INTRODUCTION TO BIOPHARMACEUTICS AND PHARMACOKINETICS

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Biopharmaceutics:

The study of various factors influencing the rate and amount of drug that reaches the systemic circulation and the use of this information to optimize the therapeutic efficacy of the drug products is known as biopharmaceutics.

Pharmacokinetics:

It is defined as the study of time course of drug ADME and their relationship with its therapeutic and toxic effects of drugs.

Bioavailability:

Rate and extent of drug enter into systemic circulation in unchanged form.

Absorption:

It is defined as the process of movement of drug from its site of administration to the systemic circulation.

Distribution:

The movement of drug between one compartment and the other (generally blood and the extravascular tissues) is referred to as drug distribution.

Elimination:

It is defined as the process that tends to remove the drug from the body and terminates its action

Takes place by two processes

1.Biotransformation

2.Excretion

Biotransformation:

It is defined as conversion from one chemical form to another. The term is used synonymously with metabolism.

Excretion:

It is the process whereby drugs and/or their metabolites are irreversibly transferred from internal to external environment.

Pharmacodynamic studies:

It is the study of relationship between the drug concentration to that of response given by the specific organ or tissue of a body.

Pharmacotherapeutic studies:

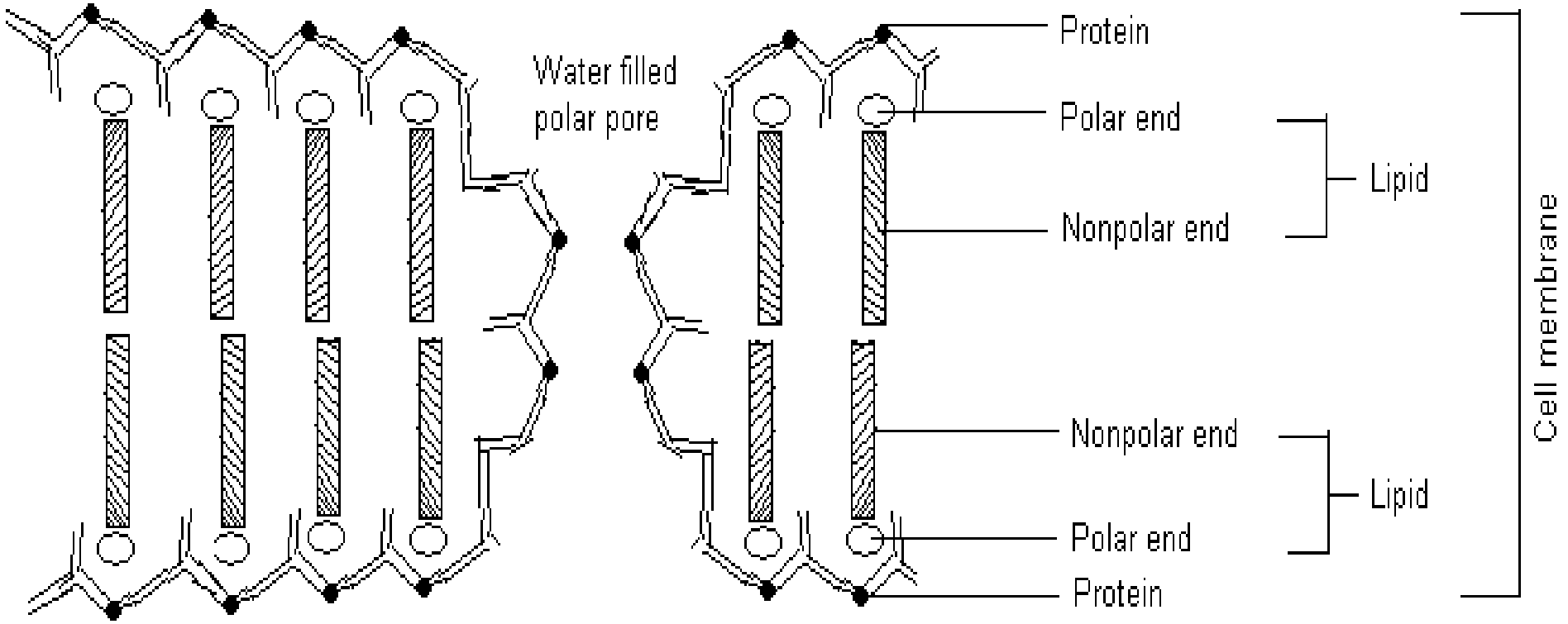
It is the study of relationship between the therapeutic efficacy of the drug to that of the clinical response given by a suitable dosage form.

Dosage regimen:

Frequency of administration of a drug in a particular dose.

ABSORPTION

Basic structure of functional cell membrane



Mechanisms of Drug Absorption

1. Passive Diffusion
2. Pore Transport
3. Facilitated Diffusion
4. Active Transport
5. Ionic or Electrochemical Diffusion
6. Ion-pair Transport
7. Endocytosis

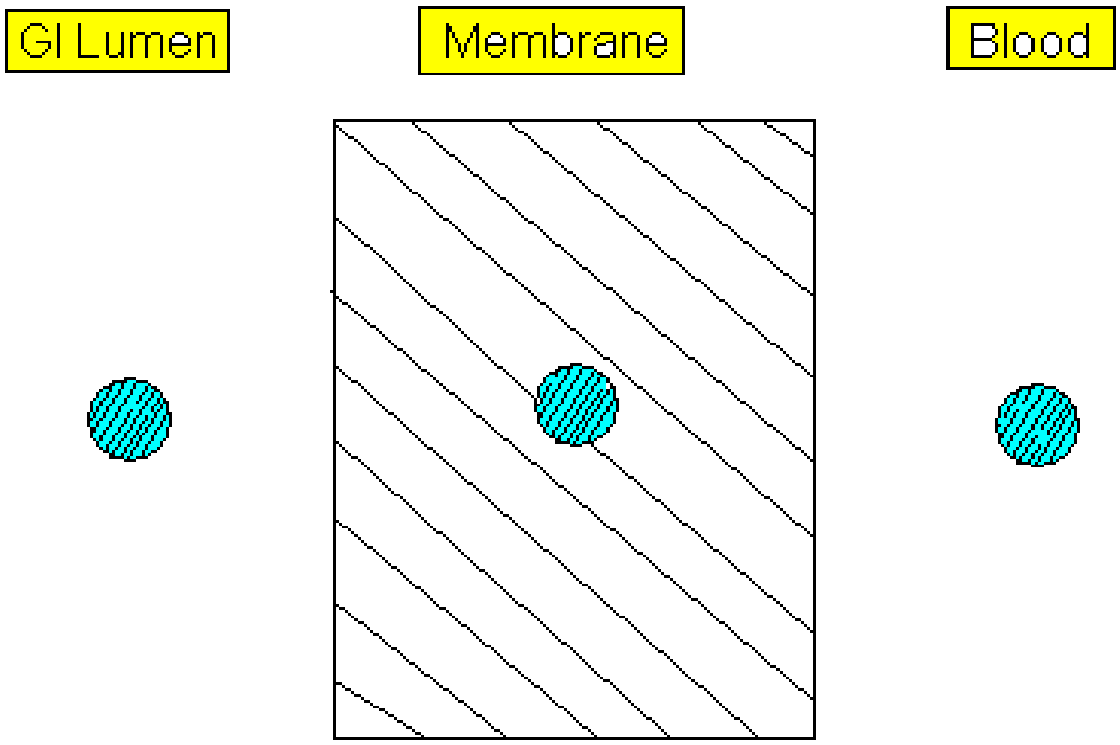
Passive Diffusion

- Also called nonionic diffusion.
- The driving force is concentration or electrochemical gradient.
- Fick's first law of diffusion

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

Permeability coefficient, P

$$dQ/dt = P\,C_{GIT}$$

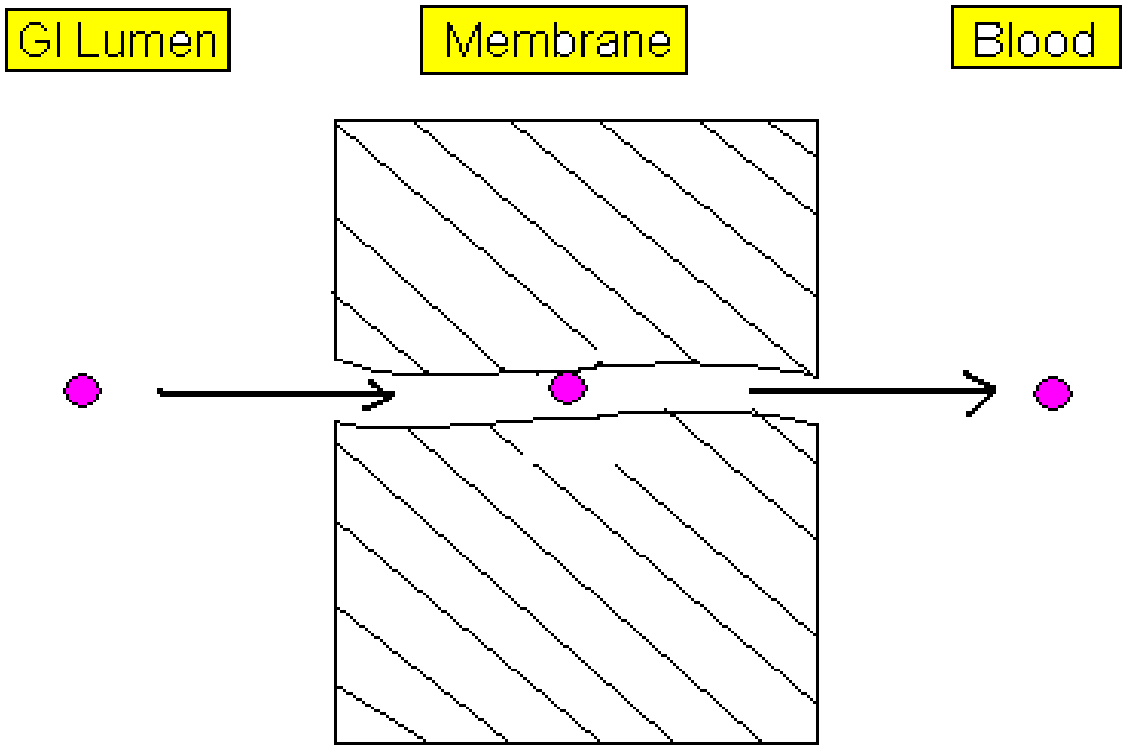


Passive Diffusion

Pore Transport

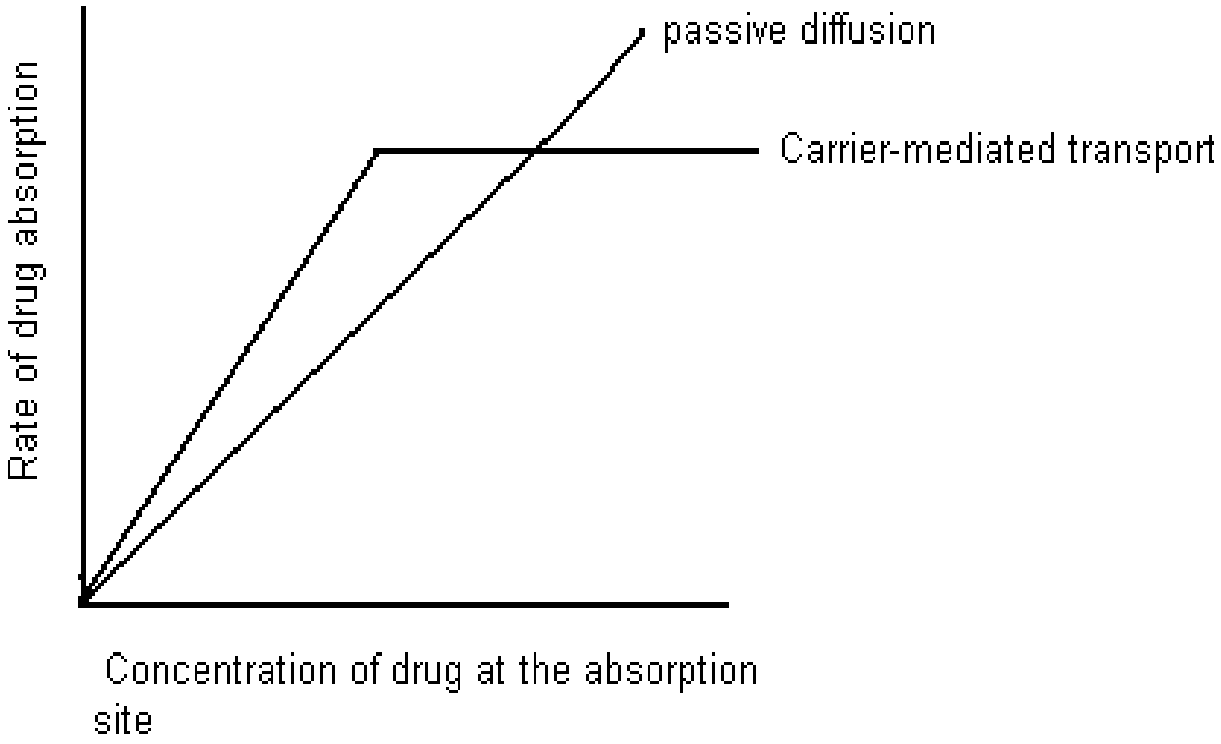
- Also called as convective transport, bulk flow or filtration.
- The driving force is hydrostatic pressure or osmotic pressure difference across the membrane due to which bulk flow of water along with small solid molecules across aqueous channels.
- Water flux that promotes such a transport is called as solvent drag.
- It is important in the absorption of low molecular weight, low molecular size and water-soluble drugs.

  Eg: urea, water and sugars.

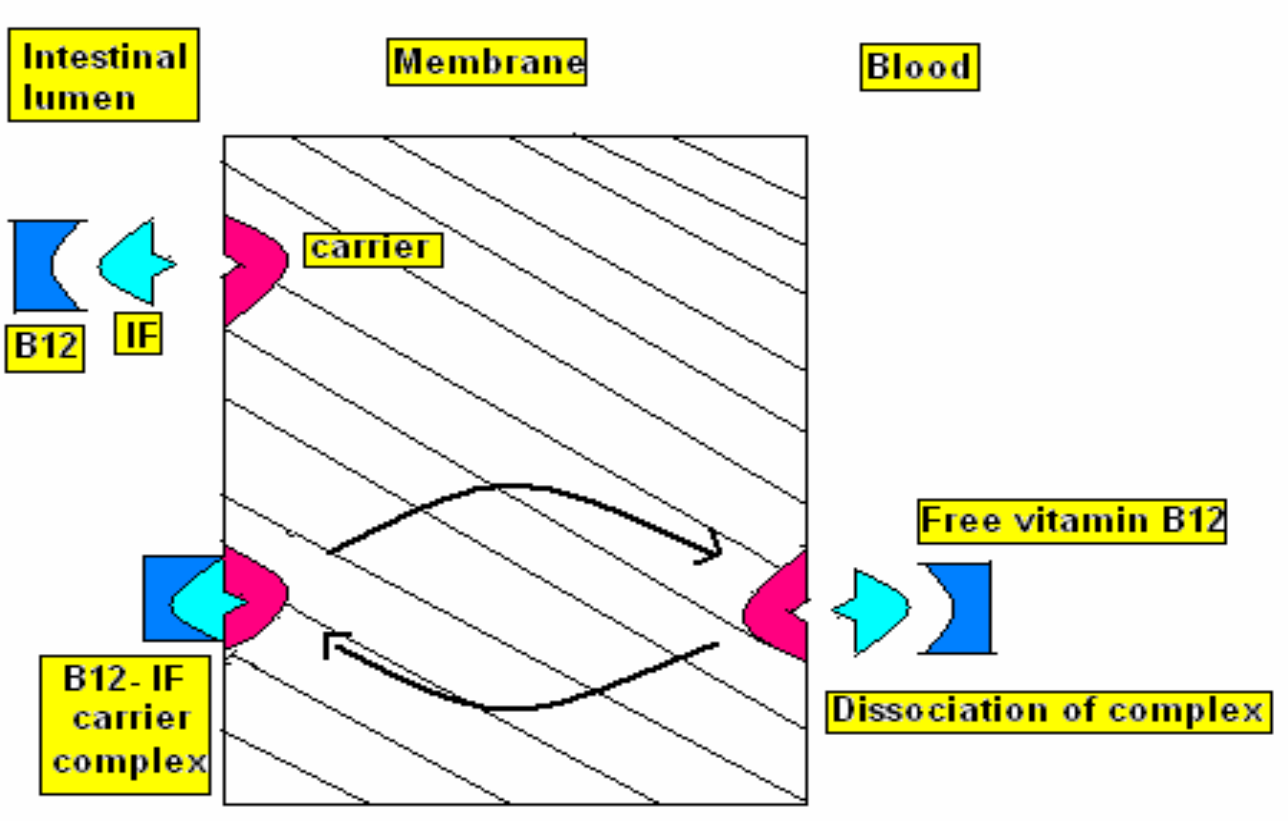


Pore Transport

Carrier-mediated Transport System

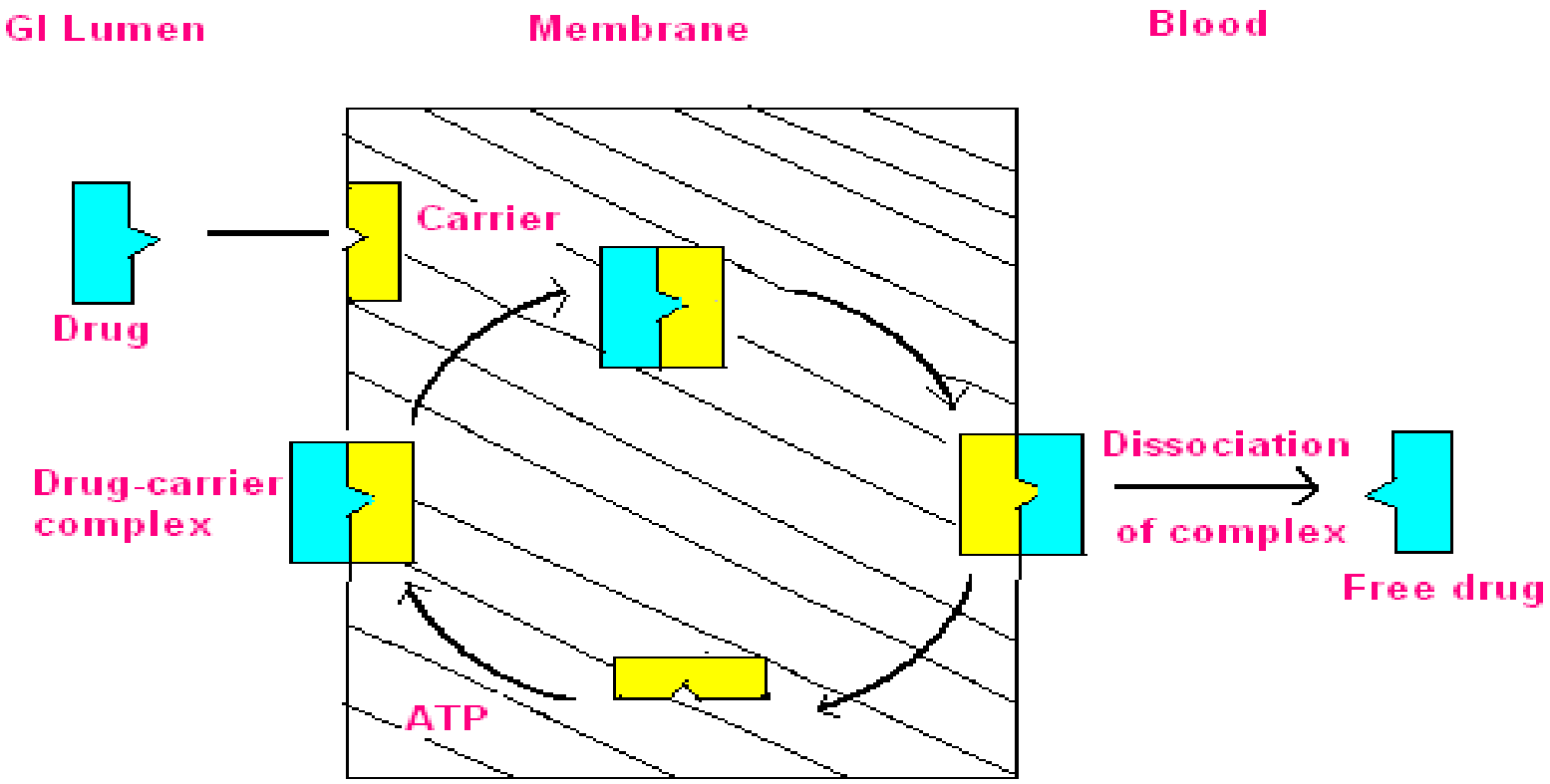


Facilitated Diffusion



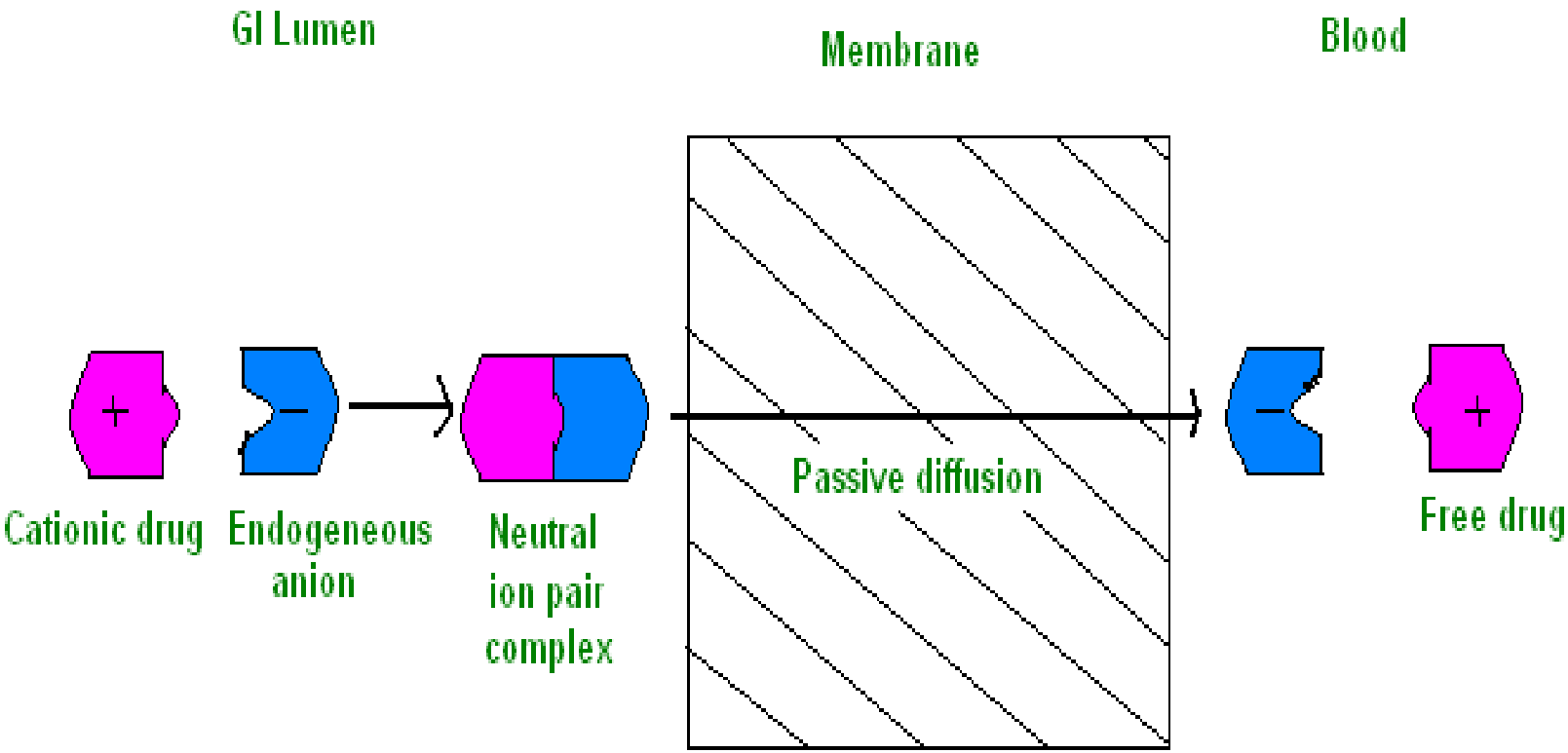
GI absorption of vitamin B_{12}

Active Transport



Absorption of 5-fluorouracil and 5- bromouracil via an pyrimidine transport system, absorption of methyl dopa and levodopa via an L-amino acid transport

Ion or Electrochemical Diffusion



The rate of permeation is in the following order:
Unionized molecules > anions > cations.

Ion-pair Transport

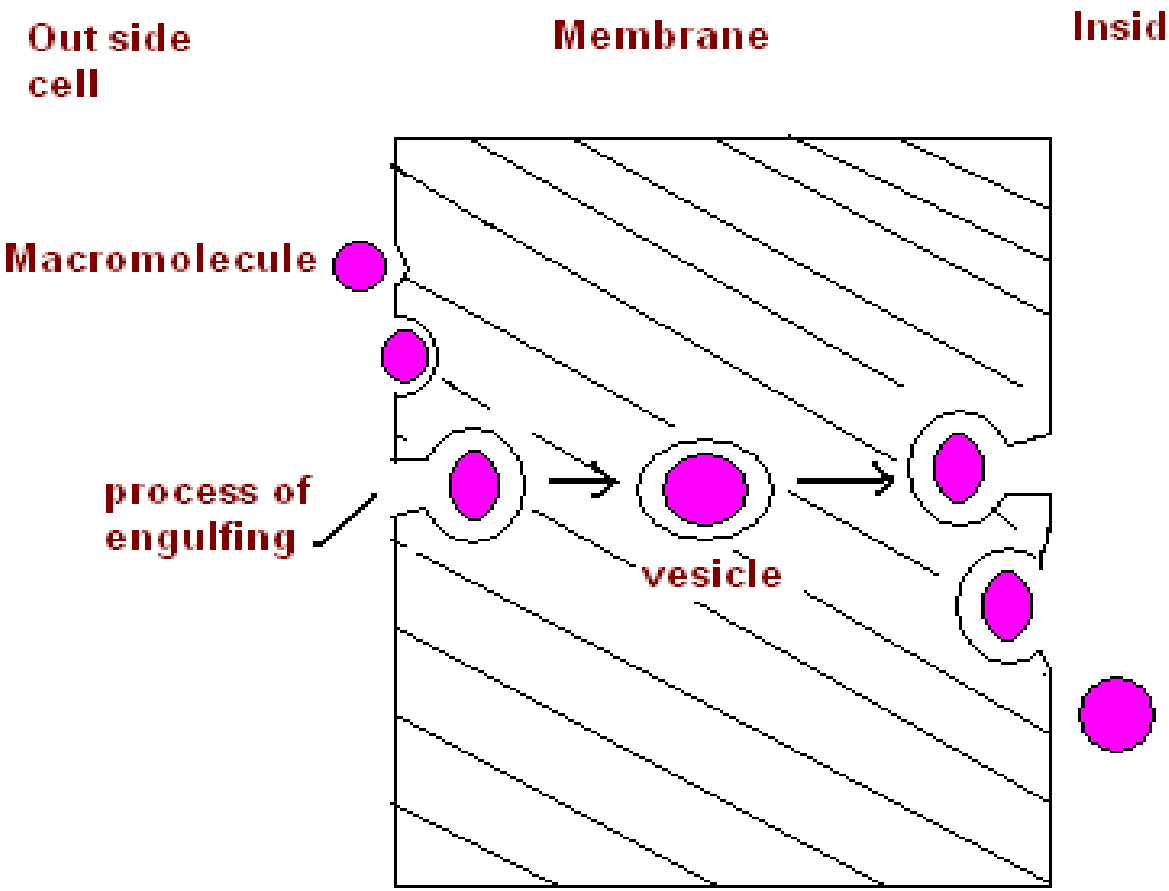
- Quaternary ammonium compounds and sulphonic acids ionize under all p^H conditions. such agents penetrate membrane by forming reversible neutral complexes with endogenous ion like mucin.
- These complexes have required lipophilicity and aqueous solubility.

Endocytosis

- It is responsible for cellular uptake of macromolecular nutrients like fats and starch, oil soluble vitamins like A,D,E,& K and drugs like insulin.

- It includes two types of process:

1. Phagocytosis(cell eating)
2. Pinocytosis (cell drinking)
3. Transcytosis (endocytic vesicle is transferred from one extra cellular compartment to another).



Endocytic uptake of Macromolecules

Biopharmaceutical factors influencing GI absorption of a drug from the dosage form

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. Pseudo polymorphism (hydrates or solvates)
5. Salt form of the drug
6. Lipophylicity of the drug
7. Pka of the drug and Ph
8. Drug stability

II. Dosage form characteristics and pharmaceutic ingredients

1. Disintegration time (tablets or capsules)
2. Dissolution time
3. Manufacturing variables
4. Pharmaceutic ingredients (excipients or adjuvants)
5. Nature and type of dosage form
6. Product age and storage conditions

PHYSICOCHEMICAL PROPERTIES AFFECTING BIOAVAILABILITY

- Drug solubility and dissolution rate
- Particle size and effective surface area
- Polymorphism and Amorphism
- Pseudopolymorphism(hydrates/solvates)
- Salt form of the drug
- Lipophilicity of the drug
- Pka of the drug and pH
- Drug stability

Dissolution:

Definition:

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

Solubility:

Definition:

It is defined as a process in which maximum amount of solute dissolved in a given solvent under standard conditions of temperature, pressure, pH is known as solubility.

Theories of drug dissolution:

a) Diffusion Layer Model/ Film theory.

b) Danckwert Model/ Surface Renewal Theory.

c) Interfacial Barrier Model / Limited solvation theory.

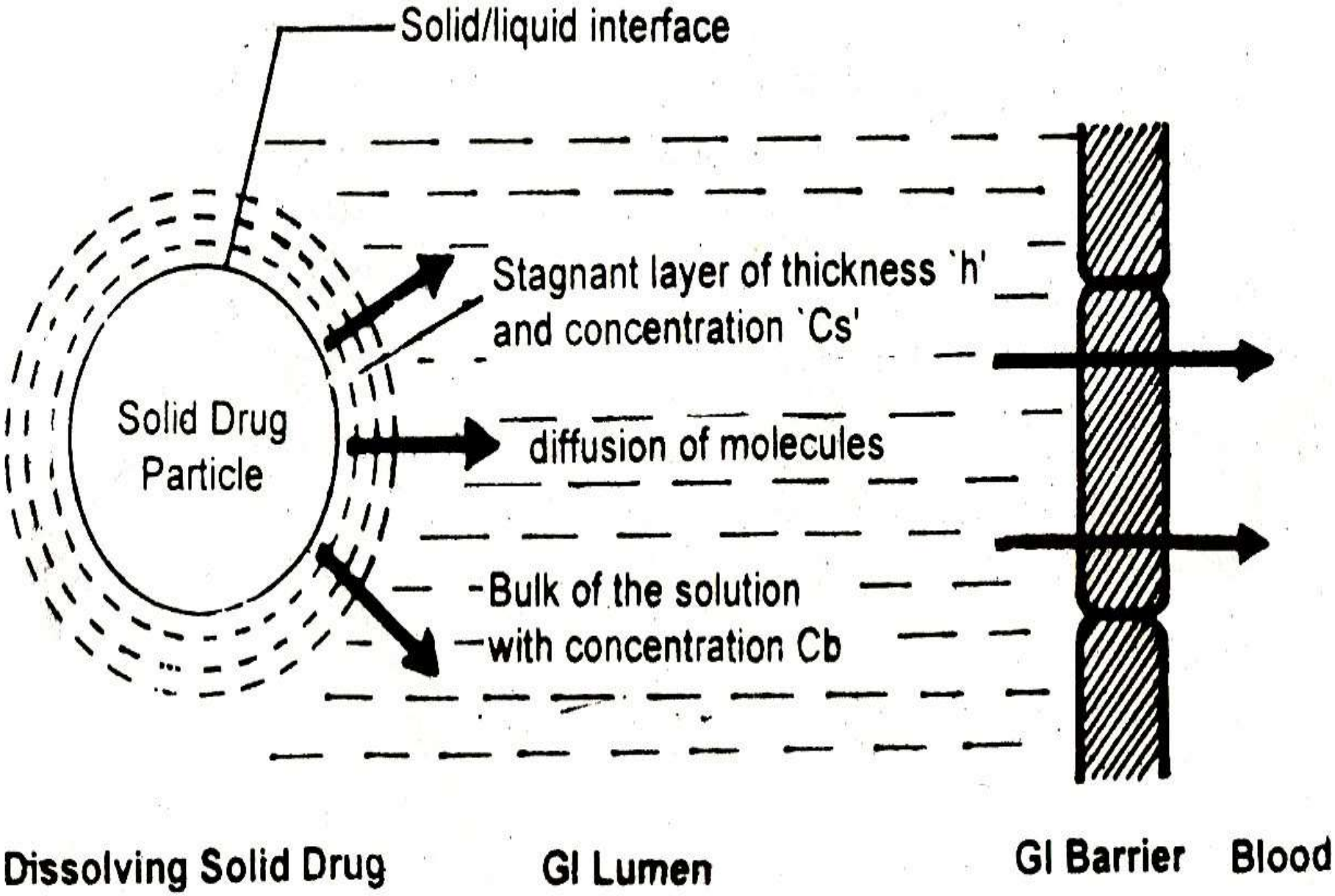


Fig. 2.11 Diffusion layer model for drug dissolution

Diffusion layer model (or)Film theory:

Noyes- whitney equation:

$$\frac{dC}{dT} = k\,(Cs - Cb)$$

dC/ dT = dissolution rate of drug

k = dissolution rate constant (first order)

Cs = Maximum drug solubility/ concentration of drug in stagnant layer

Cb = Concentration of drug in bulk of solution at time 't'

$$\frac{dC}{dT} = \frac{DAKw/o\,(Cs - Cb)}{Vh}$$

where, D = Diffusion coefficient of the drug

A = Surface area of dissolving solid

Kw/o = Water in oil partition coefficient. Intrinsic dissolution rate constant

V = Volume of dissolution medium

h = Thickness of stagnant layer

(Cs- Cb) = Concentration gradient for diffusion of drug

Sink conditions

Definition:

Sink conditions is a process in which drug concentration in a solution maintained constant at low level is known as sink conditions.

1. The saturated solubility of a drug is a key factor in the Noyes-whitney equation . The driving force for dissolution is the concentration gradient across the boundary layer.

2. The driving force depends upon the thickness of the boundary layer and the concentration of drug dissolved.

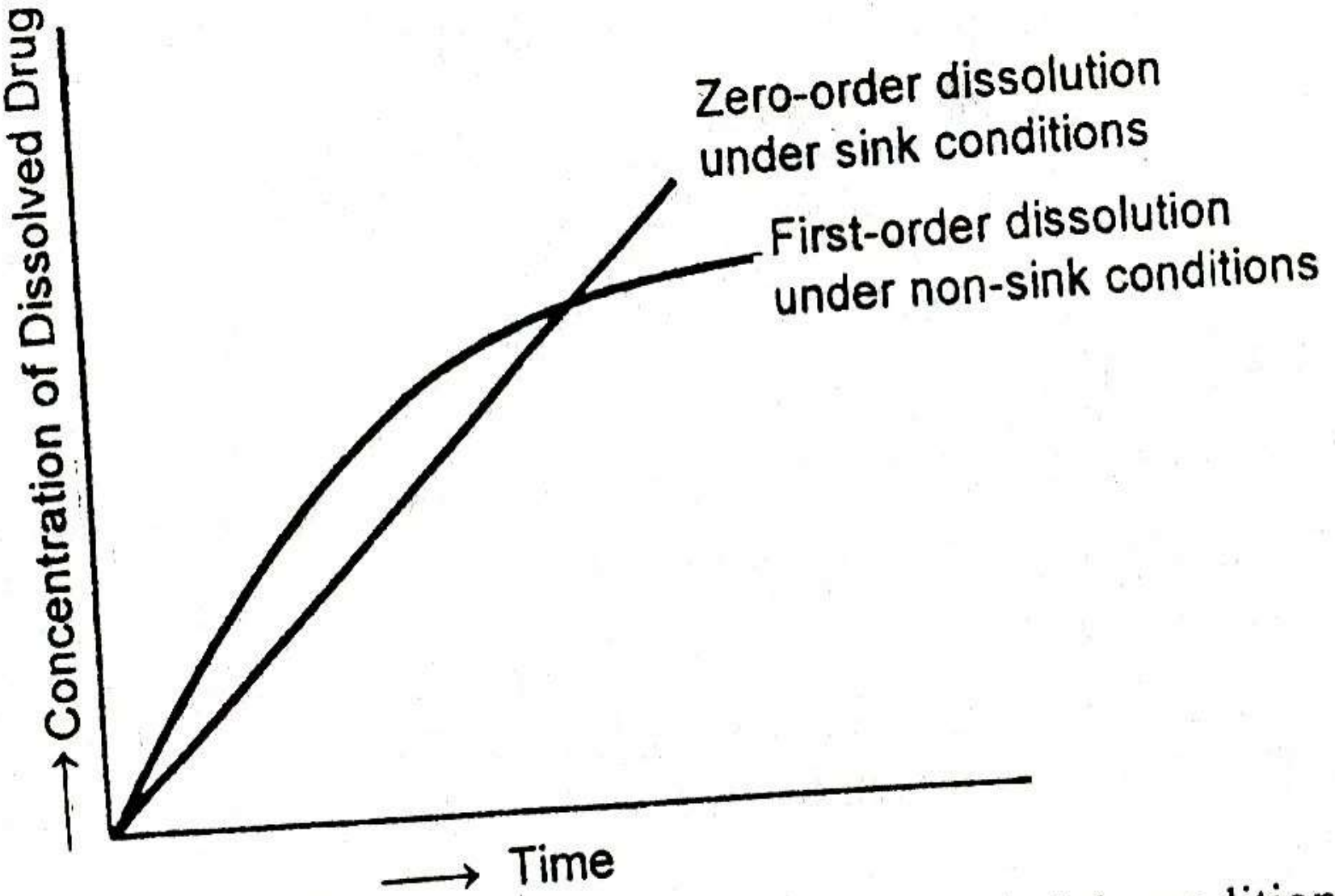


Fig. 2.12 Dissolution rate under nonsink and sink conditions.

Importance of sink conditions :

1. The driving force for dissolution is greatest when the system is under sink conditions.

2. Bathing the dissolving solid in fresh solvent from time to time.

3. Increasing the volume of dissolution fluid.

4. Removing the dissolved drug by partitioning it from the aqueous phase of the dissolution fluid into an organic phase placed either above or below the dissolution fluid .

e.g. : hexane (or) chloroform.

- *Hixson Crowell's cubic root law of* dissolution is used:

$$W_o^{1/3} - W_o^{1/3} = Kt$$

Where,

- Wo = Original mass of drug
- W = mass of drug remaining to dissolve at time t
- K = dissolution rate constant

Danckwert Model (or) Penetration (or) Surface Renewal Theory:

1. Danckwert did not approve of the existence of a stagnant layer and suggested that turbulence in the dissolution medium exists at the solid/liquid interface.

2. As a result the agitated fluid consisting of macroscopic mass of eddies (or) packets reach the solid/liquid interface in a random fashion due to eddy current absorb the solute by diffusion and carry it to the bulk of the solution.

The Danckwert's model is expressed by equation:

$$V\frac{dC}{dt} = \frac{dm}{dt} = A(Cs - Cb).\sqrt{\gamma D} \qquad (2.7)$$

where,

m = mass of solid dissolved, and

γ = rate of surface renewal (or the interfacial tension).

The model is depicted in Fig. 2.13.

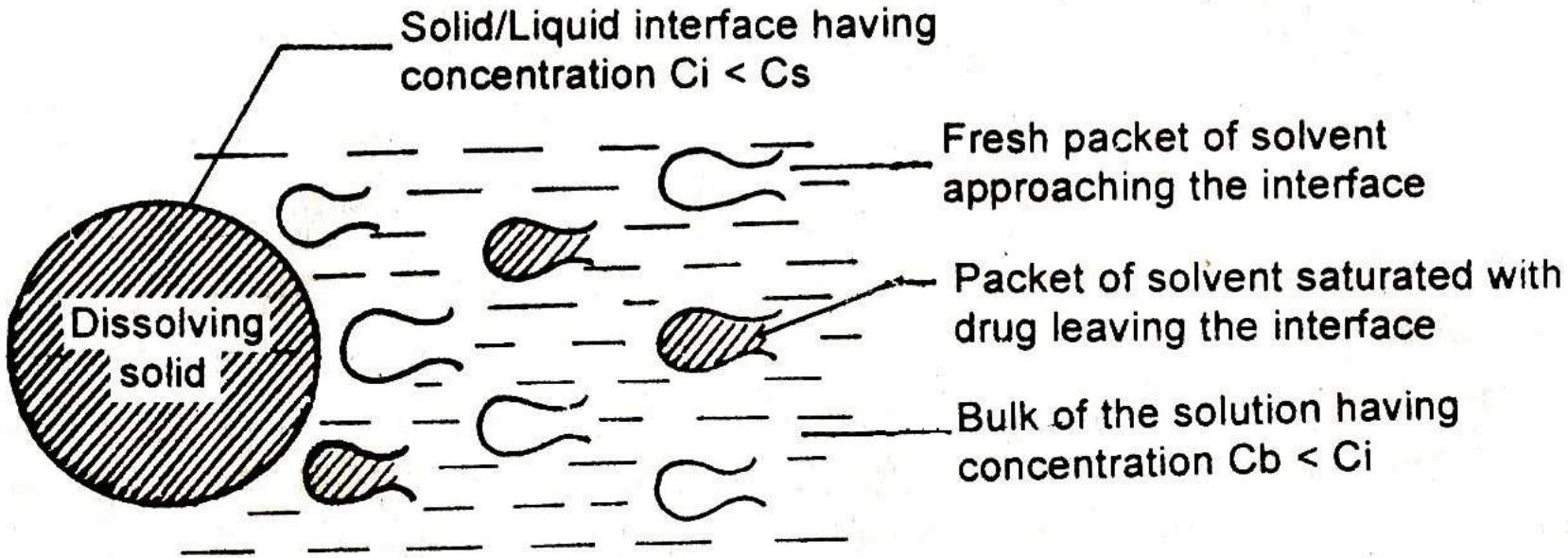


Fig. 2.13 Danckwert's model for drug dissolution

Interfacial barrier (or) Double barrier (or) Limited Solvation theory:

This model is based on the two assumptions.

1. The rate-determining steps the controls the dissolution is the mass transport.

2. Solid solution equilibrium is achieved at the solid / liquid interface.

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

Compendial methods of Dissolution :

Apparatus :1 Rotating basket apparatus.

Apparatus : 2 Paddle assembly apparatus:

Apparatus :3 Reciprocating cylindrical

Apparatus :4 flow – through cell apparatus.

Apparatus :5 Paddle over disk apparatus.

Apparatus :6 Cylinder apparatus.

Apparatus :7 Reciprocating disc method.

Alternative methods : Diffusion cell

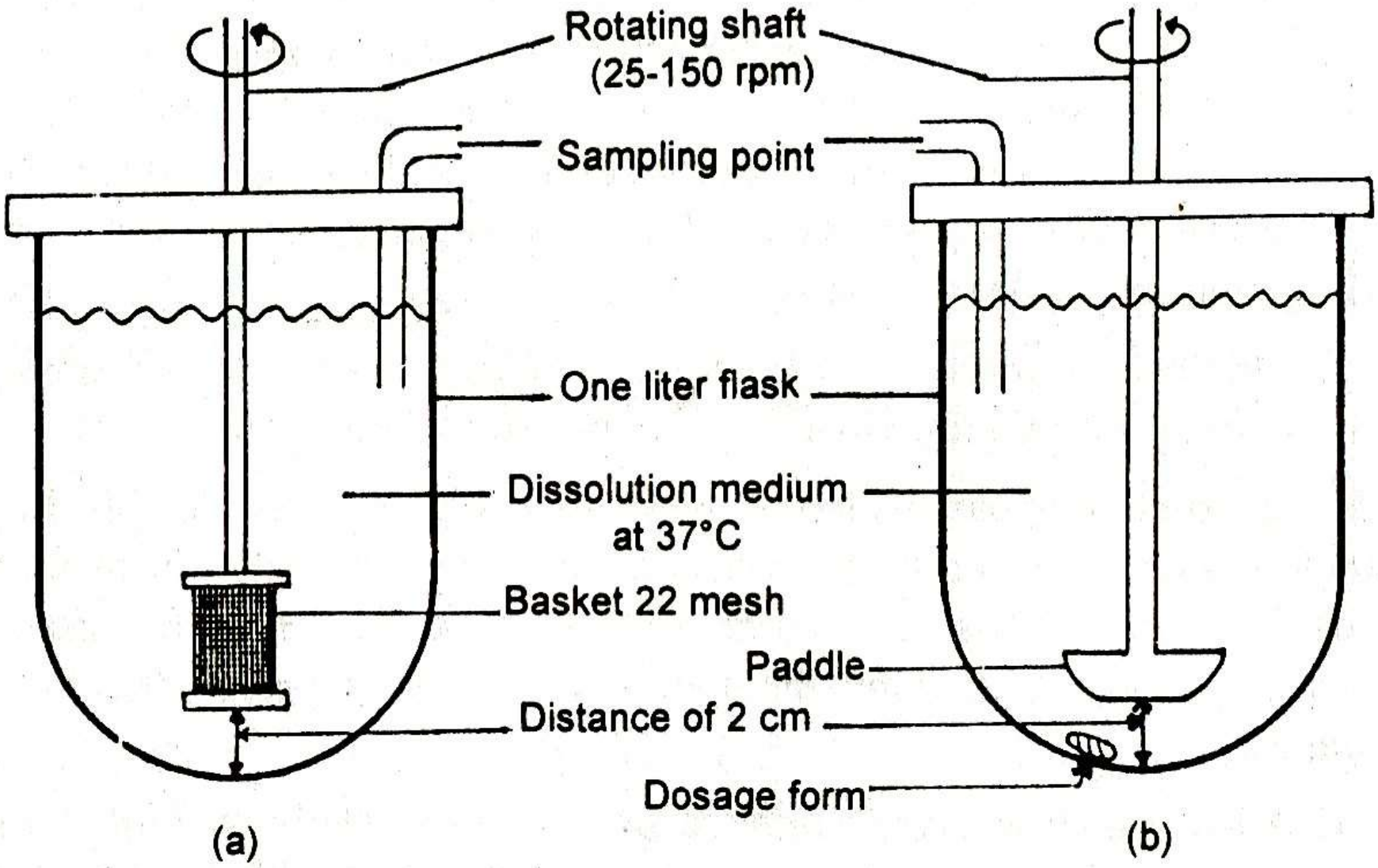


Fig. 12.3 Schematic representation of official dissolution apparatus —forced convection nonsink type (*a*) rotating basket apparatus, and (*b*) rotating paddle apparatus.

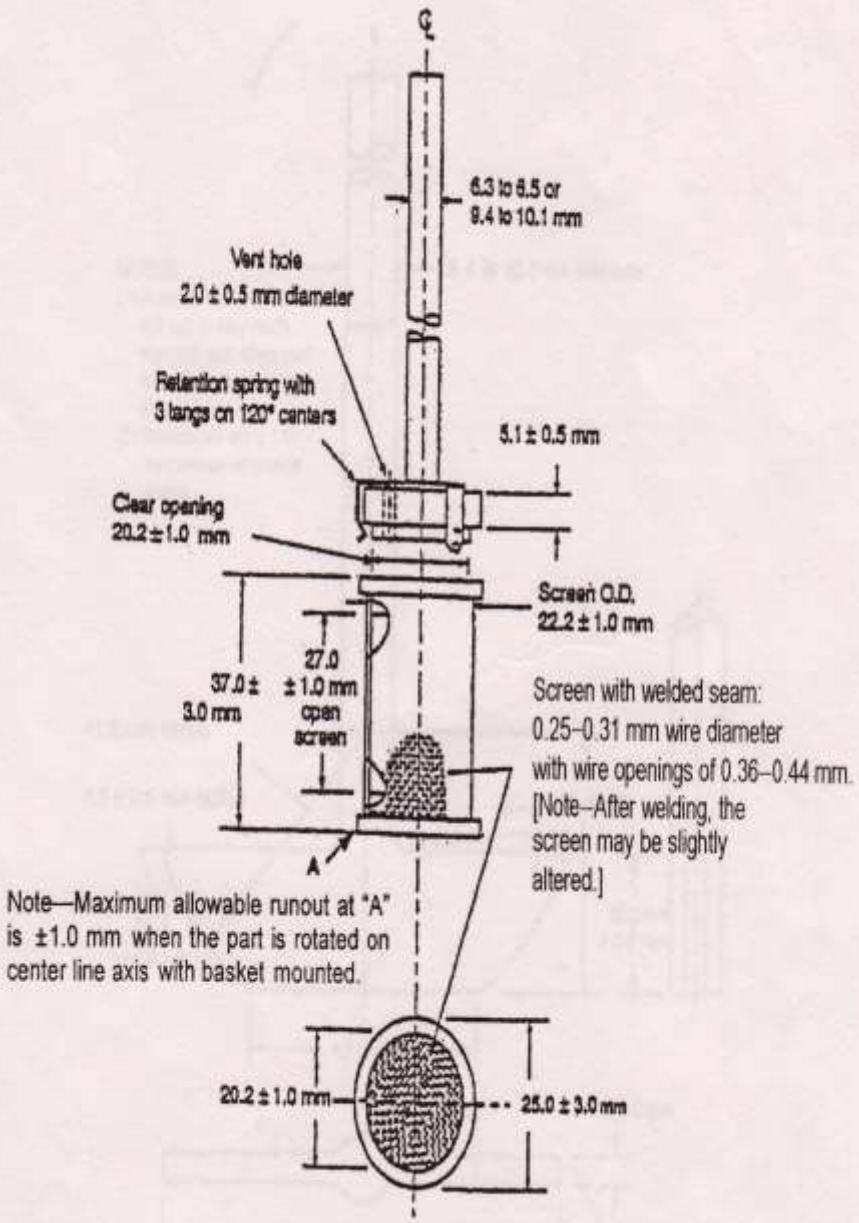


Fig. 1. Basket Stirring Element

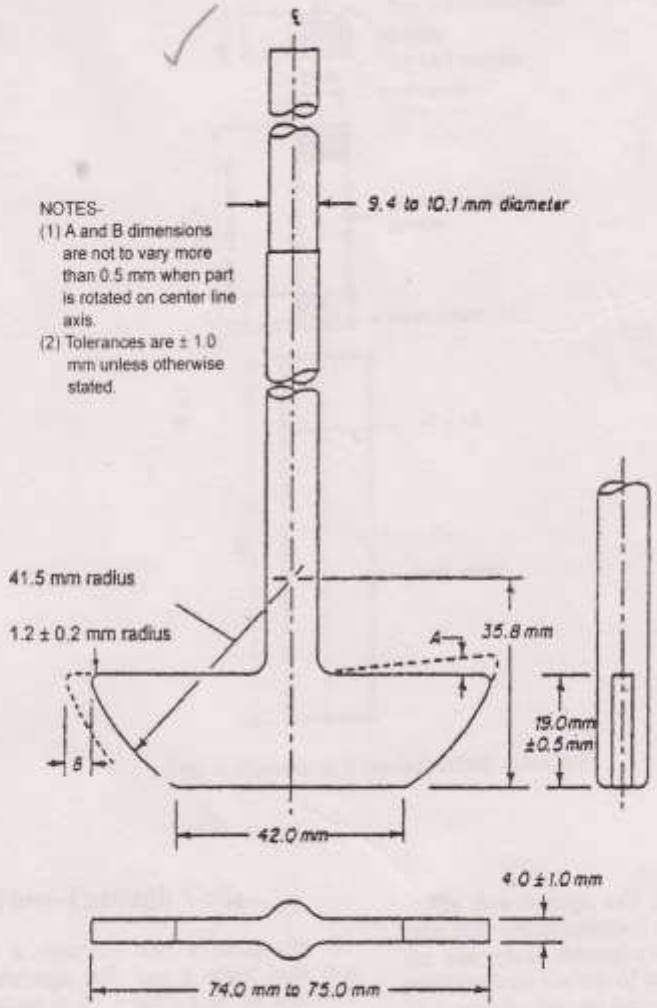


Fig. 2. Paddle Stirring Element

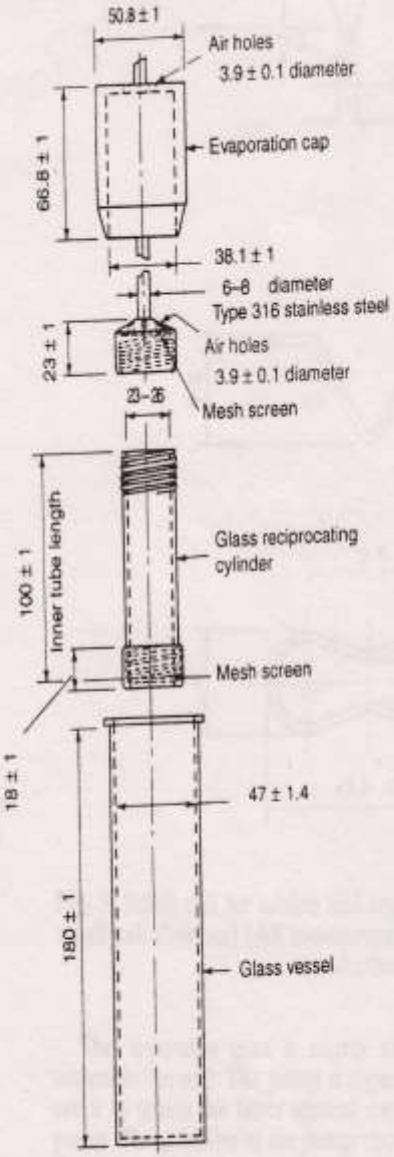
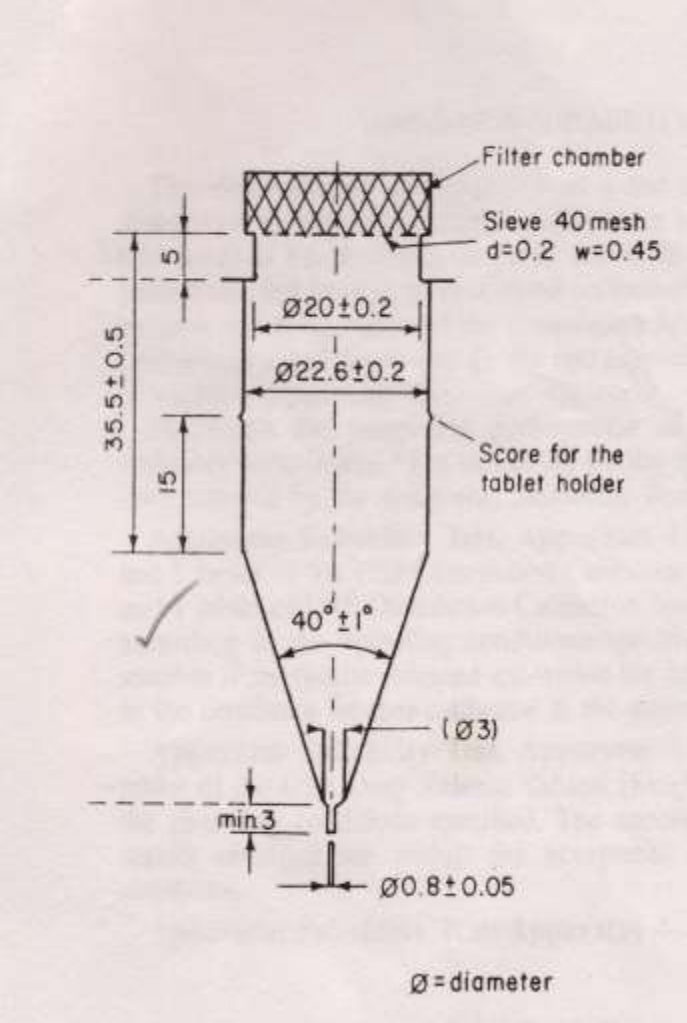
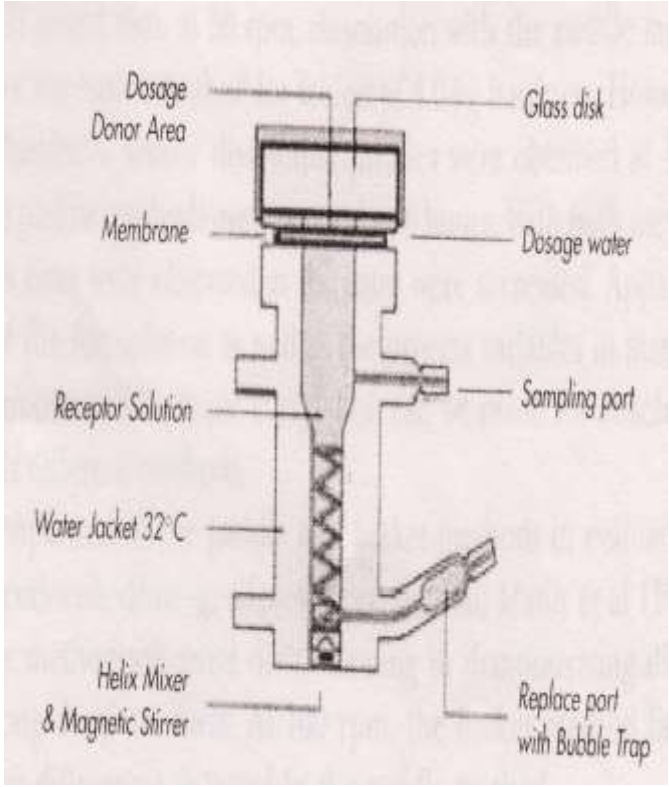


Fig. 3. Apparatus 3 (reciprocating cylinder)


Filter chamber
Sieve 40 mesh
d=0.2 w=0.45
5
Ø20±0.2
Ø22.6±0.2
35.5±0.5
15
Score for the
tablet holder
40°±1°
(Ø3)
min.3
Ø0.8±0.05
Ø=diameter


Dosage
Donor Area
Glass disk
Membrane
Dosage water
Receptor Solution
Sampling port
Water Jacket 32°C
Helix Mixer
& Magnetic Stirrer
Replace port
with Bubble Trap

Acceptance Table 1

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than $Q + 5\%$.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$.

- **Particle size and Effective surface area:**

- Particle size and surface area are inversely related to each other. Two types of surface area can be defined.

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

- Micronization of poorly aqueous soluble drugs like Griseofulvin, Chloramphenicol and several salts of Tetracycline results in superior dissolution rates in comparision to simple milled form of these drugs

- Micronization also lead to decrease in dose of drugs because of increased absorption efficiency.

- Ex; *Griseofulvin* dose was reduced to half and that of *Spironolactone* was decreased 20 times

→ In case of hydrophobic drugs like Aspirin, Phenacetin, Phenobarbital micronization results in decrease in effective surface area of such powders and fall in dissolution rate

→ Absolute surface area of hydrophobic drugs can be converted to their effective surface area by

→ Use of surfactant as a wetting agent that decrease interfacial tension and displaces the adsorbed air with the solvent

→ Ex; Tween-80 increases the bioavailability of Phenacetin by promoting its wettability

→ Adding Hydrophobic diluents such as *PEG, PVP, Dextrose* etc; which coat the surface of hydrophobic drug particles and renders them hydrophilic

- But the particle size reduction and increase in surface area and dissolution rate is not always advisable especially when the drugs are unstable and degrade in solution form

- *Ex; PenicillinG and Erythromycin* produce undesirable effects (Gastric irritation caused by Nitrofurantoin) or when a sustained effect is desired

- The second mechanism by which a reduction in particle size improves drug dissolution is through an increase in its solubility.

- Molecular dispersion or solid solution where the sparingly soluble drug is molecularly trapped in lattice of hydrophilic agent

Ex; Cyclodextrins

- Solid dispersion where drug dispersed in carrier such as PVP,PEG, Urea

- **Polymorphism and Amorphism**

Enantiotropic polymorph**:** Ex; sulfur

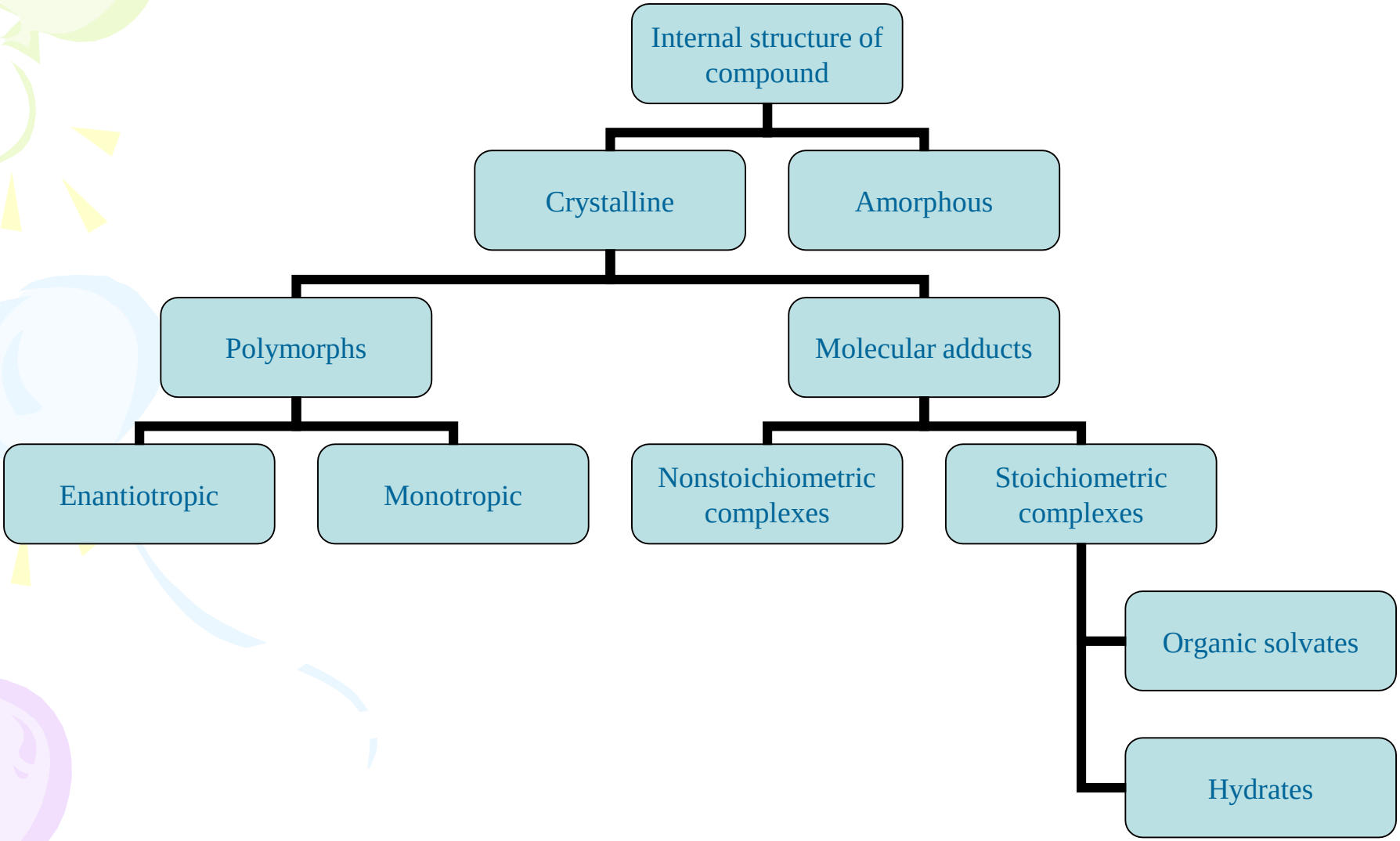
Monotropic polymorph; Ex Glyceryl monostearates

Some drugs can exist in Amorphous forms (having no internal crystal structure)**.**

- Ex Amorphous form of Novobiocin is 10 times more soluble than crystalline form.
- Chloramphenicol Palmitate , Cortisone acetate , Phenobarbital
- Order for dissolution of different solid forms of drugs is

Amorphous> Metastable> Stable

Classification of Internal Structure of a Compound



- **Hydrates / Solvates (Pseudopolymorphism):**

- **Ex;** Anhydrous form of Theophylline and Ampicillin have higher aqueous solubilities, dissolve at faster rate and show better bioavailability in comparision to their monohydrate and trihydrate forms
- Organic solvates have greater aqueous solubility than the nonsolvates
- **Ex;** n-pentanol solvate of fludrocortisone and succinylthiazole and the chloroform solvate of griseofulvin are more water soluble than their nonsolvated forms

Salt Form of Drug:

- Weakly acidic drugs, a strong base salt is prepared

- Ex; Sodium and Potassium salts of barbiturates and sulfonamides

- Weakly basic drugs, a strong acid salt is prepared

- Ex; Hydrochloride salts or sulfate salts of several alkaloidal drugs

Formation of fine precipitate

Insitu salt formation

Aspirin and Penicillin from buffered alkaline tablets.

Selection of suitable salt form

Ex: Choline and Isopropanolamine salts of Theophylline dissolve 3-4 times more rapidly than the Ethylene diamine salt and show better bioavailability

Size of counter ions :

Smaller the size of counter ion , greater the solubility of salt

Ex: Bioavailability of Novobiocin from its Sodium salt , Calcium salt and free acid form was found to be in ratio of 50:25:1

Ex; Pamoates,stearates and Palmitates of weak bases have poor aqueous solubility. These forms are used to prolong the duration of action (Steroidal salts) to overcome bad taste (Chloramphenicol palmitate), to enhance GI stability (Erythromycin estolate), or to decrease the side effects, local/ systemic

- **Drug pKa and Lipophilicity and GI pH-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 (pKa) of the drug
- *The lipid solubility of unionized drug
- *The pH at the absorption site

Drug pKa and Gastrointestinal pH:

Hendersen-Hasselbalch equations

For weak acids

$$pH = pKa + \log \frac{\text{Ionized drug concentration}}{\text{Unionized drug concentration}}$$

$$\% \text{ Drug ionized} = \frac{10^{pH - pKa}}{1 + 10^{pH - pKa}} \times 100$$

For weak bases

$$pH = pKa + \log \frac{\text{Unionized drug concentration}}{\text{Ionized drug concentration}}$$

$$\% \text{ Drug ionized} = \frac{10^{pKa - pH}}{1 + 10^{pKa - pH}} \times 100$$

For weak acids;

$$Ra = \frac{C_{GIT}}{C_{Plasma}} = \frac{1+10^{\,pH\ GIT\ -\ pKa}}{1+10^{\,pH\ Plasma-\ pKa}}$$

For weak bases:

$$Ra = \frac{C_{GIT}}{C_{Plasma}} = \frac{1+10^{\,pKa\ -pH\ GIT}}{1+10^{pKa-\ pH\ Plasma}}$$

Influence of drug pKa and GI pH on drug absorption

Very weak acids *(pKa> 8.0)*

Drugs	pKa	pH/ site of absorption
Pentobarbital	8.1	Unionized at all p H values;
Phenytoin	8.3	absorbed along the entire length of GIT

Moderately weak acids *(pKa 2.5-7.5)*

Cloxacillin	2.7	Unionized in gastric pH, Ionizein
Aspirin	3.5	intestinal pH ;better absorbed from Stomach

Stronger acids *(pKa < 2.5)*

Disodium cromoglycate	2.0	Ionized at all pH values; poorly absorbed from GIT

Very weak bases (*pKa < 5.0)*

Theophylline	0.7	Unionized at all pH values

Moderately weak bases *(pKa 5 to 11.0)*

Codeine	8.2	Ionized at gastric pH ,Unionized
Heroin	7.2	at intestinal pH;better absorbed from Intestine

Stronger bases *(pKa > 11.0)*

Mecamylamine	11.2	Ionized at all pH values;
Guanethidine	11.7	poorly absorbed from GIT

- **Lipophilicity and Drug Absorption:**

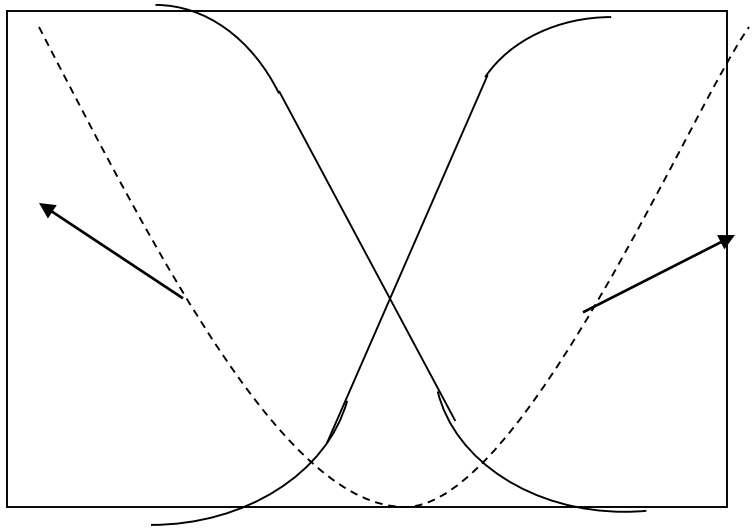
- A perfect hydrophilic-lipophilic balance (HLB) should be there in the structure of drug for optimum bioavailability

- To enhance the bioavailability of a drug, not only its dissolution rate but also its rate of permeability should be considered.

- Rate of dissolution can be increased by altering the physical properties such as particle size or crystalline structure but its permeability can only be promoted by modification of chemical structure

- **Limitations of pH –Partition Hypothesis**
- Presence of virtual membrane pH
- Absorption of ionized drugs
- Influence of GI surface area and residence time of drug
- Presence of aqueous unstirred diffusion layer

- **Presence of Virtual Membrane pH:**



pH absorption curve for acidic and basic drugs . Dotted lines indicate curves predicted by pH partition hypothesis and bold lines indicate the practical curves

- **Absorption of Ionized drugs:**

- Ex: Morphinan derivatives

- **Influence of GI surface area and Residence time of drug**

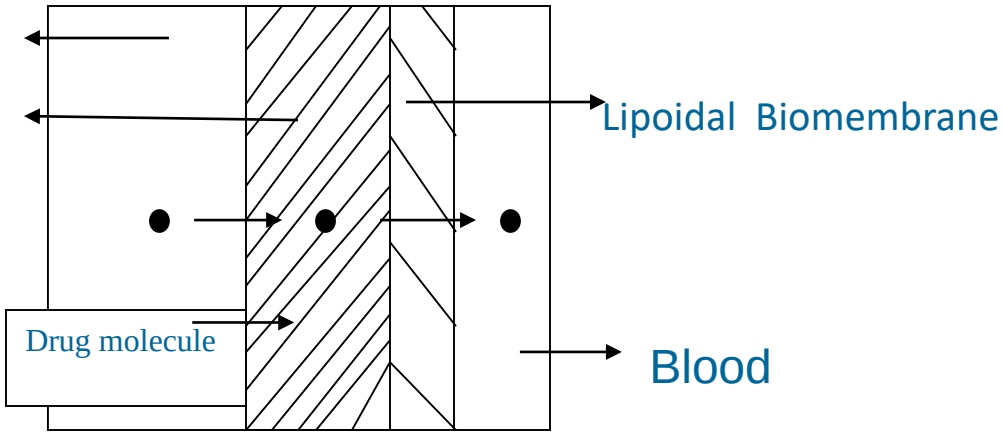
- Both acidic drugs and basic drugs are more rapidly absorbed from the intestine, because of its large surface area and secondly ,because of long residence time of drug in intestine.

Presence of Aqueous unstirred diffusion layer on the membrane surface

Ex*; High molecular weight fatty acids and bile salts*

Aqueous bulk fluid of GIT

Aqueous unstirred diffusion layer



Biopharmaceutical factors influencing GI absorption of a drug from the dosage form

B. PATIENT RELATED FACTORS

1. Age
2. Gastric emptying time
3. Intestinal transit time
4. Gastrointestinal Ph
5. Disease state

- Blood flow through the GIT
- Gastrointestinal contents: Other drugs, food, fluids, other normal GI contents
- Presystemic metabolism by:
  Lumenal enzymes, gutwall enzymes, bacterial enzymes, hepatic enzymes

Physiological factors:

- Age:

Infants: gastric pH – high

intestinal surface, blood flow to GIT – low

Therefore, altered absorption pattern compared to adults.

Elderly persons: impaired drug absorption include

altered gastric emptying, decreased intestinal surface area and GI blood flow, higher incidents of achlorhydria and bacterial over growth in small intestine .

Gastric emptying time:

- Rate limiting step in drug absorption

- Gastric emptying of a drug is delayed by co-administering food because unless the gastric contents are fluid enough or the size of the solid particles is reduced below 2mm, its passage through the pylorus into the intestine is not possible.

- Delay in gastric emptying is recommended where:

- food promotes drug dissolution and absorption(Griseofulvin)
- drugs irritate the gastric mucosa(aspirin, nitrofurantoin)
- Disintegration and dissolution is promoted by gastric fluids

- Gastric emptying is a First order process. Parameters used to quantify gastric emptying:
  - Gastric emptying rate
  - Gastric emptying time
  - Gastric emptying t1/2

- Factors influencing gastric emptying:
  - Volume of meal
  - Composition of meal
  - Physical state and viscosity of meal
  - Temperature of meal
  - Gastrointestinal Ph
  - Electrolytes and osmotic pressure
  - Body posture
  - Emotional state
  - Exercise
  - Disease states
  - drugs

- Intestinal transit:

- Long intestinal transit time is desirable for complete drug absorption
- Delayed intestinal transit is desirable for:
  - Drugs that dissolve or release slowly from their dosage form (sustained release products)
  - Drugs that dissolve only in intestine (enteric coated formulations)
  - Drugs absorbed from specific sites of intestine (several B vitamins)
- Metochlopramide promote gastric emptying and intestinal transit enhance absorption of rapidly soluble drugs.
- Laxatives also promote the rate of intestinal transit

Gastrointestinal pH:

- 10^7 fold difference in the hydrogen ion concentration is observed between the gastric and colon fluids
- GI fluid pH influence drug absorption in several ways:
    - Disintegration
    - Dissolution
    - Absorption
    - Stability

Disease states:

Gastrointestinal diseases:

- Altered GI motility
- Gastrointestinal diseases and infections
- Gastrointestinal surgery
- Cardiovascular diseases
- Hepatic diseases

Blood flow to the GIT:

The GIT is extensively supplied by blood capillary network and the lymphatic system.

since the blood flow rate to the GIT +6is 500-1000times more than the lymph flow, much drugs reach the systemic circulation verses blood.

Food influences blood flow to the git. the perfusion rate increases after and persists per hours but drug absorption is not influenced significantly.

Gastrointestinal contents:

1. Food - drug interactions
2. Fluid volume
3. Interactions of drug with normal GI constituents
4. Drug – Drug interactions in the GIT

Influence of food on drug absorption

Delayed	Decreased	Increased	Unaffected
Aspirin Paracetamol Diclofenac Nitrofurantoin Digoxin	Penicillins Erythromycin Ethanol Tetracyclines Levodopa Iron	Griseofulvin Nitrofurantoin Diazepam Actively absorbed Water soluble vitamins	Methyldopa Propylthiouracil Sulfasomide

Drug-drug interaction in the GIT:

It is two types

a) Physicochemical Drug-drug interaction

b) Physiologic Drug-drug interaction

a) Physicochemical Drug-drug interaction:

- Adsorption
- Complexation
- pH range

b) Physiologic Drug-drug interaction

» Decreased GI transit

» Increased gastric emptying

» Altered GI metabolism

Presystemic metabolism:

- For a drug administered orally 2 main reasons for its decreased bioavailability are:
  - Decreased absorption
  - First pass/presystemic metabolism
- The 4 primary systems which effect presystemic metabolism of a drug are
  - Lumenal enzymes
  - Gutwall enzymes
  - Bacterial enzymes
  - Hepatic enzymes

Dosage related factors

- Disintegration time
- Dissolution time
- Manufacturing variables
- Pharmaceutic ingredients
- Nature and type of dosage form
- Product age and storage condition

❖ Disintegration time

- Disintegration time is of particular importance in case of solid dosage forms like tablets and capsules.

- However if a solid forms does forms conform to the disintegration time, it portends problems, because the subsequent process of dissolution will be much slower and absorption much be insufficient.

❖ Manufacturing variables

- Drug dissolution is the single most important factor in the absorption of drugs, especially for conventional solid dosage forms like tablets and capsules.
- Several manufacturing processes influence drug dissolution from solid dosage forms are
- (a) Method of granulation.
- (b) Compression force.

Method of Granulation:

- The wet granulations process is the conventional technique in the manufacture of tablets.

The limitations of this methods includes:

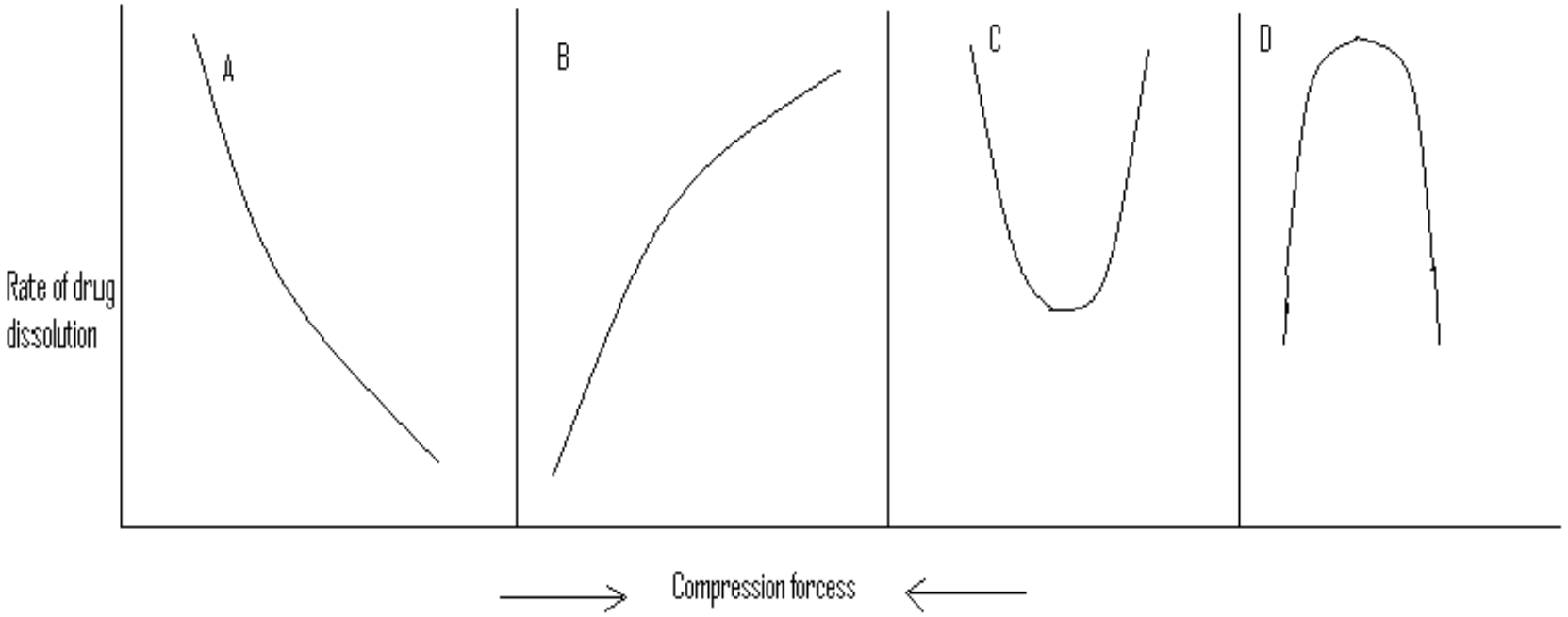
(i) Formation of crystals bridge by the presence of liquid.

(ii) The liquid may acts as a medium for effecting chemical reactions such as hydrolysis.

(iii) The drying step may harm the thermo labile drugs.

Compression Force:

- The compression force employed in tabulating process influence density, porosity, hardness, disintegration, and dissolution of tablets.
- The curve obtained by plotting compression force verses rate of dissolution can take one of the 4 possible shapes.



- On the one hand, higher compression force increases the density and hardness
- of tablet, decreases porosity and hence penetrability of the solvent in to the tablet, retards wet ability by forming a firmer and more effective sealing layer by the lubricant.
- On other hand, higher compression forces causes deformation, crushing (or) fracture of drug particle in to smaller ones (or) convert a spherical granules in to a disc shaped particle with a large increases in the effective surface area. This increases in dissolution rate of tablets.

Intensity of packing of capsule content:

- Compression force for tablets, packing density in case of capsule dosage form either inhibit (or) promote dissolution.

- Diffusion of GI fluids in to the tightly filled capsules resulting in rapid bursting and dissolution of contents.

❖ Pharmaceutical Ingredients (or) Excipients:

- A convenient dosage form to be administered by suitable route is prepared such a formulation contains no: of excipients.

- Excipients are added to ensure acceptability, physico-chemical stability during the shelf life, uniformity of composition and dosage, optimum bioavailability and functionality of the drug products.

Vehicle:

- Vehicles is the major component of liquid orals (or) parental.
- They are three categories of vehicles in use are aqueous vehicles (water, syrup) non –aqueous water miscible vehicles (propylene glycol, glycerol sorbitol) and non –aqueous water immiscible vehicles (vegetable oils).
- Bioavailability of a drug from vehicles depend to a large extent on its miscibility with biological fluid.
- Aqueous and water miscible vehicles are miscible with the body fluids and drugs from them are rapidly absorbed.

Diluents:

- Diluents are commonly added to tablet formulations if the required dose is inadequate to produce the necessary bulk.
- One of the classical example of drug-diluents interaction results in poor bioavailability is that of tetracycline complex and dicalcium phosphate.

Binders and granulating agents:

- The materials are used to hold powders together to form granules (or) promote cohesive compacts for directly compressible materials, and to ensure that the tablet remains intact after compression.

- Popular binders include polymeric materials like starch, cellulose derivatives, acacia, pvp etc.

Disintegrants:

- These agents over come the cohesive strength of tablet and break them up on contact with water which is an important prerequisite to tablet dissolution.
- All the disintegrants are hydrophilic in nature. A decrease in the amount of disintegrants can significantly lower bioavailability.

Lubricants (or) ant frictional agents:

- These agents are added to tablet formulations to aid the flow of granules, to reduce interparticle friction and sticking (or) adhesion of particles to dies and punches.

- The commonly used lubricants are hydrophobic in nature, and to inhibit wet ability, penetration of water in to tablet and their disintegration and dissolution.

Suspending agents:

- Suspending agents are hydrophilic polymers like vegetable gums, (acacia, tragcanth) semi synthetic gums (cmc, mc) and synthetic gums which stabilize the solid drug particles by reducing their rate of settling through an increase in the viscosity of the medium.

Surfactants:

- Surfactants are widely used in formulations as wetting agents, solubilizers, emulsifiers etc.

  mechanism involved in the increased absorption of drug by use of surfactants includes:

  - ✓ Promotion of wetting and dissolution of drugs':. Tween 80 with phenacetin.
  - ✓ Better membrane contact of the drug for absorption.
  - ✓ Enhanced membrane permeability of the drug.

Buffers:

- Buffers are useful in creating the right atmosphere for drug dissolution was observed for buffered aspirin tablets.
- Buffer systems containing potassium cat ions inhibit the drug absorption as seen in vitamin B2 and sulfonamide.

Complexing agents:

- Complex formation has been used to alter the physico chemical and biopharmaceutical properties of a drug.

- several examples where complexation has been used to enhance drug bioavailability are :

- 1.enhanced dissolution through formation of a solute complex.

  eg: ergotamine tartarate-caffeine complex.

Colorants:

- Low concentration of water-soluble dye can have an inhibitory effect on dissolution rate of several crystalline drugs.

- The dye molecules get absorbed on to the crystal faces and inhibit drug dissolution.

  e.g.: brilliant blue retards dissolution of sulfathiazole.

Crystal growth inhibitors:

- Crystal growth inhibitors like PVP and PEG inhibit conversion of a high energy meta stable polymorph in to stable, less soluble polymorph.

Nature and type of dosage:

- For a proper selection of a drug ,clinical success depends to a great extent on the proper selection of dosage form of that drug.
- For a given drug, 2 to 5 folds (or) perhaps more difference could be observed in the oral bioavailability of a drug depending up on the nature and type of dosage form.
- Such a difference is due to the relative rate at which a particular dosage form releases the drug to the biological fluids and the membrane.
- The relative rate at which a drug from a dosage form is presented to the body depends up on the complexity of dosage form.

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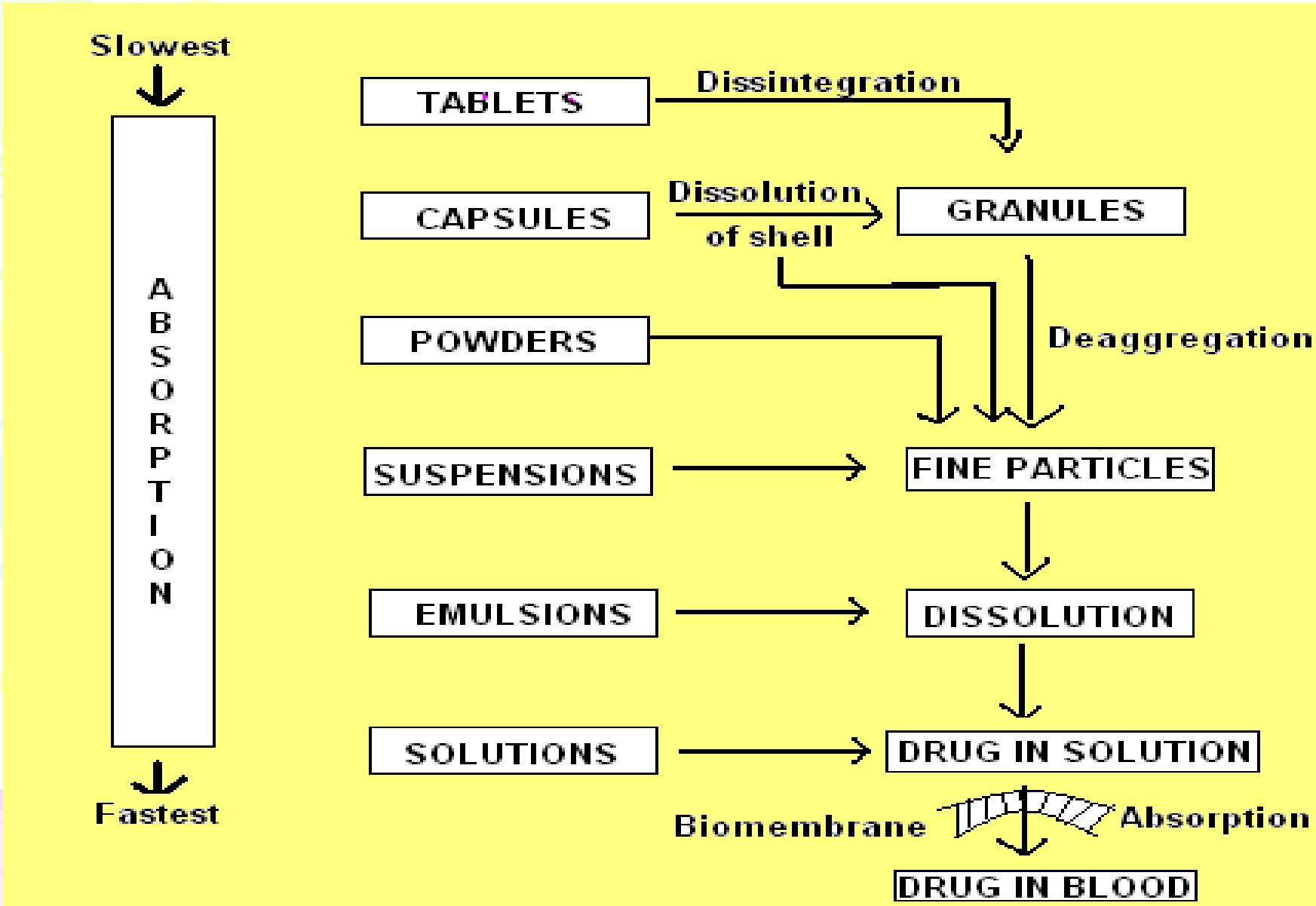


Course of events that occur following oral administration of various dosage forms

Solutions:

A Drug in solutions (syrups, elixirs) is most rapidly absorbed since the major rate- limiting step, drug dissolution is absent.

- Factors that influence bioavailability of a drug from solution dosages forms includes the nature of solvent, viscosity, surfactants, solubilizers, stabilizers etc.

Emulsions:

- Emulsion dosage forms have been found to be superior to suspensions in administering poorly aqueous soluble lipophilic drugs.
- It was observed with indoxole that when it is dissolved in a vegetable oil and emulsified in water, absorption increases 3 fold over its aqueous suspension.

Suspensions:

- The major rate- liming step in the absorption of a drug from suspension dosage form is drug dissolution which is generally rapid due to the large surface area of particles.
- Important factors in the bioavailability of a drug from suspensions include particle size, polymorphism, wetting agents, viscosity of the medium, suspending agents etc.

Powders:

- powders are superior to tablets and capsules, they are not in use now a days due to handling and palatability problems.
- Major factor to be considered in the absorption of a drug from powders are particle size, polymorphism, wettability etc.

Capsules:

- powders and granules are popularly administered in hard gelatin capsules where as viscous fluids and oils in soft elastic shells.
- In case of hard gelatin capsules include drug particle size, density, polymorphism, intensity of packing and influence of diluents and excipients.

Tablets:

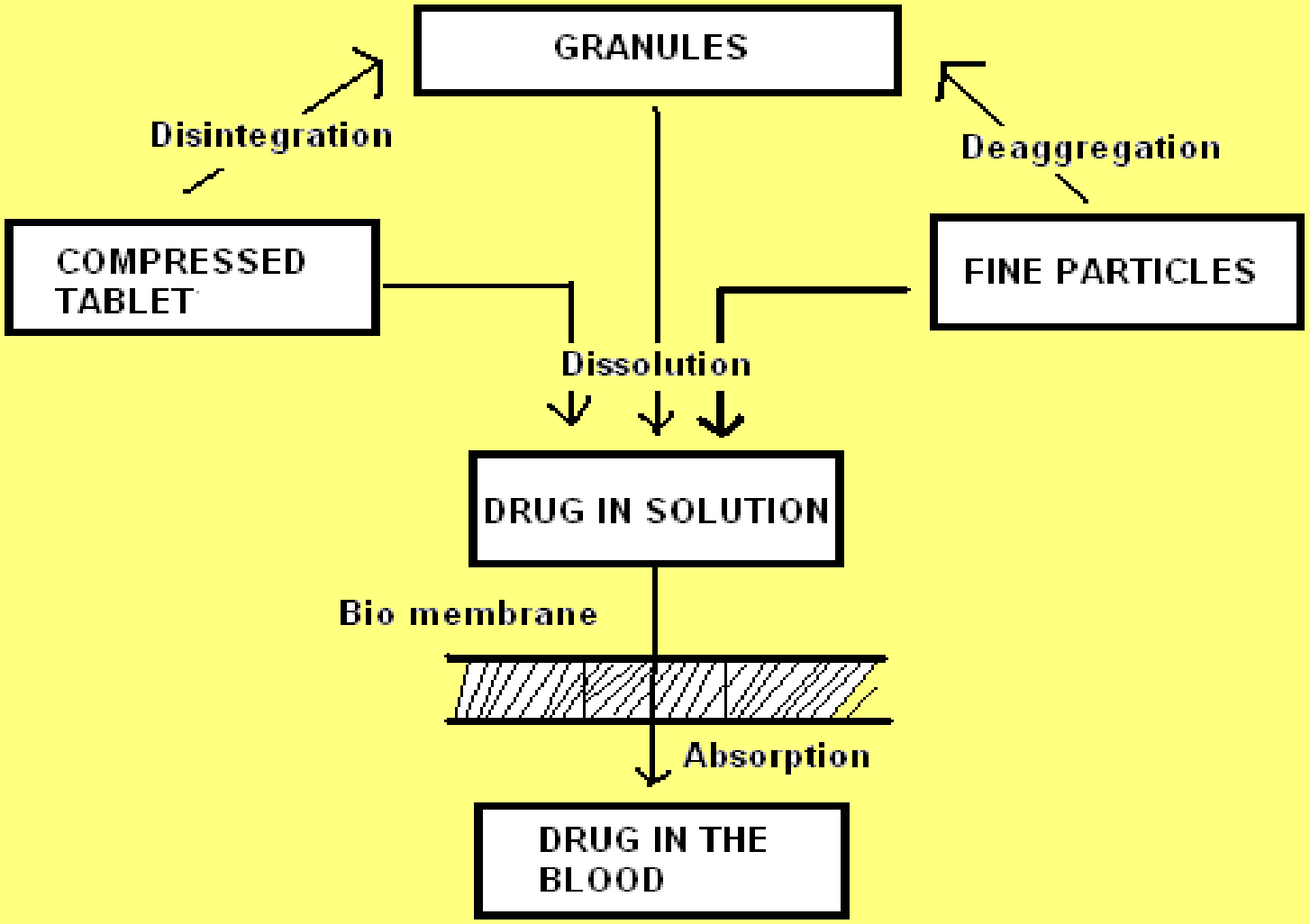
- Compressed Tablets are the most rapid widely used convenience and effective dosage forms.
- The bioavailability problems with tablets arise from the reduction in the effective surface area due to granulation and compression in to a dosage form.

Coated tablets:

- The factors that influence drug release from compressed tablets , the coating acts as another barrier which must first dissolve to give way to disintegration and dissolution of tablet.

two types of coatings are :

- ✓ Film coating.
- ✓ Sugar coating.



sequence of events in the absorption of a drug from tablet dosage form

Enteric coated tablets:

- Enteric coatings tablets have great potentials in creating bioavailability problems , because the coat dissolves only in the alkaline Ph of the intestine and it may take as long as 2 to 4 hours for such a tablet to empty from the stomach in to the intestine depending up on the meals and GI motility.

Product age and storage conditions:

- A number of changes, especially in the physic-chemical properties of a drug in dosage form, can result due to ageing and alterations n storage conditions which can adversely affect bioavailability.

- With solution dosage form, precipitation of drug due to altered solubility, especially due to conversion of metastable in to poorly soluble, stable polymorph can occur during shelf-life of the product.

- In case of solid dosage forms, especially tablets, disintegration and dissolution rates are greatly affected due to aging and storage conditions.

Parenterals:

- Oral route is the most preferred route for drug administration, however certain situations demand delivery of drugs through parental routes.

- For quick restoration of fluid and electrolyte imbalances in patients suffering from severe dehydration (or) electrolyte depletion for a variety of reasons such as severe diarrhea and vomiting electrolyte solutions are administered.

- To achieve adequate concentrations of the drug in to diseased antibiotics tissues.

- e.g.: Intraventricular injection of amino glycoside antibiotics.

ABSORPTION OF DRUGS FROM NON PER OS EXTRAVASCULAR ROUTES

ROUTE	ABSORPTION MECHANISMS	DRUGS DELIVERED
Buccal /Sublingual	Passive diffusion, Carrier mediated transport	Nitrites and Nitrates, Antianginals, Nifedipine, Morphine, Fenoterol
Rectal	Passive diffusion	Aspirin, Paracetmol, Theophylline, Few Barbiturates.
Transdermal	Passive diffusion	Nitroglycerine, Lidocaine, Scopolamine, Testosterone, Betamethasone
Intramuscular	Passive diffusion Endocytosis, Pore transport.	Phenytoin, Digoxin, Several Steroids and Antibiotics and many other drugs.

ROUTE	ABSORPTION MECHANISMS	DRUGS DELIVERED
Subcutaneous	Passive diffusion	Insulin, heparin, C.R. Implants.
Inhalation	Passive diffusion, pore transport	Salbuterol, cromolyn, Beclomethasone
Intranasal	Passive diffusion, pore transport.	Phenylpropanolamine, Antihistamines
Intraocular	Passive diffusion	Atropine, pilocarpine, Adrénaline, Antibiotics
Vaginal	Passive diffusion	Steroidal drugs and Contraceptives, Metronidazole

THANK YOU