Factors Influencing Absorption of Drugs

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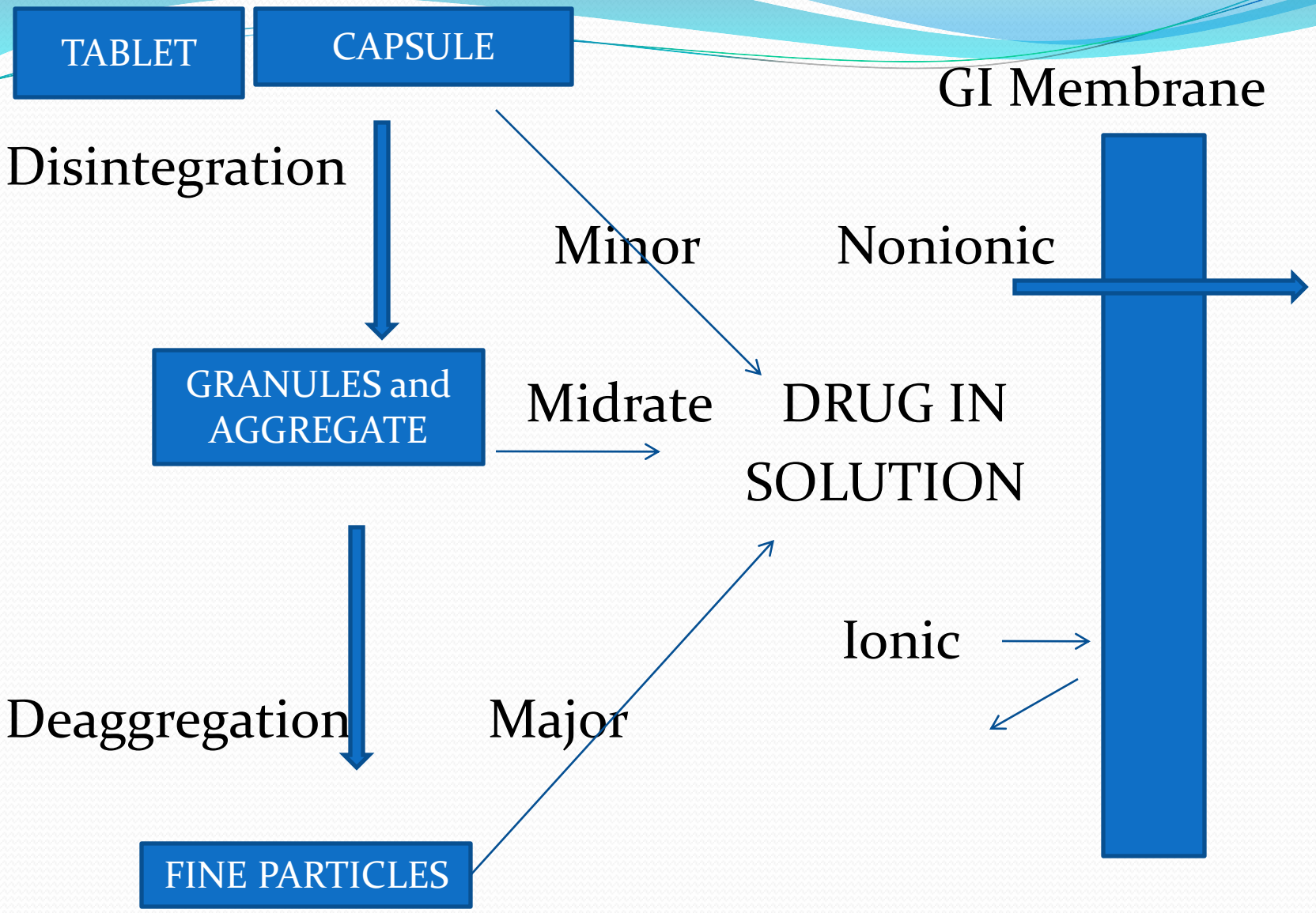
INTRODUCTION[1]

- **BIOPHARMACEUTICS** : It is combination of two terms

  1) Pharmacokinetics(ADME)

  2) Pharmacodynamics

- **Absorption** : It is defined as the process of movement of unchanged drug from site of administration to the systemic circulation…


TABLET
CAPSULE
GI Membrane
Disintegration
Minor
Nonionic
GRANULES and AGGREGATE
Midrate
DRUG IN SOLUTION
Ionic
Deaggregation
Major
FINE PARTICLES

Factors affecting.....[1]

A) PHARMACEUTICAL FACTORS:

I. Physicochemical properties of drug substances

1) Drug solubility and dissolution rate
2) Particle size and effective surface area
3) Polymorphism and amorphism
4) Salt form of drug
5) Lipophilicity of drug
6) Pseudopolymorphism
7) pka of drug and pH
8) Drug stability

II. Dosage Form Characteristics and Pharmaceutical Ingredient.

1) Disintegration Time.
2) Dissolution Time.
3) Manufacturing variables.
4) Pharmaceutical Ingredient.
5) Nature /type of dosage form.
6) Product age and storage condition.

B) PATIENT RELATED FACTORS

1)Age.

2)Gastric emptying time

3)Intestinal transit time

4)Gastrointestinal pH.

5)Disease state

6)Blood flow through the GIT

7)Gastrointestinal content-a)Other drug b)Food
c)Fluid d)Other normal GI content

8)Presystemic metabolism by

A. Drug solubility and dissolution rate:-[1]

- **Dissolution Rate:** amount of drug in solution / time(at specific pH, temp and solvent composition)

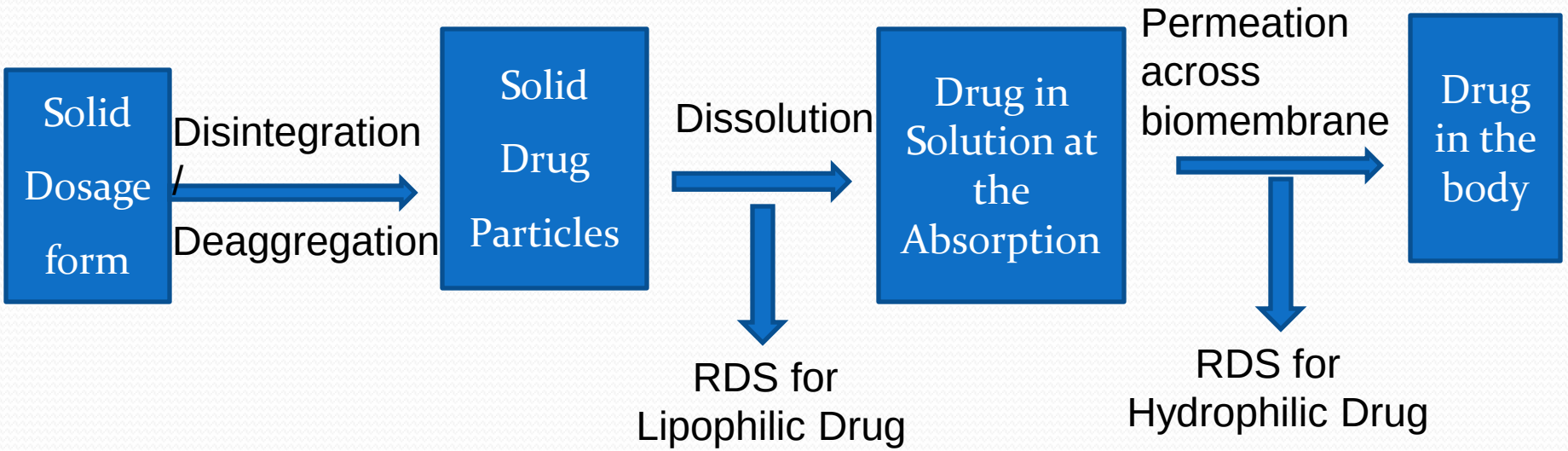
Two slowest rate-determine processes in the orally administered drugs are:

- Rate of dissolution
- Rate of drug permeation through biomembrane

Dissolution is the RDS for hydrophobic, poorly aqueous soluble drugs
e.g. griseofulvin and spironolactone,

<u>these drug are dissolution rate limited</u>

If drug is hydrophilic with high aqueous solubility e.g. cromalin sodium or neomycine, then dissolution is rapid and the RDS in the absorption of such drugs is rate of permeation through the biomembrane. In other word, absorption of such drug is said to be <u>permeation rate limited or transmembrane rate limited.</u>



❖THEORIES OF DISSOLUTION :1

- **Dissolution:** Dissolution is process in which a solid substance solubilizes in a given solvent i.e. mass transfer from the solid surface to the liquid phase.

- **The three basic theories of dissolution involves:**

1) Film theory (Diffusion layer model).

2) Permeation or Surface renewal theory (Danckwart's model).

3)Double barrier or Limited solvation theory (intefacial barrier model).

Diffusion layer model[2]

1) proposed by Nernst

2) According to this theory dissolution process completes in two steps -

A)formation of stagnant layer

B) diffusion of drug from this layer

- It involves two steps :-

a. Solution of the solid to form stagnant film or diffusive layer at the solid /liquid interface which is saturated with the drug

b. Diffusion of the soluble solute from the stagnant layer to the bulk of the solution; this is r.d.s in drug dissolution.

1. Diffusion layer model:

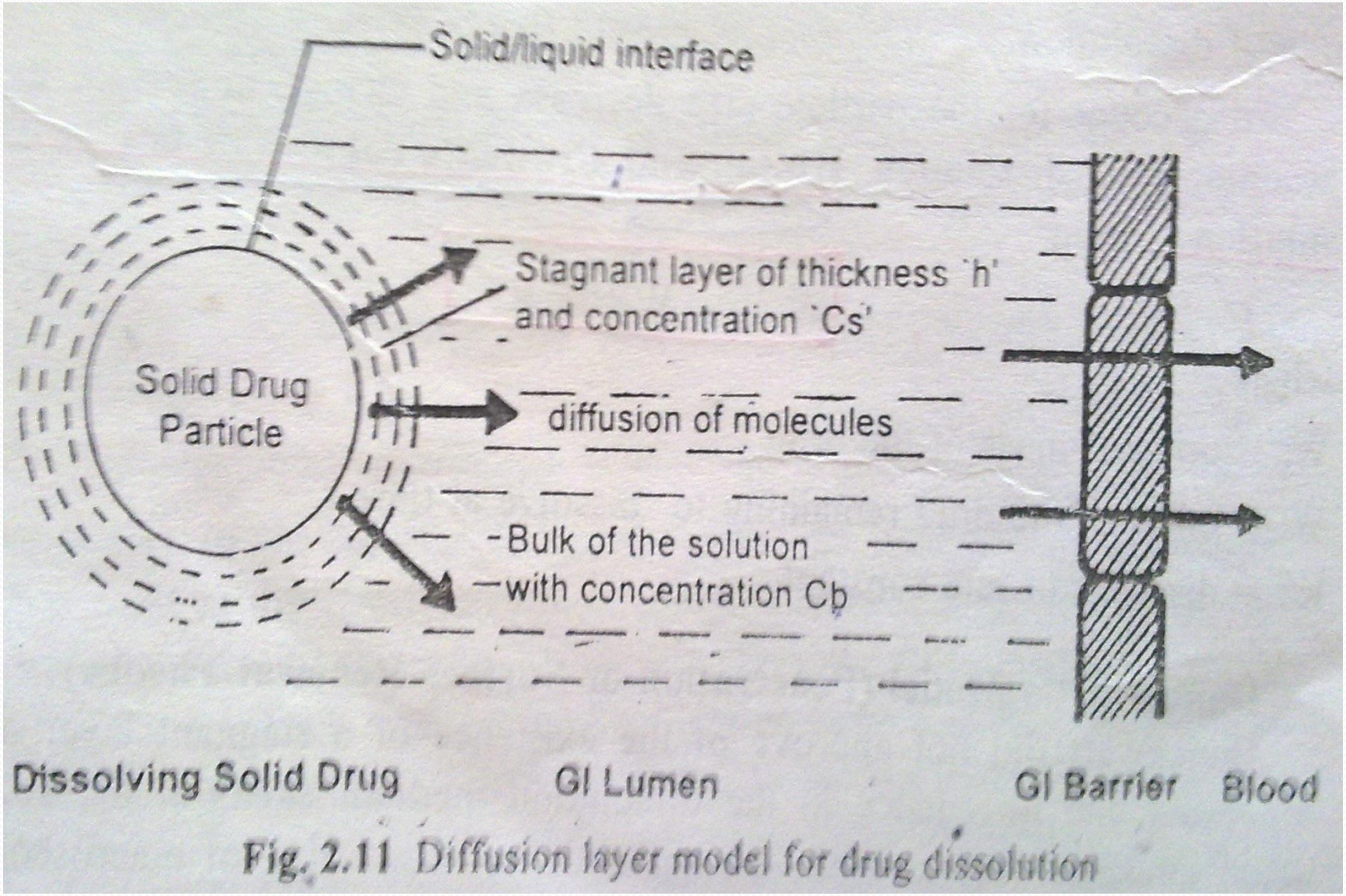


Fig. 2.11 Diffusion layer model for drug dissolution

The equation to explain the rate of dissolution when the process is diffusion controlled and involve no chemical reaction was given by Noyes and Whitney:

$$dc/dt = k(Cs-Cb)$$

Where ,

dc/dt= dissolution rate of drug

K=dissolution rate constant

Cs=concentration of drug in the stagnant layer

Cb=concentration drug in bulk of solution

Modified Noyes-Whitney's Equation -

$$\frac{dC}{dt} = \frac{DAKw/o\,(C_s - C_b)}{Vh}$$

Where,

D= diffusion coefficient of drug.

A= surface area of dissolving solid.

Kw/o= water/oil partition coefficient of drug.

V= volume of dissolution medium.

h= thickness of stagnant layer.

(Cs – Cb)= conc. gradient for diffusion of drug.

- This is first order dissolution rate process,for which the driving force is concentration gradient

- This is true for *in-vitro* dissolution which is characterized by non-sink conditions.

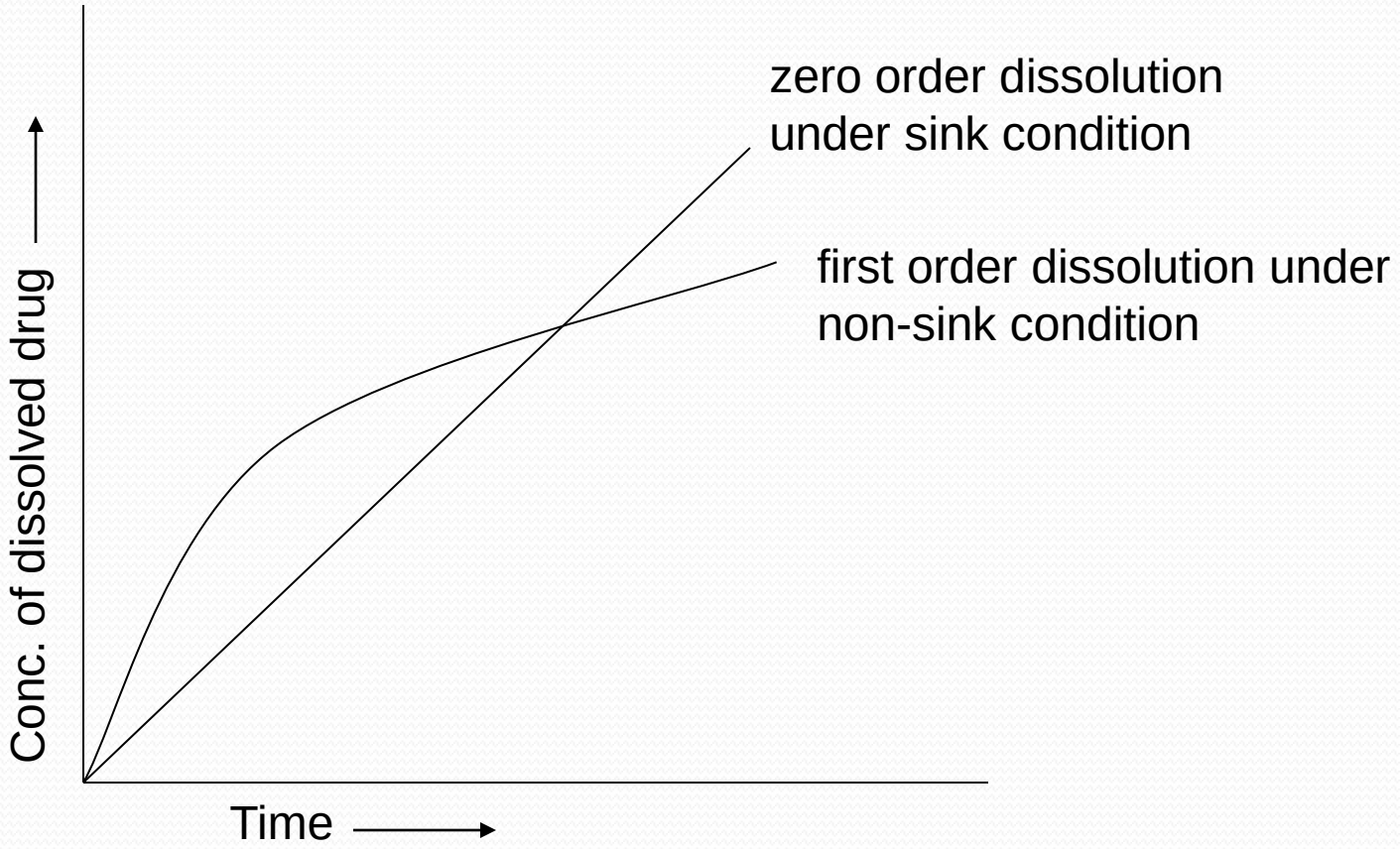
- The *in-vivo* dissolution is rapid as sink conditions are maintained by absorption of drug in systemic circulation i.e. C_b=0 and rate of dissolution is maximum.

- Under sink conditions, if the volume and surface area of the solid are kept constant, then

$$\frac{dC}{dt} = K$$

- This represents that the dissolution rate is constant under sink conditions and follows zero order kinetics.

Dissolution rate under non-sink and sink conditions.



2. Danckwert's Model: [3]

Danckwert suggested that , the turbulence in dissolution medium exists at the solid-liquid interface.

As a result ,the agitated fluid consisting of solvent packets reaches the interface in a random fashion due to eddy current, absorb the solute and carry it to the bulk of the solution.

Such solute containing packets are continuously replaced with new packets of fresh solvent

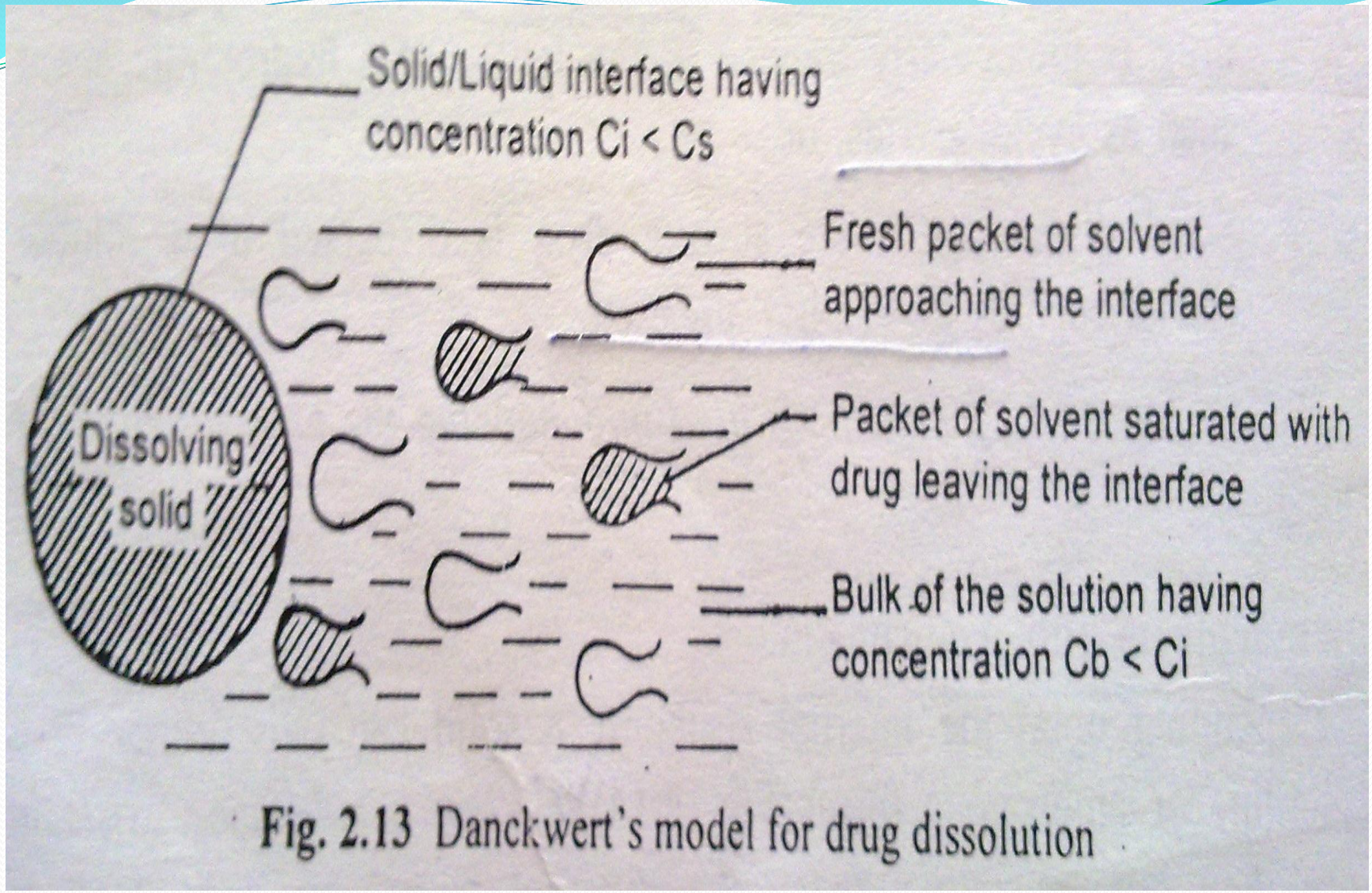


Fig. 2.13 Danckwert's model for drug dissolution

Fig. Danckwert's Model for drug dissolution

3. Interfacial barrier model :

According to interfacial barrier model ,an intermediate concentration can exist at the interface as a result of solvation mechanism and is a function of solubility rather than diffusion.

While considering the dissolution of a crystal each face of the crystal will have a different interfacial barrier

$$G = K_i (C_s - C_b)$$

B. Partical size and effective surface area

- **Absolute surface area :**
- **Effective surface area:**

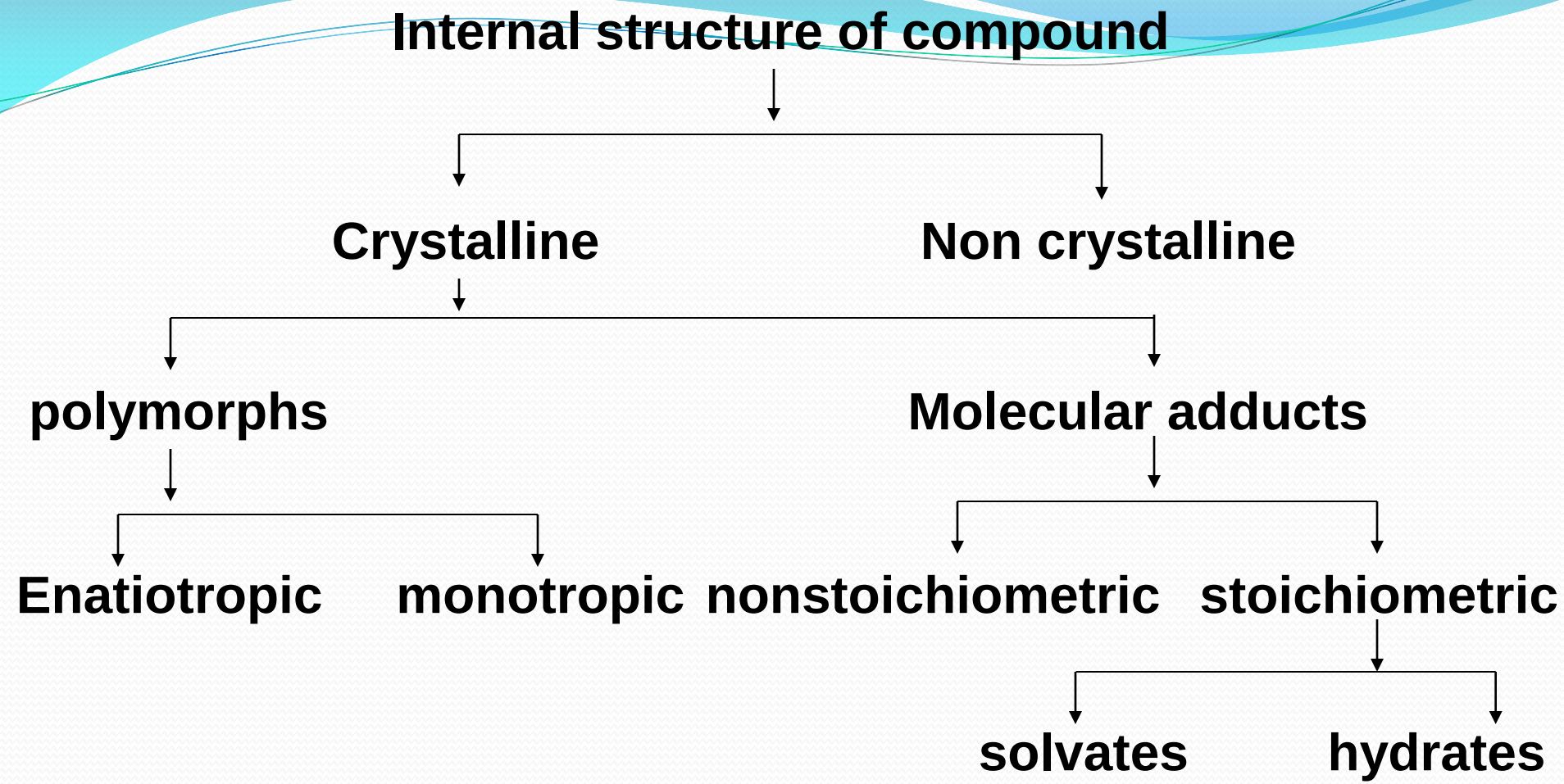
particle size = 1/surface area

from the modified Noyes and Whitney equation it is clear that larger the surface area higher the dissolution rate.

Micronisation

Hydrophilic--- Increase in ESA

Hydrophobic--- Decrease in ESA


Internal structure of compound
Crystalline
Non crystalline
polymorphs
Molecular adducts
Enatiotropic
monotropic
nonstoichiometric
stoichiometric
solvates
hydrates

C. Polymorphism and amorphism:

Existence of substance in a more than one crystalline form, the different forms are designated as polymorphism and the phenomenon as polymorphism.

two types are…..

- ✓ **Enantiotropy polymorph**: is one which can be reversibly changed in to another form by altering the temperature or pressure.

  e.g. sulfur

- ✓ **Monotropic polymorph:** is one which is unstable at all temperature and pressures

  e.g. glyceryl stearate

Stable : lower energy state, higher melting point and least aqueous solubility

Metastable : Higher energy state, low melting point and higher aqueous solubility

Amorphous :

Crystalline:

Amorphous ❯ Metastable❯ Stable

D. Pseudopolymorphism:

- **Solvate:** The stoichimetric type of adducts where solvent molecules are incorporated in crystal lattice of solid are called as **solvates** and trapped solvent as **solvent of crystallization.**

The solvates can exist in different crystalline form called as **Pseudopolymorph**

- **Hydrate:-** When solvent in association with the drug is water is known as hydrates

E. Salt form of the drug

- Solubility is pH dependent.
- **Weak acidic drug:** strong base salt prepared
- Solubility in diffusion layer is greater
- Higher pH favors solubility of weak acid.
- pH of diffusion layer (salt form) > bulk solution (free acid)
- E.g. Na and K salt of barbiturate and sulfonamide.
- **Weak basic drug :** strong acid salt
- E.g. HCL salt of alkaloids.
- Solubility in diffusion layer is greater
- Lower pH favors solubility of weak base.
- pH of diffusion layer (salt form) < bulk solution (free acid)

F.Drug pKa and liphophilicity and GI pH

Very weak acids (pKa> 8): unionized at all pH values : absorbed along the entire length of GIT (pH1 to 8). E.g. Phenytoin, Phenobarbital.

Moderately weak acids (pka 2.5 to 7.5): unionised in gastric pH: ionized in intestinal pH: better absorbed from stomach (pH 1 to 3).e.g. Aspirin. Ibuprofen.

Stronger acids (pka <2.5): ionized at all pH; poorly absorbed from GIT.

Very weak bases (pKa<5): unionized at all pH values absorbed along the entire length of GIT (pH1 to 8).

E.g. Theophyline, Caffeine, Diazepam.

Moderately weak bases (pka 5 to 11.0): ionised in gastric pH: unionized in intestinal pH: better absorbed from intestine (pH 5 to 8).

e.g. Reserpine, Codeine.

Stronger bases (pka >11): ionized at all pH; poorly absorbed from GIT.

pH partition Hypothesis[2] :

Brodie et al. proposed the pH partition Hypothesis .

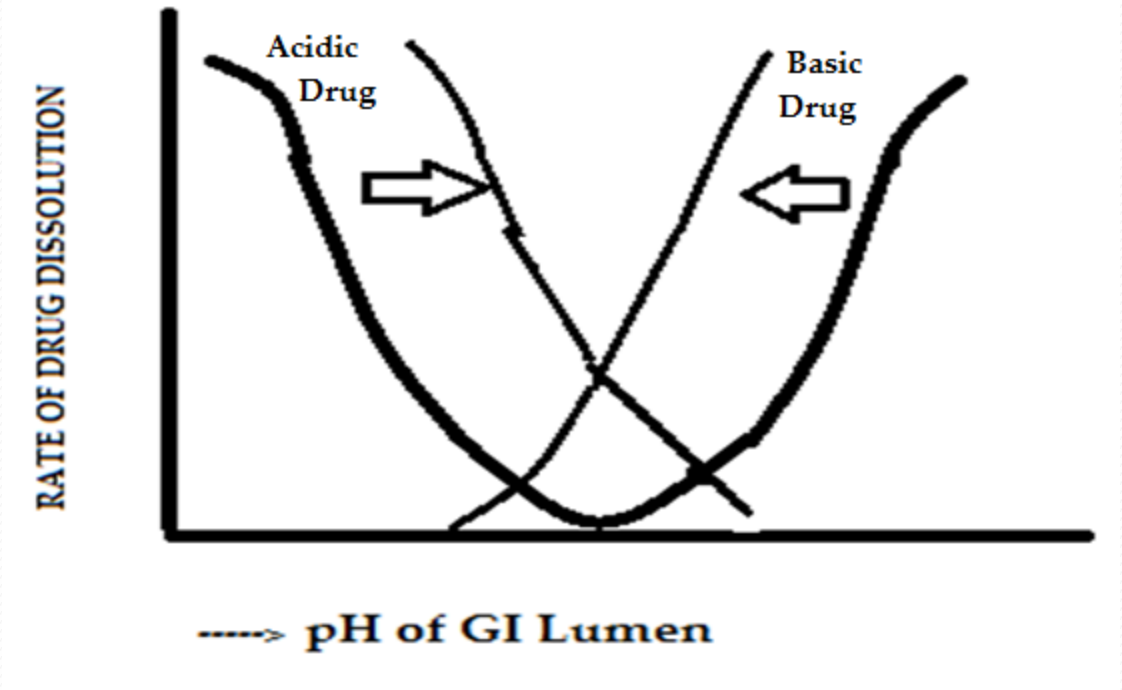
The theory states that for drug compounds of molecular weight greater than 100 which are primarily transported across the biomembrane by passive diffusion, the process of absorption is governed by,

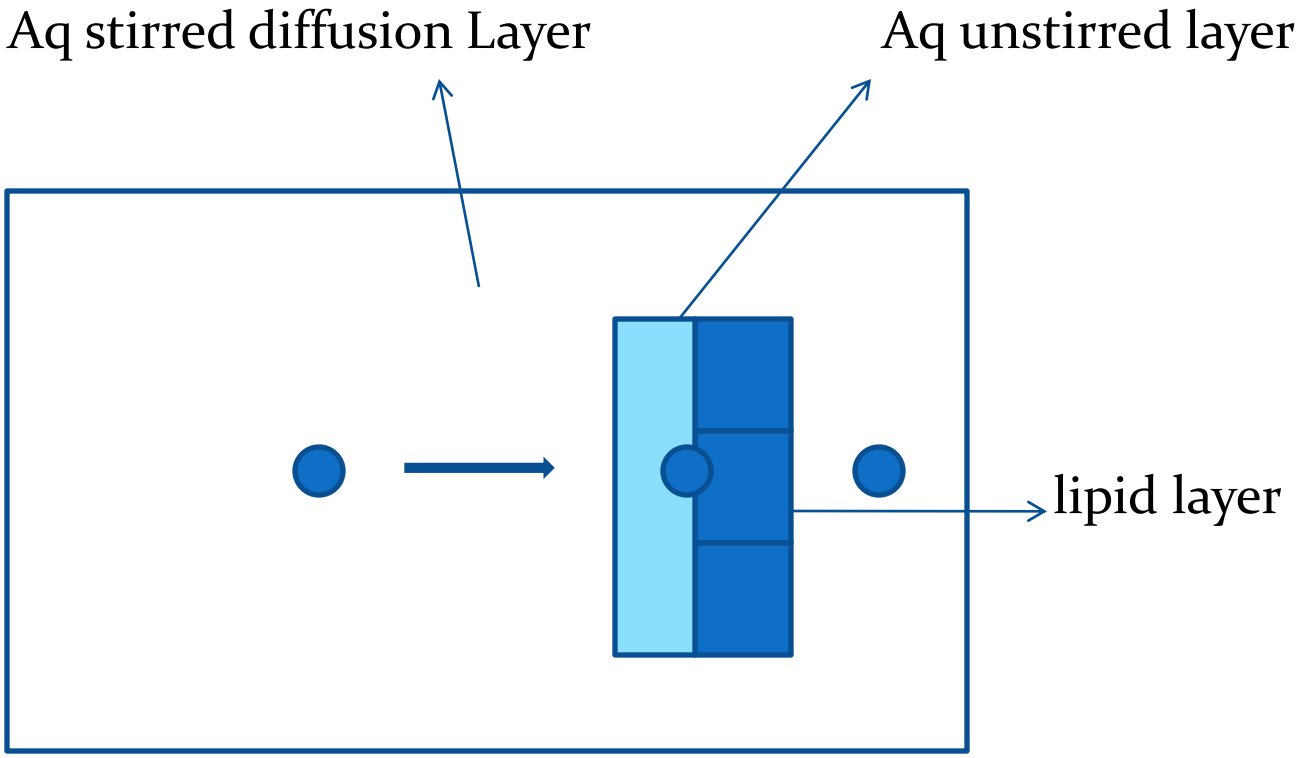
- ✓ **The dissociation constant of the drug.**
- ✓ **The lipid solubility of the unionized drug.**
- ✓ **The pH at absorption site.**

- Limitations of pH – partition hypothesis

1. Presence of virtual membrane pH
2. Absorption of ionized drug
3. Influence of GI surface area and residence time of drug
4. Presence of aqueous unstirred diffusion layer

- Presence of virtual membrane pH




Aq stirred diffusion Layer
Aq unstirred layer
lipid layer

H. Drug Stability :

- Poor B.A. due to destabilization of drug during its shelf life is due to --
- Degradation of drug in to inactive form
- Interaction with one or more different component

CONCLUSION[1,3]

- Physiochemical properties of drug are necessary while selecting proper drug delivery system.
- Solubility is pH dependent .
- Dissolution is RDS for hydrophobic & poorly aqueous soluble drugs.

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Thank you.....