHAVE PREPARATION:-

Main purpose of shave preparation is to confer a pleasant feeling of comfort and well being after shaving. This is achieved by giving slight coolness, anaesthesia, tautness or emolliency to skin. At the same time it should be aseptic also.

Formula:-(Antiseptic after shave lotion)

Hyamine……..0.25%
Alcohol……40%
Menthol……0.005%
Benzocaine……0.025%
Water……59.72%
Perfume……q.s

❖ **COSMETICS FOR NAILS:-**

Includes

1. Nail polishes
2. Nail lacquers & removers
3. Nail bleaches & Stain removers
4. Cuticle remover & softener
5. Fingernail elongations

1) NAIL POLISHES:-

A distinction between nail polishes and lacquer is that in nail polish exert the abrasive action. Due to friction it draw the blood to numerous capillaries of nail bed and increasing blood supply, and exert stimulating effect to growth of nail. Examples are stannic oxide, talc, precipitated chalk. Silica exert abrasive action.

Formula:- Stannic oxide……90%
Powdered silica……8%
Butyl stearate……2%
Pigment & Perfume…….. ..q.s

2) NAIL LACQUERS :-

- These are the preparations that cover the nail with a water and air impermeable layer which normally remains for days.

- A good Nail lacquer should fulfill the following characters:-

1) Must be innocuous to the nail & the skin
2) Must be easy and inconvenient to apply
3) Product should be stable on storage
4) The product should produce a good &satisfactory film.

- **COMPOSITION:-**

1) Film former:-Nitro cellulose, Cellulose nitrate (mostly used), Cellulose acetate, cellulose acetobutyrate, Ethyl. Cellulose.
2) Resins :- Give film more body, gloss, depth, adhesion
Natural - Gum damar, Benzoic acid, Gum copal, Shellac
Synthetic - Sulphonamide –Formaldehyde Resins
3) Solvents:-Mix of solvent is preferred, Mixing middle b.p solvents like alcohols, acetates,and aromatic solvents rate of evaporation can be retarded.
4) Diluents:-
5) Plasticizers :- Dibutyl phthalate, Castor oil ,n-butyl stearate, castor oil
6) pearlescent material :-Guanine crystals
(R.I-1.8), mica flakes, Ti02**,** Platelets coated with bismuth oxychloride.
7) colors and perfumes

Formulation (Nail Lacquer)

INGREDIENT	AMOUNT
Nitrocellulose	16 gm
Resin	9 gm
plasticizer	4.8 gm
Solvent	60.5 gm
Color	0.5 gm
Perfume	q.s

b) LACQUER REMOVERS:-
These are also called as nail cleansers which is applied to remove nail lacquers.

FORMULATION OF LACQUER REMOVERS

Ingredients	Amount
Butyl acetate	15 gm
Ethylene glycol monoethyl ether	80 gm
Propylene glycol ricinoleate	05 gm
Perfume	q.s

c) CUTICLE REMOVERS AND SOFTENERS:-
Cuticle preparations either soften or remove the cuticles.

- **COSMETICS FOR EYES:-**

Includes following preparations
1. Eye shadow
2. Mascara

3. Eyebrow pencil
4. Eye cream
5. Eye liners
6. Kajal

1) EYE SHADOW:-

- Give a back ground of color to the eye
- Formulated as cream, liquid, powder or stick.
- Ultramarine(20 part)& Ti02 --- **(BLUE)**
- Iron oxide(30 part) &Ti02 (5 part)-- **(BROWN)**

Ingredients	Amount
petroleum jelly	47.5 gm
Liquid lanolin	4.5 gm
Bees wax	4.5 gm
Micro crystalline wax	8.5 gm
Isopropyl myristate	35 gm

2) EYE LINER:-

Types

1) Pencil type
2) Liquid type (suspension in a base containing film forming material)
3) Cake eye liners

Formulation of Cake type eyeliner

Kaolin	5%
Zn Stearate	12%
Ppted Caco3	7 %
Pigment	10%
Talc to make	100 %

3) EYE BROW PENCIL:-

- Contain high proportion of wax to increase M.P so that these can be moulded into sticks.

Ingredient	Amount
Bees wax	25%
Ozokerite	25%
Butyl stearate	8%
Lanolin	2%
Castor oil	25%
Mineral oil	15%
Perfume	q.s

Antioxidant	q.s

4) MASCARA:-

- Black pigmented preparation for applying to eye lashes or eye brows ,it darkens the eye lashes & gives an illusion of their density and length.
- Type:- Cake , Cream , Liquid

Formulation:-

Carbon black	55 %
Coconut oil sodium soap	25%
Palm oil –sodium soap	22.5%

7) QUALITY CONTROL OF COSMETICS :-

We all know that "Price of a product is quickly forgotten but the quality is remembered" so quality control plays a vital role regarding monitoring different parameters that may affect quality &also helps in producing quality product every time.

Includes :-

1) RAW MATERIAL CONTROL
2) INTERMEDIATE PRODUCT CONTROL
3) FINISHED PRODUCT CONTROL
4) PACKAGING MATERIAL CONTROL

1) Q.C OF RAW MATERIAL:-

- Done by determination of **Bioburden**

The bacterias that are monitored in raw materials include:-

- Enterobacteriaceae
- E.Coli
- Salmonella
- Pseudomonas aeruginosa
- Staphylococcus aureus

2) Q.C OF INTERMEDIATES AND BULK FINISHED PRODUCT:-

Basing on the type of product few typical processing parameters are continuously to ensure quality final product. few of them have been enlisted here.

a) CREAMS & LOTIONS:-

- Mechanics,
- perfume addition temp
- addition of phases
- Viscosity
- Temp of filling
- rate of cooling

b) FACE POWDER

- Uniformity of mixing
- Apparent density
- Shade ,color

- Compression pressure (compacts)

c) LIPSTICKS

- Color match
- Texture
- Softening point
- Breaking point test

d) SHAMPOO:-

- -Foam & foam stability
- -Detergency & coloring action
- -Wetting action
- -Eye irritation
- -Oral toxicity

e) NAIL LACQUER:-

- Color match, Drying rate,
- Non volatile content,
- Smoothness,
- Gloss, Hardness, abrasion resistance, adhesion etc.

Sampling size for final Q.C:-

No of packaging	No of packing selected
Up to 3	Each
4-50	03
51-150	04
151-300	05
301-500	06
>500	07

8) COSMOCEUTICALS: - These are cosmetics with therapeutic & disease fighting property

The following substances are now recognized having cosmoceutical potentials

1) **Polysacharides** :-Fom Tamarind extract and skin beneficial acids from Coriander extract provide moisture-lipid balance preventing dryness and itching 2
2) **Wheat Germ Oil** guard skin against free radical damage.
3) **Moringa Extract** protects your skin against dust and harmful pollutants.

4) **Galanga Oil** * protects skin from harmful UV rays and fights pimple in acne prone skin. Skin beneficial fatty acids from **Coriander** boost the deposition of skin proteins, enhancing tissue repair
5) **Cococin** provides wholesome freshness and nourishment of natural tender coconut water. Natural growth promoters like kinetin and amino acids in Cococin® impart natural conditioning, suppleness and glow to the skin.
6) **Ubiquinone(CO.Q.10)** rejuvenates and increases the oxygen uptake into the cells.
7) **Tetrahydrocurcuminoids,** patented molecule from turmeric in combination with potent antioxidants - Alpha lipolic acid and Ubiquinone reduces fine lines, wrinkles, crow's feet, minimizes the UV induced signs of photo aging and pigmentation, leaving behind blemish-free, youthful skin.
8) **Isoflavons** from Soy impart luster and brightness to the skin by improving skin thickness, skin blood circulation, increased desquamation resulting in excellent surface texture and softness.
9) **Tetrahydropiperine** as Cosmoperine from Pepper improves the dermal penetration of the actives,

MISCELLANEOUS ISSUES:-

SKIN TESTING:-

Type of cosmetic Preparation	Suspected agent to cause harm
CREAMS	Mercurial & Salicylic acid
DEODORANT	Phenolic antimicrobials, Aluminium.chloride
DEPILATORIES	Sulphides of alkali (R.A)
HAIR DYE	Ammonia solution
COLD WAVE LOTIONS	Thioglycollates
LIPSTICK	Bromofluorescein dye (cause Cheilitis)
HAIR & BATH Prep	Agent which cause eye irritation

4) TEN SYNTHETIC COSMETIC INGREDIENTS TO AVOID:-

Organic consumers association has given the following list of chemicals that are to be avoided in preparation of cosmetics.

1. Imidazolidinyl Urea and Diazolidinyl Urea
2. Methyl and Propyl and Butyl and Ethyl Paraben
3. Petrolatum
4. Propylene Glycol
5. PVP/VA Copolymer
6. Sodium Lauryl Sulfate
7. Stearalkonium Chloride
8. Synthetic Colors
   Example: FD&C Red No. 6 / D&C Green No. 6
9. Synthetic Fragrances
10. Triethanolamine

Newer approaches

- **Hair Growth-accelerating preparation containing chlorogenic acid or its isomer for treating androgenic alopecia and its formulation.**
- **Cosmetic composition contain in caffeine, acetic acid and sodium hyaluronate for preventing alopecia.**

DENTAL PRODUCTS

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1) **Introduction**
2) **The teeth and common problem**
3) **Causes of oral health problems**
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    1. **Tooth pastes**
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    3. **Solid blocks**
    4. **Liquid preparations**
    5. **Mouth wash**
7) **Topical anesthetics**
8) **Tartar reducing product**
9) **Mechanical method for plaque control**
10) **Safety**
11) **Dental care product**
12) **Newer approaches**

INTRODUCTION

Dentifrice a preparation for cleansing and polishing the teeth; it may contain a therapeutic agent, such as fluoride, to inhibit dental caries.

A substance, such as a paste or powder, for cleaning the teeth.

Etymology: L, *dens* + *fricare,* to rub

a pharmaceutic compound used with a toothbrush for cleaning and polishing the teeth. It typically contains a mild abrasive, detergent, flavoring agent, fluoride, and binder. Other common ingredients are deodorants, humectants, desensitizers, and various medications to prevent dental caries. Also called **toothpaste**.

Dentifrice (toothpaste)

A pharmaceutical compound used in conjunction with the toothbrush to clean and polish the teeth. Contains a mild abrasive, a detergent, a flavoring agent, a binder, and occasionally deodorants and various medicaments designed as caries preventives (e.g., antiseptics).

Two type of Dentifrice

1. **Simple cleansing dentifrices**
2. **Therapeutics dentifrices:** Therapeutic dentifrices may contain the bactericidal, bacteriostatic, enzyme inhibiting or acid neutralizing qualities of the drugs or chemicals.

The teeth and common problem

1. Bad Breath

If you suffer from bad breath, you are not alone. Bad breath, also called halitosis, can be downright embarrassing. According to dental studies, about 85% of people with persistent bad breath have a dental condition that is to blame. Gum disease, cavities, oral cancer, dry mouth and bacteria on the tongue are some of the dental problems that can cause bad breath. Using mouthwash to cover up bad breath when a dental problem is present will only mask the odor and not cure it. If you suffer from chronic bad breath, visit your dentist to rule out any of these problems.

2. Tooth Decay

Did you know tooth decay, also known as cavities, is the second most prevalent disease in the United States (the common cold is first). Tooth decay occurs when plague, the sticky substance that forms on teeth, combines with the sugars and / or starches of the food we eat. This combination produces acids that attack tooth enamel. The best way to prevent tooth decay is by brushing twice a day, flossing daily and going to your regular dental check ups. Eating healthy foods and avoiding snacks and drinks that are high in sugar are also ways to prevent decay.

3. Gum (Periodontal) Disease

Studies have shown that periodontal disease, also known as gum disease, is linked to heart attacks and strokes. Gum disease is an infection in the gums surrounding the teeth. Gum disease is also one of the main causes of tooth loss among adults. There are two major stages of gum disease: gingivitis and periodontitis. Regular dental check ups along with brushing at least twice a day and flossing daily play an important role in preventing gum disease.

4. Oral Cancer

Oral cancer is a serious and deadly disease that affects millions of people. In fact, the Oral Cancer Foundation estimates that someone in the United States dies every hour of every day from oral cancer. Over 300,000 new cases of oral cancer are diagnosed every year, worldwide. This serious dental disease, which pertains to the mouth, lips or throat, is often highly curable if diagnosed and treated in the early stages.

5. Mouth Sores

There are several different types of mouth sores and they can be pesky and bothersome. Unless a mouth sore lasts more than two weeks, it is usually nothing to worry about and will disappear on its own. Common mouth sores are canker sores, fever blisters, cold sores, ulcers and thrush.

6. Tooth Erosion

Tooth erosion is the loss of tooth structure and is caused by acid attacking the enamel. Tooth erosion signs and symptoms can range from sensitivity to more severe problems such as cracking. Tooth erosion is more common than people might think, but it can also be easily prevented.

7. Tooth Sensitivity

Tooth sensitivity is a common problem that affects millions of people. Basically, tooth sensitivity means experiencing pain or discomfort to your teeth from sweets, cold air, hot drinks, cold drinks or ice cream. Some people with sensitive teeth even experience discomfort from brushing and flossing. The good news is that sensitive teeth can be treated.

8. Toothaches and Dental Emergencies

I can't think of much worse than suffering from a toothache. While many toothaches and dental emergencies can be easily avoided just by regular visits to the dentist, we all know that accidents can and do happen. Having a dental emergency can be very painful and scary. Fortunately, you can do several things until you are able to see your dentist.

9. Unattractive Smile

While an unattractive smile is not technically a "dental problem," it is considered a dental problem by people who are unhappy with their smile and it's also a major reason that many patients seek dental treatment. An unattractive smile can really lower a person's self-esteem. Luckily, with today's technologies and developments, anyone can have a beautiful smile. Whether it's teeth whitening, dental implants, orthodontics or other cosmetic dental work, chances are that your dentist can give you the smile of your dreams.

Causes of oral health problems

1)Pellicle

The pellicle is rapidly formed on all freshly cleaned tooth surfaces by the deposition and absorption of some salivary proteins. It is less than 0.1 mm thick and is invisible to the naked eye.

2)Plaque

Following the deposition of pellicle on a freshly cleaned tooth surface, plaque forms rapidly. Plaque is an invisible sticky film of bacteria, salivary proteins, and polysaccharides that accumulates on everyone's teeth. It is not washed away by the saliva, and the composition of bacteria depends upon the host, the site in the mouth and the age of the plaque layer. In the event of poor oral hygiene, plaque ages and there is a shift in bacterial population to more harmful organisms as the plaque age.

3)Dental calculus (tartar)

Dental plaque may itself become mineralized and this hard deposit is called calculus. It accumulates on the tooth surface mainly at the gingival margin opposite the salivary ducts. It is a hard mineral deposit, containing predominantly calcium and phosphate, very tightly bound to the tooth surface. Once it has formed, it is virtually impossible to remove it except by a dental hygienist.

CLASSIFICATION OF DENTAL PRODUCTS

Classification depending on Dental Problems.

I. **Products for carries control.**
    a. Systemic fluoride
    b. Topical fluoride
        i. Dentifrices
        ii. Gel
        iii. Rinses
        iv. Miscellaneous
II. **Products for plaque control.**
    a. Chemical agents
        i. Dentifrices

ii. Mouth washes

b. Mechanical products

i. Tooth brushes

ii. Dental floss

iii. Other aids to plaque removal.

III. **Products for tooth surface hypersensitivity.**

IV. **Topical anesthetic**.

V. **Halitosis**

TOOTHPASTE INGREDIENTS AND MANUFACTURE

Requirements of a toothpaste/dentifrice

The major requirements of oral preparations, especially toothpastes, have been summarized on many occasions in the past. For a toothpaste, these requirements were:

1. When used properly, with an efficient toothbrush, it should clean the teeth adequately, that is, remove food debris, plaque and stains.
2. It should leave the mouth with a fresh, clean sensation.
3. Its cost should be such as to encourage regular and frequent use by all.
4. It should be harmless, pleasant and convenient to use. (It should conform to the EC Cosmetics Directive in that it is 'not liable to cause damage to human health when applied under normal usage conditions'.)
5. It should be capable of being packed economically and should be stable in storage during its commercial shelf-life.
6. It should conform to accepted standards in terms of its abrasivity to enamel and dentine.
7. Claims should be substantiated by properly conducted clinical trials.

These requirements remain valid today, with perhaps only the priority and emphasis placed on any individual point being changed.

- To achieve this it is necessary to have a high solid suspension in a stable viscous form and therefore gelling agents or thickening polymers have to be incorporated.
- To prevent it from drying out it also becomes necessary to add humectants to the system. Finally, colours (if desired), and preservatives (if necessary), are also added, creating a complex matrix of ingredients which can be classified as a 'simple' cosmetic toothpaste, i.e. 1. Cleaning and polishing agents (abrasives).
  2. Surfactant (cleaning and foaming).
  3. Humectants.
  4. Binding (gelling) agents.
  5. Sweetener.
  6. Flavouring agents.
  7. Minor ingredients (colours, whitening agents, preservatives).

- In such a complex system many interactions can take place depending upon internal and external factors. Even the 'simple' formulations require extensive stability testing, over a range of temperatures and time, in order to be confident that the product quality does not change upon storage. Only in this way can the manufacturer have a high degree of confidence that the product seen by the consumer is of premium quality.

'A dentifrice should be no more abrasive than is necessary to keep the teeth clean - that is free of accessible plaque, debris and superficial stain'. Thus, considerable performance testing on the final formulation is necessary.

❖ **Ingredients used in toothpastes**

All ingredients generally have specifications approved for use in foodstuffs or are special grades available for dental preparations, especially abrasives.

1. Cleaning and polishing agents (abrasives)

Clearly the main purpose of the cleaning and polishing agent is to remove any adherent layer on the teeth, and the materials normally considered are given below.

(a) Dental grade silicas $(SiO2)n$.

- In a relatively short period of time silica has generally become the abrasive of choice because it offers great flexibility to the formulator.
- It can be produced to a high state of purity giving excellent compatibility with therapeutic additives and flavours.
- Varying the particle size can alter the finished product abrasivity.
- Clear gels can be formulated by carefully matching the refractive indices of silica used with the liquid phase of the toothpaste.
- Silica can also give additional thickening properties to the dental cream if extremely fine particle sizes are used (silica thickeners).
- When used in toothpastes, silica is generally incorporated at levels between 10 and 30%.

(b) Dicalcium phosphate dihydrate (DCPD) $CaHPO4\text{-}2H2O$.

- DCPD is one of the most commonly used dental cream abrasives, perhaps because it gives good flavour stability.
- It is normally white in colour and gives toothpaste which generally does not require additional whitening agents.
- The main drawback is that it is only fully compatible with sodium monofluorophosphate as the fluoride source because of the presence of free calcium ions. Formulating with other therapeutic fluoride sources does not appear to have been successful.
- The abrasive is usually formulated at levels between 40% and 50% to give relatively dense toothpaste.

(c) Calcium carbonate $CaCO3$.

- Calcium carbonate is probably one of the most commonly used dental cream abrasives.
- Precipitated calcium carbonate (chalk) is available with a white or off-white colour and both particle size and crystalline form can be varied, depending upon its conditions of manufacture.
- As a result of its structure and calcium content, precipitated calcium carbonate is incompatible with sodium fluoride, but is stable with the less reactive sodium monofluorophosphate.
- Calcium carbonate is also used at levels between 30% and 50% to give a relatively dense paste.

(d) Sodium bicarbonate (or baking soda $NaHCO3$).

- Sodium bicarbonate has a unique 'salty' mouth-feel that tends to polarize consumers, many finding it attractive possibly due to its heritage as a cleaner/deodorizer.
- It is a very mild abrasive, usually used at a 5-30% level, in combination with other abrasives such as silica or calcium carbonate to achieve the required cleaning action.

(e) Hydrated alumina $Al2O3 \bullet 3H2O$ or $Al(OH)3$.

- Hydrated alumina is relatively inert, cost-effective, and available as a white amorphous solid.
- It has good compatibility with sodium monofluorophosphate and other ingredients added to give a therapeutic benefit.
- The abrasive is usually formulated at levels between 40% and 50% to give a relatively dense paste.

(f) Other abrasives.

- Insoluble sodium metaphosphate (IMP) (NaPO3)x, is available as a free-flowing white powder, with moderate abrasivity and good compatibility with flavour oils, sodium monofluorophosphate and ionic fluoride sources (stannous and sodium fluorides).
- it is now only used in extremely limited amounts.
- Calcium pyrophosphate (CPP), Ca2P2O7, was the original abrasive purposely developed for its compatibility with stannous fluoride to give the first commercially available therapeutic dentifrice containing fluoride.

2. Surfactants

- Surfactants are used in the toothpaste to aid in the penetration of the surface film on the tooth by lowering the surface tension.
- They also provide the secondary benefits of providing foam to suspend and remove the debris, and the subjective perception of toothpaste performance.
- They often have better foaming properties, and are more compatible with other ingredients since their pH range is essentially neutral.
- They are also available with a higher degree of purity that can eliminate some of the bitter flavour components that affect taste.
- In general, surfactants are used at a concentration of around 1-2% by weight in the dental cream.

(a) Sodium lauryl sulphate (SLS)

- This has been the main surfactant of choice, used in nearly all toothpaste brands.
- However, while alternative surfactants have been considered, and will continue to be looked at and developed, none is in widespread use since all have some disadvantages compared to SLS.

3. Humectants

- Humectants are used to prevent the paste from drying out and hardening to an unacceptable level.
- At the same time they give shine and some plasticity to the paste.
- Generally only two major humectants are considered for use in toothpaste, often in combination with small amounts of additional minor humectants.

(a) Glycerin, CH2OHCHOHCH2OH.

- Glycerin is still the humectant used in greatest bulk quantity in toothpaste. It is one of the best humectants, producing a shiny, glossy product.
- It is stable, non-toxic, available from both synthetic and natural sources, and provides a useful sweetening function to the paste.

(b) Sorbitol, CH2OH(CHOH)4CH2OH.

- Sorbitol syrup (approximately 70%) is also extensively used throughout the industry and is sometimes considered superior to glycerin depending upon the formulation.
- It also imparts sweetness, and is a stable humectant.

(c) Propylene Glycol, CH3CHOHCH2OH and Polyethylene Glycol, CH2OH(CHOH)nCH2OH.

- Propylene glycol and polyethylene glycol are not normally used as the sole humectant in a paste since they are more expensive and, in the case of propylene glycol, can impart a slightly bitter taste.

- They are more generally used in relatively small amounts in combination with either glycerin or sorbitol.
- The amount of humectant in any formula obviously has to be adjusted depending upon the other constituents of the formula (especially abrasive nature), but generally the total humectant loading is in the range 10-30% by weight.

(d) Xylitol (CH2OH(CHOH)3CH2OH).

- Xylitol is a polyol equivalent of sorbitol, but with a five-carbon chain instead of six. Like sorbitol it is a naturally occurring material with a relative sweetness equal to sugar.
- Currently its high cost and limited availability restrict its use.

4. Gelling agents

- Gelling or binding agents are hydrophilic (water-loving) colloids which disperse and swell in the water phase of the toothpaste and are necessary to maintain the integral stability of the paste and prevent separation into component phases.
- They are probably the most widely variable components of toothpaste and the choice of gelling agent can greatly influence the dispersibility of the paste in the mouth, the generation of foam and, above all, the release of the flavor components.
- Some formulations have combinations of gelling agents in order to ahieve the desired consumer preferences.

(a) Sodium Carboxymethyl Cellulose CMC.

- Carboxymethyl cellulose is one of the preferred gelling agents for use in toothpaste.
- It can be manufactured to a high state of purity, and tailor-made for an individual requirement by varying the degree of substitution on the cellulose chain.
- This can give flexibility in terms of solubility, elasticity and some increased stability in the presence of electrolytes.

(b) Carrageenan.

- It is a purified colloid, consisting of a mixture of sulfated polysaccharides and, as with all natural products, it can be of variable quality, which could cause a problem for any formulator.
- Therefore, it is standardized either by repeated blending, or dilution with variable amounts of inert material.
- Some flexibility in the gelling properties of carrageenan can be achieved by controlling the cations present by ion exchange.

(c) Miscellaneous gelling agents

Xanthan - This is a polysaccharide produced by fermentation technology. It offers excellent properties for use in toothpaste since it gives a highly structured gel, relatively easily broken down when sheared, but which recovers rapidly. It is relatively insensitive to electrolytes and heat, but unfortunately it is generally incompatible with cellulosic materials because of contaminating enzymes that degrade cellulose.

Hydroxy ethyl cellulose HEC - This is occasionally used as an alternative to carboxymethyl cellulose (CMC), especially when a greater electrolyte tolerance is required.

Synthetic polymers – Cross linked acrylic acid polymers have become more intensively used in the past decade because of their useful thickening and suspending properties combined with their inertness and their stability to heat and ageing.

Clays - Colloidal clays, either natural processed bentonites or synthetic clays,have been used as binding agents because of their thixotropic properties. Depending upon the rest of the formula components (e.g. abrasive, amount of free water), the level of gelling agent added to a paste can vary from 0.5% to 2.0% by weight.

5. Sweetening agents

- These are important for product acceptance, since the final product must be neither too sweet nor too bitter.
- These ingredients must always be considered in partnership with the flavour because of their combined impact.

(a) Sodium saccharin.

- This is the sweetening agent in widest commercial use, and is generally used at a level between 0.05% and 0.5% by weight.

6. Flavours

- Flavours are probably the most crucial part of toothpaste because of consumer preferences.
- The flavour is a blend of many suitable oils, with peppermint and spearmint being the major base components. These are nearly always fortified with other components such as thymol, anethole, menthol (to give a pleasant cooling effect), eugenol (clove oil), cinnamon, eucalyptol, aniseed, and wintergreen (to give a medicinal effect).
- In addition, because the flavour is a mixture of sparingly soluble organic oils, its interactions with the other dentifrice components are often unpredictable and unexpected.
- Taste and stability can be influenced greatly by both the other components of the dental cream, e.g. free water content, or absorption by the abrasive (perhaps to the surface), and also by the physical properties of the dental cream, e.g. pH, viscosity etc.,
- Depending upon the formulation, e.g. the abrasive nature and level, the gelling agent used and the presence of therapeutic ingredients which may impact taste perception, the flavour level may vary from around 0.5% to 1.5% by weight.

7. Minor ingredients

(a) Titanium Dioxide TiO2- Titanium dioxide may be added to give additional whiteness and brilliance to the paste.

(b) Colours. Colours can be an integral part of the aspect of any toothpaste that may influence consumer preference and purchase intent. The EEC Cosmetics Directive (Annex IV) lists the permitted colours and only a small amount is necessary to create a large impact, <0.01% by weight.

(c) pH regulators. Occasionally buffering systems need to be added to the dental cream to adjust the pH of the final finished product.

(d) Sparkles. *A* recent introduction in the marketplace is the addition of small reflective mica particles to coloured transparent gel products. This gives toothpaste the appearance of containing 'sparkles' and is especially aimed at younger children.

8. Fluoride and other 'active' ingredients

- The earliest fluoride dentifrices contained sodium fluoride.
- However, the fluoride was biologically unavailable because the calcium in the dentifrice abrasive bound the fluoride and thus inactivated it.
- Although a number of dentifrices containing fluoride are on the market, not all provide available fluoride because the abrasive systems that some dentifrices contain inactivate the fluoride.
- Therefore, the product may contain as much fluoride as any other dentifrice but it is not available.
- Also, if the product has a short shelf life, it will be ineffective if poor marketing gets it to the consumer too late.

For these reasons, only dentifrices approved by the Council on Scientific Affairs of the American Dental.

Various topical fluoride preparations are available as given in the table.

Form of fluoride	Preparations	Concentration of fluoride
Acidulated phosphate fluoride	Topical solution Topical gel Mouth rinse Paste	1.23 % in 1 % phosphoric acid 1.23 % in 1 % phosphoric acid 0.02-0.04 % 1.2 %
Amine fluoride	Dentifrices Mouth rinse	1.6 % 2.5 %
Sodium fluoride	Topical solution Mouth rinse Dentifrice	2 % 2.5 % 0.2 % (weekly)
Sodium monofuorophosphate	Dentifrices	0.76 – 0.8 %
Stannous fluoride	Topical solution Mouth rinse Paste Gel Dentifrices	8 % 0.1 % 8 % 0.4 % 0.4 %

Currently accepted dentifrices contain sodium monofluorophosphate,sodium fluoride, or, less frequently,stannous fluoride, all of which reduce caries by approximately 25% when used daily.

The composition of some popular tooth pastes is given in table.

Brand	Fluoride	Abrasive	Sweetener	Foaming agent
Aim	0.8 % Na.MFP	10 % Hydrated silica xerogel 19 % Hydrated silica	67 % sorbitol	1.5 % SLS
Aim extra	1.2 % Na.MFP			

strength				
Aqua fresh	0.76 % Na.MFP	12.6 % calcium carbonate 12 % silica	52.8 % sorbitol	1.15 % SLS
Colgate	0.76 % Na.MFP	48.76 % dicalcium phosphate	22 % glycerin	1.2 % SLS

✳ Stannous fluoride

- Dentifrices stained teeth, particularly in pits and fissures.
- This stain is related to the tin in this compound, which adheres to plaque.
- The significance of this staining and its esthetic problems have resulted in a decreased usage in dentifrices.
- Stannous fluoride dentifrices are marketed in a plastic container because a reaction of stannous ions at an acid pH occurs when conventional soft metal tubes are used.
- Dentifrices containing stannous fluoride as an active ingredient are no longer widely marketed; however, these formulations were the first to be evaluated for caries-reducing properties.
- Effectiveness in caries reduction varied from 23 to 34%.

✳ Amine fluoride

- Amine fluorides also have strong plaque-reducing properties.
- However, although the amine fluorides may be more effective for caries reduction than other forms of fluoride, the FDA has not allowed these products to be extensively tested in this country.

✳ Sodium fluoride

- Recent studies of sodium fluoride dentifrices formulated to ensure ready availability of fluoride ions have shown anticaries benefits similar to those obtained in clinical caries trials with dentifrices containing stannous fluoride and sodium monofluorophosphate.
- Clinical caries trials conducted under well controlled, daily supervised brushing conditions have reported reductions in dental caries of approximately 25–48%.

✳ Sodium monofluorophosphate

- A number of clinical studies have been conducted with dentifrices containing 0.76% monofluorophosphate (MFP).
- The data from these controlled clinical studies of sodium MFP dentifrices have indicated reductions in dental caries ranging from approximately 17–42%.

Therapeutic effects of fluoride

✳ Caries control

M/A: fluoride ion can replace the hydroxyl ion in hydroxyapatite the major crystalline structure of enamel.

- ♦ The substituted crystals called fluorapatite is more resistant to acid, such as those produced by plaque bacteria.
- ♦ As fluoride is also an antienzyme. It may inhibit enzymatic acid production by plaque bacteria.

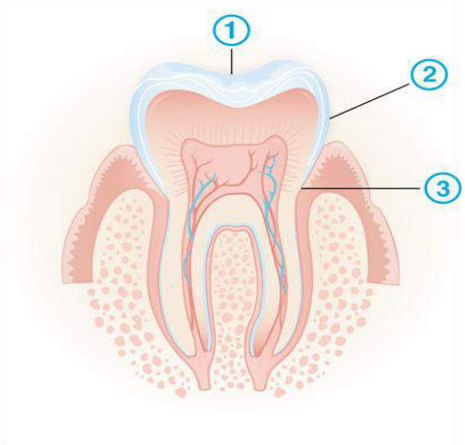
✳ Dental plaque control

- ♦ Mainly stannous fluoride is used for this purpose.

M/A: related to an alteration of bacterial aggregation and metabolism.

Caries sites

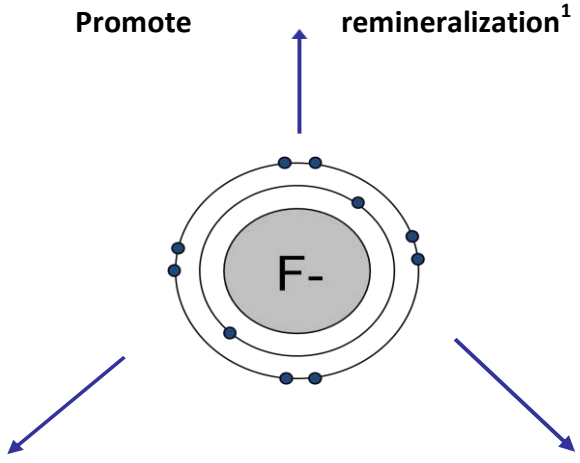
1. **Pit-and-fissure caries** develop initially in the fissures of the teeth, but can spread into the dentine
2. **Smooth-surface caries** are most common on interdental surfaces, but can occur on any smooth surface of the tooth
3. **Root caries** attack the cementum and dentine, which becomes exposed as gums recede



Sources of fluoride

- Topical agents
- Fluoridated water
- Other ingested source

■ **Fluoride effect on remineralization and demineralization of ename**



MECHANICAL PRODUCTS FOR PLAQUE CONTROL

- Toothbrush
- Toothpaste
- Dental Floss

- Tongue Scraper

1. Toothbrush

The toothbrush is the primary dental hygiene product you need to take care of your teeth. First, the regular toothbrush alone provides a plethora of options. Toothbrushes come in various sizes and styles. Various brushes differ from the handle to the bristles. That's why buying a toothbrush can be a confusing task.

In choosing a brush, most dentists recommend soft-bristled brushes more because these can best remove plaque and traces of food that gets stuck in the teeth. You should also choose a brush that does not have a big head. Small-headed brushes can reach the back areas of the mouth for thorough and complete mouth cleaning. You can also choose from squared heads or tapered ones.

As for the handle, you should go for brushes that provide good grip. The shape of the handles themselves differs a lot. But the most important part of the brush is the bristles. There are many forms of bristles, such as rippled, flat, trimmed, or domed ones. All these different types of bristles provide specific benefits that may help meet your needs.

Aside from regular brushes, however, you can also use power brushes, which is very popular among younger users. These powered brushes help clean the teeth better than children usually can.

2. Toothpaste

Another important choice you have to make is what toothpaste to use to go with that perfect brush. The toothpaste aisle in the supermarket is highly congested, and the different brands and kinds often differ in ways that are vague to consumers. That's why it is even harder to choose toothpaste than a toothbrush. The trick, however, is to follow the fluoride arrow. Look for toothpaste that contains fluoride, and the brand usually doesn't matter much. Fluoride is an essential ingredient that can provide strengthening for your teeth. Fluoride works by keeping cavities away and also by polishing tooth enamel.

Another clue to look for is the seal of approval by the American Dental Association, which will help lead you to safe and effective products that have passed clinical scrutiny. You can also consider your specific tastes, such as desensitizing toothpaste for sensitive teeth, whitening toothpaste for yellowing teeth, and tar-tar control toothpaste for those dealing with tar-tar problems.

3. Dental Floss

Another important dental hygiene product is dental floss, which is often neglected by a lot of people. Flossing should be done at least once daily, and benefits are far ranging. Flossing can help clean teeth and in between teeth to make sure no food debris are left. It can help you easily get rid of the food stuck irritatingly between your teeth, which can lead to tooth decay, gum disease, and accumulation of bacteria in the long run. Also, bacteria can lead to bad breath, so dental floss can help keep bad breath away.

4. Tongue Scraper

Another less popular product is the tongue scraper or tongue cleaner, which cleans the surface of the tongue to remove bacteria, food debris, fungi, and dead cells. The tongue is vulnerable to bacteria and fungi that can cause bad breath, oral problems and even medical conditions. Tongue cleaners come in a general form, but one thing to note is that it should be

used before brushing your teeth, since brushing might cause the stuff on your tongue to recede into the throat.

Tartar (Calculus)-Reducing Products

- A number of products, both dentifrices and mouthrinses,are available for reduction of supragingival calculus (tartar) in dental patients. Calculus reduction has been shown with dentifrices containing pyrophosphates, zinc salts, triclosan, and papain.
- The incidence of calculus formation ranges from 45 to 66%, with some variation between males and females and different age groups. Although supragingival calculus is not a major etiologic agent for gingivitis or periodontitis, its surface porosity provides an environment for plaque formation.
- In addition, it serves as a plaque-delivery system by holding plaque against gingival tissues. Although plaque formation has been well correlated with gingivitis and periodontitis, a similar correlation for calculus has not been reported.
- For this reason, the ADA does not offer an acceptance program for products that reduce calculus formation because this is considered to be a cosmetic issue, rather than an issue of disease.
- The mechanism of action of the calculus-reducing chemicals is related to the latter's ability to inhibit crystal growth and interrupt the transformation of calcium phosphate (found in foods and saliva) into dental calculus.

This effect may occur as follows:

1. The agents complex on the tooth surface to block receptor sites for calcium phosphate that precipitates from saliva and chemically absorbs to initiate calculus formation.
2. This same receptor site blockage also occurs in the calculus matrix as it begins to form.
3. The pyrophosphate complexes combine with free calcium in saliva to inhibit the attachment at the tooth surface (probably a secondary mechanism).

TYPE OF DENTIFRICES

(A) Pastes form – Tooth paste
(B) Powder form – Tooth powder
(C) Solid blocks
(D) liquids

(A) TOOTH PASTES

Tooth pastes are most popular valuable and widely used preparations for cleansing the teeth. It has largest share of dental cleansing and care preparations.

Tooth pastes are preferred over other dental preparations because of following reasons.

- Easy to take and spread on the tooth brush
- No spillage or wastage
- Attractive consistency
- Proper distribution in mouth
- Available in wide varieties

A good tooth paste should have following characteristics

- It must clean the dental surface properly without any scratches.

- Consistency should be such that it can be easily squeezed out of the tube to spread on the brush, but should not penetrate in to the brush.
- The consistency should remain constant in wide range of temperature during shelf life.
- It should be non toxic and should not sensitize buccal membrane.
- It should not interact with the container material.
- It should have pleasant taste and odour.
- It should have good appearance.

Formulation:

Method: - 1

The binder, prewetted with the humectant, it is disperse in liquid portion containing the saccharin and preservative and allow swelling to form a homogeneous gel. The swelling may be accelerated by heat and agitation. The solid abrasive is added slowly to homogeneous gel and mixed in mixer until a paste formed. The flavour and detergent are added last and distributed uniformly.

Excessive, aeration, particularly in the presence of detergent, should be avoided. The paste can then be milled, deairated and tubed.

Method: - 2

The binder is premixed with solid abrasive, which is then mixed with the liquid phase, containing humectant, preservative and sweetener into a mixer. After formation of homogeneous paste, the flavour and detergent are added, mixed, milled deairated and tubed.

(A) TOOTH POWDERS

Tooth powders are oldest and simplest preparations. Over the years their market share has been reduced due to popularity of pastes, but steel they have a considerable market share.

The main problems encountered with powders are-

- Floating of powder in air during manufacturing.
- Formation of cake on storage
- Uneven distribution in mouth

Composition

Tooth powders contain the following ingredients-

- Abrasives
- Surfactants or detergents
- Sweetening agents
- Flavours
- Colours

Abrasives are used in manufacturing of tooth powders are similar to that of tooth pastes. Though lighter calcium carbonate is used in tooth paste but in tooth powders heavier grade calcium carbonate is used.

Other ingredients are similar to that of tooth paste.

General procedure for manufacture

- This is done by simple mixing
- First ingredients of small quantity are premixed and then mixed with other ingredients.
- Ribbon type or agitator type of mixer are used.
- Flavour can be sprayed on to the bulk or can be premixed with part of some abrasive.

(3) SOLID BLOCKS

Solid dentifrice is like a soap preparation.

Basically they consist of tooth powder suspended in a base of soap powder, water, and humectant.

Solid detifrices provide a convenient and handy from of cleaning for the teeth.

Formulation

The soap first dissolved in a mixture of glycerin and water with the aid of heat. The powder (abrasive) is then mixed until soft mass formed. Mass is dried on trays, cut into blocks.

EVALUATION OF SOLID DENTAL PRODUCTS

Identification of ingredients and estimation of their contents are essential components of overall quality control and evaluation of dental care products. The products, tooth pastes and tooth powders, can be basically classified into foam forming and non-foam forming.

Some other special evaluation tests are as follows:

Abrasiveness

Various tests have been designed and reported over the year, mostly on the set of extracted teeth. The teeth were mechanically brushed with pastes or powders and then the effects were studied by observation, mechanical or other means. Abrasive character normally depended on the particle size. So, study of particle size can also give such idea.

Particle size

This can be determined by microscopic study of the particles or by sieving or other means.

Cleansing property

This is studied by measuring the change in the reflectance character of a lacquer coating on the polyester film caused by brushing with a tooth cleanser (paste or powder). Also an in vivo test has been suggested in which teeth were brushed for two weeks and condition of teeth was assessed before and after use with the help of photo graphs.

Consistency

It is important that the product , paste, should maintain the consistency to enable the product press out from the container. Study of viscosity is essential for this. Rheology of powders is also important for proper flow of the powder from the container.

pH of the product

pH of the dispersion of 10 % of the product in water is determined by P^H meter.

Foaming character

This test is specially required for foam forming tooth pastes or tooth powders. Specific amount of product can be mixed with specific amount of water and to be shaken. The foam thus formed is studied for its nature, stability, washability.

Limit test for arsenic and lead

This is very important as these are highly toxic metals. Specific tests are there to estimate these two metals; products may not have excess of such metals.

Volatile matters and moisture

A specific amount of the product required to be taken in a dish and drying is to be done till constant weight. Loss of weight will indicate percentage of moisture and volatile matters.

Effect of special ingredients

Special test should be done for the special ingredients if any, like antiseptics, enzymes, etc. for each one special and specific test are to be done.

(4) LIQUID DENTAL PREPARATIONS

- Use of liquid dentifrices are comparatively less than solid one.
- They are basically aqueous or hydroalcoholic solutions of surfactants with additional components like
  - Thickening agent
  - Sweeteners
  - Flavours etc.
- They do not contain any abrasive as they will sediment
- Action of this preparation on dental surface is less but the cleansing effect is more.
- Manufacturing process is making solution of all ingredients.

Formulations

Formula :1	
Sodium myristate sulphate	4.0 gm
Methyl cellulose	4.0 gm
Saccharine sodium	0.1 gm
Flavouring oil	0.3 gm
Glycerin	5.0 gm
Alcohol	10.0 gm
Water	85.4 gm

HALITOSIS

- Local factors, systemic factors, or a combination of both can cause halitosis.
- It is estimated that 80% of all mouth odors are caused by local factors within the oral cavity, and these odors are most often associated with caries, gingivitis, and periodontitis.
- Oral malodors occur because of the action of various microorganisms on proteinaceous substances, such as, exfoliated oral epithelium, salivary proteins, food debris, and blood.
- Studies have shown that saliva from individuals who are free of dental disease produces malodor less rapidly than saliva from patients with dental disease.
- It has also been observed that after prolonged periods of decreased salivary flow and abstinence from food and liquid malodors tend to be most severe.
- Various oral bacteria produce products that are degraded to a number of compounds, foremost of which are sulfides and mucoproteins.
- These compounds have been most often associated with oral malodor.

Specifically, it appears that oral malodor usually results from the bacterial- mediated degradative processes of methyl mercaptan and hydrogen sulfide in oral air.

- Ammonia is also produced but does not appear to contribute significantly to halitosis.
- It has even been suggested that ammonia production may improve the odor of mouth air.

- However, for many patients, systemic or local factors cannot be identified.
- Tongue scraping has been shown to reduce malodor in some patients.
- Mouthwashes and dentifrices can serve an esthetic function by reducing halitosis. They can accomplish this by masking malodors, acting as antimicrobial agents, or both.
- There are no ADA-accepted products to reduce halitosis at this time.

Safety

- While dentifrice products have a long history of safety, there is an ongoing concern associated with dental fluorosis due to fluoride ingestion in children under age six. Studies have shown that for children 1–3 years, 30–75% of the dentifrice is ingested, and for children 4–7 years 14–48% is ingested.
- As with any OTC drug product, precautions need to be taken to prevent overdose. The FDA requires labeling of all fluoride dentifrice products to include a statement "to minimize swallowing use a pea-size amount in children under six."
- Making childproof caps available on fluoride dentifrice products intended for use by children has been recommended.
- Another approach would be to provide metered dentifrice delivery systems for children under age six, which could be set to dispense the correct amount of fluoride depending on the body weight of the child.

Dental care products

- **Effervescent Polident Denture Cleansers**

Non abrasive cleaning and antibacterial action in a soaking solution with oxidizing agents and detergents to remove food particles, stains and bacteria. Cleaning action is available in variants for 3 minutes, overnight and stain removing whitening and for partials.

- **Polident Fresh Cleanse Denture Foam**

Denture Cleansing foam provides non abrasive mechanical cleaning and antibacterial action and stain removal with detergents and a long lasting flavor

- **Polident Dentu-Paste and Dentu- Gel Denture Cleansers**

Mechanical cleaning with a brush using these denture cleansers containing detergents and oxidizing agents

- **Super Poligrip Denture Adhesive Cream**

Poly (methylvinylether/maleic polymer cross linking salts to provide adhesion between denture and the alveolar ridge and the palate. The denture adhesive cream fills gaps between gum and denture for a strong hold and sealing out food particles

- **Super Poligrip Denture Adhesive Powder**

Poly(methylvinylether/maleic polymer cross linking salts to provide adhesion between a denture and the alveolar ridge and the palate. The denture adhesive powder forms a strong, thin seal to keep out food particles

- **Super Poligrip Denture Adhesive Strips**

Extruded strip with a Polyox/Carboxymethylcellulose system. The denture adhesive strips are pre cut to control the amount of the application.

Texas Dental Firm Offers Novel Tooth-Whitening Product Line

- Ultra-White Products, Inc., a tooth whitening product manufacturer in Texas, now offers an attractive alternative to marginally effective over-the-counter tooth whitening product lines and costly dental treatments.
- The company's novel tooth whitening product affords users the ability to obtain custom application trays and whitening gels at a fraction of the cost normally associated with professional cosmetic dentistry and are far more effective than Over-the-counter solutions.
- The company has a worldwide following with over 30,000 clients and is owned an managed by a practicing dentist.

NEWER FORMULATIONS OF DENTIFRICE FROM CHEMICAL ABSTRACTS

- Functional toothpaste containing nano sized silver.
- High Fluoride ion recovery dentifrice compositions.
- Stable Suspensions of composite material s for use as dentifrices containing an antimicrobial organic acid salt.
- Application of water soluble chitosan in toothpaste & mouthwash.
- Dentifrice containing silica microparticles as the sole abrasives.
- Dentifrice compositions comprising alkyl galactoside derivatives +nonionic disinfectants or +protein naturants or +vit- E gives strong coaggregation-inhibitory effect & antibacterial effect against Fusobacterial & other dental caries & periodontal disease- causing bacteria.

QUESTIONS:-

1) Define cosmetics? Put some light on its origin and development through different ages.
2) Describe in brief the cosmetics products for skin?
3) Define shampoo? Write note about it?
4) Write a note on skin colorants?
5) Classify cosmetics with examples?
6) Define cosmoceutical? How it differs from cosmetics products? explain
7) Describe different nail preparations?
8) Write in detail about quality control of cosmetics including sampling size?
9) What is powder? Classify powers ? Give formulation of any one type?
10) Classify raw materials of cosmetics? Write in brief about each with example?

Parenteral Preparations

Syllabus:
Types- General requirements, Various components, container, closure, production facilities, procedures and equipment employed in the manufacture of parenterals.
Freeze drying of parenteral formulations, quality control and packaging of parenterals. Study of official preparations like, water of injection, Calcium gluconate injection.

References
1. Remington's Pharmaceutical Sciences
2. Ansel Pharmaceutical Dosage Forms and Drug Delivery Systems
3. Banker Rhodes
4. Cooper & Gunn Dispensing

PARENTERAL PREPARATIONS

Definition:
The word '*parenteral*' came from the Greek work '*para enteron*' that means '*beside the intestine*'. So parenteral products mean the dosage forms those deliver drugs through a route other than oral route.

Types of injections
Injections may be classified according to the route of administration, which is given in the tabular form under *Routes of Administration.*

Intradermal injection
They are made into the skin between the inner layer or dermis, and the outer layer, or epidermis. The skin of the front of the left forearm is usually selected. Other details are given in the table. The drug is injected into the dermis of skin raising a bleb (e.g. BCG vaccine, sensitivity testing of drugs) or scarring / multiple puncture of the epidermis through a drop of the drug (small pox vaccine) is done.

This route is employed for testing of allergen, such as pollens, dust or microorganisms (tuberculin or histoplasmin).

Absorption is very small from this site because very small number of blood capillaries are present. The site should not be massaged.
Body sites of injection: Usually on the outer surface of the left forearm.

Subcutaneous (or Hypodermic) injection
These injections are made under the skin, into the subcutaneous tissue. The drug is deposited in the loose subcutaneous tissue which is richly supplied by nerves (so irritant drugs cannot be injected) but is less vascular (so absorption is slower).

Care must be taken to ensure that the needle is not in a blood vessel. This is checked by lightly pulling back the syringe plunger (a method known as *aspiration*) before making an injection. If the needle has pierced into a vessel then blood will appear in the syringe and in that situation the injection should not be made.
Sometimes dextrose and electrolyte solutions are given subcutaneously in amounts from 250 to 1000mL. This technique is called *hypodermoclysis*. This method is used when veins are not available in a patient or are difficult to use for further medication. In this case the hyalouronidase is co-administered with the large volume injection (LVP) that helps in hydrolysis of hyalouronic acid (the cell-cementing material that binds the cells of the tissues), increases the absorption of the liquid and decrease tissue distension.
Body sites of injection: Usually on the most portions of arms, legs and abdomen.
Advantages:
1. Self injection is possible because deep penetration is not required.
2. oily solutions or aqueous suspensions can form a depot which will release drug slowly for a prolonged period.

Disadvantages:
1. Since skin is richly supplied by nerve-endings hence irritant drugs cannot be injected.
2. Drugs administered in this route produce slower onset of action than i.m. or i.v. route.
3. This route should be avoided in shock patients.

e.g. Insulin injection.

Intramuscular injection

The drug is injected in one of the large skeletal muscles that lie below the subcutaneous layer.

Body sites of injection: Deltoid (upper arm), gluteal (buttock), vastus lateralis (lateral thigh) msucles.

It is important to aspirate before injection to ensure that the needle does not enter into a vein.

Advantages:

1. Muscle is less richly supplied with sensory nerves, hence mild irritants can be injected.
2. Muscle is more vascular hence absorption is faster (onset of action 15 to 30mins) than subcutaneous route.
3. It is less painful.
4. Depot preparations can be injected by this route and the action of the drug may be prolonged.

Disadvantages:

1. Since deep penetration is needed hence self-medication is not possible.
2. Large volume cannot be given.

e.g. Low volume injections - Vitamin A, hydrocortisone acetate, tetanus toxoid, antibiotic etc.

Intravenous injection

The drug is injected as a bolus (*venipuncture*) or infused slowly over hours (*venoclysis*) in one of the superficial veins (generally medial basilic vein).

Rug must be administered through this route slowly because irritation or an excessive drug concentration at sensitive organs such as the heart and brain (*drug shock*) may occur.

The duration of action of a drug depends on the pharamcokinetic parameters (rate of distribution and elimination)

Advantages:

(i) The drug directly reaches the blood stream and effect is produced immediately, hence, this route can be used in emergencies.

(ii) The inside of the veins is insensitive (because no nerve endings are there) and drug gets diluted with blood quickly, therefore, even highly irritant drugs can be injected intravenously.

(iii) Large volumes can be infused (e.g. normal saline).

(iv) It is useful in unconscious patients.

(v) Desired blood concentration can be achieved.

Disadvantages:

(i) Drugs that precipitate in the blood cannot be administered. Only aqueous solution can be administered.

(ii) If the needle puncture the vessel (i.e. extra vasation) then thrombophlebitis of the injected vein and necrosis of the adjoining tissues may occur.

(iii) No drug can be given in depot form - so the action is not prolonged compared to other parenteral administrations.

(iv) Untoward reactions if occur are immediate.

(v) Once administered, withdrawal of the drug is not possible.

Intra-arterial injection

The intra-arterial route involves injecting a drug directly into an artery. It is important that the artery not be missed, since serious nerve damage may occur to the nerves lying close to the arteries.

Dose given through this route must be minimum and given gradually, since, once injected, the drug effect cannot be neutralized.

This route of injection is used to administer radiopaque contrast media for viewing an organ, such as the heart or kidney, or to perfuse an antineoplastic agent at the highest possible concentration to the target organ.

Intrathecal injection

The intrathecal route is employed to administer a drug directly into the cerebrospinal fluid at any level of the cerebrospinal axis. This route is used when it is not possible to achieve sufficiently high plasma levels to accomplish adequate diffusion and penetration into the cerebrospinal fluid. Intrathecal, intraspinal, and intracisternal routes must be formulated at physiologic pH, must be isotonic and must not contain any preservatives in order to minimize nerve damage.

Local anaesthetic drugs are injected through this routes.

Specialized Large-Volume Parenteral and Sterile solutions

Large volume parenterals are designed to provide fluid (water), calories (dextrose solutions), electrolytes (saline solutions), or combinations of these materials.

Hyperalimentation solution (Total Parenteral Nutrition)

Parenteral hyperalimentation involves administration of large amount of nutrients (e.g. carbohydrates, amino acids, lipids and vitamins) to maintain a patient who is unable to take food orally for several weeks at caloric intake levels of 4000kcal/day or more. The formulation when administered through a peripheral vein intravenously at a slower rate the body does not get enough nutrition, so this type of LVP is given as hypertonic solution and given through subclavian vein so the liquid gets diluted very quickly with the blood. This formulation generally consists commonly a mixture of dextrose, amino acids and lipids (usually soybean oil, sunflower oil or mixture of two) containing added electrolytes, trace metals and vitamins.

Nutrition is supplied in this method to comatose patients, patients undergoing oesophageal obstruction, GI disease (including GI cancer), ulcerative colitis, etc.

Cardioplegic solutions

Cardioplegic solutions are large-volume parenteral solutions used in heart surgery to help prevent ischemic injury to the myocardium during the time the blood supply to the heart is clamped off and during reperfusion, as well as to maintain bloodless operating field and to make the myocardium flaccid.

This solutions are typically electrolyte solutions where the electrolyte composition is intended to maintain diastolic arrest.

These solutions are administered in cold condition in order to cool the myocardium and minimize metabolic activity.

These solutions are slightly alkaline and hypertonic in order to minimize acidosis and to minimize reperfusion injury resulting from tissue edema.

Peritoneal dialysis solutions

The sterile peritoneal dilysis solutions are infused continuously into the abdominal cavity, bathing the peritoneum, and are then continuously withdrawn.

The purpose of peritoneal dialysis is to remove toxic substances from the body and accelerates the excretion rate of the drug from the body in case of acute renal insufficiency.

These types of formulations contains

(a) glucose and ionic content similar to extraceular fluid. In some cases hypertonic glucose solutions are prepared to draw excess fluid from the patient.
(b) An antibiotic is often added to this solutions as a prophylactic measure.

Irrigating solutions

Irrigating solutions are intended to irrigate, flush, and aid in cleansing body cavities and wounds.

Normal saline may be used as irrigating solution.

Irrigating solutions are sterile and pyrogen free because while it is used to wash the wounds small amount of solution infuses inside the wound.

Formulation factors

The formulation of injections involves careful consideration of the following factors:

1. The route of administration
2. The volume of injection
3. The vehicle in which the medicament is to be dissolved or suspended.
4. The osmotic pressure of the solution.
5. The need for a preservative.
6. The pH of the solution.
7. The stability of the drug.

1. Routes of administration

Routes	Usual volume	Needle Used Length / Dia	Formulation constraints	Types of medication administered
Subcutaneous	0.5-2ml	5/8in 23gauge	Must be isotonic	Insulins, vaccines
Intramuscular	0.5-2ml	1.5in, 22gauge	Can be oils, suspensions, emulsion. Preferably isotonic.	Nearly all types of drugs.
Intravenous				
Small volume	1-1000ml	Veinpunture 1.5in,20-22gauge	Solutions, emulsions and liposomes	Nearly all types of drugs
Large volume	101 and	Venoclysis	Solutions and some emulsions	Nearly all types of drugs

(infusion)	above	1.5in, 18-19gauge	(TPN)	
Intra-arterial (Directly into an artery)	2-20ml	20-22gauge	Solutions and some emulsions	Radiopaque media, antineoplastics, antibiotics.
Intrathecal (into spinal canal)	1-4ml	24-28gauge	Must be isotonic	Local anaesthetics, analgesics, neurolytic agents.
Intraepidural (into epidural space near spinal cord)	6-30ml	5in,16-18gauge	Must be isotonic	Local anaesthetics, narcotics, α2-agonists, steroids.
Intracisternal (directly into caudal region of the brain between the cerebellum and medula oblongata)			Must be isotonic	

Routes	**Usual volume**	**Needle Used Length / Dia**	**Formulation constraints**	**Types of medication administered**
Intra-articular (directly into a joint)	2-20ml	1.5-2in, 18-22 gauge	Must be isotonic	Morphine, local anaesthetics, steroids, NSAIDs, antibiotics.
Intracardial (directly into the heart)	0.2-1	5 in 22gauge		Cardiotonic drugs (epinephrine), calcium.
Intrapleural (directly nito the pleural cavity of the lung)	2-30ml	2-5 in 16-22 gauge		Local anaesthetics, narcotics, chemotherapeutic agents
Intradermal	0.05ml	½ - 5/8 in, 25-26 gauge	Should be isotonic	Diagnostic agents for investigation of immunity and allergy to any agent.

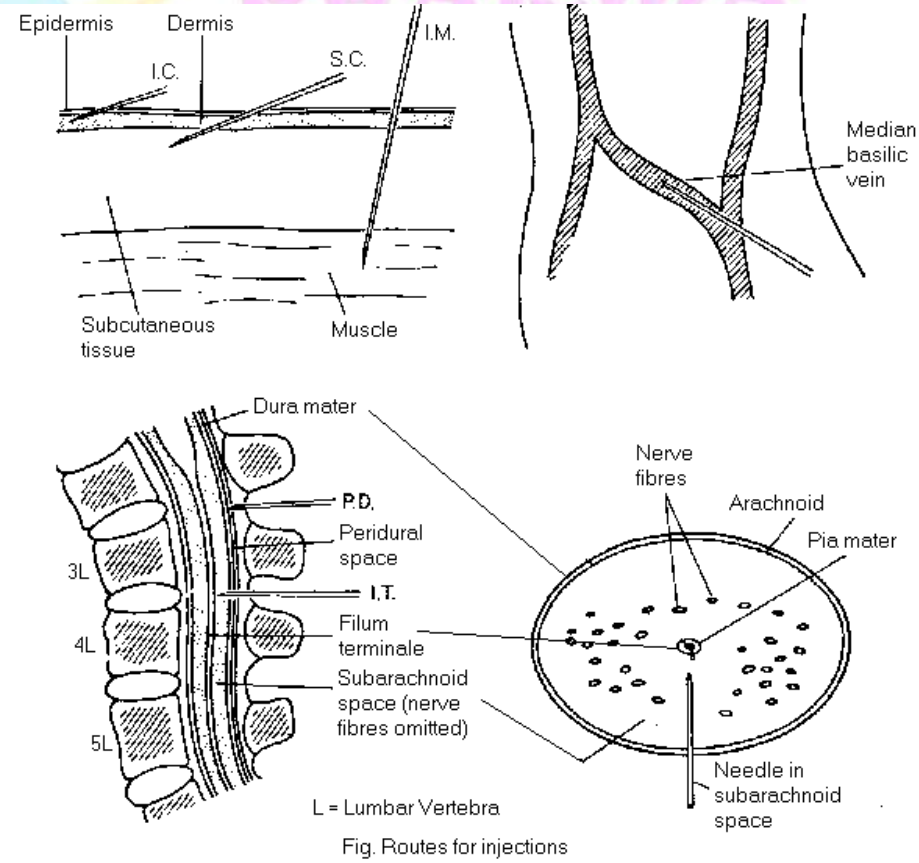


Fig. Routes for injections

2. Volume of injection

Usually the volume of an injection depends on the route of administration. Only the intravenous route is really suitable for *large volume parenterals* (LVP). In subcutaneuous route generally 0.5-2ml volume may be injected. Some times veins of a patient are unavailable. In those cases instead of intravenous infusion large volume parenterals (250 to 1000ml) may be injected subcutaneously. This technique is called *hypodermoclysis*. In most of this case the injection is given along with *hyalouronidase* an enzyme that hydrolyses the hyalouronic acid, the viscous cell-cementing agent. It helps in rapid absorption of the injection and reduces tissue distension. The hydrolysis is reversible and the acid is reformed in about 20minutes after completion of the injection.

The volume must be convenient to administer. Less than 20ml is suitable for injection with a syringe and more than 250ml injections are given as infusion.

PHARMAROCKS GPAT SUCCESS TEST SERIES 2015 CALCULATION FORMULA

MOST IMPORTANT FORMULA USE IN POSOLOGY CALCULATION

1. Young's Rule: Child dose = [Age X Adult dose] / (Age + 12)

2. Couling's Rule: Infant dose = [Age (at next birthday) X Adult dose] / 24

3. Fried's Rule: Infant dose = [Age (in months) X Adult dose] / 150

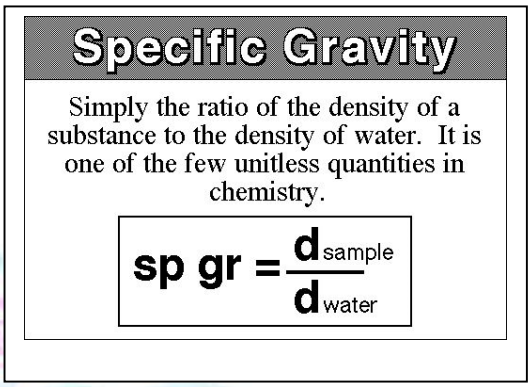
4. Clark's Rule: Child dose = [Weight (in lbs) X Adult dose] / 150

DENSITY = MASS / VOLUME

SPECIFIC GRAVITY (Sp. gr.)

Sp. gr. = W_t / V

Sp. vol = V / W_t thus sp. volume = 1 / sp. gr



Wt. of the liquid = sp. gr. of liquid X volume of the liquid

Volume of a liquid = Wt of liquid / sp. gr.

Strength X Volume = Strength X Volume

CALCULATION OF TEMPERATURE

9 X °C = 5 X °F -160

Proof Gallon = Wine gallon X Proof strength / 50%

ISOTONICITY

- Sodium chloride 0.90%
- Dextrose 5.00%
- Boric acid 1.73%

FREEZING POINT DEPRESSION OF NORMAL SALINE IS 0.52

The equivalent weight = Molecular weight / valency

Mosmol = m moles X no of ions = (wt in mg / m wt) X no of ions

pH = – Log [H+]

pOH = – log [OH]

pH = pKw – pOH = 14 – pOH

pKa = - log [Ka]

pKb = - log [Kb]

pH = pKa + log [Salt / Acid]

pH = pKa + log [Base / Salt]

pH = pKw – pKb + log [Base / Salt]

Sensitivity requirement = minimum quantity to be weighed in mg X permissible error

PHARMAROCKS

GPAT STUDY MATERIAL

ALKALOIDS

PHARMACOGNOSY

PHARMAROCKS GPAT SUCCESS TEST SERIES

ORGANISE BY MR. AMAR M. RAVAL

ALKALOIDS: SOME IMP POINTS AND DRUGS

Alkaloids are basic nitrogen containing compounds obtained from plants, animals & microorganisms having a marked physiological action

Characteristics:

Well defined crystalline substances, generally occurring as solids except nicotine which is a liquid, colourless except berberine which is a yellow coloured alkaloid. Occur in plants in the salt form.

They answer the following chemical tests:

1. **Mayer's reagent**- (potassium mercuric iodide)

Cream coloured precipitate

2. **Wagner's reagent**- (iodine in potassium iodide)

Reddish brown precipitate

3. **Hager's reagent**- (salt solution of picric acid)

Yellow precipitate

4. **Dragendroff's reagent**- (potassium bismuth iodide)

Reddish brown precipitate

Caffeine is a pseudo alkaloid drug which does not answer this test

Extraction:

- The powdered drug is defatted using petroleum ether if necessary
- The powder is further basified using lime to break the salt form of the alkaloid & liberate free base which can be extracted using an organic solvent
- Alkaloidal salts can be directly extracted using an acidified aqueous solvent

Classification:

1. Pharmacological method
2. Taxonomic method
3. Biosynthetic method
4. Chemical method – true & proto alkaloids

- **TRUE ALKALOIDS**

1. Pyrrole & Pyrrolidine Eg- Coca
2. Pyridine & Piperidine Eg- Coniine
3. Tropane Eg- Atropine

4. Quinoline Eg- Cinchona
5. Indole Eg- Rauwolfia
6. Purine Eg- Caffeine
7. Steroidal Eg- Kurchi
8. Isoquinoline Eg- Opium

- **PROTO ALKALOIDS**

Eg- Ephedrine

INDOLE ALKALOIDS

ERGOT / ARGOT / ST. ANTHONY'S FIRE

BIOLOGICAL SOURCE:

Schlerotium of fungus claviceps purpurea, at the ovary of rye plant secale cereale

Family: graminae (fungus belongs to family clavicipitaceae)

GEOGRAPHICAL SOURCE: Switzerland

Known to have caused gangrene (ergotism) in Germany

Life cycle:

1. Sexual / sphacelial stage
2. Asexual / schlerotium stage

Sexual stage:

The ascospores infect the ovary of the rye plant & if conditions are favourable it develops hyphal strands, it forms a white mass over the ovary known as the mycelium

Asexual stage:

The hyphal strands further develop invading the ovary & converting it to a hard violet schlerotium, Schlerotium contains stromatum which shows a globular stalk

It encloses bag like structures known as ascus containing ascospores

If these ascospores are liberated they infect another rye plant

Morphology of schlerotium:

Hard, violet, odourless, with an unpleasant taste

Chemistry:

Derivatives of lysergic acid

Water soluble ones are ergometrine & ergometrinine

Water insoluble ones are ergotamine & ergotoxine

Only the levo isomer is active

Uses:

Ergometrine is an oxytocic drug but its methyl derivative is preferred as it causes less hypertension

Ergotamine is analgesic in migraine

Chemical Test:

1. Gives a blue colour with Van Curk's reagent (para dimethyl amino benzaldehyde)
2. Gives blue fluorescence in water
3. When treated with ether, H2SO4 followed by sodium bicarbonate, aqueous layer shows a red violet colour
4. Ergotamine + glacial acetic acid + ethyl acetate + H2SO4 gives a blue solution with a red tinge. When further treated with FeCl3 the blue colour disappears

VINCA / PERIWINKLE

BIOLOGICAL SOURCE: aerial parts of catharanthus roseus

Family: apocynaceae

GEOGRAPHICAL SOURCE: India, Madagascar

Morphology:

Leaves are small, opaque, dark green, odourless & bitter to taste

Chemistry:

Indole alkaloids such as vinblastine, vincristine, ajamlicine & serpentine

Use:

Potent anti-cancer agent, hypotensive & anti-diabetic

NUXVOMICA

BIOLOGICAL SOURCE: dried seeds of strychnos nuxvomica

Family: Loganiaceace

GEOGRAPHICAL SOURCE: srilanka, India

MORPHOLOGY:

Seeds are circular, flat, grayish green, covered with trichomes & extremely bitter to taste

Chemistry:

Contains two main indole alkaloids strychnine & brucine

Use:

Rarely used as a nerve tonic as it is poisonous in large doses

Chemical Test:

1. Section when treated with concentrated HNO3 shows a yellow colour with brucine
2. Section when treated with ammonium vanadate & H2SO4 shows a purple colour with strychnine
3. Strychnine when treated with H2SO4 & K2Cr2O7 develops a violet to yellow colour

RAUWOLFIA / SARPAGANDHA

BIOLOGICAL SOURCE: dried roots of rauwolfia serpentina

Family: apocynaceae

GEOGRAPHICAL SOURCE: Asia, America

Morphology:

Snake shaped, brown coloured, longitudinal wrinkles tapering towards the end

Chemistry:

Reserpine, ajamlicine, serpentine

Use:

Antihypertensive by preventing uptake of adrenaline

Chemical Test:

1. Freshly fractured surface of the root when treated with concentrated HNO3 shows red coloured medullary rays
2. Reserpine gives a violet colour with vanillin in acetic acid

TROPANE ALKALOIDS

BELLADONA

BIOLOGICAL SOURCE: dried leaves of atropa belladonna

Family: solanaceae

GEOGRAPHICAL SOURCE: England, Europe, India

Morphology:

Leaves are greenish brown, ovate in shape with an entire margin & bitter to taste

Microscopic Characters:

- Dorsiventral leaf
- Collenchyma above & below the mid rib
- Unicellular covering trichomes, unicellular glandular trichomes
- Microsphaenoidal calcium oxalate crystals

Chemistry:

Atropine, hyoscyanine, belladonine

Use:

Atropine is a parasympatholytic, thus decreases secretion & spasms

Chemical Test:

Vitali morin test – to the drug fuming nitric acid is added & it is evaporated to dryness.

Methanolic KOH is added to the acetone solution of the nitrated residue

It develops a violet colour

STRAMONIUM

BIOLOGICAL SOURCE: dried leaves & flowering tops of datura stramonium

Family: solanaceae

GEOGRAPHICAL SOURCE: America, France

Morphology:

Leaves are grayish green with a crenate margin & unequal base

Microscopic Characters:

- Dorsiventral leaf
- Collenchyma above & below the mid rib
- Unicellular covering & glandular trichomes
- Xylem surrounded by phloem
- Anisocytic stomata

Chemistry:

Hyoscine, atropine, belladonine

Use:

Hyoscine is an anti-emetic

Chemical Test:

Vitali morin test

COCA LEAVES

BIOLOGICAL SOURCE:

Dried leaves of erythroxylon coca (Bolivian variety) Erythroxylon truxillense (Peruvian variety)

Family: erythroxylaceae

GEOGRAPHICAL SOURCE: Bolivia, Peru

Morphology:

Peruvian leaves are pale green, fragile, thin, and elliptical in shape

Bolivian leaves are greenish brown, oval in a shape with a prominent mid rib

Microscopic Characters:

- Dorsiventral leaf
- Collenchyma above & below mid rib
- Xylem surrounded by phloem & pericyclic fibres
- Paracytic stomata

Chemistry:

Cocaine, cinnamoyl cocaine, tropocaine, benzoylecgonine

Extraction:

The leaf powder is basified with lime & extracted using an organic solvent

The free bases are converted to their hydrohlorides by using HCl

Due to this procedure cocaine liberates ecgonine, methanol & benzoic acid whereas cinnamoyl cocaine generates ecgonine, methanol & cinnamic acid

The ecgonine thus obtained is used to synthesize cocaine by treating it with benzoic anhydride, methyl iodide, and methanol & sodium methoxide

Use:

Local anaesthetic

Chemical Test:

Drug powder when heated with concentrated H2SO4 gives a typical odour of methyl benzoate

QUINAZOLINE ALKALOIDS

VASAKA LEAF / ADULSA

BIOLOGICAL SOURCE: dried & fresh leaves of adhatoda vasica

Family: acanthaceae

GEOGRAPHICAL SOURCE: India

Morphology:

Leaves are dark green, lanceolate in shape, have a crenate margin with a characteristic odour & bitter taste

Chemistry:

Vasicine, vasicinone & adhatodic acid

Uses:

Vasicine is an expectorant. It gets oxidized to vasicinone which in an abortifacient in large doses, otherwise a bronchodilator

PYRIDINE ALKALOIDS

LOBELIA HERB / INDIAN TOBACCO / ASTHMA WEED

BIOLOGICAL SOURCE: dried aerial parts of lobelia nicotianefolia

Family: campanulaceae

GEOGRAPHICAL SOURCE: India

Morphology:

Leaves are sessile, large, dark green & possess an acrid taste

Chemistry:

Lobeline, lobelidine & isolobanine

Use:

Respiratory stimulant

Chemical Test:

1. Lobeline solution if heated gives typical odour of acetophenone
2. Lobeline in H2SO4 when treated with formaldehyde develops red colour

IMIDAZOLE ALKALOIDS

PILOCARPUS

BIOLOGICAL SOURCE: dried leaves of pilocarpus jaborandi, Pilocarpus microphyllus

Family: rutaceae

GEOGRAPHICAL SOURCE: south America

Morphology:

Leaves are greyish green with an asymmetrical base & possesses aromatic odour & bitter taste

Chemistry:

Contains pilocarpine, pseudopilocarpine, pilosine & limonene

Uses:

Antagonist to atropine, causes miosis, increases salivation & sweating

Chemical Test:

Pilocarpine solution when treated with H2SO4, H2O2, benzene & K2Cr2O4, the organic layer appears bluish violet in colour whereas aqueous layer shows yellow colour

INDOLE ALKALOIDS

CALABAR BEANS

BIOLOGICAL SOURCE: dried type seeds of physostigma venenosum

Family: leguminosae

GEOGRAPHICAL SOURCE: Africa

Morphology:

Reddish brown in colour, hard, shiny & rough to touch

Chemistry:

Contains physostigmine, starch & proteins

Use:

Helps in contraction of pupil, retards respiration & causes bradycardia

OPIUM / POPPY PLANT

BIOLOGICAL SOURCE: dried latex obtained from capsules of papaver somniferum

Family: papaveraceae

GEOGRAPHICAL SOURCE: India (MP), turkey, Pakistan, Afghanistan

Collection:

- Collection is started when capsules change colour from dark green to yellowish green.
- Longitudinal incisions about 2mm deep are given on the capsules to exude the latex
- The latex is allowed to solidify overnight & later scraped off
- The process is repeated 4 times with a gap of 2 days

Morphology:

The dried latex is dark brown, extremely bitter to taste & has a strong odour

Chemistry:

Contains phenanthrene type of alkaloids such as morphine & codeine & benzyl isoquinoline type of alkaloids such as papaverine & noscapine

These occur as salts of meconic acid

Use:

- Morphine is a narcotic analgesic & stimulant
- Codeine is an anti tussive
- Papverine is a smooth muscle relaxant

Chemical Test:

1. Aqueous solution of meconic acid shows a deep reddish purple colour with ferric chloride
2. Morphine when sprinkled with concentrated HNO3 shows an orange red colour. This is not allowed by codeine
3. Morphine solution when treated with ferric chloride & potassium ferricyanide gives a bluish green colour
4. Papaverine solution in HCl & potassium ferricyanide develops a lemon yellow colour

Varieties of opium:

Indian, Turkish, Persian, European, manipulated Persian & European

QUINOLINE AKALOIDS

CINCHONA BARK / JESUIT'S BARK / PERUVIAN BARK

BIOLOGICAL SOURCE:

Dried bark of cultivated trees of cinchona calisaya

Cinchona officinalis

Cinchona ledgeriana

Cinchona succirubra

Family: rubiaceae

GEOGRAPHICAL SOURCE: India, Bolivia, srilanka

Collection:

It is collected by coppicing method

Vertical incisions are made on branches, trunk of the tree & these incisions are connected by horizontal circles

The bark is then stripped off & dried in sunlight & further by artificial heat (175 degree F)

The root bark is collected by uprooting trees & separating manually

Morphology:

Stem bark is rough with transverse fissures

Outer surface is grey & inner surface is pale yellowish brown to deep reddish brown

Root bark is curved, outer surface is scaly, outer & inner surface with same colour

Microscopic Characters:

- Cork cells are thin walled
- Cortex has phloem fibres
- Medullary rays with radially arranged cells
- Idioblast of calcium oxalate is a specific characteristic
- Starch grains in parechymatous tissues
- Stone cells rarely present

Chemistry:

Contains quinine, quinidine, cinchonine & cinchonidine

Also contains quinic acid & cinchotannic acid

Chemical Test:

1. On heating the drug in a dry test tube with glacial acetic acid, purple vapours are produced
2. Thalleoquin test: drug + bromine water + dilute ammonia gives an emerald green colour
3. Drug when treated with quinidine solution gives a white precipitate with silver nitrate which is soluble in nitric acid

Uses:

Anti-malarial, anti-pyretic, quinine is used in arrhythmias against atrial fibrillation

ISOQUINOLINE ALKALOIDS

IPECAC

BIOLOGICAL SOURCE:

Dried roots of cephalis ipecacuanha (Brazilian / Rio), Cephalis acuminata (panama / Cartagena)

Family: rubiaceae

GEOGRAPHICAL SOURCE: Brazil, panama

Morphology:

Brazilian ipecac is dark brick red as compared to greyish brown panama ipecae

Both possess faint odour & bitter taste

Chemistry:

Brazilian – emetine: cephalin ratio is 4:1

Panama – emetine: cephalin ratio is 1:1

Uses:

Expectorant in mild doses & as an emetic in large doses

Emetine also possesses anti protozoal activity

Chemical Test:

1. Emetine shows a bright green colour with H2SO4 & molybdic acid

2. Emetine when shaken with water & small amount of HCl, filtered & to the filtrate potassium chlorate is added gives a yellow colour changing to red

PYRIDINE- PIPERIDINE ALKALOIDS

TOBACCO

BIOLOGICAL SOURCE: dried leaves of nicotiana tabacum

Family: solanaceae

GEOGRAPHICAL SOURCE: India, France

Morphology:

Leaves are large, green with a dentate margin

It has a characteristic strong odour & bitter taste

Chemistry:

Nicotine, nornicotine & anabasine

Use:

Stimulant

PROTO ALKALOIDS

EPHEDRA / MA HUANG

BIOLOGICAL SOURCE: dried stem of ephedra gerardiana

Family: ephedreaceae / gnetaceae

GEOGRAPHICAL SOURCE: china, Pakistan

Morphology:

Greyish green, thin, cylindrical stem bearing scaly leaves & internodes

No typical odour but has a bitter taste

Chemistry:

Contains amino alkaloids like ephedrine, norephedrine & pseudo ephedrine

Uses:

Sympathomimetic & bronchodilator

Chemical Test:

Aqueous solution of ephedrine shows a violet colour when treated with dilute HCl & CuSO4 followed by dilute NaOH

COLCHICUM / AUTUMN CROCUS

BIOLOGICAL SOURCE: dried seeds & corms of colchicum luteum

Family: liliaceae

GEOGRAPHICAL SOURCE: Europe

Morphology:

Seeds are hard, reddish brown, rough to touch whereas corms are yellowish in colour with a longitudinal groove & bitter to taste

Chemistry:

Contains amino alkaloid colchicine & demecolchicine

Uses:

Rheumatism, treatment of gout, anti-tumour activity & polyploidy

ACONITE / BACHNAG

BIOLOGICAL SOURCE: dried roots of aconitum napellus

Family: ranunculaceae

GEOGRAPHICAL SOURCE: Germany, Spain

Morphology:

Roots are dark brown, longitudinally wrinkled & tapering towards one end

They have slight odour & taste

Chemistry:

Diterpene alkaloids such as aconitine, neopelline, neoline & small amount of ephedrine

Aconitine is an active constituent but if hydrolysed forms benzoyl aconine & aconine which are less active

Uses:

Externally in neuralgia & sciatica

PSEUDO ALKALOIDS

COFFEE

BIOLOGICAL SOURCE: dried seeds of coffee Arabica

Family: rubiaceae

GEOGRAPHICAL SOURCE: southern part of India, Indonesia

Collection:

The unripe coffee fruit is dark green & is collected when it turns red

Each fruit has two locules containing one seed each

The seeds are separated, roasted because of which they develop a dark brown colour & a typical odour

Chemistry:

Contains caffeine which is a salt of chlorogenic acid, volatile oil known as caffeol, enzymes & other phenolic compounds

Uses:

Stimulant, diuretic (due to theophylline), & source of caffeine

Chemical Test:

1. Murexide test: caffeine when heated with HCl & potassium chlorate give a residue which turns purple when exposed to ammonia vapours
2. Caffeine forms a white precipitate with tannin solution

TEA

BIOLOGICAL SOURCE: prepared leaves of thea sinensis

Family: theaceae

GEOGRAPHICAL SOURCE: India, srilanka

Collection:

The tea plant is a small green shrub wherein younger leaves are picked & allowed to undergo fermentation

Polyphenol oxidase carries out oxidation to produce furfural & other phenolic compounds

The process imparts a dark brown or black colour & a typical odour of tea powder

For preparation of green tea, fresh leaves are dried & roasted in copper pans & finally powdered

Chemistry:

Contains caffeine, theophylline, theobromine, oxidase enzyme & tannins

Use:

Stimulant, diuretic, source of caffeine

Chemical Test:

Murexide test

KOLA NUTS / BISSY SEEDS

BIOLOGICAL SOURCE: seeds of cola nitida

Family: sterculiaceae

GEOGRAPHICAL SOURCE: west Africa, Brazil

Morphology:

Seeds are Plano convex in shape & reddish brown with a bitter taste

Chemistry:

Contains caffeine, theobromine & a red pigment known as kola catechin

Use:

Stimulant

COCOA SEEDS

BIOLOGICAL SOURCE: seeds of theobroma cacao

Family: sterculiaceae

Collection:

The fruits are ellipsoidal in shape with a white pulp & contain about 40 to 50 seeds

Fermentation is carried out in boxes for about 3 days at a temperature below 60 degree Celsius

The seeds acquire a different coulour, taste & odour

Seeds are then roasted to evaporate the water

It also facilitates removal of the seed coat

Seeds are then powdered to obtain cocoa powder

Chemistry:

Caffeine. Theobromine, other phenolic compounds

Use: Stimulant

STEROIDAL ALKALOIDS

KURCHI

BIOLOGICAL SOURCE: dried bark of holarrhena antidysenterica

Family: apocynaceae

GEOGRAPHICAL SOURCE: India

Chemistry:

Steroidal alkaloid conessine & norconessine

Use:

Amoebic dysentery

ASHWAGANDHA

BIOLOGICAL SOURCE: dried roots of withania somnifera

Family: solanaceae

GEOGRAPHICAL SOURCE: India, Afghanistan

Morphology:

Roots are cylindrical, buff coloured, have a characteristic odour & are tasteless

Microscopic Characters:

Outermost layer of cork cells followed by cortex

Vascular bundle consists of phloem parenchyma & xylem blocking the pith

Chemistry:

2 types of chemical constituents

1. Steroidal lactones called withanolides like withaferine

2. Alkaloids like withanine, somniferine, anaferine

Also contains alcohols known as somnitol & somnirol

Uses:

Sedative, hypnotic, hypotensive & immunomodulatory

PYRAZOLINE ALKALOIDS

PEPPER

BIOLOGICAL SOURCE: dried fruits of piper nigrum

Family: piperaceae

GEOGRAPHICAL SOURCE: south India, Indonesia

Morphology:

Fruits are green when unripe but turn dark black after drying

The dried fruits are wrinkled with an aromatic odour & pungent taste

Chemistry:

Alkaloid piperine is responsible for pungent taste aong with piperetine, resins, volatile oils containing limonene & pinen responsible for the odour

Uses:

Bronchitis & gonorrhoea

- DO OTHER TOPICS FROM BOOK **C.K KOKATE**
- DO MICROSCOPY FROM **KHANDELWAL BOOK**
- THE TABLES GIVEN IN C.K KOKATE ARE IMP FOR GPAT EXAM
- PREPARE WELL ALL THE TABLES GIVEN IN C.K. KOKATE BOOK

PHARMAROCKS

GPAT STUDY MATERIAL

ALKALOIDS

PHARMACOGNOSY

PHARMAROCKS GPAT SUCCESS TEST SERIES

ORGANISE BY MR. AMAR RAVAL

ALKALOIDS: SOME IMP POINTS AND DRUGS

Alkaloids are basic nitrogen containing compounds obtained from plants, animals & microorganisms having a marked physiological action

Characteristics:

Well defined crystalline substances, generally occurring as solids except nicotine which is a liquid, colourless except berberine which is a yellow coloured alkaloid. Occur in plants in the salt form.

They answer the following chemical tests:

1. **Mayer's reagent**- (potassium mercuric iodide)

Cream coloured precipitate

2. **Wagner's reagent**- (iodine in potassium iodide)

Reddish brown precipitate

3. **Hager's reagent**- (salt solution of picric acid)

Yellow precipitate

4. **Dragendroff's reagent**- (potassium bismuth iodide)

Reddish brown precipitate

Caffeine is a pseudo alkaloid drug which does not answer this test

Extraction:

- The powdered drug is defatted using petroleum ether if necessary
- The powder is further basified using lime to break the salt form of the alkaloid & liberate free base which can be extracted using an organic solvent
- Alkaloidal salts can be directly extracted using an acidified aqueous solvent

Classification:

1. Pharmacological method
2. Taxonomic method
3. Biosynthetic method
4. Chemical method – true & proto alkaloids

- **TRUE ALKALOIDS**

1. Pyrrole & Pyrrolidine Eg- Coca
2. Pyridine & Piperidine Eg- Coniine
3. Tropane Eg- Atropine

4. Quinoline Eg- Cinchona
5. Indole Eg- Rauwolfia
6. Purine Eg- Caffeine
7. Steroidal Eg- Kurchi
8. Isoquinoline Eg- Opium

- **PROTO ALKALOIDS**

Eg- Ephedrine

INDOLE ALKALOIDS

ERGOT / ARGOT / ST. ANTHONY'S FIRE

BIOLOGICAL SOURCE:

Schlerotium of fungus claviceps purpurea, at the ovary of rye plant secale cereale

Family: graminae (fungus belongs to family clavicipitaceae)

GEOGRAPHICAL SOURCE: Switzerland

Known to have caused gangrene (ergotism) in Germany

Life cycle:

1. Sexual / sphacelial stage
2. Asexual / schlerotium stage

Sexual stage:

The ascospores infect the ovary of the rye plant & if conditions are favourable it develops hyphal strands, it forms a white mass over the ovary known as the mycelium

Asexual stage:

The hyphal strands further develop invading the ovary & converting it to a hard violet schlerotium, Schlerotium contains stromatum which shows a globular stalk

It encloses bag like structures known as ascus containing ascospores

If these ascospores are liberated they infect another rye plant

Morphology of schlerotium:

Hard, violet, odourless, with an unpleasant taste

Chemistry:

Derivatives of lysergic acid

Water soluble ones are ergometrine & ergometrinine

Water insoluble ones are ergotamine & ergotoxine

Only the levo isomer is active

Uses:

Ergometrine is an oxytocic drug but its methyl derivative is preferred as it causes less hypertension

Ergotamine is analgesic in migraine

Chemical Test:

1. Gives a blue colour with Van Curk's reagent (para dimethyl amino benzaldehyde)
2. Gives blue fluorescence in water
3. When treated with ether, H2SO4 followed by sodium bicarbonate, aqueous layer shows a red violet colour
4. Ergotamine + glacial acetic acid + ethyl acetate + H2SO4 gives a blue solution with a red tinge. When further treated with FeCl3 the blue colour disappears

VINCA / PERIWINKLE

BIOLOGICAL SOURCE: aerial parts of catharanthus roseus

Family: apocynaceae

GEOGRAPHICAL SOURCE: India, Madagascar

Morphology:

Leaves are small, opaque, dark green, odourless & bitter to taste

Chemistry:

Indole alkaloids such as vinblastine, vincristine, ajamlicine & serpentine

Use:

Potent anti-cancer agent, hypotensive & anti-diabetic

NUXVOMICA

BIOLOGICAL SOURCE: dried seeds of strychnos nuxvomica

Family: Loganiaceace

GEOGRAPHICAL SOURCE: srilanka, India

MORPHOLOGY:

Seeds are circular, flat, grayish green, covered with trichomes & extremely bitter to taste

Chemistry:

Contains two main indole alkaloids strychnine & brucine

Use:

Rarely used as a nerve tonic as it is poisonous in large doses

Chemical Test:

1. Section when treated with concentrated HNO3 shows a yellow colour with brucine
2. Section when treated with ammonium vanadate & H2SO4 shows a purple colour with strychnine
3. Strychnine when treated with H2SO4 & K2Cr2O7 develops a violet to yellow colour

RAUWOLFIA / SARPAGANDHA

BIOLOGICAL SOURCE: dried roots of rauwolfia serpentina

Family: apocynaceae

GEOGRAPHICAL SOURCE: Asia, America

Morphology:

Snake shaped, brown coloured, longitudinal wrinkles tapering towards the end

Chemistry:

Reserpine, ajamlicine, serpentine

Use:

Antihypertensive by preventing uptake of adrenaline

Chemical Test:

1. Freshly fractured surface of the root when treated with concentrated HNO3 shows red coloured medullary rays
2. Reserpine gives a violet colour with vanillin in acetic acid

TROPANE ALKALOIDS

BELLADONA

BIOLOGICAL SOURCE: dried leaves of atropa belladonna

Family: solanaceae

GEOGRAPHICAL SOURCE: England, Europe, India

Morphology:

Leaves are greenish brown, ovate in shape with an entire margin & bitter to taste

Microscopic Characters:

- Dorsiventral leaf
- Collenchyma above & below the mid rib
- Unicellular covering trichomes, unicellular glandular trichomes
- Microsphaenoidal calcium oxalate crystals

Chemistry:

Atropine, hyoscyanine, belladonine

Use:

Atropine is a parasympatholytic, thus decreases secretion & spasms

Chemical Test:

Vitali morin test – to the drug fuming nitric acid is added & it is evaporated to dryness.

Methanolic KOH is added to the acetone solution of the nitrated residue

It develops a violet colour

STRAMONIUM

BIOLOGICAL SOURCE: dried leaves & flowering tops of datura stramonium

Family: solanaceae

GEOGRAPHICAL SOURCE: America, France

Morphology:

Leaves are grayish green with a crenate margin & unequal base

Microscopic Characters:

- Dorsiventral leaf
- Collenchyma above & below the mid rib
- Unicellular covering & glandular trichomes
- Xylem surrounded by phloem
- Anisocytic stomata

Chemistry:

Hyoscine, atropine, belladonine

Use:

Hyoscine is an anti-emetic

Chemical Test:

Vitali morin test

COCA LEAVES

BIOLOGICAL SOURCE:

Dried leaves of erythroxylon coca (Bolivian variety) Erythroxylon truxillense (Peruvian variety)

Family: erythroxylaceae

GEOGRAPHICAL SOURCE: Bolivia, Peru

Morphology:

Peruvian leaves are pale green, fragile, thin, and elliptical in shape

Bolivian leaves are greenish brown, oval in a shape with a prominent mid rib

Microscopic Characters:

- Dorsiventral leaf
- Collenchyma above & below mid rib
- Xylem surrounded by phloem & pericyclic fibres
- Paracytic stomata

Chemistry:

Cocaine, cinnamoyl cocaine, tropocaine, benzoylecgonine

Extraction:

The leaf powder is basified with lime & extracted using an organic solvent

The free bases are converted to their hydrohlorides by using HCl

Due to this procedure cocaine liberates ecgonine, methanol & benzoic acid whereas cinnamoyl cocaine generates ecgonine, methanol & cinnamic acid

The ecgonine thus obtained is used to synthesize cocaine by treating it with benzoic anhydride, methyl iodide, and methanol & sodium methoxide

Use:

Local anaesthetic

Chemical Test:

Drug powder when heated with concentrated H2SO4 gives a typical odour of methyl benzoate

QUINAZOLINE ALKALOIDS

VASAKA LEAF / ADULSA

BIOLOGICAL SOURCE: dried & fresh leaves of adhatoda vasica

Family: acanthaceae

GEOGRAPHICAL SOURCE: India

Morphology:

Leaves are dark green, lanceolate in shape, have a crenate margin with a characteristic odour & bitter taste

Chemistry:

Vasicine, vasicinone & adhatodic acid

Uses:

Vasicine is an expectorant. It gets oxidized to vasicinone which in an abortifacient in large doses, otherwise a bronchodilator

PYRIDINE ALKALOIDS

LOBELIA HERB / INDIAN TOBACCO / ASTHMA WEED

BIOLOGICAL SOURCE: dried aerial parts of lobelia nicotianefolia

Family: campanulaceae

GEOGRAPHICAL SOURCE: India

Morphology:

Leaves are sessile, large, dark green & possess an acrid taste

Chemistry:

Lobeline, lobelidine & isolobanine

Use:

Respiratory stimulant

Chemical Test:

1. Lobeline solution if heated gives typical odour of acetophenone
2. Lobeline in H2SO4 when treated with formaldehyde develops red colour

IMIDAZOLE ALKALOIDS

PILOCARPUS

BIOLOGICAL SOURCE: dried leaves of pilocarpus jaborandi, Pilocarpus microphyllus

Family: rutaceae

GEOGRAPHICAL SOURCE: south America

Morphology:

Leaves are greyish green with an asymmetrical base & possesses aromatic odour & bitter taste

Chemistry:

Contains pilocarpine, pseudopilocarpine, pilosine & limonene

Uses:

Antagonist to atropine, causes miosis, increases salivation & sweating

Chemical Test:

Pilocarpine solution when treated with H2SO4, H2O2, benzene & K2Cr2O4, the organic layer appears bluish violet in colour whereas aqueous layer shows yellow colour

INDOLE ALKALOIDS

CALABAR BEANS

BIOLOGICAL SOURCE: dried type seeds of physostigma venenosum

Family: leguminosae

GEOGRAPHICAL SOURCE: Africa

Morphology:

Reddish brown in colour, hard, shiny & rough to touch

Chemistry:

Contains physostigmine, starch & proteins

Use:

Helps in contraction of pupil, retards respiration & causes bradycardia

OPIUM / POPPY PLANT

BIOLOGICAL SOURCE: dried latex obtained from capsules of papaver somniferum

Family: papaveraceae

GEOGRAPHICAL SOURCE: India (MP), turkey, Pakistan, Afghanistan

Collection:

- Collection is started when capsules change colour from dark green to yellowish green.
- Longitudinal incisions about 2mm deep are given on the capsules to exude the latex
- The latex is allowed to solidify overnight & later scraped off
- The process is repeated 4 times with a gap of 2 days

Morphology:

The dried latex is dark brown, extremely bitter to taste & has a strong odour

Chemistry:

Contains phenanthrene type of alkaloids such as morphine & codeine & benzyl isoquinoline type of alkaloids such as papaverine & noscapine

These occur as salts of meconic acid

Use:

- Morphine is a narcotic analgesic & stimulant
- Codeine is an anti tussive
- Papverine is a smooth muscle relaxant

Chemical Test:

1. Aqueous solution of meconic acid shows a deep reddish purple colour with ferric chloride
2. Morphine when sprinkled with concentrated HNO3 shows an orange red colour. This is not allowed by codeine
3. Morphine solution when treated with ferric chloride & potassium ferricyanide gives a bluish green colour
4. Papaverine solution in HCl & potassium ferricyanide develops a lemon yellow colour

Varieties of opium:

Indian, Turkish, Persian, European, manipulated Persian & European

QUINOLINE AKALOIDS

CINCHONA BARK / JESUIT'S BARK / PERUVIAN BARK

BIOLOGICAL SOURCE:

Dried bark of cultivated trees of cinchona calisaya

Cinchona officinalis

Cinchona ledgeriana

Cinchona succirubra

Family: rubiaceae

GEOGRAPHICAL SOURCE: India, Bolivia, srilanka

Collection:

It is collected by coppicing method

Vertical incisions are made on branches, trunk of the tree & these incisions are connected by horizontal circles

The bark is then stripped off & dried in sunlight & further by artificial heat (175 degree F)

The root bark is collected by uprooting trees & separating manually

Morphology:

Stem bark is rough with transverse fissures

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Microscopic Characters:

- Cork cells are thin walled
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- Medullary rays with radially arranged cells
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- Starch grains in parechymatous tissues
- Stone cells rarely present

Chemistry:

Contains quinine, quinidine, cinchonine & cinchonidine

Also contains quinic acid & cinchotannic acid

Chemical Test:

1. On heating the drug in a dry test tube with glacial acetic acid, purple vapours are produced
2. Thalleoquin test: drug + bromine water + dilute ammonia gives an emerald green colour
3. Drug when treated with quinidine solution gives a white precipitate with silver nitrate which is soluble in nitric acid

Uses:

Anti-malarial, anti-pyretic, quinine is used in arrhythmias against atrial fibrillation

ISOQUINOLINE ALKALOIDS

IPECAC

BIOLOGICAL SOURCE:

Dried roots of cephalis ipecacuanha (Brazilian / Rio), Cephalis acuminata (panama / Cartagena)

Family: rubiaceae

GEOGRAPHICAL SOURCE: Brazil, panama

Morphology:

Brazilian ipecac is dark brick red as compared to greyish brown panama ipecae

Both possess faint odour & bitter taste

Chemistry:

Brazilian – emetine: cephalin ratio is 4:1

Panama – emetine: cephalin ratio is 1:1

Uses:

Expectorant in mild doses & as an emetic in large doses

Emetine also possesses anti protozoal activity

Chemical Test:

1. Emetine shows a bright green colour with H2SO4 & molybdic acid

2. Emetine when shaken with water & small amount of HCl, filtered & to the filtrate potassium chlorate is added gives a yellow colour changing to red

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TOBACCO

BIOLOGICAL SOURCE: dried leaves of nicotiana tabacum

Family: solanaceae

GEOGRAPHICAL SOURCE: India, France

Morphology:

Leaves are large, green with a dentate margin

It has a characteristic strong odour & bitter taste

Chemistry:

Nicotine, nornicotine & anabasine

Use:

Stimulant

PROTO ALKALOIDS

EPHEDRA / MA HUANG

BIOLOGICAL SOURCE: dried stem of ephedra gerardiana

Family: ephedreaceae / gnetaceae

GEOGRAPHICAL SOURCE: china, Pakistan

Morphology:

Greyish green, thin, cylindrical stem bearing scaly leaves & internodes

No typical odour but has a bitter taste

Chemistry:

Contains amino alkaloids like ephedrine, norephedrine & pseudo ephedrine

Uses:

Sympathomimetic & bronchodilator

Chemical Test:

Aqueous solution of ephedrine shows a violet colour when treated with dilute HCl & CuSO4 followed by dilute NaOH

COLCHICUM / AUTUMN CROCUS

BIOLOGICAL SOURCE: dried seeds & corms of colchicum luteum

Family: liliaceae

GEOGRAPHICAL SOURCE: Europe

Morphology:

Seeds are hard, reddish brown, rough to touch whereas corms are yellowish in colour with a longitudinal groove & bitter to taste

Chemistry:

Contains amino alkaloid colchicine & demecolchicine

Uses:

Rheumatism, treatment of gout, anti-tumour activity & polyploidy

ACONITE / BACHNAG

BIOLOGICAL SOURCE: dried roots of aconitum napellus

Family: ranunculaceae

GEOGRAPHICAL SOURCE: Germany, Spain

Morphology:

Roots are dark brown, longitudinally wrinkled & tapering towards one end

They have slight odour & taste

Chemistry:

Diterpene alkaloids such as aconitine, neopelline, neoline & small amount of ephedrine

Aconitine is an active constituent but if hydrolysed forms benzoyl aconine & aconine which are less active

Uses:

Externally in neuralgia & sciatica

PSEUDO ALKALOIDS

COFFEE

BIOLOGICAL SOURCE: dried seeds of coffee Arabica

Family: rubiaceae

GEOGRAPHICAL SOURCE: southern part of India, Indonesia

Collection:

The unripe coffee fruit is dark green & is collected when it turns red

Each fruit has two locules containing one seed each

The seeds are separated, roasted because of which they develop a dark brown colour & a typical odour

Chemistry:

Contains caffeine which is a salt of chlorogenic acid, volatile oil known as caffeol, enzymes & other phenolic compounds

Uses:

Stimulant, diuretic (due to theophylline), & source of caffeine

Chemical Test:

1. Murexide test: caffeine when heated with HCl & potassium chlorate give a residue which turns purple when exposed to ammonia vapours
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TEA

BIOLOGICAL SOURCE: prepared leaves of thea sinensis

Family: theaceae

GEOGRAPHICAL SOURCE: India, srilanka

Collection:

The tea plant is a small green shrub wherein younger leaves are picked & allowed to undergo fermentation

Polyphenol oxidase carries out oxidation to produce furfural & other phenolic compounds

The process imparts a dark brown or black colour & a typical odour of tea powder

For preparation of green tea, fresh leaves are dried & roasted in copper pans & finally powdered

Chemistry:

Contains caffeine, theophylline, theobromine, oxidase enzyme & tannins

Use:

Stimulant, diuretic, source of caffeine

Chemical Test:

Murexide test

KOLA NUTS / BISSY SEEDS

BIOLOGICAL SOURCE: seeds of cola nitida

Family: sterculiaceae

GEOGRAPHICAL SOURCE: west Africa, Brazil

Morphology:

Seeds are Plano convex in shape & reddish brown with a bitter taste

Chemistry:

Contains caffeine, theobromine & a red pigment known as kola catechin

Use:

Stimulant

COCOA SEEDS

BIOLOGICAL SOURCE: seeds of theobroma cacao

Family: sterculiaceae

Collection:

The fruits are ellipsoidal in shape with a white pulp & contain about 40 to 50 seeds

Fermentation is carried out in boxes for about 3 days at a temperature below 60 degree Celsius

The seeds acquire a different coulour, taste & odour

Seeds are then roasted to evaporate the water

It also facilitates removal of the seed coat

Seeds are then powdered to obtain cocoa powder

Chemistry:

Caffeine. Theobromine, other phenolic compounds

Use: Stimulant

STEROIDAL ALKALOIDS

KURCHI

BIOLOGICAL SOURCE: dried bark of holarrhena antidysenterica

Family: apocynaceae

GEOGRAPHICAL SOURCE: India

Chemistry:

Steroidal alkaloid conessine & norconessine

Use:

Amoebic dysentery

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Family: solanaceae

GEOGRAPHICAL SOURCE: India, Afghanistan

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Roots are cylindrical, buff coloured, have a characteristic odour & are tasteless

Microscopic Characters:

Outermost layer of cork cells followed by cortex

Vascular bundle consists of phloem parenchyma & xylem blocking the pith

Chemistry:

2 types of chemical constituents

1. Steroidal lactones called withanolides like withaferine

2. Alkaloids like withanine, somniferine, anaferine

Also contains alcohols known as somnitol & somnirol

Uses:

Sedative, hypnotic, hypotensive & immunomodulatory

PYRAZOLINE ALKALOIDS

PEPPER

BIOLOGICAL SOURCE: dried fruits of piper nigrum

Family: piperaceae

GEOGRAPHICAL SOURCE: south India, Indonesia

Morphology:

Fruits are green when unripe but turn dark black after drying

The dried fruits are wrinkled with an aromatic odour & pungent taste

Chemistry:

Alkaloid piperine is responsible for pungent taste aong with piperetine, resins, volatile oils containing limonene & pinen responsible for the odour

Uses:

Bronchitis & gonorrhoea

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PHARMA-ROCKS IMPORTANT SYNONYMS

Synonyms

CARBOHYDRATES		Vasaka	Adulsa	Product	Animal used
Indian gum	Gum Arabic, Acacia			Digitalis	Pigeon
Guar gum	Jaguar gum,	**Punarnava**	Hog weed	Glycogen	Cat
Gum karaya	Ind. Tragacanth, Sterculia gum	**Colchicum**	Atumun seed	Insulin inj.	Rabbit
Isabgol	Ind. Psyllium, flea seed	**Lobelia**	Ind. Tobacco	Oxytocin	Chicken
Bael	Bengal Quince	**Areca nut**	Betel nut	Parathyroid	Dog
Agar	Japnese Isinglass, vegetable gelatin	**Pilocarpus**	Jaborandi	Vasopressin	Rat
Carragenan	Irish moss extract	**Aconite**	Wolfsbane root Mokshood	Posterior pitutary	Chicken
Inulin	Alant starch, Dehlia	**OILS**		Tubocurarine chloride	Rabbit
Locust bean	Aroban, Carob gum, Ceratonia	**Arachis oil**	Peanut oil	Chorionic gonadotropin	Male rat
Starch	Amylum	**Chaulmogra oil**	Hydnocarpus oil, Gynocardia oil	Cod liver oil	Rachitic rat
GLYCOSIDES				Heparin sodium	Sheep
Aloe	Mussaber, Kumari	**Sesame oil**	Gingelly oil Benne oil	Iron dextran inj.	Microbial cultures
Rhubarb	Revandchini	**Corn oil**	Maize oil	Antiseptics & disinfectants	Frog
Cascara	Sacred bark chittem bark	**Mustard oil**	Sarson oil	Diphthria toxoid	Rat
Hypericum	St. John wort, Millepertuis, goat weed	**Nemm oil**	Margosa oil	Atropine	Rabbit
Digitalis	Foxglove	**Cocca butter**	Theobroma oil	Insulin Prod.	Guinea pig
Digitalis latanata	Woolly foxglove, Austrial digitalis	**Kokum butter**	Goa butter, Mango steen oil	Elastomeric closures	Guinea pig
Thevetia	Yellow oleander, Trumpet flower, Luckey nut tree	**Hydrous wool fat**	Lanolin	Fungicides and germicides	
Urgenia Indian squill	Jangli pyaj, Sea onion	**Lard**	Adeps		
Eur. squill	White squill	**Carnauba wax**	Brazil wax		
Dioscorea	Yam	**Linseed**	Flaxseed		
Liquorice	Mulethi	**TERPENOIDS**			
Senega	Rattlesnake root	**Chenopodium**	American wormseed oil		
Quilllia	Panama wood, Soap bark	**Eucalyptous**	Dinkum		
Gokhru	Puncture vine	**Peppermint**	Colepermin		
Bitter Almond	Amygdala amara	**Dill**	Anethum		
WildCherry Bark	Virginian prune bark	**Cinnamon**	Kalmi Cinnamon, Ceylon Cinnamon		
Silymarin	Marian Thistle, Milk Thistle, Our ladyâ s thistle	**Jatamansi**	Indian spike nard		
Ginkgo	Maiden hair tree, kew tree	**Tulsi**	Sacred basil		
Visnga	Khella, Picktooth tree	**Kapur kachri**	Spiked ginger lily		
Psoralea	Bavchi	**Oil of Vetiver**	Khus oil		
Canthrides	Spanish flies	**Cummin**	Jira		
Bearberry	Busserole	**Gaultheria**	Betula		
Picrorrhiza	Kutcki	**Artemisia**	Santonica		
Henna	Lawsonia	**Arnica**	Leopard bane,		

			Mountain tobacco, Wolfs bane		
TANNINS		**Hops**	Humulus		
Myrobalan	Harde	**Sausserea**	Kuth, Kostus		
Black Catechu	Kattha	**Acorus**	Bach, Ghoda vaj, Sweet Flag		
Pterocrpus	Bijasal	DITERPENOIDS			
Nux vomica	Crow fig Semen Strychni	**Taxus**	Yew, Talispatra		
Physostigma	Calabar bean	**Crocus**	Saffron		
Rawolfia	Sarpagandha	**RESINS**			
Vinca	Periwinkle	**Guggul**	Scented Bdellium		
Belladona	Deadly Nightshade	**Asafoetida**	Devils dung		
Hyscamous	Henbane	**Coloycynth**	Bitter apple		
Stramonium	Thorn apple leaf	**Cannabis**	Ind. Hemp		
Cinchona	Jesuit bark, Peruvian Bark	**Male fern**	Filixmas, Aspidium		
Ephedra	Ma-huang	**Kaladana**	Pharbitis		
		Guggul	Scented Bdellium		

Name of the test	Test for	Result/examine
Dragendroffs test	Alkaloids	Reddish brown ppt
Mayers reagent	Alkaloids	Cream colour ppt
Wagenrs reagent	Alkaloids	Reddish brown ppt
Hagers reagent	Alkaloids	Yellow ppt
Tannic acid test	Alkaloids	Buff colour
Picnolic acid test	Alkaloids	Yellow colour
millions test	amino acids	White ppt
Ninhydrine test	Amino acids	Violet colour
Molischs test	carbohydrates	Purple to violet colour
Barfoeds test	Carbohydrates	Red cupric oxide
Selivanhoffs test	Carbohydrate/ ketones	Rose colour **ex**: fructose,honey
Pentose test	Pentose/carbohydrates	Red colour
osazone	Carbohydrates	Yellow colour
Thinone test	Cellulose /lignin	Blue/bluish violet
……	Volatile oil+ Sudan III solution	Red colour by globules
Saponification test	Fats & fixed oils	Partial neutralization of alkali
Shinoda test	Flavoniods	Pink scarlet, crimson red, green to blue colour
Alkaline reagent test	Flavonoids	Yellow colour
Zinc hydrochloride	Flavonoids	Red colour
Borntragers test	Anthraquinone glycosides	Rose pink to red colour
Modified borntragers test	Anthraquinone glycosides	Rose pink to red colour
……..	Anthraquinone glycosides+ methanolic magenisum acetate	Pink colour
……	Hydroxyl anthraquinone + KOH	Red colour
Keddes test	Cardiac glycosides	Purple colour
Keller- killani test	Cardiac glycosides	Blue colour
Raymonds test	Cardiac glycosides	Violet colour
Legal test	Cardiac glycosides	Blood red colour
Balijets test	Cardiac glycosides	Orange colour
Froth formation test	Saponin glycosides	Stable foam is formed
Haemolysis test	Saponin glycosides	Red supernatant
Gold beaters skin	Tannins	Brown/black colour
Ferric chloride test	Tannins	Green colour
Phenazone test	Tannins	Bulky ppt is formed
Gelatin test	Tannins	Ppt formed
Test for catechin	Tannins	Pink to phlorong luminol
Test for chlorogenic acid	Tannins	Green colour
Liberman burchard test	Steroids and triterpenoids	Green →steriods, deep red colour →triterpinoids
Salkowski test	Steroids,	Red colour
Salkowski test	triterpinoids	Yellow coloured

Sulfur powder test	Steroids,& triterpinoids	Sinks of steroids & triterpinoids
Fehling solution A & B	Carbohydrates	Brick red

Identification test for enzymes

- Papin +aqueous $kmno_4$ solution ……decolourises
- Esbachs for protein
- Enrichs test for urobilinogen in urine
- Kavous for indole
- Millions test for protein estimation

Laxatives					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Aloe	*Aloe barbadensis,* Mill. *A. Indica,* Royle. *A. Littoralis,* Koening *A. Vera,* Tourn. Ex Linn. (Liliaceae; Agavaceae)	Curacao Aloe, Barbados Aloe, Indian Aloe, Jaffarabad Aloe, Kummari	Juice	glyburide, anthraquinone glycosides – aloin, acemannan.	purgative (causes griping), gel—topically emollient, anti-inflammatory, antimicrobial - used for wound healing, sunburn.
Rhubarb	*Rheum officinale*, Baill. *Rheum Palmatum*, Linn. (Polygonaceae)	Rhubarb	Rhizome, root	chrysophan, chrysophanic acid, emodin, aporetin, phæoretin, erythroretin, rheumic acid, and rheotannic acid	purgative, astringent, aperient. used for constipation and atonic dyspepsia
Ispaghula	*Plantago ovata*, Forsk. (Plantaginaceae)	Blond Psyllium, Indian Plantago, Ispagol, Pale Psyllium, Spogel	Seed, husk	essential oils with alpha-pinene, dipentene, linalool, cineol, methyl salicylate, decyl aldehyde, eugenol, anisaldehyde, bergapten, indole, salicylic and benzoic acids as major constituents.	seed -astringent. seed coat -demulcent.
Senna	*Cassia senna*, Linn. *Cassia angustifolia*, Vahl. (Leguminosae)	Alexandrian Senna, Cassia acutifolia Delite, Khartoum Senna Indian Senna, Tinnevelly Senna	Fruit (pod), leaves	contains rhein, aloe-emodin, kaempferol, isormamnetin, both free and as glucosides, together with mycricyl alcohol the purgative principles are largely attributed to anthraquinone derivatives and their glucosides.	purgative (free from astringent action of rhubarb type herbs, but causes gripe), used in compounds for treating biliousness, distention of stomach, vomiting and hiccups.

Cardiotonics					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Digitalis	*Digitalis lanata*, Ehrh. *Digitalis purpurea*, Ehrh. (Scrophulariaceae)	Grecian Foxglove	Leaves	cardiac glycosides found throught entire plant	cardiac stimulant diuretic emetic
Adulsa	*Adhatoda zeylanica*, Medic. *Adhatoda vasica*, Nees. (Acanthaceae)	Malabarnut, Vasaka Adulsa	Leaves along with tender stem	quinazoline alkaloids - vasicoline, adhatodine, vasicolinone and anisotine . vasicinol, vasicinone, deoxyvasicinone, deoxyvasicine	cold. cough, whooping-cough and chronic bronchitis and asthma as sedative-expectorant
Carminatives and GI regulators					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Coriander	*Coriandrum sativum*, Linn. (Umbelliferae)	Dhaanyaka, Kustumburu, Dhaanyeyaka, Dhanika	Fruits	contains volatile oil, consisting mainly of delta-linalool, alpha-pinene and terpinine. it also contains flavonoids, coumarins, phthalides and phenolic acids (including caffeic and chlorogenic)	stimulant, stomachic, carminative, antispasmodic, diuretic; also hypoglycaemic and anti-inflammatory. oil—bactericidal and larvicidal.
Fennel	*Foeniculum vulgare*, Mill. (Umbelliferae)	Mishreyaa, Mishi, Madhurikaa, Madhuraa, Shatapushpaa	Fruits	fennel seed contain volatile oils anethole, among others fenchone and methylchavicol), flavonoids, coumarins (including bergapten) and sterols	carminative, stomachic, antispasmodic, emmenagogue, galactagogue, anti-inflammatory, diuretic.
Ajowan	*Trachyspermum ammi*, Linn. *Carum copticum*, Benth. (Umbelliferae)	Ammi, Lovage, Carum,	Fruits Leaf juice Root	the seeds contain a phenolic glucoside, principal constituents of the	fruits—carminative, antispasmodic, anticholerin,

		Ajowan, Yavaani		ajowan oil are the phenols, mainly thymol and some carvacrol.	antidiarrhoeal, bechic, stimulant. leaf juice— anthelmintic. root— carminative, diuretic, febrifuge.
Cardamom	*Elettaria cardamomum*, Maton (Zingiberaceae)	Lesser Cardamom , Elaa, Sukshmailaa.	Seed	seeds yield an essential oil the major constituents are, 1,8-cineole and alpha-terpinylacetate, with limonene, alpha-terpineol, sabinene and linalool.	seed - carminative antiemetic, stomachic, orexigenic, anti-gripe, antiasthmatic, bechic, oil - antispasmodic, antiseptic.
Ginger	*Zingiber officinale*, Roscoe. (Zingiberaceae)	Fresh rhizome— Aardraka, Aadrikaa, Shrngibera. Dried rhizome— Shunthi, Naagara.	Rhizome	contains an essential oil containing monoterpenes, mainly geranial and neral; sesquiterpenes mainly beta-sesquiphellandrene, betabisabolene; aromatic curcumene and alphazingiberene; pungent principles, consisting of gingerols, shogaols and related phenolic ketone derivatives.	antiemetic, antiflatulent, hypocholesterolaemic, anti-inflammatory, antispasmodic, expectorant, circulatory stimulant, diaphoretic, increases bioavailability of prescription drugs.
Black pepper	*Piper nigrum*, Linn. (Piperaceae)	Black Pepper , Maricha, Vellaja	Fruits	the fruit yielded piperine, piperatine and piperidine; amides, piperyline, piperoleins a and b, and n-isobutyl- cicosa-trans-2-trans-4-dienamide.	stimulant, carminative, diuretic, anticholerin, sialagogue, bechic, antiasthmatic. used in fevers, dyspepsia, flatulence, indigestion, and as mucous

					membrane and gastro-intestinal stimulant.
Asafoetida	*Ferula assafoetida* Linn. *Ferula rubricaulis* Boiss. *Ferula foetida* Bunge. (Apiaceae / Umbelliferae)	Asafetida, Asant, Devil's Dung, Gum Asafetida	Oleo gum resin obtained by incising the living rhizomes and roots.	ferula foetida contains: resins consisting of asaresionotannols and their esters; farnesiferols, ferulic acid and other acids; gum; volatile oil, major constituent being sec-propenylisobutyl disulphide; sulphated terpenes, pinene, cadinene and vanillin; sesquiterpenoid coumarins.	olea-gum-resin—stimulates the intestinal and respiratory tracts and the nervous system.
Nutmeg	*Myristica fragrans* Houtt. (Myristicaceae)	Nutmeg, Mace, Jaatiphala, Jaatishasya.	Dried seed and Aril	contains anti-inflammatory principle, and licarin-b and dehydro diisoeugenol, eugenol and isoeugenol, myristicin.	nutmeg is used in flatulency, diarrhoea, nausea and vomiting. mace is used in rheumatism, chronic bowel complaints and asthma.
Cinnamon	*Cinnamomum zeylanicum* Bl. *Cinnamomum loureirii* Nees. *Cinnamomum burmanii* (Nees) Bl. (Lauraceae)	Ceylon Cinnamon, Cinnamomum verum J.S. Presl., True Cinnamon Cinnamomum obtusifolium Nees var.loureirii Perr. & Eb., Saigon Cassia, Saigon Cinnamon	Inner bark	cinnamaldehyde, alpha- and beta-pinene, pcymene and limonene, linalool	leaf—carminative, antidiarrhoeal, spasmolytic, antirheumatic, hypoglycaemic. essential oil—fungicidal.

		Batavia Cassia, Batavia Cinnamon, Padang-Cassia, Panang Cinnamon			
Clove	*Syzygium aromaticum* (Linn.) Merr. & Perry. *Caryophyllus aromaticus* Linn., *Eugenia aromatica* (Linn.) Baill., *Eugenia caryophyllata* Thunb., (Myrtaceae)	Lavanga, Devakusum, Devapushpa, Shrisangya, Shriprasuunaka	Clove (dried flowerbud)	eugenin, triterpene acids, crategolic acid, steroid glucosides. Eugenol a major component of the oil, is antibacterial.	carminative, antiinflammatory, antibacterial. Flower buds— antiemetic, stimulant, carminative, used in dyspepsia, gastric irritation. oil— employed as a local analgesic for hypersensitive dentlines and carious cavaties; internally as a carminative and antispasmodic
Astringent					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Catechu	*Uncaria gambier,* Roxb. (Rubiaceae)	Pale Catechu, Gambier, Khadira	extract of the leaves and shoots	contains tannins ─ mainly catechins and catechu tannic acid, indole alkaloids ─including gambirine, gambiridine; flavonoids ─ quercetin; pigments and gambirfluorescin.	demulcent, emollient, expectorant, diuretic, intestinal astringent.

Drugs acting on Nervous System					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Hyoscymus	*Hyoscyamus niger*, Linn. (Solanaceae)	Indian Henbane, Black Henbane, Paarsika-yavaani, Ajwaayin.	Leaves and flowering tops	tropane alkaloids – hyoscyamine, and hyoscine.	Sedative. Narcotic drug. Used for convulsions. Action similar to Belladonna
Belladonna	*Atropa belladonna,* Auct. (Solanaceae)	Belladonna, Deadly Nightshade, Suuchi	fruits, leaves	atropine, (dl-hyoscyamine), l- scopalomine (tropane alkaloid) (atropine is converted to l-hyoscyamine by an enzyme when the plant is dry, therefore the plant is more active when dry) starch, sugar, mucilage	antispasmodic, parasympathetic, depressant, vasoconstrictor, smooth muscle inhibitor, bronchodilator.
Aconite	*Aconitum ferox Wall.* ex Ser. *Aconitum napellus* Linn. (Ranunculaceae)	Aconitum, Indian aconite, Monkshood	tuber	aconitia, aconitine or nepalline	narcotic, sedative, antileprotic, anti-inflammatory. extremely poisonous. (roots possess depressant activity, but after mitigation in cow's milk for 2–3 days, they exhibit stimulant activity.)
Ashwa-gandha	*Withania ashwagandha*, Kaul. (cultivated variety) *W. somnifera* Linn.	Winter Cherry, Ashwagandhaa, Hayagandhaa,	root	alkaloids – withanine, withananine, withananinine,	root—used as an antiinflammatory drug for swellings,

	(Solanaceae)	Ashwakanda, Gandharvagandhaa.		pseudo-withanine, somnine, somniferine, somniferinine. steroidal lactones – withanolide,	tumours, scrofula and rheumatism; and as a sedative and hypnotic in anxiety neurosis.
Ephedra	*Ephedra sinica*, Stapf. *E. Equisetina*, Bunge. *E. Intermedia*, Shrenk. ex Meyer. *E. Gerardiana*, Wallich. ex Meyer. (Ephedraceae)	Cao Ma Huang, E. Mahuang Liu, Ephedra (and some other herbs) has also been referred to as 'herbal ecstasy		arial: alkaloids ephedrine, phytosterols. root: ephedrine, tannin, saponin, flavone, oil	arial parts: diaphoretic stimulant astringent decongestant expectorant diuretic root: diaphoretic
Opium	*Papaver somniferum*, Linn. (Papaveraceae)	Opium Poppy, Ahiphena, Aaphuuka, Afyum.	dried poppy juice	isoquinoline alkaloids – morphine, narcotine, codeine, papaverine and thebaine.	opium is obsolete as a drug. narcotic, sedative, hypnotic, analgesic, sudorific, anodyne, antispasmodic.
Cannabis	*Cannabis sativa,* Linn. (Cannabinaceae)	Hemp, Indian Hemp, Vijayaa, Bhangaa, Maadani, Maatulaani, Indraasana.	dried leaves or juice	cannabis yields 421 chemicals of various classes—cannabinoids, cannabispirans, and many alkaloids, of which δ -9- tetrahydrocannabinol (thc) is important.	hallucinogenic, hypnotic, sedative, analgesic, antiinflammatory, hemp derivatives are suggested for treating glaucoma and as an antiemetic in cancer chemotherapy.
Nux vomica	*Strychnos Nux-vomica*, Linn. (Loganiacoe)	Semina Strychni	seeds	strychnine, brucine, caffeotannic acid, igasuric acid, loganin	bitter stomachic and tonic
Antihypertensive					

Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Rauvolfia	*Rauvolfia serpentine*, Benth. (Apocynaceae)	Snake root, Sarpgandha	root	indole alkaloids (more than 50 alkaloids identified, reserpine - best known) anti-hypertensive alkaloids (alseroxylone, corganthine, voxinil, rescinamine) anti-arrhythmic alkaloids ─ ajmaline	anti-arrhythmic anti-hypertensive
Antitussive					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) used	Constituents	Indications / use
Vasaka	*Adhatoda zeylanica,* Medic *Adhatoda vasica*, Nees. (Acanthaceae)	Malabarnut, Vasaka Adulsa	leaves along with tender stem	quinazoline alkaloids - vasicoline, adhatodine, vasicolinone and anisotine . vasicinol, vasicinone, deoxyvasicinone, deoxyvasicine	cold. cough, whooping-cough and chronic bronchitis and asthma as sedative-expectorant
Tolu Balsam	*Toluifera Balsamum,* Linn. (Leguminosae)	Balsamum Tolutanum	balsam of the plant	toluene, benzylic benzoate, benzylic cinnamate, benzoic acid, cinnamic acid, resins	expectorant
Tulsi	*Ocimum Sanctum*, Linn. (Labiatae)	Holy Basil, Sacred Basil, Tulsi, Surasa	seed, leaves	Major components of the essential oil are eugenol, carvacrol, nerol and eugenolmethylether. Leaves have been reported to contain ursolic acid, apigenin, luteolin, apigenin-7-O-glucuronide, luteolin-7-O-glucuronide, orientin and molludistin.	leaf— expectorant, carminative, stomachic, antispasmodic, antiasthmatic, antirheumatic, stimulant, hepatoprotective, antipyretic and diaphoretic. seed— used in

					genitourinary diseases.
Antirhumatics					
Plant Name	Biological name	Synonym(s)	part(s) used	constituents	indications / use
Guggul	*Commiphora mukul*, Hooker. (Burseraceae)	Indian Bdellium, Guggulu	gum – resin exudes	guggolestrones E, Z.	anti-cholesterol, antirhumatic
Colchicum	*Colchicum autumnale*, Linn. (Liliaceae)		seed and the corn of colchicum	colchicine	antirhumatic, as emetic in poisioning
Antitumour					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Vinca	*Vinca major*, Linn. (Apocynaceae)	Periwinkle, amaranth	whole plant extract	indole alkaloids (vincamine, cinblastine) tannins	anticancer, circulatory stimulant (increases blood flow to the brain) hypotensive
Antileprotics					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Chaulmoogra oil / Oleum Chaulmoogra e	*Taraktogenos Kurzii*, King. (Hydnocarpus)	Taraktogenos. Chaulmoogra. Chaulmoogra.	Seed oil	fixed oil, 25-50 % contains palmitin, linolein, but chiefly glycerides of two fatty acids—chaulmoogric, cho, and hydnocarpic, cho, starch, proteins, tannin, coloring matter	leprosy
Antidiabetics					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Pterocarpous	*Pterocarpus Marsupium*, Rozburgh. (Papilionaceae; Fabaceae)	Gummi (Resina) Kino, Vengay, Bastard	bark juice	kino-tannic acid, kino-red, kinoin, pyrocatechin (pyrocatechuic acid, catechol),	diabetes, diarrhea, pyrosis, menorrhagia, dysentery, leucorrhea, ulcers,

Gymnema sylvestre	*Gymnema sylvestre* B. Br. (Asclepiadaceae)	Australian Cow Plant, Ipecacuanha (Indian). Meshashringi, Meshavishaanikaa,	leaves or whole plant	gymnemagenin, gymnemic acids	leaf—antidiabetic. stimulates the heart and circulatory system, activates the uterus. used in parageusia and furunculosis. whole plant—diuretic, antibilious. root— emetic, expectorant, astringent, stomachic.
Diuretics					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Gokhru	*Tribulus terrestris*, Linn. (Zygophyllaceae)	Gokshura, Gokshuraka, Kshudra (Laghu) Gokharu, Shvadamshtraa, Swaadu-kantaka	fruit, leaves, root.	plant contains saponins, which on hydrolysis yield sapogenins—diosgenin, gitogenin, chlorogenin, ruscogenin, 25d-spirosta-3, 5-diene, among others. flavonoids—rutin, quercetin, kaempferol, kaempferol-3-glucoside and-rutinoside, and tribuloside have been isolated fromthe leaves and fruits. theseeds contain carboline alkaloids— harmane and harmine.	fruits—diuretic, demulcent, anti-inflammatory, anabolic, spasmolytic, muscle relaxant, hypotensive, hypoglycaemic. leaf—diuretic, haemostatic. root—stomachic, diuretic.

				harmol is also reported from the herb.	
Punarnava	*Boerhavia diffusa,* Linn. (Nyctaginaceae)	Horse-purslane, Hogweed, Rakta-punarnavaa, Punarnavaa, Katthilla, Shophaghni.	whole plant	xanthone, beta-ecdysone. flavonoid, arbinofuranoside	diuretic, anti-inflammatory, antiarthritic, spasmolytic, antibacterial (used for inflammatory renal diseases, nephrotic syndrome, in cases of ascites resulting from early cirrhosis of liver and chronic peritonitis, dropsy associated with chronic bright's diseases
Antidysenterics					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Ipecacuanha	*Cephaelis ipecacuanha*, A. Richard (Rubiacae)	Ipecacuanha. Ipecac	dried root	emetine, cephaeline, cephaelic acid, epecacuanhic acid, tannic acid, volatile oil, starch, gum	antidysenterics, emetic
Antiseptic and disinfectant					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Benzoin	*Styrax benzoin*, Dryander. (Styraceoe)	Sumatra benzoin	resinous exudates obtained by injury to the tree	benzaldehyde, vanillin (1 %), phenylpropyl cinnamate, styrol, and styracin, cinnamic acid, benzoic acid	antiseptic and disinfectant
Myrrh	*Commiphora myrrha* Nees.	African Myrrh,	oleo-gum-resin	the gum contains acidic	antiseptic and

	(Burseraceae)	Arabian Myrrh, Balsamodendron Myrrha, Bitter Myrrh, Commiphora,		polysaccharides, volatile oil including other constituents, eugenol, heerabolene, monoterpenes and furanosequiterpenes.	disinfectant
Neem	*Melia Azadirachta*, Linn. (Meliaceoe)	Neem, Limb, Nila	leaves, bark, seed oil.	amorphous resin, a crystalline, bitter alkaloid (margosine), margosia acid, a crystalline substance and tannin	insect repellant, bitter tonic, antiseptic and disinfectant
Curcuma	*Curcuma Longa*, Roxb (Zingiberaceae)	Turmeric, haridra, haldi, halad.	the dried rhizome	contains volatile oil 5-10%, turmerones which are sesquiterpene, ketones, Curcumin, Curcuminoids, bitter principles, sugars, starch, resin.	antiseptic and disinfectant, stomachic, aromatic, stimulant; dyspepsia, flatulence
Antimalarial					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Cinchona	*Calisaya Weddell*, Linn. *Cinchona officinalis*, Linn. (Rubiaceae)	Cinchona bark, Jesuit bark.	Quills or in curved pieces of bark	quinine, quinidine, cinchonine, cinchonidine, quinamine, quinic acid, quinovic acid	malaria
Oxytocics					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Ergot	*Claviceps purpurea*, (Clavicititaceae)	Rye ergot	dried sclerotium	alkaloids (ergotamine) ergotic/ergotinic acid, sclerotic	oxytocic, hemostatic, motor excitant
Vitamins					
Amla	*Emblica officinalis*, Gaertn. (Euphorbiaceae)	Phyllanthus emblica, Aamalaki, Aamalaka	Fruit pericarp	vitamin C (ascorbic acid), zeatin, phyllembin,	antianaemic, anabolic, antiemetic, bechic,

				minerals and amino acids	astringent, antihaemorrhagic.
Enzymes					
Papaya	*Carica Papaya*, Linn. (Caricaceae)	Papain or Papayotin	papain enzyme	plant enzyme	digestive in dyspepsia stomachic, carminative, diuretic, galactagogue. useful in bleeding piles, haemoptysis, dysentery and chronic diarrhoea.
Perfumes and Flavoring Agents					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Peppermint oil	*Mentha piperata*, Linn. (Labiatae; Lamiaceae)	Pudinaa, Peppermint, Brandy Mint	steam distilled volatile oil of the plant	menthol, menthone, pulegone, enthofuran,1,8-cineole, menthyl acetate, isomenthone, the leaves contain flavonoid glycosides, eriocitrin, luteolin 7-0-rutinoside, hesperidin, isorhoifolin, diosmin, eriodictyol 7-O-glucoside and narirutin, besides rosmarinic acid, azulenes, cholene, carotenes.	digestive, carminative, chloretic, antispasmodic, diuretic, antiemetic, mild sedative, diaphoretic, antiseptic, antiviral, used in many mixtures of indigestion and colic and cough and cold remedies.
Lemon oil	*Citrus limon*, Linn. (Rutaceae)	Jambira, Jambh, Jambhir, Jaamphal, Nimbu, Nimbuka, neebu	peel oil	volatile oil (about 2.5% of the peel) consists of about 75% limonene, alpha-and beta-pinenes, alpha-terpinene, citral, hesperidin, rutin.	antiscorbutic, carminative, stomachic, antihistaminic, antibacterial. used during coughs, colds, influenza and

					onset of fever
Sandalwood	*Santalum album*, Linn. (Santalaecae)	Chandan, Sandal, Sandalwood	Heartwood of the plant	phenols - santalol, borneol, alcohols - α-norisoborneol	aromatic therapy, perfumary
Miscellaneous					
Plant Name	Biological name/ Synonym(s)	Other names	Part(s) Used	Constituents	Indications / Use
Liquorice	*Glycyrrhiza glabra*, Linn. (Papilionaceae, Fabaceae)	Gan Cao (root/rhizome), Glycyrrhiza glabra L. Var. Glabra, G.glabra L. Subsp. Glandulifera (Waldst. & Kit.) Ponert, Licorice	root, stolon	glycyrrhizin 2-8%, triterpene saponin, glycyrrhetinic acid, isoflavonoids, chalcones, coumarins, triterpenoids and sterols, lignans, amino acids, amines, gums and volatile oils	demulcent, expectorant, antiallergic, anti-inflammatory, spasmolytic, mild laxative, antistress, antidepressive
Garlic	*Allium sativum*, Linn. (Liliaceae, Alliaceae)	Ajo, Allium, Lashuna, Rasona, Yavaneshta, Ugragandha	bulb (clove)	disulphide compounds allicin (via allinase) alliin, diallyl disulphide, lipids, mucilage, albumin vitamins A, B, C, E.	anti-microbial hypotensive hypolipidemic
Picrorhiza	*Picrorhiza kurroa*, Royle ex Benth (Scrophulariaceae)	Katukaa, Katurohini, Kutki.	root	glycosidal bitter principle, kutkin found to be a mixture of two iridoid glycosides, picroside i and kutkoside also obtained were D-mannitol, kutkiol, kutkisterol and a ketone (identical with apocynin).	in jaundice, intermittent fever, dyspnoea and skin diseases
Dioscorea	*Dioscorea anguina*, Roxb. *Dioscorea bulbifera*, Linn. (Dioscoreaceae)	Wild yam, Colic-root, Dioscorea villosa	tubers	dioscorine , furanoid norditerpenes, contain nearly 83% starch	tubers—used for ulcer, to kill worms in wounds. plant parts— used in whitlow, sores, boils.

Linseed	*Linum usitatissimum*, Linn. (Linaceae)	Flaxseed, Flax, Lint-bells, Winter lien	ripe seed	fixed oil 35-40%, tannin, amygdalin, mucilage, oleic acid, linoleic acid	inflammation of mucous membranes of respiratory, digestive, and urinary organs, renal and vesical irritation, catarrh, dysentery,
Shatavari	*Asparagus racemosus Willd.* (Asparagaceae)	Indian asparagus , Shataavari, Shatmuuli, Atirasaa, Bahusutaa, Shatpadi, Shatviryaa	dried root	saponins— shatavarins I–IV. shatavarin IV is a glycoside of sarsasapogenin, sitosterol etc.	as galactagogue, for disorders of female genitourinary tract, ulcer-healing agent, intestinal disinfectant and astringent in diarrhea, nervine tonic and in sexual debility for spermatogenesis
Shankh-pushpi	*Evolvulus alsinoides, Linn.* (Convolvulaceae)	E. Angustifolius Roxb. Convolvulus alsinoides L. Shankhphuli, Shivakrandi	aqueous extract of whole plant	evolvine, beta-sitosterol, stearic, oleic, linoleic acids, pentatriacontane and triacontane	brain tonic, an aid in conception, astringent, antidysenteric.
Pyrethrum	*Anacyclus Pyrethrum*, Linn. (Compositae)	Pellitory, Officinarum Hayne, Aakallaka, Aakulakrit, Agragraahi	root	an acrid, brown resin, inulin, anacycline, isobutylamide, inulin and a trace of essential oil.	sialogogue, stimulant, cordial, rubefacient, insulin-dependent diabetes mellitus
Tobacco	*Nicotiana tabacum*, Linn. (Solanaceae)	Indian tobacco, Taamraparna, Dhuumrapatraa	herb	nicotine	muscle relaxation in dislocation, strangulated hernia and orchitis arthralgia, lumbago, rheumatism and gout

PHARMAROCKS

GPAT -2016 BOOKLET

VITAMINS IMPORTANT INFORMATION

TABLE WISE NOTES

MR. AMAR M. RAVAL

CONTACT US +91 9016312020

FAT SOLUBLE VITAMINS (A D E K)

VITAMIN	PHYSIOLOGIC FUNC.	DEFICIENCY	Toxicity	U.S. RDA	SOURCES
VITAMIN A (Retinol): Retin = Retina ol = alcohol B-carotene → Retinol → 11 cis retinol	▪ Proper night vision ▪ Formation & maintenance of healthy epithelial tissue. ▪ Growth of skeletal / soft tissues bone & teeth ▪ Deficiency can be due to: o Inadequate dietary intake o Poor absorption o Inadequate hepatic conversion of B carotene	▪ Night blindness ▪ Keratinization of corneal epithelium → Xerophthalmia ▪ Keratinization of epithelium of skin / mucous membrane leading to Infections ▪ Faulty tooth formation. ▪ Retarded growth ▪ Loss of appetite	▪ Toxic in large amounts. ▪ Loss of hair, joint pain, jaundice, L. bone thicken ▪ **In children:** hyperstoses (bone hypertrophy) ▪ **In adults & children:** o Peeling of skin o Headache, Nystagmus o Lymph node enlarge	▪ Adult: 3,000 IU ▪ Inf: 1,300 – 2,600 ▪ Ped. prepn. must contain > 1,000 IU ▪ Adult prepn. must contain > 1,600 IU ▪ No prepn. should contain > 10,000 ▪ 1IU = 0.3 μ retinol, 0.6 μ carotene	▪ Liver, fish oil ▪ Butter, whole milk, egg yolk ▪ Green & yellow vegetables ▪ Yellow fruits (apricots)
VITAMIN D: Formed in the body by skin exposure to UV from sun or lamp **(CALCIFEROL)**	▪ Para-hormone (involved in Ca / P metabolism) ▪ Absorption of Ca & P from GIT ▪ Tubular reabsorption of Ca ▪ Calcification of bones (Ca mobilization from bone to blood)	▪ In children: faulty bone formation & rickets (cranial bones soften, bowed thighs & knock-knees) ▪ In adults: osteomalasia & hypo-parathyroidism.	o Calcification of soft tissues lungs / kidney o Hyper-calcemia o Bone fragility. o ↑ Digitalis tox. , MI	400 IU (children; pregnant or lactating women) 1 IU vitamin D = 0.025 μg vitamin D_2.	▪ Fish oil / yeast ▪ Fortified or irradiated milk. ▪ In few foods: cod liver oil, little in milk, egg yolk
VITAMIN E: Anti-sterility vitamin (proven in rats)	▪ Related to action of Selenium ▪ Antioxidant (protects # peroxides which can destroy RBCs & capillary walls) ▪ Normal development of muscles ▪ Safe in large doses	▪ Hemolysis of RBCs ▪ Anemia. ▪ Sterility in males. ▪ Habitual abortion in females ▪ Muscular dystrophy	▪ Safe in large doses	▪ Adult: 5 - 10 IU ▪ Increases vitamin A absorption ▪ Anti-oxidant	▪ Vegetable oil. ▪ Seed oils. ▪ Others: milk, eggs, meat & fish.
VITAMIN K: **(MENADIONE)**	▪ Blood clotting, necessary for hepatic synthesis of prothrombin. ▪ Toxic in large amounts.	▪ Hemorrhagic tendencies → ↑ PT time. ▪ Xss oral AB → inhibits flora → Vitamin K deficiency.	o Inf: hemorrhagic anemia, kernicterus, & ↑ bilirubin. o In adults: ↓ liver functn. → Jaundice.	▪ UNKNOWN ▪ Synthesized by normal GIT flora	▪ Green leafy vegetables, ▪ Cheese, egg yolk, liver.

WATER SOLUBLE VITAMINS (VITAMIN B-COMPLEX & VITAMIN C)

VITAMIN	PHYSIOL. FUNCTIONS	Deficiency	Toxicity	U.S. RDA	SOURCES
THIAMINE (B 1) Anti-beriberi factor (Oral / IM / SC)	▪ Coenzyme in carbohydrate metabolism (2 C atom metabolism getting rid of pyruvic).	▪ Results from eating white wheat polished rice & alcoholics →Beriberi ▪ GI: Anorexia, ↓ HCl ▪ CNS: Fatigue, Mental Disorders, Periph neuritis, ▪ CV: Card. failure / LVH, TC	▪ Very safe; toxicity not marked.	Adults > 0.6 mg Infants > 0.4 mg Uses: Beriberi Periph neuritis in DM Neuralgia Mental Disorders	▪ Beef, liver, pork, fish, eggs. ▪ Whole or enriched grains. ▪ Yeast ▪ Vitamin B1 is thermolabile.
RIBOFLAVIN (B 2) The yellow green florescent pigment in milk	▪ Coenzyme in protein metabolism (proton carrier). ▪ Deficiency → tissue inflammation. (def. occurs in conjunctn. with other B vit.)	▪ Wound aggravation ▪ Cheilosis (cracks at corners of mouth). ▪ Glossitis, eye irritation. ▪ Seborrheic dermatitis.		Adults > 1.0 mg Infants > 0.6 mg ▪ Never given alone but with other B vit. (Oral, IM, SC)	▪ Milk, liver, kidney ▪ Enriched cereals ▪ Absorbed from upper GIT
NIACIN (B 3) As nicotinic acid or nicotinamide (when vasodilatation is contraindicated we can use nicotinamide instead of nicotinic a	▪ Coenzyme in tissue oxidation as H+ carrier → energy (ATP productn in respiratory chain). ▪ Metabolism of Fat, protein, glucose. ▪ Uses: ttt of pellagra. ▪ Nicot. a (not nicotinamide) > 3 gm / day, hypocholest.	▪ Pellagra characterized by scaly dermatitis, photosensitivity & fatal effects on CNS ▪ Weakness, lassitude ▪ Anorexia, indigestion. ▪ CNS: neuritis, confusion, apathy, schizophrenia.	▪ Vasodilatatn, flushing ▪ Hepatotoxicity ▪ GI irritatn/ ulceration ▪ Hyperuricemia ▪ Glucose intolerance (hyperglycemia)	Adults: > 6 - 45 mg Infants > 4 mg (niacin equivalent) 60 mg tryptophan = 1 mg nicotinic acid B3 & B2 are closely interrelated in cell metabolism. If one is deficient the other is.	▪ Meats ▪ Peanuts, beans, peas ▪ Enriched grains.
PYRIDOXINE (B 6) Pyridoxal is more stable than pyridoxine	▪ Coenzyme in amino acid metabolism (in decarboxylation & transamination) ▪ Production of GABA (a neurotransmitter inhibitor that prevents convulsions)	▪ Anemia (hypo chromic, microcytic). ▪ CNS: epileptic convulsions, peripheral neuritis.	B6 is contraindicated wit L-dopa (Why)	2 mg (Pregnancy & estrogen/progest OC ↓ B6 → additional B6) INH, hydralazine & penicillamine deplete tryptophan → B6 def.	▪ Wheat, corn, yeast ▪ Meat, liver, Kidney ▪ GIT flora → B6 but significance not determined

VITAMIN	PHYSIOLOGIC FUNC.	Deficiency	Toxicity	U.S. RDA	SOURCES
PANTOTHENIC ACID (B5) Found throughout body tissues	▪ Coenzyme in overall body metabolism ▪ Converted to Co-A (Ac Ch synthesis & fatty a metabolism)	Contributes to: ▪ Amino acid activation ▪ Formation of Cholesterol ▪ Excretion of drugs	▪ Locally to aid wound healing. ▪ IM to aid motility of the intestine after surgical op (post-op paralytic ileus.	GIT flora syn. a considerable amount + wide spread in nat. sources → def. not common	▪ Liver, kidney ▪ Yeast, egg yolk ▪ Skimmed milk. ▪ Leafy vegetable
FOLIC ACID	▪ Important in cell growth & blood forming factors. ▪ Essential for synth. of purine & pyrimidine nucleotides	▪ Megaloplasic anemia ▪ Sprue (GIT disease characterized by severe diarrhea).	▪ Not toxic by oral route ▪ Pern. anemia (doesn't control neurologic sym) ▪ Megaloblastic anemia. ▪ Sprue treatment.	50 ug	▪ Liver, kidney ▪ Green leafy vegetables ▪ Asparagus.
COBOLAMINE (B12)	▪ Coenzyme in protein synthesis ▪ Formation of red blood cells.	▪ Pernicious anemia ▪ Sprue treatment + folic a		6 ug.	▪ Liver, meat, egg. milk, cheese.
BIOTIN	▪ Coenzyme in CO_2 reactions in energy metabolism. ▪ Involved in fatty a synthesis & in carboxylation reactns.	▪ Undetermined.	▪ Synthesized by GIT flora or with ingested food (nat. def. unknown) ▪ Large amounts of egg white → deficiency.	"micronutrient" bec minute traces → metabolic task	▪ Egg yolk, ▪ Liver, kidney. ▪ Tomato, yeast
CHOLINE	▪ Essential for synthesis of phosphatidyl-choline involved in lipid transport & acetylcholine synthesis	▪	▪ Synth. in body from amino acid methionine		

VITAMIN C (ASCORBIC ACID)	▪ Building & maintaining collagen, cartilage, bone matrix & connective tissue. ▪ Wound healing, tissue ▪ GIT absorption of iron ▪ Redox reactions in the body → Cellular respiration	▪ Scurvy * ▪ Megahemoglobinemia (bec of its reducing properties) ▪ Wound healing, tissue formation (cementing connective tissue) ▪ Fever, infections ↓ stored vitamin C ▪ Stress reactions ▪ Growth period. ▪ ttt of alcohol overdose → stimulates alcohol dehydrogenase	▪ Increased stone formation in UT. ▪ Diarrhea ▪ 10 gm daily of vit C followed by rapid withdrawal → frank symptoms of scurvy. ▪ Scurvy develops in newborns to mothers who suddenly stop large daily doses of vitamin C.	Adult > 150 mg Child > 20 mg Women have higher vitamin C levels than men. Smoking ↓ vitamin C levels in blood.	Citrus fruits, tomatoes, green & yellow vegetables (cabbage, potatoes) & strawberries.

MEDICINAL CHEMISTRY NOTES MR. AMAR M. RAVAL

AMINOGLYCOSIDES

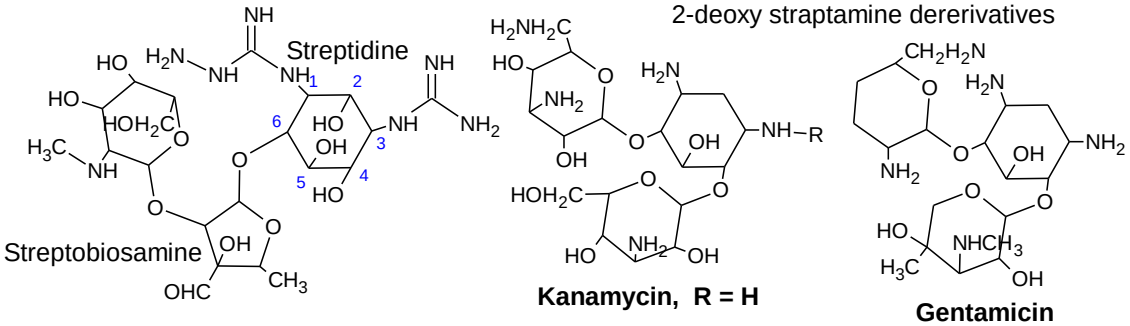
An **aminoglycoside** is a molecule or a portion of a molecule composed of amino-modified sugars. These are glycosides of amino sugars. Aglycone part in streptomycin is inositol derivative streptidine that contains two guanido groups at 1 and 3-position of inositol. Streptomycin is tri-acidic base on hydrolysis it produces streptidine and streptobiosamine. Streptobiosamine further breaks in streptose and N-methyl glucosamine. Other aminoglycosides like gentamicin, tobramycin, kanamycin, neomycin are 2-deoxy streptamine derivatives.

Several aminoglycosides function as antibiotics that are effective against certain types of bacteria. They include amikacin, arbekacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, rhodostreptomycin, streptomycin, tobramycin, and apramycin.

NOMENCLATURE

Aminoglycosides that are derived from bacteria of the *Streptomyces* genus are named with the suffix *-mycin*, whereas those that are derived from *Micromonospora* are named with the suffix *-micin*.

This nomenclature system is not specific for aminoglycosides. For example, vancomycin is a glycopeptide antibiotic and erythromycin, which is produced from the species *Saccharopolyspora erythraea* (previously misclassified as *Streptomyces*) along with its synthetic derivatives clarithromycin and azithromycin, is a macrolide.



Streptomycin

Amikacin, R = COCH(OH)$CH_2CH_2NH_2$

DIFFERENT SOURCES OF ANTIBIOTICS:-

1. Gentamicin — *Micromonospora purpurea*
2. Neomycin — *Streptomyces fradiae*
3. Streptomycin — *Streptomyces griseus*
4. Tobramycin — *Streptomyces tenebrarius*
5. Framycetin — *Streptomyces decaries*
6. Kanamycin — *Streptomyces kanamyceticus*
7. Amikacin — It is 1-L-(-)-4-amino-2-hydroxybutyryl kanamycin

MECHANISMS OF ACTION

Aminoglycosides have several potential antibiotic mechanisms, some as protein synthesis inhibitors, although their exact mechanism of action is not fully known:

- They interfere with the proofreading process, causing increased rate of error in synthesis with premature termination.
- Also, there is evidence of inhibition of ribosomal translocation where the peptidyl-tRNA moves from the A-site to the P-site.
- They can also disrupt the integrity of bacterial cell membrane.

They bind to the bacterial 30S ribosomal subunit (some work by binding to the 50S subunit
There is a significant variability in the relationship between the dose administered and the resultant plasma level in blood. Therapeutic drug monitoring (TDM) is necessary to obtain the correct dose. These agents exhibit a post-antibiotic effect in which there is no or very little drug level detectable in blood, but there still seems to be inhibition of bacterial re-growth. This is due to strong, irreversible binding to the ribosome, and remains intracellular long after plasma levels drop. This allows a prolonged dosage interval. Depending on their concentration they act as bacteriostatic or bactericidal agents.
The protein synthesis inhibition of aminoglycosides does not usually produce a bactericidal effect, let alone a rapid one as is frequently observed on susceptible Gram-negative bacilli. Aminoglycosides competitively displace cell biofilm-associated Mg^{2+} and Ca^{2+} that link the polysaccharides of adjacent lipopolysaccharide molecules. "The result is shedding of cell membrane blebs, with formation of transient holes in the cell wall and disruption of the normal permeability of the cell wall. This action alone may be sufficient to kill most susceptible Gram-negative bacteria before the aminoglycoside has a chance to reach the 30S ribosome."
The antibacterial properties of aminoglycosides were believed to result from inhibition of bacterial protein synthesis through irreversible binding to the 30S bacterial ribosome. This explanation, however, does not account for the potent bactericidal properties of these agents, since other antibiotics that inhibit the synthesis of proteins (such as tetracycline) are not bactericidal. Recent experimental studies show that the initial site of action is the outer bacterial membrane. The cationic antibiotic molecules create fissures in the outer cell membrane, resulting in leakage of intracellular contents and enhanced antibiotic uptake. This rapid action at the outer membrane probably accounts for most of the bactericidal activity. Energy is needed for aminoglycoside uptake into the bacterial cell. Anaerobes have less energy available for this uptake, so aminoglycosides are less active against anaerobes.
Aminoglycosides are useful primarily in infections involving aerobic, gram-negative bacteria, such as *Pseudomonas*, *Acinetobacter*, and *Enterobacter*. In addition, some *Mycobacteria*, including the bacteria that cause tuberculosis, are susceptible to aminoglycosides. The most frequent use of aminoglycosides is empiric therapy for serious infections such as septicemia, complicated intraabdominal infections, complicated urinary tract infections, and nosocomial respiratory tract infections. Usually, once cultures of the causal organism are grown and their susceptibilities tested, aminoglycosides are discontinued in favor of less toxic antibiotics.
Streptomycin was the first effective drug in the treatment of tuberculosis, though the role of aminoglycosides such as streptomycin and amikacin has been eclipsed (because of their toxicity and inconvenient route of administration) except for multiple drug resistant strains.

Infections caused by gram-positive bacteria can also be treated with aminoglycosides, but other types of antibiotics are more potent and less damaging to the host. In the past the aminoglycosides have been used in conjunction with beta-lactam antibiotics in streptococcal infections for their synergistic effects, particularly in endocarditis. One of the most frequent combinations is ampicillin (a beta-lactam, or penicillin-related antibiotic) and gentamicin. Often, hospital staff refer to this combination as "amp and gent" or more recently called "pen and gent" for penicillin and gentamicin.

Aminoglycosides are mostly ineffective against anaerobic bacteria, fungi, and viruses

Nonsense suppression

The interference with DNA proofreading has been exploited to treat genetic diseases which result from premature stop codes (leading to early termination of protein synthesis and truncated proteins). Aminoglycosides can cause the cell to overcome the stop code, insert a random amino acid, and express a full-length protein.

The aminoglycoside gentamicin has been used to treat cystic fibrosis (CF) cells in the laboratory to induce them to grow full-length proteins. CF is caused by a mutation in the gene coding for the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) protein. In approximately 10% of CF cases, the mutation in this gene causes its early termination during translation, leading to the formation of is truncated and non-functional CFTR protein. It is believed that gentamicin distorts the structure of the ribosome-RNA complex, leading to a mis-reading of the termination codon, causing the ribosome to "skip" over the stop sequence and to continue with the normal elongation and production of the CFTR protein.

Routes of administration

Since they are not absorbed from the gut, they are administered intravenously and intramuscularly. Some are used in topical preparations for wounds. Oral administration can be used for gut decontamination (e.g., in hepatic encephalopathy). Tobramycin may be administered in a nebulized form.

Clinical use

The recent emergence of infections due to Gram-negative bacterial strains with advanced patterns of antimicrobial resistance has prompted physicians to reevaluate the use of these antibacterial agents. This revived interest in the use of aminoglycosides has brought back to light the debate on the two major issues related to these compounds, namely the spectrum of antimicrobial susceptibility and toxicity. Current evidence shows that aminoglycosides do retain activity against the majority of Gram-negative clinical bacterial isolates in many parts of the world. Still, the relatively frequent occurrence of nephrotoxicity and ototoxicity during aminoglycoside treatment makes physicians reluctant to use these compounds in everyday practice. Recent advances in the understanding of the effect of various dosage schedules of aminoglycosides on toxicity have provided a partial solution to this problem, although more research still needs to be done in order to overcome this problem entirely.

Resistance Development

Aminoglycosides develops resistance very fastly. These are inactivated by N-acetyl transferase, N-adenyl transferase and O-Phosphorylase. These enzymes inactivate the antibiotics so newer antibiotics like kanamycin and gentamicin are 2-deoxy streptamine derivative and amikacin has no free amino group on 1-position.

ANTI ARRHYTHMIC DRUGS

Heart is the major organ that supplies oxygen to the whole body. Heart contains two atria (right and left) and two ventricles. There is coronary artery that supplies 11% of total oxygen to the heart and other nutrients. Heart is composed of cardiac muscle that has intrinsic activity and spontaneous impulse are generated by pace maker (Sinoartrial node) that sweeps over atria AV nodes and his purkinje fibres; so there is contraction and relaxation of cardiac muscle. Total 0.8 tme is required, 0.1 for contraction of artrias and 0.3 second for contraction of ventricles and then complete relaxation of 0.4 second. Both atrias and ventricles beat at the same time.

Physiology of heart muscle

Normal heart muscle electrical activity curve Heart beats 72 times/minute

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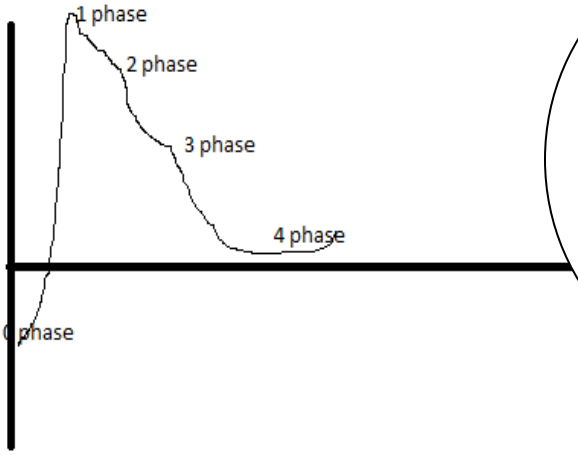
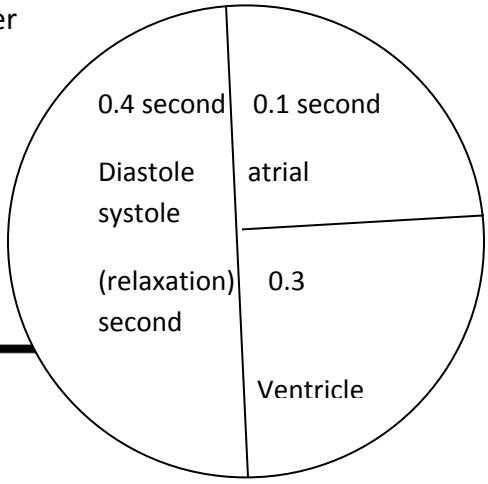




At the resting stage the potential inside the muscle is negative. At 0 phase there is influx of Na^+ ions that causes rapid depolarization of cell and muscle contract as potential reaches to maximum and generate action potential. After that in 1 phase, there is partial repolarization. Further in 2 phase (Plateau phase) there is release of $caCa^{2+}$ ions from sarcoplasmic reticulum that causes slow inward current. In 3 phase there is repolarization causes influx of k^+ ions and then at last 4 phase comes.

Antiarrhythmic agents are a group of pharmaceuticals that are used to suppress abnormal rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.

Many attempts have been made to classify antiarrhythmic agents. The problem arises from the fact that many of the antiarrhythmic agents have multiple modes of action, making any classification imprecise.

Vaughan Williams classification

The Singh Vaughan Williams classification, introduced in 1970 based on the seminal work of Bramah N. Singh in his doctoral thesis at Oxford where Vaughan Williams was his advisor and on subsequent work by Singh and his colleagues in the United States, is one of the most widely used classification schemes for antiarrhythmic agents. This scheme classifies a drug based on the primary mechanism of its antiarrhythmic effect. However, its dependence on primary mechanism is one of the limitations of the Singh-VW classification, since many antiarrhythmic agents have multiple action mechanisms. Amiodarone, for example, has effects consistent with all of the first four classes. Another limitation is the lack of consideration within the Singh-VW classification system for the effects of drug metabolites. Procainamide—a class Ia agent whose metabolite N- acetyl procainamide (NAPA) has a class III action—is one such example. A historical limitation was that drugs such as digoxin and adenosine – important antiarrhythmic agents – had no place at all in the VW classification system. This has since been rectified by the inclusion of class V

There are five main classes in the Singh Vaughan Williams classification of antiarrhythmic agents:

- **Class I** agents interfere with the sodium (Na^+) channel.
- **Class II** agents are anti-sympathetic nervous system agents. Most agents in this class are beta blockers.
- **Class III** agents affect potassium (K^+) efflux.
- **Class IV** agents affect calcium channels and the AV node.
- **Class V** agents work by other or unknown mechanisms.

Overview table

Class	Known as	Examples	Mechanism	Clinical uses [1]
Ia	fast-channel blockers	• Quinidine • Procainamide • Disopyramide	(Na^+) channel block (intermediate association/dissociation)	• Ventricular arrhythmias • prevention of paroxysmal recurrent atrial fibrillation (triggered by vagal overactivity), *procainamide in Wolff-Parkinson-White syndrome
Ib		• Lidocaine • Phenytoin • Mexiletine	(Na^+) channel block (fast association/dissociation)	• treatment and prevention during and immediately after myocardial infarction, though this practice is now discouraged given the increased risk of asystole o ventricular tachycardia o atrial fibrillation
Ic		• Flecainide • Propafenone • Moricizine	(Na^+) channel block (slow association/dissociation)	• prevents paroxysmal atrial fibrillation • treats recurrent tachyarrhythmias of abnormal conduction system. • contraindicated immediately post-myocardial infarction.
II	Beta-blockers	• Propranolol • Esmolol • Timolol • Metoprolol	beta blocking Propranolol also shows some class I action	• decrease myocardial infarction mortality • prevent recurrence of

		• Atenolol • Bisoprolol		tachyarrhythmias
III		• Amiodarone • Sotalol • Ibutilide • Dofetilide • E-4031	K^+ channel blocker Sotalol is also a beta blocker	• In Wolff-Parkinson-White syndrome • (sotalol:) ventricular tachycardias and atrial fibrillation • (Ibutilide:) atrial flutter and atrial fibrillation
IV	slow-channel blockers	• Verapamil • Diltiazem	Ca^{2+} channel blocker	• prevent recurrence of paroxysmal supraventricular tachycardia • reduce ventricular rate in patients with atrial fibrillation
V		• Adenosine • Digoxin	Work by other or unknown mechanisms (Direct nodal inhibition).	Used in supraventricular arrhythmias, especially in Heart Failure with Atrial Fibrillation, contraindicated in ventricular arrhythmias.

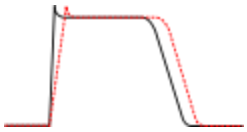
Class I agents

The class I antiarrhythmic agents interfere with the sodium channel. Class I agents are grouped by what effect they have on the Na^+ channel, and what effect they have on cardiac action potentials.

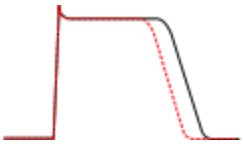
Class 1 agents are called Membrane Stabilizing agents. The 'stabilizing' is the word used to describe the decrease of excitogenicity of the plasma membrane which is brought about by these agents. (Also noteworthy is that a few class 2 agents like propranolol also have a membrane stabilizing effect.)

Class I agents are divided into three groups (1a, 1b and 1c) based upon their effect on the length of the action potential.

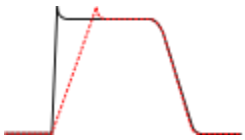
- 1A lengthens the action potential (right shift)
- 1B shortens the action potential (left shift)
- 1C does not significantly affect the action potential (no shift)



Class Ia agent decreasing V_{max}, thereby increasing action potential duration.



Class Ib



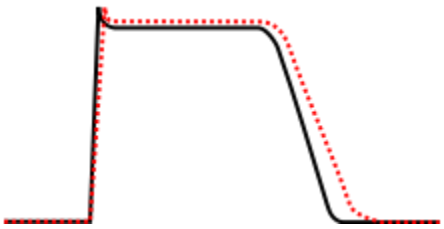
Class Ic

Class II agents

Class II agents are conventional beta blockers. They act by blocking the effects of catecholamines at the β_1-adrenergic receptors, thereby decreasing sympathetic activity on the heart. These agents are particularly useful in the treatment of supraventricular tachycardias. They decrease conduction through the AV node.

Class II agents include atenolol, esmolol, propranolol, and metoprolol.

Class III agents



Class III

Class III agents predominantly block the potassium channels, thereby prolonging repolarization.[5] Since these agents do not affect the sodium channel, conduction velocity is not decreased. The prolongation of the action potential duration and refractory period, combined with the maintenance of normal conduction velocity, prevent re-entrant arrhythmias. (The re-entrant rhythm is less likely to interact with tissue that has become refractory). Drugs include: amiodarone, ibutilide, sotalol, dofetilide, and dronedarone.

Class IV agents

Class IV agents are slow calcium channel blockers. They decrease conduction through the AV node, and shorten phase two (the plateau) of the cardiac action potential. They thus reduce the contractility of the heart, so may be inappropriate in heart failure. However, in contrast to beta blockers, they allow the body to retain adrenergic control of heart rate and contractility.

Class IV agents include verapamil and diltiazem.

Other agents ("Class V")

Since the development of the original Vaughan-Williams classification system, additional agents have been used that don't fit cleanly into categories I through IV.

Some sources use the term "Class V". However, they are more frequently identified by their precise mechanism.

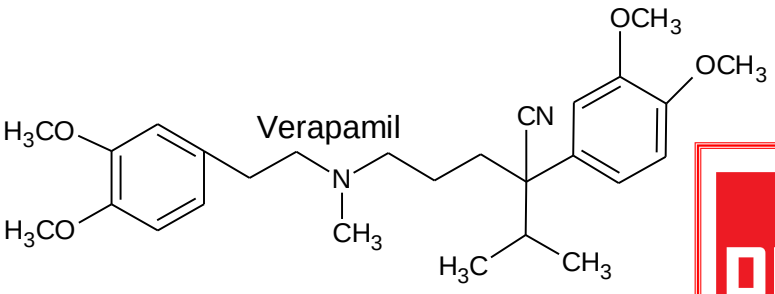
Agents include:

- Digoxin, which decreases conduction of electrical impulses through the AV node and increases vagal activity via its central action on the central nervous system.
- Adenosine
- Magnesium sulfate, which has been used for torsades de pointes.

Sicilian Gambit classification

Another approach, known as the "Sicilian Gambit", placed a greater approach on the underlying mechanism.

It presents the drugs on two axes, instead of one, and is presented in tabular form. On the Y axis, each drug is listed, in approximately the Vaughan Williams order. On the X axis, the channels, receptors, pumps, and clinical effects are listed for each drug, with the results listed in a grid. It is therefore not a true classification in that it does not aggregate drugs into categories.[14]



NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs, usually abbreviated to **NSAIDs** or **NAIDs**, but also referred to as **nonsteroidal anti-inflammatory agents/analgesics** (**NSAIAs**) or **nonsteroidal anti-inflammatory medicines** (**NSAIMs**), are drugs with analgesic and antipyretic (fever-reducing) effects and which have, in higher doses, anti-inflammatory effects.
The term "nonsteroidal" is used to distinguish these drugs from steroids, which, among a broad range of other effects, have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic.
The most prominent members of this group of drugs are aspirin, ibuprofen, and naproxen, all of which are available over the counter in many areas.

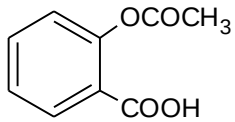
Mechanism of action

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A_2). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. This mechanism of action was elucidated by John Vane (1927–2004), who later received a Nobel Prize for his work (see Mechanism of action of aspirin). Many aspects of the mechanism of action of NSAIDs remain unexplained, for this reason further COX pathways are hypothesized. The COX-3 pathway was believed to fill some of this gap but recent findings make it appear unlikely that it plays any significant role in humans and alternative explanation models are proposed.
NSAIDS have antipyretic activity and can be used to treat fever. Fever is caused by elevated levels of prostaglandin E2, which alters the firing rate of neurons within the hypothalamus that control thermoregulation. Antipyretics work by inhibiting the enzyme COX, which causes the general inhibition of prostanoid biosynthesis (PGE2) within the hypothalamus. PGE2 signals to the hypothalamus to increase the body's thermal set point. Ibuprofen has been shown to be more effective as an antipyretic than acetaminophen. Arachidonic acid is the precursor substrate for cyclooxygenase leading to the production of prostaglandins F,D & E.

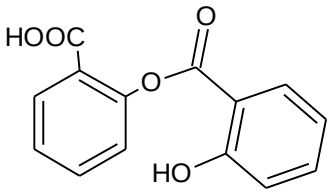
Classification

NSAIDs can be classified based on their chemical structure or mechanism of action. Older NSAIDs were known long before their mechanism of action was elucidated and were for this reason classified by chemical structure or origin. Newer substances are more often classified by mechanism of action.

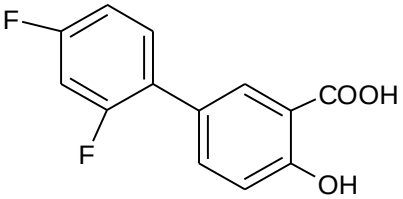
Salicylates:-



Aspirin

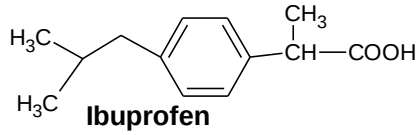


Salsalate



Diflunisal

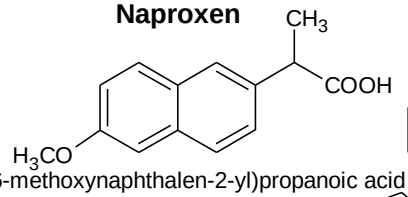
Propionic Acid Derivatives:-



Ibuprofen

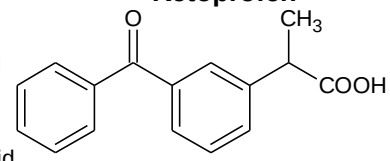
2-[p-(isobutyl)phenyl]propanoic acid

Naproxen



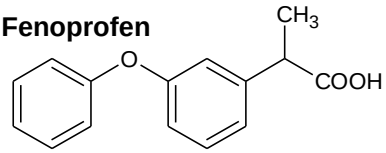
2-(6-methoxynaphthalen-2-yl)propanoic acid

Ketoprofen



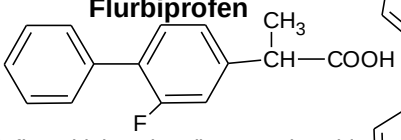
2-(3-benzoylphenyl)propanoic acid

Fenoprofen



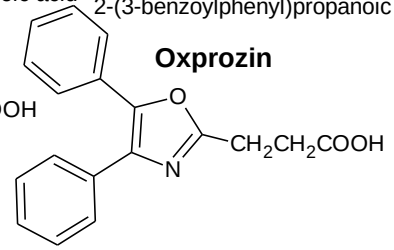
2-(3-phenoxyphenyl)propanoic acid

Flurbiprofen

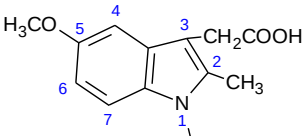


2-(2-fluorobiphenyl-4-yl)propanoic acid

Oxprozin



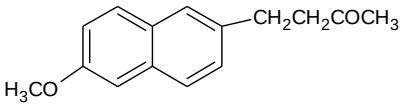
Acetic Acid Derivatives:-



Indomethacin

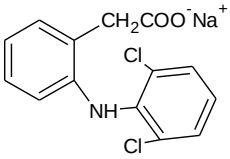
[1-(4-chlorophenyl)-6-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

Nabumetone(Prodrug)



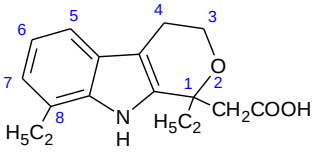
4-(6-methoxynaphthalen-2-yl)butan-2-one

Diclofenac Sod.



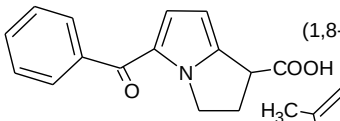
{2-[(2,6-dichlorophenyl)amino]phenyl}acetic acid

Etodolac



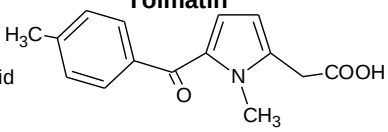
(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid

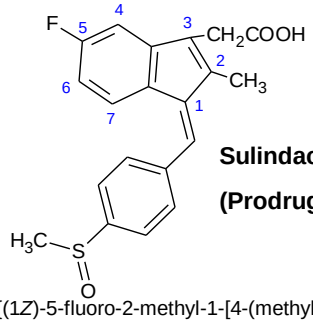
Ketorolac



5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid

Tolmatin





Sulindac (Prodrug)

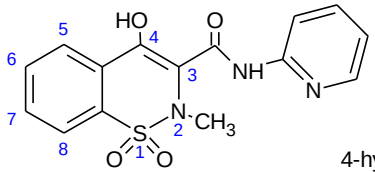
{(1*Z*)-5-fluoro-2-methyl-1-[4-(methylsulfinyl)-benzylidene]-1*H*-inden-3-yl}acetic acid

[Enolic acid (Oxicam) derivatives

Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam

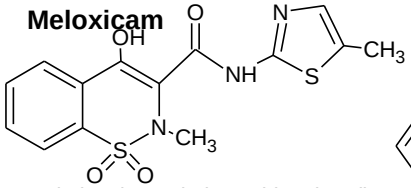
Oxicam Derivatives:-

Piroxicam



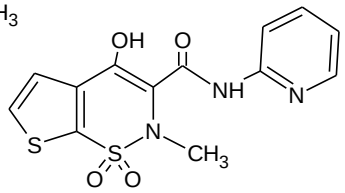
4-hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide

Meloxicam



4-hydroxy-2-methyl-*N*-(5-methyl-1,3-thiazol-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide

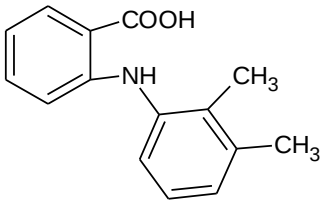
Tenoxicam



4-hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-thieno[3,2-*e*][1,2]thiazine-3-carboxamide 1,1-dioxide

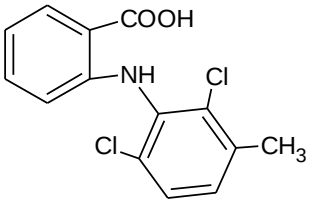
Anthranilic Acid (Fenamic) Derivatives:-

Mefenamic Acid



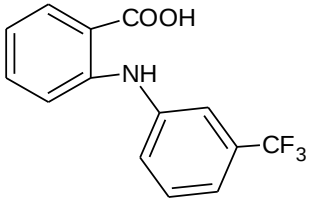
2-[(2,3-dimethylphenyl) amino]benzoic acid

Meclofenamic acid



2-[(2,6-dichloro-3-methylphenyl) amino]benzoic acid

Flufenamic acid



2-{[3-(trifluoromethyl)phenyl] amino}benzoic acid

Tolfenamic acid

Selective COX-2 inhibitors (Coxibs)

- Celecoxib (FDA alert)
- Rofecoxib (withdrawn from market)
- Valdecoxib (withdrawn from market)
- Parecoxib FDA withdrawn
- Lumiracoxib TGA cancelled registration
- Etoricoxib FDA withdrawn
- Firocoxib used in dogs and horses

Sulphonanilides

- Nimesulide (systemic preparations are banned by several countries for the potential risk of hepatotoxicity)

Others

- Acetaminophen acts by inhibiting COX-2 and to a lesser degree COX-1
- Licofelone acts by inhibiting LOX (lipooxygenase) & COX and hence known as 5-LOX/COX inhibitor

Main practical differences

NSAIDs within a group will tend to have similar characteristics and tolerability. There is little difference in clinical efficacy among the NSAIDs when used at equivalent doses. Rather, differences among compounds tend to be with regards to dosing regimens (related to the compound's elimination half-life), route of administration, and tolerability profile.

Regarding adverse effects, selective COX-2 inhibitors have lower risk of gastrointestinal bleeding, but a substantially more increased risk of myocardial infarction than the increased risk from nonselective inhibitors.[13] Some data also supports that the partially selective nabumetone is less likely to cause gastrointestinal events. The nonselective naproxen appears to be risk-neutral with regard to cardiovascular events.

A consumer report noted ibuprofen, naproxen and salsalate to be less expensive than other NSAIDs and to be essentially as effective and safe as any of them when used appropriately in treating osteoarthritis and pain.

Uses

NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. Research continues into their potential for prevention of colorectal cancer, and treatment of other conditions, such as cancer and cardiovascular disease.

NSAIDs are generally indicated for the symptomatic relief of the following conditions:

- Rheumatoid arthritis
- Osteoarthritis
- Inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
- Acute gout
- Dysmenorrhoea (menstrual pain)
- Metastatic bone pain
- Headache and migraine
- Postoperative pain
- Mild-to-moderate pain due to inflammation and tissue injury
- Pyrexia (fever)
- Ileus
- Renal colic
- They are also given to neonate infants whose ductus arteriosus is not closed within 24 hours of birth

Aspirin, the only NSAID able to irreversibly inhibit COX-1, is also indicated for inhibition of platelet aggregation. This is useful in the management of arterial thrombosis and prevention of adverse cardiovascular events. Aspirin inhibits platelet aggregation by inhibiting the action of thromboxane -A.

In 2001 NSAIDs accounted for 70,000,000 prescriptions and 30 billion over-the-counter doses sold annually in the United States.

Pharmacokinetics

Most nonsteroidal anti-inflammatory drugs are weak acids, with a pKa of 3-5. They are absorbed well from the stomach and intestinal mucosa. They are highly protein-bound in plasma (typically >95%), usually to albumin, so that their volume of distribution typically approximates to plasma volume. Most NSAIDs are metabolised in the liver by oxidation and conjugation to inactive metabolites which are typically excreted in the urine, although some drugs are partially excreted in bile. Metabolism may be abnormal in certain disease states, and accumulation may occur even with normal dosage.

Ibuprofen and diclofenac have short half-lives (2–3 hours). Some NSAIDs (typically oxicams) have very long half-lives (e.g. 20–60 hours).

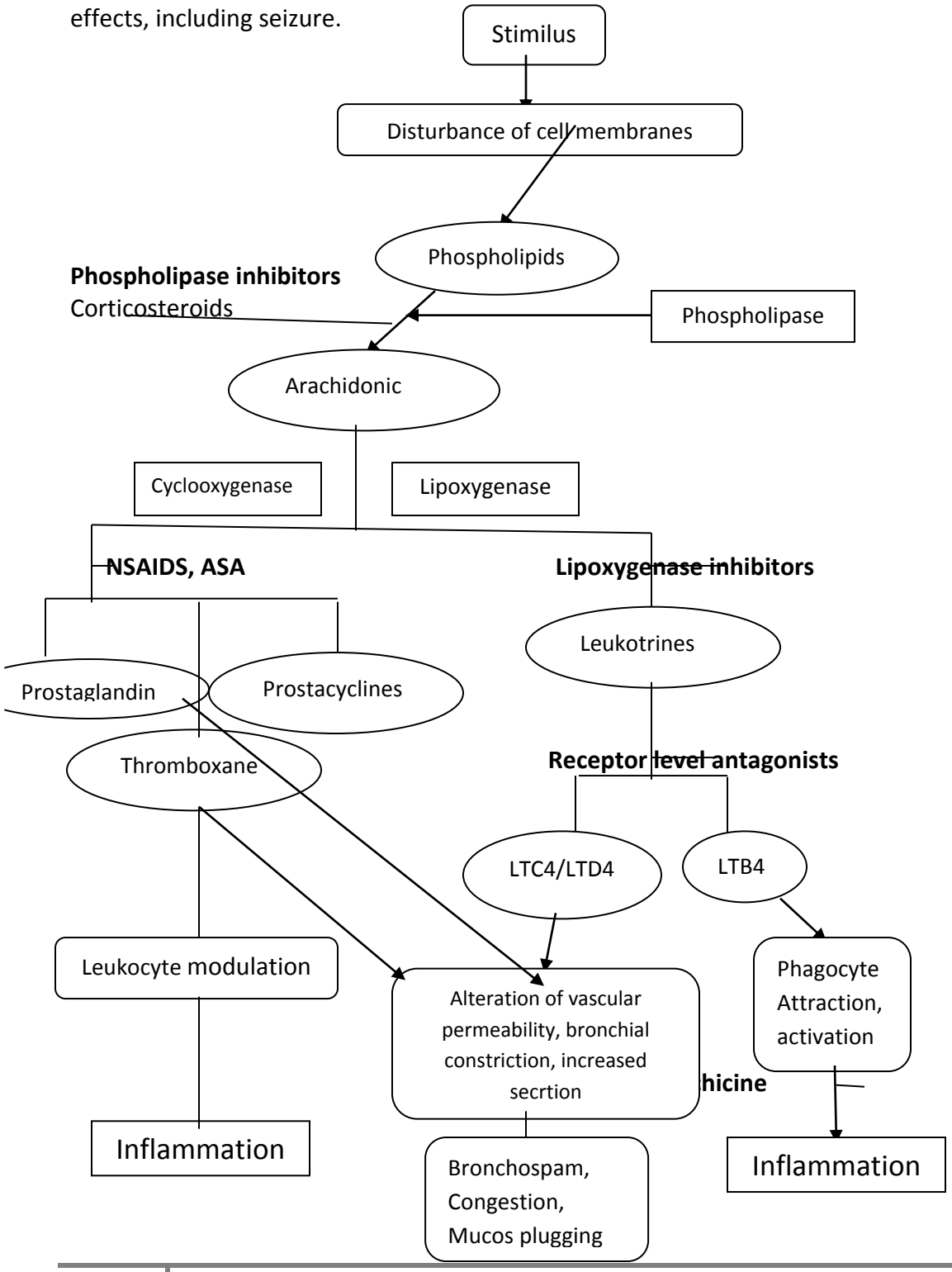
Adverse effects

The widespread use of NSAIDs has meant that the adverse effects of these drugs have become increasingly prevalent. The two main adverse drug reactions (ADRs) associated with NSAIDs relate to gastrointestinal (GI) effects and renal effects of the agents.

These effects are dose-dependent, and in many cases severe enough to pose the risk of ulcer perforation, upper gastrointestinal bleeding, and death, limiting the use of NSAID therapy. An estimated 10-20% of NSAID patients experience dyspepsia, and NSAID-associated upper gastrointestinal adverse events are estimated to result in 103,000 hospitalizations and 16,500

deaths per year in the United States, and represent 43% of drug-related emergency visits. Many of these events are avoidable; a review of physician visits and prescriptions estimated that unnecessary prescriptions for NSAIDs were written in 42% of visits.

NSAIDs, like all drugs, may interact with other medications. For example, concurrent use of NSAIDs and quinolones may increase the risk of quinolones' adverse central nervous system effects, including seizure.



Scheme for mediators from arachidonic acid and site of drug action

Combinational risk

If a COX-2 inhibitor is taken, one should not use a traditional NSAID (prescription or over-the-counter) concomitantly.[20] In addition, patients on daily aspirin therapy (e.g. for reducing cardiovascular risk) need to be careful if they also use other NSAIDs, as the latter may block[the cardioprotective effects of aspirin.

Cardiovascular

A recent meta-analysis of all trials comparing NSAIDs found an 80% increase in the risk of myocardial infarction with both newer COX-2 antagonists and high dose traditional anti-inflammatories compared with placebo.

NSAIDs aside from (low-dose) aspirin are associated with a doubled risk of symptomatic heart failure in patients without a history of cardiac disease. In patients with such a history, however, use of NSAIDs (aside from low-dose aspirin) was associated with more than 10-fold increase in heart failure.[22] If this link is found to be causal, NSAIDs are estimated to be responsible for up to 20 percent of hospital admissions for congestive heart failure.

In patients with already established heart failure, NSAIDs increase mortaility with a hazard ratio of approximately 1.2-1.3 for naproxen and ibuprofen, 1.7 for rofecoxib and celecoxib, and 2.1 for diclofenac.

Gastrointestinal

The main adverse drug reactions (ADRs) associated with use of NSAIDs relate to direct and indirect irritation of the gastrointestinal (GI) tract. NSAIDs cause a dual insult on the GI tract: the acidic molecules directly irritate the gastric mucosa, and inhibition of COX-1 and COX-2 reduces the levels of protective prostaglandins. Inhibition of prostaglandin synthesis in the GI tract causes increased gastric acid secretion, diminished bicarbonate secretion, diminished mucus secretion and diminished trophic effects on epithelial mucosa.

Common gastrointestinal ADRs include:

- Nausea/Vomiting
- Dyspepsia
- Gastric ulceration/bleeding.
- Diarrhea

Risk of ulceration increases with duration of therapy, and with higher doses. In attempting to minimise GI ADRs, it is prudent to use the lowest effective dose for the shortest period of time, a practice which studies show is not often followed. Recent studies show that over 50% of patients taking NSAIDs have sustained damage to their small intestine. Studies show that risk of ulceration is less with nabumetone than with ibuprofen alone.

There are also some differences in the propensity of individual agents to cause gastrointestinal ADRs. Indomethacin, ketoprofen and piroxicam appear to have the highest prevalence of gastric ADRs, while ibuprofen (lower doses) and diclofenac appear to have lower rates.

Certain NSAIDs, such as aspirin, have been marketed in enteric-coated formulations which are claimed to reduce the incidence of gastrointestinal ADRs. Similarly, there is a belief that rectal formulations may reduce gastrointestinal ADRs. However, in consideration of the mechanism of

such ADRs and indeed in clinical practice, these formulations have not been shown to have a reduced risk of GI ulceration.

Commonly, gastric (but not necessarily intestinal) adverse effects can be reduced through suppressing acid production, by concomitant use of a proton pump inhibitor, e.g. omeprazole, esomeprazole; or the prostaglandin analogue misoprostol. Misoprostol is itself associated with a high incidence of gastrointestinal ADRs (diarrhea). While these techniques may be effective, they prove to be expensive for maintenance therapy.

Inflammatory bowel disease

NSAIDs are never to be used in individuals with inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) due to their tendency to cause gastric bleeding and form ulceration in the gastric lining. Pain relievers such as paracetamol (also known as acetaminophen) or drugs containing codeine (which slows down bowel activity) are safer medications for pain relief in IBD.

Renal

NSAIDs are also associated with a relatively high incidence of renal adverse drug reactions (ADRs). The mechanism of these renal ADRs is due to changes in renal haemodynamics (blood flow), ordinarily mediated by prostaglandins, which are affected by NSAIDs. Prostaglandins normally cause vasodilation of the afferent arterioles of the glomeruli. This helps maintain normal glomerular perfusion and glomerular filtration rate (GFR), an indicator of renal function. This is particularly important in renal failure where the kidney is trying to maintain renal perfusion pressure by elevated angiotensin II levels. At these elevated levels, angiotensin II also constricts the afferent arteriole into the glomerulus in addition to the efferent arteriole one it normally constricts. Prostaglandins serve to dilate the afferent arteriole; by blocking this prostaglandin-mediated effect, particularly in renal failure, NSAIDs cause unopposed constriction of the afferent arteriole and decreased renal perfusion pressure. Horses are particularly prone to these adverse affects compared with other domestic animal species.

Common ADRs associated with altered renal function include:

- Salt and fluid retention
- Hypertension (high blood pressure)

These agents may also cause renal impairment, especially in combination with other nephrotoxic agents. Renal failure is especially a risk if the patient is also concomitantly taking an ACE inhibitor and a diuretic - the so-called "triple whammy" effect.

In rarer instances NSAIDs may also cause more severe renal conditions:

- Interstitial nephritis
- Nephrotic syndrome
- Acute renal failure
- Acute tubular necrosis

NSAIDs in combination with excessive use of phenacetin and/or paracetamol may lead to analgesic nephropathy.

Photosensitivity

Photosensitivity is a commonly overlooked adverse effect of many of the NSAIDs. It is somewhat ironic that these anti-inflammatory agents may themselves produce inflammation in combination with exposure to sunlight. The 2-arylpropionic acids have proven to be the most

likely to produce photosensitivity reactions, but other NSAIDs have also been implicated including piroxicam, diclofenac and benzydamine.

Benoxaprofen, since withdrawn due to its hepatotoxicity, was the most photoactive NSAID observed. The mechanism of photosensitivity, responsible for the high photoactivity of the 2-arylpropionic acids, is the ready decarboxylation of the carboxylic acid moiety. The specific absorbance characteristics of the different chromophoric 2-aryl substituents, affects the decarboxylation mechanism. While ibuprofen is somewhat of an exception, having weak absorption, it has been reported to be a weak photosensitising agent.

During pregnancy

NSAIDs are not recommended during pregnancy, particularly during the third trimester. While NSAIDs as a class are not direct teratogens, they may cause premature closure of the fetal ductus arteriosus and renal ADRs in the fetus. Additionally, they are linked with premature birth. Aspirin, however, is used together with heparin in pregnant women with antiphospholipid antibodies.

In contrast, paracetamol (acetaminophen) is regarded as being safe and well-tolerated during pregnancy. Doses should be taken as prescribed, due to risk of hepatotoxicity with overdoses.

In France, the country's health agency contraindicates the use of NSAIDs, including aspirin, after the sixth month of pregnancy.

Other

Common adverse drug reactions (ADR), other than listed above, include: raised liver enzymes, headache, dizziness. Uncommon ADRs include: hyperkalaemia, confusion, bronchospasm, rash. Rapid and severe swelling of the face and/or body. Ibuprofen may also rarely cause irritable bowel syndrome symptoms.

Most NSAIDs penetrate poorly into the central nervous system (CNS). However, the COX enzymes are expressed constitutively in some areas of the CNS, meaning that even limited penetration may cause adverse effects such as somnolence and dizziness.

In very rare cases, ibuprofen can cause aseptic meningitis.

As with other drugs, allergies to NSAIDs might exist. While many allergies are specific to one NSAID, up to 1 in 5 people may have unpredictable cross-reactive allergic responses to other NSAIDs as well.

Drug Interactions

NSAIDs reduce renal blood flow and thereby decrease the efficacy of diuretics, and inhibit the elimination of lithium and methotrexate.

NSAIDs cause hypocoagulability, which may be serious when combined with other drugs that also decrease blood clotting, such as warfarin.

NSAIDS may aggravate hypertension (high blood pressure) and thereby antagonize the effect of antihypertensives, such as ACE Inhibitors.

Chirality

Most NSAIDs are chiral molecules (diclofenac is a notable exception). However, the majority are prepared in a racemic mixture. Typically, only a single enantiomer is pharmacologically active. For some drugs (typically profens), an isomerase enzyme exists *in vivo* which converts the inactive enantiomer into the active form, although its activity varies widely in individuals. This phenomenon is likely to be responsible for the poor correlation between NSAID efficacy and

plasma concentration observed in older studies, when specific analysis of the active enantiomer was not performed.

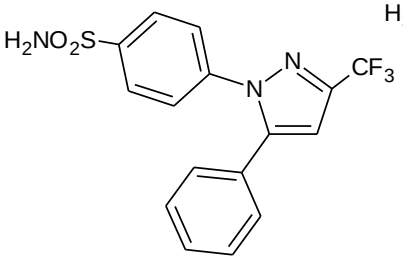
Ibuprofen and ketoprofen are now available in single, active enantiomer preparations (**dexibuprofen** and **dexketoprofen**), which purport to offer quicker onset and an improved side-effect profile. Naproxen has always been marketed as the single active enantiomer.

Selective COX inhibitors

The discovery of COX-2 in 1991 by Daniel L. Simmons at Brigham Young University raised the hope of developing an effective NSAID without the gastric problems characteristic of these agents. It was thought that selective inhibition of COX-2 would result in anti-inflammatory action without disrupting gastroprotective prostaglandins.

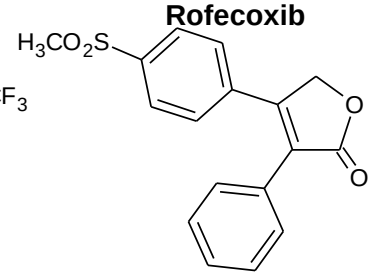
Selective COX-2 Inhibitors:-

Celecoxib



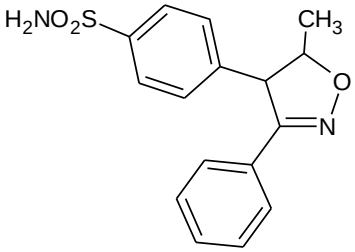
4-[5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

Rofecoxib



4-[4-(methylsulfonyl)phenyl]-3-phenylfuran-2(5*H*)-one

Valdecoxib



4-(5-methyl-3-phenyl-4,5-dihydro-1,2-oxazol-4-yl)benzenesulfonamide

COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. One of these is in the stomach lining, where prostaglandins serve a protective role, preventing the stomach mucosa from being eroded by its own acid. When nonselective COX-1/COX-2 inhibitors (such as aspirin, ibuprofen, and naproxen) lower stomach prostaglandin levels, these protective effects are lost and ulcers of the stomach or duodenum and potentially internal bleeding can result. COX-2 is an enzyme facultatively expressed in inflammation, and it is inhibition of COX-2 that produces the desirable effects of NSAIDs.

The relatively selective COX-2 inhibiting oxicam, meloxicam, was the first step towards developing a true COX-2 selective inhibitor. Coxibs, the newest class of NSAIDs, can be considered as true COX-2 selective inhibitors, and include celecoxib, rofecoxib, valdecoxib, parecoxib and etoricoxib.

Acetaminophen does also work mainly by blocking COX-2, unlike the newly developed COX-2 inhibitors it has weaker peripheral inhibitory activity.

Controversies with COX-2 inhibitors

While it was hoped that this COX-2 selectivity would reduce gastrointestinal adverse drug reactions (ADRs), there is little conclusive evidence that this is true. The original study touted by Searle (now part of Pfizer), showing a reduced rate of ADRs for celecoxib, was later revealed to be based on preliminary data - the final data showed no significant difference in ADRs when compared with diclofenac.

Rofecoxib however, which has since been withdrawn, had been shown to produce significantly fewer gastrointestinal ADRs compared with naproxen. This study, the VIGOR trial, raised the

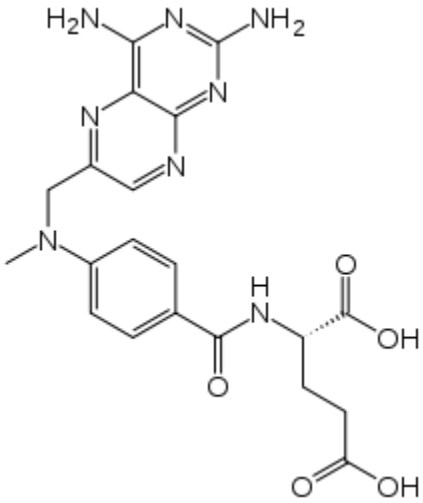
issue of the cardiovascular safety of the coxibs - a statistically insignificant increase in the incidence of myocardial infarctions was observed in patients on rofecoxib. Further data, from the APPROVe trial, showed a relative risk of cardiovascular events of 1.97 versus placebo - a result which resulted in the worldwide withdrawal of rofecoxib in October 2004.

COX-3 inhibitors

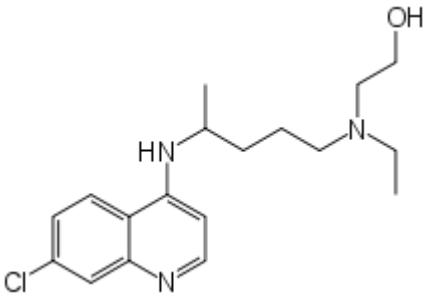
Simmons also co-discovered COX-3 in 2002 and analyzed this new isozyme's relation to paracetamol (acetaminophen), arguably the most widely used analgesic drug in the world. The authors postulated that inhibition of COX-3 could represent a primary central mechanism by which these drugs decrease pain and possibly fever.

The relevance of this research has been called into question as the putative COX-3 gene encodes proteins with completely different amino acid sequences than COX-1 or COX-2.

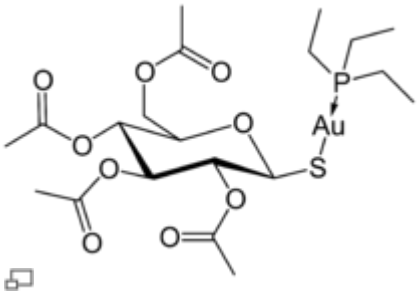
Disease-modifying antirheumatic drugs



Methotrexate



Hydroxychloroquine



Auranofin, a gold salt

Disease-modifying antirheumatic drugs (**DMARDs**) is a category of otherwise unrelated drugs defined by their use in rheumatoid arthritis to slow down disease progression. The term is often used in contrast to non-steroidal anti-inflammatory drug, which refers to agents that treat the inflammation but not the underlying cause.

The term "antirheumatic" can be used in similar contexts, but without making a claim about an effect on the course.

Terminology

Although their use was first propagated in rheumatoid arthritis (hence their name) the term has come to pertain to many other diseases, such as Crohn's disease, lupus erythematosus (SLE), idiopathic thrombocytopenic purpura (ITP), myasthenia gravis and various others. Many of these are autoimmune disorders, but others, such as ulcerative colitis, are probably not (there is no consensus on this).

The term was originally introduced to indicate a drug that reduced evidence of processes thought to underlie the disease, such as a raised erythrocyte sedimentation rate, reduced haemoglobin level, raised rheumatoid factor level and more recently, raised C-reactive protein level. More recently, the term has been used to indicate a drug that reduces the rate of damage to bone and cartilage. DMARDs can be further subdivided into traditional small molecular mass drugs synthesised chemically and newer 'biological' agents produced through genetic engineering.

Some DMARDs (eg the Purine synthesis inhibitors) are mild chemotherapeutics but use a side-effect of chemotherapy - *immunosuppression* - as its main therapeutical benefit.

Members

Drug	**Mechanism**
adalimumab	TNF inhibitor
azathioprine	Purine synthesis inhibitor
chloroquine and hydroxychloroquine (antimalarials)	Suppression of IL-1 & TNF-alpha, induce apoptosis of inflammatory cells and increase chemotactic factors
ciclosporin (Cyclosporin A)	calcineurin inhibitor
D-penicillamine	Reducing numbers of T-lymphocytes etc.
etanercept	TNF inhibitor
golimumab	TNF inhibitor
gold salts (sodium aurothiomalate, auranofin)	unknown - proposed mechanism: inhibits macrophage activation
infliximab	TNF inhibitor
leflunomide	Pyrimidine synthesis inhibitor

methotrexate (MTX)	Antifolate
minocycline	5-LO inhibitor
rituximab	chimeric monoclonal antibody against CD20 on B-cell surface
sulfasalazine (SSZ)	Suppression of IL-1 & TNF-alpha, induce apoptosis of inflammatory cells and increase chemotactic factors

Although these agents operate by different mechanisms, many of them can have similar impact upon the course of a condition.
Some of the drugs can be used in combination.

Alternatives

When treatment with DMARDs fails, cyclophosphamide or steroid pulse therapy is often used to stabilise uncontrolled autoimmune disease. Some severe autoimmune diseases are being treated with bone marrow transplants in clinical trials, usually after cyclophosphamide therapy has failed.
Combinations of DMARDs are often used together, because each drug in the combination can be used in smaller dosages than if it were given alone, thus reducing the risk of side effects.
Many patients receive an NSAID and at least one DMARD, sometimes with low-dose oral glucocorticoids. If disease remission is observed, regular NSAIDs or glucocorticoid treatment may no longer be needed. DMARDs help control arthritis but do not cure the disease. For that reason, if remission or optimal control is achieved with a DMARD, it is often continued at a maintenance dosage. Discontinuing a DMARD may reactivate disease or cause a “rebound flare”, with no assurance that disease control will be reestablished upon resumption of the medication, according to Arthritis & Rheumatism.
These agents are used to treat gout

Antigout agents

Gout also known as **podagra** when it involves thebig toe is a medical condition usually characterized by recurrent attacks of acute inflammatory arthritis—a red, tender, hot, swollen joint. The metatarsal-phalangeal joint at the base of the big toe is the most commonly affected (~50% of cases). However, it may also present as tophi, kidney stones, or urate nephropathy. It is caused by elevated levels of uric acid in the blood which crystallize and are deposited in joints, tendons, and surrounding tissues.
Diagnosis is confirmed clinically by the visualization of the characteristic crystals in joint fluid. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, or colchicine improves symptoms. Once the acute attack has subsided, levels of uric acid are usually lowered via lifestyle changes, and in those with frequent attacks allopurinol or probenicid

provide long-term prevention.
Gout has increased in frequency in recent decades affecting approximately 1–2% of the Western population at some point in their lives. The increase is believed to be due to increasing risk factors in the population, such as metabolic syndrome, longer life expectancy and changes in diet. Gout was historically known as "the disease of kings" or "rich man's disease".

Signs and symptoms

Gout presenting in the metatarsal-phalangeal joint of the big toe. Note the slight redness of the skin overlying the joint.

Gout can present in a number of ways, although the most usual is a recurrent attack of acute inflammatory arthritis (a red, tender, hot, swollen joint). The metatarsal-phalangeal joint at the base of the big toe is affected most often, accounting for half of cases. Other joints, such as the heels, knees, wrists and fingers, may also be affected. Joint pain usually begins over 2–4 hours and during the night. The reason for onset at night is due to the lower body temperature then. Other symptoms that may occur along with the joint pain include fatigue and a high fever.
Long-standing elevated uric acid levels (hyperuricemia) may result in other symptomatology, including hard, painless deposits of uric acid crystals known as tophi. Extensive tophi may lead to chronic arthritis due to bone erosion. Elevated levels of uric acid may also lead to crystals precipitating in the kidneys, resulting in stone formation and subsequent urate nephropathy.

Cause

Hyperuricemia is the underlying cause of gout. This can occur for a number of reasons, including diet, genetic predisposition, or underexcretion of urate, the salts of uric acid. Renal underexcretion of uric acid is the primary cause of hyperuricemia in about 90% of cases, while overproduction is the cause in less than 10%.[1] About 10% of people with hyperuricemia develop gout at some point in their lifetimes.[7] The risk, however, varies depending on the degree of hyperuricemia. When levels are between 415 and 530 µmol/L (7 and 8.9 mg/dL), the risk is 0.5% per year, while in those with a level greater than 535 µmol/L (9 mg/dL), the risk is 4.5% per year.

Lifestyle

Dietary causes account for about 12% of gout, and include a strong association with the consumption of alcohol, fructose-sweetened drinks, meat, and seafood. Other triggers include

physical trauma and surgery. Recent studies have found dietary factors once believed to be associated are in fact not, including the intake of purine-rich vegetables and total protein. Coffee, vitamin C and dairy products consumption and physical fitness appear to decrease the risk. This is believed to be partly due to their effect in reducing insulin resistance.

Genetics

The occurrence of gout is partly genetic, contributing to about 60% of variability in uric acid level. A few rare genetic disorders, including familial juvenile hyperuricemic nephropathy, medullary cystic kidney disease, phosphoribosylpyrophosphate synthetase superactivity, and hypoxanthine-guanine phosphoribosyltransferase deficiency as seen in Lesch-Nyhan syndrome, are complicated by gout.

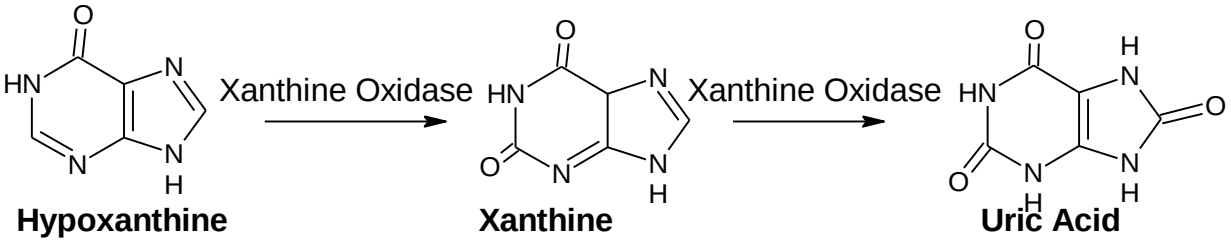
Medical conditions

Gout frequently occurs in combination with other medical problems. Metabolic syndrome, a combination of abdominal obesity, hypertension, insulin resistance and abnormal lipid levels occurs in nearly 75% of cases. Other conditions which are commonly complicated by gout include: polycythemia, lead poisoning, renal failure, hemolytic anemia, psoriasis, and solid organ transplants. A body mass index greater than or equal to 35 increases a male's risk of gout threefold. Chronic lead exposure and lead-contaminated alcohol are risk factors for gout due to the harmful effect of lead on kidney function.. Lesch-Nyhan syndrome is often associated with gouty arthritis.

Medication

Diuretics have been associated with attacks of gout. However, a low dose of hydrochlorothiazide does not seem to increase the risk. Other medicines that have been associated include niacin and aspirin (acetylsalicylic acid). Cyclosporine is also associated with gout, particularly when used in combination with hydrochlorothiazide, as are the immunosuppressive drugs ciclosporin and tacrolimus.

Pathophysiology



Gout is a disorder of purine metabolism, and occurs when its final metabolite, uric acid, crystallizes in the form of monosodium urate, precipitating in joints, on tendons, and in the surrounding tissues. These crystals then trigger a local immune-mediated inflammatory

reaction with one of the key proteins in the inflammatory cascade being interleukin 1β. An evolutionary loss of uricase, which breaks down uric acid, in humans and higher primates is what has made this condition so common.
The triggers for precipitation of uric acid are not well understood. While it may crystallize at normal levels, it is more likely to do so as levels increase. Other factors believed to be important in triggering an acute episode of arthritis include cool temperatures, rapid changes in uric acid levels, acidosis, articular hydration, and extracellular matrix proteins, such as proteoglycans, collagens, and chondroitin sulfate. The increased precipitation at low temperatures partly explains why the joints in the feet are most commonly affected. Rapid changes in uric acid may occur due to a number of factors, including trauma, surgery, chemotherapy, diuretics, and stopping or starting allopurinol.

Diagnosis

Gout on X-ray of a left foot. Typical location at the big toe joint. Note also the soft tissue swelling at the lateral border of the foot.

Gout may be diagnosed and treated without further investigations in someone with hyperuricemia and the classic podagra. Synovial fluid analysis should be done, however, if the diagnosis is in doubt. X-rays, while useful for identifying chronic gout, have little utility in acute attacks.

Synovial fluid

Spiked rods of uric acid (MSU) crystals from a synovial fluid sample photographed under a microscope with polarized light. Formation of uric acid crystals in the joints is associated with gout.

A definitive diagnosis of gout is based upon the identification of monosodium urate (MSU) crystals in synovial fluid or a tophus. All synovial fluid samples obtained from undiagnosed inflamed joints should be examined for these crystals. Under polarized light microscopy, they have a needle-like morphology and strong negative birefringence. This test is difficult to perform, and often requires a trained observer. The fluid must also be examined relatively quickly after aspiration, as temperature and pH affect their solubility.

Blood tests

Hyperuricemia is a classic feature of gout; gout occurs, however, nearly half of the time without hyperuricemia, and most people with raised uric acid levels never develop gout. Thus, the diagnostic utility of measuring uric acid level is limited. Hyperuricemia is defined as a

plasma urate level greater than 420 μmol/L (7.0 mg/dL) in males and 360 μmol/L (6.0 mg/dL) in females. Other blood tests commonly performed are white blood cell count, electrolytes, renal function, and erythrocyte sedimentation rate (ESR). However, both the white blood cells and ESR may be elevated due to gout in the absence of infection. A white blood cell count as high as 4.0×10^9/L (40,000/mm^3) has been documented.

Differential diagnosis

The most important differential diagnosis in gout is septic arthritis. This should be considered in those with signs of infection or those who do not improve with treatment. To help with diagnosis, a synovial fluid Gram stain and culture may be performed. Other conditions which present similarly include pseudogout and rheumatoid arthritis. Gouty tophi, in particular when not located in a joint, can be mistaken for basal cell carcinoma, or other neoplasms.

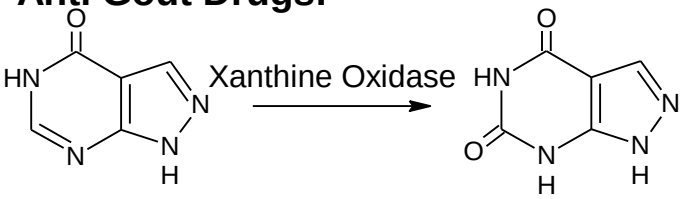
Prevention

Both lifestyle changes and medications can decrease uric acid levels. Dietary and lifestyle choices that are effective include reducing intake of food such as meat and seafood, consuming adequate vitamin C, limiting alcohol and fructose consumption, and avoiding obesity. A low-calorie diet in obese men decreased uric acid levels by 100 µmol/L (1.7 mg/dL). Vitamin C intake of 1,500 mg per day decreases the risk of gout by 45% compared to 250 mg per day.[1] Coffee, but not tea, consumption is associated with a lower risk of gout.[28] Gout may be secondary to sleep apnea via the release of purines from oxygen-starved cells. Treatment of apnea can lessen the occurrence of attacks.

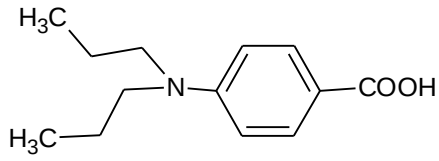
Treatment

The initial aim of treatment is to settle the symptoms of an acute attack. Repeated attacks can be prevented by different drugs used to reduce the serum uric acid levels. Ice applied for 20 to 30 minutes several times a day decreases pain. Options for acute treatment include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine and steroids, while options for prevention include allopurinol, probenecid and febuxostat. Lowering uric acid levels can cure the disease. Treatment of comorbidities is also important.

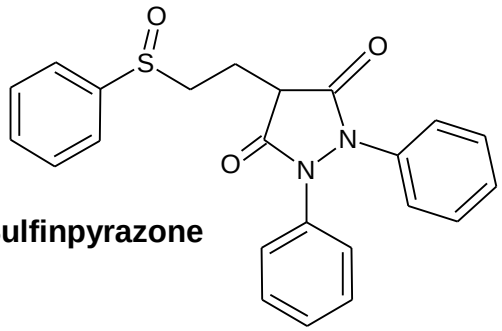
Anti Gout Drugs:-



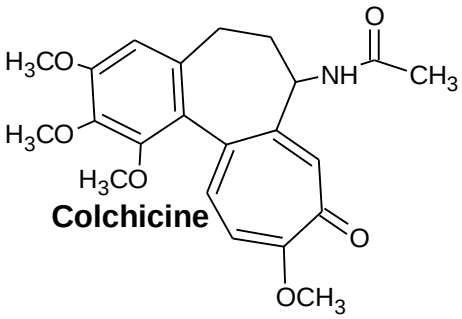
Allopurinol **Alloxanthine**



Probenicid



Sulfinpyrazone



Colchicine

NSAIDs

NSAIDs are the usual first-line treatment for gout, and no specific agent is significantly more or less effective than any other. Improvement may be seen within 4 hours, and treatment is recommended for 1–2 weeks. They are not recommended, however in those with certain other health problems, such as gastrointestinal bleeding, renal failure, or heart failure. While indomethacin has historically been the most commonly used NSAID, an alternative, such as ibuprofen, may be preferred due to its better side effect profile in the absence of superior effectiveness. For those at risk of gastric side effects from NSAIDs, an additional proton pump inhibitor may be given.

Colchicine

Colchicine is an alternative for those unable to tolerate NSAIDs. Its side effects (primarily gastrointestinal upset) limit its usage. Gastrointestinal upset, however, depends on the dose, and the risk can be decreased by using smaller yet still effective doses. Colchicine may interact with other commonly prescribed drugs, such as atorvastatin and erythromycin, among others.

Steroids

Glucocorticoids have been found to be as effective as NSAIDs and may be used if contraindications exist for NSAIDs.[1] They also lead to improvement when injected into the joint; the risk of a joint infection must be excluded, however, as they worsen this condition.

Pegloticase

Pegloticase (Krystexxa) was approved to treat gout in 2010. It will be an option for the 3% of people who are not adequately treated with other medications due to their association with severe allergic reactions. Pegloticase is administered as an intravenous infusion every two weeks. As of March 2010, however, no double blind, placebo controlled trials have been completed.

Prophylaxis

A number of medications are useful for preventing further episodes of gout, including allopurinol, probenecid, and febuxostat. They are not usually commenced until one to two weeks after an acute attack has resolved, due to theoretical concerns of worsening the attack, and are often used in combination with either an NSAID or colchicine for the first 3–6 months. They are not recommended until a person has suffered two attacks of gout, unless destructive joint changes, tophi, or urate nephropathy exist, as it is not until this point that medications have been found to be cost effective. Urate-lowering measures should be increased until serum uric acid levels are below 300-360 µmol/L (5.0-6.0 mg/dL) and are continued indefinitely. If these medications are being used chronically at the time of an attack, it is recommended they be continued.
Allopurinol blocks uric acid production, and is the most commonly used hypourecemic agent. Long term therapy is safe and well tolerated, and can be used in people with renal impairment or urate stones, although hypersensitivity occurs in a small number of individuals. Probenecid is effective for treating hyperuricemia, but has been found to be less effective than allopurinol. Febuxostat, a nonpurine inhibitor of xanthine oxidase, is now available as an alternative to allopurinol. It is approved in both Europe and the United States.

Prognosis

Without treatment, an acute attack of gout will usually resolve in 5 to 7 days. However, 60% of people will have a second attack within one year.[1] Those with gout are at increased risk of hypertension, diabetes mellitus, metabolic syndrome, and renal and cardiovascular disease and thus at increased risk of death. This may be partly due to its association with insulin resistance and obesity, but some of the increased risk appears to be independent.
Without treatment, episodes of acute gout may develop into chronic gout with destruction of joint surfaces, joint deformity, and painless tophi. These tophi occur in 30% of those who are untreated for five years, often in the helix of the ear, over the olecranon processes, or on the Achilles tendons. With aggressive treatment, they may dissolve. Kidney stones also frequently complicate gout, affecting between 10 and 40% of people, and occur due to low urine pH promoting the precipitation of uric acid. Other forms of chronic renal dysfunction may occur.

Epidemiology

Gout affects around 1–2% of the Western population at some point in their lifetimes, and is

becoming more common. Rates of gout have approximately doubled between 1990 and 2010. This rise is believed to be due to increasing life expectancy, changes in diet, and an increase in diseases associated with gout, such as metabolic syndrome and high blood pressure. A number of factors have been found to influence rates of gout, including age, race, and the season of the year. In men over the age of 30 and women over the age of 50, prevalence is 2%.

In the United States, gout is twice as likely in African American males as it is in European Americans. Rates are high among the peoples of the Pacific Islands and the Māori of New Zealand, but rare in Australian aborigines, despite a higher mean concentration of serum uric acid in the latter group. It has become common in China, Polynesia, and urban sub-Saharan Africa. Some studies have found attacks of gout occur more frequently in the spring. This has been attributed to seasonal changes in diet, alcohol consumption, physical activity, and temperature.

History

The word *gout* was initially used by Randolphus of Bocking, around 1200 AD. It is derived from the Latin word *gutta*, meaning "a drop" (of liquid).

Gout has, however, been known since antiquity. Historically, it has been referred to as "the king of diseases and the disease of kings" or "rich man's disease". The first documentation of the disease is from Egypt in 2,600 BC in a description of arthritis of the big toe. The Greek physician Hippocrates around 400 BC commented on it in his *Aphorisms*, noting its absence in eunuchs and premenopausal women. Aulus Cornelius Celsus (30 AD) described the linkage with alcohol, later onset in women, and associated kidney problems:

Again thick urine, the sediment from which is white, indicates that pain and disease are to be apprehended in the region of joints or viscera... Joint troubles in the hands and feet are very frequent and persistent, such as occur in cases of podagra and cheiragra. These seldom attack eunuchs or boys before coition with a woman, or women except those in whom the menses have become suppressed... some have obtained lifelong security by refraining from wine, mead and venery.

While in 1683, Thomas Sydenham, an English physician, described its occurrence in the early hours of the morning, and its predilection for older males:

Gouty patients are, generally, either old men, or men who have so worn themselves out in youth as to have brought on a premature old age - of such dissolute habits none being more common than the premature and excessive indulgence in venery, and the like exhausting passions. The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep. The pain is like that of a dislocation, and yet parts feel as if cold water were poured over them. Then follows chills and shivers, and a little fever... The night is passed in torture, sleeplessness, turning the part affected, and perpetual change of posture; the tossing about of body being as incessant as the pain of the tortured joint, and being worse as the fit comes on.

The Dutch scientist Antonie van Leeuwenhoek first described the microscopic appearance of

urate crystals in 1679. In 1848 English physician Alfred Baring Garrod realized that this excess uric acid in the blood was the cause of gout.

Research

A number of new medications are under study for treating gout, including anakinra, canakinumab, and rilonacept. A recombinant uricase enzyme (rasburicase) is available; its use, however, is limited, as it triggers an autoimmune response. Less antigenic versions are in development.

Opioid

An **opioid** is a chemical that works by binding to opioid receptors, which are found principally in the central nervous system and the gastrointestinal tract. The receptors in these organ systems mediate both the beneficial effects and the side effects of opioids.

The analgesic (painkiller) effects of opioids are due to decreased perception of pain, decreased reaction to pain as well as increased pain tolerance. The side effects of opioids include sedation, respiratory depression, and constipation. Opioids can cause cough suppression, which can be both an indication for opioid administration or an unintended side effect. Physical dependence can develop with ongoing administration of opioids, leading to a withdrawal syndrome with abrupt discontinuation. Opioids can produce a feeling of euphoria, motivating some to recreationally use opioids.

Although the term *opiate* is often used as a synonym for *opioid*, the term *opiate* is properly limited to only the natural alkaloids found in the resin of the opium poppy *(Papaver somniferum)*.

Classification

There are a number of broad classes of opioids:

- **Natural** opiates: alkaloids contained in the resin of the opium poppy, primarily morphine, codeine, and thebaine, but not papaverine and noscapine which have a different mechanism of action; The following could be considered natural opiates: The leaves from Mitragyna speciosa (also known as Kratom) contain a few naturally-occurring opioids, active via Mu- and Delta receptors. Salvinorin A, found naturally in the Salvia divinorum plant, is a kappa-opioid receptor agonist.
- **Semi-synthetic** opioids: created from the natural opiates, such as hydromorphone, hydrocodone, oxycodone, oxymorphone, desomorphine, diacetylmorphine (heroin), nicomorphine, dipropanoylmorphine, benzylmorphine and ethylmorphine and buprenorphine;

- **Fully synthetic** opioids: such as fentanyl, pethidine, methadone, tramadol and dextropropoxyphene;
- **Endogenous** opioid peptides, produced naturally in the body, such as endorphins, enkephalins, dynorphins, and endomorphins.
- There are also drugs such as tramadol and tapentadol that are chemically not of the opioid class, but do have agonist actions at the μ-opioid receptor. Although their exact mechanism of action is not fully understood, they both have a dual mode of action, the second mode of action appearing to be on the noradrenergic and serotonergic systems. This second mechanism of action was discovered during testing in where the drugs showed signs of analgesia even when naloxone, an opioid antagonist, was administered.

Some minor opium alkaloids and various substances with opioid action are also found elsewhere, including molecules present in Kratom, *Corydalis*, and *Salvia divinorum* plants and some species of poppy aside from *Papaver somniferum* and there are strains which produce copious amounts of thebaine, an important raw material for making many semi-synthetic and synthetic opioids. Of all of the more than 120 poppy species, only two produce morphine.

Amongst analgesics are a small number of agents which act on the central nervous system but not on the opioid receptor system and therefore have none of the other (narcotic) qualities of opioids although they may produce euphoria by relieving pain—a euphoria that, because of the way it is produced, does not form the basis of habituation, physical dependence, or addiction. Foremost amongst these are nefopam, orphenadrine, and perhaps phenyltoloxamine and/or some other antihistamines. Tricyclic antidepressants have painkilling effect as well, but they're thought to do so by indirectly activating the endogenous opioid system. The remainder of analgesics work peripherally (i.e., not on the brain or spinal cord). Research is starting to show that morphine and related drugs may indeed have peripheral effects as well, such as morphine gel working on burns. Paracetamol is predominantly a centrally acting analgesic (non-narcotic) which mediates its effect by action on descending serotoninergic (5-hydroxy triptaminergic) pathways, to increase 5-HT release (which inhibits release of pain mediators). It also decreases cyclo-oxygenase activity. It has recently been discovered that most or all of the therapeutic efficacy of paracetamol is due to a metabolite (AM404, making paracetamol a prodrug) which enhances the release of serotonin and also interacts as with the cannabinoid receptors by inhibiting the uptake of anandamide.

It has been discovered in 1953, that the human body, as well as those of some other animals, naturally produce minute amounts of morphine and codeine and possibly some of their simpler derivatives like heroin and dihydromorphine, in addition to the well known endogenous opioid peptides. Some bacteria are capable of producing some semi-synthetic opioids such as hydromorphone and hydrocodone when living in a solution containing morphine or codeine respectively.

Many of the alkaloids and other derivatives of the opium poppy are not opioids or narcotics; the best example is the smooth-muscle relaxant papaverine. Noscapine is a marginal case as it does have CNS effects but not necessarily similar to morphine, and it is probably in a category

all its own. Dextromethorphan (the stereoisomer of levomethorphan, a semi-synthetic opioid agonist) and its metabolite dextrorphan have no opioid analgesic effect at all despite their structural similarity to other opioids; instead they are potent NMDA antagonists and sigma 1 and 2-receptor agonists and are used in many over-the-counter cough suppressants. Salvinorin A is a unique selective, powerful κ-opioid receptor agonist. It is not properly considered an opioid nevertheless, because 1) chemically, it is not an alkaloid; and 2) it has no typical opioid properties: absolutely no anxiolytic or cough-suppressant effects. It is instead a powerful hallucinogen.

Pharmacology

Opioids bind to specific opioid receptors in the central nervous system and other tissues. There are three principal classes of opioid receptors, μ, κ, δ (mu, kappa, and delta), although up to seventeen have been reported, and include the ε, ι, λ, and ζ (Epsilon, Iota, Lambda and Zeta) receptors. Conversely, σ (Sigma) receptors are no longer considered to be opioid receptors because: their activation is not reversed by the opioid inverse-agonist naloxone, they do not exhibit high-affinity binding for classical opioids, and they are stereoselective for dextro-rotatory isomers while the other opioid receptors are stereo-selective for laevo-rotatory isomers. In addition, there are three subtypes of μ-receptor: μ_1 and μ_2, and the newly discovered μ_3. Another receptor of clinical importance is the opioid-receptor-like receptor 1 (ORL1), which is involved in pain responses as well as having a major role in the development of tolerance to μ-opioid agonists used as analgesics. These are all G-protein coupled receptors acting on GABAergic neurotransmission.The pharmacodynamic response to an opioid depends upon the receptor to which it binds, its affinity for that receptor, and whether the opioid is an agonist or an antagonist. For example, the supraspinal analgesic properties of the opioid agonist morphine are mediated by activation of the μ_1 receptor; respiratory depression and physical dependence by the μ_2 receptor; and sedation and spinal analgesia by the κ receptor. Each group of opioid receptors elicits a distinct set of neurological responses, with the receptor subtypes (such as μ_1 and μ_2 for example) providing even more [measurably] specific responses. Unique to each opioid is its distinct binding affinity to the various classes of opioid receptors (e.g. the μ, κ, and δ opioid receptors are activated at different magnitudes according to the specific receptor binding affinities of the opioid). For example, the opiate alkaloid morphine exhibits high-affinity binding to the μ-opioid receptor, while ketazocine exhibits high affinity to κ receptors. It is this combinatorial mechanism that allows for such a wide class of opioids and molecular designs to exist, each with its own unique effect profile. Their individual molecular structure is also responsible for their different duration of action, whereby metabolic breakdown (such as N-dealkylation) is responsible for opioid metabolism.

Drug	Relative Potency[3]	Nonionized Fraction	Protein Binding	Lipid Solubility[4]
Morphine	*1*	++	++	+
Meperidine	0.1	+	+++	++
Hydromorphone	10			
Alfentanil	10-25	++++	++++	+++
Fentanyl	75-125	+	+++	++++
Remifentanil	250	+++	+++	++
Sufentanil	500-1000	++	++++	++++
Etorphine	1000-3000			
		+ very low, ++ low, +++ high, ++++ very high		

Uses

Prescription use

Opioids have long been used to treat acute pain (such as post-operative pain). They have also been found to be invaluable in palliative care to alleviate the severe, chronic, disabling pain of terminal conditions such as cancer, and degenerative conditions such as rheumatoid arthritis. Contrary to popular belief, high doses are not necessarily required to control the pain of advanced or end-stage disease, so long as the effects of tolerance (which means a physical reaction which makes the body immune to analgesic as well as mental effects of opiates, narcotics, and others) allow patients to often require a median dose in such patients being only 15 mg oral morphine every four hours (90 mg/24 hours). This means that 50% of patients manage on lower doses, and requirements can level off for many months at a time, depending on severity of pain, which varies. This is despite the fact that opioids have some of the greatest potential for tolerance of any category of drugs, which essentially means in many cases, opioids are a successful long-term care strategy for those in chronic pain as well as acute pain.

In recent years there has been an increased use of opioids in the management of non-malignant chronic pain. This practice has grown from over 30 years experience in palliative care of long-term use of strong opioids which has shown that addiction is rare when the drug is being used for pain relief. The basis for the occurrence of iatrogenic addiction to opioids in this setting being several orders of magnitude lower than the general population is the result of a combination of factors. Open and voluminous communication and meticulous documentation amongst patient, caretakers, physicians, and pharmacists is one part of this; the aggressive and consistent use of opioid rotation, adjuvant analgesics, potentiators, and drugs which deal with other elements of the pain (NSAIDS) and opioid side effects both improve the prognosis for the patient and appear to contribute to the rarity of addiction in these cases. Unfortunately, in

most countries the use of opioids is subject to complex legal regulations, which often impede proper medical use for pain control and thus result in unnecessary suffering for patients.

United States

The sole clinical indications for opioids in the United States, according to *Drug Facts and Comparisons,* 2005, are:

- Moderate to severe pain, *i.e.*, to provide analgesia or, in surgery, to induce and maintain anesthesia, as well as allaying patient apprehension right before the procedure. Fentanyl, oxymorphone, hydromorphone, and morphine are most commonly used for this purpose, in conjunction with other drugs such as scopolamine, short and intermediate-acting barbiturates, and benzodiazepines, especially midazolam which has a rapid onset of action and lasts shorter than diazepam(Valium) or similar drugs. The combination of morphine (or sometimes hydromorphone) with alprazolam(Xanax) or midazolam(Dormicum) or other similar benzodiazepines with or without scopolamine (rarely replaced with or used alongside Compazine, Zofran or other anti-nauseants) is colloquially called "Milk of Amnesia" amongst anesthesiologists, hospital pharmacists, physicians, radiologists, patients and others. The enhancement of the effects of each drug by the others is useful in troublesome procedures like endoscopies, complicated and difficult deliveries (pethidine and its relatives and piritramide where it is used are favoured by many practitioners with morphine and derivatives as the second line), incision & drainage of severe abcesses, intraspinal injections, and minor and moderate-impact surgical procedures in patients unable to have general anesthesia due to allergy to some of the drugs involved or other concerns.
- Cough (codeine, dihydrocodeine, ethylmorphine (dionine), hydromorphone and hydrocodone, with morphine or methadone as a last resort.)
- Diarrhea (generally loperamide, difenoxin or diphenoxylate; but paregoric, powdered opium or laudanum or morphine may be used in some cases of severe diarrheal diseases, e.g. cholera); also diarrhea secondary to Irritable Bowel Syndrome (Codeine, paregoric, diphenoxylate, difenoxin, loperamide, laudanum)
- Anxiety due to shortness of breath (oxymorphone and dihydrocodeine only)
- Opioid dependence (methadone and buprenorphine only)

In the U.S., doctors virtually never prescribe opioids for psychological relief (with the narrow exception of anxiety due to shortness of breath), despite their extensively reported psychological benefits, and the widespread use of opiates in depression and anxiety up until the mid 1950s. There are virtually no exceptions to this practice, even in circumstances where researchers have reported opioids to be especially effective and where the possibility of addiction or diversion is very low—for example, in the treatment of senile dementia, geriatric depression, and psychological distress due to chemotherapy or terminal diagnosis.

Opioids are often used in combination with adjuvant analgesics (drugs which have an indirect effect on the pain). In palliative care, opioids are not recommended for sedation or anxiety

because experience has found them to be ineffective agents in these roles. Some opioids are relatively contraindicated in renal failure because of the accumulation of the parent drug or their active metabolites (e.g. morphine and oxycodone). Age (young or old) is not a contraindication to strong opioids. Some synthetic opioids such as pethidine have metabolites which are actually neurotoxic and should therefore be used only in acute situations.

History

Non-clinical use was criminalized in the U.S by the Harrison Narcotics Tax Act of 1914, and by other laws worldwide. Since then, nearly all non-clinical use of opioids has been rated zero on the scale of approval of nearly every social institution. However, in United Kingdom the 1926 report of the Departmental Committee on Morphine and Heroin Addiction under the Chairmanship of the President of the Royal College of Physicians reasserted medical control and established the "British system" of control—which lasted until the 1960s; in the U.S. the Controlled Substances Act of 1970 markedly relaxed the harshness of the Harrison Act.

Before the twentieth century, institutional approval was often higher, even in Europe and America. In some cultures, approval of opioids was significantly higher than approval of alcohol.

Global shortage of poppy-based medicines

Morphine and other poppy-based medicines have been identified by The World Health Organization as essential in the treatment of severe pain. However, only six countries use 77% of the world's morphine supplies, leaving many emerging countries lacking in pain relief medication. The current system of supply of raw poppy materials to make poppy-based medicines is regulated by the International Narcotics Control Board under the provision of the 1961 Single Convention on Narcotic Drugs. The amount of raw poppy materials that each country can demand annually based on these provisions must correspond to an estimate of the country's needs taken from the national consumption within the preceding two years. In many countries, underprescription of morphine is rampant because of the high prices and the lack of training in the prescription of poppy-based drugs. The World Health Organization is now working with different countries' national administrations to train healthworkers and to develop national regulations regarding drug prescription to facilitate a greater prescription of poppy-based medicines.

Another idea to increase morphine availability is proposed by the Senlis Council, who suggest, through their proposal for Afghan Morphine, that Afghanistan could provide cheap pain relief solutions to emerging countries as part of a second-tier system of supply that would complement the current INCB regulated system by maintaining the balance and closed system that it establishes while providing finished product morphine to those suffering from severe pain and unable to access poppy-based drugs under the current system.

Adverse effects

Common adverse reactions in patients taking opioids for pain relief include: nausea and vomiting, drowsiness, itching, dry mouth, miosis, and constipation.

Infrequent adverse reactions in patients taking opioids for pain relief include: dose-related respiratory depression (especially with more potent opioids), confusion, hallucinations, delirium, urticaria, hypothermia, bradycardia/tachycardia, orthostatic hypotension, dizziness, headache, urinary retention, ureteric or biliary spasm, muscle rigidity, myoclonus (with high doses), and flushing (due to histamine release, except fentanyl and remifentanil).

Opioid-induced hyperalgesia has been observed in some patients, whereby individuals using opioids to relieve pain may paradoxically experience more pain as a result of their medication. This phenomenon, although uncommon, is seen in some palliative care patients, most often when dose is escalated rapidly. If encountered, rotation between several different opioid analgesics may mitigate the development of hyperalgesia.

Both therapeutic and chronic use of opioids can compromise the function of the immune system. Opioids decrease the proliferation of macrophage progenitor cells and lymphocytes, and affect cell differentiation (Roy & Loh, 1996). Opioids may also inhibit leukocyte migration. However the relevance of this in the context of pain relief is not known.

Men who are taking moderate to high doses of an opioid analgesic long-term are likely to have subnormal testosterone levels, which can lead to osteoporosis and decreased muscle strength if left untreated. Therefore, total and free testosterone levels should be monitored in these patients; if levels are suboptimal, testosterone replacement therapy, preferably with patches or transdermal preparations, should be given. Also, prostate-specific antigen levels should be monitored.

Treating opioid adverse effects

Nausea: tolerance occurs within 7–10 days, during which antiemetics (e.g. low dose haloperidol 1.5–3 mg once at night) are very effective.[Due to severe side effects such as tardive dyskinesia, haloperidol is currently rarely used. A related drug, Compazine (prochlorperazine) is more often used, although it has similar risks. (Stronger antiemetics such as ondansetron or tropisetron may be indicated if nausea is severe or continues for an extended period, although these tend to be avoided due to their high cost unless nausea is really problematic. A cheaper alternative is dopamine antagonists, e.g. domperidone and metoclopramide. Domperidone does not cross the blood-brain barrier, so blocks opioid emetic action in the chemoreceptor trigger zone without adverse central anti-dopaminergic effects (not available in the U.S.) Some antihistamines with anti-cholinergic properties (e.g. orphenadrine or diphenhydramine) may also be effective. The first-generation anti-histamine hydroxyzine is very commonly used, with the added advantages of not causing movement disorders, and also possessing analgesic-sparing properties.

- 5-HT_3 antagonists (e.g. ondansetron)
- Dopamine antagonists (e.g. domperidone)
- Anti-cholinergic antihistamines (e.g. diphenhydramine)

Vomiting: this is due to gastric stasis (large volume vomiting, brief nausea relieved by vomiting, oesophageal reflux, epigastric fullness, early satiation), besides direct action on the vomiting centre of the brain. Vomiting can thus be prevented by prokinetic agents (e.g. domperidone or metoclopramide 10 mg every eight hours). If vomiting has already started, these drugs need to be administered by a non-oral route (e.g. subcutaneous for metoclopramide, rectally for domperidone).

- Prokinetic agents (e.g. domperidone)
- Anti-cholinergic agents (e.g. orphenadrine)

Drowsiness: tolerance usually develops over 5–7 days, but if troublesome, switching to an alternative opioid often helps. Certain opioids such as morphine and diamorphine (heroin) tend to be particularly sedating, while others such as oxycodone and meperidine (pethidine) tend to produce less sedation, but individual patients responses can vary markedly and some degree of trial and error may be needed to find the most suitable drug for a particular patient. Treatment is at any rate possible - CNS stimulants are generally effective.

- Stimulants (e.g. caffeine, modafinil, amphetamine)

Itching: tends not to be a severe problem when opioids are used for pain relief, but if required then antihistamines are useful for counteracting itching. Non-sedating antihistamines such as fexofenadine are preferable so as to avoid increasing opioid induced drowsiness, although some sedating antihistamines such as orphenadrine may be helpful as they produce a synergistic analgesic effect which allows smaller doses of opioids to be used while still producing effective analgesia. For this reason some opioid/antihistamine combination products have been marketed, such as Meprozine (meperidine/promethazine) and Diconal (dipipanone/cyclizine), which may also have the added advantage of reducing nausea as well.

- Antihistamines (e.g. fexofenadine)

Constipation: develops in 99% of patients[on opioids and since tolerance to this problem does not develop, nearly all patients on opioids will need a laxative. Over 30 years experience in palliative care has shown that most opioid constipation can be successfully prevented: "Constipation ... is treated [with laxatives and stool-softeners]" (Burton 2004, 277). According to Abse, "It is very important to watch out for constipation, which can be severe" and "can be a very considerable complication" (Abse 1982, 129) if it is ignored. Peripherally acting opioid antagonists such as alvimopan (Entereg) and methylnaltrexone (Relistor) have been found to effectively relieve opioid induced constipation without affecting analgesia or triggering withdrawal symptoms, although alvimopan is contraindicated in patients who have taken opioids for more than seven days, is only FDA-approved for 15 doses or less, and may increase

risk of heart attack. For mild cases, a lot of water (around 1.5 L/day) and fiber might suffice (in addition to the laxative and stool-softeners).

- Stool-softening and peristalsis-promoting laxatives (e.g. docusate in combination with bisacodyl or senna).
- Peripherally-acting opioid antagonists (e.g. methylnaltrexone)
- High water intake and dietary fiber

For more severe and/or chronic cases, the drugs that are used work by not increasing peristalsis, but by preventing water uptake in the intestine, leading to a softer stool with a larger component of water, and, additionally, by acidifying the environment inside the intestine, which both decreases water uptake and enhances peristalsis (e.g. lactulose, which is controversially noted as a possible probiotic). The following drugs are generally efficacious:

- Polyethylene glycol 3350±10% dalton powder for solution (MiraLax, GlycoLax) 8.5-34g daily.
- Lactulose syrup 10g/15mL 30-45mL twice daily.

One medicine provider, Napp, claim to have solved this problem by combining Oxicodone with an opioid suppressor, Naloxone, in a form which does not pass through the body-brain barrier. Thus, the constipation effect is suppressed, but not the pain reduction. Their product is marketed under the names Targiniq or Targinact.

Respiratory depression: although this is the most serious adverse reaction associated with opioid use it usually is seen with the use of a single, intravenous dose in an opioid-naive patient. In patients taking opioids regularly for pain relief, tolerance to respiratory depression occurs rapidly, so that it is not a clinical problem. Several drugs have been developed which can block respiratory depression completely even from high doses of potent opioids, without affecting analgesia, although the only respiratory stimulant currently approved for this purpose is doxapram, which has only limited efficacy in this application. Newer drugs such as BIMU-8 and CX-546 may however be much more effective.

- Respiratory stimulants: carotid chemoreceptor agonists (e.g. doxapram), 5-HT_4 agonists (e.g. BIMU8), δ-opioid agonists (e.g. BW373U86)
- Opioid antagonists (e.g. naloxone)

Finally, *all* opioid effects (adverse or otherwise) can readily be reversed with an opioid antagonist (more exactly, an inverse agonist) such as naloxone or naltrexone. These competitive antagonists bind to the opioid receptors with higher affinity than agonists but do not activate the receptors. This displaces the agonist, attenuating and/or reversing the agonist effects. However, the elimination half-life of naloxone can be shorter than that of the opioid itself, so repeat dosing or continuous infusion may be required, or a longer acting antagonist such as nalmefene may be used. In patients taking opioids regularly it is essential that the opioid is only partially reversed to avoid a severe and distressing reaction of waking in

excruciating pain. This is achieved by not giving a full dose (e.g. naloxone 400 µg) but giving this in small doses (e.g. naloxone 40 µg) until the respiratory rate has improved. An infusion is then started to keep the reversal at that level, while maintaining pain relief.

Safety

Studies over the past 20 years have repeatedly shown opioids to be safe when they are used correctly. In the UK two studies have shown that double doses of bedtime morphine did not increase overnight deaths, and that sedative dose increases were not associated with shortened survival (n=237). Another UK study showed that the respiratory rate was not changed by morphine given for breathlessness to patients with poor respiratory function (n=15). In Australia, no link was found between doses of opioids, benzodiazepines or haloperidol and survival. In Taiwan, a study showed that giving morphine to treat breathlessness on admission and in the last 48 hours did not affect survival. The survival of Japanese patients on high dose opioids and sedatives in the last 48 hours was the same as those not on such drugs.[25] In U.S. patients whose ventilators were being withdrawn, opioids did not speed death, while benzodiazepines resulted in longer survival (n=75). Morphine given to elderly patients in Switzerland for breathlessness showed no effect on respiratory function (n=9, randomised controlled trial). Injections of morphine given subcutaneously to Canadian patients with restrictive respiratory failure did not change their respiratory rate, respiratory effort, arterial oxygen level, or end-tidal carbon dioxide levels. Even when opioids are given intravenously, respiratory depression is not seen.

Carefully titrating the dose of opioids can provide for effective pain relief while minimizing adverse effects. Morphine and diamorphine have been shown to have a wider therapeutic range or "safety margin" than some other opioids. It is impossible to tell which patients need low doses and which need high doses, so all have to be started on low doses, unless changing from another strong opioid.

Opioid analgesics do not cause any specific organ toxicity, unlike many other drugs, such as aspirin and acetaminophen. They are not associated with upper gastrointestinal bleeding and renal toxicity.

Tolerance

Tolerance is the process whereby neuroadaptation occurs (through receptor desensitization) resulting in reduced drug effects. Tolerance is more pronounced for some effects than for others; tolerance occurs quickly to the effects on mood, itching, urinary retention, and respiratory depression, but occurs more slowly to the analgesia and other physical side effects. However, tolerance does not develop to constipation or miosis (the constriction of the pupil of the eye to less than or equal to two millimeters).Tolerance to opioids is attenuated by a number of substances, including:

- calcium channel blockers

- intrathecal magnesium and zinc
- NMDA antagonists, such as dextromethorphan or ketamine
- cholecystokinin antagonists, such as proglumide
- Newer agents such as the phosphodiesterase inhibitor ibudilast have also been researched for this application.

Magnesium and zinc deficiency speed up the development of tolerance to opioids and relative deficiency of these minerals is quite common due to low magnesium/zinc content in food and use of substances which deplete them including diuretics (such as alcohol, caffeine/theophylline) and smoking. Reducing intake of these substances and taking zinc/magnesium supplements may slow the development of tolerance to opiates.

Dependence

Dependence is characterised by extremely unpleasant withdrawal symptoms that occur if opioid use is abruptly discontinued after tolerance has developed. The withdrawal symptoms include severe dysphoria, sweating, nausea, rhinorrea, depression, severe fatigue, vomiting and pain. Slowly reducing the intake of opioids over days and weeks will reduce or eliminate the withdrawal symptoms. The speed and severity of withdrawal depends on the half-life of the opioid; heroin and morphine withdrawal occur more quickly and are more severe than methadone withdrawal, but methadone withdrawal takes longer. The acute withdrawal phase is often followed by a protracted phase of depression and insomnia that can last for months. The symptoms of opioid withdrawal can also be treated with other medications, such as clonidine, antidepressants and benzodiazepines, but with a low efficacy.

Addiction

Addiction is the process whereby physical and/or psychological dependence develops to a drug - including opioids. The withdrawal symptoms can reinforce the addiction, driving the user to continue taking the drug. Psychological addiction is more common in people taking opioids recreationally.

Misuse

Drug misuse is the use of drugs for reasons other than what the drug was prescribed for. Opioids are primarily misused due to their ability to produce euphoria.

Examples

Endogenous opioids

Opioid-peptides that are produced in the body include:

- Endorphins
- Enkephalins
- Dynorphins
- Endomorphins

β-endorphin is expressed in Pro-opiomelanocortin (POMC) cells in the arcuate nucleus and in a small population of neurons in the brainstem, and acts through μ-opioid receptors. β-endorphin has many effects, including on sexual behavior and appetite. β-endorphin is also secreted into the circulation from pituitary corticotropes and melanotropes. α-neoendorphin is also expressed in POMC cells in the arcuate nucleus.

[met]-enkephalin is widely distributed in the CNS; [met]-enkephalin is a product of the proenkephalin gene, and acts through μ and δ-opioid receptors. [leu]-enkephalin, also a product of the proenkephalin gene, acts through δ-opioid receptors.

Dynorphin acts through κ-opioid receptors, and is widely distributed in the CNS, including in the spinal cord and hypothalamus, including in particular the arcuate nucleus and in both oxytocin and vasopressin neurons in the supraoptic nucleus.

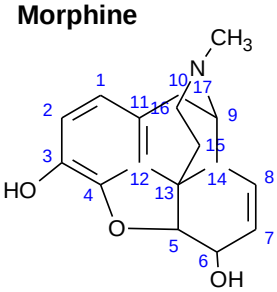
Endomorphin acts through μ-opioid receptors, and is more potent than other endogenous opioids at these receptors.

Opium alkaloids

Phenanthrenes naturally occurring in opium:

- Codeine
- Morphine
- Thebaine, Oripavine

Morphine



1) 3-methylation produce codeine (3-methyl morphine)

2) 3,6-dimethylation produce thiabaine (3,6-dimethyl morphine)

3) 3,6-diacetyl morphine is known as heroin

4) 7,8-dihydro-6-keto morphine is hydromorphone

5) 7,8-dihydro-6-keto-14 hydroxy morphine is oxomorphone

6) N-allyl-7,8-dihydro-6-keto-14 hydroxy normorphine is naloxone

N-cyclopropyl methyl-7,8-dihydro-6-keto-14 hydroxy normorphine (Naltreoxone)

SAR (Structure Activity relationship) of morphine

1. If 3-hydroxyl group is replaced by 3-H, activity decrease ten times
2. If 3-hydroxyl group is replaced by 3-methoxy group, analgesic activity decrease but compound becomes anti-tussive (codeine)
3. If 3-hydroxyl group is replaced by 3-acetyl group, activity decrease.
4. If 6-hydroxyl group is replaced by 6-acetyl group, activity increase ten times
5. If 7,8 double bound is reduced and 6-hydroxy is oxidized to keto group then activity increase 8 to 10 times (hydromorphone)
6. If 14-position of morphine is hydroxylated, activity increase (oxomorphome)
7. If basic nitrogen contains methyl then the drug is agonist on μ receptor (morphine) but methyl is replace by 3 – 5 carbon aliphatic or carbocyclic group compound becomes antagonist at μ receptor (Naloxone, naltreoxone) but k receptor agonist (pentazocin, nalbupine, butorphanol), when chain is increased 8-10 carbon then the compound becomes again μ receptor agonist (Fentanyl).

Preparations of mixed opium alkaloids, including papaveretum, are still occasionally used.**Semisynthetic derivatives**

- Diacetylmorphine (heroin)
- Dihydrocodeine
- Hydrocodone
- Hydromorphone
- Nicomorphine
- Oxycodone
- Oxymorphone

Synthetic opioids

Anilidopiperidines

- Fentanyl

- Alphamethylfentanyl
- Alfentanil
- Sufentanil
- Remifentanil
- Carfentanyl
- Ohmefentanyl

Phenylpiperidines

- Pethidine (meperidine)
- Ketobemidone
- MPPP
- Allylprodine
- Prodine
- PEPAP

Diphenylpropylamine derivatives

- Propoxyphene
- Dextropropoxyphene
- Dextromoramide
- Bezitramide
- Piritramide
- Methadone
- Dipipanone
- Levomethadyl Acetate (LAAM)
- Difenoxin
- Diphenoxylate
- Loperamide (used for diarrhoea, does not cross the blood-brain barrier)

Benzomorphan derivatives

- Dezocine - agonist/antagonist
- Pentazocine - agonist/antagonist
- Phenazocine

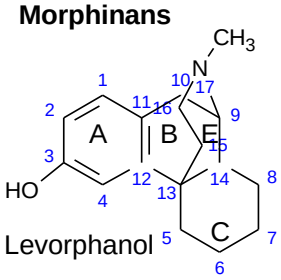
[edit] Oripavine derivatives

- Buprenorphine - partial agonist
- Dihydroetorphine
- Etorphine

Morphinan derivatives

- Butorphanol - agonist/antagonist
- Nalbuphine - agonist/antagonist
- Levorphanol
- Levomethorphan

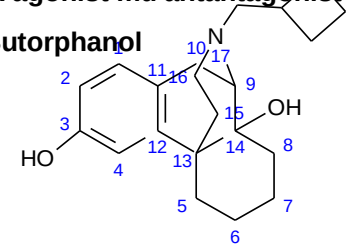
Morphinans



If D ring in morphine is removed or (epoxide) the remaining 4 ring skelton is known as morphinans (Levorphanol). leavo form of morphinan acts as analgesic but dextroform shows anti-tussive activity like Dextromethorphan (dextro rotatary methyl form of levorphanol)

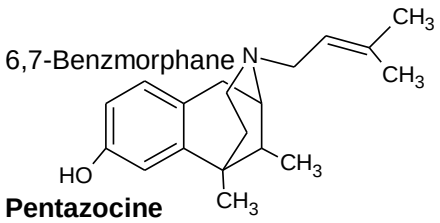
k agonist mu antantagonist

Butorphanol



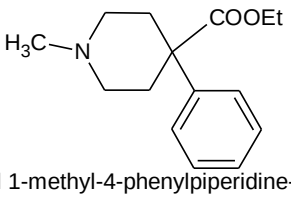
Others

- Lefetamine
- Meptazinol
- Tilidine
- Tramadol
- Tapentadol



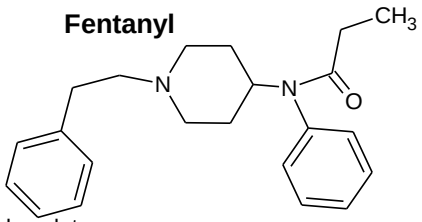
Pentazocine

Meperidine



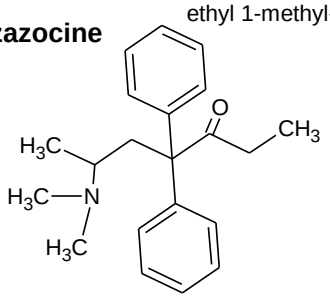
ethyl 1-methyl-4-phenylpiperidine-4-carboxylate

Fentanyl

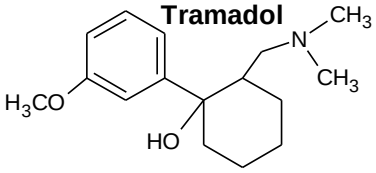


2,6 metheno-3-benzazocine

Methadone



Tramadol



Opioid antagonists

- Nalmefene
- Naloxone
- Naltrexone

ANTIPSYCHOTIC

An **antipsychotic** (or **neuroleptic**) is a tranquilizing psychiatric medication primarily used to manage psychosis (including delusions or hallucinations, as well as disordered thought), particularly in schizophrenia and bipolar disorder. A first generation of antipsychotics, known as typical antipsychotics, was discovered in the 1950s. Most of the drugs in the second generation, known as atypical antipsychotics, have been developed more recently, although the first atypical antipsychotic, clozapine, was discovered in the 1950s and introduced clinically in the 1970s. Both generations of medication tend to block receptors in the brain's dopamine pathways, but antipsychotic drugs encompass a wide range of receptor targets.

A number of harmful and undesired (adverse) effects have been observed, including lowered life expectancy, weight gain, enlarged breasts and milk discharge in men and women (hyperprolactinaemia), lowered white blood cell count (agranulocytosis), involuntary repetitive body movements (tardive dyskinesia), diabetes, an inability to sit still or remain motionless (akathisia), sexual dysfunction, a return of psychosis requiring increasing the dosage due to cells producing more neurochemicals to compensate for the drugs (tardive psychosis), and a potential for permanent chemical dependence leading to psychosis much worse than before treatment began, if the drug dosage is ever lowered or stopped (tardive dysphrenia).

Temporary withdrawal symptoms including insomnia, agitation, psychosis, and motor disorders may occur during dosage reduction of antipsychotics, and can be mistaken for a return of the underlying condition.

The development of new antipsychotics with fewer of these adverse effects and with greater relative effectiveness as compared to existing antipsychotics (efficacy), is an important ongoing field of research. The most appropriate drug for an individual patient requires careful consideration.

History

The original antipsychotic drugs were happened upon largely by chance and then tested for their effectiveness. The first, chlorpromazine, was developed as a surgical anesthetic. It was first used on psychiatric patients because of its powerful calming effect; at the time it was regarded as a "chemical lobotomy". Lobotomy at the time was used to treat many behavioral disorders, including psychosis, although its effect was to markedly reduce behavior and mental functioning of all types. However, chlorpromazine proved to reduce the effects of psychosis in a

more effective and specific manner than the extreme lobotomy-like sedation it was known for. The underlying neurochemistry involved has since been studied in detail, and subsequent antipsychotic drugs have been discovered by an approach that incorporates this sort of information.

Antipsychotics have long been known as neuroleptic drugs. The word *neuroleptic* was derived from the Greek: "νεῦρον" (*neuron*, originally meaning "sinew" but today referring to the nerves) and "λαμβάνω" (*lambanō*, meaning "take hold of"). Thus, the word means *taking hold of one's nerves*. This may refer to common side effects such as reduced activity, lethargy, and impaired motor control. Although these effects are unpleasant and in some cases harmful, they were at one time considered a reliable sign that the drug was working. The term "neuroleptic" is being abandoned in favor of "antipsychotic," which refers to the drug's desired effects. Typical antipsychotics have also been referred to as the major **tranquilizers**, because of their tendency to tranquilize and sedate. As with the term "neuroleptics," the term "major tranquilizers" is falling out of common and scientific use. The term "tranquilizers" now generally refers to drugs that are primarily intended to sedate—mostly the barbiturates and benzodiazepines, which were once referred to as the "minor tranquilizers."

Antipsychotics are broadly divided into two groups, the typical or first-generation antipsychotics and the atypical or second-generation antipsychotics. The typical antipsychotics are classified according to their chemical structure while the atypical antipsychotics are classified according to their pharmacological properties. These include serotonin-dopamine antagonists (see dopamine antagonist and serotonin antagonist), multi-acting receptor-targeted antipsychotics (MARTA, those targeting several systems), and dopamine partial agonists, which are often categorized as atypicals.

Usage

Common conditions with which antipsychotics might be used include schizophrenia, bipolar disorder and delusional disorder. Antipsychotics might also be used to counter psychosis associated with a wide range of other diagnoses, such as psychotic depression. However, not all symptoms require heavy medication and hallucinations and delusions should only be treated if they distress the patient or produce dangerous behaviors.

In addition, "antipsychotics" are increasingly used to treat non-psychotic disorders. For example, they are sometimes used off-label to manage aspects of Tourette syndrome or autism spectrum disorders. They have multiple off-label uses as an augmentation agent (i.e. in addition to another medication), for example in "treatment-resistant" depression or OCD. Despite the name, the off-label use of "antipsychotics" is said to involve deploying them as antidepressants, anti-anxiety drugs, mood stabilizers, cognitive enhancers, anti-aggressive, anti-impulsive, anti-suicidal and hypnotic (sleep) medications.

Antipsychotics have also been increasingly used off-label in cases of dementia in older people, and for various disorders and difficulties in children and teenagers. A survey of children with

pervasive developmental disorder found that 16.5% were taking an antipsychotic drug, most commonly to alleviate mood and behavioral disturbances characterized by irritability, aggression, and agitation. Recently, risperidone was approved by the US FDA for the treatment of irritability in children and adolescents with autism.

Antipsychotics are sometimes used as part of compulsory treatment via inpatient (hospital) commitment or outpatient commitment. This may involve various methods to persuade a person to take the medication, or actual physical force. Administration may rely on an injectable form of the drug rather than tablets. The injection may be of a long-lasting type known as a depot injection, usually applied at the top of the buttocks.

Due to the chronic nature of the treated disorders, antipsychotic medications, once started, are seldom discontinued, and the aim of the treatment is often to gradually reduce dosage to a minimum safe maintenance dose that is enough to control the symptoms. Only when the side-effects have become too severe and/or a patient have been symptom-free for a long periods of time, is discontinuation carefully attempted. One reason for this strategy is that discontinuation and restarting of neuroleptics tends to cause increasing nervous system malfunction, affecting the brainstem and autonomous nervous system that control vital body functions.

Side-effects

Antipsychotics are associated with a range of side effects. It is well-recognized that many people stop taking them (around two-thirds even in controlled drug trials) due in part to adverse effects. Extrapyramidal reactions include acute dystonias, akathisia, parkinsonism (rigidity and tremor), tardive dyskinesia, tachycardia, hypotension, impotence, lethargy, seizures, intense dreams or nightmares, and hyperprolactinaemia. Some of the side-effects will appear after the drug has been used only for a long time.

The most serious adverse effect associated with long-term antipsychotic use is lowered life expectancy. This has proved most controversial in regard to the use of antipsychotics in dementia in older people, worsened by alleged use to control and sedate rather than necessarily to treat. A 2009 systematic review of studies of schizophrenia also found decreased life expectancy associated with use of antipsychotics and argued that more studies were urgently needed, a call that had already been made when similar results were found in 2006.

In "healthy" individuals without psychosis, doses of antipsychotics can produce the so-called "negative symptoms" (e.g. emotional and motivational difficulties) associated with schizophrenia.

From a subjective perspective, antipsychotics heavily influence one's perceptions of pleasurable sensations, causing a severe reduction in feelings of desire, motivation, pensive thought, and awe. This does not coincide with the apathy and lack of motivation experienced by the negative symptoms of schizophrenia. Detrimental effects on short term memory, which affect the way one figures and calculates (although this also may be purely subjective), may also be observed

on high enough dosages. These are all the reasons why they are thought to affect "creativity". Also, for some individuals with schizophrenia, too much stress may cause "relapse".

Following are details concerning some of the side effects of antipsychotics:

- Antipsychotics, particularly atypicals, appear to cause diabetes mellitus and fatal diabetic ketoacidosis, especially (in US studies) in African Americans.
- Antipsychotics may cause pancreatitis.
- The atypical antipsychotics (especially olanzapine) seem to cause weight gain more commonly than the typical antipsychotics. The well-documented metabolic side effects associated with weight gain include diabetes, which can be life-threatening.
- Antipsychotics increase the likelihood of a fatal heart attack, with the risk of death increasing with dose and the length of time on the drug.
- Clozapine also has a risk of inducing agranulocytosis, a potentially dangerous reduction in the number of white blood cells in the body. Because of this risk, patients prescribed clozapine may need to have regular blood checks to catch the condition early if it does occur, so the patient is in no danger.
- One of the more serious of these side effects is tardive dyskinesia, in which the sufferer may show repetitive, involuntary, purposeless movements often of the lips, face, legs, or torso. It is believed that there is a greater risk of developing tardive dyskinesia with the older, typical antipsychotic drugs, although the newer antipsychotics are now also known to cause this disorder.
- A potentially serious side effect of many antipsychotics is that they tend to lower an individual's seizure threshold. Chlorpromazine and clozapine, in particular, have a relatively high seizurogenic potential. Fluphenazine, haloperidol, pimozide and risperidone exhibit a relatively low risk. Caution should be exercised in individuals that have a history of seizurogenic conditions such as epilepsy, or brain damage.
- Neuroleptic malignant syndrome, in which the drugs appear to cause the temperature regulation centers to fail, resulting in a medical emergency, as the patient's temperature suddenly increases to dangerous levels.
- Dysphoria.
- Sexual dysfunction, which may rarely continue after withdrawal, similar to Post-SSRI sexual dysfunction (PSSD).
- Dystonia, a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures.
- Hyperprolactinaemia. The breasts may enlarge and discharge milk, in both men and women due to abnormally-high levels of prolactin in the blood. Prolactin secretion in the pituitary is normally suppressed by dopamine. Drugs that block the effects of dopamine at the pituitary or deplete dopamine stores in the brain may cause the pituitary to secrete prolactin.
- There is evidence that exposure may cause demyelinating disease in laboratory animals.
- Following controversy over possible increased mortality (death) related to antipsychotics in indivdiuals with dementia, warnings have been added to packaging.

Continuous use of neuroleptics has been shown to decrease the total brain volume by 10% in macaque monkeys.

Some people suffer few apparent side effects from taking antipsychotic medication, whereas others may have serious adverse effects. Some side effects, such as subtle cognitive problems, may go unnoticed.

There is a possibility that the risk of tardive dyskinesia can be reduced by combining the anti-psychotics with diphenhydramine or benzatropine, although this remains to be established. Central nervous system damage is also associated with irreversible tardive akathisia and/or tardive dysphrenia.

Withdrawal

Withdrawal symptoms from antipsychotics may emerge during dosage reduction and discontinuation. Withdrawal symptoms can include nausea, emesis, anorexia, diarrhea, rhinorrhea, diaphoresis, myalgia, paresthesia, anxiety, agitation, restlessness, and insomnia. The psychological withdrawal symptoms can include psychosis, and can be mistaken for a relapse of the underlying disorder. Conversely, the withdrawal syndrome may also be a trigger for relapse. Better management of the withdrawal syndrome may improve the ability of individuals to discontinue antipsychotics.

Tardive dyskinesia can emerge as a physical withdrawal symptom, and may either gradually abate during the withdrawal phase, or become persistent. Withdrawal-related psychosis from antipsychotics is called "supersensitivity psychosis", and is attributed to increased number and sensitivity of brain dopamine receptors, due to blockade of dopaminergic receptors by the antipsychotics, which often leads to exacerbated symptoms in the absence of neuroleptic medication. Efficacy of antipsychotics may likewise be reduced over time, due to this development of drug tolerance.

Withdrawal effects may also occur when switching a person from one antipsychotic to another, (presumably due to variations of potency and receptor activity). Such withdrawal effects can include cholinergic rebound, an activation syndrome, and motor syndromes including dyskinesias. These adverse effects are more likely during rapid changes between antipsychotic agents, so making a gradual change between antipsychotics minimises these withdrawal effects. The British National Formulary recommends a gradual withdrawal when discontinuing antipsychotic treatment to avoid acute withdrawal syndrome or rapid relapse.

Efficacy

There have been a large number of studies of the efficacy of typical antipsychotics, and an increasing number on the more recent atypical antipsychotics.

The American Psychiatric Association and the UK National Institute for Health and Clinical Excellence recommend antipsychotics for managing acute psychotic episodes in schizophrenia or bipolar disorder, and as a longer-term maintenance treatment for reducing the likelihood of further episodes. They state that response to any given antipsychotic can be variable so that trials may be necessary, and that lower doses are to be preferred where possible. A number of studies have looked at levels of "compliance" or "adherence" with antipsychotic regimes and found that discontinuation (stopping taking them) by patients is associated with higher rates of relapse, including hospitalization.

Nevertheless, a 2009 systematic review and meta-analysis of trials in people diagnosed with schizophrenia found that less than half (41%) showed any therapeutic response to an antipsychotic, compared to 24% on placebo, and that there was a decline in treatment response over time, and possibly a bias in which trial results were published. In addition, a 2010 Cochrane Collaboration review of trials of Risperidone, one of the biggest selling antipsychotics and the first of the new generation to become available in generic form, found only marginal benefit compared with placebo and that, despite its widespread use, evidence remains limited, poorly reported and probably biased in favor of risperidone due to pharmaceutical company funding of trials. Another Cochrane review in 2009, of bipolar disorder, found the efficacy and risk/benefit ratio better for the traditional mood stabilizer lithium than for the antipsychotic Olanzapine as a first line maintenance treatment.

Antipsychotic polypharmacy (prescribing two or more antipsychotics at the same time for an individual) is said to be a common practice but not necessarily evidence-based or recommended, and there have been initiatives to curtail it. Similarly, the use of excessively high doses (often the result of polypharmacy) continues despite clinical guidelines and evidence indicating that it is usually no more effective but is usually more harmful.

A review by the US Agency for Healthcare Research and Quality found that much of the evidence for the off-label use of antipsychotics (for example, for depression, dementia, OCD, PTSD, Personality Disorders, Tourette's) was of insufficient scientific quality to support such use, especially as there was strong evidence of increased risks of stroke, tremors, significant weight gain, sedation, and gastrointestinal problems. A UK review of unlicensed usage in children and adolescents reported a similar mixture of findings and concerns.

Aggressive challenging behavior in adults with intellectual disability is often treated with antipsychotic drugs despite lack of an evidence base. A recent randomized controlled trial, however, found no benefit over placebo and recommended that the use of antipsychotics in this way should no longer be regarded as an acceptable routine treatment.

A 2006 Cochrane Collaboration review of controlled trials of antipsychotics in old age dementia reported that one or two of the drugs showed a modest benefit compared to placebo in managing aggression or psychosis, but that this was combined with a significant increase in serious adverse events. They concluded that this confirms that antipsychotics should not be

used routinely to treat dementia patients with aggression or psychosis, but may be an option in the minority of cases where there is severe distress or risk of physical harm to others.

Some doubts have been raised about the long-term effectiveness of antipsychotics for schizophrenia, in part because two large international World Health Organization studies found individuals diagnosed with schizophrenia tend to have better long-term outcomes in developing countries (where there is lower availability and use of antipsychotics and mental health problems are treated with more informal, community-led methods only) than in developed countries. The reasons for the differences are not clear, however, and various explanations have been suggested.

Some argue that the evidence for antipsychotics from discontinuation-relapse studies may be flawed, because they do not take into account that antipsychotics may sensitize the brain and provoke psychosis if discontinued, which may then be wrongly interpreted as a relapse of the original condition. Evidence from comparison studies indicates that at least some individuals with schizophrenia recover from psychosis without taking antipsychotics, and may do better in the long term than those that do take antipsychotics. Some argue that, overall, the evidence suggests that antipsychotics only help if they are used selectively and are gradually withdrawn as soon as possible and have referred to the "Myth of the antipsychotic".

A review of the methods used in trials of antipsychotics, despite stating that the overall quality is "rather good," reported issues with the selection of participants (including that in schizophrenia trials up to 90% of people who are generally suitable do not meet the elaborate inclusion and exclusion criteria, and that negative symptoms have not been properly assessed despite companies marketing the newer antipsychotics for these); issues with the design of trials (including pharmaceutical company funding of most of them, and inadequate experimental "blinding" so that trial participants could sometimes tell whether they were on placebo or not); and issues with the assessment of outcomes (including the use of a minimal reduction in scores to show "response," lack of assessment of quality of life or recovery, a high rate of discontinuation, selective highlighting of favorable results in the abstracts of publications, and poor reporting of side-effects).

Typicals versus atypicals

While the atypical (second-generation) antipsychotics were marketed as offering greater efficacy in reducing psychotic symptoms while reducing side effects (and Extrapyramidal symptoms in particular) than typical medications, the results showing these effects often lacked robustness, and the assumption was increasingly challenged even as atypical prescriptions were soaring. One review concluded there were no differences while another found that atypicals were "only moderately more efficacious". These conclusions were, however, questioned by another review, which found that clozapine, amisulpride, and olanzapine and risperidone were more effective Clozapine has appeared to be more effective than other atypical antipsychotics, although it has previously been banned due to its potentially lethal side effects. While controlled clinical trials of atypicals reported that extrapyramidal symptoms occurred in 5–15%

of patients, a study of bipolar disorder in a real world clinical setting found a rate of 63%, questioning the generalizability of the trials.

In 2005 the US government body NIMH published the results of a major independent (not funded by the pharmaceutical companies) multi-site, double-blind study (the CATIE project). This study compared several atypical antipsychotics to an older typical antipsychotic, perphenazine, among 1493 persons with schizophrenia. The study found that only olanzapine outperformed perphenazine in discontinuation rate (the rate at which people stopped taking it due to its effects). The authors noted an apparent superior efficacy of olanzapine to the other drugs in terms of reduction in psychopathology and rate of hospitalizations, but olanzapine was associated with relatively severe metabolic effects such as a major weight gain problem (averaging 44 pounds over 18 months) and increases in glucose, cholesterol, and triglycerides. The mean and maximal doses used for olanzapine were considerably higher than standard practice, and this has been postulated as a biasing factor that may explain olanzapine's superior efficacy over the other atypical antipsychotics studied, where doses were more in line with clinically relevant practices. No other atypical studied (risperidone, quetiapine, and ziprasidone) did better than the typical perphenazine on the measures used, nor did they produce fewer adverse effects than the typical antipsychotic perphenazine (a result supported by a meta-analysis by Dr. Leucht published in Lancet), although more patients discontinued perphenazine owing to extrapyramidal effects compared to the atypical agents (8% vs. 2% to 4%, P=0.002).

A phase 2 part of this CATIE study roughly replicated these findings. This phase consisted of a second randomization of the patients that discontinued taking medication in the first phase. Olanzapine was again the only medication to stand out in the outcome measures, although the results did not always reach statistical significance (which means they were not reliable findings) due in part to the decrease of power. The atypicals again did not produce fewer extrapyramidal effects than perphenazine. A subsequent phase was conducted that allowed clinicians to offer clozapine which was more effective at reducing medication drop-outs than other neuroleptic agents. However, the potential for clozapine to cause toxic side effects, including agranulocytosis, limits its usefulness.

It had been hoped that patient adherence to antipsychotics would be higher with the atypicals, but a 2008 review found that the data have failed to substantiate the notion that novel antipsychotic drug use leads to improved medication compliance and favorable clinical outcomes.[62]

Overall evaluations of the CATIE and other studies have led many researchers to question the first-line prescribing of atypicals over typicals, or even to question the distinction between the two classes.[63][64] In contrast, other researchers point to the significantly higher risk of tardive dyskinesia and EPS with the typicals and for this reason alone recommend first-line treatment with the atypicals, notwithstanding a greater propensity for metabolic adverse effects in the latter. The UK government organization NICE recently revised its recommendation favoring atypicals, to advise that the choice should be an individual one based on the particular profiles of the individual drug and on the patient's preferences.

The re-evaluation of the evidence has not necessarily slowed the bias towards prescribing the atypicals, however.

Common antipsychotics

First generation antipsychotics (Typical antipsychotic**)**

Phenothiazines

- **(Aliphatic Chain analogoues):-** Chlorpromazine (Thorazine, Largactil), Promazine, Trifluprомazine (Vesprin) Levomepromazine (Nozinan), Promethazine (Phenergan)
- **(Piperidinyl side chain analogoues):-** Thioridazine (Mellaril, Melleril), Mesoridazine
- **(Piperizinyl side chain analogoues):-**Trifluoperazine (Stelazine), Fluphenazine (Prolixin) - Available in decanoate (long-acting) form, Perphenazine (Trilafon), Prochlorperazine (Compazine), Periciazine
- **(Diphenyl butyl piperidine derivative):-**Pimozide (Orap)

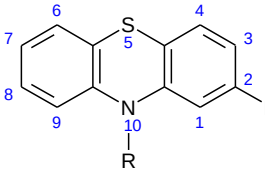
Butyrophenones

- Haloperidol (Haldol, Serenace), Droperidol (Droleptan)

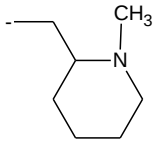
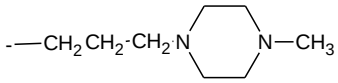
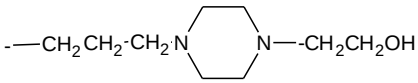
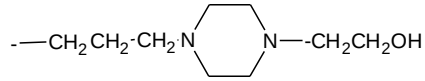
Thioxanthenes

- Chlorprothixene (Cloxan, Taractan, Truxal), Clopenthixol (Sordinol), Flupenthixol (Depixol, Fluanxol), Thiothixene (Navane), Zuclopenthixol (Cisordinol, Clopixol, Acuphase)

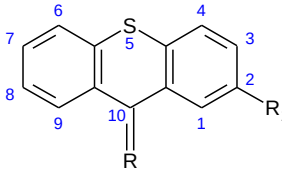
Phenothiazine Derivatives



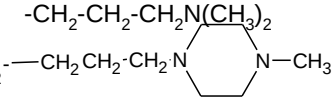
Phenothiazine nucleus

Name	R_1	R
(Aliphatic side Chain)		
Chlorpromazine	-Cl	$-CH_2-CH_2-CH_2N(CH_3)_2$
Triflupromazine	$-CF_3$	$-CH_2-CH_2-CH_2N(CH_3)_2$
(Piperidine side Chain)		
Thioridazine	$-SCH_3$	
(Piperizine side Chain)		
Trifluoperzine	$-CF_3$	
Perphenazine	-Cl	
Fluphenazine	$-CF_3$	

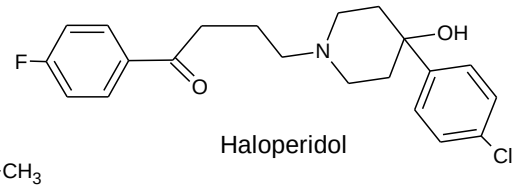
Thioxanthene Derivatives



Substituting C for N in the nucleus

Name	R_1	R
Chlorprothixene	-Cl	$-CH_2-CH_2-CH_2N(CH_3)_2$
Thiothixene	$-SONH_2$	

Butyrophenone



Haloperidol

Metabolic Product of phenothiazine is **7-O-Glu-Nor-CPZ-SO**

Commonly used antipsychotic medications are listed above by drug group. Trade names appear in parentheses.

SAR of Phenothiazines

1. 2-position is substituted by electron withdrawing groups like –Cl, CF_3, SCH_3 etc. for antipsychotic activity.
2. Aliphatic side chain at 10-position must contain three carbon chain; lengthening or shortening of the chain diminish neuroleptic activity.
3. Nitrogen in side chain must be tertiary for antipsychotic activity.
4. Piperidine, piperizine ring in side chain increase the potency of drugs.

Second generation antipsychotics (Atypical antipsychotic**)**

- Clozapine (Clozaril) - Requires weekly to biweekly complete blood count due to risk of agranulocytosis.
- Olanzapine (Zyprexa) - Used to treat psychotic disorders including schizophrenia, acute manic episodes, and maintenance of bipolar disorder. Dosing 2.5 to 20 mg per day.

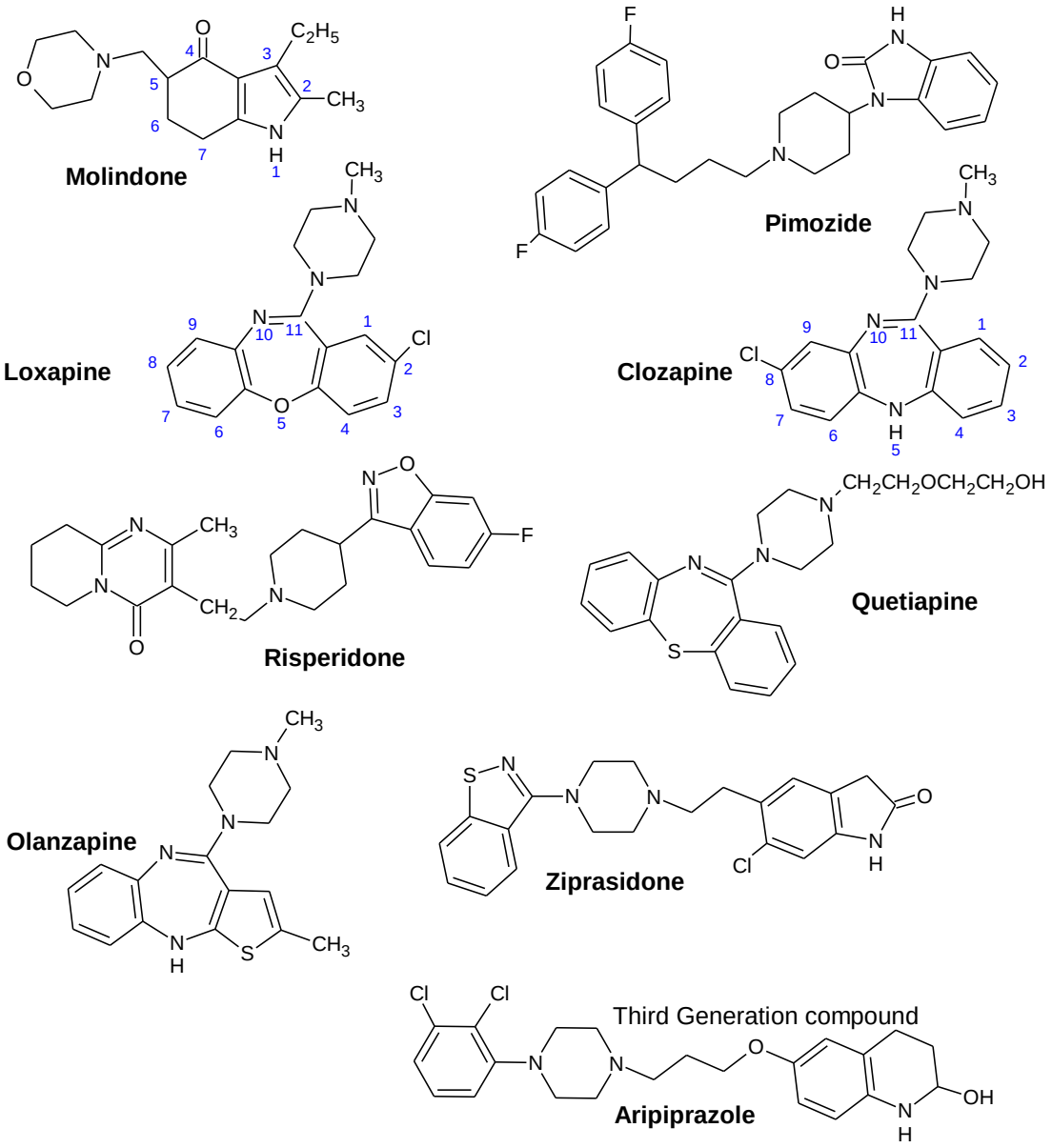


Figure:- Structural formulas of some newer antipsychotic drugs (Second Generation)

- Risperidone (Risperdal) - Dosing 0.25 to 6 mg per day and is titrated upward; divided dosing is recommended until initial titration is completed, at which time the drug can be administered once daily. Used off-label to treat Tourette syndrome and anxiety disorder.
- Quetiapine (Seroquel) - Used primarily to treat bipolar disorder and schizophrenia, and "off-label" to treat chronic insomnia and restless legs syndrome; it is a powerful sedative. Dosing starts at 25 mg and continues up to 800 mg maximum per day, depending on the severity of the symptom(s) being treated.
- Ziprasidone (Geodon) - Approved in 2004 to treat bipolar disorder. Dosing 20 mg twice daily initially up to 80 mg twice daily. Side-effects include a prolonged QT interval in the

heart, which can be dangerous for patients with heart disease or those taking other drugs that prolong the QT interval.

- Amisulpride (Solian) - Selective dopamine antagonist. Higher doses (greater than 400 mg) act upon post-synaptic dopamine receptors resulting in a reduction in the positive symptoms of schizophrenia, such as psychosis. Lower doses, however, act upon dopamine autoreceptors, resulting in increased dopamine transmission, improving the negative symptoms of schizophrenia. Lower doses of amisulpride have also been shown to have antidepressant and anxiolytic effects in non-schizophrenic patients, leading to its use in dysthymia and social phobias. Amisulpride has not been approved for use by the Food and Drug Administration in the United States.
- Asenapine (Saphris) is a 5-HT2A- and D2-receptor antagonist under development for the treatment of schizophrenia and acute mania associated with bipolar disorder.
- Paliperidone (Invega) - Derivative of risperidone that was approved in 2006.
- Iloperidone (Fanapt) - Approved by the FDA on May 6, 2009.
- Zotepine (Nipolept, Losizopilon, Lodopin, Setous)- An atypical antipsychotic indicated for acute and chronic schizophrenia. It was approved in Japan circa 1982 and Germany in 1990, respectively.
- Sertindole (Serdolect, and Serlect in Mexico). Sertindole was developed by the Danish pharmaceutical company H. Lundbeck. Like the other atypical antipsychotics, it is believed to have antagonist activity at dopamine and serotonin receptors in the brain.

Third generation antipsychotics

- Aripiprazole (Abilify) - Dosing 1 mg up to maximum of 30 mg has been used. Mechanism of action is thought to reduce susceptibility to metabolic symptoms seen in some other atypical antipsychotics. The extent to which these effects differ from other atypical antipsychotics is debated.
- Partial agonists of dopamine.

Other options

- Cannabidiol is one of the main components of *Cannabis sativa*. Cannabidiol differs from the active drug in cannabis, tetrahydrocannabinol, in that cannabidiol lacks the typical intoxicating and recreational effects. One study has suggested that cannabidiol may be as effective as atypical antipsychotics in treating schizophrenia.[71] Some further research has supported these results, and found fewer side effects with cannabidiol than with amisulpride.
- Tetrabenazine is similar in function to antipsychotic drugs, though is not, in general, considered an antipsychotic itself. Its main usefulness is the treatment of hyperkinetic movement disorders such as Huntington's disease and Tourette syndrome, rather than for conditions such as schizophrenia. Also, rather than having the potential to cause tardive dyskinesia, which most antipsychotics have, tetrabenazine can be an effective treatment for the condition.

- Metabotropic glutamate receptor 2 agonism has been seen as a promising strategy in the development of novel antipsychotics. When tested in patients, the research substance *LY2140023* yielded promising results and had few side effects. The active metabolite of this prodrug targets the brain glutamate receptors mGluR2/3 rather than dopamine receptors.
- Glycine transporter 1 inhibition. RG1678 has been shown in phase 2 clinical trials to be selectively effective for the negative symptoms of schizophrenia.

Drug action

All antipsychotic drugs tend to block D_2 receptors in the dopamine pathways of the brain. This means that dopamine released in these pathways has less effect. Excess release of dopamine in the mesolimbic pathway has been linked to psychotic experiences. It is the blockade of dopamine receptors in this pathway that is thought to control psychotic experiences.

Typical antipsychotics are not particularly selective and also block dopamine receptors in the mesocortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway. Blocking D_2 receptors in these other pathways is thought to produce some of the unwanted side effects that the typical antipsychotics can produce (see below). They were commonly classified on a spectrum of low potency to high potency, where potency referred to the ability of the drug to bind to dopamine receptors, and not to the effectiveness of the drug. High-potency antipsychotics such as haloperidol, in general, have doses of a few milligrams and cause less sleepiness and calming effects than low-potency antipsychotics such as chlorpromazine and thioridazine, which have dosages of several hundred milligrams. The latter have a greater degree of anticholinergic and antihistaminergic activity, which can counteract dopamine-related side effects.

Atypical antipsychotic drugs have a similar blocking effect on D_2 receptors. Some also block or partially block serotonin receptors (particularly $5HT_{2A,\ C}$ and $5HT_{1A}$ receptors):ranging from risperidone, which acts overwhelmingly on serotonin receptors, to amisulpride, which has no serotonergic activity. The additional effects on serotonin receptors may be why some of them can benefit the "negative symptoms" of schizophrenia.

Structural effects

Many studies now indicate that chronic treatment with antipsychotics affects the brain at a structural level, for example increasing the volume of the basal ganglia (especially the caudate nucleus), and reducing cortical grey matter volume in different brain areas. The effects may differ for typical versus atypical antipsychotics and may interact with different stages of disorders. Death of neurons in the cerebral cortex, especially in women, has been linked to the use of both typical and atypical antipsychotics for individuals with Alzheimers.

Recent studies on macaque monkeys have found that administration of haloperidol or olanzapine for about two years led to a significant overall shrinkage in brain tissue, in both gray

and white matter across several brain areas, with lower glial cell counts, due to a decrease in astrocytes and oligodendrocytes, and increased neuronal density. It has been said that these studies require serious attention and that such effects were not clearly tested for by pharmaceutical companies prior to obtaining approval for placing the drugs on the market.

Anxiolytic

An **anxiolytic** (also **antipanic** or **antianxiety agent**) is a drug used for the treatment of symptoms of anxiety. Anxiolytics have been shown to be useful in the treatment of anxiety disorders.

Beta-receptor blockers such as propranolol and oxprenolol, although not anxiolytics, can be used to combat the somatic symptoms of anxiety.

Anxiolytics are also known as "minor tranquilizers", though their use and effects are by no means minor; this term is less common in modern texts, and was originally derived from a dichotomy with major tranquilizers, also known as neuroleptics or antipsychotics.

Types of anxiolytics

Benzodiazepine

Benzodiazepines are prescribed for short-term relief of severe and disabling anxiety. Benzodiazepines may also be indicated to cover the latent periods associated with the medications prescribed to treat an underlying anxiety disorder. They are used to treat a wide variety of conditions and symptoms and are usually a first choice when short-term CNS sedation is needed. Longer-term uses include treatment for severe anxiety. There is a risk of a benzodiazepine withdrawal and rebound syndrome after continuous usage for longer than two weeks. There is also the added problem of the accumulation of drug metabolites and adverse effects. Benzodiazepines include:

- Alprazolam (Xanax)
- Chlordiazepoxide (Librium)
- Clonazepam (Klonopin)
- Diazepam (Valium)
- Lorazepam (Ativan)

Benzodiazepines exert their anxiolytic properties at moderate dosage. At higher dosage hypnotic properties occur.

- Tofisopam (Emandaxin and Grandaxin) is a drug which is a benzodiazepine derivative. Like other benzodiazepines, it possesses anxiolytic properties but unlike other benzodiazepines it does not have anticonvulsant, sedative, skeletal muscle relaxant, motor skill-impairing or amnestic properties.

SSRIs

Selective serotonin reuptake inhibitors or **serotonin-specific reuptake inhibitor** (**SSRIs**) are a class of compounds typically used as antidepressants in the treatment of depression, anxiety disorders, and some personality disorders. SSRIs are primarily classified as antidepressants and typically higher dosages are required to be effective against anxiety disorders than to be effective against depression but nevertheless most SSRIs have anxiolytic properties.

Azapirone

Azapirones are a class of 5-HT_{1A} receptor agonists. They lack the sedation and the dependence associated with benzodiazepines and cause much less cognitive impairment. They may be less effective than benzodiazepines in patients who have been previously treated with benzodiazepines as they do not provide the sedation that these patients may expect or equate with anxiety relief. Currently approved azapirones include buspirone (Buspar) and tandospirone (Sediel). Gepirone (Ariza, Variza) is also in clinical development.

Barbiturates

Barbiturates exert an anxiolytic effect linked to the sedation they cause. The risk of abuse and addiction is high. Many experts consider these drugs obsolete for treating anxiety but valuable for the short-term treatment of severe insomnia, though only after benzodiazepines or non-benzodiazepines have failed. They are rarely prescribed anymore.

Hydroxyzine

Hydroxyzine (Atarax) is an old antihistamine originally approved for clinical use by the FDA in 1956. It possesses anxiolytic properties in addition to its antihistamine properties and is also licensed for the treatment of anxiety and tension. It is also used for its sedative properties as a premed before anesthesia or to induce sedation after anesthesia.[6] It has been shown to be as effective as benzodiazepines in the treatment of generalized anxiety disorder while producing fewer side effects.

Pregabalin

Pregabalin's therapeutic effect appears after 1 week of use and is similar in effectiveness to lorazepam, alprazolam and venlafaxine but pregabalin has demonstrated superiority by producing more consistent therapeutic effects for psychic and somatic anxiety symptoms. Long-term trials have shown continued effectiveness without the development of tolerance and

additionally unlike benzodiazepines it does not disrupt sleep architecture and produces less severe cognitive and psychomotor impairment; it also has a low potential for abuse and dependence and may be preferred over the benzodiazepines for these reasons.

Herbal treatments

Certain herbs are reputed to have anxiolytic properties, including the following:

- *Rhodiola rosea* (Arctic Weed/Golden Root)
- *Bacopa monnieri* (Brahmi)
- *Hypericum perforatum* (St. John's Wort)
- *Matricaria recutita* (German Chamomile)
- *Mitragyna speciosa* (Kratom)
- *Cannabis sativa* (Marijuana)
- *Nepeta persica* (Catnip)
- *Piper methysticum* (Kava)
- *Sceletium tortuosum* (Kanna)
- *Scutellaria spp.* (Skullcap)
- *Valeriana officinalis* (Valerian)

Of these, only Kava and Brahmi have shown anxiolytic effects in randomized clinical trials, and only Kava's effect has been independently replicated.

In mice, trials have shown anxiolytic effects at 50 mg/kg. However an increase in the dose of *N. persica* exerted stimulation rather than sedation as is the case for many other herbs.

A team from Brazil found cannabidiol (a constituent of cannabis; also called CBD) to be an effective anti-psychotic and anxiolytic. "CBD induced a clear anxiolytic effect and a pattern of cerebral activity compatible with anxiolytic activity. Therefore, similar to the data obtained in animal models, results from studies on healthy volunteers have strongly suggested an anxiolytic-like effect of CBD."

Pineapple sage, or salvia elegans, is used as a treatment for anxiety in traditional Mexican medicine, and a preliminary study on mice has yielded some support for both anxiolytic and antidepressant properties.

Over-the-counter

Chlorpheniramine (Chlor-Trimeton) and diphenhydramine (Benadryl) have hypnotic and sedative effects with mild anxiolytic-like properties(off-label use). These drugs are approved by the FDA for allergies, rhinitis, and urticaria.

FLUOROQUINOLONES

The **quinolones** are a family of synthetic broad-spectrum antibiotics. The term quinolone(s) refers to potent synthetic chemotherapeutic antibacterials,.

The first generation of the quinolones begins with the introduction of nalidixic acid in 1962 for treatment of urinary tract infections in humans. Nalidixic acid was discovered by George Lesher and coworkers in a distillate during an attempt at chloroquine synthesis.

They prevent bacterial DNA from unwinding and duplicating. (See Mechanism of Action later.)

Quinolones in comparison to other antibiotic classes have the highest risk of causing colonization with MRSA and Clostridium difficile. A general avoidance of fluoroquinolones is recommended based on the available evidence and clinical guidelines. The majority of quinolones in clinical use belong to the subset of **fluoroquinolones**, which have a fluorine atom attached to the central ring system, typically at the 6-position or C-7 position.

History

Nalidixic acid is considered to be the predecessor of all members of the quinolone family, including the second, third and fourth generations commonly known as fluoroquinolones. This first generation also included other quinolone drugs such as pipemidic acid, oxolinic acid, and cinoxacin, which were introduced in the 1970s. They proved to be only marginal improvements over nalidixic acid. Though it is generally accepted that nalidixic acid is to be considered the first quinolone drug, this has been disputed over the years by a few researchers that believe that chloroquine, from which nalidixic acid is derived, is to be considered the first quinolone drug, rather than nalidixic acid.

Since the introduction of nalidixic acid in 1962, more than 10,000 analogs have been synthesized, but only a handful have found their way into clinical practice. The fluoroquinolone drugs are the most toxic and dangerous antibiotics in clinical practice today.

Indications

It continues to be debatable as to whether or not the effectiveness of fluoroquinolones for the treatment of respiratory disorders is similar to that of other antibiotic classes.

Fluoroquinolone use for pneumonia is increasing, and with it so is bacterial resistance to fluoroquinolones. The majority of the prescribing of fluoroquinolones is inappropriate, with less than 4 percent of people prescribed quinolones being appropriate according to clinical guidelines. Clinical guidelines in Canada recommend fluoroquinolones only for outpatient treatment of pneumonia in a small number of patients, such as those with certain co-morbid conditions, e.g., patients with a history of COPD, or those with recent use of antibiotics. For severe forms of community-acquired pneumonia, the fluoroquinolones are associated with improved treatment rates, but with no differences found in mortality between other antibiotic classes.

Fluoroquinolones are not recommended as first-line antibiotics for acute sinusitis, as this condition is usually self-limiting, and the risks outweigh the benefits in comparison to other antibiotic classes.

Antibiotics including fluoroquinolones can be effective in some cases of bronchitis. However, only about 5-10% of bronchitis cases are caused by a bacterial infection; most cases of bronchitis are caused by a viral infection and are self-limiting and resolve themselves in a few weeks. It has been recommended that antibiotics are limited in most cases to those whose symptoms fail to resolve on their own.

Fluoroquinolones are often used for genitourinary infections; in general they are recommended only after other antibiotic regimens have failed. However, for serious acute cases of pyelonephritis or bacterial prostatitis where the patient may need to be hospitalised, fluoroquinolones are recommended as first-line therapy. Prostatitis has been termed "the waste basket of clinical ignorance" by prominent Stanford University urologist Dr. Thomas Stamey. *Campbell's Urology*, the urologist's most authoritative reference text, identifies only about 5% of all patients with prostatitis as having bacterial prostatitis, which can be "cured" at least in the short term by antibiotics. In other words, 95% of men with prostatitis have little hope for a cure with antibiotics alone, since they do not actually have any identifiable bacterial infection.

The American Thoracic Society recommends that fluoroquinolones are not used as a first-line agent, instead recommending macrolide or doxycycline as first-line agents. The Drug-Resistant *Streptococcus pneumoniae* Working Group recommends that fluoroquinolones be used only after other antibiotic classes have been tried and failed, or in those with demonstrated drug-resistant Streptococcus pneumoniae. The Centers for Disease Control are concerned that fluoroquinolones are being used as a "one-size-fits-all" treatment unnecessarily by doctors without considering suitability and differences due to age and other risk factors. Effective interventions have been recommended to reduce the excessive fluoroquinolone prescribing in the United States.

Adverse effects

In general, fluoroquinolones are well tolerated, with most side-effects being mild to moderate. On occasion, serious adverse effects occur. Some of the serious adverse effects that occur more commonly with fluoroquinolones than with other antibiotic drug classes include CNS and tendon toxicity. The currently marketed quinolones have safety profiles similar to that of other antimicrobial classes. Fluoroquinolones are sometimes associated with an QTc interval prolongation and cardiac arrhythmias, convulsions, tendon rupture, torsade de pointes and hypoglycemia.

These adverse reactions are a class effect of all quinolones; however, certain quinolones are more strongly associated with increased toxicity to certain organs. For example, moxifloxacin carries a higher risk of QTc prolongation, and gatifloxacin has been most frequently linked to disturbed blood sugar levels, although all quinolones carry these risks. Some quinolones were withdrawn from the market because of these adverse events (for example, sparfloxacin was associated with phototoxicity and QTc prolongation, thrombocytopenia and nephritis were seen with tosufloxacin, and hepatotoxicity with trovafloxacin). Simultaneous use of corticosteroids is present in almost one-third of quinolone-associated tendon rupture. The risk of adverse events is further increased if the dosage is not properly adjusted, for example if there is renal insufficiency.

The serious events may occur during therapeutic use at therapeutic dose levels or with acute overdose. At therapeutic doses they include: central nervous system toxicity, cardiovascular

toxicity, tendon / articular toxicity, and, rarely, hepatic toxicity. Caution is required in patients with liver disease. Events that may occur in acute overdose are rare, and include renal failure and seizure. Susceptible groups of patients, such as children and the elderly, are at greater risk of adverse reactions during therapeutic use. Adverse reactions may manifest during, as well as after fluoroquinolone therapy has been completed.

Fluoroquinolones are considered high-risk antibiotics for the development of *Clostridium difficile* and MRSA infections. A previously rare strain of *C. difficile* that produces a more severe disease with increased levels of toxins is becoming epidemic, and may be connected to the use of fluoroquinolones. Fluoroquinolones are more strongly associated with *C. difficile* infections than other antibiotics, including clindamycin, third-generation cephalosporins, and beta lactamase inhibitors. One study found that fluoroquinolones were responsible for 55% of *C. difficile* infections. The European Center for Disease Prevention and Control recommends that fluoroquinolones and the antibiotic clindamycin should be avoided in clinical practice due to their high association with *Clostridium difficile*, a potentially life-threatening super-infection.

The central nervous system is an important target for fluoroquinolone-mediated neurotoxicity. Adverse event reporting in Italy by doctors showed fluoroquinolones among the top 3 prescribed drugs for causing adverse neurological and psychiatric effects. These neuropsychiatric effects included tremor, confusion, anxiety, insomnia, agitation, and, in severe cases, psychosis. Moxifloxacin came out worst among the quinolones for causing CNS toxicity. Some support and patient advocacy groups refer to these adverse events as "fluoroquinolone toxicity". Some people from these groups claim to have suffered serious long-term harm to their health from using fluoroquinolones. This has led to a class-action lawsuit by people harmed by the use of fluoroquinolones as well as action by the consumer advocate group Public Citizen. Partly as a result of the efforts of Public Citizen, the FDA ordered black box warnings on all fluoroquinolones, advising consumers of the possible toxic effects of fluoroquinolones on tendons.

Contraindications

Quinolones are contraindicated if a patient has epilepsy, QT prolongation, pre-existing CNS lesions, central nervous system inflammation or those who have suffered a stroke. There are safety concerns of fluoroquinolone use during pregnancy and, as a result, are contraindicated except for when no other safe alternative antibiotic exists. They are also contraindicated in children due to the risks of damage to the musculoskeletal system. Their use in children is not absolutely contraindicated, however. For certain severe infections where other antibiotics are not an option, their use can be justified. Quinolones should also not be given to people with a known hypersensitivity to the drug.

Boxed warnings

U.S. Boxed Warning: Increased risk of developing tendonitis and tendon rupture in patients of all ages taking fluoroquinolones for systemic use. This risk is further increased in individuals over 60 years of age, taking corticosteroid drugs, and have received kidney, heart, or lung transplants.

Musculoskeletal disorders attributed to use of quinolone antibiotics were first reported in the medical literature in 1972, as an adverse reaction to nalidixic acid. Rheumatic disease after use of a fluoroquinolone (norfloxacin) was first reported eleven years later. In response to a 1995 letter published in the *New England Journal of Medicine*, representatives of the U.S. Food and

Drug Administration (FDA) stated that the agency would "update the labeling [package insert] for all marketed fluoroquinolones to include a warning about the possibility of tendon rupture." By August 1996, the FDA had not taken action, and the consumer advocacy group Public Citizen filed a petition with the FDA, prompting the agency to act. Two months later, the FDA published an alert in the *FDA Medical Bulletin* and requested that fluoroquinolone package inserts be amended to include information on this risk.

Nine years later, in 2005, the Illinois Attorney General filed a second petition with the FDA again seeking black box warnings and "Dear Doctor" letters emphasizing the risk of tendon rupture; the FDA responded that it had not yet been able to reach a decision on the matter. In 2006, Public Citizen, supported by the Illinois Attorney General, renewed its demand of ten years prior for black box warnings by filing a third petition requesting such changes be made. When the FDA failed to respond to these two petitions as required by law, Public Citizen, in January 2008, filed suit to compel the FDA to respond to their 2006 petition. On July 7, 2008 the FDA requested that the makers of systemic-use fluoroquinolones add a boxed warning regarding spontaneous tendon ruptures, and to develop a Medication Guide for patients. The package inserts for ciprofloxacin, Avelox (moxifloxacin), Proquin XR, Factive (gemifloxacin), Floxin (ofloxacin), Noroxin (norfloxacin) and Levaquin (levofloxacin) were amended on September 8, 2008 to include these new warnings. Bayer, which manufactures Cipro, Avelox and Proquin XR, issued a Dear Healthcare Professional letter on October 22 concerning these changes. Ortho-McNeil, the manufacturers of Levaquin, issued a similar letter in November. through the Health Care Notification Network, a registration-only website that distributes drug alerts to licensed healthcare professionals.

A review of the FDA website indicates that the majority of the generic versions of the fluoroquinolones have *not* been updated to include this Boxed Warning as of September 2009. In addition, there are numerous reports that claim that this information has not been disseminated to the pharmacist, the name brand products continue to contain the previous labels that are absent of this warning, and the Medication Guide has not been made available to the pharmicist or physician for distribution.

Pharmacology

The basic pharmacophore, or active structure, of the fluoroquinolone class is based upon the quinoline ring system. The addition of the fluorine atom at C6 is what distinguishes the successive-generation fluoroquinolones from the first-generation quinolones. It has since been demonstrated that the addition of the C6 fluorine atom is not a necessary requirement for the antibacterial activity of this class (circa 1997).

Various substitutions made to the quinoline ring resulted in the development of numerous fluoroquinolone drugs available today. Each substitution is associated with a number of specific adverse reactions, as well as increased activity against bacterial infections, whereas the quinoline ring, in and of itself, has been associated with severe and even fatal adverse reactions.

Mechanism of action

Quinolones and fluoroquinolones are chemotherapeutic bactericidal drugs, eradicating bacteria by interfering with DNA replication. The other antibiotics used today, (e.g., tetracyclines, lincomycin, erythromycin, and chloramphenicol) do not interact with components of eukaryotic ribosomal particles and, thus, have not been shown to be toxic to eukaryotes,[64] as opposed to

the fluoroquinolone class of drugs. Other drugs used to treat bacterial infections, such as penicillins and cephalosporins, inhibit cell wall biosynthesis, thereby causing bacterial cell death, as opposed to the interference with DNA replication as seen within the fluoroquinolone class of drugs.

Quinolones inhibit the bacterial DNA gyrase or the topoisomerase II enzyme, thereby inhibiting DNA replication and transcription. Recent evidence has shown that topoisomerase II is also a target for a variety of quinolone-based drugs. Thus far, most of the compounds that show high activity against the eukaryotic type II enzyme contain aromatic substituents at their C-7 positions.

Quinolones can enter cells easily via porins and, therefore, are often used to treat intracellular pathogens such as *Legionella pneumophila* and *Mycoplasma pneumoniae*. For many Gram-negative bacteria, DNA gyrase is the target, whereas topoisomerase IV is the target for many Gram-positive bacteria. It is believed that eukaryotic cells do not contain DNA gyrase or topoisomerase IV. However, there is debate concerning whether the quinolones still have such an adverse effect on the DNA of healthy cells, in the manner described above, hence contributing to their adverse safety profile. This class has been shown to damage mitochondrial DNA.

Interactions

Theophylline, nonsteroidal anti-inflammatory drugs and corticosteroids enhance the toxicity of fluoroquinolones.

Products containing multivalent cations, such as aluminum- or magnesium-containing antacids and products containing calcium, iron, or zinc, invariably result in marked reduction of oral absorption of fluoroquinolones.

Other drugs that interact with fluoroquinolones include antacids, Sucralfate, Probenecid, Cimetidine, Warfarin, antiviral agents, Phenytoin, Cyclosporine, Rifampin, Pyrazinamide, and Cycloserine.

Many fluoroquinolones, especially ciprofloxacin, inhibit the cytochrome P450 isoform CYP1A2. This inhibition causes an increased level of, for example, antidepressants such as amitriptyline and imipramine, clozapine (an atypical antipsychotic), caffeine, Olanzapine (an atypical antipsychotic), Ropivacaine (a local anaesthetic), Theophylline (a xanthine), and Zolmitriptan (a serotonin receptor agonist).

Antibiotic misuse and bacterial resistance

See also: Antibiotic misuse and Antibiotic resistance

Resistance to quinolones can evolve rapidly, even during a course of treatment. Numerous pathogens, including *Staphylococcus aureus*, enterococci, and *Streptococcus pyogenes* now exhibit resistance worldwide. Widespread veterinary usage of quinolones, in particular in Europe, has been implicated.

Fluoroquinolones have been recommended to be reserved for the use in patients that are seriously ill and may soon require immediate hospitalization. Though considered to be a very important and necessary drugs required to treat severe and life-threatening bacterial infections, the associated antibiotic misuse remains unchecked, which has contributed to the problem of bacterial resistance. The overuse of antibiotics such as happens with children suffering from otitis media has given rise to a breed of super-bacteria that are resistant to antibiotics entirely.

For example, the use of the fluoroquinolones had increased threefold in an emergency room environment in the United States between 1995 and 2002, while the use of safer alternatives, such as macrolides, declined significantly. Fluoroquinolones had become the most commonly prescribed class of antibiotics to adults in 2002. Nearly half (42%) of these prescriptions were for conditions not approved by the FDA, such as acute bronchitis, otitis media, and acute upper respiratory tract infection, according to a study that was supported in part by the Agency for Healthcare Research and Quality. In addition, they are commonly prescribed for medical conditions, such as acute respiratory illness, that are usually caused by viral infections.

Within a recent study concerning the proper use of this class in the emergency room, it was revealed that 99% of these prescriptions were in error. Out of the one hundred total patients studied, eighty-one received a fluoroquinolone for an inappropriate indication. Out of these cases, forty-three (53%) were judged to be inappropriate because another agent was considered first line, twenty-seven (33%) because there was no evidence of a bacterial infection to begin with (based on the documented evaluation), and eleven (14%) because of the need for such therapy was questionable. Out of the nineteen patients who received a fluoroquinolone for an appropriate indication, only *one patient* out of one hundred received both the correct dose and duration of therapy.

There are three known mechanisms of resistance. Some types of efflux pumps can act to decrease intracellular quinolone concentration. In Gram-negative bacteria, plasmid-mediated resistance genes produce proteins that can bind to DNA gyrase, protecting it from the action of quinolones. Finally, mutations at key sites in DNA gyrase or topoisomerase IV can decrease their binding affinity to quinolones, decreasing the drugs' effectiveness.

Social and economic impact

Increased hospitalizations attributed to adverse drug reactions alone account for billions of dollars each year within the US healthcare system. Severe reactions do occur with the fluoroquinolone class and can add significantly to the cost of care. Antibacterial adverse effects account for nearly 25% of all adverse drug reactions among hospitalized patients.

Adverse effects of fluoroquinolones can lead to patients attending hospital emergency rooms. Many of the important adverse effects of fluoroquinolones are widely underappreciated by physicians, and are often misdiagnosed as other medical or psychiatric conditions. Physicians typically fail to enquire about antibiotic use to explain with an acute presentation of new symptoms. The important adverse effects of fluoroquinolones include hypoglycemia or hyperglycemia, QTc prolongation, central nervous system toxicity, gastrointestinal, skin, musculoskeletal, cardiotoxicity, and respiratory effects, phototoxicity, tendinopathy, angioedema, and *Clostridium difficile* infections. A further factor that leads to misdiagnosis of quinolone adverse effects is that some symptoms can persist or occur for the first time quite some time after a course of quinolone has been finished, so inquiring about distant-past use of quinolones has been recommended. Quinolones are probably the worst offending antibiotic for causing *C. difficile* infections. Some of the adverse effects can present similar to acute dementia, confusion, and psychosis. Quinolones are a common cause of cerebral dysfunction, with neuropsychiatric disturbances being the most common quinolone adverse effects. One study found that, of all drug classes prescribed by doctors including psychotropic drugs, fluoroquinolones were the most common cause of neuropsychiatric adverse effects.

Patent extensions

Under the George W. Bush administration (2001–2008), patent extension legislation that allowed Bayer AG, as well as other drug companies, a six-month patent extension for testing their products for safety in children was signed into law. It has been estimated that Bayer AG's revenue increased an extra $358 million due to ciprofloxacin's pediatric patent extension. The legislation was drafted after extensive lobbying of numerous members of Congress by Bayer AG and others. One of the four sponsors of this legislation was Chris Dodd (D-CT), who, at the time, ranked as one of the top three beneficiaries of campaign contributions by drug companies. Sen. Edward Kennedy (D-MA), who chaired the committee with jurisdiction over the bill, refused to fight over the language that (if it had been included) would have reduced the drug company's profits due to these patent extensions. The reasons for Sen. Edward Kennedy's decision not to fight for the inclusion of this language were not made known.

The results of these pediatric trials indicated that arthropathy occurred more frequently in patients that received ciprofloxacin (within these studies). The affected joints included the knees, elbows, ankles, hips, wrists, and shoulders of the pediatric patients. In one study, at six weeks arthropathy was seen in 9.3% of ciprofloxacin patients. These rates increased significantly after one year to 13.7% of the ciprofloxacin patients. Such arthropathy occurred more frequently in patients treated with ciprofloxacin than any other control drug, regardless of whether they received IV ciprofloxacin or the oral version of the drug. Ciprofloxacin patients reported more than one event and on more than one occasion when compared to the control patients. The overall incidence of adverse events at six weeks was 41% in those patients being treated with ciprofloxacin. Serious adverse events were seen in 7.5% of these patients and 3% of the patients discontinued the drug due to adverse events. Despite these results the FDA stated that “The data support updating the package insert to include safety; and treatment recommendations for pediatric patients between 1 and 17 years of age with complicated urinary tract infection or pyelonephritis.”

Within a 2005 memo, the FDA reviewed seventeen unique pediatric cases reported to the FDA during the thirteen-month period after the pediatric exclusivity for ciprofloxacin had been granted. During this period, there was one report of death, two of disability, and four of hospitalization. The disabilities involved the inability to walk (in a 12-year-old female patient) and the inability to run (in a 12-year-old male patient). The hospital admissions were for pseudomembranous colitis, pancytopenia, tendonitis, and Stevens Johnson syndrome. The female patient received 5 weeks of ciprofloxacin oral therapy at the recommended doses. Even though ciprofloxacin was discontinued, she could not stand or ambulate and required a wheelchair one month later. These seventeen unique pediatric cases showed mostly hematological, musculoskeletal, allergic/hypersensitivity, and central nervous system adverse events. It does not appear that this executive summary was ever released to the medical community.

- Economic impact: adverse reactions:

The adverse drug reaction profile of ciprofloxacin and other fluoroquinolone drugs has spawned a grass-roots movement of those so affected to lobby for Black Box Warnings and Dear Doctor Letters as well as the petitioning of the FDA for the removal of some fluoroquinolone drugs from clinical practice

Current litigation

The effectiveness and the proven clinical need for the drugs found within this class have rarely been called into question. They have a proven track record with regard to eradicating bacterial infections and are to be considered an essential tool within the medical community. However, there is controversy concerning the safety profile of quinolones, as well as their proper use.

At present, there is a significant number of cases pending before the United States District Court, District of Minnesota, involving the drug Levaquin. On June 13, 2008 a Judicial Panel On Multidistrict Litigation (MDL) granted the Plaintiffs' motion to centralize individual and class-action lawsuits involving Levaquin in the District of Minnesota over objection of Defendants, Johnson and Johnson / Ortho McNeil.

Most recently, on July 6, 2009, the New Jersey Supreme Court had also designated litigation over Levaquin as a mass tort and has assigned it to an Atlantic County, N.J., judge. The suits charge that the drug has caused Achilles tendon ruptures and other permanent damage.

Several class action lawsuits had been filed in regards to the adverse reactions suffered by those exposed to ciprofloxacin during the anthrax scare of 2001, as well.

Generations

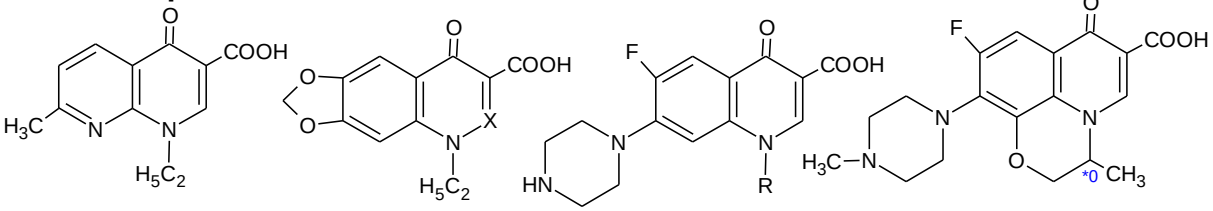
Researchers divide the quinolones into generations based on their antibacterial spectrum. The earlier-generation agents are, in general, more narrow-spectrum than the later ones, but there is no standard employed to determine which drug belongs to which generation. The only universal standard applied is the grouping of the non-fluorinated drugs found within this class (quinolones) within the *first-generation* heading. As such, there exists a wide variation within the literature dependent upon the methods employed by the authors.

- Some researchers group these drugs by patent dates
- Some by a specific decade (i.e., '60s, '70s, '80s, etc.)

- Others by the various structural changes

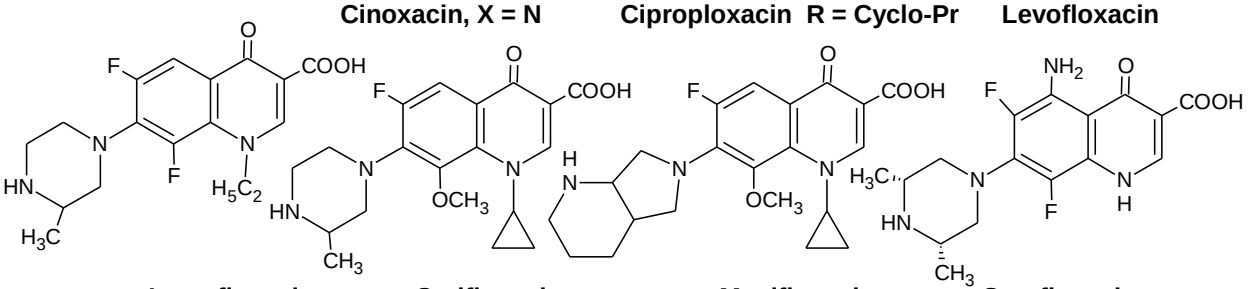
The first generation is rarely used today. Nalidixic acid was added to the OEHHA Prop 65 list as a carcinogen on May 15, 1998. A number of the second-, third-, and fourth-generation drugs have been removed from clinical practice due to severe toxicity issues or discontinued by their manufacturers. The drugs most frequently prescribed today consist of Avelox (moxifloxacin), Cipro (ciprofloxacin), Levaquin (levofloxacin), and, to some extent, their generic equivalents.

Fluoroquinolones:-



Nalidixic acid **Oxolinic Acid X = CH** **Norfloxacin R = C_2H_5** **Ofloxacin**

Cinoxacin, X = N **Ciproploxacin R = Cyclo-Pr** **Levofloxacin**



Lomefloxacin **Gatifloxacin** **Moxifloxacin** **Sparfloxacin**

First-generation

- cinoxacin (Cinobac) (Removed from clinical use)
- flumequine (Flubactin) (Genotoxic carcinogen)(Veterinary use)
- nalidixic acid (NegGam, Wintomylon) (Genotoxic carcinogen)
- oxolinic acid (Uroxin) (Currently unavailable in the United States)
- piromidic acid (Panacid) (Currently unavailable in the United States)
- pipemidic acid (Dolcol) (Currently unavailable in the United States)
- rosoxacin (Eradacil) (Restricted use, currently unavailable in the United States)

Second-generation

The second-generation class is sometimes subdivided into "Class 1" and "Class 2".

- ciprofloxacin (Zoxan, Ciprobay, Cipro, Ciproxin)
- enoxacin (Enroxil, Penetrex) (Removed from clinical use)
- fleroxacin (Megalone, Roquinol) (Removed from clinical use)
- lomefloxacin (Maxaquin) (Discontinued in the United States)
- nadifloxacin (Acuatim, Nadoxin, Nadixa) (Currently unavailable in the United States)
- norfloxacin (Lexinor, Noroxin, Quinabic, Janacin) (restricted use)
- ofloxacin (Floxin, Oxaldin, Tarivid) (Only as ophthalmic in the United States)
- pefloxacin (Peflacine) (Currently unavailable in the United States)
- rufloxacin (Uroflox) (Currently unavailable in the United States)

Third-generation

Unlike the first- and second-generations, the third-generation is active against streptococci.

- balofloxacin (Baloxin) (Currently unavailable in the United States)
- grepafloxacin (Raxar) (Removed from clinical use)
- levofloxacin (Cravit, Levaquin)
- pazufloxacin (Pasil, Pazucross) (Currently unavailable in the United States)
- sparfloxacin (Zagam) (Currently unavailable in the United States),
- temafloxacin (Omniflox) (Removed from clinical use)

- tosufloxacin (Ozex, Tosacin) (Currently unavailable in the United States)
- **Fourth-generation**

Fourth generation fluoroquinolones act at DNA gyrase and topoisomerase IV. This dual action slows development of resistance.

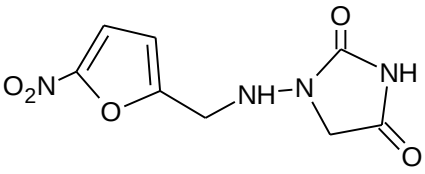
- clinafloxacin (Currently unavailable in the United States)
- gatifloxacin (Zigat, Tequin) (Zymar -opth.) (Tequin removed from clinical use)
- gemifloxacin (Factive)(Currently unavailable in the United States)
- moxifloxacin (Avelox,Vigamox (restricted use).
- sitafloxacin (Gracevit) (Currently unavailable in the United States)
- trovafloxacin (Trovan) (Removed from clinical use)
- prulifloxacin (Quisnon) (Currently unavailable in the United States)

In development

- garenoxacin (Geninax)(Application withdrawn due to toxicity issues)
- delafloxacin

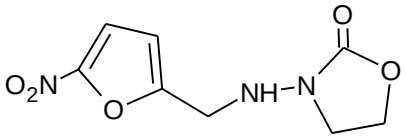
Urinary Antiseptics:- Nitrofurantion and furazolidone are also used as urinary antiseptic that inhibit DNA gyrase. Specially effective in E. coli infection. Nitrofurantoin is given in micro particle form to increase the absorption of the drug from intestine (Microdantin).

Nitrofuranton



1-{[(5-nitrofuran-2-yl)methyl]amino}imidazolidine-2,4-dione

Furazolidone



3-{[(5-nitrofuran-2-yl)methyl]amino}-1,3-oxazolidin-2-one

Furazolidone is red color dye that causes discoloration (Pink color) of urine.

GENERAL ANESTHETICS

General anesthetic are the agents that cause reversible loss of consciousness. These are useful in surgical anesthesia for surgery. There are two types, inhalational and intravenous. When diethyl ether is used as surgical anesthetic; this is characterized by Guedel's sign of anesthesia and divided in four stages 1) analgesia 2) delirium 3) surgical anesthesia 4) respiratory depression.

Stages of anaesthesia

The four stages of anaesthesia were described in 1937. Despite newer anaesthetic agents and delivery techniques, which have led to more rapid onset and recovery from anaesthesia, with greater safety margins, the principles remain.

- Stage 1: Stage 1 anaesthesia, also known as the "induction", is the period between the initial administration of the induction agents and loss of consciousness. During this stage, the patient progresses from analgesia without amnesia to analgesia with amnesia. Patients can carry on a conversation at this time.
- Stage 2: Stage 2 anaesthesia, also known as the "excitement stage", is the period following loss of consciousness and marked by excited and delirious activity. During this stage, respirations and heart rate may become irregular. In addition, there may be uncontrolled movements, vomiting, breath holding, and pupillary dilation. Since the combination of spastic movements, vomiting, and irregular respirations may lead to airway compromise, rapidly acting drugs are used to minimize time in this stage and reach stage 3 as fast as possible.
- Stage 3: Stage 3, "surgical anaesthesia". During this stage, the skeletal muscles relax, and the patient's breathing becomes regular. Eye movements slow, then stop, and surgery can begin. It has been divided into 4 planes:

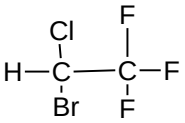
1. eyes initially rolling, then becoming fixed
2. loss of corneal and laryngeal reflexes
3. pupils dilate and loss of light reflex
4. intercostal paralysis, shallow abdominal respiration, dilated pupils

- Stage 4: Stage 4 anaesthesia, also known as "overdose", is the stage where too much medication has been given relative to the amount of surgical stimulation and the patient has severe brain stem or medullary depression. This results in a cessation of respiration and potential cardiovascular collapse. This stage is lethal without cardiovascular and respiratory support. This can be fatal.

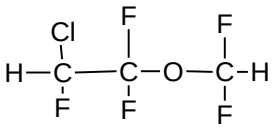
Other agents are chloroform, halothane, nitrous oxide, enflurane, desflurane, sevoflurane and methoxyflurane. These are easily converted in gaseous form and are used to maintain

anesthesia. The agents that are given in intravenous form are thiopental, propafol, ketamine, midazolam and etodimate.

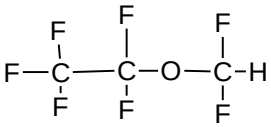
Inhalational anesthetics



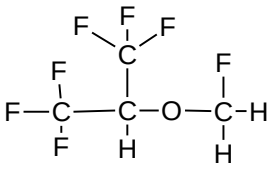
Halothane



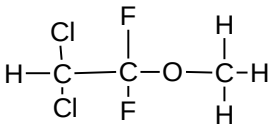
Enflurane



Desflurane

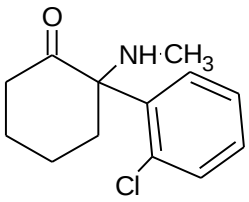


Sevoflurane

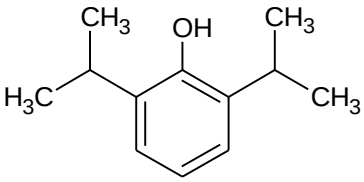


Methoxyflurane

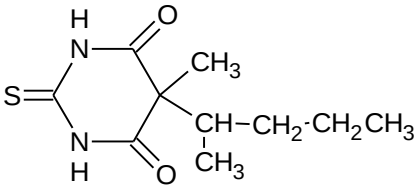
Intravenous anesthetics



Ketamine



Propofol



Thiopantal

HISTAMINE ANTAGONIST

A **histamine antagonist** is an agent that inhibits action of histamine via histamine receptors. H_1 antihistamines are used as treatment for symptoms of allergies such as runny nose. Allergies are caused by an excessive type 1 hypersensitivity response of the body to allergens, such as pollen released by plants. An allergic reaction, which if severe enough can lead to anaphylaxis, results in excessive release of histamines and other mediators by the body. Other uses of H_1 antihistamines help with symptoms of local inflammation that results from various conditions, such as insect stings, even if there is no allergic reaction. Other commonly used examples of antihistamines include the H_2 antagonists (Cimetidine) which are widely used for the treatment of acid reflux and stomach ulcers as they decrease gastric acid production.

Clinical effects

Histamines will produce increased vascular permeability causing fluid to escape from capillaries into the tissues, which leads to the classic symptoms of an allergic reaction – a runny nose and watery eyes.

Antihistamines suppress the histamine-induced wheal (swelling) and flare (vasodilation) response by blocking the binding of histamine to its receptors on nerves, vascular smooth muscle, glandular cells, endothelium, and mast cells. They effectively exert competitive antagonism of histamine for H1-receptors. Itching and sneezing are suppressed by antihistamine blockade of H1-receptors on nasal sensory nerves. Antihistamines are commonly used for relief of allergies caused by intolerances of proteins.

Clinical: H_1- and H_2-receptor antagonists

H_1-receptor antagonists

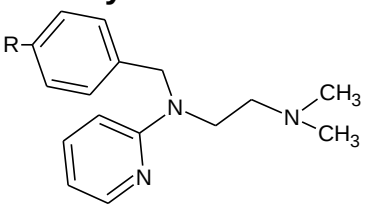
In common use, the term antihistamine refers only to H_1 antagonists, also known as H_1 antihistamines. It has been discovered that these H_1-antihistamines are actually inverse agonists at the histamine H_1-receptor, rather than antagonists *per se*. Clinically, H_1 antagonists are used to treat allergic reactions. Sedation is a common side effect, and some H_1 antagonists, such as diphenhydramine and doxylamine, are also used to treat insomnia. However, second generation antihistamines do not cross the blood brain barrier, and as such do not cause drowsiness

Classification

1. **Ethylene diamine derivatives**
   Mepyramine (Pyrilamine), Tripelennamine
2. **Amino Alkyl Ethers**
   Diphenhydramine (Benadryl), Clemastine, Doxylamine , Medrylamine, Dimenhydrinate
3. **Cyclic basic chain analogoues**
   Hydroxazine, cyclizine, chlorcyclizine, buclizine, cinnarzine, Meclizine (most commonly used as an antiemetic)
4. **Mono amino propyl analogos**
   Pheniramine, Chlorpheniramine, dexchlorpheniramine
5. **Tricyclic antihistaminic**
   Promethazine, cyproheptadiene, azatadine, ketotiphene, dimethindene
6. **Newer antihistaminic with fewer sedation (second generation)**
   Loratadine, Desloratadine, Fexofenadine, Cetirizine, Ebastine, Levocetirizine, Olopatadine (used locally), Quetiapine (antipsychotic), embramine

- Vitamin C (also known as ascorbic acid)

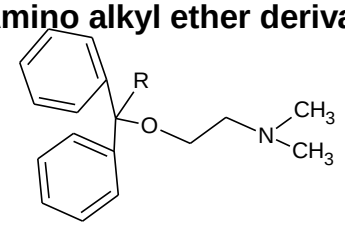
Ethylene diamine derivatives



$R = OCH_3$ Mepyramine

R = H Tripelennamine

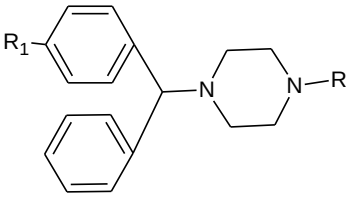
Amino alkyl ether derivatives



$R = CH_3$ Doxylamine

R = H Diphenhydramine

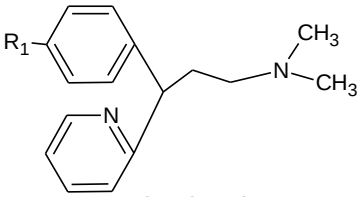
Cyclic Basic Chain derivatives



$R_1 = H$, $R = CH_3$, Cyclizine

R_1= Cl, $R = CH_3$, Chorcyclizine

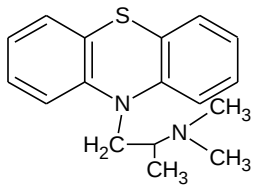
Monopropylamino derivatives



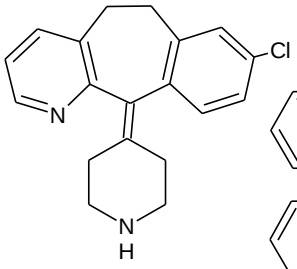
R = H , Pheniramine

R = Cl Chorpheniramine

TriCyclic derivatives

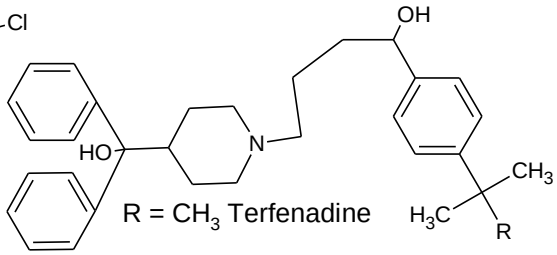


Promethazine



Desloratadine

Newer Drugs



$R = CH_3$ Terfenadine

R = COOH Fexofenadine

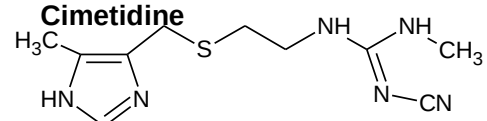
H_2-receptor antagonists

H_2 antagonists, like H_1 antagonists, are also inverse agonists and not true antagonists. H_2 histamine receptors are found principally in the parietal cells of the gastric mucosa. H_2 antagonists are used to reduce the secretion of gastric acid, treating gastrointestinal conditions including peptic ulcers and gastroesophageal reflux disease.

- Cimetidine
- Famotidine
- Ranitidine
- Nizatidine
- Roxatidine
- Lafutidine

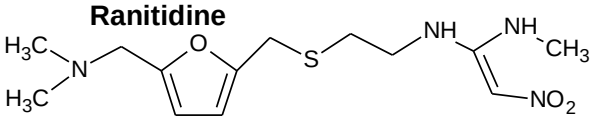
H_2 - Antagonist

Cimetidine

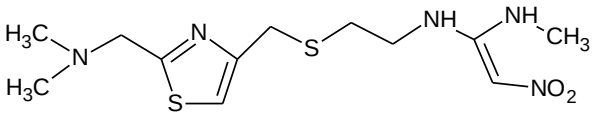


2-cyano-1-methyl-3-(2-{[(5-methyl-1*H*-imidazol-4-yl) methyl]sulfanyl}ethyl)guanidine

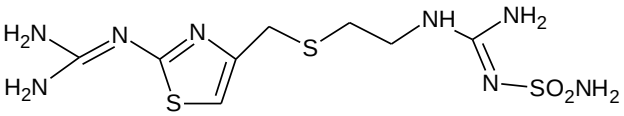
Ranitidine



(*E*)-*N*-{2-[({5-[(dimethylamino)methyl]furan-2-yl}methyl) sulfanyl]ethyl}-*N*'-methyl-2-nitroethene-1,1-diamine



Nizatidine

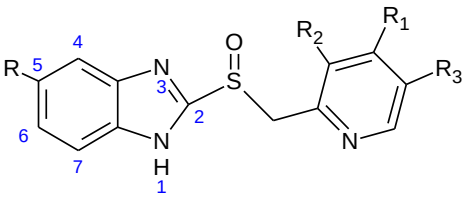


Famotidine

Proton Pump Inhibitors (PPI)

Proton pump inhibitors are used as ulcer healing substances like omeprazole, esomeprazole, lansoperazole, pantoperazole and rabeprazole.

Proton Pump Inhibitors:-



	R	R_1	R_2	R_3
1. Omeprazole	OCH_3	OCH_3	CH_3	CH_3
2. Pantoprazole	$OCHF_2$	OCH_3	OCH_3	
3. Lansoprazole	H	OCH_2CF_3	CH_3	
4. Rabeprazole	H	$OCH_2CH_2CH_2OCH_3$	CH_3	

Experimental: H_3- and H_4-receptor antagonists

These are experimental agents and do not yet have a defined clinical use, although a number of drugs are currently in human trials. H_3-antagonists have a stimulant and nootropic effect, and are being investigated for the treatment of conditions such as ADHD, Alzheimer's Disease, and schizophrenia, whereas H_4-antagonists appear to have an immunomodulatory role and are being investigated as anti-inflammatory and analgesic drugs.

H_3-receptor antagonists

- Ciproxifan
- Clobenpropit
- Thioperamide

H_4-receptor antagonists

- Thioperamide

Mast cell stabilizers

Mast cell stabilizers appear to stabilize the mast cells to prevent degranulation and mediator release. These drugs are not usually classified as histamine antagonists, but have similar indications.

- Cromoglicate (cromolyn)
- Nedocromil
- β2 adrenergic agonists

Serotonin receptor agonist

A **serotonin receptor agonist** is a compound that activates serotonin receptors, mimicking the effect of the neurotransmitter serotonin. There are various serotonin receptors and ligands.

5-HT_{1A} receptor

Azapirones such as buspirone, gepirone, and tandospirone are 5-HT_{1A} agonists marketed primarily as anxiolytics, but also recently as antidepressants.

5-HT_{1B} receptor

Triptans such as sumatriptan, rizatriptan, and naratriptan, are 5-HT_{1B} receptor agonists that are used to abort migraine and cluster headache attacks.

5-HT_{1D} receptor

In addition to being 5-HT_{1B} agonists, triptans are also agonists at the 5-HT_{1D} receptor, which contributes to their anti-migraine effect.

5-HT_{1F} receptor

LY-334,370 was a selective 5-HT_{1F} agonist that was being developed by Eli Lilly and Company for the treatment of migraine and cluster headaches. Development was halted however due to toxicity detected in animal test subjects. Lasmiditan has successfully completed Phase II clinical trials in early 2010.

5-HT_{2A} receptor

Psychedelic drugs such as LSD, mescaline, psilocin, DMT, and 2C-B act as 5-HT_{2A} agonists. Their action at this receptor is responsible for their hallucinogenic effects.

It is now known that many of these drugs inhibit many other 5HT receptors in addition to the 5-HT2A.

5-HT_{2C} receptor

Lorcaserin is a thermogenic and anorectic weight-loss drug which acts as a selective 5-HT_{2C} agonist.

5-HT_4 receptor

Cisapride is a 5-HT_4 receptor agonist that has been used to treat disorders of gastrointestinal motility.

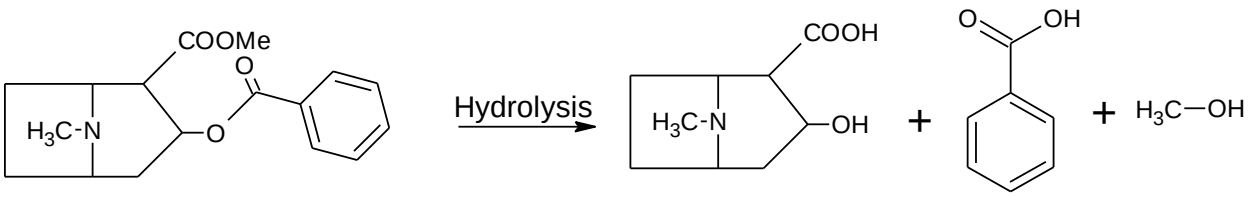
LOCAL ANESTHETICS

Local anesthetic reversibly blocks impulse conduction in peripheral nervous system; there by producing transient loss of sensation in circumscribed area of the body, without causing general loss of consciousness. These are given either topically or parentrally to a localized area.

Mechanism of action: Local anesthetics block voltage sensitive sodium channel that causes depolarization. The channel is composed of glycoprotein and has selective filters (pores for sodium ions). These pores have twelve times more speed than other cation like K^+. When depolarization occurs these selective filters open and local anesthetic blocks this voltage sensitive sodium channel. There are other two chemicals tetrodoxin and saxitoxin that block the voltage sensitive sodium channel in the same manner.
Local anesthetics are tertiary amines that contain pH between7.5 – 9 so these form water soluble salts [BH^+] and bind to the receptor. The drug(B) can bind directly to the receptor also. According to Henderson Hesselbalch equation

$$pH = pK_a - \log_{10} [B]/[BH^+]$$

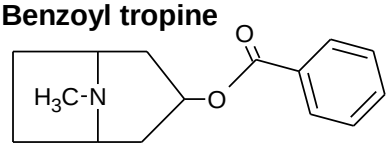
Discovery: The initial lead derived from the leaves of Erythroxylon coca plant. Native of peru country used to chew the leaves for general feeling of well being and to prevent hunger. Saliva after chewing the leaves was used to relieve the painful wounds. Niemann isolated crystalline form of cocaine from the leaves of coca in1860. Von Anrep recommended as clinical agent for after experiments on animals. Koller (1884) used first time in surgery of teeth.



Cocaine **Ecgonine** **Benzoic acid** **Methanol**

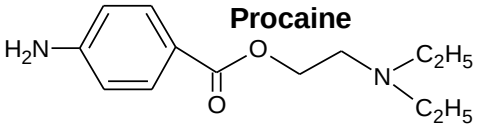
The major drawback of this drug is adducting property. This was disappeared when carboxymethyl group was removed. The cocaine is ester of benzoic acid with ecgonine and methyl alcohol. Ecgonine contain bicyclic tropane ring which is not essential for local anesthetic activity so bezoyl tropane and procaine was the new drugs to improve the side effects of cocaine.

Benzoyl tropine



8-methyl-8-azabicyclo[3.2.1]oct-3-yl benzoate

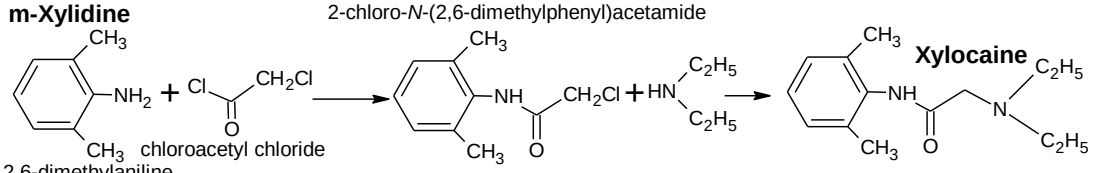
Procaine



2-(diethylamino)ethyl 4-aminobenzoate

These above drugs (Benzoyltropine and Procaine) are free from addicting properties but due to short duration of action and less intrinsic activity; epinephrine was administered with these drugs. Other side effects of these drugs are 1) allergic reactions 2) tissue irritability and 3) poor stability in aqueous medium. To improve these properties, Euler discover other natural plant origin drug Isogramine. Further new synthetic bioisoster of this drug was Lidocaine (Xylocaine or Lignocaine). The drug lidocaine is free from these side effects and most widely used drug.

m-Xylidine



2,6-dimethylaniline

chloroacetyl chloride

2-chloro-*N*-(2,6-dimethylphenyl)acetamide

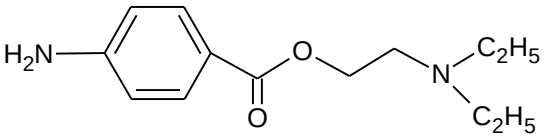
Xylocaine

2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide

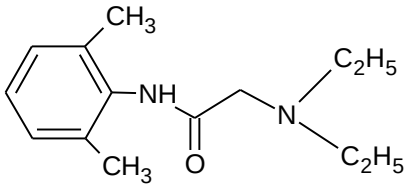
Benzocaine is lipophilic drug that is used as local anesthetic. Tetracaine is most widely used drug in amino ester group drugs.

SAR (structure activity relationship):- There are three portion of the drug lipophilic – Aliphatic chain - hydrophilic in which hydrophilic group is tertiary amino, the carbon chain is from one to three carbon and lipophilic group is PABA, benzoic acid of dimethyl aniline. If ortho and para position is replaced by electron releasing groups then they increase the potency by resonance and positive inductive effect. The zwitterions is most suitable for binding to the receptor like procaine and lidocaine.

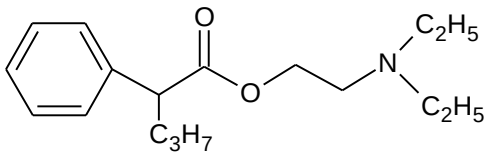
Procaine



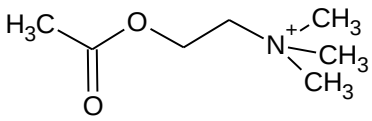
Lidocaine



Propivane



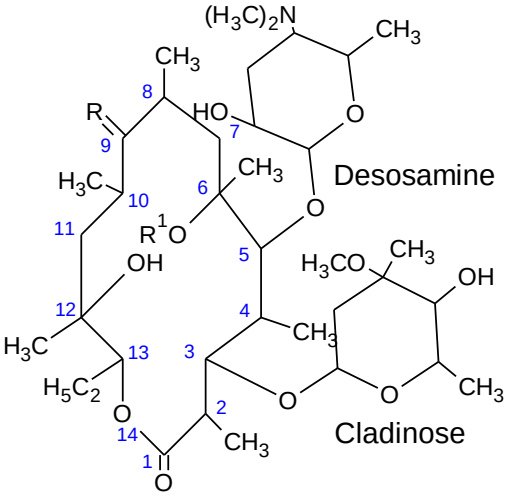
Acetylcholine



Metabolism:- Esters are hydrolyzed by enzyme esterase in the liver and inactivated. Amides are some stable to hydrolysis. The drug compete with sulpha drugs so increase in duration of action when administered with PABA antagonists.

MACROLIDE

The **macrolides** are a group of drugs (typically antibiotics) whose activity stems from the presence of a *macrolide ring*, a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached. The lactone rings are usually 14-, 15-, or 16-membered. Macrolides belong to the polyketide class of natural products.



Erythromycin R = O and R^1 = H

Clarithromycin R = O and $R^1 = CH_3$

Roxithromycin R = $NOCH_2OCH_2CH_2OCH_3$ and R^1 = H

Clarithromycin: It is 6-methyl ether of erythromycin. This group inhibits peroxide formation with 12-OH group in the macrolacton ring.

Roxithromycin: It is produced by reaction of substituted hydroxyl amine at C-9 of macrolide ketone to produce oxime that also inhibit formation of ketal .

Azithromycin: It is prepared by Beckmann rearrangement inserting N-CH3 between 9 and 10-position of macrolide ring. It has 15 membered macrolactone ring

Antibiotic macrolides

US FDA approved :

- Azithromycin (does not inhibit CYP3A4)
- Clarithromycin
- Dirithromycin
- Erythromycin
- Roxithromycin
- Telithromycin

Not US FDA approved:

Carbomycin A
Josamycin
Kitasamycin
Midecamycin/midecamycin acetate
Oleandomycin
Spiramycin - approved in Europe and other countries

Troleandomycin - used in Italy and Turkey

Tylosin/tylocine - used in animals

Non-antibiotic macrolides

The drugs tacrolimus, pimecrolimus and sirolimus which are used as immunosuppressants or immunomodulators are also macrolides. They have similar activity to ciclosporin.

Ketolides

Ketolides are a new class of antibiotics that are structurally related to the macrolides. They are used to fight respiratory tract infections caused by macrolide-resistant bacteria. Ketolides are especially resistant, as they have a double-binding site. Cladinose sugar of erythromycin is replaced with keto group in telithromycin
Macrolides include:

- Telithromycin, Cethromycin, Spiramycin - used for treating toxoplasmosis, Ansamycin, Oleandomycin, Carbomycin, Tylocine

Uses

Antibiotic macrolides are used to treat infections caused by Gram positive bacteria, *Streptococcus pneumoniae*, and *Haemophilus influenzae* infections such as respiratory tract and soft tissue infections. The antimicrobial spectrum of macrolides is slightly wider than that of penicillin, and, therefore, macrolides are a common substitute for patients with a penicillin allergy. Beta-hemolytic streptococci, pneumococci, staphylococci, and enterococci are usually susceptible to macrolides. Unlike penicillin, macrolides have been shown to be effective against mycoplasma, mycobacteria, some rickettsia, and chlamydia.
Macrolides are *not* to be used on non-ruminant herbivores, such as horses and rabbits. They rapidly produce a reaction causing fatal digestive disturbance. It can be used in horses less than one year old, but care must be taken that other horses (such as a foal's mother) do not come in contact with the macrolide treatment.

Mechanism of action

Antibacterial

Macrolides are protein synthesis inhibitors. The mechanism of action of macrolides is inhibition of bacterial protein biosynthesis, and they are thought to do this by preventing peptidyltransferase from adding the peptidyl attached to tRNA to the next amino acid (similarly to chloramphenicol) as well as inhibiting ribosomal translocation. Another potential mechanism is premature dissociation of the peptidyl-tRNA from the ribosome.
Macrolide antibiotics do so by binding reversibly to the P site on the subunit 50S of the bacterial ribosome. This action is mainly bacteriostatic, but can also be bactericidal in high

concentrations. Macrolides tend to accumulate within leukocytes, and are, therefore, transported into the site of infection.

Immunomodulation

Diffuse panbronchiolitis

The macrolide antibiotics erythromycin, clarithromycin, and roxithromycin have proven to be an effective long-term treatment for the idiopathic, Asian-prevalent lung disease diffuse panbronchiolitis (DPB). The successful results of macrolides in DPB stems from controlling symptoms through immunomodulation (adjusting the immune response), with the added benefit of low-dose requirements.
With macrolide therapy in DPB, great reduction in bronchiolar inflammation and damage is achieved through suppression of not only neutrophil granulocyte proliferation, but also lymphocyte activity and obstructive secretions in airways. The antimicrobial and antibiotic effects of macrolides, however, are not believed to be involved in their beneficial effects toward treating DPB. This is evident, as the treatment dosage is much too low to fight infection, and in DPB cases with the occurrence of the macrolide-resistant bacterium *Pseudomonas aeruginosa*, macrolide therapy still produces substantial anti-inflammatory results.

Resistance

The primary means of bacterial resistance to macrolides occurs by post-transcriptional methylation of the 23S bacterial ribosomal RNA. This acquired resistance can be either plasmid-mediated or chromosomal, i.e., through mutation, and results in cross-resistance to macrolides, lincosamides, and streptogramins (an MLS-resistant phenotype).
Two other types of acquired resistance rarely seen include the production of drug-inactivating enzymes (esterases or kinases), as well as the production of active ATP-dependent efflux proteins that transport the drug outside of the cell.
Azithromycin has been used to treat strep throat (Group A streptococcal (GAS) infection caused by *Streptococcus pyogenes*) in penicillin-sensitive patients, however macrolide-resistant strains of GAS are not uncommon. Cephalosporin is another option for these patients.

Side-effects

A 2008 British Medical Journal article highlights that the combination of macrolides and statins (used for lowering cholesterol) is not advisable and can lead to debilitating myopathy. This is because macrolides are potent inhibitors of the cytochrome P450 system, particularly of CYP3A4. Macrolides, mainly erythromycin and clarithromycin, also have a class effect of QT prolongation, which can lead to torsade de pointes. Macrolides exhibit enterohepatic recycling; that is, the drug is absorbed in the gut and sent to the liver, only to be excreted into the duodenum in bile from the liver. This can lead to a build-up of the product in the system, thereby causing nausea.

Antibacterial that bind on 30 S ribosome in protein biosynthesis:-

Aminoglycosides (initiation inhibitors)

-mycin (Streptomyces):- Streptomycin, Neomycin (Framycetin, Paromomycin, Ribostamycin), Kanamycin (Amikacin, Arbekacin, Bekanamycin, Dibekacin, Tobramycin)

Spectinomycin· Hygromycin B

Paromomycin

-micin (Micromonospora):- Gentamicin (Netilmicin, Sisomicin, Isepamicin)

Verdamicin

Astromicin

Tetracycline antibiotics(tRNA binding):- Doxycycline# •Chlortetracycline • Clomocycline • Demeclocycline • Lymecycline • Meclocycline • Metacycline • Minocycline • Oxytetracycline • Penimepicycline • Rolitetracycline • Tetracycline

Glycylcyclines:-Tigecycline

Antibacterial that bind on 50 S ribosome in protein biosynthesis

Oxazolidinone (initiation inhibitors:-) Linezolid • Torezolid · Eperezolid · Posizolid · Radezolid

Peptidyl transferase inhibitors:-

Amphenicols:- Chloramphenicol · Azidamfenicol · Thiamphenicol · Florfenicol

Pleuromutilins:- Retapamulin · Tiamulin · Valnemulin

MLS (transpeptidation/translocation inhibitors)

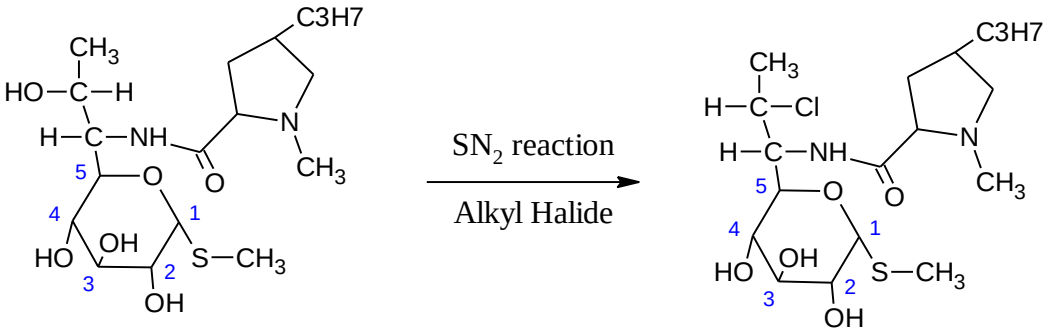
Macrolides:- Erythromycin · Azithromycin · Spiramycin · Midecamycin · Oleandomycin ·Roxithromycin · Josamycin · Troleandomycin · Clarithromycin · Miocamycin · Rokitamycin · Dirithromycin · Flurithromycin · Ketolide (Telithromycin, Cethromycin)

Lincosamides:- Clindamycin · Lincomycin

Streptogramins:- Pristinamycin · Quinupristin/dalfopristin · Virginiamycin

Lincomycin:-

Lincomycin is a lincosamide antibiotic that comes from the actinomyces *Streptomyces lincolnensis*. It has been structurally modified by thionyl chloride to its more commonly known 7-chloro-7-deoxy derivative, clindamycin.



Lincomycin **Clindamycin**

Although similar in structure, antibacterial spectrum, and in mechanism of action to macrolides, they are also effective against other species as well, i.e., actinomycetes, mycoplasma, and some species of *Plasmodium*.

However, because of its adverse effects and toxicity, it is rarely used today and reserved for patients allergic to penicillin or where bacteria has developed resistance.Clinical pharmacology

Intramuscular administration of a single dose of 600 mg of Lincomycin produces average peak serum levels of 11.6 micrograms/ml at 60 minutes, and maintains therapeutic levels for 17 to 20 hours, for most susceptible gram-positive organisms. Urinary excretion after this dose ranges from 1.8 to 24.8 percent (mean: 17.3 percent).

A two-hour intravenous infusion of 600 mg of Lincomycin achieves average peak serum levels of 15.9 micrograms/ml and yields therapeutic levels for 14 hours for most susceptible gram-positive organisms. Urinary excretion ranges from 4.9 to 30.3 percent (mean: 13.8 percent).

The biological half-life after IM or IV administration is 5.4 ± 1.0 hours. The serum half-life of lincomycin may be prolonged in patients with severe impairment of renal function, compared to patients with normal renal function. In patients with abnormal hepatic function, serum half-life may be twofold longer than in patients with normal hepatic function. Hemodialysis and peritoneal dialysis are not effective in removing lincomycin from the serum.

Tissue level studies indicate that bile is an important route of excretion. Significant levels have been demonstrated in the majority of body tissues. Although lincomycin appears to diffuse in the cerebrospinal fluid (CSF), levels of lincomycin in the CSF appear inadequate for the treatment of meningitis.

Dosage and administration

Adults

Serious infections - 600 mg (2 ml) IM every 24 hours. More severe infections - 600mg (2 ml) every 12 hours. The IV dose will be determined by the seriousness of the infection. For serious infections, doses of 600 mg to 1000 mg are given every 8 to 12 hours. For more severe infections, these doses may have to be increased. In life-threatening situations, daily IV administration of as much as 8000 mg have been given.

Pediatric Patients

Pediatric patients over one month of age: Serious infections—one IM injection of 10mg/kg every 24 hours. More severe infections—one IM injection of 10 mg/kg every 12 hours, or more

often as indicated by susceptibility testing, renal and hepatic functioning. IV dosing is 10 to 20 mg/kg/day in divided doses every 8 to 12 hours.

Subconjunctival injections

An injection of 0.75 mg, given subconjuctivally, will result in ocular fluid levels of antibiotic (lasting for at least 5 hours) with Minimum Inhibitory Concentrations sufficient for most susceptible pathogens.

Patients with diminished renal function

When therapy with lincomycin is required in individuals with severe impairment of renal function, an appropriate dose is 25 to 30 percent of that recommended for patients with normally functioning kidneys.

Side effect:- Pseudo membrane colitis is major side effect. It can be treated by vancomycin antibiotics.

PENICILLIN

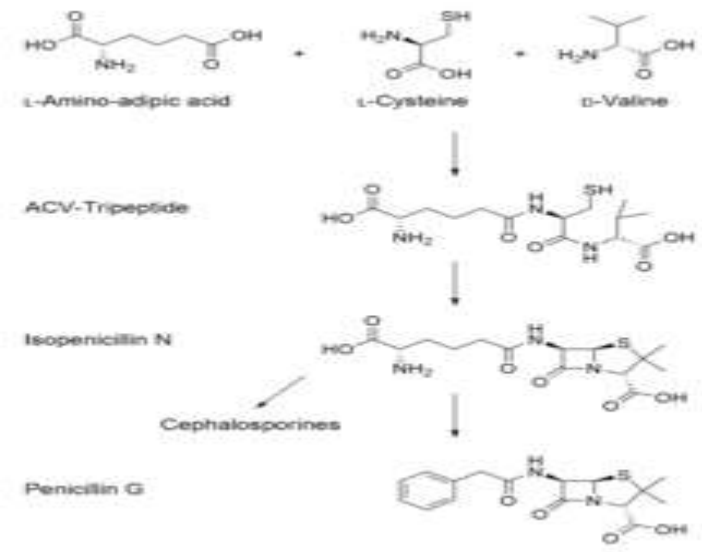
Penicillin (sometimes abbreviated **PCN** or **pen**) is a group of antibiotics derived from *Penicillium* fungi.[1] Penicillin antibiotics are historically significant because they are the first drugs that were effective against many previously serious diseases such as syphilis and Staphylococcus infections. Penicillins are still widely used today, though many types of bacteria are now resistant. All penicillins are Beta-lactam antibiotics and are used in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms.

The term "penicillin" can also refer to the *mixture* of substances that are naturally, and organically, produced.

Structure

The term "penam" is used to describe the core skeleton of a member of a penicillin antibiotic. This skeleton has the molecular formula R-$C_9H_{11}N_2O_4S$, where R is a variable side chain.

Normal penicillin has a molecular weight of 313 to 334 g/mol (latter for penicillin G). Penicillin types with additional molecular groups attached may have a molar mass around 500 g/mol. For example, cloxacillin has a molar mass of 476 g/mol and dicloxacillin has a molar mass of 492 g/mol



Biosynthesis

Penicillin biosynthesis.

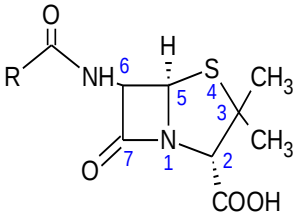
Overall, there is a total of three main and important steps to the biosynthesis of penicillin G (benzylpenicillin)

- The first step in the biosynthesis of penicillin G is the condensation of three amino acids L-α-aminoadipic acid, L-cysteine, L-valine into a tripeptide. Before condensing into a tripeptide, the amino acid L-valine will undergo epimerization and become D-valine. After the condensation, the tripeptide is named δ-(L-α-aminoadipyl)-L-cysteine-D-valine,

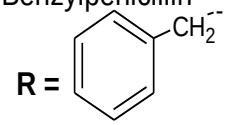
which is also known as ACV. While this reaction occurs, we must add in a required catalytic enzyme ACVS, which is also known as δ-(L-α-aminoadipyl)-L-cysteine-D-valine synthetase. This catalytic enzyme ACVs is required for the activation of the three amino acids before condensation and the epimerization of transforming L-valine to D-valine.

- The second step in the biosynthesis of penicillin G is to use an enzyme to change ACV into isopenicillin N. The enzyme is isopenicillin N synthase with the gene pcbC enclosed. The tripeptide on the ACV will then undergo oxidation, which then allows a ring closure so that a bicyclic ring is formed.[7][8] Isopenicillin N is a very weak intermediate because it does not show much antibiotic activity.[10]
- The last step in the biosynthesis of penicillin G is the exchange of the side-chain group so that isopenicillin N will become penicillin G. Through the catalytic coenzyme isopenicillin N acyltransferase (IAT), the alpha-aminoadipyl side-chain of isopenicillin N is removed and exchanged for a phenylacetyl side-chain. This reaction is encoded by the gene penDE, which is unique in the process of obtaining penicillins.

Penicillins:-

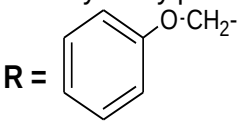


Benzylpenicillin



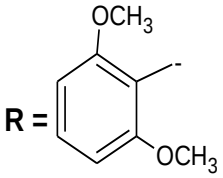
Penicillin G

Phenoxymethylpenicillin



Penicillin V

Penicillinase resistant Parenteral Penicillin



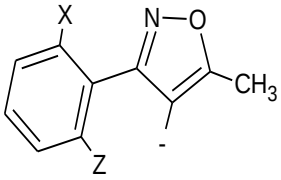
Methicillin

Oral Penicillins

Oxacillin X = Z = H

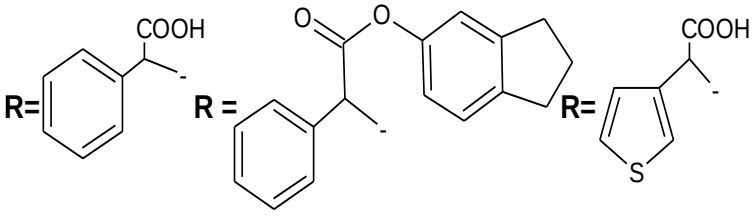
Cloxacillin X = Cl Z = H

Dicloxacillin X = Z = Cl



Penicillinase sensitive (Broad-Spectrum) Parenteral Penicillin

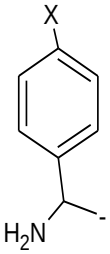
Oral Penicillins



Carbenicillin **Carindacillin** **Ticarcillin**

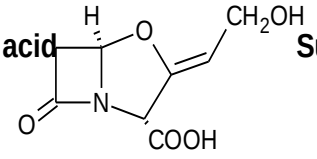
X = H Ampicillin

X = OH Amoxicillin

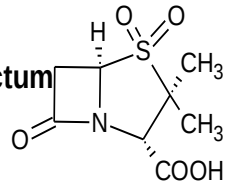


Beta-Lactamase Inhibitors:-

Clavulanic acid



Sulbactum



History

Discovery

The discovery of penicillin is attributed to Scottish scientist and Nobel laureate Alexander Fleming in 1928. He showed that, if *Penicillium notatum* were grown in the appropriate substrate, it would exude a substance with antibiotic properties, which he dubbed penicillin. This serendipitous observation began the modern era of antibiotic discovery. The development of penicillin for use as a medicine is attributed to the Australian Nobel laureate Howard Walter Florey together with the German Nobel laureate Ernst Chain and the English biochemist Norman Heatley.

However, several others reported the bacteriostatic effects of *Penicillium* earlier than Fleming. The use of bread with a blue mould (presumably penicillium) as a means of treating suppurating wounds was a staple of folk medicine in Europe since the Middle Ages. The first published reference appears in the publication of the Royal Society in 1875, by John Tyndall.[13] Ernest Duchesne documented it in an 1897 paper, which was not accepted by the Institut Pasteur because of his youth. In March 2000, doctors at the San Juan de Dios Hospital in San José, Costa Rica published the manuscripts of the Costa Rican scientist and medical doctor Clodomiro (Clorito) Picado Twight (1887–1944). They reported Picado's observations on the inhibitory actions of fungi of the genus *Penicillium* between 1915 and 1927. Picado reported his discovery to the Paris Academy of Sciences, yet did not patent it, even though his investigations started years before Fleming's. Joseph Lister was experimenting with penicillum in 1871 for his Aseptic surgery. He found that it weakened the microbes but then he dismissed the fungi.

These early investigations could not have yielded more intellectual ferment in antibiotic theory because they not only occurred in practical obscurity, but also because at the time of their earliest observation, infectious agent theory was not widespread in understanding, nor fully accepted as medical science fact.

Sanitation/sterilization measures and methods were heuristically known to limit the outbreak and spread of disease. However, the actual mechanism of what the specific parasite, bacteria, or virus, agents were, their vectors and mechanisms of transmission & biological attack, how they progressed in the body at the cellular level, and the bio-chemical mechanism of their natural course in the bodies of living organisms was wholly unknown, and was unimaginable to the minds of 19th century medical science and medical practice.

With the rise in the late 19th century of a rigorous fundamental investigative scientific method and practices in all of the physical sciences, the anecdotal heuristic information regarding “cures” stemming from the application of natural agents against the progress of disease could be put to rigorous examination. This work led to the concurrent discovery of how living organisms receive infection, how they manage infections once they have begun; and, most importantly (in penicillin’s case) what agents, natural and man-made could do, to affect the progress of the infection within the living organism.

Fleming recounted that the date of his discovery of penicillin was on the morning of Friday, September 28, 1928. It was a fortuitous accident: in his laboratory in the basement of St. Mary's Hospital in London (now part of Imperial College), Fleming noticed a petri dish containing *Staphylococcus* plate culture he had mistakenly left open, which was contaminated by blue-green mould, which had formed a visible growth. There was a halo of inhibited bacterial growth around the mould. Fleming concluded that the mould was releasing a substance that was

repressing the growth and lysing the bacteria. He grew a pure culture and discovered that it was a *Penicillium* mould, now known to be *Penicillium notatum*. Charles Thom, an American specialist working at the U.S. Department of Agriculture, was the acknowledged expert, and Fleming referred the matter to him. Fleming coined the term "penicillin" to describe the filtrate of a broth culture of the *Penicillium* mould. Even in these early stages, penicillin was found to be most effective against Gram-positive bacteria, and ineffective against Gram-negative organisms and fungi. He expressed initial optimism that penicillin would be a useful disinfectant, being highly potent with minimal toxicity compared to antiseptics of the day, and noted its laboratory value in the isolation of "*Bacillus influenzae*" (now *Haemophilus influenzae*).[15] After further experiments, Fleming was convinced that penicillin could not last long enough in the human body to kill pathogenic bacteria, and stopped studying it after 1931. He restarted clinical trials in 1934, and continued to try to get someone to purify it until 1940.

Medical application

In 1930, Cecil George Paine, a pathologist at the Royal Infirmary in Sheffield, attempted to use penicillin to treat sycosis barbae–eruptions in beard follicles, but was unsuccessful, probably because the drug did not penetrate the skin deeply enough. Moving on to ophthalmia neonatorum; a gonococcal infection in infants, he achieved the first recorded cure with penicillin, on November 25, 1930. He then cured four additional patients (one adult and three infants) of eye infections, failing to cure a fifth.

In 1939, Australian scientist Howard Florey (later Baron Florey) and a team of researchers (Ernst Boris Chain, A. D. Gardner, Norman Heatley, M. Jennings, J. Orr-Ewing and G. Sanders) at the Sir William Dunn School of Pathology, University of Oxford made significant progress in showing the *in vivo* bactericidal action of penicillin. Their attempts to treat humans failed because of insufficient volumes of penicillin (the first patient treated was Reserve Constable Albert Alexander), but they proved it harmless and effective on mice.[18]

Some of the pioneering trials of penicillin took place at the Radcliffe Infirmary in Oxford, England. These trials continue to be cited by some sources as the first cures using penicillin, though the Paine trials took place earlier. On March 14, 1942, John Bumstead and Orvan Hess saved a dying patient's life using penicillin.

Mass production

The chemical structure of penicillin was determined by Dorothy Crowfoot Hodgkin in 1945. Penicillin has since become the most widely used antibiotic to date, and is still used for many Gram-positive bacterial infections. A team of Oxford research scientists led by Australian Howard Florey and including Ernst Boris Chain and Norman Heatley devised a method of mass-producing the drug. Florey and Chain shared the 1945 Nobel prize in medicine with Fleming for their work. After World War II, Australia was the first country to make the drug available for civilian use. Chemist John C. Sheehan at MIT completed the first total synthesis of penicillin and some of its analogs in the early 1950s, but his methods were not efficient for mass production.

The challenge of mass-producing this drug was daunting. On March 14, 1942, the first patient was treated for streptococcal septicemia with U.S.-made penicillin produced by Merck & Co. Half of the total supply produced at the time was used on that one patient. By June 1942, there was just enough U.S. penicillin available to treat ten patients. A moldy cantaloupe in a Peoria, Illinois market in 1943 was found to contain the best and highest-quality penicillin after a worldwide search. The discovery of the cantaloupe, and the results of fermentation research on

corn steep liquor at the Northern Regional Research Laboratory at Peoria, Illinois, allowed the United States to produce 2.3 million doses in time for the invasion of Normandy in the spring of 1944. Large-scale production resulted from the development of deep-tank fermentation by chemical engineer Margaret Hutchinson Rousseau.

G. Raymond Rettew made a significant contribution to the American war effort by his techniques to produce commercial quantities of penicillin. During World War II, penicillin made a major difference in the number of deaths and amputations caused by infected wounds among Allied forces, saving an estimated 12%–15% of lives. Availability was severely limited, however, by the difficulty of manufacturing large quantities of penicillin and by the rapid renal clearance of the drug, necessitating frequent dosing. Penicillin is actively excreted, and about 80% of a penicillin dose is cleared from the body within three to four hours of administration. Indeed, during the early penicillin era, the drug was so scarce and so highly valued that it became common to collect the urine from patients being treated, so that the penicillin in the urine could be isolated and reused.

This was not a satisfactory solution, so researchers looked for a way to slow penicillin excretion. They hoped to find a molecule that could compete with penicillin for the organic acid transporter responsible for excretion, such that the transporter would preferentially excrete the competing molecule and the penicillin would be retained. The uricosuric agent probenecid proved to be suitable. When probenecid and penicillin are administered together, probenecid competitively inhibits the excretion of penicillin, increasing penicillin's concentration and prolonging its activity. Eventually, the advent of mass-production techniques and semi-synthetic penicillins resolved the supply issues, so this use of probenecid declined.[26] Probenecid is still useful, however, for certain infections requiring particularly high concentrations of penicillins.

Developments from penicillin

The narrow range of treatable diseases or *spectrum of activity* of the penicillins, along with the poor activity of the orally active phenoxymethylpenicillin, led to the search for derivatives of penicillin that could treat a wider range of infections. The isolation of 6-APA, the nucleus of penicillin, allowed for the preparation of semisynthetic penicillins, with various improvements over benzylpenicillin (bioavailability, spectrum, stability, tolerance).

The first major development was ampicillin, which offered a broader spectrum of activity than either of the original penicillins. Further development yielded beta-lactamase-resistant penicillins including flucloxacillin, dicloxacillin and methicillin. These were significant for their activity against beta-lactamase-producing bacteria species, but are ineffective against the methicillin-resistant *Staphylococcus aureus* strains that subsequently emerged.

Another development of the line of true penicillins was the antipseudomonal penicillins, such as carbenicillin, ticarcillin, and piperacillin, useful for their activity against Gram-negative bacteria. However, the usefulness of the beta-lactam ring was such that related antibiotics, including the mecillinams, the carbapenems and, most important, the cephalosporins, still retain it at the center of their structures.

Mechanism of action

Bacteria constantly remodel their peptidoglycan cell walls, simultaneously building and breaking down portions of the cell wall as they grow and divide. β-Lactam antibiotics work by inhibiting the formation of peptidoglycan cross-links in the bacterial cell wall. The β-lactam moiety (functional group) of penicillin binds to the enzyme (DD-transpeptidase) that links the peptidoglycan molecules in bacteria. The enzymes that hydrolyze the peptidoglycan cross-links continue to function, which weakens the cell wall of the bacterium (in other words, the antibiotic causes cytolysis or death due to osmotic pressure). In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases and autolysins, which further digest the bacteria's existing peptidoglycan.

Gram-positive bacteria are called protoplasts when they lose their cell wall. Gram-negative bacteria do not lose their cell wall completely and are called spheroplasts after treatment with penicillin.

Penicillin shows a synergistic effect with aminoglycosides, since the inhibition of peptidoglycan synthesis allows aminoglycosides to penetrate the bacterial cell wall more easily, allowing its disruption of bacterial protein synthesis within the cell. This results in a lowered MBC for susceptible organisms.

Penicillins, like other β-lactam antibiotics, block not only the division of bacteria, including cyanobacteria, but also the division of cyanelles, the photosynthetic organelles of the glaucophytes, and the division of chloroplasts of bryophytes. In contrast, they have no effect on the plastids of the highly developed vascular plants. This supports the endosymbiotic theory of the evolution of plastid division in land plants.

Variants in clinical use

The term "penicillin" is often used in the generic sense to refer to one of the narrow-spectrum penicillins, in particular, benzylpenicillin (penicillin G).

Other types include:

- Phenoxymethylpenicillin
- Procaine benzylpenicillin
- Benzathine benzylpenicillin

Adverse effects

Main article: Penicillin drug reaction

Common adverse drug reactions (≥1% of patients) associated with use of the penicillins include diarrhea, hypersensitivity, nausea, rash, neurotoxicity, urticaria, and superinfection (including candidiasis). Infrequent adverse effects (0.1–1% of patients) include fever, vomiting, erythema, dermatitis, angioedema, seizures (especially in epileptics), and pseudomembranous colitis.

Production

Penicillin is a secondary metabolite of fungus *Penicillium* that is produced when growth of the fungus is inhibited by stress. It is not produced during active growth. Production is also limited by feedback in the synthesis pathway of penicillin.

α-ketoglutarate + AcCoA → homocitrate → L-α-aminoadipic acid → L-Lysine + β-lactam

The by-product L-Lysine inhibits the production of homocitrate, so the presence of exogenous lysine should be avoided in penicillin production.

The Penicillium cells are grown using a technique called fed-batch culture, in which the cells are constantly subject to stress and will produce plenty of penicillin. The carbon sources that are available are also important: Glucose inhibits penicillin, whereas lactose does not. The pH and

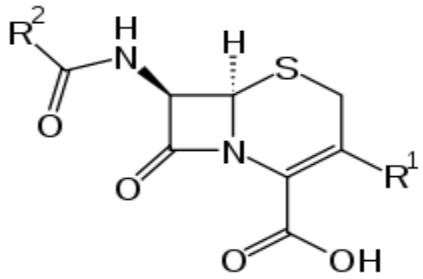
the levels of nitrogen, lysine, phosphate, and oxygen of the batches must be controlled automatically.

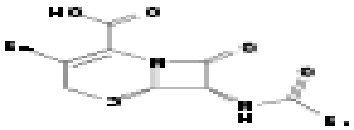
Penicillin production emerged as an industry as a direct result of World War II. During the war, there was an abundance of jobs available in the U.S. on the home front. The War Production Board was founded to monitor job distribution and production. Penicillin was produced in huge quantities during the war and the industry prospered. In July 1943, the War Production Board drew up a plan for the mass distribution of penicillin stocks to Allied troops fighting in Europe. At the time of this plan, 425 million units per year were being produced. As a direct result of the war and the War Production Board, by June 1945 over 646 billion units per year were being produced.

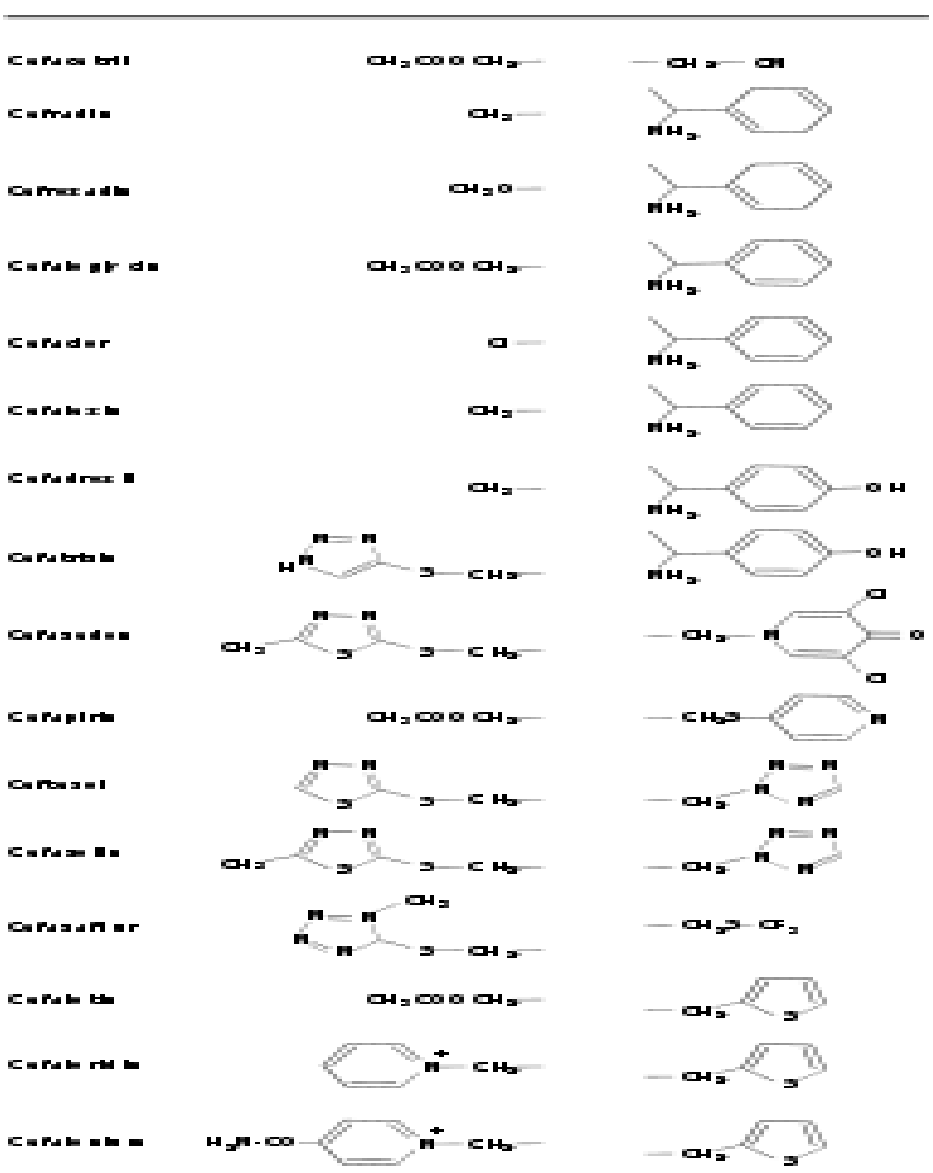
CEPHALOSPORIN

The **cephalosporins** are a class of β-lactam antibiotics originally derived from *Acremonium*, which was previously known as "Cephalosporium".

Together with cephamycins they constitute a subgroup of β-lactam antibiotics called cephems.







Structure of the classical cephalosporins

History

Cephalosporin compounds were first isolated from cultures of *Cephalosporium acremonium* from a sewer in Sardinia in 1948 by Italian scientist Giuseppe Brotzu. He noticed that these cultures produced substances that were effective against *Salmonella typhi*, the cause of typhoid fever, which had beta-lactamase. Guy Newton and Edward Abraham at the Sir William Dunn School of Pathology at the University of Oxford isolated cephalosporin C. The cephalosporin nucleus, 7-aminocephalosporanic acid (7-ACA), was derived from cephalosporin C and proved to be analogous to the penicillin nucleus 6-aminopenicillanic acid, but it was not sufficiently potent for clinical use. Modification of the 7-ACA side-chains resulted in the development of useful antibiotic agents, and the first agent cephalothin (cefalotin) was launched by Eli Lilly and Company in 1964.

Mechanism of action

Cephalosporins are bactericidal and have the same mode of action as other beta-lactam antibiotics (such as penicillins) but are less susceptible to penicillinases. Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin-binding proteins (PBPs). PBPs bind to the D-Ala-D-Ala at the end of muropeptides (peptidoglycan precursors) to crosslink the peptidoglycan. Beta-lactam antibiotics mimic this site and competitively inhibit PBP crosslinking of peptidoglycan.

Clinical use

Indications

Cephalosporins are indicated for the prophylaxis and treatment of infections caused by bacteria susceptible to this particular form of antibiotic. First-generation cephalosporins are predominantly active against Gram-positive bacteria, and successive generations have increased activity against Gram-negative bacteria (albeit often with reduced activity against Gram-positive organisms).

Adverse effects

Common adverse drug reactions (ADRs) (≥1% of patients) associated with the cephalosporin therapy include: diarrhea, nausea, rash, electrolyte disturbances, and/or pain and inflammation at injection site. Infrequent ADRs (0.1–1% of patients) include: vomiting, headache, dizziness,

oral and vaginal candidiasis, pseudomembranous colitis, superinfection, eosinophilia, and/or fever.

The commonly quoted figure of 10% of patients with allergic hypersensitivity to penicillins and/or carbapenems also having cross-reactivity with cephalosporins originated from a 1975 study looking at the original cephalosporins, and subsequent "safety first" policy meant this was widely quoted and assumed to apply to all members of the group. Hence it was commonly stated that they are contraindicated in patients with a history of severe, immediate allergic reactions (urticaria, anaphylaxis, interstitial nephritis, etc.) to penicillins, carbapenems or cephalosporins. This, however, should be viewed in the light of recent epidemiological work suggesting that, for many second-generation (or later) cephalosporins, the cross-reactivity rate with penicillin is much lower, having no significantly increased risk of reactivity in the studies examined. The British National Formulary previously issued blanket warnings of 10% cross reactivity, but, since the September 2008 edition, suggests in the absence of suitable alternatives that oral cefixime or cefuroxime and injectable cefotaxime, ceftazidine, and ceftriaxone can be used with caution, but to avoid cefaclor, cefadrocil, cefalexin, and cefradine.

Several cephalosporins are associated with hypoprothrombinemia and a disulfiram-like reaction with ethanol. These include latamoxef, cefmenoxime, moxalactam, cefoperazone, cefamandole, cefmetazole, and cefotetan. This is thought to be due to the N-methylthiotetrazole (NMTT) side-chain of these cephalosporins, which blocks the enzyme vitamin K epoxide reductase (likely causing hypothrombinemia) and aldehyde dehydrogenase (causing alcohol intolerance).

Classification

The cephalosporin nucleus can be modified to gain different properties. Cephalosporins are sometimes grouped into "generations" by their antimicrobial properties. The first cephalosporins were designated first-generation cephalosporins, whereas, later, more extended-spectrum cephalosporins were classified as second-generation cephalosporins. Each newer generation of cephalosporins has significantly greater Gram-negative antimicrobial properties than the preceding generation, in most cases with decreased activity against Gram-positive organisms. Fourth-generation cephalosporins, however, have true broad-spectrum activity.

The classification of cephalosporins into "generations" is commonly practiced, although the exact categorization of cephalosporins is often imprecise. For example, the fourth generation of cephalosporins is not recognized as such, in Japan.[*citation needed*] In Japan, cefaclor is classed as a first-generation cephalosporin, even though in the United States it is a second-generation one; and cefbuperazone, cefminox, and cefotetan are classed as second-generation cephalosporins. Cefmetazole and cefoxitin are classed as third-generation cephems. Flomoxef, latamoxef are in a new class called oxacephems.

Most first-generation cephalosporins were originally spelled "ceph-" in English-speaking countries. This continues to be the preferred spelling in the United States and Australia, while European countries (including the United Kingdom) have adopted the International Nonproprietary Names, which are always spelled "cef-". Newer first-generation cephalosporins and all cephalosporins of later generations are spelled "cef-", even in the United States.

Some state that, although cephalosporins can be divided into five or even six generations, the usefulness of this organization system is of limited clinical relevance.
Fourth generation Cephalosporins as of March, 2007 were considered to be *"a class of highly potent antibiotics that are among medicine's last defenses against several serious human infections"* according to the *Washington Post*.

	Members	Description
1	Cefacetrile (cephacetrile), Cefadroxil (cefadroxyl; Duricef), Cephalexin (cephalexin; Keflex), Cefaloglycin (cephaloglycin), Cefalonium (cephalonium), Cefaloridine (cephaloradine), Cefalotin (cephalothin; Keflin), Cefapirin (cephapirin; Cefadryl), Cefatrizine, Cefazaflur, Cefazedone, Cefazolin (cephazolin; Ancef, Kefzol), Cefradine (cephradine; Velosef), Cefroxadine, Ceftezole.	**Gram positive:** Activity against penicillinase-producing, methicillin-susceptible staphylococci and streptococci (though they are not the drugs of choice for such infections). No activity against methicillin-resistant staphylococci or enterococci. **Gram negative:** Activity against *Proteus mirabilis*, some *Escherichia coli*, and *Klebsiella pneumoniae* ("PEcK"), but have no activity against *Bacteroides fragilis*, *Pseudomonas*, *Acinetobacter*, *Enterobacter*, indole-positive *Proteus*, or *Serratia*.
2	Cefaclor (Ceclor, Distaclor, Keflor, Raniclor), Cefonicid (Monocid), Cefprozil (cefproxil; Cefzil), Cefuroxime (Zefu, Zinnat, Zinacef, Ceftin, Biofuroksym,[13] Xorimax), Cefuzonam. Second generation cephalosporins with antianaerobe activity: Cefmetazole, Cefotetan, Cefoxitin. The following cephems are also sometimes grouped with second-generation cephalosporins: Carbacephems: loracarbef (Lorabid); Cephamycins: cefbuperazone, cefmetazole (Zefazone), cefminox, cefotetan (Cefotan), cefoxitin (Mefoxin).	**Gram positive:** Less than first generation. **Gram negative:** Greater than first generation: HEN (*Haemophilus influenzae*, *Enterobacter aerogenes* and some *Neisseria* + the PEcK described above.
3	Cefcapene, Cefdaloxime, Cefdinir (Zinir, Omnicef, Kefnir), Cefditoren, Cefetamet, Cefixime (Zifi, Suprax), Cefmenoxime, Cefodizime, Cefotaxime (Claforan), Cefovecin (Convenia), Cefpimizole, Cefpodoxime (Vantin, PECEF), Cefteram, Ceftibuten (Cedax), Ceftiofur, Ceftiolene, Ceftizoxime (Cefizox),	**Gram positive:** Some members of this group (in particular, those available in an oral formulation, and those with anti-pseudomonal activity) have decreased activity against Gram-positive organisms. **Gram negative:** Third-generation cephalosporins have a broad spectrum of

Ceftriaxone (Rocephin). Third-generation cephalosporins with antipseudomonal activity: Cefoperazone (Cefobid), Ceftazidime (Fortum, Fortaz). The following cephems are also sometimes grouped with third-generation cephalosporins: Oxacephems: latamoxef (moxalactam).

activity and further increased activity against Gram-negative organisms. They may be particularly useful in treating hospital-acquired infections, although increasing levels of extended-spectrum beta-lactamases are reducing the clinical utility of this class of antibiotics. They are also able to penetrate the CNS, making them useful against meningitis caused by pneumococci, meningococci, *H. influenzae*, and susceptible *E. coli*, *Klebsiella*, and penicillin-resistant *N. gonorrhoeae*. Since 2007, third-generation cephalosporins (ceftriaxone or cefixime) have been the only recommended treatment for gonorrhea in the United States.[14]

Gram positive: They are extended-spectrum agents with similar activity against Gram-positive organisms as first-generation cephalosporins.

4 Cefclidine, Cefepime (Maxipime), Cefluprenam, Cefoselis, Cefozopran, Cefpirome (Cefrom), Cefquinome. The following cephems are also sometimes grouped with fourth-generation cephalosporins: Oxacephems: flomoxef

Gram negative: Fourth-generation cephalosporins are zwitterions that can penetrate the outer membrane of Gram negative bacteria. They also have a greater resistance to beta-lactamases than the third-generation cephalosporins. Many can cross the blood-brain barrier and are effective in meningitis. They are also used against Pseudomonas aeruginosa.

5 Ceftobiprole, Ceftaroline

Ceftobiprole has been described as "fifth-generation" cephalosporin, though acceptance for this terminology is not universal. Ceftobiprole (and the soluble prodrug medocaril) are on the FDA fast-track. Ceftobiprole has powerful antipseudomonal characteristics and *appears* to be less susceptible to development of resistance. Ceftaroline has also been described as "fifth-

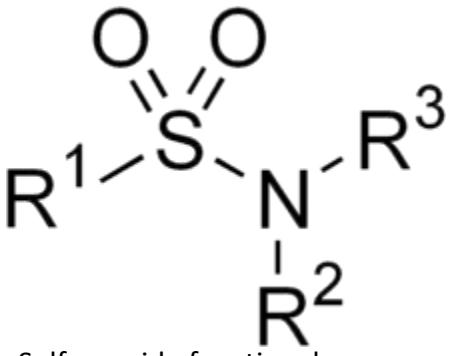
generation" cephalosporin.

These cephems have progressed far enough to be named, but have not been assigned to a particular generation: Cefaloram, Cefaparole, Cefcanel, Cefedrolor, Cefempidone, Cefetrizole, Cefivitril, Cefmatilen, Cefmepidium, Cefoxazole, Cefrotil, Cefsumide, Ceftaroline, Ceftioxide, Cefuracetime

SULFONAMIDE (MEDICINE)

Sulfonamide is the basis of several groups of drugs. The original antibacterial sulfonamides (sometimes called simply sulfa drugs) are synthetic antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, e.g., the anticonvulsant sultiame. The sulfonylureas and thiazide diuretics are newer drug groups based on the antibacterial sulfonamides.

Sulfa allergies are common, hence medications containing sulfonamides are prescribed carefully. It is important to make a distinction between sulfa drugs and other sulfur-containing drugs and additives, such as sulfates and sulfites, which are chemically unrelated to the sulfonamide group, and do not cause the same hypersensitivity reactions seen in the sulfonamides.



Sulfonamide functional group

Antimicrobial (Dihydropteroate synthetase inhibitor)

In bacteria, antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS), an enzyme involved in folate synthesis.

Other uses

The sulfonamide chemical moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochlorothiazide, metolazone, and indapamide, among others), loop diuretics (including furosemide, bumetanide and torsemide) sulfonylureas (including glipizide, glyburide, among others), some COX-2 inhibitors (e. g. celecoxib) and acetazolamide.

Sulfasalazine, in addition to its use as an antibiotic, is also utilized in the treatment of inflammatory bowel disease.

History

Sulfonamide drugs were the first antimicrobial drugs, and paved the way for the antibiotic revolution in medicine. The first sulfonamide, trade named Prontosil, was actually a prodrug. Experiments with Prontosil began in 1932 in the laboratories of Bayer AG, at that time a component of the huge German chemical trust IG Farben. The Bayer team believed that coal-tar dyes able to preferentially bind to bacteria and parasites might be used to target harmful organisms in the body. After years of fruitless trial-and-error work on hundreds of dyes, a team led by physician/researcher Gerhard Domagk (working under the general direction of Farben executive Heinrich Hoerlein) finally found one that worked: a red dye synthesized by Bayer chemist Josef Klarer that had remarkable effects on stopping some bacterial infections in mice. The first official communication about the breakthrough discovery was not published until 1935, more than two years after the drug was patented by Klarer and his research partner Fritz Mietzsch. Prontosil, as Bayer named the new drug, was the first medicine ever discovered that could effectively treat a range of bacterial infections inside the body. It had a strong protective action against infections caused by streptococci, including blood infections, childbed fever, and erysipelas, and a lesser effect on infections caused by other cocci. However, it had no effect at all in the test tube, exerting its antibacterial action only in live animals. Later it was accidentally discovered by a French research team, led by Ernest Fourneau **(French)**, at the Pasteur Institute that the drug was metabolized into two pieces inside the body, releasing from the inactive dye portion a smaller, colorless, active compound called sulfanilamide. The discovery helped establish the concept of "bioactivation" and dashed the German corporation's dreams of enormous profit; the active molecule sulfanilamide (or sulfa) had first been synthesized in 1906 and was widely used in the dye-making industry; its patent had since expired and the drug was available to anyone.

The result was a sulfa craze. For several years in the late 1930s, hundreds of manufacturers produced tens of thousands of tons of myriad forms of sulfa. This and nonexistent testing requirements led to the Elixir Sulfanilamide disaster in the fall of 1937, during which at least 100 people were poisoned with diethylene glycol. This led to the passage of the Federal Food, Drug, and Cosmetic Act in 1938. As the first and only effective antibiotic available in the years before penicillin, sulfa drugs continued to thrive through the early years of World War II. They are credited with saving the lives of tens of thousands of patients including Franklin Delano Roosevelt, Jr. (son of President Franklin Delano Roosevelt) (in 1936) and Winston Churchill. Sulfa had a central role in preventing wound infections during the war. American soldiers were issued a first-aid kit containing sulfa pills and powder and were told to sprinkle it on any open wound.

During the years 1942 to 1943, Nazi doctors conducted sulfanilamide experiments on prisoners in concentration camps.

The sulfanilamide compound is more active in the protonated form, which in case of the acid works better in a basic environment. The solubility of the drug is very low and sometimes can crystallize in the kidneys, due to its first pK_a of around 10. This is a very painful experience so patients are told to take the medication with copious amounts of water. Newer compounds have a pK_a of around 5–6 so the problem is avoided.

Many thousands of molecules containing the sulfanilamide structure have been created since its discovery (by one account, over 5,400 permutations by 1945), yielding improved formulations with greater effectiveness and less toxicity. Sulfa drugs are still widely used for

conditions such as acne and urinary tract infections, and are receiving renewed interest for the treatment of infections caused by bacteria resistant to other antibiotics.

Sulpha is an alternate (British English) spelling of the common name for sulfonamide antibiotics.

Preparation

Sulfonamides are prepared by the reaction of a sulfonyl chloride with ammonia or an amine. Certain sulfonamides (sulfadiazine or sulfamethoxazole) are sometimes mixed with the drug trimethoprim, which acts against dihydrofolate reductase.

List of sulfonamides

Antibiotics / Dihydropteroate synthetase inhibitors

Short-acting

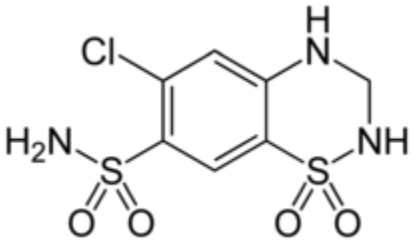
- Sulfamethoxazole
- Sulfisomidine (also known as sulfaisodimidine)
- Sulfanilamides (e.g. sulfadiazine, sulfamethoxazole)

Intermediate-acting

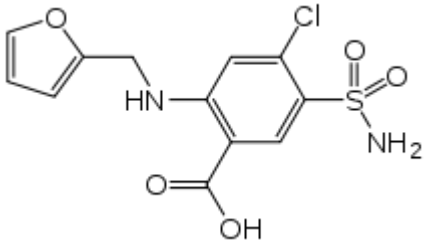
- Sulfacetamide, Sulfadoxine

Diuretics

- Acetazolamide, Bumetanide, Chlorthalidone, Clopamide, Furosemide, Hydrochlorothiazide (HCT, HCTZ, HZT), Indapamide, Mefruside, Metolazone, Xipamide



Hydrochlorothiazide is a sulfonamide & a thiazide.



Furosemide is a sulfonamide.

Ophthalmologicals

- Dichlorphenamide (DCP), Dorzolamide

Anticonvulsants

- Acetazolamide, Ethoxzolamide, Sultiame, Zonisamide

Dermatologicals

- Mafenide

Other

- Celecoxib (COX-2 inhibitor)
- Darunavir (Protease Inhibitor)
- Probenecid (PBN)
- Sulfasalazine (SSZ)
- Sumatriptan (SMT)

Side effects

Patient Suffering from Stevens–Johnson syndrome

Sulfonamides have the potential to cause a variety of untoward reactions, including urinary tract disorders, haemopoietic disorders, porphyria and hypersensitivity reactions. When used in

large doses, they may cause a strong allergic reaction. Two of the most serious are Stevens Johnson syndrome and toxic epidermal necrolysis (also known as Lyell syndrome).

Adverse reactions

Approximately 3% of the general population have adverse reactions when treated with sulfonamide antimicrobials. Of note is the observation that patients with HIV have a much higher prevalence, at about 60%. People who have a hypersensitivity reaction to one member of the sulfonamide class are likely to have a similar reaction to others.

Hypersensitivity reactions are less common in non-antibiotic sulfonamides, and, though controversial, the available evidence suggests those with hypersensitivity to sulfonamide antibiotics do not have an increased risk of hypersensitivity reaction to the non-antibiotic agents.

Allergic urticaria on the skin induced by an antibiotic

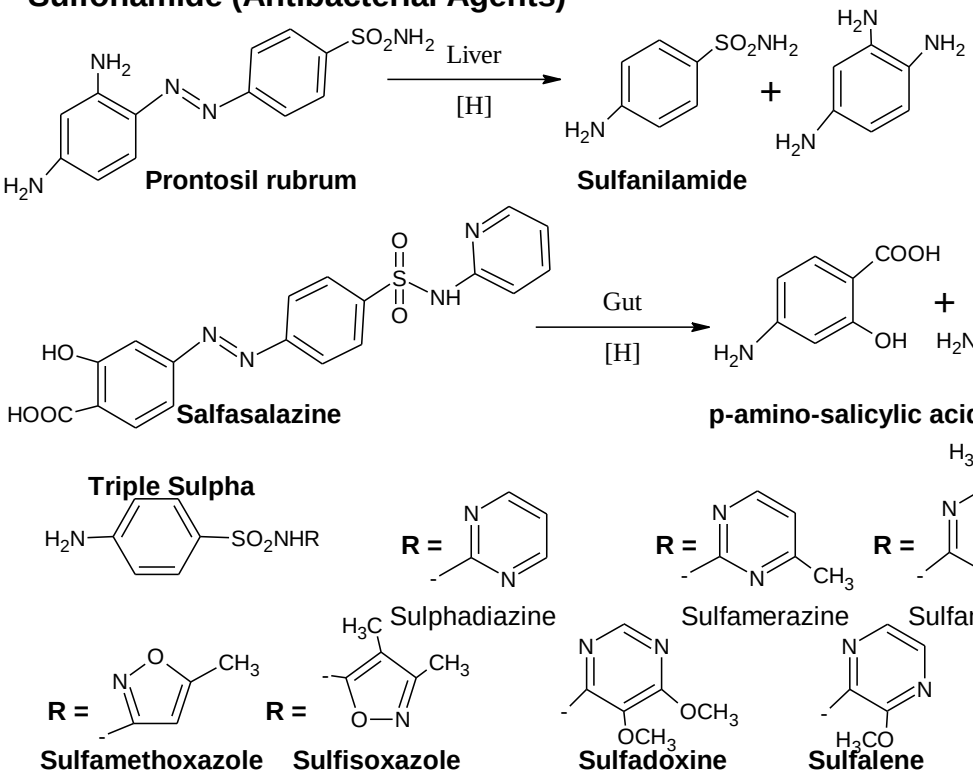
Two regions of the sulfonamide antibiotic chemical structure are implicated in the hypersensitivity reactions associated with the class.

- The first is the N1 heterocyclic ring, which causes a type I hypersensitivity reaction.
- The second is the N4 amino nitrogen that, in a stereospecific process, forms reactive metabolites that cause either direct cytotoxicity or immunologic response.

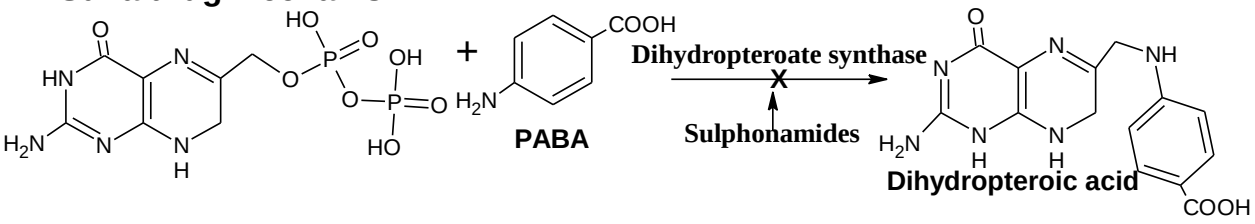
The non-antibiotic sulfonamides lack both of these structures.

The most common manifestations of a hypersensitivity reaction to sulfa drugs are rash and hives. However, there are several life-threatening manifestations of hypersensitivity to sulfa drugs, including Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, hemolytic anemia, thrombocytopenia, and fulminant hepatic necrosis, among others.

Sulfonamide (Antibacterial Agents)



Sulfa drug Mechanism:-



Trimethoprim-sulfamethoxazole

Sulphonamides are co-administered with dihydrofolate reductase inhibitors such as trimethoprim and sulphamethoxazole is known as cotrimoxazole is very useful drug combinations because both drugs act at different phases with synergistic effect.

Trimethoprim-sulfamethoxazole

Combination of	
Trimethoprim	Dihydrofolate reductase inhibitor

(16.7%)

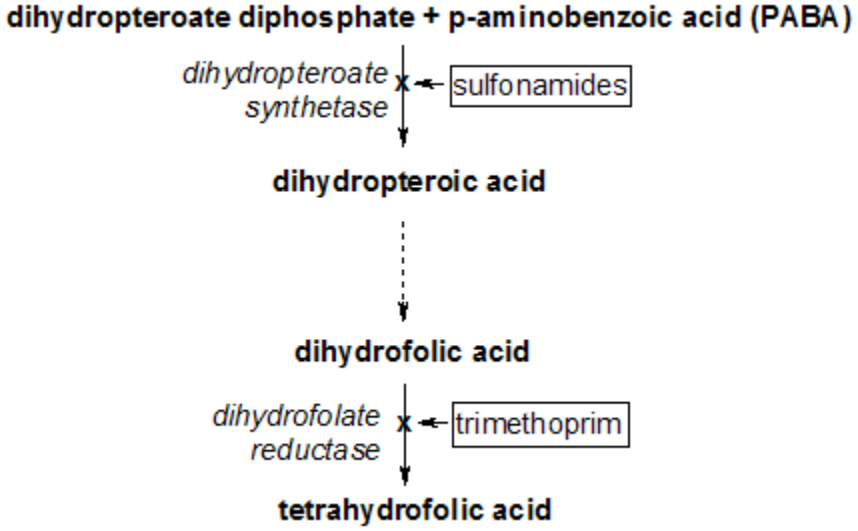
Sulfamethoxazole Sulfonamide antibiotic (83.3%)

Trimethoprim-sulfamethoxazole or **Co-trimoxazole** (abbreviated SXT, TMP-SMX, TMP-SMZ or TMP-sulfa) is a sulfonamide antibiotic combination of trimethoprim and sulfamethoxazole, in the ratio of 1 to 5, used in the treatment of a variety of bacterial infections. The name co-trimoxazole is the British Approved Name, and has been marketed worldwide under many trade names including **Septra** (GSK), **Bactrim** (Roche), and various generic preparations. Sources differ as to whether co-trimoxazole usually is bactericidal or bacteriostatic.

Synergistic action

The synergy between trimethoprim and sulphamethoxazole was first described in a series of *in vitro* and *in vivo* experiments published in the late 1960s. Trimethoprim and sulfamethoxazole have a greater effect when given together than when given separately; the reason is because they inhibit successive steps in the folate synthesis pathway (see diagram below).

It is unclear whether this synergy occurs at doses used in humans, because, at the concentrations seen in blood and tissues, the ratio of trimethoprim to sulphamethoxazole is 1:20,[5] which is less than the 1:5 ratio needed *in vitro* for synergy to occur.



Tetrahydrofolate synthesis pathway

Sulfamethoxazole acts as a false-substrate inhibitor of dihydropteroate synthetase. Sulfonamides such as sulfamethoxazole are analogues of *p*-aminobenzoic acid (PABA) and, thus, are competitive inhibitors of the enzyme, inhibiting the production of dihydropteroic acid.

Trimethoprim acts by interfering with the action of bacterial dihydrofolate reductase, inhibiting synthesis of tetrahydrofolic acid.

Folic acid is an essential precursor in the *de novo* synthesis of the DNA nucleosides thymidine and uridine. Bacteria are unable to take up folic acid from the environment (i.e., the infection host) and, thus, are dependent on their own de novo synthesis - inhibition of the enzyme starves the bacteria of two bases necessary for DNA replication and transcription.

Clinical indications

Co-trimoxazole was claimed to be more effective than either of its components individually in treating bacterial infections, although this was later disputed. Along with its associated greater incidence of adverse effects including allergic responses (see below), its widespread use has been restricted in many countries to very specific circumstances where its improved efficacy is demonstrated. It may be effective in a variety of upper and lower respiratory tract infections, renal and urinary tract infections, gastrointestinal tract infections, skin and wound infections, septicaemias and other infections caused by sensitive organisms. The global problem of advancing antimicrobial resistance has led to a renewed interest in the use of co-trimoxazole in various settings more recently.[8]

Specific indications for its use include:

HIV

Being an antibiotic, co-trimoxazole does not have any activity against HIV itself, but it is often prescribed to immunocompromised patients as Pneumocystis jiroveci pneumonia prophylaxis.

Bacterial

- infections caused by *Listeria monocytogenes*, *Nocardia* spp., *Stenotrophomonas maltophilia* (*Zanthomonas maltophilia*)
- Staphylococcus saprophyticus infections presenting as urinary tract infection or cystitis
- melioidosis
- shigellosis
- Whipple's disease
- traveller's diarrhea

Protozoan

- Isosporiasis
- prophylaxis of cerebral toxoplasmosis in HIV patients
- Cyclospora cayetanensis

Fungal

- treatment and prophylaxis of pneumonia caused by *Pneumocystis jirovecii* (formerly identified as *P. carinii* and commonly seen in immunocompromised patients including those suffering from cancer or HIV/AIDS)

Safety

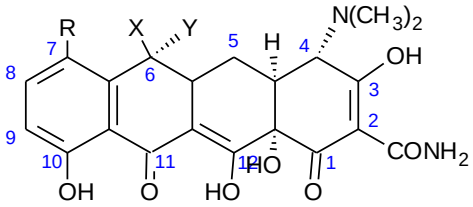
There has been some concern about its use, however, since it has been associated with both frequent mild allergic reactions and serious adverse effects including Stevens-Johnson syndrome, myelosuppression, mydriasis, agranulocytosis, as well as severe liver damage (cholestatic hepatosis, hepatitis, liver necrosis, fulminant liver failure).[*citation needed*] Due to displacement of bilirubin from albumin, there is an increased risk of kernicterus in the newborn during the last 6 weeks of pregnancy. Also renal impairment up to acute renal failure and anuria have been reported. These side-effects are seen especially in the elderly and may be fatal. (Joint Formulary Committee, 2004). Both Folic acid and Folinic acid were found equally effective in reducing the adverse effects of TMP-SMX, so unless new evidence is found for Folinic acid that shows it is more effective than the cheaper Folic acid, Folic acid will continue to be the preferred treatment method.

In some countries, co-trimoxazole has been withdrawn due to these toxic effects.

TETRACYCLINE ANTIBIOTICS

Tetracyclines are a group of broad-spectrum antibiotics whose general usefulness has been reduced with the onset of bacterial resistance. Despite this, they remain the treatment of choice for some specific indications.

They are so named for their four ("tetra-") hydrocarbon rings ("-cycl-") derivation ("-ine"). To be specific, they are defined as "a subclass of polyketides having an octahydrotetracene-2-carboxamide skeleton". They are collectively known as "derivatives of polycyclic naphthacene carboxamide".

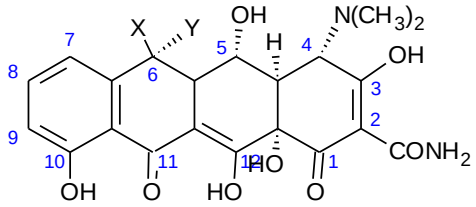


Tetracycline, R = H, X = OH, Y = CH_3

Demeclocycline, R = Cl, X = OH, Y = H

Minocycline, R = $N(CH_3)_2$, X = Y = H

Sanocycline, R = X = Y = H



Oxytetracycline, X = OH, Y = CH_3

Methacycline, X = Y = CH_2

Doxycycline, X = H, Y = CH_3

History

The first member of the group to be discovered is Chlortetracycline (Aureomycin) in the late 1940s by Dr. Benjamin Duggar, a scientist employed by Lederle Laboratories who derived the substance from a golden-colored, fungus-like, soil-dwelling bacterium named *Streptomyces aureofaciens*. Oxytetracycline (Terramycin) was discovered shortly afterwards by AC Finlay et al.; it came from a similar soil bacterium named *Streptomyces rimosus*. Robert Burns Woodward determined the structure of Oxytetracycline enabling Lloyd H. Conover to successfully produce tetracycline itself as a synthetic product. The development of many chemically altered antibiotics formed this group. In June 2005, tigecycline, the first member of a new subgroup of tetracyclines named glycylcyclines, was introduced to treat infections that are resistant to other antimicrobics including conventional tetracyclines. While tigecycline is the first tetracycline approved in over 20 years, other, newer versions of tetracyclines are currently in human clinical trials.

Mechanism of action

Tetracycline antibiotics are protein synthesis inhibitors, inhibiting the binding of aminoacyl-tRNA to the mRNA-ribosome complex. They do so mainly by binding to the 30S ribosomal subunit in the mRNA translation complex.

Tetracyclines also have been found to inhibit matrix metalloproteinases. This mechanism does not add to their antibiotic effects, but has led to extensive research on chemically modified

tetracyclines or CMTs (like incyclinide) for the treatmet of rosacea, acne, and various types of neoplasms. Since incyclinide was announced to be ineffective for rosacea in September 2007, no drugs of this group will be marketed in the near-future.

Mechanism and resistance

Tetracycline inhibits cell growth by inhibiting translation. It binds to the 16S part of the 30S ribosomal subunit and prevents the amino-acyl tRNA from binding to the A site of the ribosome. The binding is reversible in nature.

Cells become resistant to tetracycline by at least three mechanisms: enzymatic inactivation of tetracycline, efflux, and ribosomal protection. Inactivation is the rarest type of resistance, where an acetyl group is added to the molecule, causing inactivation of the drug. In efflux, a resistance gene encodes a membrane protein that actively pumps tetracycline out of the cell. This is the mechanism of action of the tetracycline resistance gene on the artificial plasmid pBR322. In ribosomal protection, a resistance gene encodes a protein that can have several effects, depending on what gene is transferred. Six classes of ribosomal protection genes/proteins have been found, all with high sequence homology, suggesting a common evolutionary ancestor.

Possible mechanisms of action of these protective proteins include:

1. blocking tetracyclines from binding to the ribosome
2. binding to the ribosome and distorting the structure to still allow t-RNA binding while tetracycline is bound
3. binding to the ribosome and dislodging tetracycline.

All of these changes to ribosomes are reversible (non-covalent) because ribosomes isolated from both tetracycline-resistant and susceptible organisms bind tetracycline equally well *in vitro*.

Indication

Tetracyclines are generally used in the treatment of infections of the respiratory tract, sinuses, middle ear, urinary tract, and intestines, and is used in the treatment of gonorrhoea, especially in patients allergic to β-lactams and macrolides; however, their use for these indications is less popular than it once was due to widespread resistance development in the causative organisms.

Their most common current use is in the treatment of moderately severe acne and rosacea (tetracycline, oxytetracycline, doxycycline, or minocycline).

Doxycycline is also used as a prophylactic treatment for infection by *Bacillus anthracis* (anthrax) and is effective against *Yersinia pestis*, the infectious agent of bubonic plague. It is also used for malaria treatment and prophylaxis, as well as treating elephantiasis.

Tetracyclines remain the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and *L. venereum* infection), Rickettsia (typhus, Rocky Mountain spotted fever), brucellosis, and spirochetal infections (borreliosis, syphilis, and Lyme disease). In addition, they may be used to treat anthrax, plague, tularemia, and Legionnaires' disease.

They may have a role in reducing the duration and severity of cholera, although drug-resistance is occurring, and their effects on overall mortality is questioned.

Demeclocycline has an additional use in the treatment of SIADH.

Tetracycline derivatives are currently being investigated for the treatment of certain inflammatory disorders.

Administration

When ingested, it is usually recommended that the more water-soluble, short-acting tetracyclines (plain tetracycline, chlortetracycline, Oxytetracycline, demeclocycline and methacycline) be taken with a full glass of water, either two hours after eating, or two hours before eating. This is partly because most tetracyclines bind with food and also easily with magnesium, aluminium, iron, and calcium, which reduces their ability to be completely absorbed by the body. Dairy products, antacids, or preparations containing iron are particularly recommended to be avoided near the time of taking the drug. Partial exceptions to these rules occur for doxycycline and minocycline, which may be taken with food (though not iron, antacids, or calcium supplements). Minocycline, can be taken with dairy products because it does not chelate calcium as readily, although dairy products do decrease absorption of minocycline slightly.

Cautions

Tetracyclines should be used with caution in those with liver impairment and those that are soluble in water and urine worsen renal failure (this is not true of the lipid soluble agents doxycycline and minocycline). They may increase muscle weakness in myasthenia gravis and exacerbate systemic lupus erythematosus. Antacids reduce the absorption of all tetracyclines, and dairy products reduce absorption greatly for all but minocycline.

The breakdown products of tetracyclines are toxic and can cause Fanconi Syndrome, a potentially fatal disease affecting proximal tubular function in the nephrons of the kidney. Prescriptions of these drugs should be discarded once expired.

It was once believed that tetracycline antibiotics impair the effectiveness of many types of hormonal contraception. Recent research has shown no significant loss of effectiveness in oral contraceptives while using most tetracyclines. Despite these studies, many physicians still recommend the use of barrier contraception for people taking any tetracyclines to prevent unwanted pregnancy.

Contraindications

Tetracycline use should be avoided in pregnant or lactating women, and in children with developing teeth because they may result in permanent staining (dark yellow-gray teeth with a darker horizontal band that goes across the top and bottom rows of teeth), and possibly affect the growth of teeth and bones.

In tetracycline preparation, stability must be considered in order to avoid formation of toxic epi-anhydrotetracyclines.

Side-effects

Side-effects from tetracyclines are not always common, but of particular note is possible photosensitive allergic reaction that increases the risk of sunburn under exposure to UV light from the sun or other sources. This may be of particular importance for those intending to take on vacations long-term doxycyline as a malaria prophylaxis.

They may cause stomach or bowel upsets, and, on rarely occasions, allergic reactions. Very rarely, severe headache and vision problems may be signs of dangerous secondary intracranial hypertension, also known as pseudotumor cerebri.

Tetracyclines are teratogens due to the likelihood of causing teeth discolouration in the fetus as they develop in infancy. For this same reason, tetracyclines are contraindicated for use in children under 8 years of age. They are, however, safe to use in the first 18 weeks of pregnancy. Some patients taking tetracyclines require medical supervision because they can cause steatosis and hepatotoxicity.

Examples of tetracyclines

According to source:

- **Naturally-occurring**
  Tetracycline, Chlortetracycline, Oxytetracycline, Demeclocycline
- **Semi-synthetic**
  Doxycycline, Lymecycline, Meclocycline, Methacycline, Minocycline
  Rolitetracycline (Prodrug)

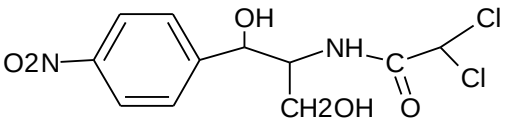
According to duration of action:

- **Short-acting (Half-life is 6-8 hrs)**
  Tetracycline, Chlortetracycline, Oxytetracycline
- **Intermediate-acting (Half-life is ~12 hrs)**
  Demeclocycline, Methacycline
- **Long-acting (Half-life is 16 hrs or more)**
  Doxycycline, Minocycline, Tigecycline

Tigecycline may also be considered a tetracycline antibiotic, though it is usually classified as a glycylcycline antibiotic.

Chloramphenicol

Chloramphenicol



Chloramphenicol (INN) is a bacteriostatic antimicrobial. It is considered a prototypical broad-spectrum antibiotic, alongside the tetracyclines.

Chloramphenicol is effective against a wide variety of Gram-positive and Gram-negative bacteria, including most anaerobic organisms. Due to resistance and safety concerns, it is no longer a first-line agent for any indication in developed nations, although it is sometimes used topically for eye infections. Nevertheless, the global problem of advancing bacterial resistance to newer drugs has led to renewed interest in its use. In low-income countries, chloramphenicol is still widely used because it is inexpensive and readily available.

The most serious adverse effect associated with chloramphenicol treatment is bone marrow toxicity, which may occur in two distinct forms: bone marrow suppression, which is a direct toxic effect of the drug and is usually reversible, and aplastic anemia, which is idiosyncratic (rare, unpredictable, and unrelated to dose) and generally fatal.

Spectrum of activity

Because it functions by inhibiting bacterial protein synthesis, chloramphenicol has a very broad spectrum of activity: it is active against Gram-positive bacteria (including most strains of MRSA), Gram-negative bacteria and anaerobes. It is not active against *Pseudomonas aeruginosa*, *Chlamydiae*, or *Enterobacter* species. It has some activity against *Burkholderia pseudomallei*, but is no longer routinely used to treat infections caused by this organism (it has been superseded by ceftazidime and meropenem). In the West, chloramphenicol is mostly restricted to topical uses because of the worries about the risk of aplastic anaemia.

Therapeutic uses

The original indication of chloramphenicol was in the treatment of typhoid, but the now almost universal presence of multi-drug resistant *Salmonella typhi* has meant that it is seldom used for this indication except when the organism is known to be sensitive. Chloramphenicol may be used as a second-line agent in the treatment of tetracycline-resistant cholera.

Because of its excellent BBB penetration (far superior to any of the cephalosporins), chloramphenicol remains the first choice treatment for staphylococcal brain abscesses. It is also useful in the treatment of brain abscesses due to mixed organisms or when the causative organism is not known.

Chloramphenicol is active against the three main bacterial causes of meningitis: *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. In the West, chloramphenicol remains the drug of choice in the treatment of meningitis in patients with severe penicillin or cephalosporin allergy and GPs are recommended to carry intravenous chloramphenicol in their bag. In low income countries, the WHO recommend that oily chloramphenicol be used first-line to treat meningitis.

Chloramphenicol has been used in the U.S. in the initial empirical treatment of children with fever and a petechial rash, when the differential diagnosis includes both *Neisseria meningitidis* septicaemia as well as Rocky Mountain spotted fever, pending the results of diagnostic investigations.

Chloramphenicol is also effective against *Enterococcus faecium*, which has led to it being considered for treatment of vancomycin-resistant enterococcus.

Although unpublished, recent research suggests that chloramphenicol could also be applied to frogs to prevent their widespread destruction from fungal infections. Chloramphenicol has recently been discovered to be a life-saving cure for chytridiomycosis in amphibians. Chytridiomycosis is a fungal disease, blamed for the extinction of one-third of the 120 frog species lost since 1980.

Adverse effects

Aplastic anemia

The most serious side effect of chloramphenicol treatment is aplastic anaemia. This effect is rare and is generally fatal: there is no treatment and there is no way of predicting who may or may not get this side effect. The effect usually occurs weeks or months after chloramphenicol treatment has been stopped and there may be a genetic predisposition. It is not known whether monitoring the blood counts of patients can prevent the development of aplastic anaemia, but it is recommended that patients have a blood count checked twice weekly while on treatment. The highest risk is with oral chloramphenicol (affecting 1 in 24,000–40,000) and the lowest risk occurs with eye drops (affecting less than 1 in 224,716 prescriptions).

Thiamphenicol is a related compound with a similar spectrum of activity that is available in Italy and China for human use, and has never been associated with aplastic anaemia. Thiamphenicol is available in the U.S. and Europe as a veterinary antibiotic, and is not approved for use in humans.

Bone marrow suppression

It is common for chloramphenicol to cause bone marrow suppression during treatment: this is a direct toxic effect of the drug on human mitochondria. This effect manifests first as a fall in hemoglobin levels and occurs quite predictably once a cumulative dose of 20 g has been given. This effect is fully reversible once the drug is stopped and does not predict future development of aplastic anaemia.

Leukemia

There is an increased risk of childhood leukemia as demonstrated in a Chinese case-controlled study, and the risk increases with length of treatment.

Possible Related Adverse Effects Chloramphenicol is particularly toxic to people sensitive to benzene based preservatives like preservatives 210 and 211. Chloramphenicol poisoning can cause sensitivity reactions to organic acids and salicylates. Chloramphenicol is also known to cause tinnitus and balance problems through inner ear damage. It also causes folic acid depletion resulting in adverse effects to the thyroid, pituitary and prostate through effects on PABA levels. There may also be links to chronic lymphocytic leukemia(CLL) through folic acid "depletion" and resultant high levels of folic acid in the mutant lymphocytes that characterize CLL Chloramphenicol stops the body's production of vitamin D and pregnenolone. This results in major hormone depletion, including DHEA and testosterone, that can result in death and also lowers the body's resistance to viral infection. Chloramphenicol can cause testes pain, possibly through hormone effects. Chinese research shows that chloramphenicol affects motor neurones. It also affects insulin Igf1 levels and glutamate levels. Both of these conditions are considered indicative of a type of motor neurone disease. The adverse genetic effects of chloramphenicol are considered heritable.

Gray baby syndrome

Intravenous chloramphenicol use has been associated with the so called gray baby syndrome. This phenomenon occurs in newborn infants because they do not yet have fully functional liver enzymes (i.e. UDP-glucuronyl transferase), and so chloramphenicol remains unmetabolized in the body. This causes several adverse effects, including hypotension and cyanosis. The condition can be prevented by using chloramphenicol at the recommended doses and monitoring blood levels.

Pharmacokinetics

Chloramphenicol is extremely lipid soluble, it remains relatively unbound to protein and is a small molecule: it has a large apparent volume of distribution of 100 litres and penetrates effectively into all tissues of the body, including the brain. The concentration achieved in brain and cerebrospinal fluid (CSF) is around 30 to 50% even when the meninges are not inflamed; this increases to as high as 89% when the meninges are inflamed.

Chloramphenicol increases the absorption of iron.

Use in special populations

Chloramphenicol is metabolised by the liver to chloramphenicol glucuronate (which is inactive). In liver impairment, the dose of chloramphenicol must therefore be reduced. There is no

standard dose reduction for chloramphenicol in liver impairment, and the dose should be adjusted according to measured plasma concentrations. Chloramphenicol is also noted for its cause of "Gray Baby Syndrome" because of infants lack of the enzyme glucoronyl transferase which is the main pathway conjugational excretion, which leads to a buildup of the chemical in infants system- contraindication.

The majority of the chloramphenicol dose is excreted by the kidneys as the inactive metabolite, chloramphenicol glucuronate. Only a tiny fraction of the chloramphenicol is excreted by the kidneys unchanged. It is suggested that plasma levels be monitored in patients with renal impairment, but this is not mandatory. Chloramphenicol succinate ester (the inactive intravenous form of the drug) is readily excreted unchanged by the kidneys, more so than chloramphenicol base, and this is the major reason why levels of chloramphenicol in the blood are much lower when given intravenously than orally.

Chloramphenicol passes into breast milk and should therefore be avoided during breastfeeding if possible.

Dose monitoring

Plasma levels of chloramphenicol must be monitored in neonates and in patients with abnormal liver function. It is recommended that plasma levels be monitored in all children under the age of 4, the elderly and patients with renal failure. Peak levels (1 hour after the dose is given) should be 15–25 mg/l; trough levels (taken immediately before a dose) should be less than 15 mg/l. Drug interactions

Administration of chloramphenicol concomitantly with bone marrow depressant drugs is contraindicated, although concerns over aplastic anaemia associated with ocular chloramphenicol have largely been discounted.

Chloramphenicol is a potent inhibitor of the cytochrome P450 isoforms CYP2C19 and CYP3A4 in the liver. Inhibition of CYP2C19 causes decreased metabolism and therefore increased levels of, for example, antidepressants, antiepileptics and proton pump inhibitors if they are given concomitantly. Inhibition of CYP3A4 causes increased levels of, for example, calcium channel blockers, immunosuppressants, chemotherapeutic drugs, benzodiazepines, azole antifungals, tricyclic antidepressants, macrolide antibiotics, SSRIs, statins and PDE5 inhibitors. Mechanism of action

Chloramphenicol is bacteriostatic (that is, it stops bacterial growth). It is a protein synthesis inhibitor, inhibiting peptidyl transferase activity of the bacterial ribosome, binding to A2451 and A2452 residues in the 23S rRNA of the 50S ribosomal subunit, preventing peptide bond formation. While chloramphenicol and the macrolide class of antibiotics both interact with ribosomes, chloramphenicol is not a macrolide. Chloramphenicol directly interferes with substrate binding, macrolides sterically block the progression of the growing peptide.

Resistance

There are three mechanisms of resistance to chloramphenicol: reduced membrane permeability, mutation of the 50S ribosomal subunit and elaboration of chloramphenicol acetyltransferase. It is easy to select for reduced membrane permeability to chloramphenicol *in vitro* by serial passage of bacteria, and this is the most common mechanism of low-level chloramphenicol resistance. High-level resistance is conferred by the *cat*-gene; this gene codes for an enzyme called chloramphenicol acetyltransferase which inactivates chloramphenicol by covalently linking one or two acetyl groups, derived from acetyl-S-coenzyme A, to the hydroxyl

groups on the chloramphenicol molecule. The acetylation prevents chloramphenicol from binding to the ribosome. Resistance-conferring mutations of the 50S ribosomal subunit are rare.

Chloramphenicol resistance may be carried on a plasmid that also codes for resistance to other drugs. One example is the ACCoT plasmid (A=ampicillin, C=chloramphenicol, Co=co-trimoxazole, T=tetracycline) which mediates multi-drug resistance in typhoid (also called R factors).

Formulations

Chloramphenicol is available as 250 mg capsules or as a liquid (125 mg/5 ml). In some countries, chloramphenicol is sold as chloramphenicol palmitate ester. Chloramphenicol palmitate ester is inactive, and is hydrolysed to active chloramphenicol in the small intestine. There is no difference in bioavailability between chloramphenicol and chloramphenicol palmitate.

The intravenous (IV) preparation of chloramphenicol is the succinate ester, because pure chloramphenicol does not dissolve in water. This creates a problem: chloramphenicol succinate ester is an inactive prodrug and must first be hydrolysed to chloramphenicol; the hydrolysis process is incomplete and 30% of the dose is lost unchanged in the urine, therefore serum concentrations of chloramphenicol are only 70% of those achieved when chloramphenicol is given orally. For this reason, the chloramphenicol dose needs to be increased to 75 mg/kg/day when administered IV in order to achieve levels equivalent to the oral dose. The oral route is therefore preferred to the intravenous route.

Manufacture of oral chloramphenicol in the U.S. stopped in 1991, because the vast majority of chloramphenicol-associated cases of aplastic anaemia are associated with the oral preparation. There is now no oral formulation of chloramphenicol available in the U.S.

Oily

Dose: 100 mg/kg (maximum dose 3 g) as a single intramuscular injection. The dose is repeated if there is no clinical response after 48 hours. A single injection costs approximately US$5.

Oily chloramphenicol (or chloramphenicol oil suspension) is a long-acting preparation of chloramphenicol first introduced by Roussel in 1954; marketed as Tifomycine, it was originally used as a treatment for typhoid. Roussel stopped production of oily chloramphenicol in 1995; the International Dispensary Association has manufactured it since 1998, first in Malta and then in India from December 2004.

Oily chloramphenicol is recommended by the World Health Organization (WHO) as the first line treatment of meningitis in low-income countries and appears on the essential drugs list. It was first used to treat meningitis in 1975 and there have been numerous studies since demonstrating its efficacy It is the cheapest treatment available for meningitis (US$5 per treatment course, compared to US$30 for ampicillin and US$15 for five days of ceftriaxone). It has the great advantage of requiring only a single injection, whereas ceftriaxone is traditionally given daily for five days. This recommendation may yet change now that a single dose of ceftriaxone (cost US$3) has been shown to be equivalent to one dose of oily chloramphenicol.

Oily chloramphenicol is not currently available in the U.S. or Europe.

Eye drops

In the West, chloramphenicol is still widely used in topical preparations (ointments and eye drops) for the treatment of bacterial conjunctivitis. Isolated cases report of aplastic anaemia following chloramphenicol eyedrops exist, but the risk is estimated to be less than 1 in 224,716 prescriptions

History

Chloramphenicol was originally derived from the bacterium *Streptomyces venezuelae*, isolated by David Gottlieb, & introduced into clinical practice in 1949, under the trade name Chloromycetin. It was the first antibiotic to be manufactured synthetically on a large scale.

STEREOCHEMISTRY

STEREOISOMERS are isomers which have the same pattern of bonding but with atoms arranged differently in space. Stereoisomers are also known as **geometric isomers** but confusingly this latter term is often used to refer only to 'cis/trans isomers'.There are two types of stereoisomer:

Enantiomers

two isomers which are mirror images of each other; also known as **optical isomers** due to the fact that two enantiomers will rotate plane-polarized light in equal, but opposite directions. **Chirality** is (yet) another term for enantiomerism.

Diastereomers

stereoisomers which are not enantiomers.

Stereoisomerism can be caused by:

Stereocenters

if a carbon atom has four different groups attached to it, it will exhibit enantiomerism. Other causes of enantiomerism include helical structures.

Non-rotation of bonds

the C=C bond cannot rotate and is the most common cause of diastereomerism. Other causes are cyclic compounds and steric hindrance.

CONFIGURATION AND CONFORMATION

Conformation is the set of possible shapes a molecule can have by means of **rotation about single bonds only**. Configuration is the relative position of the atoms in a molecule that can be changed exclusively by cleaving and forming *new* chemical bonds. Isomers have different configurations, although the distinction may be blurred in compounds where steric hindrance occurs.

NAMING CONVENTIONS

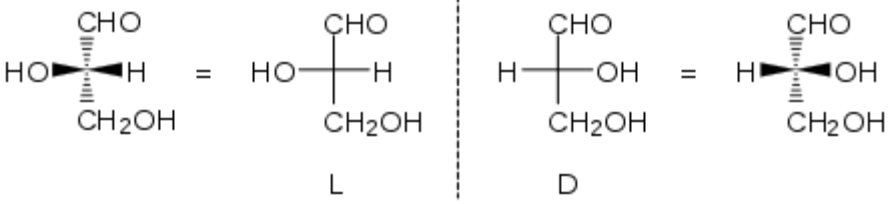
There are three main systems for describing configuration: the oldest, the *relative* whose use is now deprecated, and the current, or *absolute*. The relative configuration description is still used mainly in glycochemistry. Configuration can also be assigned on the purely empirical basis of the optical activity.

OPTICAL ACTIVITY : (+) & (-)

An optical isomer can be named by the direction in which it rotates the plane of polarized light. If an isomer rotates the plane clockwise as seen by a viewer towards whom the light is traveling, that isomer is labeled (+). Its counterpart is labeled (-). The (+) and (-) isomers have also been termed d- and l-, respectively (for dextrorotatory and levorotatory). This labeling is easy to confuse with D- and L-.The fact that an enantiomer can rotate polarised light clockwise (*d*- or *+*- enantiomer) does not relate with the relative configuration (D- or L-) of it.

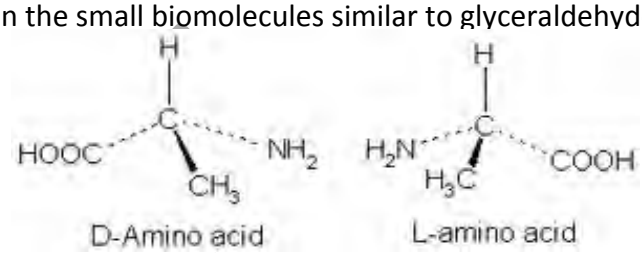
RELATIVE CONFIGURATION: D- AND L-

Fischer, whose research interest was in carbohydrate chemistry, took glyceraldehyde (the simplest sugar, systematic name 2,3-dihydroxyethanal) as a template chiral molecule and denoted the two possible configurations with D- and L-, which rotated polarised light clockwise and counterclockwise, respectively.



All other molecules are assigned the D- or L- configuration if the chiral centre can be formally obtained from glyceraldehyde by substitution. For this reason the D- or L- naming scheme is called ***relative configuration***.

An optical isomer can be named by the spatial configuration of its atoms. The D/L system does this by relating the molecule to glyceraldehyde. Glyceraldehyde is chiral itself, and its two isomers are labeled D and L. Certain chemical manipulations can be performed on glyceraldehyde without affecting its configuration, and its historical use for this purpose (possibly combined with its convenience as one of the smallest commonly-used chiral molecules) has resulted in its use for nomenclature. In this system, compounds are named by analogy to glyceraldehyde, which generally produces unambiguous designations, but is easiest to see in the small biomolecules similar to glyceraldehyde.



One example is the amino acid alanine: alanine has two optical isomers, and they are labeled according to which isomer of glyceraldehyde they come from. Glycine, the amino acid derived from glyceraldehyde, incidentally, does not retain its optical activity, since its central carbon is not chiral. Alanine, however, is essentially methylated glycine and shows optical activity.

The D/L labeling is unrelated to (+)/(-); it does not indicate which enantiomer is dextrorotatory and which is levorotatory. Rather, it says that the compound's stereochemistry is related to that of the dextrorotatory or levorotatory enantiomer of glyceraldehyde. Nine of the nineteen L-amino acids commonly found in proteins are dextrorotatory (at a wavelength of 589 nm), and D-fructose is also referred to as levulose because it is levorotatory.

The dextrorotatory isomer of glyceraldehyde is in fact the D isomer, but this was a lucky guess. At the time this system was established, there was no way to tell which configuration was dextrorotatory. (If the guess had turned out wrong, the labeling situation would now be even more confusing.)

A rule of thumb for determining the D/L isomeric form of an amino acid is the "CORN" rule. The groups:

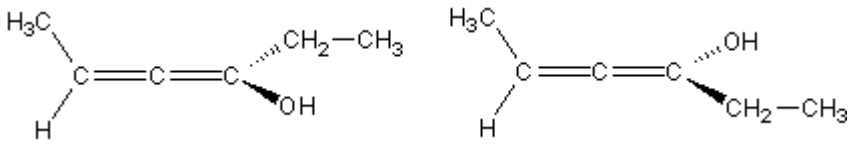
COOH, R, NH2 and H (where R is an unnamed carbon chain)
are arranged around the chiral center carbon atom. If these groups are arranged counter-clockwise around the carbon atom, then it is the D-form. If clockwise, it is the L-form.

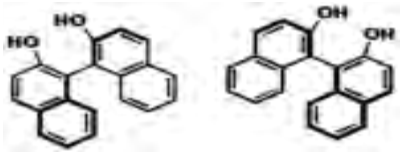
ABSOLUTE CONFIGURATION: R- AND S-

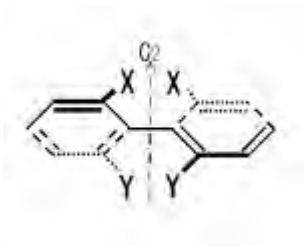
The absolute configuration system stems from the Cahn-Ingold-Prelog priority rules, which allow a precise description of a stereocenter without using any reference compound. In fact the basis is now the atomic number of the stereocenter substituents. The R/S system is another way to name an optical isomer by its configuration, without involving a reference molecule such as glyceraldehyde. It labels each chiral center R or S according to a system by which its ligands are each assigned a priority, according to the Cahn Ingold Prelog priority rules, based on atomic number.This system labels each chiral center in a molecule (and also has an extension to chiral molecules not involving chiral centers). It thus has greater generality than the D/L system, and can label, for example, an (R,R) isomer versus an (R,S) — diastereomers. The R/S system has no fixed relation to the (+)/(-) system. An R isomer can be either dextrorotatory or levorotatory, depending on its exact ligands.The R/S system also has no fixed relation to the D/L system. For example, one of glyceraldehyde's ligands is a hydroxy group, -OH. If a thiol group, -SH, were swapped in for it, the D/L labeling would, by its definition, not be affected by the substitution. But this substitution would invert the molecule's R/S labeling, due to the fact that sulfur's atomic number is higher than carbon's, whereas oxygen's is lower. [Note: This seems incorrect. Oxygen has a higher atomic number than carbon.]For this reason, the D/L system remains in common use in certain areas, such as amino acid and carbohydrate chemistry. It is convenient to have all of the common amino acids of higher organisms labeled the same way. In D/L, they are all L. In R/S, they are not, conversely, all S — most are, but cysteine, for example, is R, again because of sulfur's higher atomic number. The word “racemic” is derived from the Latin word for grape; the term having its origins in the work of Louis Pasteur who isolated racemic tartaric acid from wine.

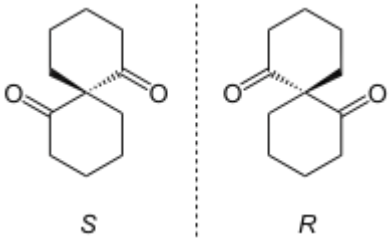
CHIRAL COMPOUNDS WITHOUT STEREOCENTERS

It is also possible for a molecule to be chiral without having actual point chirality (stereocenters). Commonly encountered examples include 1,1'-bi-2-naphthol (BINOL) and 1,3-dichloro-allene which have axial chirality, and (E)-cyclooctene which has planar chirality.For example, the isomers which are shown by the following figure are different. The two isomers cannot convert from one to another spontaneously because of restriction of rotation of double bonds. Other types of chiral compounds without stereocenters (like restriction of rotation of a single bond because of steric hindrance) also exist. Consider the following example of the R and S binol molecules:





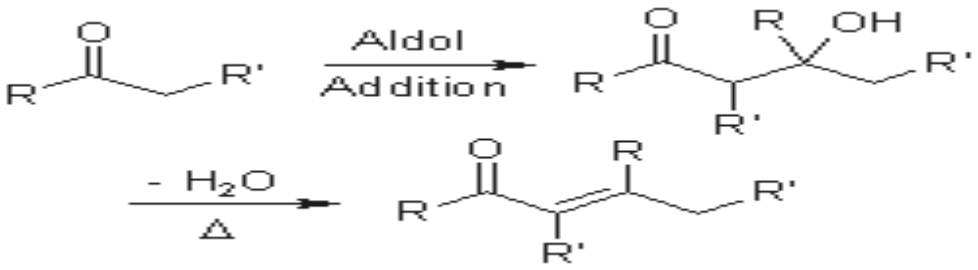




The biphenyl C-C bond cannot rotate if the X and Y groups cause steric hindrance. This compound exhibits spiral chirality.

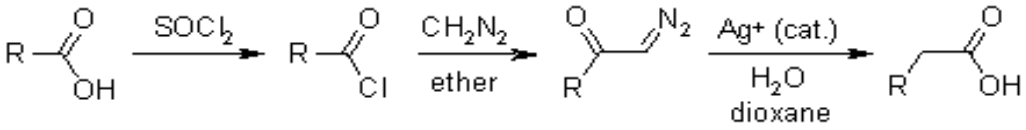
IMPORTANT NAME REACTION

ALDOL CONDENSATION



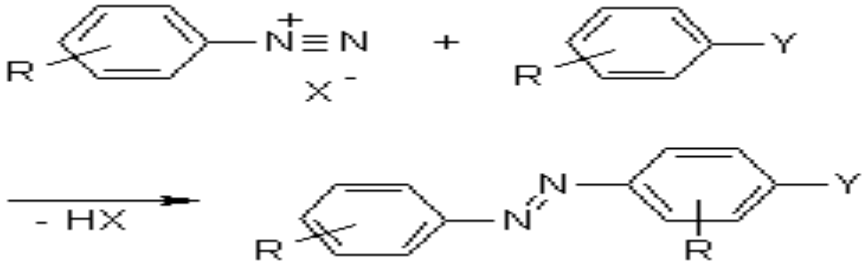
In some cases, the adducts obtained from the Aldol Addition can easily be converted to α,β-unsaturated carbonyl compounds, either thermally or under acidic or basic catalysis..

ARNDT-EISTERT SYNTHESIS



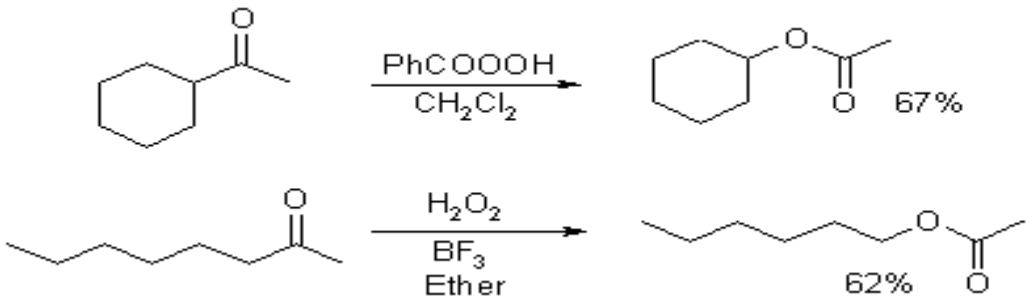
The Arndt-Eistert Synthesis allows the formation of homologated carboxylic acids or their derivatives by reaction of the activated carboxylic acids with diazomethane and subsequent Wolff-Rearrangement of the intermediate diazoketones in the presence of nucleophiles such as water, alcohols, or amines

AZO COUPLING



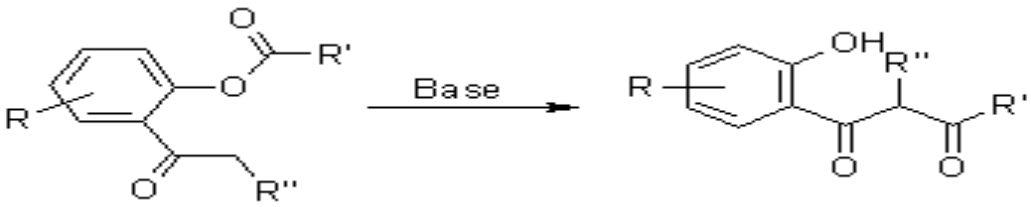
Azo coupling is the most widely used industrial reaction in the production of dyes, lakes and pigments. Aromatic diazonium ions acts as electrophiles in coupling reactions with activated aromatics such as anilines or phenols. The substitution normally occurs at the para position, except when this position is already occupied, in which case *ortho* position is favoured. The pH of solution is quite important; it must be mildly acidic or neutral, since no reaction takes place if the pH is too low.

BAEYER-VILLIGER OXIDATION



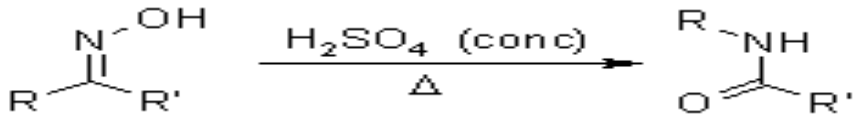
The Baeyer-Villiger Oxidation is the oxidative cleavage of a carbon-carbon bond adjacent to a carbonyl, which converts ketones to esters and cyclic ketones to lactones. The Baeyer-Villiger can be carried out with peracids, such as MCBPA, or with hydrogen peroxide and a Lewis acid.so,it is called as oxy-insert reaction.

BAKER-VENKATARAMAN REARRANGEMENT



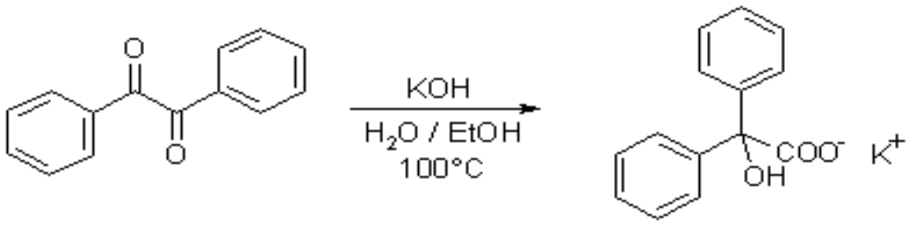
The base-induced transfer of the ester acyl group in an *o*-acylated phenol ester, which leads to a 1,3-diketone. This reaction is related to the Claisen Condensation, and proceeds through the formation of an enolate, followed by intramolecular acyl transfer

BECKMANN REARRANGEMENT



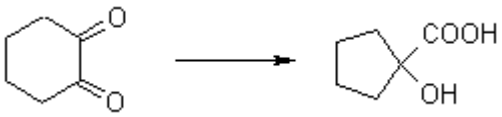
An acid-induced rearrangement of oximes to give amides.This reaction is related to the Hofmann and Schmidt Reactions and the Curtius Rearrangement, in that an electropositive nitrogen is formed that initiates an alkyl migration.

BENZILIC ACID REARRANGEMENT



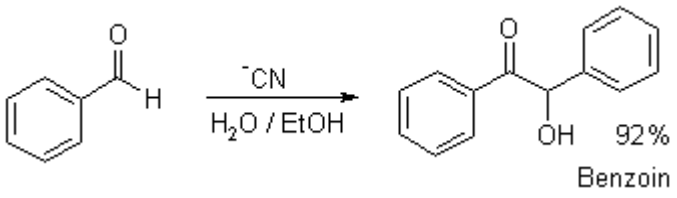
1,2-Diketones undergo a rearrangement in the presence of strong base to yield α-hydroxycarboxylic acids. The best yields are obtained when the subject diketones do not have enolizable protons.

The reaction of a cyclic diketone leads to an interesting ring contraction:



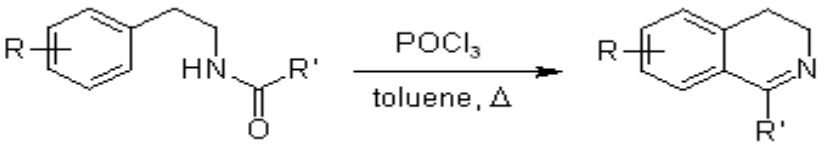
Ketoaldehydes do not react in the same manner, where a hydride shift is preferred
(in Cannizzaro Reaction)

BENZOIN CONDENSATION



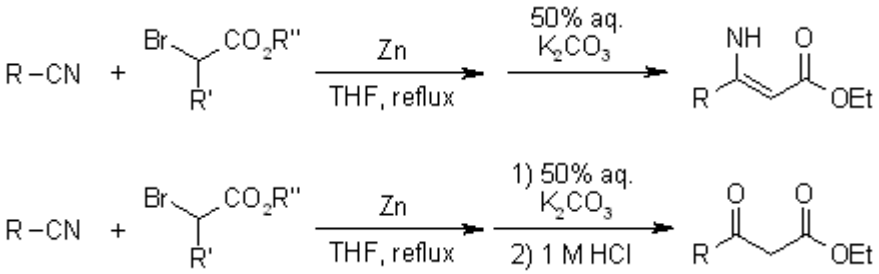
The Benzoin Condensation is a coupling reaction between two aldehydes that allows the preparation of α-hydroxyketones. The first methods were only suitable for the conversion of aromatic aldehydes

BISCHLER-NAPIERALSKI REACTION



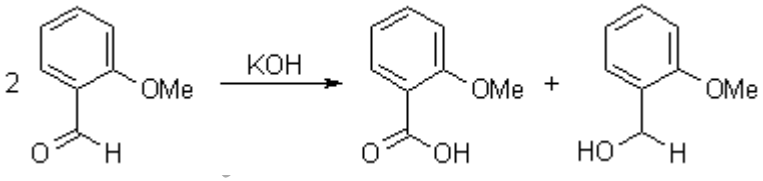
The Bischler-Napieralski Reaction allows the synthesis of 3,4-dihydroisoquinolines from the β-ethylamides of electron-rich arenes using condensation reagents such as P_2O_5, $POCl_3$ or $ZnCl_2$.

BLAISE REACTION

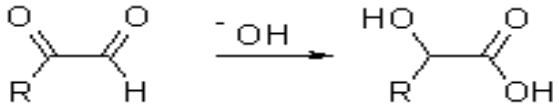


The Blaise Reaction allows the synthesis of β-enamino esters or β-keto esters (depending on the work-up conditions) via the zinc-mediated reaction of nitriles with α-haloesters.

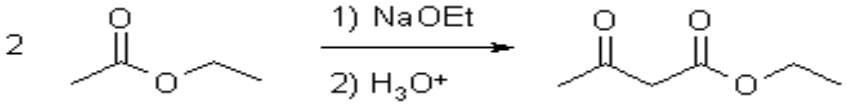
CANNIZZARO REACTION



This redox disproportionation of non-enolizable aldehydes to carboxylic acids and alcohols is conducted in concentrated base. α-Keto aldehydes give the product of an intramolecular disproportionation in excellent yields.



CLAISEN CONDENSATION



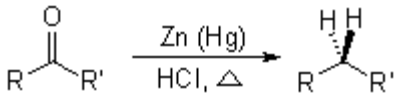
The Claisen Condensation between esters containing α-hydrogens, promoted by a base such as sodium ethoxide, affords β-ketoesters. The driving force is the formation of the stabilized anion of the β-keto ester. If two different esters are used, an essentially statistical mixture of all four products is generally obtained, and the preparation does not have high synthetic utility.

However, if one of the ester partners has enolizable α-hydrogens and the other does not (e.g., aromatic esters or carbonates), the mixed reaction (or crossed Claisen) can be synthetically useful. If ketones or nitriles are used as the donor in this condensation reaction, a β-diketone or a β-ketonitrile is obtained, respectively.

The use of stronger bases, e.g. sodium amide or sodium hydride instead of sodium ethoxide, often increases the yield.

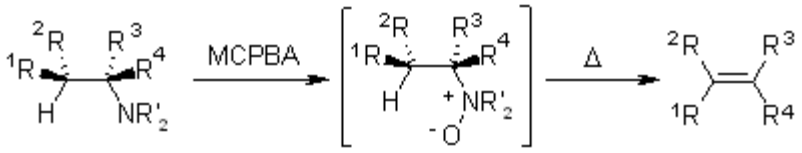
The intramolecular version is known as Dieckmann Condensation.

CLEMMENSEN REDUCTION



The Clemmensen Reduction allows the deoxygenation of aldehydes or ketones, to produce the corresponding hydrocarbon. The substrate must be stable to strong acid. The Clemmensen Reduction is complementary to the Wolff-Kishner Reduction, which is run under strongly basic conditions. Acid-labile molecules should be reduced by the Wolff-Kishner protocol.

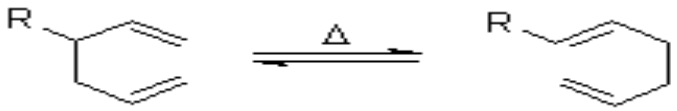
COPE ELIMINATION



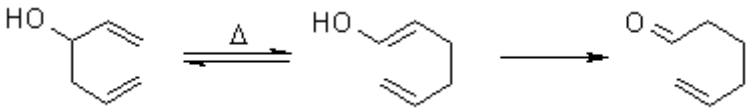
The Cope Reaction of *N*-oxides, which can easily be prepared *in situ* from amines with an oxidant such as peracid, leads to alkenes via a thermally induced *syn*-elimination in aprotic solvents

COPE REARRANGEMENT

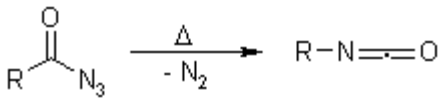
The Cope Rearrangement is the thermal isomerization of a 1,5-diene leading to a regioisomeric 1,5-diene. The main product is the thermodynamically more stable regioisomer. The Oxy-Cope has a hydroxyl substituent on an sp^3-hybridized carbon of the starting isomer.



The driving force for the neutral or anionic Oxy-Cope Rearrangement is that the product is an enol or enolate (resp.), which can tautomerize to the corresponding carbonyl compound. This product will not equilibrate back to the other regioisomer.

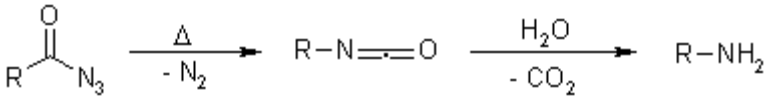


CURTIUS REARRANGEMENT

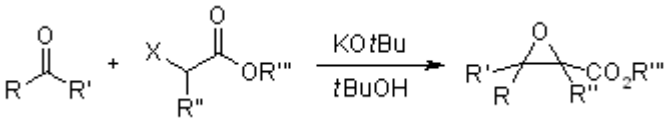


The Curtius Rearrangement is the thermal decomposition of carboxylic azides to produce an isocyanate. These intermediates may be isolated, or their corresponding reaction or hydrolysis products may be obtained.

The reaction sequence - including subsequent reaction with water which leads to amines - is named the Curtius Reaction. This reaction is similar to the Schmidt Reaction with acids, differing in that the acyl azide in the present case is prepared from the acyl halide and an azide salt.

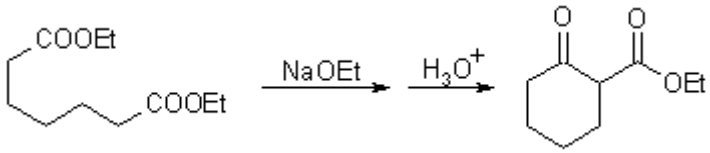


DARZENS CONDENSATION



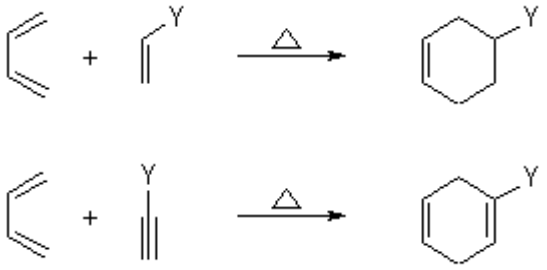
The Darzens Reaction is the condensation of a carbonyl compound with an α-halo ester in the presence of a base to form an α,β-epoxy ester.

DIECKMANN CONDENSATION



The base-catalyzed intramolecular condensation of a diester. The Dieckmann Condensation works well to produce 5- or 6-membered cyclic ß-keto esters, and is usually effected with sodium alkoxide in alcoholic solvent.

DIELS-ALDER REACTION



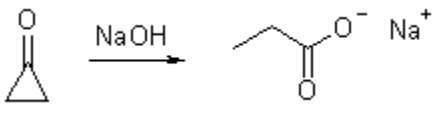
The [4+2]-cycloaddition of a conjugated diene and a dienophile (an alkene or alkyne), an electrocyclic reaction that involves the 4 π-electrons of the diene and 2 π-electrons of the dienophile. The driving force of the reaction is the formation of new σ-bonds, which are energetically more stable than the π-bonds.

In the case of an alkynyl dienophile, the initial adduct can still react as a dienophile if not too sterically hindered. In addition, either the diene or the dienophile can be substituted with cumulated double bonds, such as substituted allenes.

With its broad scope and simplicity of operation, the Diels-Alder is the most powerful synthetic method for unsaturated six-membered rings.

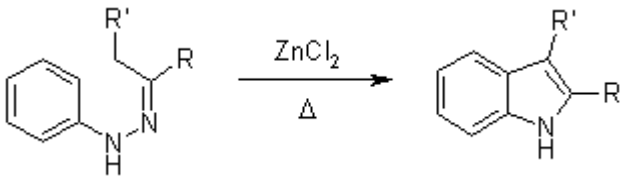
A variant is the hetero-Diels-Alder, in which either the diene or the dienophile contains a heteroatom, most often nitrogen or oxygen. This alternative constitutes a powerful synthesis of six-membered ring heterocycles

FAVORSKII REACTION



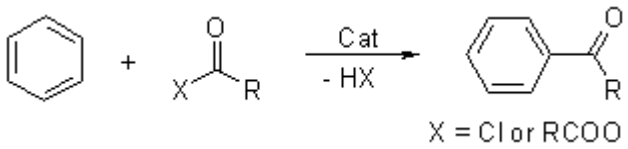
The rearrangement of cyclopropanones, often obtained as intermediates from the base-catalyzed reaction of α-halo ketones, leading to carboxylic acids and derivatives.

FISCHER INDOLE SYNTHESIS



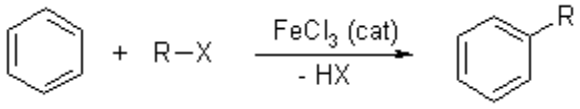
The conversion of aryl hydrazones to indoles; requires elevated temperatures and the addition of Brønsted or Lewis acids. Some interesting enhancements have been published recently; for example a milder conversion when *N*-trifluoroacetyl enehydrazines are used as substrates.

FRIEDEL-CRAFTS ACYLATION



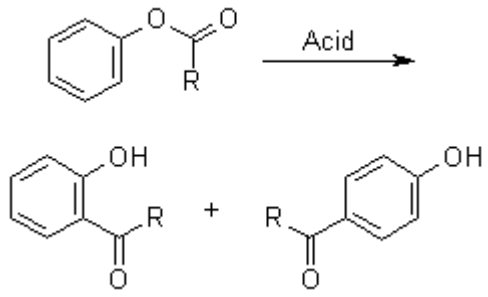
This electrophilic aromatic substitution allows the synthesis of monoacylated products from the reaction between arenes and acyl chlorides or anhydrides. The products are deactivated, and do not undergo a second substitution. Normally, a stoichiometric amount of the Lewis acid catalyst is required, because both the substrate and the product form complexes.

FRIEDEL-CRAFTS ALKYLATION



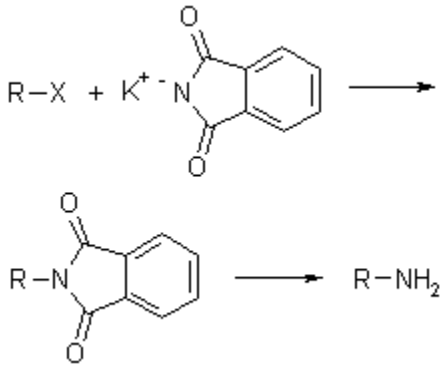
This Lewis acid-catalyzed electrophilic aromatic substitution allows the synthesis of alkylated products via the reaction of arenes with alkyl halides or alkenes. Since alkyl substituents activate the arene substrate, polyalkylation may occur. A valuable, two-step alternative is Friedel-Crafts Acylation followed by a carbonyl reduction.

FRIES REARRANGEMENT



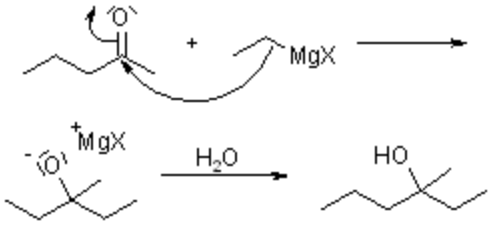
The Fries Rearrangement enables the preparation of acyl phenols.

GABRIEL SYNTHESIS



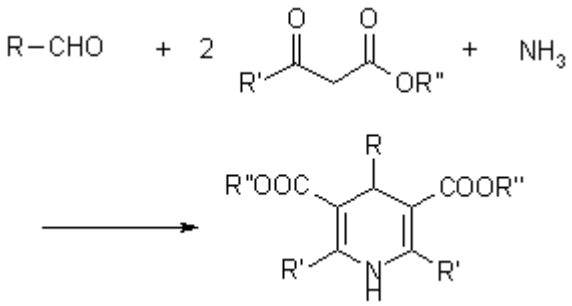
Potassium phthalimide is a $^{-}NH_2$-synthon which allows the preparation of primary amines by reaction with alkyl halides. After alkylation, the phthalimid is not nucleophile and does not react anymore. Product is cleaved by reaction with base or hydrazine, which leads to a stable cyclic product.

GRIGNARD REACTION



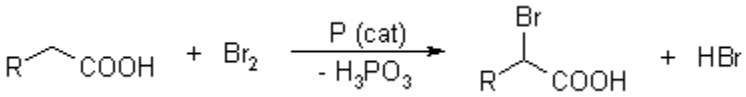
The Grignard Reaction is the addition of an organomagnesium halide (Grignard reagent) to a ketone or aldehyde, to form a tertiary or secondary alcohol, respectively. The reaction with formaldehyde leads to a primary alcohol.

HANTZSCH DIHYDROPYRIDINE (PYRIDINE) SYNTHESIS



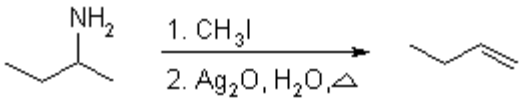
This reaction allows the preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents of a β-ketoester in the presence of ammonia. Subsequent oxidation (or dehydrogenation) gives pyridine-3,5-dicarboxylates, which may also be decarboxylated to yield the corresponding pyridines

HELL-VOLHARD-ZELINSKY REACTION



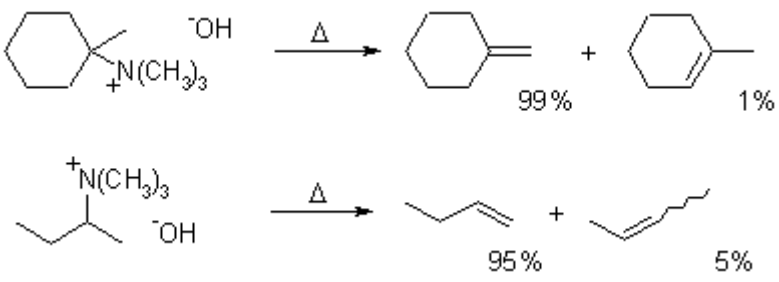
Treatment with bromine and a catalytic amount of phosphorus leads to the selective α-bromination of carboxylic acids.

HOFMANN ELIMINATION

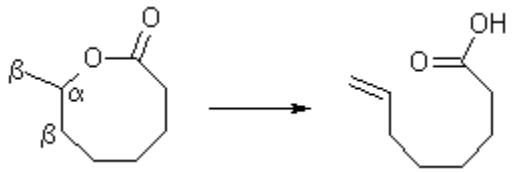


Sometimes referred to as the Hofmann Degradation. This elimination reaction of alkyl trimethyl amines proceeds with *anti*-stereochemistry, and is generally suitable for producing alkenes with one or two substituents. The reaction follows the Hofmann Rule.

HOFMANN'S RULE

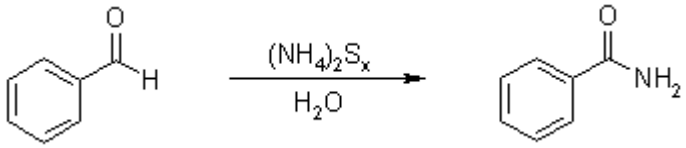


Hofmann's Rule implies that steric effects have the greatest influence on the outcome of the Hofmann or similar eliminations. The loss of the β-hydrogen occurs preferably from the most unhindered (least substituted) position [$-CH_3 > -CH_2-R > -CH(R_2)$]. The product alkene with fewer substitutents will predominate. Ester Pyrolysis also obeys this preference, and the Hofmann Rule is generally followed whenever a reaction passes through a cyclic transition state.



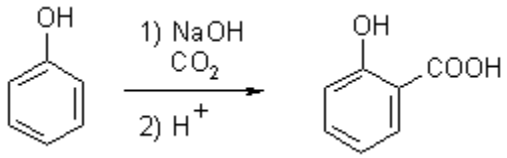
Hofmann's Rule is valid for all intramolecular eliminations and for the Hofmann Elimination. Most bimolecular eliminations will follow Saytzeff's Rule.

WILLGERODT-KINDLER REACTION



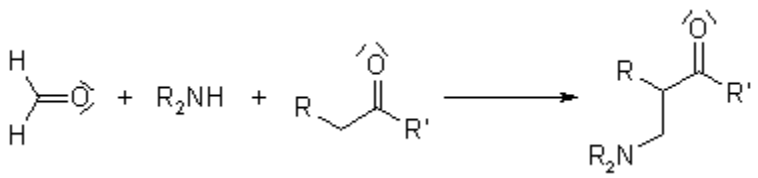
The Willgerodt Reaction allows the synthesis of amides from aryl ketones under the influence of a secondary amine and a thiating agent.

KOLBE-SCHMITT REACTION



A base-promoted carboxylation of phenols that allows the synthesis of salicylic acid derivatives.

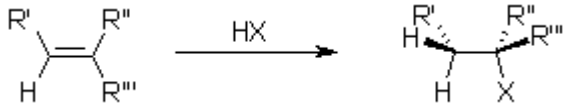
MANNICH REACTION



This multi-component condensation of a nonenolizable aldehyde, a primary or secondary amine and an enolizable carbonyl compound affords aminomethylated products. The iminium derivative of the aldehyde is the acceptor in the reaction.The involvement of the

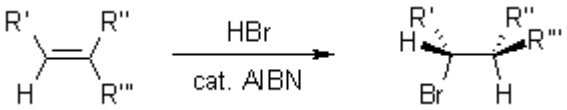
Mannich Reaction has been proposed in many biosynthetic pathways, especially for alkaloids

MARKOVNIKOV'S RULE



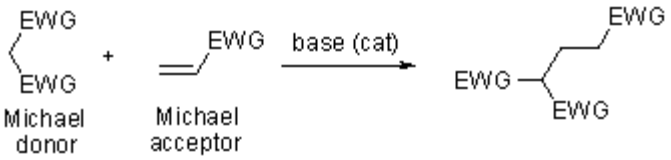
Markovnikov Rule predicts the regiochemistry of HX addition to unsymmetrically substituted alkenes.The halide component of HX bonds preferentially at the more highly substituted carbon, whereas the hydrogen prefers the carbon which already contains more hydrogens.

ANTI-MARKOVNIKOV



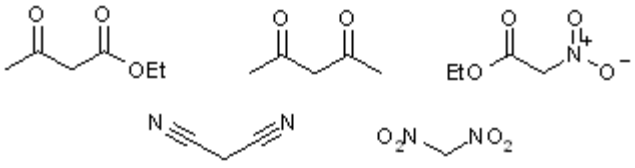
Some reactions do not follow Markovnikov's Rule, and *anti*-Markovnikov products are isolated. This is a feature for example of radical induced additions of HX and of Hydroboration.

MICHAEL ADDITION

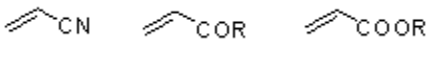


The 1,4-addition (or conjugate addition) of resonance-stabilized carbanions. The Michael Addition is thermodynamically controlled; the reaction donors are active methylenes such as malonates and nitroalkanes, and the acceptors are activated olefins such as α,β-unsaturated carbonyl compounds.

Examples:

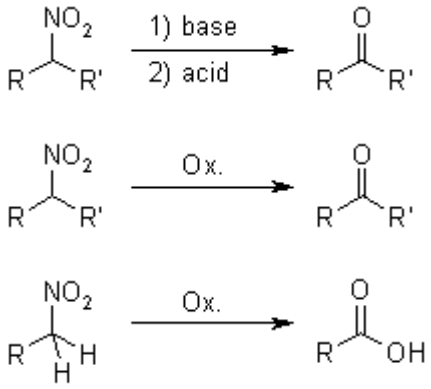


donors



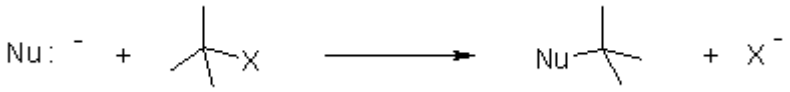
acceptors

NEF REACTION



The conversion of nitro compounds into carbonyls is known as the Nef Reaction.

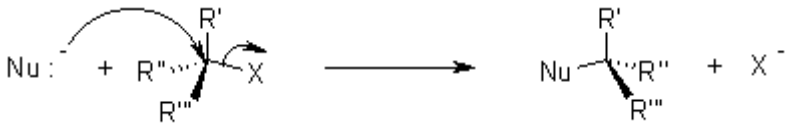
NUCLEOPHILIC SUBSTITUTION (S_N1-S_N2)



Nucleophilic substitution is the reaction of an electron pair donor (the nucleophile, Nu) with an electron pair acceptor (the electrophile). An sp^3-hybridized electrophile must have a leaving group (X) in order for the reaction to take place.

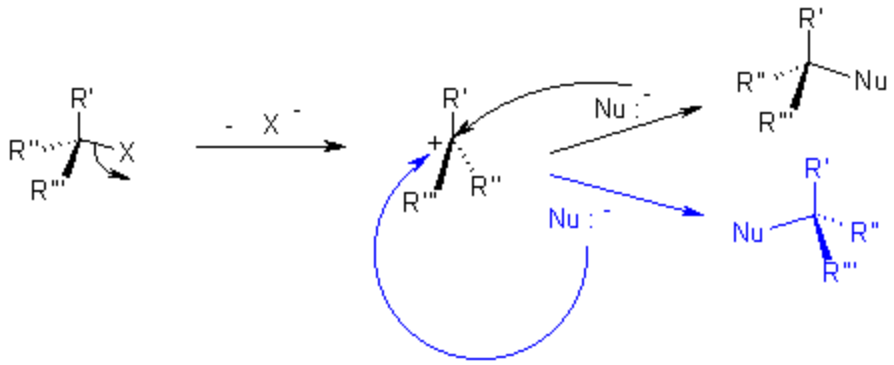
Mechanism of Nucleophilic Substitution

The term S_N2 means that two molecules are involved in the actual transition state:



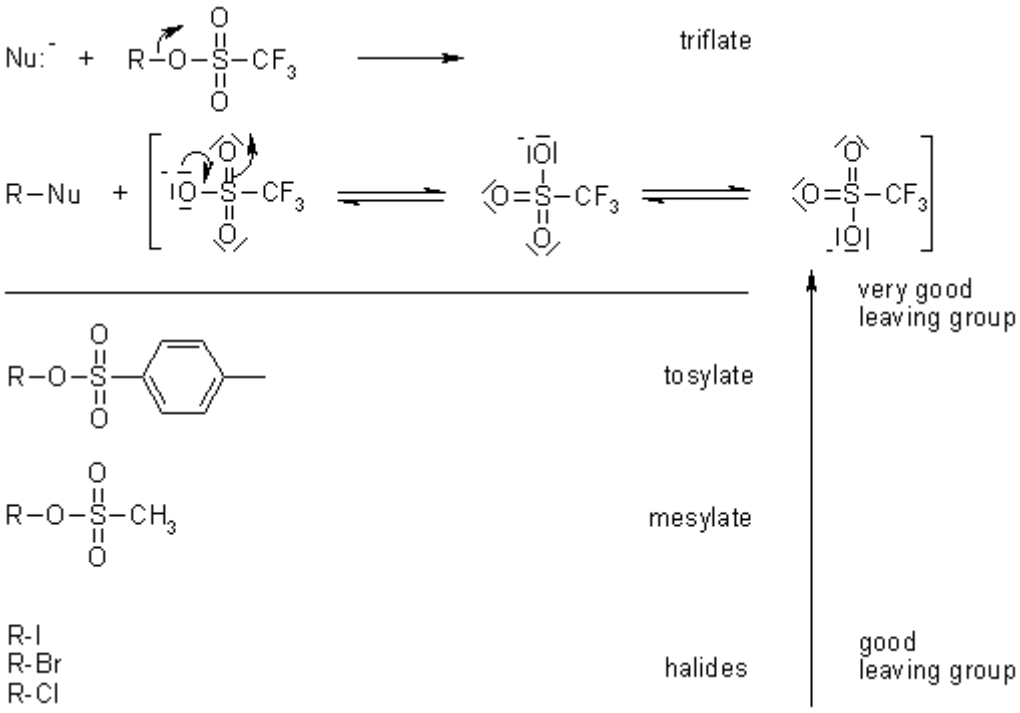
The departure of the leaving group occurs simultaneously with the backside attack by the nucleophile. The S_N2 reaction thus leads to a predictable configuration of the stereocenter - it proceeds with inversion (reversal of the configuration).

In the S_N1 reaction, a planar carbenium ion is formed first, which then reacts further with the nucleophile. Since the nucleophile is free to attack from either side, this reaction is associated with racemization.



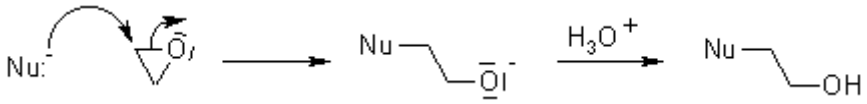
In both reactions, the nucleophile competes with the leaving group. Because of this, one must realize what properties a leaving group should have, and what constitutes a good nucleophile. For this reason, it is worthwhile to know which factors will determine whether a reaction follows an S_N1 or S_N2 pathway.

Very good leaving groups, such as triflate, tosylate and mesylate, stabilize an incipient negative charge. The delocalization of this charge is reflected in the fact that these ions are not considered to be nucleophilic.



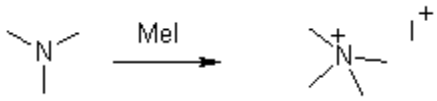
Hydroxide and alkoxide ions are not good leaving groups; however, they can be activated by means of Lewis or Brønsted acids.

Epoxides are an exception, since they relieve their ring strain when they undergo nucleophilic substitution, with activation by acid being optional:

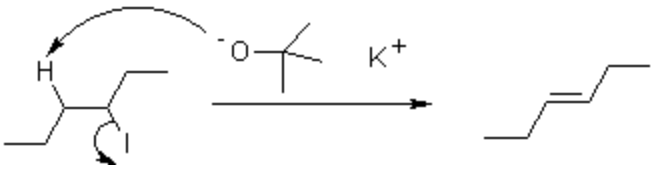


Triflate, tosylate and mesylate are the anions of strong acids. The weak conjugate bases are poor nucleophiles. Nucleophilicity increases in parallel with the base strength. Thus, amines, alcohols and alkoxides are very good nucleophiles. Base strength is a rough measure of how reactive the nonbonding electron pair is; thus, it is not necessary for a nucleophile to be anionic.

Under substitution conditions, amines proceed all the way to form quaternary salts, which makes it difficult to control the extent of the reaction.

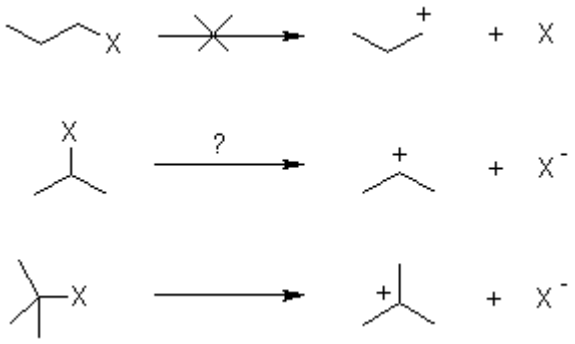


However, as a nucleophile's base strength and steric hindrance increase, its basicity tends to be accentuated. If there are abstractable protons at the β-position of the electrophile, an elimination pathway can compete with the nucleophilic substitution.



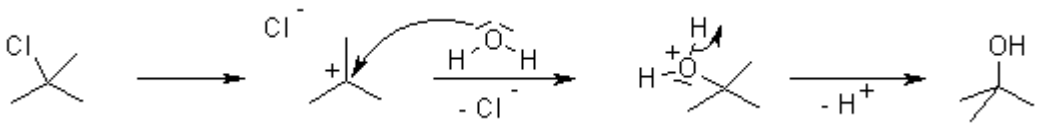
An additional factor that plays a role is the character of the solvent. Increasing stabilization of the nucleophile by the solvent results in decreasing reactivity. Thus, polar protic solvents will stabilize the chloride and bromide ions through the formation of hydrogen bonds to these smaller anions. Iodide is a comparatively better nucleophile in these solvents. The reverse behavior predominates in aprotic polar media.

The solvent also plays an important role in determining which pathway the reaction will take, S_N1 versus S_N2. It may safely be assumed that a primary-substituted leaving group will follow an S_N2 pathway in any case, since the formation of the corresponding unstable primary carbenium ion is disfavored. Reaction by the S_N1 pathway is highly probable for compounds with tertiary substitution, since the corresponding tertiary carbenium ion is stabilized through hyperconjugation:

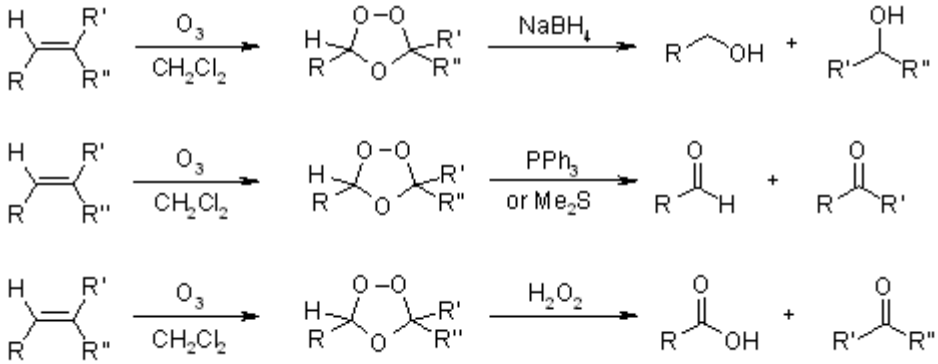


The better the solvent stabilizes the ions, the more probable that the reaction will follow an S_N1 pathway (e.g., in polar protic solvents such as water/acetone). The more highly substituted is the incipient carbenium ion, the more probable that the reaction will follow an S_N1 pathway. The more unreactive the nucleophile, the more probable it becomes that a reaction with secondary and tertiary electrophiles will follow an S_N1 pathway. A weaker nucleophile is not as effective in the backside attack, since this location is sterically shielded, especially in the case of tertiary substrates. Carbenium ions are planar and therefore less sterically hindered, and are naturally more reactive as electrophiles than the uncharged parent compound.

The hydrolysis of *tert*-butyl chloride is a typical S_N1 reaction:

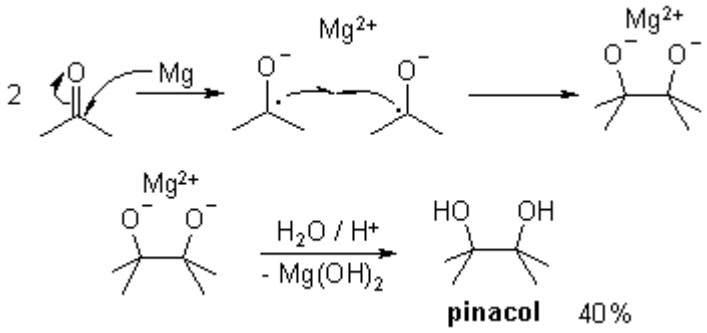


OZONOLYSIS
CRIEGEE MECHANISM



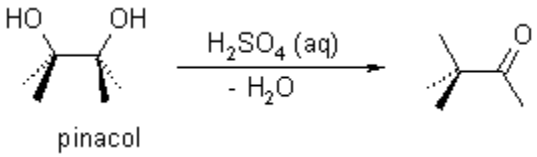
Ozonolysis allows the cleavage of alkene double bonds by reaction with ozone. Depending on the work up, different products may be isolated: reductive work-up gives either alcohols or carbonyl compounds, while oxidative work-up leads to carboxylic acids or ketones.

PINACOL COUPLING REACTION



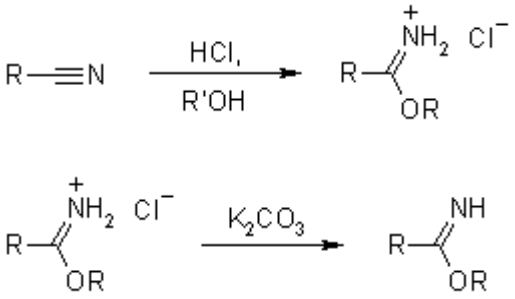
This reaction involves the reductive homo-coupling of a carbonyl compound to produce a symmetrically substituted 1,2-diol. The first step is single electron transfer of the carbonyl bond, which generates radical ion intermediates that couple via carbon-carbon bond formation to give a 1,2-diol. The example depicted above shows the preparation of pinacol itself.Pinacol and other highly substituted 1,2-diols tend to undergo dehydration with rearrangement under acid-catalysis (see Pinacol Rearrangement).

PINACOL REARRANGEMENT



In the conversion that gave its name to this reaction, the acid-catalyzed elimination of water from pinacol gives *t*-butyl methyl ketone.

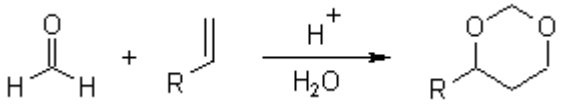
PINNER REACTION



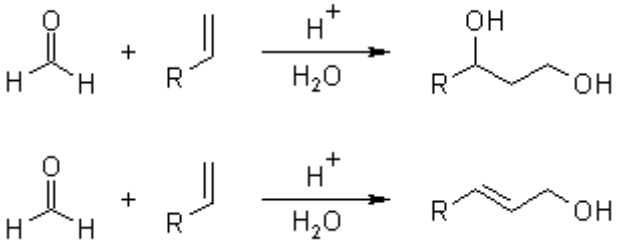
The Pinner Reaction is the partial solvolysis of a nitrile to yield an iminoether. Treatment of the nitrile with gaseous HCl in a mixture of anhydrous chloroform and an alcohol produces the imino ether hydrochloride. These salts are known as Pinner Salts, and may react further with various nucleophiles

PRINS REACTION

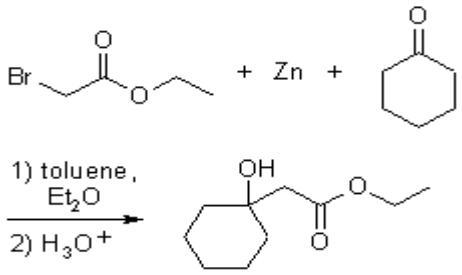
The Prins Reaction is the acid-catalyzed of addition aldehydes to alkenes, and gives different products depending on the reaction conditions. It can be thought of conceptually as the addition of the elements of the gem-diol carbonyl hydrate of the aldehyde across the double bond.



An excess of aldehyde and temperatures < 70 °C lead to the formation of acetals. When one equivalent of aldehyde is used and temperatures are > 70 °C diols or allylic alcohols may be isolated.

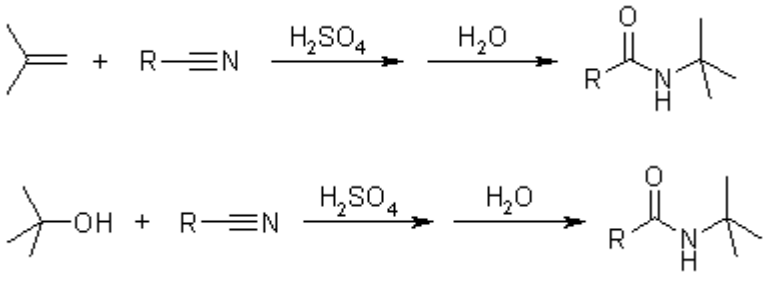


REFORMATSKY REACTION



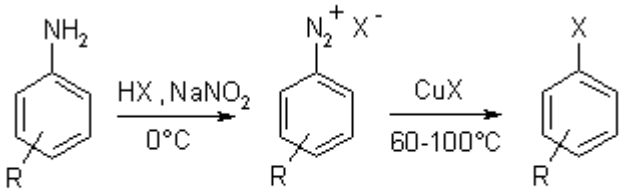
The formation of ester-stabilized organozinc reagents and their addition to carbonyl compounds

RITTER REACTION



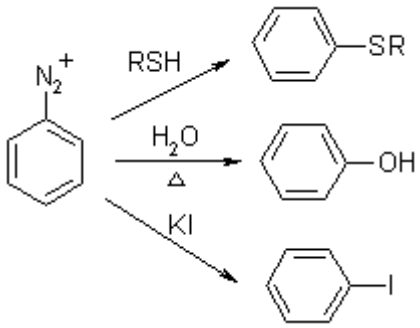
The acid-induced nucleophilic addition of a nitrile to a carbenium ion, followed by hydrolysis to the corresponding amid

SANDMEYER REACTION



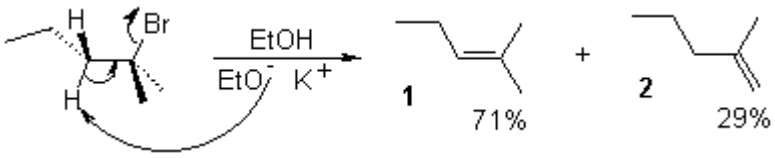
X= CN, Br, Cl, SO_3H

The substitution of an aromatic amino group is possible via preparation of its diazonium salt and subsequent displacement with a nucleophile (Cl-, I-, CN-, RS-, HO-). Many Sandmeyer Reactions proceed under copper(I) catalysis, while the Sandmeyer-type reactions with thiols, water and potassium iodide don't require catalysis.

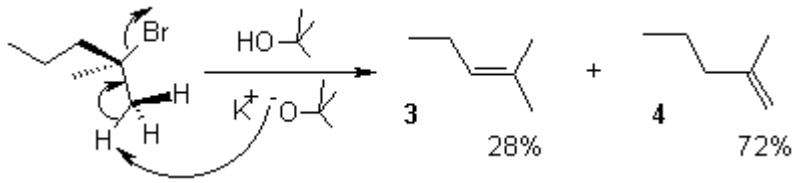


The Sandmeyer Reaction is a very important transformation in aromatic chemistry, because it can result in some substitution patterns that are not achievable by direct substitution.Fluorination is possible by using the related Schiemann Reaction

SAYTZEFF'S RULE

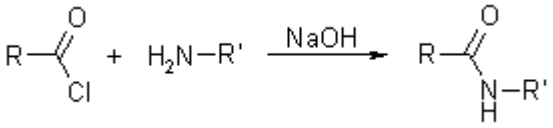


Saytzeff Rule implies that base-induced eliminations (E2) will lead predominantly to the olefin in which the double bond is more highly substituted, i.e. that the product distribution will be controlled by thermodynamics.



The use of sterically hindered bases raises the activation energy barrier for the pathway to the product predicted by Saytzeff's Rule. Thus, a sterically hindered base will preferentially react with the least hindered protons, and the product distribution will be controlled by kinetics

SCHOTTEN-BAUMANN REACTION

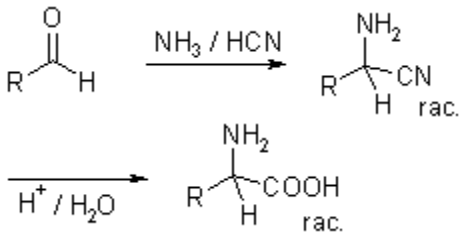


The use of added base to drive the equilibrium in the formation of amides from amines and acid chlorides.

The acylation of amines with carboxylic acid chlorides leads to the production of one equivalent acid, which will form a salt with unreacted amine and diminish the yield. The addition of an additional equivalent of base to neutralise this acid is a way to optimise the conditions. Normally, aqueous base is slowly added to the reaction mixture.

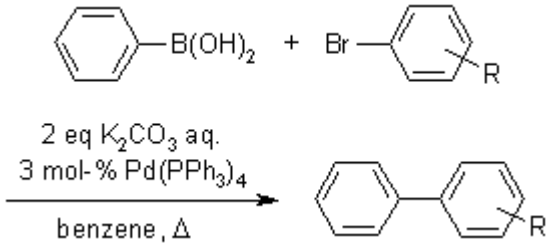
In general, the use of biphasic aqueous basic conditions is often named "Schotten-Baumann conditions".

STRECKER SYNTHESIS



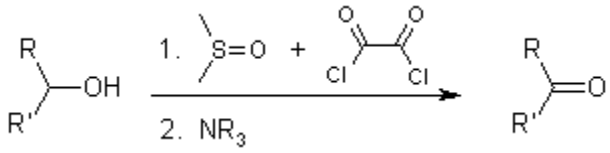
The Strecker Synthesis is a preparation of α-aminonitriles, which are versatile intermediates for the synthesis of amino acids via hydrolysis of the nitrile.

SUZUKI COUPLING



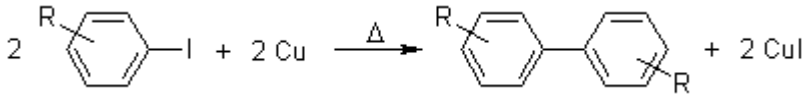
The scheme above shows the first published Suzuki Coupling, which is the palladium-catalysed cross coupling between organoboronic acid and halides. Recent catalyst and methods developments have broadened the possible applications enormously, so that the scope of the reaction partners is not restricted to aryls, but includes alkyls, alkenyls and alkynyls. Potassium trifluoroborates and organoboranes or boronate esters may be used in place of boronic acids. Some pseudohalides (for example triflates) may also be used as coupling partners.

SWERN OXIDATION



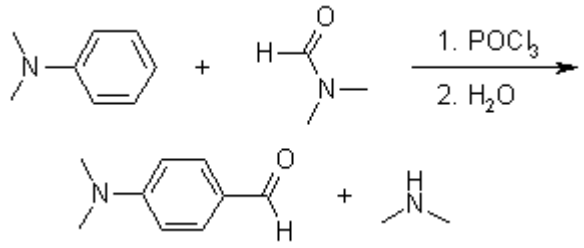
The Swern Oxidation of alcohols avoids the use of toxic metals such as chromium, and can be carried out under very mild conditions. This reaction allows the preparation of aldehydes and ketones from primary and secondary alcohols, resp. . Aldehydes do not react further to give carboxylic acids. A drawback is the production of the malodorous side product dimethyl sulphide

ULLMANN REACTION



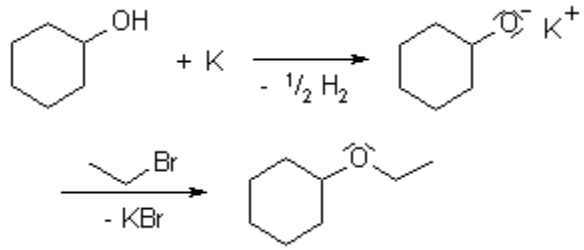
There are two different transformations referred as the Ullmann Reaction. The "classic" Ullmann Reaction is the synthesis of symmetric biaryls via copper-catalyzed coupling

VILSMEIER-HAACK REACTION



The Vilsmeier Reaction allows the formylation of electron-rich arenes

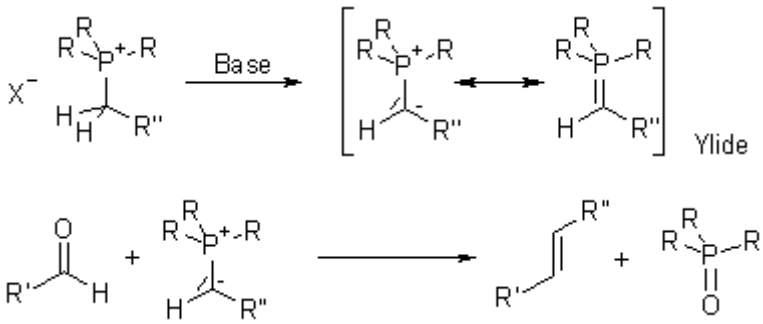
WILLIAMSON SYNTHESIS



This method is suitable for the preparation of a wide variety of unsymmetric ethers. The nucleophilic substitution of halides with alkoxides leads to the desired products.

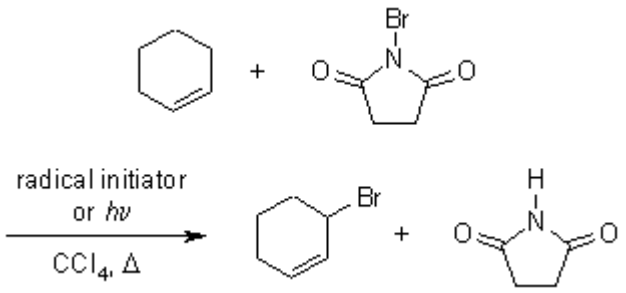
If the halides are sterically demanding and there are accessible protons in the β-position, the alkoxide will act as a base, and side products derived from elimination are isolated instead

WITTIG REACTION



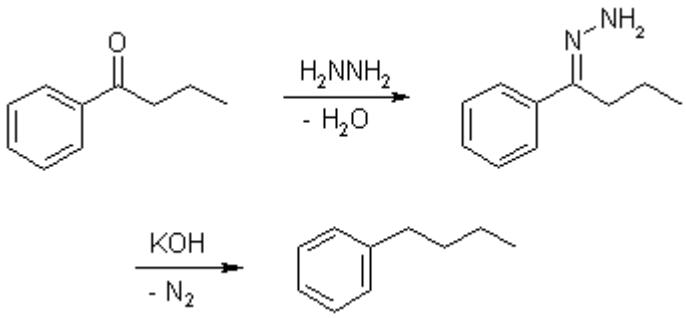
The Wittig Reaction allows the preparation of an alkene by the reaction of an aldehyde or ketone with the ylide generated from a phosphonium salt. The geometry of the resulting alkene depends on the reactivity of the ylide. If R is Ph, then the ylide is stabilized and is not as reactive as when R = alkyl. Stabilized ylides give (*E*)-alkenes whereas non-stabilized ylides lead to (*Z*)-alkenes (see Wittig-Horner Reaction)

WOHL-ZIEGLER REACTION



The bromination of allylic positions with *N*-bromosuccinimide (NBS) follows a radical pathway

WOLFF-KISHNER REDUCTION



The reduction of aldehydes and ketones to alkanes. Condensation of the carbonyl compound with hydrazine forms the hydrazone, and treatment with base induces the reduction of the carbon coupled with oxidation of the hydrazine to gaseous nitrogen, to yield the corresponding alkane.

The Clemmensen Reduction can effect a similar conversion under strongly acidic conditions, and is useful if the starting material is base-labile.

Stereochemistry: an introduction

Chem 30A Fall 2002

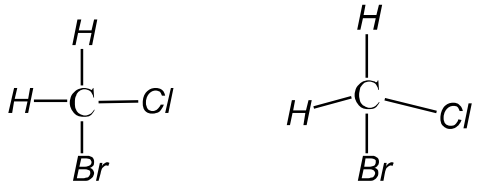
Grazia Piizzi, Steve Hardinger

Stereochemistry of Tetrahedral Carbons

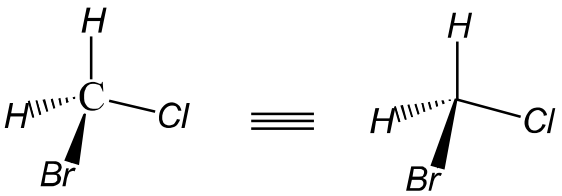
We need:

- ***one Carbon sp^3-hybridized, at least***
- ***to represent molecules as 3D objects***

For example:



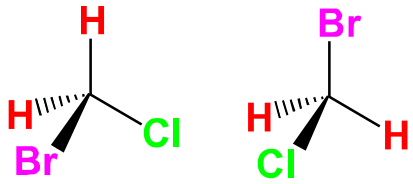
2D drawing
Not appropriate for Stereochem



3D drawing
Appropriate for Stereochem

Let's consider some molecules……

First pair

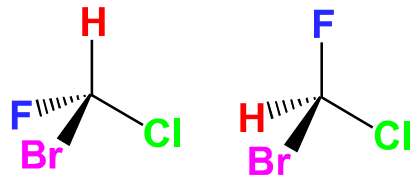


A B

- same molecular formula (CH_2BrCl)
- same atom connectivity
- superposable

➡ **identical (same compound)**

Second pair



C D

- same molecular formula (CHFBrCl)
- same atom connectivity
- nonsuperposable

➡ **stereoisomers (two different compounds)**

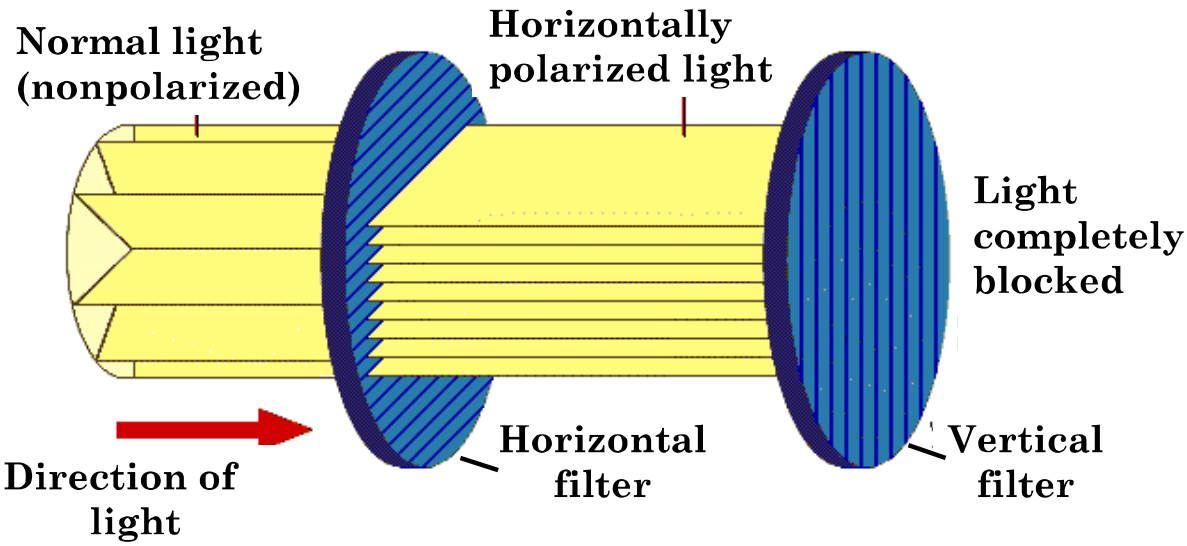
Thus, we can define……

***Stereoisomers**: isomers that have same formula and connectivity <u>but</u> differ in the position of the atoms in space*

***Stereochemistry**: chemistry that studies the properties of stereoisomers*

Historical perspective

Christiaan Huygens (1629-1695). Dutch astronomer, mathematician, and physicist. He discovers plane polarized light:

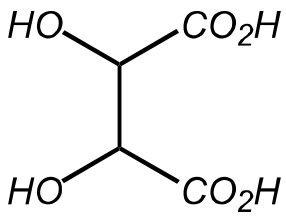


Historical perspective

Carl Wilhelm Scheele (1742-1786)

"Oh, how happy I am! No care for eating or drinking or dwelling, no care for my pharmaceutical business, for this is mere play to me. But to watch new phenomena this is all my care, and how glad is the enquirer when discovery rewards his diligence; then his heart rejoices"

In 1769, he discovers Tartaric Acid from tartar (the potassium salt of tartaric acid, deposited on barrels and corks during fermentation of grape juice).

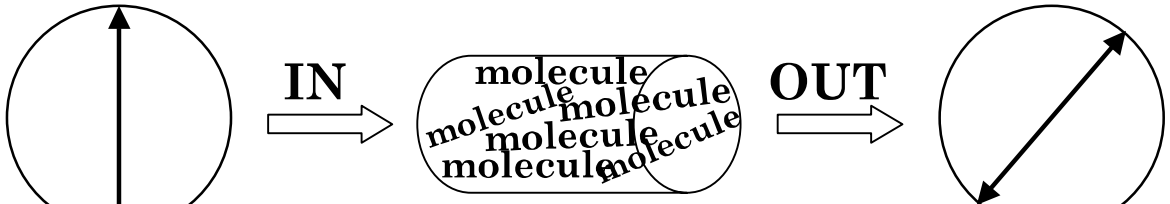


Tartaric Acid

Historical perspective

Jean Baptiste Biot (1774-1862)

In 1815, he notes that certain natural organic compounds (liquids or solutions) rotate plane polarized light (Optical Activity).



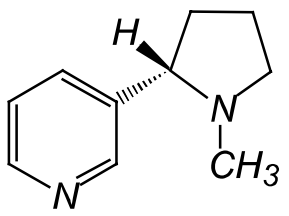
plane polarized light

tube containing a liquid organic compound or solution

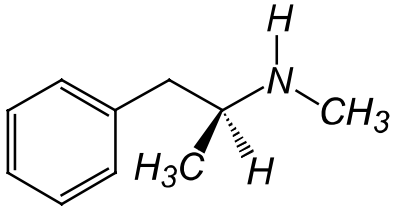
plane polarized light

Definitions

- ***Optically Active**: the ability of some compounds to rotate plane polarized light.*
- ***Dextrorotatory (+)**: an optically active compound that rotates plane polarized light in a clockwise direction.*
- ***Levorotatory (-)**: an optically active compound that rotates plane polarized light in a counterclockwise direction.*



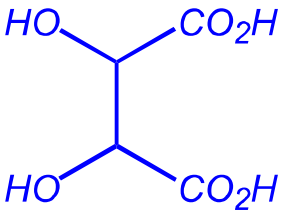
(-)-Nicotine



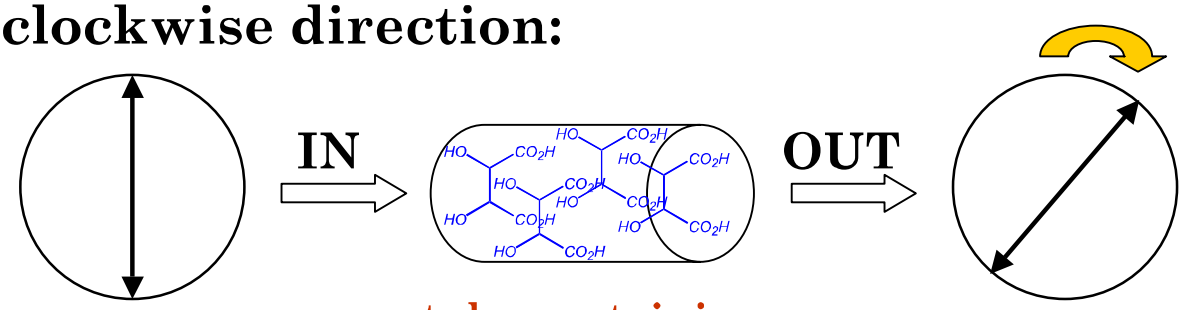
(+)-Methamphetamine

Historical perspective

In 1819, Racemic Acid was discovered. Later shown to have the same formula as Tartaric Acid.



In 1832, Biot notes that Tartaric Acid from grape juice fermentation rotates plane polarized light in a clockwise direction:



plane polarized light

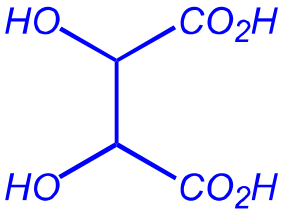
tube containing solution of Tartaric Acid (TA)

plane polarized light, rotated clockwise

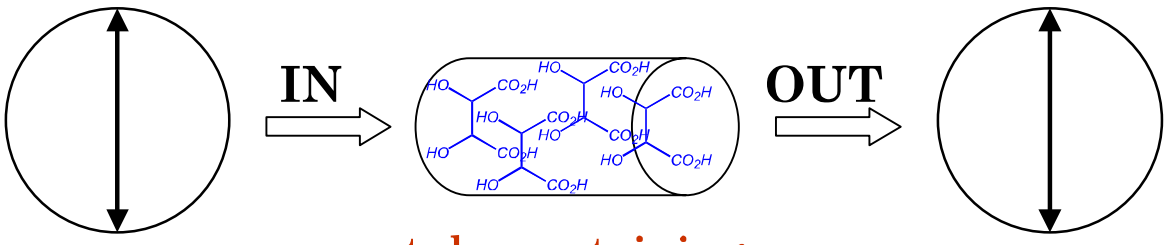
TA is dextrorotatory

Historical perspective

In 1819, Racemic Acid was discovered. Later shown to have the same formula as Tartaric Acid.



In 1838, Biot notes that Racemic Acid does not rotate plane polarized light:



plane polarized light

tube containing solution of Racemic Acid (RA)

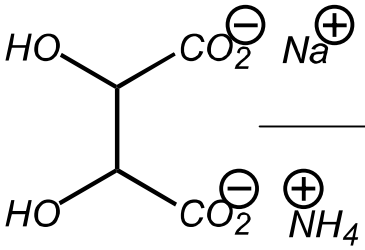
plane polarized light, unchanged

RA is not optically active

Historical perspective

Louis Pasteur (1822-1895)

In 1847, he repeats earlier work on Racemic Acid. Crystallization of sodium ammonium salt gives mirror image crystals that he separated by hand. Equimolar solutions of separated crystals have equal but opposite optical activity:



separate crystals

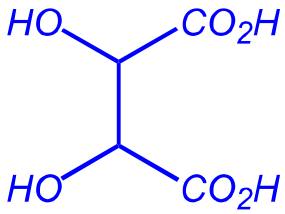
$[\alpha]_D = +12.7^o$ (+)-Tartaric Acid (dextrorotatory, natural)

$[\alpha]_D = -12.7^o$ (-)-Tartaric Acid (levorotatory, unnatural)

Racemic acid salt

Historical perspective

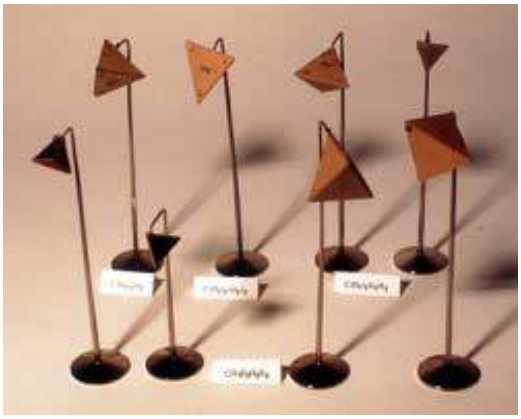
In 1853, Pasteur studies Mesotartaric Acid (same formula as Racemic and Tartaric Acid) but fails to separate into (+) and (-) crystals.



In 1854, he notes that certain plant mold metabolizes (+)-tartaric acid but not (-)-tartaric acid.

Historical perspective

Joseph A. LeBel
(1847-1930)



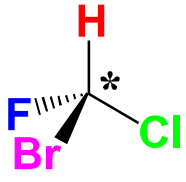
Jacobus H. van't Hoff
(1852-1930)

In 1874, they propose:

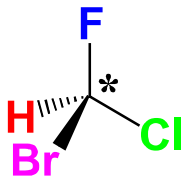
- **Carbon with 4 attachments is Tetrahedral.**
- **A molecule having a tetrahedral carbon with 4 different attachments may exist as a pair of isomers.**

Therefore…..

- ***Stereoisomers: isomers that differ only in the position of atoms in space, and that cannot be interconverted by rotation around a single bond.***
- ***Stereocenter: a carbon atom bearing 4 different atoms or group of atoms.***



C

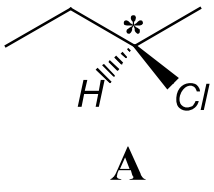


D

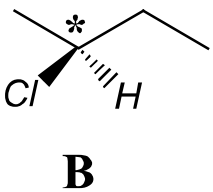
C,D are a pair of stereoisomers
Carbon * is a stereocenter

…..another example

Stereoisomers of 2-chlorobutane



A



B

A,B are stereoisomers
Carbons * are stereocenters
A,B are nonsuperposable mirror images

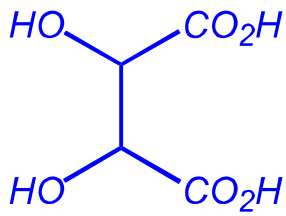
Enantiomers

Enantiomers: stereoisomers that are nonsuperposable mirror images.
Chiral: any molecule that is nonsuperposable with its mirror image (i.e. A and B are chiral).
Achiral: any molecule that is not chiral.
Racemic mixture: a 1:1 (equimolar) mixture of two enantiomers.

Unsolved Issues

Joseph A. LeBel
(1847-1930)

Jacobus H. van't Hoff
(1852-1930)



Mesotartaric Acid
could not be separated into (+) crystals and (-) crystals

- **Carbon with 4 attachments is Tetrahedral.**
- **A molecule having a tetrahedral carbon with 4 <u>different</u> attachments may exist as a pair of isomers.**

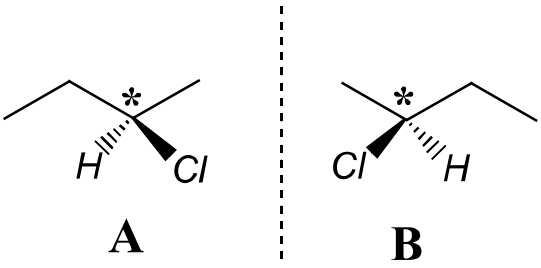
In 1877, Hermann Kolbe, one of the best organic chemist of the time wrote:

"Not long ago, I expressed the view that the lack of general education and of through training in chemistry was one of the reasons of the causes of the deterioration of chemical research in Germany.....Will anyone to whom my worries seem exaggerated please read, if he can, a recent memoir by a Herr van't Hoff on "The Arrangement of Atoms in Space", a document crammed to the hilt with the outpouring of childish fantasy...This Dr. J. H. van't Hoff, employed by the Veterinary College at Utrecht, has, so it seems, no taste for accurate chemical research. He finds it more convenient to mount his Pegasus (evidently taken from the stables of the Veterinary College) and to announce how, on his bold flight to Mount Parnassus, he saw the atoms arranged in in space."

In 1901 van't Hoff received the first Nobel Prize in Chemistry.

Take-home problem

Stereoisomers of 2-chlorobutane



Enantiomers

➨ ***Remember:***

Enantiomers: stereoisomers that are nonsuperposable mirror images.

Racemic mixture: a 1:1 (equimolar) mixture of two enantiomers.

➨ ***Explain why:***

- **A and B cannot be physically separated.**
- **a racemic mixture of A and B has no optical activity (no rotation of plane polarized light).**

Summary

***Stereoisomers**: isomers that have same formula and connectivity <u>but</u> differ in the position of the atoms in space. They possess one or more stereocenters.*

***Stereocenter**: a carbon atom bearing 4 different atoms or group of atoms.*

***Chiral**: any molecule that is nonsuperposable with its mirror image.*

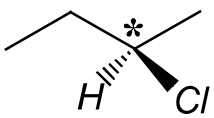
***Enantiomers**: stereoisomers that are non superposable mirror images.*

***Racemic mixture**: a 1:1 (equimolar) mixture of two enantiomers.*

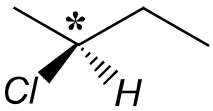
***Optically Active**: the ability of some compounds to rotate plane polarized light.*

Configuration of Stereocenters

Enantiomers of 2-chlorobutane:



A

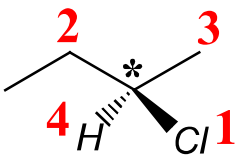


B

The Cahn-Ingold-Prelog (CIP) rule assigns R or S configuration to the two enantiomers.

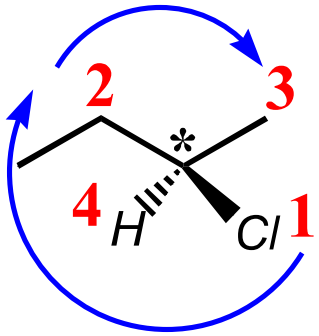
1) Assign the priorities to the groups attached to the stereocenter. Priority is based on the atomic number, i.e. H has lower priority than Cl.
But methyl and ethyl both are attached to the stereocenter through carbon! In these cases, priority assignments proceed outward, to the next atoms. The Methyl carbon has 3 Hs attached while the Ethyl carbon has 2Hs and and a carbon (the terminal methyl group). Therefore, the latter gets higher priority.

Configuration of Stereocenters



A

2) Orient the molecule so that the group of priority four (lowest priority) points away from the observer.

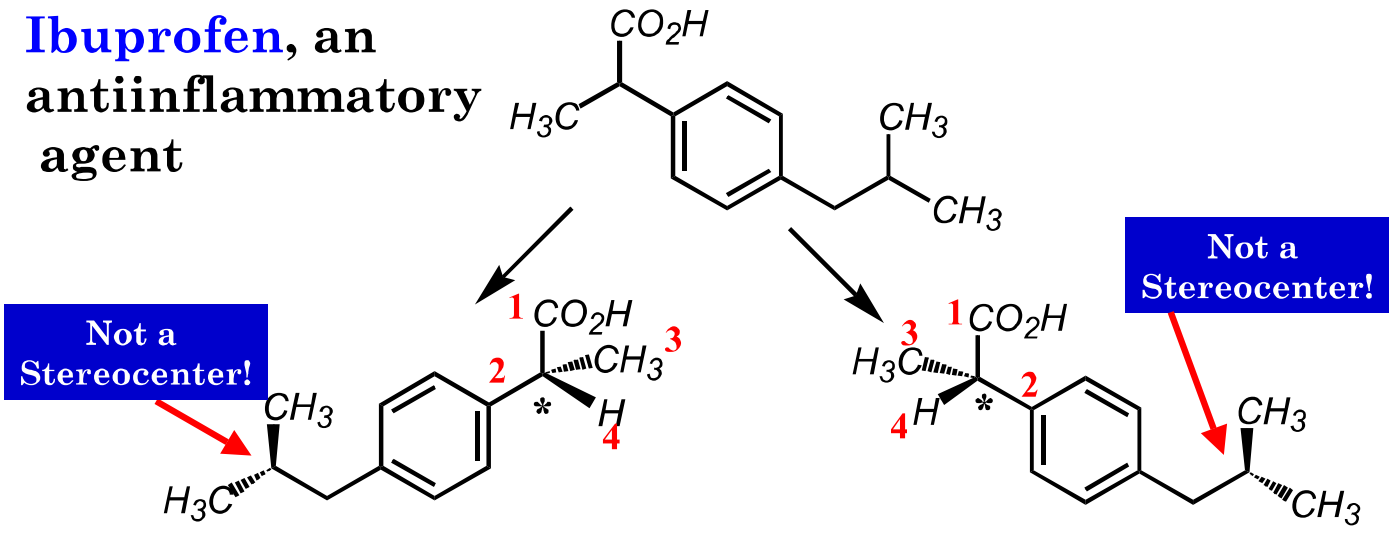


3) Draw a circular arrow from the group of first priority to the group of second priority.

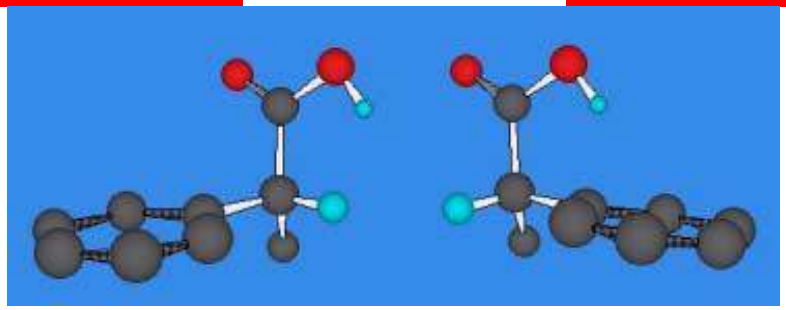
4) If this circular motion is clockwise, the enantiomer is the R enantiomer. If it is counterclockwise, it is the S enantiomer. Thus, A is the R enantiomer of 2-chlorobutane.

Configuration of Stereocenters

Ibuprofen, an antiinflammatory agent



R enantiomer **S enantiomer**

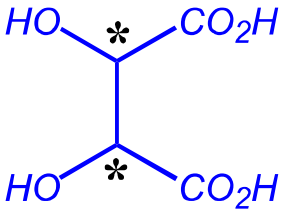


Molecules with multiple stereocenters

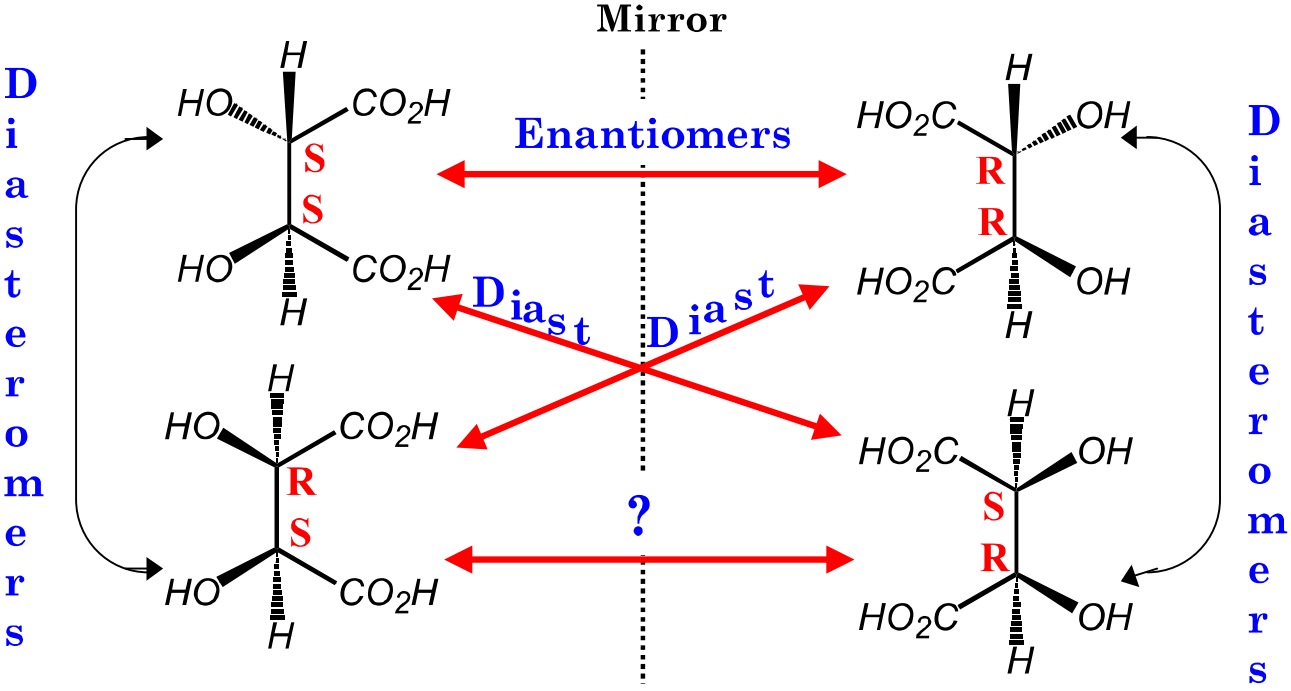
Molecules with 1 stereocenter can be R or S → **2 possible stereoisomers**

Molecules with *n* stereocenters can have all the possible combinations of R and S for each stereocenter → **2^n possible stereoisomers**

Tartaric Acid



2 stereocenters → **4 possible stereoisomers**

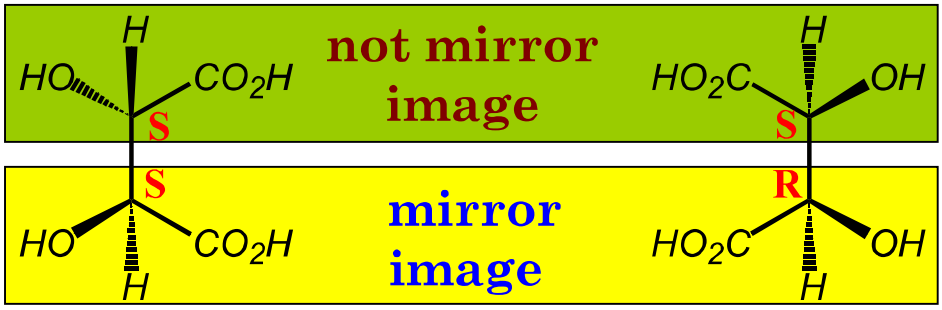


Remember

Enantiomers: stereoisomers that are non superposable mirror images.

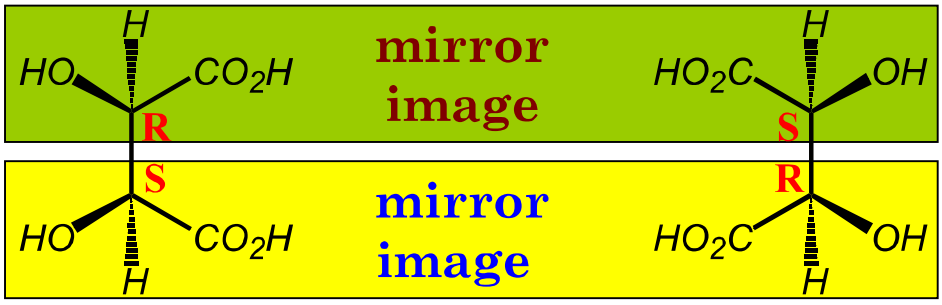
Diastereomers: stereoisomers that are not mirror images.

For example:



(S, S)-Tartaric acid **(S, R)-Tartaric acid**

DIASTEREOMERS



(R, S)-Tartaric acid ⇩ **(S, R)-Tartaric acid**

Enantiomers

?

Why not Enantiomers?

Enantiomers:

√ same molecular formula

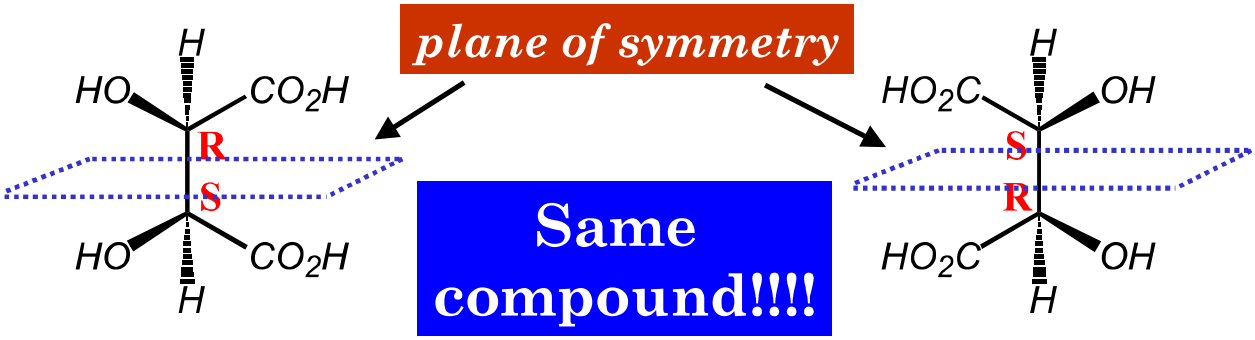
√ same connectivity

√ mirror images

X nonsuperposable ➡ Superposable

Achiral compound

Why not Enantiomers?



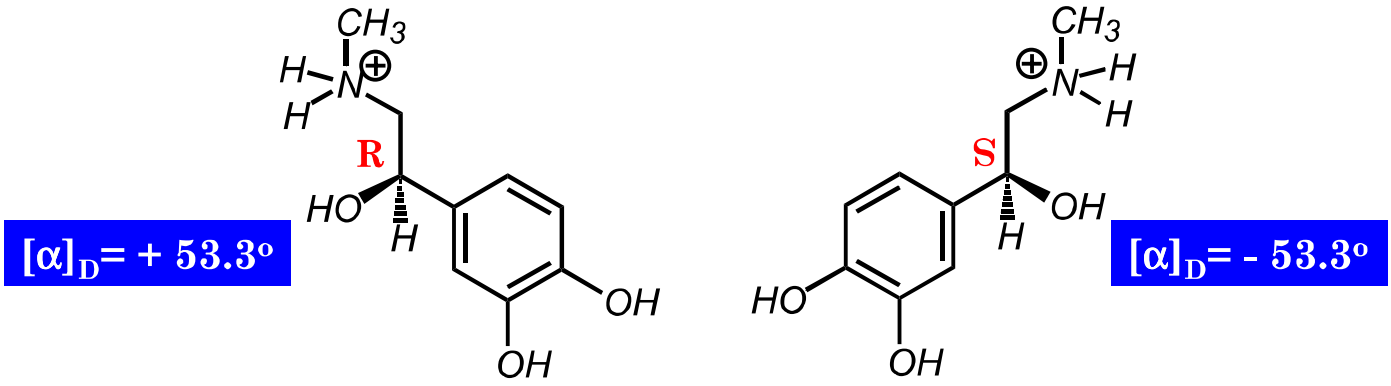
Meso compound

A compound with at <u>least 2 stereocenters</u> that is <u>achiral</u> due to the presence of a plane of symmetry

Properties of Stereoisomers

Enantiomers: have same chemical and physical properties in an achiral environment but they differ on the sign of rotation of plane polarized light.

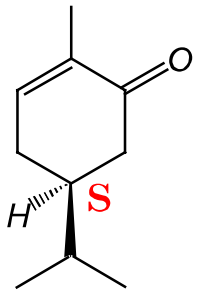
For example: Enantiomers of Epinephrine (Adrenaline)



Same melting/boiling point, same rate of reaction with achiral reagents, same degree of rotation of plane polarized light.....thus difficult to separate!

Properties of Stereoisomers

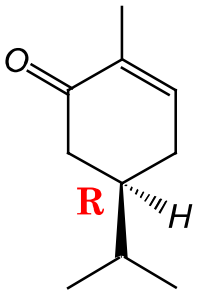
Carvone exists as a pair of enantiomers:



(+)-carvone

smells like caraway

$[\alpha]_D$ = + 62.5



(-)-carvone

smells like spearmint

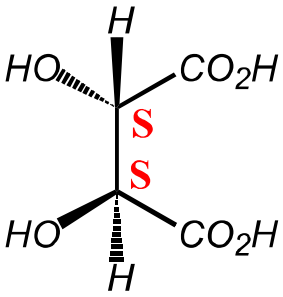
$[\alpha]_D$= – 62.5

Note:

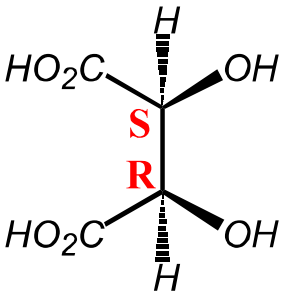
- **No relationship exists between the S/R configuration and the sign or the magnitude of rotation of plane polarized light.**
- **A 1:1 mixture of enantiomers (racemic mixture) has always no optical activity (rotation equal to zero) because the rotation of 50% of one enantiomer is cancelled out by the rotation (equal but opposite) of 50% of the other enantiomer.**

Properties of Stereoisomers

Diastereomers: have different chemical and physical properties in any type of environment.



(S,S)-Tartaric Acid



Mesotartaric Acid

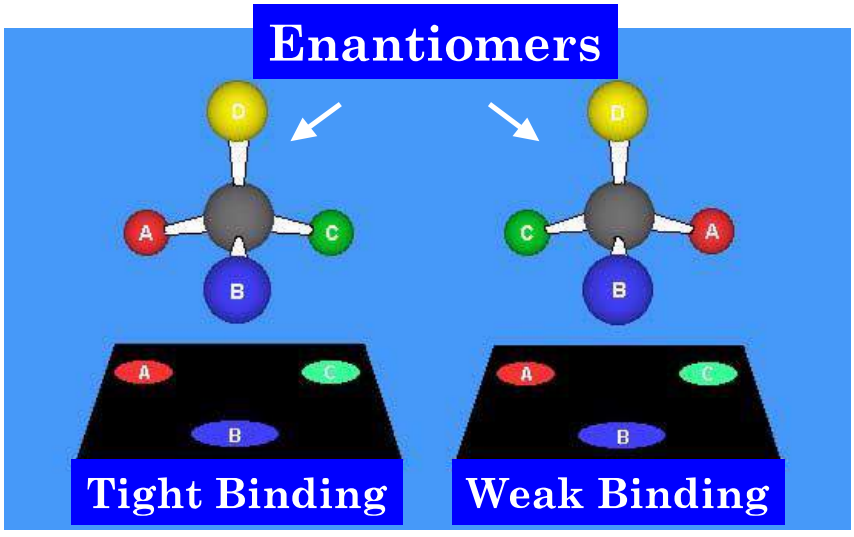
$[\alpha]_D$	- 12.7	0 (achiral)
Melting p. (°C)	171-174	146-148
Density (g/cm^3)	1.7598	1.660
Solubility in H_2O	139	125

Biological Significance of Chirality

Since most of the natural (biological) environment consists of enantiomeric molecules (amino acids, nucleosides, carbohydrates and phospholipids are chiral molecules), then enantiomers will display different properties. Then, in our body:

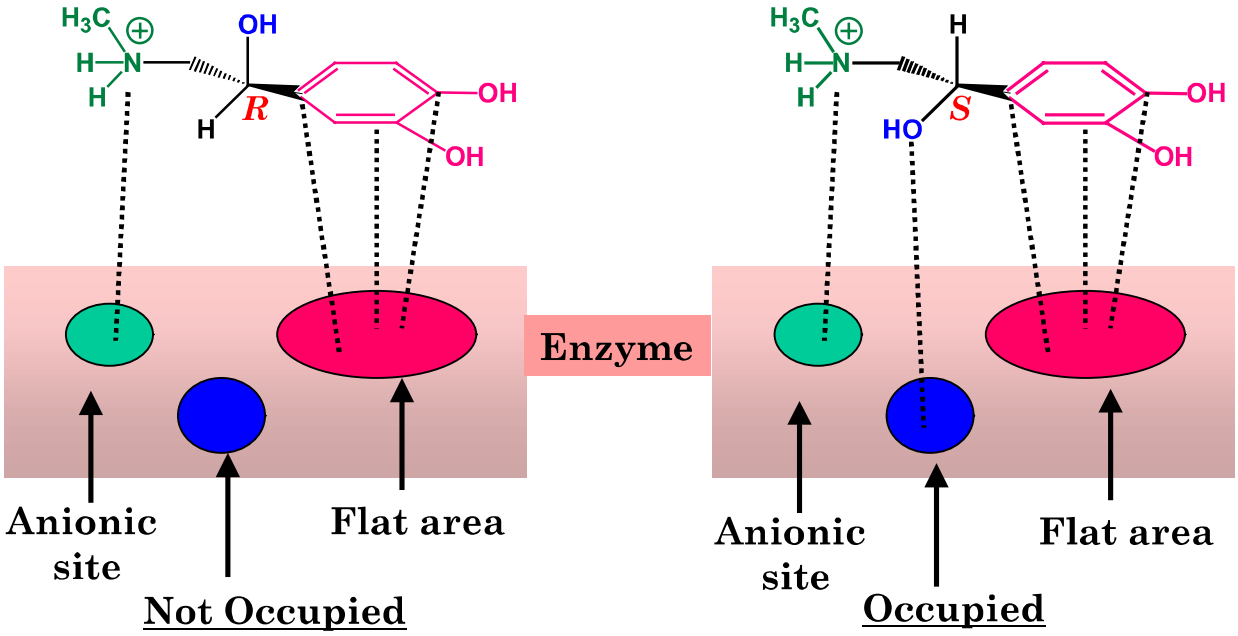
Drug ➡

Enzyme ➡



Biological Significance of Chirality

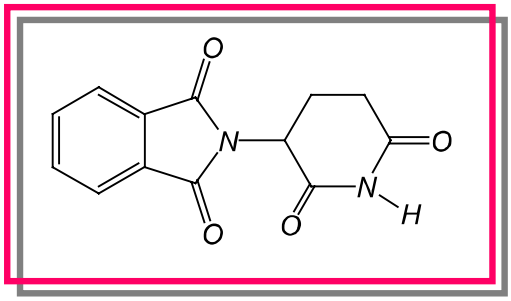
Enantiomers of Epinephrine



(+)-Epinephrine — ***Poorer Fit*** ⇨ ***Less Active***

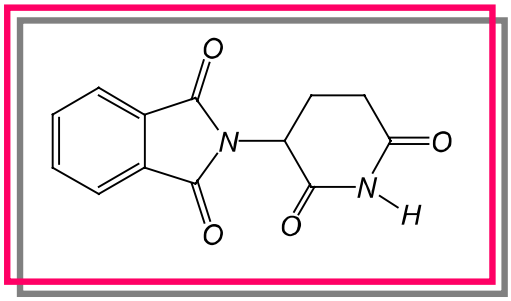
(-)-Epinephrine — ***Better Fit*** ⇨ ***More Active***

The case of Thalidomide



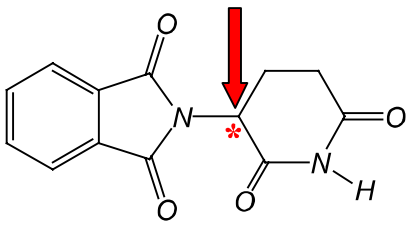
Thalidomide was synthesized in West Germany in 1953 by Chemie Grünenthal. It was marketed (available to patients) from **October 1, 1957** *(West Germany) into the early 1960's. Sold in at least 46 countries (US not included), Thalidomide was hailed as a "wonder drug" that provided a "safe, sound sleep". It was a sedative that was found to be effective when given to pregnant women to combat many of the symptoms associated with morning sickness. No clinical testing was available to show that Thalidomide molecules could cross the placental wall affecting the fetus until it was too late.*

The case of Thalidomide

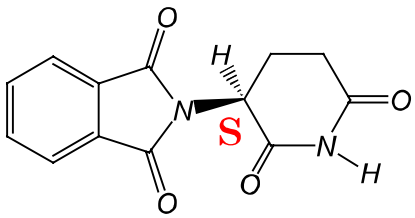


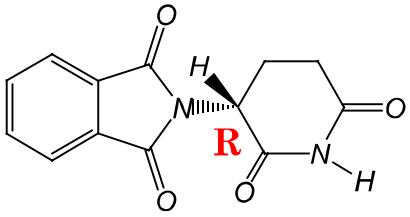
Thalidomide was a catastrophic drug with tragic side effects. Not only did a percentage of the population experience the effects of peripheral neuritis, a devastating and sometimes irreversible side effect, but Thalidomide became notorious as the killer and disabler of thousands of babies. When Thalidomide was taken during pregnancy (particularly during a specific window of time in the first trimester), it caused startling birth malformations, and death to babies. Any part of the fetus that was in development at the time of ingestion could be affected.

The case of Thalidomide



1 stereocenter = 2 stereoisomers





S-thalidomide

R-thalidomide

Sedative

Teratogen

(to calm nervousness)

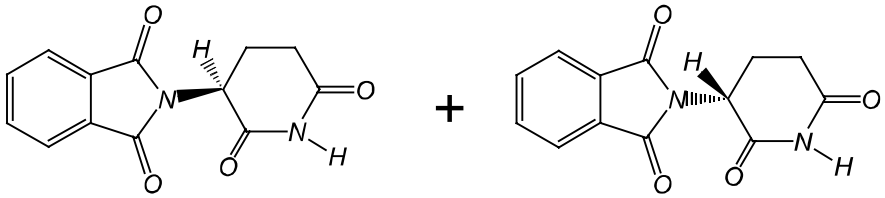
(to cause birth defects)

Why did the two enantiomers display different biological activity?

Enantiomers differ in the arrangement of atoms in space. Therefore, the **S enantiomer** of Thalidomide can fit the active site of a specific enzyme (like a "key" for a specific "lock") producing the desired effect (sedative). On the other hand, the **R enantiomer** cannot interact with the same site due to a different arrangement of atoms (3D shape). As consequence, it fits a different enzyme active pocket triggering a different biological effect (toxic).

How to solve this problem?

Chemical synthesis of Thalidomide from achiral starting materials



S R

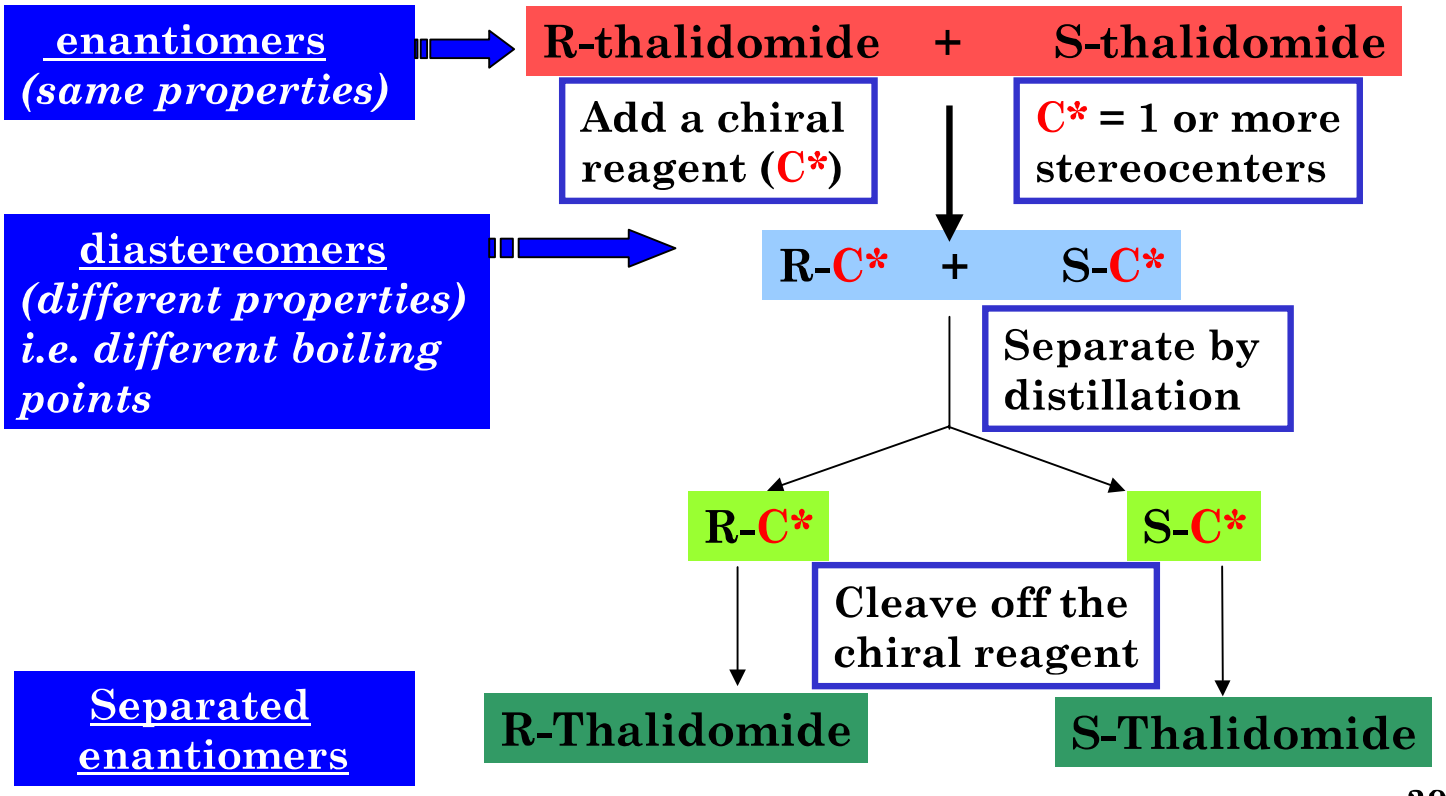
1 : 1

(racemic mixture)

Separate enantiomers (Resolution)

Resolution of Enantiomers

Enantiomers are temporarily converted into a pair of diastereomers by adding a chiral reagent.....



Conclusions

- Some organic molecules possess one or more (*n*) stereocenters, thus several (2^n) stereoisomers are possible.
- Enantiomers and diastereomers differ only in the position of atoms in space.
- Unlike Diastereomers, Enantiomers display the same chemical/physical properties in an achiral environment.
- In the human body (chiral environment) two enantiomers can be discriminated producing different biological responses.