Date
Page

* Non compartmental *

(1) Statistical moment Theory

- It is a mathematical description of discrete distribution of data.
- It calculated from conc^n/time data.
- It provide unique way to study time related changes in macroscopic event.
- Assume the drug molecule are ~~elimi~~ eliminated accor. to kinetic function

$$f(t) = C_0 e^{-kt}$$

$f(t)$ = probability density function
t = time

Now $f(t)$ multiplied by t^m & on integration to moment curve

$$\text{Mm or } m^{th} \text{ moment} = \int_0^\infty t^m f(t)\, dt \quad -(1)$$

$F(t)$ = PDF, t = time, m = moment.

- when $m = 0$ then yield M_0

$$M_0 = \int_0^\infty f(t)\, dt \quad -(2)$$

If distribution is true function, then AUC = 1.

Now at 1st function μ_1

$$\mu_1 = \int_0^t t^1 f(t)\,dt$$

⇒ AUC at time t called AUMC
area under moment curve

Similarly μ_2 & $n=2$

$$\mu_2 = \int_0^t t^2 f(t)\,dt$$

μ_2 variance of distribution
⇒ Higher moment represent skewness & kurtosis distribution

Q. MRT.

⇒ Element of distribution curve describe the distribution of drug molecule after administration & the residence time of drug molecule in body.

⇒ Here, Amount of drug in body proportional to concentration in plasma at all time points.

$$MRT = \frac{AUMC}{AUC}$$

MRT: Mean Residence time
AUMC & AUC

MRT defined as avg time spent by drug in body before elimination.

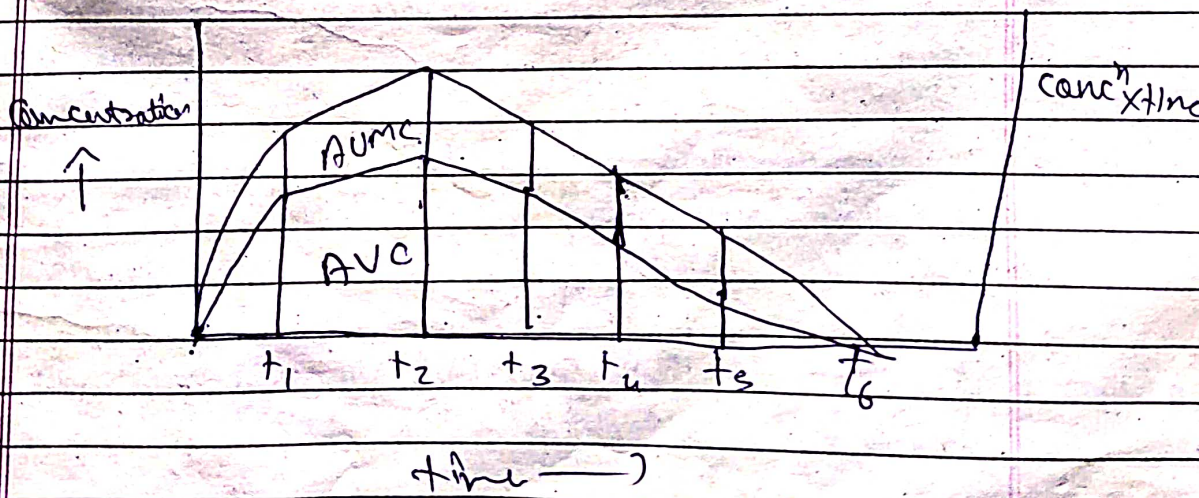
AUMC obtained from plot of product of plasma drug conc^n & time vs. time(t) from 0 to ∞

$$AUMC = \int_0^\infty C\,t\,dt.$$

AUC obtained from plot of plasma drug conc^n vs time(t) 0 to ∞.

$$AUC = \int_0^\infty C\,dt.$$

By trapezoidal rule calculate AUC & AUMC.



Date
Page

Adv:-
① Simple algebric eqn
② Applied to many drug that follow 1st order kinetic

Disadv:-
① Do not follow Non linear case
② also provide less info regarding plasma drug conc" time profile.

28/1/24

Date
Page

* BPPK Answer *

15 Difference between compartment modelling and physiological modelling.

Compartment modelling	Physiological modelling
1. It is an hypothetical approach.	1. It is an relastic approach.
2. Experimentally simple & flexible as data collection is concerned.	2. Difficult Experimentally since exhaustic data collection required
3. Widely used & often the "first model"	3. Not widely use due to complexity
4. Complex multiexponential mathematical necessary for curve fitting	4. Mathematical is straight forward.
5. Data fitting required for prediction of drug conc"	5. Data fitting not require Since drug conc" practically determine
6. Used when little info of tissue	6. Used when tissue drug conc" & binding are known.
7. Easy monitor with limited data	7. Exhaustic data require to monitor

8.	Mechanism of ADME not given	∴ Easy to explain ADME
9.	Effect of pathological condition on drugs ADME not given	∴ ... given easily
10.	Commonly used for data comparision	10. Not used for data comparision

Q12 Define pharmacokinetic model & classify.

→ It is a mathematical model used to calculate ADME of synthetic or natural product are known as pharmacokinetic model.

→ It express the time course of drug throughout body.

→ It also predict concentration of drug in body fluid after administration of dose

→ There are 3 type of pharmacokinetic model

(i) Compartment model
(ii) Physiological model
(iii) Non-Compartment model

1) Compartment models

- It assumed that body consist of series of compartment
- A compartment is not real physiologic or anatomic region.
- Rate of movement of drug within compartment follow first order kinetic.
- There are 2 type of Compartment model.

[i] Mammillary Model

- Here this model are further divide into
  (a) Central compartment
  (b) Peripheral compartment.

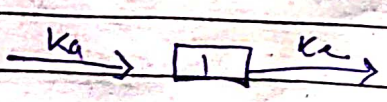
(a) Central compartment :- It comprise of blood and highly perfused tissue like lungs, liver, kidney, heart, brain

(b) Peripheral :- It comprise of poorly perfused tissue like muscle, skin, adipose etc.

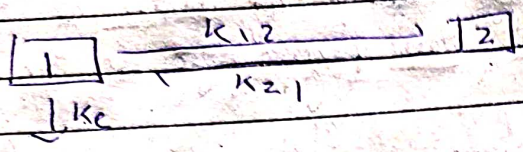
- Here 6 type of model present.

1. 1 compart open, IV

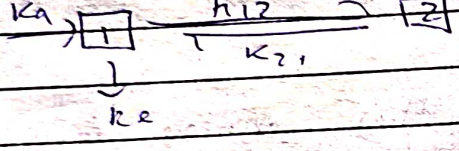
2. 1 comp open, 1st order absorption



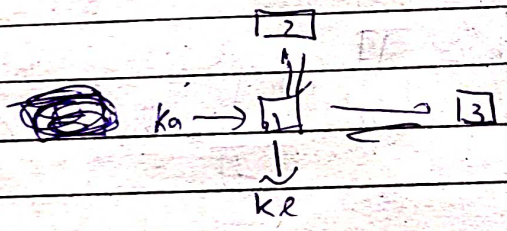
3. 2-comp, Open, IV



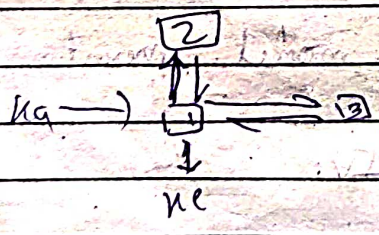
4) 2-comp Open IS ab



5 3 comp Open IV



6) 3 comp Open, Extravascular



[iv] Catenary Model.

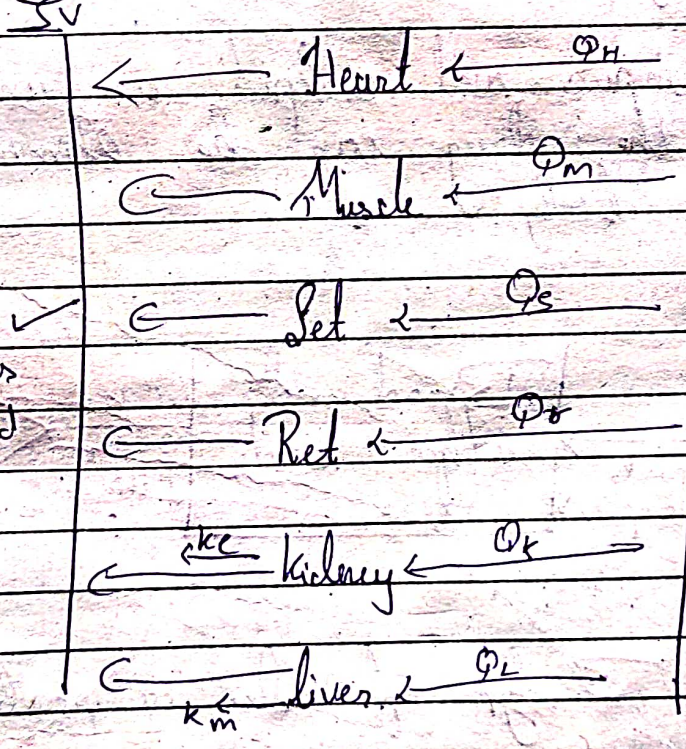
→ It consist all compartment joint to one another

[2] physiological Model.

↳ Here overall drug concentration profile result from sum of processing of drug by different organ.

↳ The distribution depend on blood flow and the organ & it size

↳ lungs, liver, brain & kidney are rapidly equilibrating tissue whereas skin, muscle etc are slowly equilibrating tissue.



[3] Non Compartment model :-

→ This are independent because they do not rely upon assumption about body compartment, but relies on algebric equation which make it less complex.

By calculating MRT the pharmacokinetic of drug

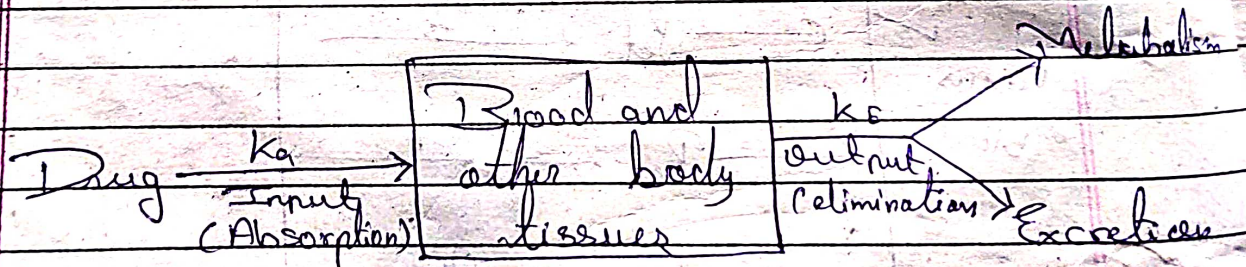
Resume.

Q13. Note an One Compartment model. (20)

→ The one compartment open model is the simplest model which represent the body as a single, kinetically homogeneous unit that has no barries to movement of drug.

→ The final distribution equilibrium b/w drug in plasma and other body fluid attained instantaneously and maintained at all times.

→ Here the input and output are unidirectional and that the drug can be eliminated from the body.



→ There are 3 type of One compartment model.

a. One compartment open model, IV injection (Bolus)
b. One compartment open model, IV infusion
c. One compartment open model, Extra vascular administration which follows zero order & first order absorption

(a) One compartment open model, IV injection (Bolus)

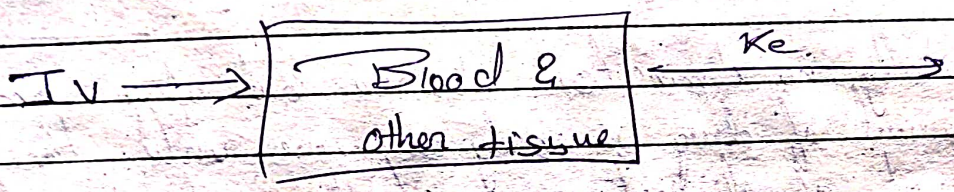
→ When drug distributes rapidly in body given in form of rapid IV injection

↓

It takes about one to three minutes for complete circulation

↓

This show rate of absorption is neglected



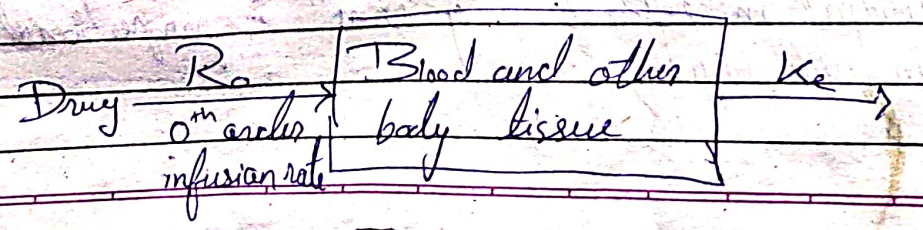
→ General expression for rate of drug presentation to

$$\frac{dx}{dt} = -K_e X$$

where dX/dt = rate of process
K_e = 1st order elimination rate constant
X = Amount of drug in body

(b) One compartment open model, IV infusion

→ Rapid IV injection is undesirable to drug produce precipitation of toxicity, thus IV infusion is beneficial due to no peaks & lows and remain stable



Date
Page

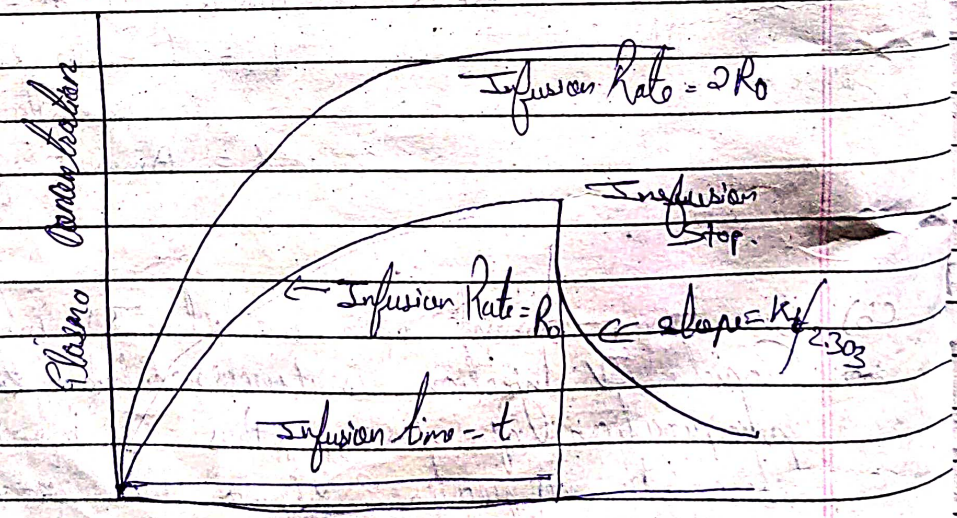
- Rate of change of amount of drug at any time (t) (dX/dt) is given as difference b/w 0th order R_0 & 1st order elimination $-K_eX$

$$dX/dt = R_0 - K_eX$$

Rearrange equation

$$X = \frac{R_0}{K_e}(1 - e^{-K_e t})$$

- Initially no elimination observe but after some time amount of drug in body increase until the rate of elimination equal to rate of infusion.
- This is called steady state, plateau or equilibrium



- Initial increase in drug conc^n is proportional to infusion rate.

Date
Page

w) The rate of change of amount of drug in body at zero state $dX/dt = 0$

$$dX/dt = R_0 - K_e X \quad \text{— (1)}$$

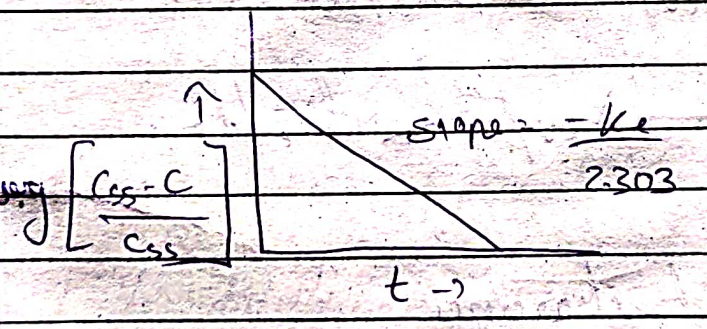
$$0 = R_0 - K_e X$$

or

$$R_0 = K_e X$$

w) Transform to Conc^n & rearranging.

$$C_{ss} = \frac{R_0}{K_e V_d} = \frac{R_0}{Cl_T} = \frac{\text{Infusion Rate}}{\text{Clearance}}$$

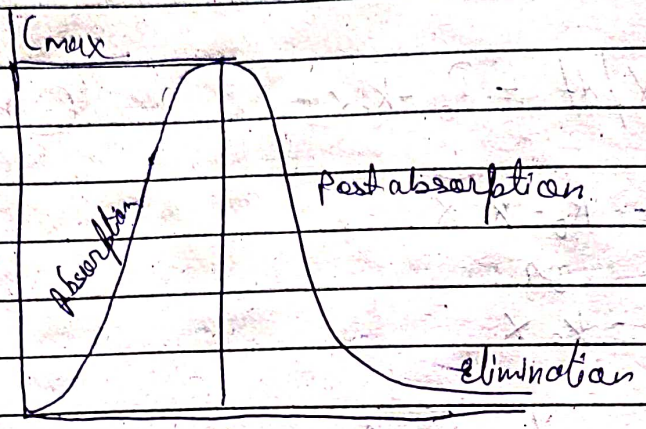


(c) One compartment open model, Extravascular administration

w) Zero order absorption refer to constant absorption & thus independent of ARA & show linear graph.

w) Where first order absorption is differentiated by decreasing ARA thus have straight line

$\therefore dX/dt = dX_{ev}/dt - dX_e/dt$



- During Absorption

$dX_{ev}/dt > dX_e/dt$

- At C_{max} $dX_{ev}/dt = dX_e/dt$
- At Elimination $dX_{ev}/dt < dX_e/dt$

Q12 Note on Renal clearance

Q11 Note on Statistical moment theory

- Statistical moment theory is a mathematical description of discrete ~~data~~ distribution of data.
- It calculated from concentration v/s time data
- It provide unique way to study the time related macroscopic event.

Date
Page

w Assume the drug molecule eliminated according to kinetic function

$$f(t) = C_0 e^{-kt}$$

w probability density function ($f(t)$) multiplied by t^m & integrated over ∫ yield the moment curve.

∴ Than moment curve show distribution

$$\mu_m \text{ or } m^{th} \text{ moment} = \int_0^\infty t^m f(t)\, dt \qquad -(1)$$

for example, when $m=0$ than yield moment is μ_0.

$$\therefore \mu_0 = \int_0^\infty t^0 f(t)\, dt$$

$$\therefore \mu_0 = \int_0^\infty f(t)\, dt \qquad -(2)$$

w If the distribution is true probability function

↓

Area under zero moment curve is 1.

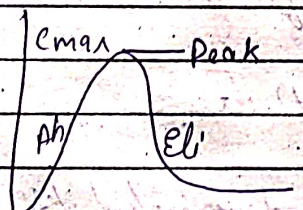
∴ Equation for 1st moment μ_1 is.

$$\mu_1 = \int_0^\infty t^1 f(t)\, dt \qquad -(3)$$

∴ AUC at time (t) called AUMC (Area under moment curve).

Q10. Define term. (i) Maximum concentration
(ii) Therapeutic windows

(i) Maximum concentration
- The point of maximum concentration of drug in plasma is called peak and the concentration of drug at peak is known as ~~plasma~~ peak plasma concentration.
- It is also called peak height concentration
- C_{max} expressed in mcg/ml
- Peak plasma level depend on
  - Administered dose
  - Rate of absorption
  - Rate of elimination

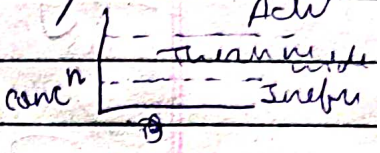


- Peak show rate of absorption equal to rate of elimination
- Curve left to the peak is absorption phase while right to peak is elimination phase

(ii) Therapeutic windows
- The close range of a drug that provide safe and effective therapy with minimal adverse effect.

Date
Page

~) At low concentration, a drug run the risk of being ineffective, at high concentration the risk of adverse effect, thus dosing regimen are designed to maintain drug concentration within therapeutic window.



Q9. Note on biotransformation.

~) It is defined as the chemical conversion of one form to another.

~) The chemical changes are unequally affected enzymetically in body.

~) The foreign substances that are not nutrient for the body but entry into body through any route called xenobiotics.

~) Drug biotransformation is one type of detoxification process.

~) The process of biotransformation helps to convert most lipophilic toxicant into hydrophilic metabolite that are less likely to pass through membrane of critical cell.

~) The loss of drug through biotransformation by eliminating organ during it passage to blood is called 1st pass metabolism.

Date
Page

- The last metabolism occur in skin & most metabolism occur in liver

- Drug biotransformation reaction are classified as

(a) Phase I :- functionalisation reaction
(b) Phase II :- Biosynthetic reaction

(a) Phase I reaction :- In these reactions a functional group [OH, NH_2, SH) is introduced on the parent compound usually to convert the parent drug to more polar metabolite

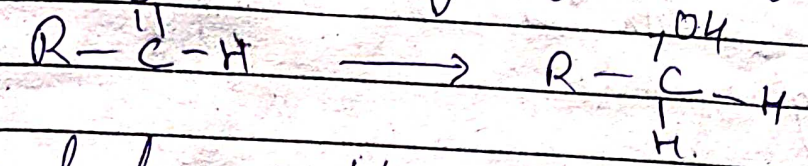
- These reaction make chemical less toxic,
  - more water soluble
  - Easier to excrete

- It further divided into 3 part
  - Oxidation :- In these reaction there is an addition of oxygen & removal of hydrogen.

- This include cytochrome P450

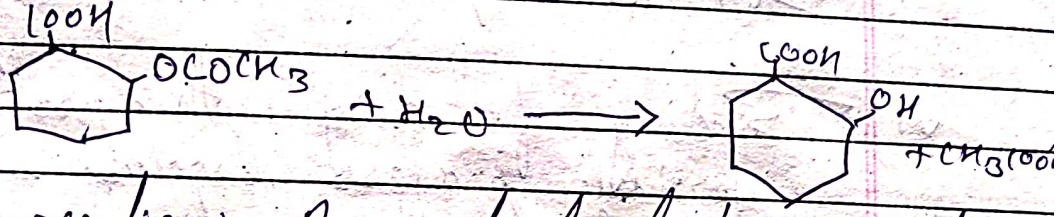
$$RH + O_2 + NADPH + H^+ \longrightarrow ROH + H_2O + NADP^+$$

② Reduction :- Here the substrate gain the electron or addition of hydrogen to the compound.



② Hydrolysis :- Here the addition of water divides the large fragment into a smaller fragment or molecule

e.g.



(b) Phase II reaction :- A covalent linkage is formed b/w functional group on the parent compound with endogenously substrate such as glucuronic acid, sulphate amino acid.

- This compound are highly polar & have poor ability to cross membrane

- This are further divided into 6 type

① Conjugation ~ glucuronic acid.
② Conjugation ~ sulphate moiety
③ Conjugation ~ amino acid
④ Conjugation ~ glutathione & mercapturic acid
⑤ Acetylation
⑥ Methylation

Q8. Note on protein binding

i) The phenomenon of complex formation of drug with a protein is known as protein binding of drug.

ii) When a drug enter a body, it may undergo interaction with several tissue component of body, usually, protein, DNA or eclipose.

iii) Binding of drug with a protein is a reversible process because in this type of binding the weak chemical force such as ~~hydrogen bonding~~ hydrogen bond, hydrophobic bonds, ionic bond or vandar Waal's forces are involved.

iv) Whenever irreversible binding take place b/w protein and drug as a result of covalent binding, then carcinogenicity or tissue toxicity of the drug may occur.

Tissue

Drug - receptor
⇅
Receptor + Drug ⇌

kidney
carrier + Drug ⇌
Drug-carrier

plasma
protein + Drug ⇌ Drug - protein

liver
Drug + enzyme
⇅
metabolize

Plasma protein Drug binding

After entry of drug into systemic circulation the first thing with which drug interact are blood component like plasma protein, Blood cell and haemoglobin.

- Mainly interact with plasma protein due to leerge amount and lerge variety.
- Binding of drug with plasma protein is reversible

Albumin > α_1-acid glycoprotein > lipoprotein > Globerlin.

⇒ Binding of drug to human serum Albumin

A lerge variety of drug → weak acid
neutral and weak base bind to HSA.

4 different side on HSA identified for drug binding.

Site 1 :- Warfarin binding site

Site 2 :- Diazepam binding site

Step 3 :- Digitoxin binding site

Site 4 :- Tamoxifen binding site

⇒ Binding of drug to α-acid glycoprotein :-

↳ Bind to member of basic drug like

- Imipramine
- Amitriptyline
- Nortriptyline
- Lidocaine
- Propranolol
- Quinidine

E.g. for

⇒ Binding of drug to lipoprotein :-

↳ As per density classify as

① ~~chylo~~ chylomicron (least dense)
② VLDL
③ LDL
④ HDL

↳ Drugs - Diclofenac
- cyclosporin
- Chlorpromazine bind to lipoprotein and facilitate transport of drug to tissue.

⇒ Bineling of drug to Globulin.

↳ There are 5 type

① α_1 globulin :- Transcortin or CBG (Corticosteroid binding globulin)
② α_2 globulin :- Ceruloplasmin

oprotein :
g like

dense)

lipoprotein
to tissue.

Corticosteroid

(3) β_1 :- Transferin

(4) β_2 :- Bind to Corticosteroid

(5) γ globulin :- Bind to antigen

Q7 Note on pulmonary drug administration.

- Pulmonary administration involves the inhalation of drug formulation through mouth or nose.
- Since the area of alveoli is large thus provide high permeability of alveolar epithelial.
- Drug used are bronchodilator;
  - beclomethasone
  - cromolyn.
- Drug administered by inhalation either as gas or aerosal.
- Here the particle size of droplet of aerosol affect the effect of drug.
- 10 micron size droplet may remain in upper respiratory & do not reach pulmonary tree.
- where as 0.5 micron ~~may~~ get to alveoli & absorbed but may exhale sometimes.

+ Advantages

(1) Inhaled drug delivery put drug where it needed.

(2) It require low and fraction of oral dose

(3) Onset of action is quick

(4) Degradation of drug in liver is avoided.

+ Disadvantage

(1) Irritant vapour cause inflammation of respiratory tract and increase secretion.

Q6 Limitation of dissolution test.

Ans

Q5 Note on ~~IVIVC~~ in vivo & in vitro correlation.

IVIVC is a scientific approach to describe the relationship b/w in vitro property of dosage form and relavant in vivo response.

This concept of corelation have been decided based on their ability to reflect the plasma concentration time profile upon the administration.

They ar
(1) Le
(2) ly
(3) le

(1) Level A
It repre
between
rate of
The in v
route e
mathema
in sam

- Advanta
(1) This is
act as
predictiv

(2) Level B
→ Utilise
analysis
Mean
product
time

They are
① level A
② level B
③ level C
~~④ level D~~ Multiple level D

① level A :- Highest category of correlation.
- It represent a point to point relationship between in vitro dissolution and the in vivo rate of absorption.
- The in vitro dissolution and in vivo absorption rate curve are superimposable and mathematical description for both curves is same. Wagner-Nelson

- Advantage:
① This is the highest category of relation which act as a meaningful quality control procedure predictive of in vivo performance of formulation.

② Level B :-
→ Utilises the principle of statistical moment analysis. Mean in vitro dissolution time (MDT in vivo) / (MDT in vivo)

- Utilise the principle of statistical moment analysis.
- Mean in vitro dissolution time ($MDT_{in\ vitro}$) of product is compared to mean in vivo residence time ($MRT_{in\ vivo}$).

Such a correlation is not a point to point correlation. so far this reason that one cannot rely on level B.

(3) Level C :- It is a single point correlation. It relate one dissolution time point to one pharmacokinetic parameter such as AUC, T_{max} or C_{max}

level	In vitro	In vivo
A	Dissolution curve	Absorption curve
B	Mean dissolution time (MDT)	Mean Resident time (MRT)
C	Disintegration time, dissolution rate, dissolution efficacy	C_{max}, T_{max}, K_a, AUC.
Multiple C		
D.		

Q4 Explain noyes whitney equation.

Dissolution rate in quantitative manner was proposed by Noyes & Whitney

$dC_b/dt = K(C_s - C_b)$

where
dC_b/dt is dissolution rate it is linear function of difference b/w bulk conc^n C_s at time t.

C_s is Saturation solubility
K = dissolution rate constant

This equation are modified by Nerst & Brunner.

The modification is dissolution rate constant is directly proportional to diffusion coefficient and surface area of dissolved drug and inversly related to volume of medium and thickness of diffusion layer.

$$dC/dt = DS(C_s - C_b)/V_0 \times h$$

where, dC/dt = rate of diffusion
D = Diffusion coefficient
S = Surface area of dissolved drug
V = Volume of dissolution medium
h = Thickness of diffusion layer

$$\frac{dC}{dt} = \frac{DS(C_s - C_b)}{Vh}$$

Date
Page

Q3 Differena between active transport & passive transport

(w) Active transport	Passive transport
① Movement of molecule from a region of low concentration to high concentration	① Movement of molecule from a region of high concentration to low concentration
② Here molecule move against the concentration gradient	② Here molecule move along the concentration gradient
③ Occur via Semipermeable membra	③ Occur even in absence of membrane
④ Here the energy require and in form of ATP	④ Here the energy is not required
⑤ It is a Selective process	⑤ It is a common process
⑥ Here there is requirement of carrier	⑥ The carrier molecule is not require
⑦ It is a rapid process	⑦ It is slow process
⑧ It is unidirectional & affected by temprature	⑧ It is bidirectional & do not affected by timprature
⑨ It disrupt the equilibrium b/w cytosol & Extracellular environment	⑨ It maintain the equilibrium b/w cytosol & Extracellular environment

⑩ Large
molecul

④ Enfuey
blood
pump
active

⑫ Influe
inhib

Q2 Classif

(w) The
the

①
②
③
④
⑤
⑥
⑦

① Passi

(w) The
of hi
concen

(10)	Large molecule, insoluble molecule are transported	(10) Small & soluble molecule are transpeerted
(11)	Endocytosis, secretion into blood stream, Na^+-K^+ pump are example of active transport	(11) Diffusion, facilated diffusion, osmosis are types of passive transport
(12)	Influenced by metabolic inhibiter	(12) Not influenced by metabolic inhibitor

Q2 Classification of drug transport mechanism

(iii) The principle for transport of drug molecule across the cell membrane are.

1. Passive diffusion
2. Active transport
3. Facilitate diffusion
4. Pore transport
5. Ionic or electrochemical diffusion
6. Ion pair
7. Endocytosis

(1) Passive diffusion

(iii) The process by which molecule diffuse from a region of higher concentration to a region of lower concentration.

- There is no external energy is expended
- Fick's law explain the rate of diffusion is proportional to both surface area & concentration difference & inversely proportional to thickness of membrane

$$\text{Rate of diffusion} = \frac{\text{Surface area} \times \text{Concentration difference}}{\text{Thickness of membrane}}$$

Or

$$\frac{dQ}{dt} = \frac{DAK}{h}(C_{GIT} - C_{Blood})$$

where dQ/dt = rate of diffusion
D = Diffusion coefficient
A = Surface Area
K = partition coefficient
$C_{GIT} - C$ = Concentration difference b/w GIT & plasma
h = thickness

(2) Active transport :
- It is carrier mediated transmembrane process that involve a carrier molecule.
- The transport of drug against a concentration gradient from low concentration to high concentration
- Here energy used in the form of ATP

i) Drug like 5 Fluorouracil absorbed from GIT & enter to circulation via active transport.

(3) Pore transport 100 m.c

i) less than 100 molecular weight molecule are transported using pore transport.

ii) The driving force is constituted by the hydrostatic pressure or osmotic difference across the membrane bulk flow

(4) Facilitate transport

i) It is a carrier mediated transport system operated down the concentration gradient.

ii) It is a passive transport mechanism

iii) No energy expenditure, not inhibited by metabolic poisons.

iv) Vitamin B_{12} is absorbed by this process.

(5) Endocytosis

i) Process of capturing a substance as particle from outside the cell by engulfing it with cell membrane

ii) It involve pinocytosis & phagocytosis

(6) Ion pairing.

i) The charges on membrane influence the permeation of drug.

iv) These agents penetrate the membrane by forming reversible neutral complex ± endogeneous ion of GIT.

Q) Define drug absorption and various route of drug absorption.

i) The process of transporting the drug substance from the GI lumen into systemic circulation.

ii) If drug is poor water soluble then it will effect rate of absorption.

iii) Rate of absorption depends on route of administration.

iv) When drug given in IV, absorption not require.

v) There are certain Route of absorption like.

I Parentral Route.

1) Intravenous (IV) → 100% Bioavailibility

2) Intramuscular (IM) → Rapid absorption from aqueous solution.

3) Subcutaneous (SC) injection - Rapid absorption aqueous solution.

II Entral Route.

1) Buccal or Sublingual (SL) :- Rapid absorption of lipid soluble drug

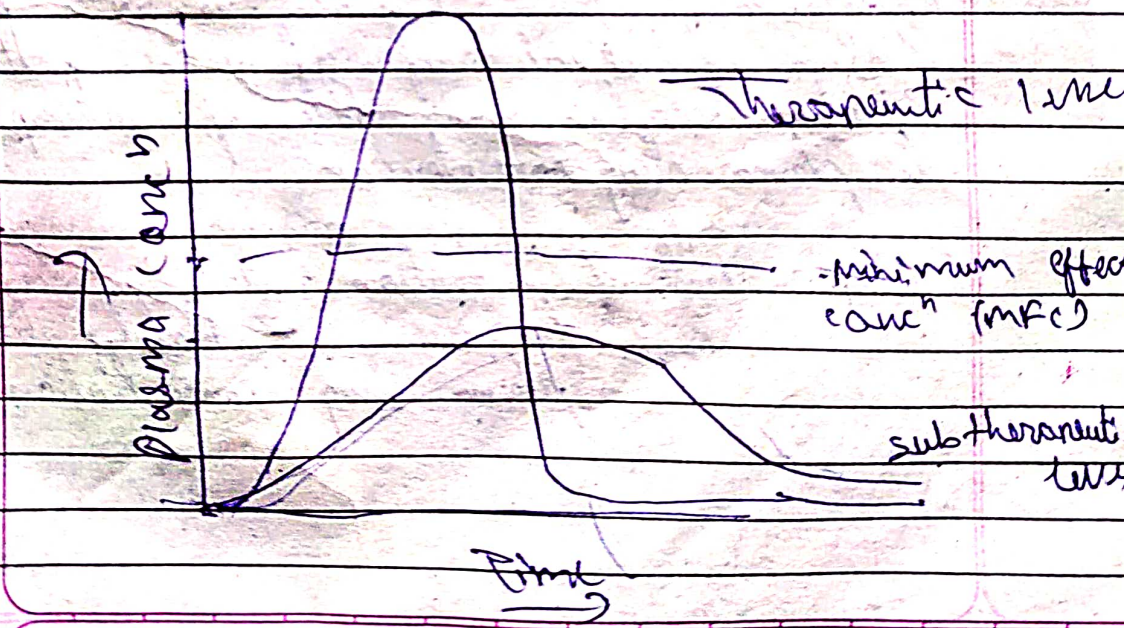
2) Oral (PO) :- Absorption may vary.
- Slower than IV or IM

3) Rectal (PR) :- Absorption vary from suppository

III Other Route

1) Transdermal :- Slow absorption
- Occlusive dressing increase absorption

2) Inhalation :- Rapid absorption
- Total dose absorbed is variable.



Q.17 Define renal clearance & Wn about determination of clearance

↳ Clearance is defined as hypothetical vol of body fluid containing drug.

- From which the drug is removed / cleared completely in specific period of time

$$Cl = \frac{\text{Elimination Rate}}{\text{Plasma drug conc}^n}$$

↳ Renal clearance :- Vol of blood / Plasma which is completely cleared of unchanged drug by kidney per unit time expressed as

$$Clr = \frac{\text{Rate of Urinary excretion}}{\text{Plasma drug conc}^n}$$

Physiologically Renal Clearance is ratio of "Sum of Rate of glomerular filtration & active secretion minus rate of reabsorption to plasma drug concentration

$$Clr = \frac{\text{Rate of filtration + Rate of Secretion} - \text{Rate of absorption}}{\text{plasma drug concentration}}$$

Date
Page

Relationship b/w Clr value & Mechanisms of Clearance.

Renal clearance (ml/min)	Renal clearance Ratio	Mechanism of Renal clearance	Example
0 (least value)	0	Drug filtered & reabsorbs completely	Glucose
<130	Above 0, Below 1	Drug filtered & reabsorbs completely	Lipophilic drug
130 (GFR)	1	Drug filtered only	Creatinine, Inselin
>130	>1	Drug filtered as well as secreted actively	Polar, ionic drug
550	5	Clearance equal to renal plasma flow rate	Iodopyracet PAH.

* Factor affecting renal clearance

1. Physiological Properties of drug
   Mol. Size, Pka & lipid Solubility
2. Plasma concentration of drug & drug that is not bound to plasma protein & excreted by filtration only linear relation b/w rate of excretion &

Plasma drug concentration.

3. Distribution & Binding characteristic of drug clearance $\propto \frac{1}{\text{vol of distribution}}$

Only unbound drug appear in glomerular filtrate
Fraction of drug bound to plasma Protein.

$f_u = \frac{C_u}{C}$ where f_u = fraction of unbound drug in plasma
C_u = conc^n of unbound drug
C = total plasma conc^n.

4. Blood flow to Kidney = renal blood flow is imp in case of drug excreted by glomerular filtration & those that are actively secreted.

5. Biological factor :- Age, Sex, species & Strain difference, ~~Disease~~ Cardiac rhythm, after drug excretion

6. Drug interaction - drug interaction result in alteration of Protein - drug binding, renal blood flow, active secretion, Urine pH & forced ~~diuresis~~ diuresis

7. Diseases state - Renal impairment
Renal dysfunction impairs elimination of drug especially those primarily excreted by kidney.

Mid - 3

Q: Define drug absorption. Discuss the various factor influencing GI absorption of a drug.

⇒ Absorption is defined as the process of transporting the drug substance from the gastrointestinal lumen into systemic circulation.

⇒ By main 3 factor the absorbtion is affected.

① Physiological

② Physiochemical

③ formulation

① Physiological :- It include 9 main factor such as

[RD, SE, GI, PPF]

① Route of administration :- IV has nearly 100% of bioavailibility

② Diseases state :- Malabsorption, thyrotoxicosis, cirrhosis etc affect & decrease the rate of absorption.

③ Splanchnic blood flow :- Presence of food in stomach cause ↑es blood flow in GI. cause decrease of absorbtion of Aspirin & L-dopa.

④ Enterohepatic circulation :- Enterohepatic circulation enhance drug bioavaibility for absorbtion.

⑤ Gastric motility :- Static & Rapid GI motility decrease the rate of absorption

⑥ Ionization & GI emptying :- Acidic drug absorb fast in acidic pH & Basic drug absorb fast in basic pH.
Also fast GI time & prolong GI emptying time affect absorbtion.

⑦ Pharmacogenetic factor :- Different races have different absorbtion rate for substance.
e.g. Male can tolerate more alcohol than female.

⑧ Presence of other substance :- In presence of iron vit C get readily absorb

⑨ First pass metabolism :- Bioavaibility ↓es in 1st pass metabolism

② Physicochemical factor
[SS, D, 3PB]

① Salt form of drug :- Salts of drug more readily dissolve & absorb
e.g. Na^+, K^+, Penicillin.

② Solvates & hydrate :- Solvate have greater solubility & readily absorb than non solvate form.

③ Dissolution :- lipid soluble drug more rapidly absorb.

④ Particle size & Surface area :- Smaller particle size larger S.A & high absorbtion

⑤ pH :- weak acid or basic drug have more effect of pH. & it absorbtion

⑥ polymorphism :- when substance exists in more than one crystal lattice called polymorphism. Metastable have higher absorbtion

③ Formulation factor

① Disintegration time
② Manufacturing variable
③ Type of dosage form
④ Ingredient.

Q2 M.O.A of Absorption.

* By 6 way the absorption done

① Passive
② Pore
③ Active
④ Endocytosis
⑤ Ion pairing
⑥ Facilitated

① Passive : The process in which molecules diffuse from a region of higher conc^n to a lower concentration.
- No ATP use as energy.
- Here the fick's law explain, "rate of diffusion is proptional to both surface area & concentration difference and inversely proptional to thickness of membrane".

Rate of diffusion $\propto$ $\frac{A \times \text{Conc}^n \text{ difference}}{\text{thickness}}$.

$$\frac{dQ}{dt} = \frac{DAK(C_{GIT} - C)}{h}$$

(2) Pore :- less than 100 mol compound pass through the pore of membrane.

(3) Active :- Here the molecule move from lower conc^{n} to higher conc^{n}.
- Due to movement against conc^{n} gradient ATP used as energy.
e.g. :- Fluorouracil.
- The carrier bind to drug & whole complex move across membrane.

(4) Endocytosis :- Capturing substance by engulfing with cell membrane & bringing into cell.
It is twelve pinocytosis & phagocytosis
↓ ↓
cell drinking cell eating
- This facilited by formation of vessels
This an active process & hence usage of energy.
This important for large molecule, proteins etc.

(5) Ion pair :- The agent penetrate membrane by forming reversible neutral complex.
This compound have lipophicity & aqueous solubility.

② Facilitated

- It involve carrier molecule to move across membrane.
- It do not require energy to move across membrane
- e.g. Vit B12.

③ Physiological barrier of distribution
Note on BBB.

- There are certain barrier that prevent permeability of certain compound.
- physiological barrier is a capillary membrane b/w plasma & brain.

- There are 6 type of physiological barrier

① Simple capillary endothelial barrier
② Simple cell membrane barrier
③ BBB
④ CSF
⑤ Blood placental Barrier
⑥ Blood testis barier

① Simple capillary endothelial barrier :-
Capillary are blood vessel that supply blood to most inner tissue.
- Simple endothelium layer arrange on basement membrane.
- Drug with less than 600 dalton can pass throug barrier

② Cell membrane barrier :- cell membrane is selective permeable membrane & act as barrier for certain molecule.
- Non polar & lipid soluble can pass threough.

③ BBB :- Capillary of brain consist endothelial joint together to one another by continuous tight intracellular junction called BBB
- BBB highly regulate interface that separate pheriral circulation & CNS.
- Astrocyte cell projection provide support the BBB cell.
- Molecule cross BBB by paracellular or transcellular pathway.

In paracellular, ion & solute utilize conc" gradient to pass BBB by passive diffusion.

In transcellular diff mechanism like passive diffusion, receptor-mediated transport & transcytosis involved.

- Factor like weight, charge, solubility, S.A affect BBB crossing.

- lipid Soluble & less or equal to 400-600 Dalton molecular weight particle access BBB and highly ionized not cross BBB.

4) There are 5 drug delivery strategies

(a) lipophilic analogue use.
(b) Use of penetration enhancer like dimethyl sulphoxide.
(c) Use of carrier mediated pathway
(d) Use of Osmatic pressure like intracarotid injection of hypertonic solution like mannitol or arabinose.
(e) Use of IV or IA route of administration

(4) CSF :- pair of membrane that separate blood from CSF & CSF to brain.
- colourless liquid contain glucose.

form in choroid plexus of lateral ventricle, made up of capillaries covered by ependymal cell.
- molecule pass through pinocytosis.
- The flap valves prevent CSF back flow.
- This valve opened when the hydrostatic pressure in subarachnoid space is greater than venous sinues.

(5) Blood placental barrier :- Placenta is an organ unite the foetus to uterus of the mother.
Metabolite & nutrients are exchanged through placenta.
- It consist number of tissue layer made up of trophoblast cell & endothelium.
O_2 - CO_2 & H_2O easily pass through it
- large molecule pass through vesicular transport.

(6) Blood test barrier :- It is the highest barrier in mammalian.
It divide the seminiferous epithelium into basal and the apical compartment.

Q4 Explain brief following terms.

- Mean residence time
- Hepatic clearance
- Renal clearance

① Renal clearance.

Volume of plasma from which drug is cleared in unit time through kidney.

$$R.C = \frac{\text{Rate of urinary excretion}}{\text{Plasma drug conc}^n.}$$

$$Cl_R = \frac{dD_u/dt}{C_p}$$

Rate of urinary excretion work on 3 main factor.

1. filtration
2. Secretion
3. Reabsorbtion.

On putting in equation

$$Cl_R = \frac{\text{filtration rate} + \text{secretion} - \text{Reabsorption}}{\text{Plasma conc}^n.}$$

② Hepatic Clearance

Volume of blood that perfuse the liver which is cleared of drug per unit time

$$Cl_R = Cl_T - Cl_P$$

Here quantitative expression shows clearance of total body - clearance of Renal.

Hepatic clearance = Rate of drug cleared by liver / plasma conc.

For organ clearance

$$C_R = Q_R E_{R_R}$$

Q_R = Hepatic blood flow

ER_R = Hepatic Excretion rate

③ Mean Residence time

→ MRT describe the average time for all the drug molecule reside in body

MRT = Total residence time for drug molecule in body / Total number of drug molecule

On putting in graph the equation form as

$$MRT = \frac{AUMC}{AUC}$$

MRT :- Mean Resident time

AUMC :- Area under first moment curve

AUC :- Area under zero moment curve

(5) Write a note on method to enhance the bioavailability through enhancement of dissolution rate.

~~adjs~~ [EMC HIM SS NN PP]

① Microemulsion :- Optically clear, pre concentrate, isotropic, thermodynamically stable transparent system.

consist a mixture of oil, hydrophilic surfactant & solvent that dissolve poorly soluble drug.

It enhance the solubility of drug that are poorly soluble.

② Co-solvency :- Solubility increase by adding water miscible solvent or co-solvent

It is mixture of water & one or more water miscible solvent that increases solubility

③ Hydrotrophy :- It is solubilization process

- large amount of 2nd solute incorporated result in 1st solute solubility increase

- This are ionic organic salt

④ Inclusion complexes :- Lipophilic drug cyclodextrin known as inclusion complexes
This are group having more than 10000 Da M.W
- They are cyclic oligosaccharide have polar cavity & hydrophilic surface.

⑤ Micellar solubilization :- This decrease surface tension & improve dissolution of lipophilic drug in aqueous medium.
Non ionic form is used e.g. Castor oil, glyceride, fatty acid, ester, glycol etc.

⑥ Solid dispersion :- Poorly soluble drug dispersed in highly soluble solid hydrophilic matrix.
e.g. PVP, PEG 4000, SLS etc.

(7) Super critical fluid :- It is novel nano-sizing technique.

This are those fluid whose temperature & pressure are more than critical temp & critical press. which allow to have liquid & gas both property

(8) Nano ~~suspension~~ :- Nano sized drug particle used that increase dissolution.
- Nano crystal, Nanopure, Nano edge are some technique

(9) Nano crystallization :- A way of diminishing drug particle to size, range of 1-1000 nanometer.

- Two method use bottom-up and top bottom.

(10) Particle size reduction :- S.A Tes with les particle size & Tes solubility

(11) pH :- By changing pH value of less water soluble drug, part of molecule that may be protonated (base) or deprotonated (acid) may acquire potential to dissolve

Q) Explain Wagner Nelson method.

→ It is an alternative method of curve fitting method.

→ method use to estimate k_a from percent unabsorbed - time plot.

→ After administration of drug, the amount of drug absorbed into systemic circulation X_A is the sum of amount of drug in body X_b and amount of drug eliminated from body X_e

$$X_A = X + X_e \quad \text{---(1)}$$

Here, amount of drug in body $X = V_d C$ and amount of drug eliminated at any time t calculated as

$$X_e = K_e V_d [AUC]_0^t \quad \text{---(2)}$$

By substituting X & X_e in eq (1)

$$X_A = V_d C + K_e V_d [AUC]_0^t \quad \text{---(3)}$$

At time Zero to infinity

$$X_A^\infty = V_d C^\infty + K_e V_d [AUC]_0^\infty$$

At t^{∞}, C^{∞} is zero.

$$X_A^{\infty} = K_e V_d [AUC]_0^{\infty}$$

Fraction of drug absorbed at time t is

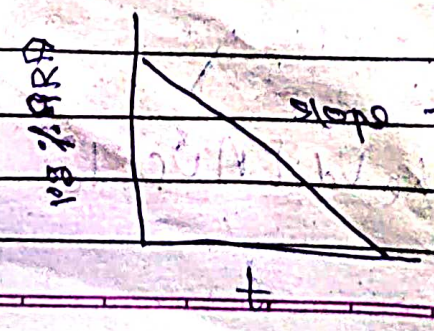
$$\frac{X_A}{X_A^{\infty}} = \frac{V_d C + K_e V_d [AUC]_0^t}{K_e V_d [AUC]_0^{\infty}}$$

$$= \frac{C + K_e [AUC]_0^t}{K_e [AUC]_0^{\infty}}$$

∴ To calculate percentage drug unabsorbed at any time is

$$\% ARA = \left[1 - \frac{X_A}{X_A^{\infty}}\right] 100$$

$$\therefore \% ARA = \left[1 - \frac{C + K_e [AUC]_0^t}{K_e [AUC]_0^{\infty}}\right] 100$$



7. Merit & demerit of non compartment model

Advantage

① Derivation of PK parameter is easy, because of simple algebric equation

② Mathematical treatment remain same, for drug or metabolite, provide elimination follows first order kinetics.

③ Drug disposition kinetics need not be described in detail.

Dis advantage

① Information regarding plasma drug conc^n time profile is expressed as an average

② Generally not useful for describing time course of drug in blood.

③ It is applicable only for linear pharmacokinetics.

Date
Page

Protocol of bioequivalence

1. Title.
   (a) principle investigator
   (b) project number & date

2. Study objective

3. Study design title.
   (a) Design
   (b) Drug product
      (i) Test product
      (ii) Reference product.
   (c) Dosage regimen
   (d) Sample collection
   (e) Housing
   (f) Fasting / meal schedule.
   (g) Analytical method

4. Study population.
   (a) Subjective
   (b) Subject selection
   (c) (i) Medical history
      (ii) Physical examination
      (iii) Laboratory test

(c) Inclusion / exclusion criteria
(d) Restriction / prohibition

(5) Clinical procedure :-

(a) Dosage & drug administration
(b) Biological sampling schedule
(c) Acitivity of subject

(6) Ethical consideration

(a) Basic principle
(b) Institutional review board
(c) Informed consent
(d) Indication fee subject withdrawal
(e) Adverse reaction and emergency procedure

(7) Facilities

(8) Data analysis

(a) Analytical validation procedure
(b) Statistical treatment of data

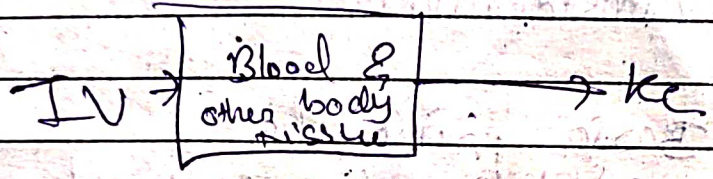
(9) Drug accountability

(10) Appendix

Q Describe open one compartment model IV bolus administration.

⇒ Here, there is no absorption phase because dose directly enter the systemic circulation as given IV.

⇒ Distribution of drug is rapid.



⇒ Drug administered IV, distribute in blood & other tissue & then elimination

⇒ Hence Rate of process follow 1st order kinetic which represented as

$$dX/dt = -K_e X$$

dX/dt. Rate of process

Ke = 1st order rate of elimination constant

X = Amount of drug at time t.

100 Latin square design in Bioequivalence study.

~~More than two formulations to apply~~

A standard approach for conducting a comparative bioavailability study is to use a randomized, balance, cross-over design called latin square.

In this design

- Each subject receives just once each formulation
- Each formulation is administered just once study protocol

- There are two way, three way & four way crossover

• Example

latin square for six human volunteers

Subj	Treatment period		
	I	II	III
1	A	B	C
2	B	C	A
3	A	A	B
4	A	C	B
5	C	B	A
6	B	A	C

Date
Page

- Advantages
- It minimize the effect of inter subject variability in study ~~by~~ ~~study~~
- Minimize carry over effect
- Minimize the time effect on bioavailability.

- Disadvantage
- Take longer time to complete study
- Time to complete trail depend on number of formation.
- Increased number of study period lead to high subject droplet.

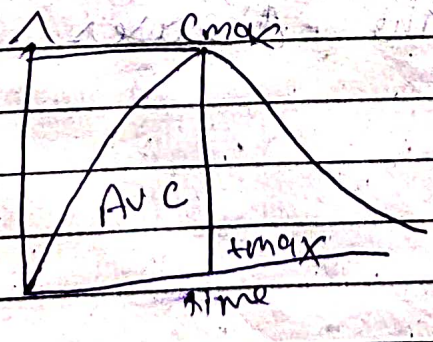
11) Define bioavailability. Explain various method used for determination of bioavailability.

ans) Bioavailability is a measurement of rate and extent to which active ingredient are absorbed from it dosage form into systemic circulation from site of action in sufficient amount to give pharmacological response.

Method to determine bioavailability

- Pharmacokinetic
  - 1) plasma concentration
    - tmax
    - Cmax
    - AUC
  - 2) Urinary drug excretion
    - Amount of drug excreted in urine (D_u)
    - Rate of excretion vs time
    - Tmax of excretion
- Pharmacodynamic
  - 1) Acute pharmacological response
  - 2) Therapeutic response

1) Plasma drug conc^n.



① Tmax :- Time at which the maximum plasma concentration achieved

② Cmax :- Maximum plasma conc^n achieved after drug administered.

③ AUC :- Area under plasma level time curve. It is measurement the extent of drug absorbed.

1] Urinary drug excretion.

(a) D_u^∞ :- It is cumulative amount of drug excreted in urine.
It related directly to amount of drug absorbed.

(b) dD_u/dt :- 1st order elimination rate constant (K) & conc^n of drug in plasma (Cp).

(c) t^∞ :- Value decrease as absorption rate increase.

2] pharmacodynamic method.

(a) Acute pharmacological response :- Include change of parameter in ECG, pupil dilation, B.P etc

(b) Therapeutic response :- It includ response of drug to the diseases.

(12) Clearance & Renal clearance
Same as Q4.

(13) Same as Q1

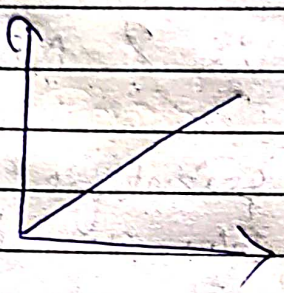
(14) What is IVIVC? Note on level of IVIVC

- IVIVC is a scientific approach to describe the relationship b/w an in vitro property of dosage form and relevant in vivo response.
- This concept of correlation have been decided based on their ability to reflect the plasma conc" time profile upon the administration.
- They are
  1. level A.
  2. level B
  3. level C
  4. Multiple C
  5. level D.

1. level A :- It represent a point to point relationship b/w invitro dissolution and invivo rate of absorption

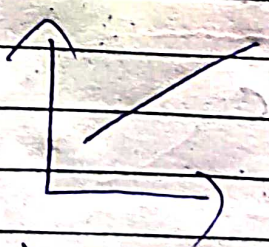
iv) This level of correlation is highest category of correlation.

v) The in vitro dissolution and in vivo rate of absorption curve are superimposible and calculated by Wagner - Nelson.

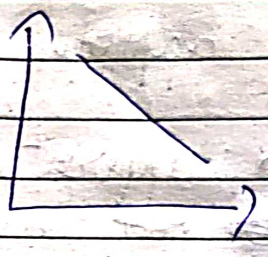


② level B :- Utilize the principle of statistical moment theory.

- Mean in vitro dissolution time (MDT_{vitro}) of product is compared to either mean in vivo resident time (MRT) or the mean in vivo dissolution time (MDT_{vivo}).
- Such correlation is not point to point & thus level B is not used.

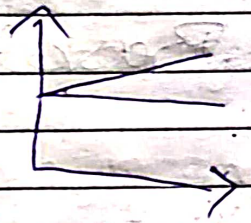


③ level C :- It is single point correlation
iv) One dissolution time point is compared to one mean pharmacokinetic parameter such as AUC, t_{max} or C_{max}



④ Multiple c correlation

It relate one or several pharmacokinetic parameter to the amount of drug dissolved at several time point of dissolution profile.



⑤ level D correlation.

It is a rank order & qualitative analysis and is not consider useful

level	Invitro	Invivo	Groups
A	Dissolution curve	Absorption curve	
B	Mean dissolution time (MDT)	Mean Residental time (MRT)	
C	Disintegration time dissolution rate, dissolution efficacy	C_{max}, t_{max} AUC	

Q5 Explain Dissolution apparatus type I & type II

→ The dissolution apparatus are of many type but main two type are listed below as per USP.

① type I :- Basket apparatus

② type II :- Paddle apparatus

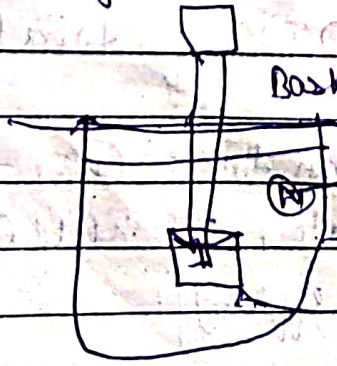
① type I :- Basket

Vessel :- Borosilicate glass
- Semi hemispherical bottom
- 1000 ml capacity

Shaft :- Stainless steel 316
Speed :- 50-100 rpm.

Water bath :- Maintain 37 ± 0.5°C
- thermometer

→ Rotating basket :-



Type II :- Paddle.

Vessel :- Same

Shaft :- fused with blade at bottom

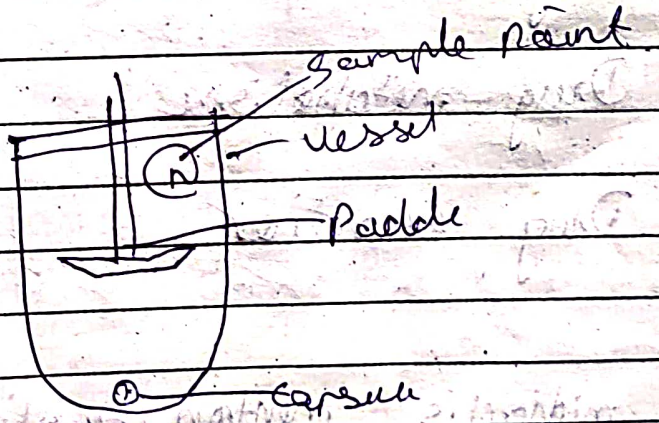
Stirring element :- coated with teflon.
- for lab purpose
- stainless steel.

Speed :- 25-50 rpm

Water bath :- Maintain 37 ± 0.5°C

Sinker :- platinium wire prevent tab/cap floating

- Dosage form should remain at bottom centre of vessel.



16. Same as Q2

(17) Regulatory requirement for conducting of bioequivalence study

pending

(18) Non linear factor & Michaelis menton equation

⇒ The nonlinearity mainly cause by 4 main factor

① Absorption of drug

② Drug distribution

③ Drug metabolism

④ Drug excretion

* The michaelis menton equation

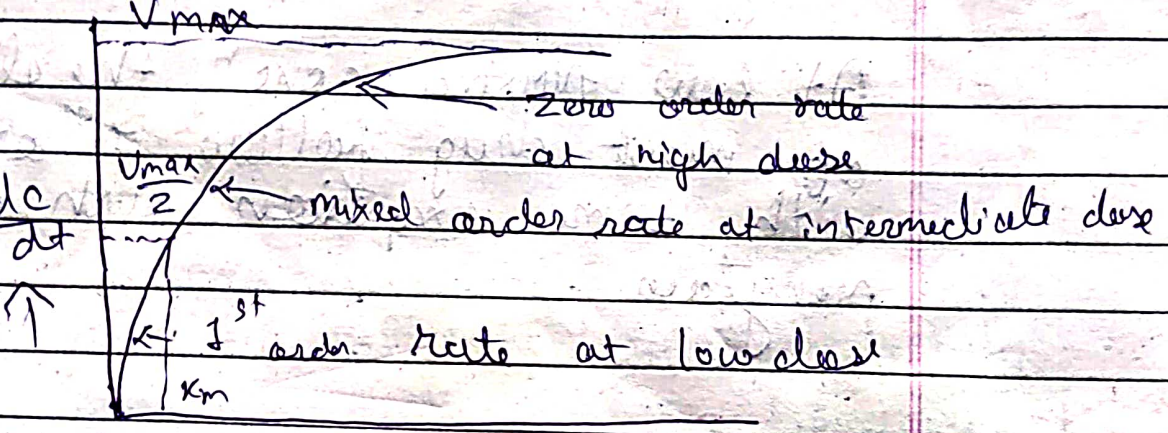
⇒ It is used to describe the kinetics of capacity limited or saturable process

$$-\frac{dC}{dt} = \frac{V_{max} C}{K_m + C} \quad \text{---(1)}$$

$-dC/dt$:- rate of decrease of drug conc^n with respect to time

V_{max} :- Maximum rate of process

K_m :- Michaelis constant.



1. When the value of $K_m = C$

In this condition, equation (1) will

$$\frac{-dC}{dt} = \frac{V_{max} \cdot C}{2C}$$

or.

$$\frac{-dC}{dt} = \frac{V_{max}}{2}$$

The equation indicate that rate of process is half (1/2) the maximum rate.

2. At low conc^{n} ($K_m >> C$), $K_m + C$ is approximat equal to K_m.

$$-\frac{dC}{dt} = \frac{V_{max} \cdot C}{K_m}$$

At low plasma conc^{n}, the elimination of most drug follow 1st order kinetic with some exception such as ethanol, phenytoin.

3. At high drug conc^{n} ($K_m << C$), $K_m + C$ is equal to C.

$$-\frac{dC}{dt} = V_{max}$$

This equation indicate zero order kinetic

19) S.N on Protein Binding
last mid ans Q.8

20) Explain Catenary & Mammillary model
last Mid ans Q.14

21) Absolute & relative bioavailability. Pharmacokinetic method for bioavailability measure:

Absolute	Relative
→ Measure of actual percentage of the administered dose, which is absorb intact into systemic circulation relative to equivalent IV dose.	→ Measure of fraction of given drug that is absorbed intact in systemic circulation from a dosage form relative to established Standard dosage form of that drug.
→ Compare drug exposure following extravascular administration of the tested dosage form with that IV administra	→ Compare bioavailability of a formulation of a certain drug with another formulation of same drug

Used

Used to characterize a drug inherent absorption properties from extravascular site

Used to characterize absorption of drug from it formulation.

- pharmacokinetic model model

→ This method is of two type.
① plasma drug concentration
② Urinary drug excretion.

① Plasma drug concentration
- There are main 3 type include in this method.

ⓐ T_{max} :- It is a time at which the maximum plasma concentration (C_{max}) is achieved after drug administration.
- At t_{max}, rate of absorption is equal to the rate of elimination.
- It expressed in hours.