FACTORS AFFECTING BIOAVAILABILITY

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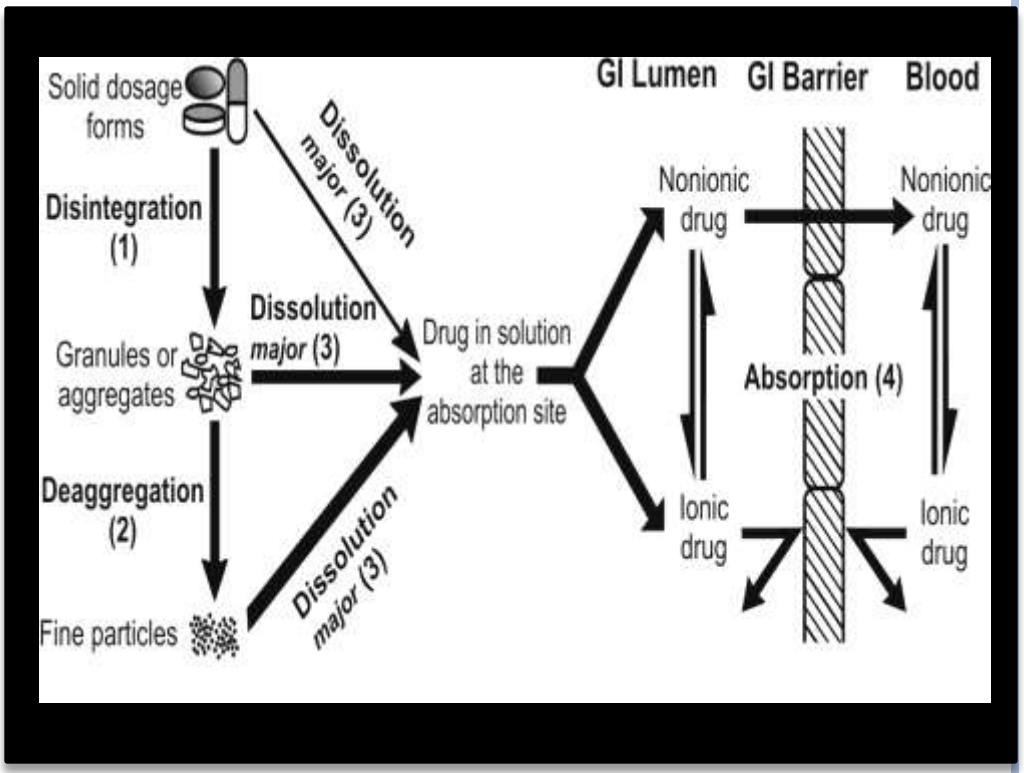
Biopharmaceutic Considerations in Dosage Form Design

- To achieve the desired therapeutic objective, the drug product must deliver the active drug at an optimal rate and amount.

- By proper biopharmaceutic design, the rate and extent of drug absorption (also called as bioavailability) or the systemic delivery of drug to the body can be varied from rapid and complete absorption to slow and sustained absorption depending upon the desired therapeutic objective.

The process consists of four steps:

- Disintegration of the drug product.
- Deaggregation and subsequent release of the drug.
- Dissolution of the drug in the aqueous fluids at the absorption site.
- Absorption i.e. movement of the dissolved drug through the GI membrane into the systemic circulation and away from the absorption site



FACTORS INFLUENCING BIOAVAILABILITY

- Pharmaceutical factors
  - Physicochemical factors of drug molecules
  - Dosage Form factors
- Patient Related factors

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.Pseudopolymorphism (hydrates/solvates)
5.Salt form of the drug
6.Lipophilicity of the drug
7.pKa of the drug and gastrointestinal pH
8.Drug stability
9.Stereochemical nature of the drug

DOSAGE FORM CHARACTERISTICS AND PHARMACEUTICAL INGREDIENTS (PHARMACO-TECHNICAL FACTORS)

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

PATIENT RELATED FACTORS

Include factors relating to the anatomical, physiological and pathological characteristics of the patient

1. Age
2. Gastric emptying time
3. Intestinal transit time
4. Gastrointestinal pH
5. Disease states
6. Blood flow through the GIT
7. Gastrointestinal contents:
    a. Other drugs
    b. Food
    c. Fluids
    d. Other normal GI contents
8. Presystemic metabolism by:
    a. Luminal enzymes
    b. Gut wall enzymes
    c. Bacterial enzymes
    d. Hepatic enzymes

PHARMACEUTICAL FACTORS

•In order to design a formulation that will deliver the drug in the most bioavailable form, the pharmacist must consider –

- Physicochemical properties of the drug, and
- Type of formulation (e.g. solution, suspension, tablet, etc.), and
- Nature of excipients in the formulation.

PHYSICOCHEMICAL FACTORS AFFECTING DRUG ABSORPTION

DRUG SOLUBILITY AND DISSOLUTION RATE

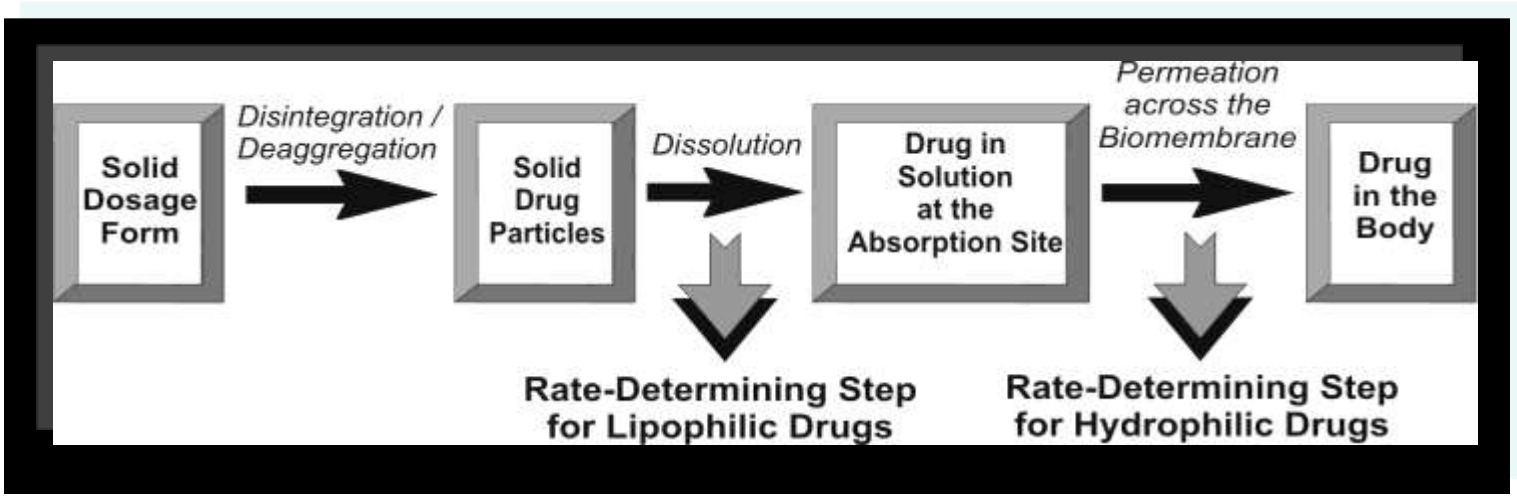
- Except in case of controlled-release formulations, disintegration and deaggregation occur rapidly if it is a well-formulated dosage form.
- Two critical slower rate-determining processes in the absorption of orally administered drugs are:

1. Rate of dissolution
2. Rate of drug permeation through the biomembrane.

- Dissolution is the RDS for hydrophobic, poorly aqueous soluble drugs , absorption of such drugs is often said to be

Dissolution rate-limited.

- If the drug is hydrophilic with high aqueous solubility then dissolution is rapid and RDS in the absorption of such drugs is rate of permeation through the biomembrane.Absorption of such drugs is said to be **Permeation Rate-limited or Transmembrane Rate-limited**



THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM FOR DRUGS

Class	Solubility	Permeability	Absorption Pattern	Rate-Limiting Step in Absorption	Drug Examples
I	High	High	Well absorbed	Gastric emptying	Diltiazem
II	Low	High	Variable	Dissolution	Nifedipine
III	High	Low	Variable	Permeability	Insulin
IV	Low	Low	Poorly absorbed	Case by case	Taxol

- An important prerequisite for the absorption of a drug by all mechanisms except endocytosis is that it must be present in aqueous solution.

- This in turn depends on the drug's aqueous solubility and its dissolution rate.

- Absolute or intrinsic solubility is defined as the maximum amount of solute dissolved in a given solvent under standard conditions of temperature, pressure and pH. It is a static property.

- Dissolution rate is defined as the amount of solid substance that goes into solution per unit time under standard conditions of temperature, pH and solvent composition and constant solid surface area.

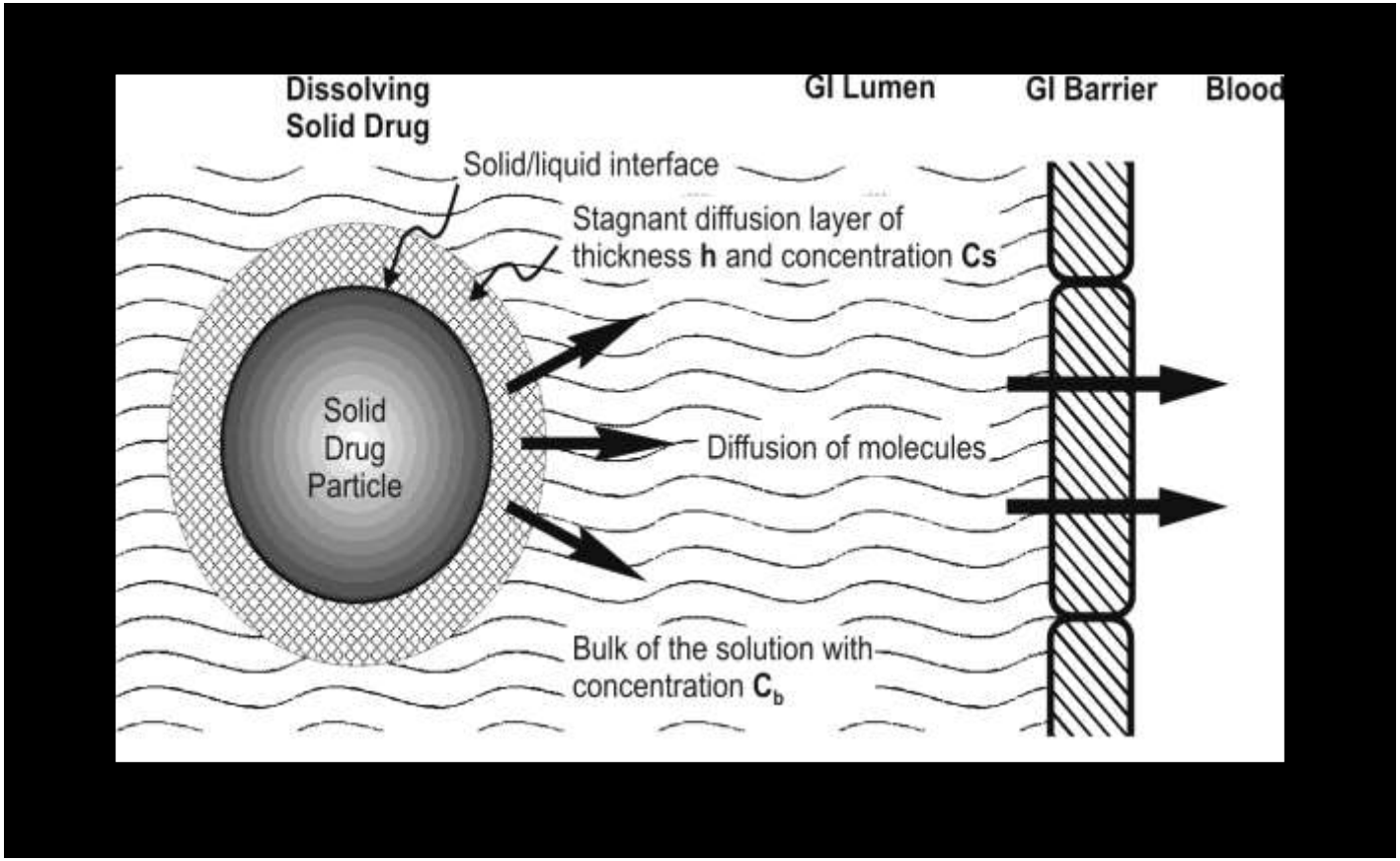
THEORIES OF DRUG DISSOLUTION

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

- Several theories drug dissolution ....

  - ✓ Diffusion layer model/Film theory,
  - ✓ Danckwert's model/Penetration or Surface renewal theory,
  - ✓ Interfacial barrier model/Double-barrier or Limited solvation theory.

DIFFUSION LAYER MODEL/FILM THEORY

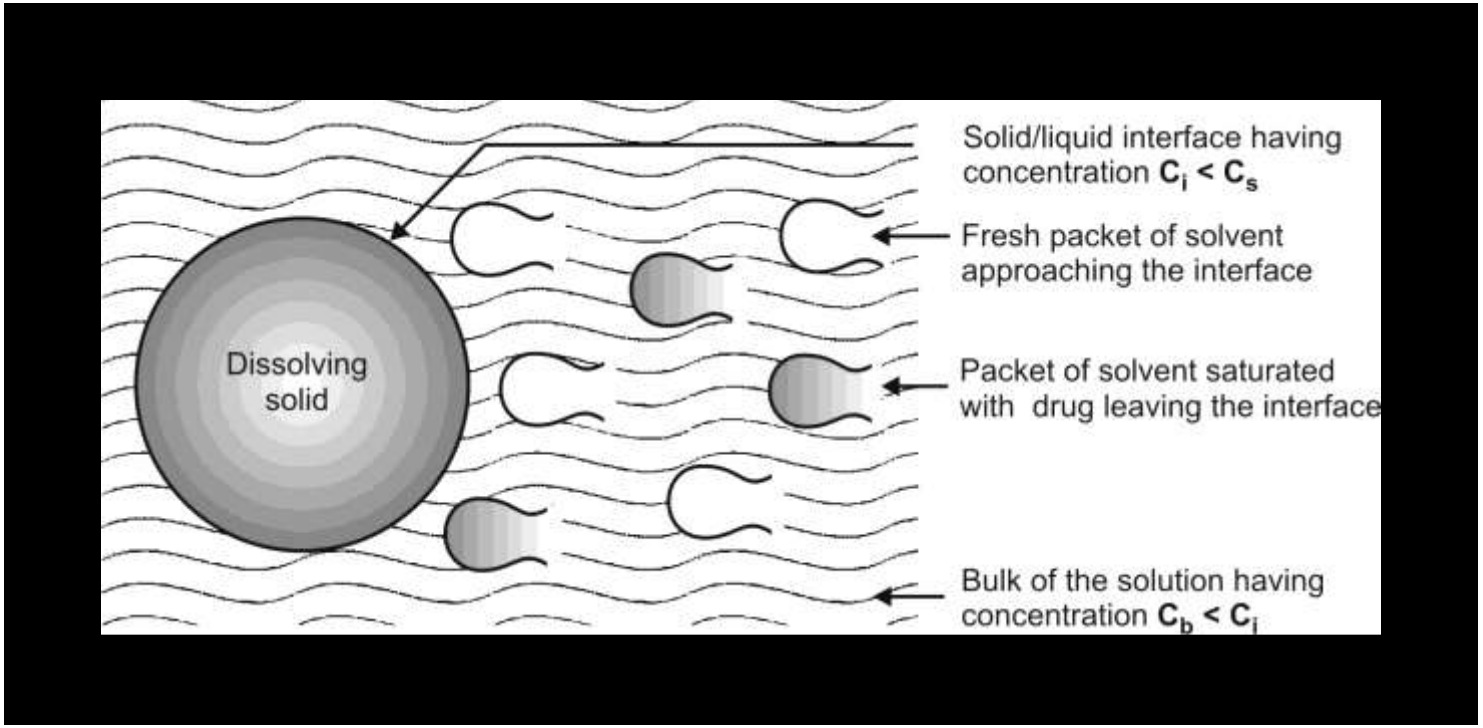


- To obtain good *in vitro-in vivo* dissolution rate correlation, the *in vitro* dissolution must always be carried under sink conditions. This can be achieved in one or more of the following ways:

  - ✓ Bathing the dissolving solid in fresh solvent from time to time.
  - ✓ Increasing the volume of dissolution fluid.
  - ✓ 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—for example, hexane or chloroform.
  - ✓ Adding a water miscible solvent such as alcohol to the dissolution fluid, or
  - ✓ By adding selected adsorbents to remove the dissolved drug.

- The *in vitro* sink conditions are so maintained that C_b is always less than 10% of C_s.

DANCKWERT'S MODEL/PENETRATION OR SURFACE RENEWAL THEORY



INTERFACIAL BARRIER MODEL
(DOUBLE BARRIER OR LIMITED SOLVATION THEORY)

- The diffusion layer model and the Danckwert's model were based on two assumptions:
  - ✓ The rate-determining step that controls dissolution is the mass transport.
  - ✓ Solid-solution equilibrium is achieved at the solid/liquid interface.

- According to the 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.

PARTICLE SIZE AND EFFECTIVE SURFACE AREA OF THE DRUG

- Particle size and surface area of a solid drug are inversely related to each other. Smaller the drug particle, greater the surface area. Two types of surface area of interest can be defined:
  - **Absolute surface area** *which is the total area of solid surface of any particle*
  - **Effective surface area** *which is the area of solid surface exposed to the dissolution medium.*
- However, it is important to note that it is not the absolute surface area but the effective surface area that is proportional to the dissolution rate.
- Greater the effective surface area, more intimate the contact between the solid surface and the aqueous solvent and faster the dissolution.
- But it is only when micronisation reduces the size of particles below 0.1 microns that there is an increase in the intrinsic solubility and dissolution rate of the drug.
- The surface of such small particles has energy higher than the bulk of the solid resulting in an increased interaction with the solvent.

- Micronisation decrease the dose of certain drugs because of increased absorption efficiency—for example, the griseofulvin dose was reduced to half and that of spironolactone was decreased 20 times following micronisation.
- In drugs like aspirin, phenacetin and phenobarbital, micronisation actually results in a decrease in the effective surface area of such powders and thus, a fall in the dissolution rate.

- Three reasons have been suggested for such an outcome —
  - The hydrophobic surface of the drug adsorbs air onto their surface which inhibit their wettability.
  - The particles re-aggregate to form larger particles due to their high surface free energy, which either float on the surface or settle at the bottom of the dissolution medium.
  - Electrically induced agglomeration owing to surface charges prevents intimate contact of the drug with the dissolution medium.

- The absolute surface area of hydrophobic drugs can be converted to their effective surface area by:

  - Use of surfactant as a wetting agent that -
    - Decreases the interfacial tension, and
    - Displaces the adsorbed air with the solvent.

  - Adding hydrophilic diluents such as PEG, PVP, dextrose, etc. which coat the surface of hydrophobic drug particles and render them hydrophilic.

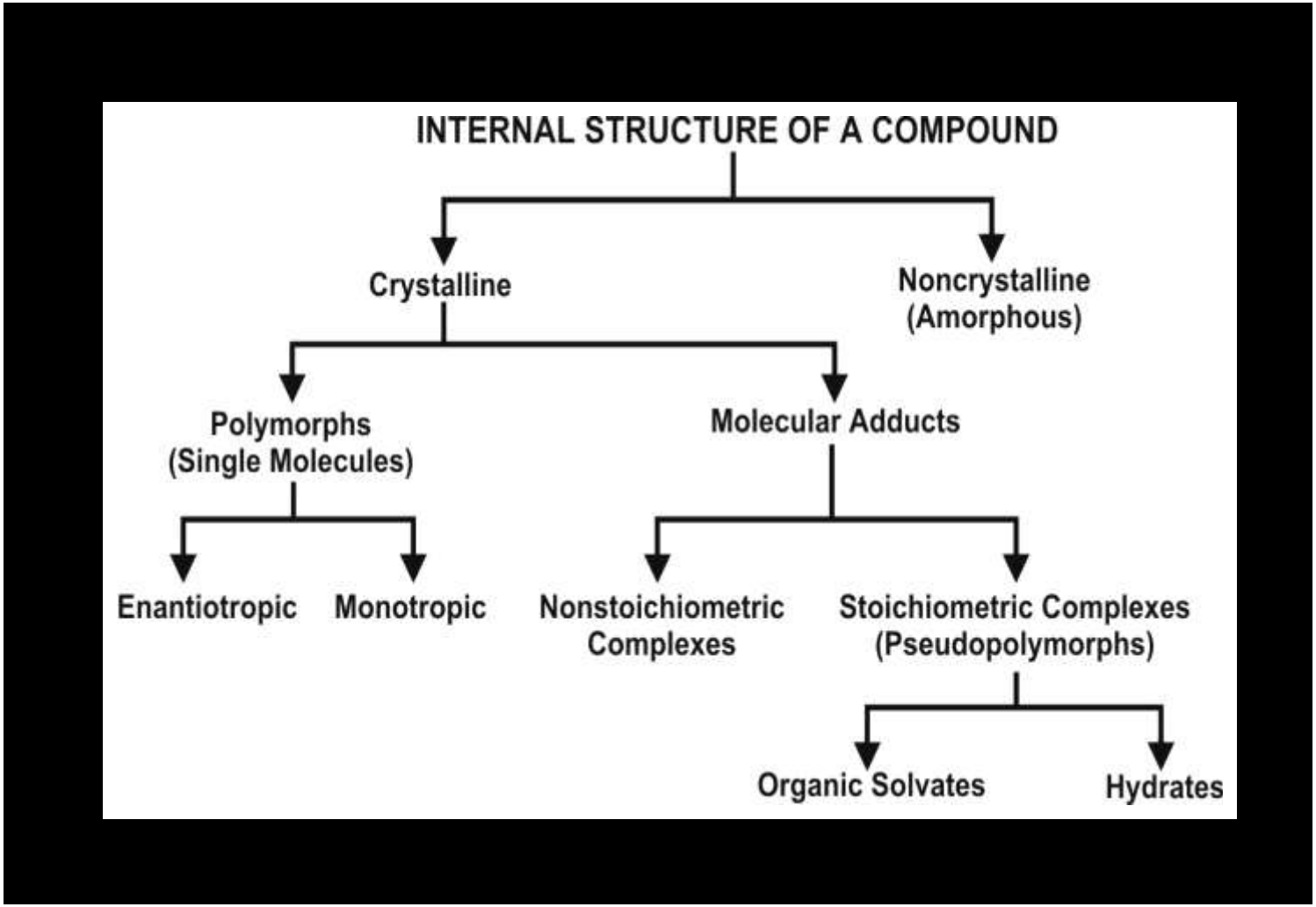
POLYMORPHISM AND AMORPHISM

- When a substance exists in more than one crystalline form, the different forms are designated as POLYMORPHS

- The polymorphs differ from each other with respect to their physical properties such as solubility, melting point, density, hardness and compression characteristics.

- They can be prepared by crystallizing the drug from different solvents under diverse conditions.

- The existence of the polymorphs can be determined by using techniques such as optical crystallography, X-ray diffraction, differential scanning calorimetry, etc.


INTERNAL STRUCTURE OF A COMPOUND
Crystalline
Noncrystalline
(Amorphous)
Polymorphs
(Single Molecules)
Molecular Adducts
Enantiotropic
Monotropic
Nonstoichiometric
Complexes
Stoichiometric Complexes
(Pseudopolymorphs)
Organic Solvates
Hydrates

DRUG pK_a AND LIPOPHILICITY AND GI pH

[pH PARTITION HYPOTHESIS]

- The pH partition theory explains in simple terms, the process of drug absorption from the GIT and its distribution across all biological membranes.

- 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 the unionised drug (a function of drug Ko/w).
  - The pH at the absorption site.

- If the pH on either side on the membrane is different, then the compartment whose pH favours greater ionisation of the drug will contain greater amount of drug, and only the unionised or undissociated fraction of drug, if sufficiently lipid soluble, can permeate the membrane passively until the concentration of unionised drug on either side of the membrane becomes equal i.e. until equilibrium is attained.

- pH partition hypothesis was based on the *assumptions* that:

  - The GIT is a simple lipoidal barrier to the transport of drug.
  - Larger the fraction of unionised drug, faster the absorption.
  - Greater the lipophilicity (Ko/w) of the unionised drug, better the absorption.

DRUG pKa & GASTROINTESTINAL pH

- The amount of drug that exists in unionised form is a function of dissociation constant (pKa) of the drug and pH of the fluid at the absorption site.

- It is customary to express the dissociation constants of both acidic and basic drugs by pKa values.

- The lower the pKa of an acidic drug, stronger the acid i.e. greater the proportion of ionised form at a particular pH. Higher the pKa of a basic drug, stronger the base.

- The relative amount of ionised and unionised drug in solution at a particular pH and the percent of drug ionised at this pH can be determined by *Henderson-Hasselbach equations*:

DRUGS	pK_a	PH/SITE OF ABSORPTION
VERY WEAK ACIDS (pKa > 8.0)		
PENTOBARBITAL	8.1	UNIONISED AT ALL PH VALUES; ABSORBED ALONG THE ENTIRE LENGTH OF GIT
HEXOBARBITAL	8.2	
PHENYTOIN	8.2	
ETHOSUXIMIDE	9.3	
MODERATELY WEAK ACIDS (pKa 2.5 to 7.5)		
CLOXACILLIN	2.7	UNIONISED IN GASTRIC PH AND IONISED IN INTESTINAL PH; BETTER ABSORBED FROM STOMACH
ASPIRIN	3.5	
IBUPROFEN	4.4	
PHENYLBUTAZONE	4.5	
STRONGER ACIDS (pKa < 2.5)		
DISODIUM CROMOGLYCATE	2.0	IONISED AT ALL PH VALUES; POORLY ABSORBED FROM GIT.
VERY WEAK BASES (pKa < 5.0)		
THEOPHYLLINE	0.7	UNIONISED AT ALL PH VALUES; ABSORBED ALONG THE ENTIRE LENGTH OF GIT
CAFFEINE	0.8	
OXAZEPAM	1.7	
DIAZEPAM	3.7	
MODERATELY WEAK BASES (pKa 5 to 11.0)		
RESERPINE	6.6	IONISED AT GASTRIC PH, RELATIVELY UNIONISED AT INTESTINAL PH; BETTER ABSORBED FROM INTESTINE
HEROIN	7.8	
CODEINE	8.2	
AMITRIPTYLINE	9.4	
STRONGER BASES (pKa > 11.0)		
MECAMYLAMINE	11.2	IONISED AT ALL PH VALUES; POORLY ABSORBED FROM GIT
GUANETHIDINE	11.7	

- Besides pKa, total aqueous solubility, S_T, of an ionisable drug is an important factor in the passive absorption of drugs.

- It is defined as the sum of concentration of ionised drug in solution and concentration of unionised drug in solution.

- The solubility of unionised form of the drug is known as the intrinsic solubility of the drug.

- If Sa is the intrinsic solubility of weakly acidic drugs and Sb that of weakly basic drugs, then –

For acidic drugs,

- $St = S_a [1 + 10(pH - pKa)]$

For basic drugs,

- $St = S_b [1 + 10(pKa - pH)]$

- *For weakly acidic drugs*,
  - When pH > pKa, ST >> Sa because ionisation of drug increases tremendously.
  - When pH = pKa, ST = 2Sa, because the drug is 50% ionised.
  - When pH < pKa, ST ≅ Sa since the drug exists predominantly in unionised form.
- *For weakly basic drugs,*
  - When pH > pKa, ST ≅ Sb since the drug exists predominantly in unionised form.
  - When pH = pKa, ST = 2Sb, because the drug is 50% ionised.
  - When pH < pKa, ST >> Sb because ionisation of drug increases tremendously.

LIPOPHILICITY AND DRUG ABSORPTION

- It is the pKa of a drug that determines the degree of ionisation at a particular pH and that only the unionised drug, if sufficiently lipid soluble, is absorbed into the systemic circulation. .

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

- The lipid solubility of a drug is measured by a parameter called as *log P* where P is oil/water partition coefficient (*Ko/w* or simply *P*) value of the drug.

- This value is a measure of the degree of distribution of drug between lipophilic solvents such as n-octanol and an aqueous phase (water or a suitable buffer).

LIMITATIONS OF pH-PARTITION HYPOTHESIS

- The pH-partition hypothesis over-simplified the otherwise complicated process of drug absorption and therefore has its own limitations.

- Some of the deviations from the theory are:

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

DRUG PERMEABILITY AND ABSORPTION

- Most orally administered drugs enter the systemic circulation by passive diffusion and their absorption is expressed mathematically by equation –

$$M = P_{eff} A C_{app} t_{res}$$

where,

- M = amount of drug absorbed
- P_{eff} = effective membrane permeability
- A = surface area available for absorption
- C_{app} =apparent luminal drug concentration
- t_{res} = residence time of drug in GI lumen.

DOSAGE FORM (PHARMACO-TECHNICAL) FACTORS AFFECTING DRUG ABSORPTION

DISINTEGRATION TIME

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

- *In vitro* disintegration test is by no means a guarantee of drug's bioavailability because if the disintegrated drug particles do not dissolve, absorption is not possible

- However, if a solid dosage form does not conform to the DT, it portends bioavailability problems because the subsequent process of dissolution will be much slower and absorption may be insufficient.

- Coated tablets, especially sugar coated ones have long DT.

- DT of a tablet is directly related to the amount of binder present and the compression force (hardness) of a tablet.
- A harder tablet with large amount of binder has a long DT.
- Disintegration can be aided by incorporating disintegrants in suitable amounts during formulation.
- After disintegration of a solid dosage form into granules, the granules must deaggregate into fine particles, as dissolution from such tiny particles is faster than that from granules.

MANUFACTURING/PROCESSING VARIABLES

- Drug dissolution is the single most important factor in the absorption of drugs, especially from the most widely used conventional solid dosage forms, tablets and capsules.

- The dosage form related factors that influence dissolution and hence absorption of a drug from such formulations are:

  1. Excipients (formulation ingredients apart from the active principles)
  2. Manufacturing processes.

- Several manufacturing processes influence drug dissolution from solid dosage forms. Processes of such importance in the manufacture of tablets are:

  - 1. Method of granulation, and
  - 2. Compression force.

METHOD OF GRANULATION

- The wet granulation process is the most conventional technique in the manufacture of tablets and was once thought to yield tablets that dissolve faster than those made by other granulation methods.

- The limitations of this method include—
  - Formation of crystal bridge by the presence of liquid,
  - The liquid may act as a medium for affecting chemical reactions such as hydrolysis, and
  - The drying step may harm the thermolabile drugs.

- Involvement of large number of steps each of which can influence drug dissolution—method and duration of blending, method, time and temperature of drying, etc.

- The method of direct compression has been utilized to yield tablets that dissolve at a faster rate.

- One of the more recent methods that have resulted in superior product is **Agglomerative Phase of Communition (APOC).**

- The process involves grinding of drugs in a ball mill for time long enough to affect spontaneous agglomeration.

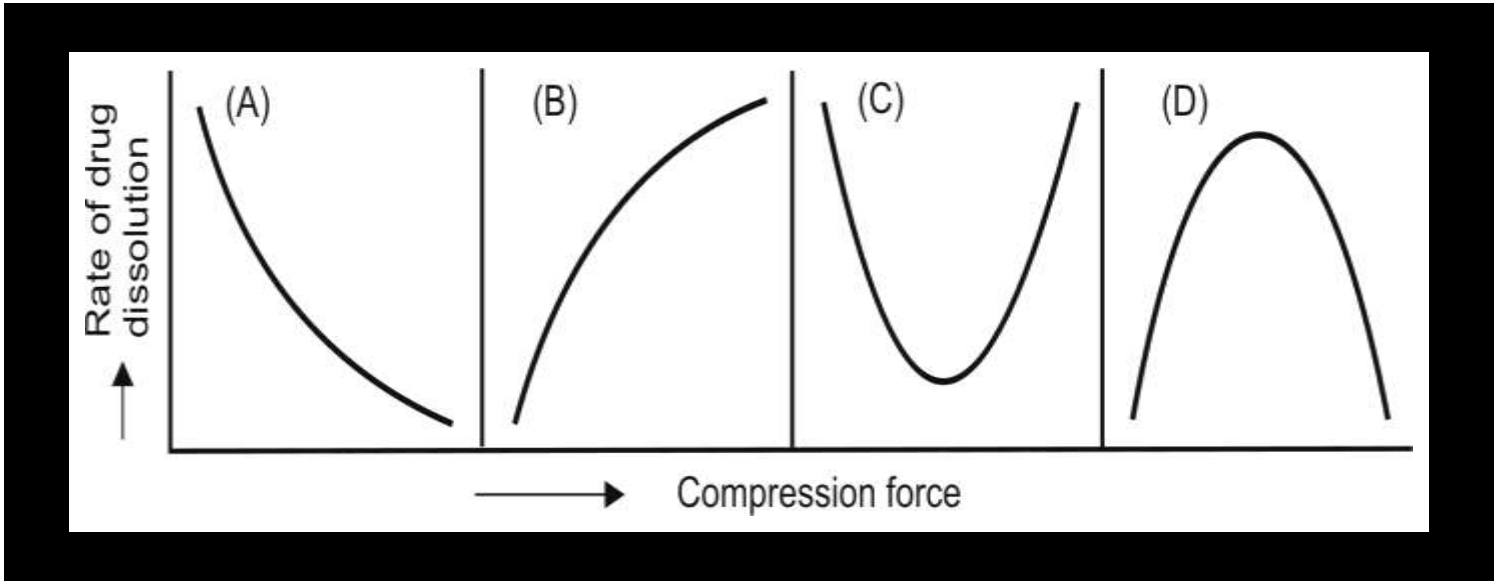
- The tablets so produced were stronger and showed rapid rate of dissolution in comparison to tablets made by other methods.

- The reason attributed to it was an increase in the internal surface area of the granules prepared by **APOC** method.

COMPRESSION FORCE

- The compression force employed in tabletting process influence density, porosity, hardness, disintegration time and dissolution of tablets.

- The curve obtained by plotting compression force versus rate of dissolution



PHARMACEUTICAL INGREDIENTS/EXCIPIENTS (FORMULATION FACTORS)

- A drug is rarely administered in its original form. Almost always, a convenient dosage form to be administered by a suitable route is prepared.

- Such a formulation contains a number of excipients (*non-drug components of a formulation*)

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

- Despite their inertness and utility in the dosage form, excipients can influence absorption of drugs.

- The more the number of excipients in a dosage form, the more complex it is and greater the potential for absorption and bioavailability problems.

- Commonly used excipients in various dosage forms are vehicles, diluents (fillers), binders and granulating agents, disintegrants, lubricants, coatings, suspending agents, emulsifiers, surfactants, buffers, complexing agents, colorants, sweeteners, crystal growth inhibitors, etc.

VEHICLE

- Vehicle or solvent system is the major component of liquid orals and parenterals.

- The 3 categories of vehicles in use are—
  - Aqueous vehicles (water, syrup, etc.),
  - Nonaqueous water miscible vehicles (propylene glycol, glycerol, sorbitol) and
  - Nonaqueous water immiscible vehicles (vegetable oils).

- Bioavailability of a drug from vehicles depends to a large extent on its miscibility with biological fluids.

- Aqueous and water miscible vehicles are miscible with the body fluids and drugs from them are rapidly absorbed.

- Drug is more soluble in water miscible vehicles like propylene glycol (serving as a *co-solvent*) and show better bioavailability.

- Solubilisers such as polysorbate 80 are sometimes used to promote solubility of a drug in aqueous vehicles.

- In case of water immiscible vehicles, the rate of drug absorption depends upon it's partitioning from the oil phase to the aqueous body fluids, which could be a rate-limiting step.

- Viscosity of the vehicles is another factor in the absorption of drugs. Diffusion into the bulk of GI fluids and thus absorption of a drug from a viscous vehicle may be slower.

DILUENTS (FILLERS)

- Diluents are commonly added to tablet (and capsule) formulations if the required dose is inadequate to produce the necessary bulk.

- A diluent may be organic or inorganic. Among organic diluents, carbohydrates are very widely used—for example, starch, lactose, microcrystalline cellulose, etc.

- These hydrophilic powders are very useful in promoting the dissolution of poorly water-soluble, hydrophobic drugs like spironolactone and triamterene by forming a coat onto the hydrophobic surface of drug particles and rendering them hydrophilic.

BINDERS AND GRANULATING AGENTS

- These 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 (natural, semisynthetic and synthetic) like starch, cellulose derivatives, acacia, PVP, etc.

- Others include gelatin and sugar solution. In general, like fillers, the hydrophilic (aqueous) binders show better dissolution profile with poorly wettable drugs like phenacetin by imparting hydrophilic properties to the granule surface.

DISINTEGRANTS

- These agents overcome the cohesive strength of tablet and break them up on contact with water which is an important prerequisite to tablet dissolution.

- Almost all the disintegrants are hydrophilic in nature.

- A decrease in the amount of disintegrant can significantly lower bioavailability.

- Adsorbing disintegrants like bentonite and veegum should be avoided with low dose drugs like digoxin, alkaloids and steroids since a large amount of dose is permanently adsorbed and only a fraction is available for absorption

- Microcrystalline cellulose is a very good disintegrant (and a binder too) but at high compression forces, it may retard drug dissolution.

LUBRICANTS/ANTIFRICTIONAL AGENTS

- These agents are added to tablet formulations to aid 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 (several metallic stearates and waxes) and known to inhibit wettability, penetration of water into tablet and their disintegration and dissolution.

- This is because the disintegrant gets coated with the lubricant if blended simultaneously which however can be prevented by adding the lubricant in the final stage.

- The best alternative is use of soluble lubricants like SLS and carbowaxes which promote drug dissolution.

COATINGS

- In general, the deleterious effect of various coatings on drug dissolution from a tablet dosage form is in the following order……

Enteric coat > Sugar coat > Non-enteric film coat.

- The dissolution profile of certain coating materials change on aging

e.g. shellac coated tablets, on prolonged storage, dissolve more slowly in the intestine. This can, however, be prevented by incorporating little PVP in the coating formulation.

SUSPENDING AGENTS/VISCOSITY IMPARTERS

- Popular suspending agents are hydrophilic polymers like vegetable gums (acacia, tragacanth, etc.), semisynthetic gums (CMC, MC) and synthetic gums which primarily stabilize the solid drug particles by reducing their rate of settling through an increase in the viscosity of the medium.

- These agents and some sugars are also used as viscosity imparters to affect palatability and pourability of solution dosage forms.

- Such agents can influence drug absorption in several ways. The macromolecular gums often form unabsorbable complexes with drugs—for example, sodium CMC forms a poorly soluble complex with amphetamine.

- An increase in viscosity by these agents acts as a mechanical barrier to the diffusion of drug from the dosage form into the bulk of GI fluids and from GI fluids to the mucosal lining by forming a viscid layer on the GI mucosa. They also retard the GI transit of drugs.

SURFACTANTS

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

- Their influence on drug absorption is very complex. They may enhance or retard drug absorption either by interacting with the drug or the membrane or both.

- Mechanisms involved in the increased absorption of drug by use of surfactants include:

    1. Promotion of wetting (through increase in effective surface area) and dissolution of drugs e.g. polysorbate 80 with phenacetin.

    2. Better membrane contact of the drug for absorption.

    3. Enhanced membrane permeability of the drug.

BUFFERS

- Buffers are sometimes useful in creating the right atmosphere for drug dissolution as was observed for buffered aspirin tablets.

- However, certain buffer systems containing potassium cations inhibit the drug absorption as seen with vitamin B2 and sulphanilamide.

The reason attributed to it was the uptake of fluids by the intestinal epithelial cells due to which the effective drug concentration in the tissue is reduced and the absorption rate is decreased.

- Inhibitory effect of the various buffer cations on the drug transfer rate is in the following order:

$K^+ > NH_4^+ > Li^+ > Na^+$

- Hence, the buffer system for a salt of a drug should contain the same cation as the drug salt and introduce no additional cations.

COMPLEXING AGENTS

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

- A complexed drug may have altered stability, solubility, molecular size, partition coefficient and diffusion coefficient

- Basically, such complexes are pharmacologically inert and must dissociate either at the absorption site or following absorption into the systemic circulation.

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

  - Enhanced dissolution through formation of a soluble complex e.g. ergotamine tartarate-caffeine complex and hydroquinone-digoxin complex.

  - Enhanced lipophilicity for better membrane permeability e.g. caffeine-PABA complex.

  - Enhanced membrane permeability e.g. enhanced GI absorption of heparin (normally not absorbed from the GIT) in presence of EDTA which chelates calcium and magnesium ions of the membrane.

- Complexation can be deleterious to drug absorption due to formation of poorly soluble or poorly absorbable complex e.g. complexation of tetracycline with divalent and trivalent cations like calcium (milk, antacids), iron (haematinics), magnesium (antacids) and aluminium (antacids).

- *Reasons for poor bioavailability of some complexes* are –
  - Failure to dissociate at the absorption site, and
  - Large molecular size of the complex that cannot diffuse through the cell membrane—for example, drug-protein complex.

COLORANTS

- Even a very low concentration of water-soluble dye can have an inhibitory effect on dissolution rate of several crystalline drugs.

- The dye molecules get adsorbed onto the crystal faces and inhibit drug dissolution—for example, brilliant blue retards dissolution of sulphathiazole.

- Dyes have also been found to inhibit micellar solubilisation effect of bile acids which may impair the absorption of hydrophobic drugs like steroids.

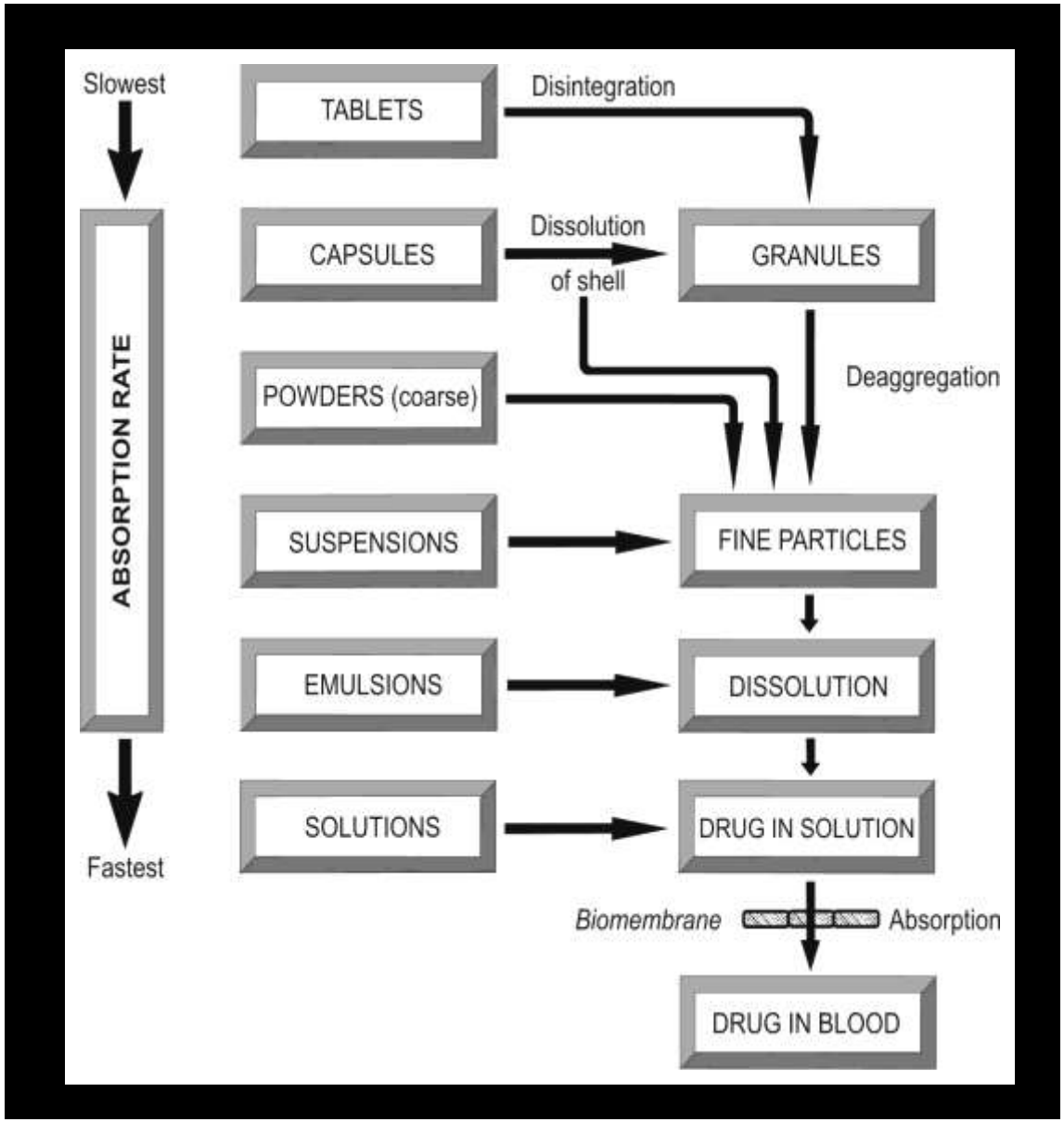
- Cationic dyes are more reactive than the anionic ones due to their greater power for adsorption on primary particles.

PRECIPITATION/CRYSTAL GROWTH INHIBITORS

- When a significant increase in *free drug concentration* above saturation or equilibrium solubility occurs, it results in supersaturation which in turn lead to drug precipitation or crystallization.

- Precipitation or crystal growth inhibitors such as PVP, HPMC, PEG, PVA (polyvinylalcohol) and similar such hydrophilic polymers prevent or prolong supersaturation thus preventing precipitation or crystallization by –
  - Increasing the viscosity of vehicle.
  - Prevent conversion of a high-energy metastable polymorph into stable, less soluble polymorph.
  - Adsorbing on the faces of crystal and reduce crystal growth.

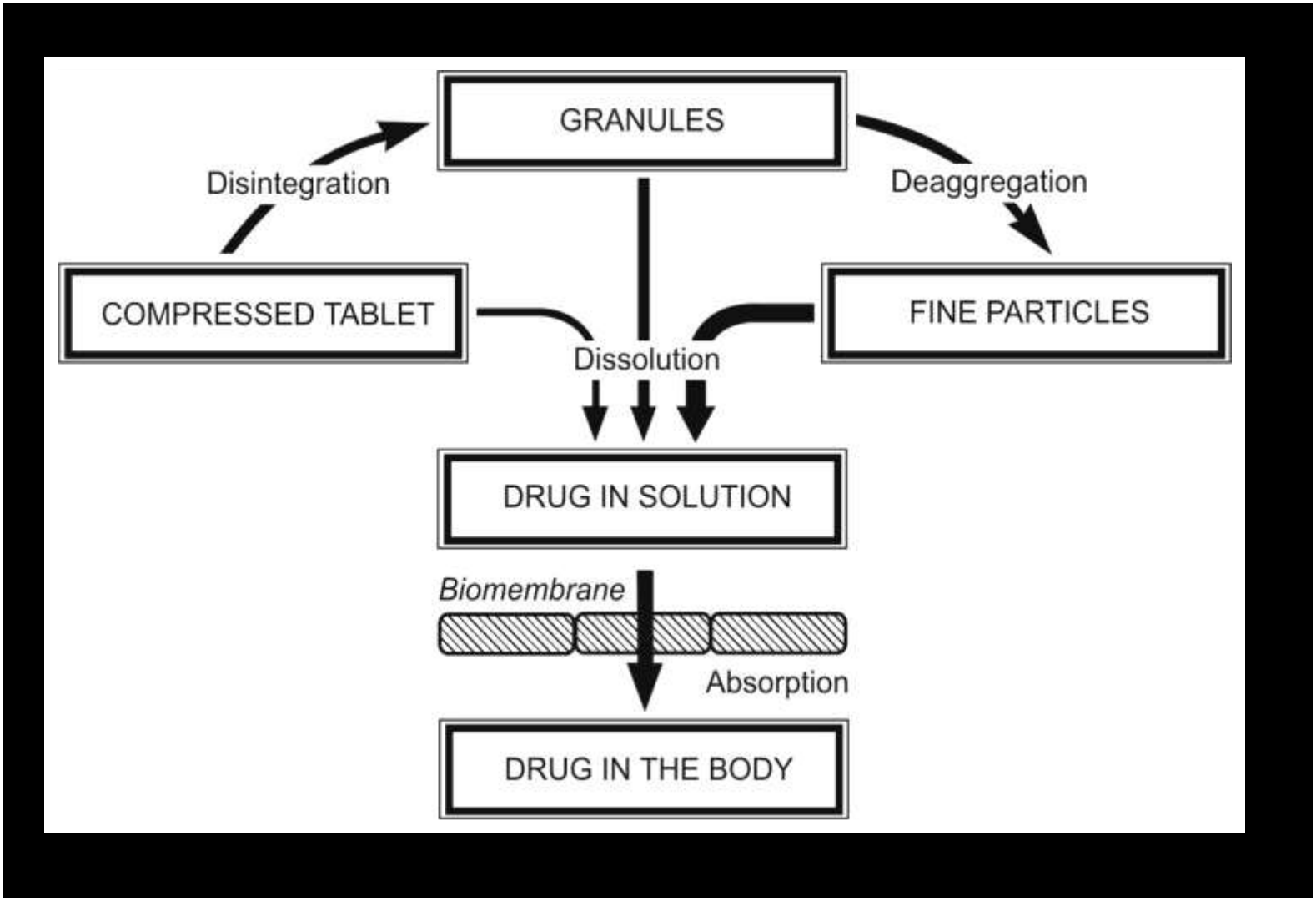
NATURE AND TYPE OF DOSAGE FORM



- The bioavailability of a drug from various dosage forms decreases in the following order:

Solutions > Emulsions > Suspensions > Capsules > Tablets > Coated Tablets > Enteric Coated Tablets > Sustained Release Products.

SEQUENCE OF EVENTS
IN THE
ABSORPTION OF A DRUG FROM TABLET DOSAGE FORM



ENHANCEMENT OF BIOAVAILABILITY

- As far as the definition of bioavailability is concerned, a drug with poor bioavailability is the one with

  - *Poor aqueous solubility* and/or *slow dissolution rate* in biological fluids.

  - *Poor permeability* through the biomembrane owing to inadequate partition coefficient or lipophilicity or large molecular size such as that of protein or peptide drugs such as insulin.

- Both solubility as well as permeability of a drug depends upon its physicochemical characteristics

CLASS	SOLUBILITY	PERMEABILITY	ABSORPTION PATTERN	EXAMPLES	CHALLENGES IN DRUG DELIVERY
I	High	High	Well absorbed	Diltiazem Propranolol Metoprolol	No major challenges for immediate release forms but CR forms need to limit drug release or dissolution since absorption of released drug is rapid.
II	Low	High	Variable	Nifedipine Carbamazepine Naproxen	Formulations are designed to overcome solubility or dissolution problems by various means
III	High	Low	Variable	Insulin Metformin Cimetidine	Approaches are employed to enhance permeability
IV	Low	Low	Poorly absorbed	Taxol Chlorthiazide Furosemide	Combination of strategies used for Class II and Class III drugs are employed to improve both dissolution and permeability.

Class V drugs: are those that are metabolically or chemically unstable thus limiting their bioavailability. The various approaches to overcome these problems are aimed at enhancing their stability by use of methods such as –

- Prodrug design.
- Enteric coating (protection from stomach acid).
- Enzyme inhibition or lymphatic delivery (to prevent presystemic metabolism).
- Lipid technologies.

- ***Class I drugs (high solubility/high permeability)*** are well absorbed orally since they have neither solubility nor permeability limitation.

- ***Class II drugs (low solubility/high permeability)*** show variable absorption owing to solubility limitation.

- ***Class III drugs (high solubility/low permeability)*** also show variable absorption owing to permeability limitation.

- ***Class IV drugs (low solubility/low permeability)*** are poorly absorbed orally owing to both solubility and permeability limitations.

- ***Class V drugs*** – are the ones that do not come under the purview of BCS classification but includes drugs whose absorption is limited owing to their poor stability in GI milieu –
  - Gastric instability (omeprazole).
  - Complexation in GI lumen.
  - First pass metabolism – by intestinal enzymes (peptide drugs), hepatic enzymes, microbial enzymes, etc.

SOLUBILITY DETERMINATION

Methods for determining drug solubility are –

- pH-solubility profile of test drug in aqueous media with a pH range of 1 to 7.5.
- Shake-flask or titration method.

PERMEABILITY DETERMINATION

- *Determination of extent of absorption in humans*:
  - ✓ Mass-balance pharmacokinetic studies.
  - ✓ Absolute bioavailability studies.
- *Intestinal permeability methods*:
  - ✓ *In vivo* intestinal perfusions studies in humans.
  - ✓ *In vivo* or *in situ* intestinal perfusion studies in animals.
  - ✓ *In vitro* permeation experiments with excised human or animal intestinal tissue.
  - ✓ *In vitro* permeation experiments across epithelial cell monolayers.

DISSOLUTION DETERMINATION

Methods for determining drug product dissolution are …

- USP apparatus I (basket) at 100 rpm or USP apparatus II (paddle) at 50 RPM.

- Dissolution media (900 ml): 0.1 N HCl or simulated gastric fluid, pH 4.5 buffer, and pH 6.8 buffer or simulated intestinal fluid.

- Compare dissolution profiles of test and reference products using a similarity factor (*f2*).

THREE CONCEPTUAL APPROACHES IN OVERCOMING THE BIOAVAILABILITY PROBLEMS OF DRUGS ARE

1. The Pharmaceutical Approach

- Involves modification of formulation, manufacturing process or the physicochemical properties of the drug without changing the chemical structure.

2.The Pharmacokinetic Approach

- The pharmacokinetics of the drug is altered by modifying its chemical structure.
- This approach is further divided into two categories –
  - Development of new chemical entity (NCE) with desirable features
  - Prodrug design.

3. The Biological Approach

whereby the route of drug administration may be changed such as changing from oral to parenteral route.

BIOAVAILABILITY ENHANCEMENT THROUGH ENHANCEMENT OF DRUG SOLUBILITY OR DISSOLUTION RATE

- Micronization
- Nanonisation
- Supercritical Fluid Recrystallization
- Use of Surfactants
- Use of Salt Forms
- Use of Precipitation Inhibitors
- Alteration of pH of the Drug Microenvironment
- Use of Amorphs, Anhydrates, Solvates and Metastable Polymorphs
- Solvent Deposition
- Precipitation
- Selective Adsorption on Insoluble Carriers
- Solid Solutions
    - Use of solid solutions,
    - Use of eutectic mixtures, and
    - Use of solid dispersions.
- Molecular Encapsulation with Cyclodextrins

MICRONIZATION

- The process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of air attrition methods (fluid energy or jet mill).

- The process is also called as ***micro-milling***.

- Examples of drugs whose bioavailability have been increased by micronization include ….
  - **Griseofulvin**
  - **several Steroidal drugs**
  - **Sulpha drugs.**

NANONISATION

- It's a process whereby the drug powder is converted to nanocrystals of sizes 200 - 600 nm,

  e.g. Amphotericin B.

- The main production technologies currently in use to produce drug nanocrystals yield as a product a dispersion of drug nanocrystals in a liquid, typically water **(*Nanosuspension*)**

- There are three basic technologies currently in use to prepare nanoparticles:
  - Pearl milling
  - Homogenisation in water (wet milling as in a colloid mill)
  - Homogenisation in non-aqueous media or in water with water-miscible liquids.

SUPERCRITICAL FLUID RECRYSTALLIZATION

- Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction *via* supercritical fluid (SCF) processes.

- Supercritical fluids (e.g. carbon dioxide) are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas.

- At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power.

- Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle sizes.

USE OF SURFACTANTS

- Surfactants are very useful as absorption enhancers and enhance both dissolution rate as well as permeability of drug.

- They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles.

- They are generally used in concentration below their critical micelle concentration (CMC) values since above CMC, the drug entrapped in the micelle structure fails to partition in the dissolution fluid.

- Nonionic surfactants like polysorbates are widely used.

- Examples of drugs whose bioavailability have been increased by use of surfactants in the formulation include steroids like **Spironolactone.**

USE OF SALT FORMS

- Salts have improved solubility and dissolution characteristics in comparison to the original drug.

- It is generally accepted that a minimum difference of 3 units between the pKa value of the group and that of its counterion is required to form stable salts.

- Alkali metal salts of acidic drugs like penicillins and strong acid salts of basic drugs like atropine are more water-soluble than the parent drug.

- Factors that influence salt selection are physical and chemical properties of the salt, safety of counterion, therapeutic indications and route of administration.

LIMITATIONS OF SALT FORMATION TECHNIQUE

- It is not feasible to form salts of neutral compounds.
- It may be difficult to form salts of very weak bases or acids.
- The salt may be hygroscopic, exhibit polymorphism or has poor processing characteristics.
- Conversion of salt to free acid or base form of the drug on surface of solid dosage form that prevents or retards drug release.
- Precipitation of unionised drug in the GI milieu that has poor solubility.

USE OF PRECIPITATION INHIBITORS

- A significant increase in free drug concentration above equilibrium solubility results in supersaturation, which can lead to drug precipitation or crystallization.

- This can be prevented by use of inert polymers such HPMC, PVP, PVA, PEG, etc. which act by one or more of the following mechanisms -
  - Increase the viscosity of crystallization medium thereby reducing the crystallization rate of drugs.
  - Provide a steric barrier to drug molecules and inhibit crystallization through specific intermolecular interactions on growing crystal surfaces.
  - Adsorb onto faces of host crystals, reduce the crystal growth rate of the host and produce smaller crystals.

ALTERATION OF pH OF THE DRUG MICROENVIRONMENT

✓ This can be achieved in two ways—*in situ* salt formation, and addition of buffers to the formulation e.g. buffered aspirin tablets.

USE OF AMORPHS, ANHYDRATES, SOLVATES & METASTABLE POLYMORPHS

✓ Depending upon the internal structure of the solid drug, selection of proper form of drug with greater solubility is important.

✓In general, amorphs are more soluble than metastable polymorphs, anhydrates are more soluble than hydrates and solvates are more soluble than non-solvates.

SOLVENT DEPOSITION

In this method, the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose by evaporation of solvent.

PRECIPITATION

- In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nanosize particles.

- The product so prepared is also called as ***hydrosol***.

SELECTIVE ADSORPTION ON INSOLUBLE CARRIERS

- A highly active adsorbent such as the inorganic clays like Bentonite can enhance the dissolution rate of poorly water-soluble drugs such as Griseofulvin, Indomethacin and PREDNISONE by maintaining the concentration gradient at its maximum.

- The two reasons for the rapid release of drugs from the surface of clays are—
  - The weak physical bonding between the adsorbate and the adsorbent,
  - Hydration and swelling of the clay in the aqueous media.

SOLID SOLUTIONS

- The three means by which the particle size of a drug can be reduced to submicron level are—
  - Use of solid solutions,
  - Use of eutectic mixtures, and
  - Use of solid dispersions.
- In all these cases, the solute is frequently a poorly water-soluble drug acting as the ***guest*** and the solvent is a highly water-soluble compound or polymer acting as a ***host*** *or* ***carrier.***

- A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent.

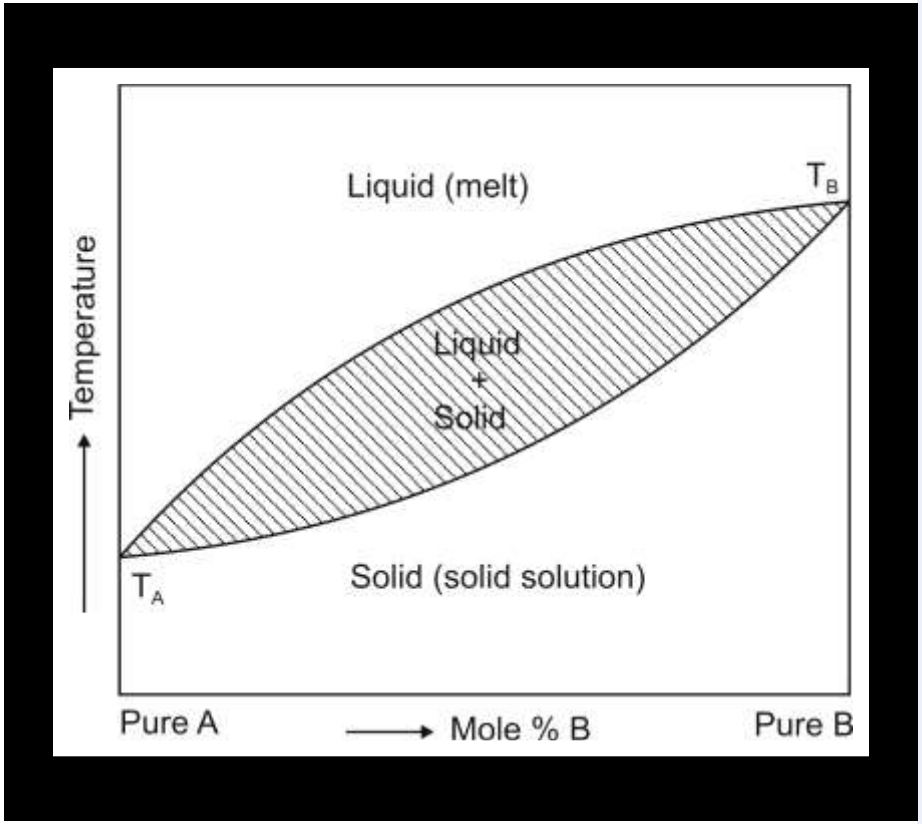
- Since the two components crystallize together in a homogeneous one phase system, solid solutions are also called as molecular dispersions or mixed crystals.

- Because of reduction in particle size to the molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersions.

- They are generally prepared by fusion method whereby a physical mixture of solute and solvent are melted together followed by rapid solidification.

- Such systems, prepared by fusion, are often called as ***melts*** e.g. griseofulvin-succinic acid

- The griseofulvin from such solid solution dissolves 6 to 7 times faster than pure griseofulvin



- If the diameter of solute molecules is less than 60% of diameter of solvent molecules or its volume less than 20% of volume of solvent molecule, the solute molecule can be accommodated within the intermolecular spaces of solvent molecules

  e.g. digitoxin-PEG 6000 solid solution.

- Such systems show faster dissolution.

- When the resultant solid solution is a homogeneous transparent and brittle system, it is called as ***Glass solution***

- Carriers that form glassy structure are citric acid, urea, PVP and PEG and sugars such as dextrose, sucrose and galactose.

- Solid solutions can be classified on two basis –
  - ✓ Miscibility between the drug and the carrier
  - ✓ Distribution of drug in carrier structure

Miscibility between the drug and the carrier

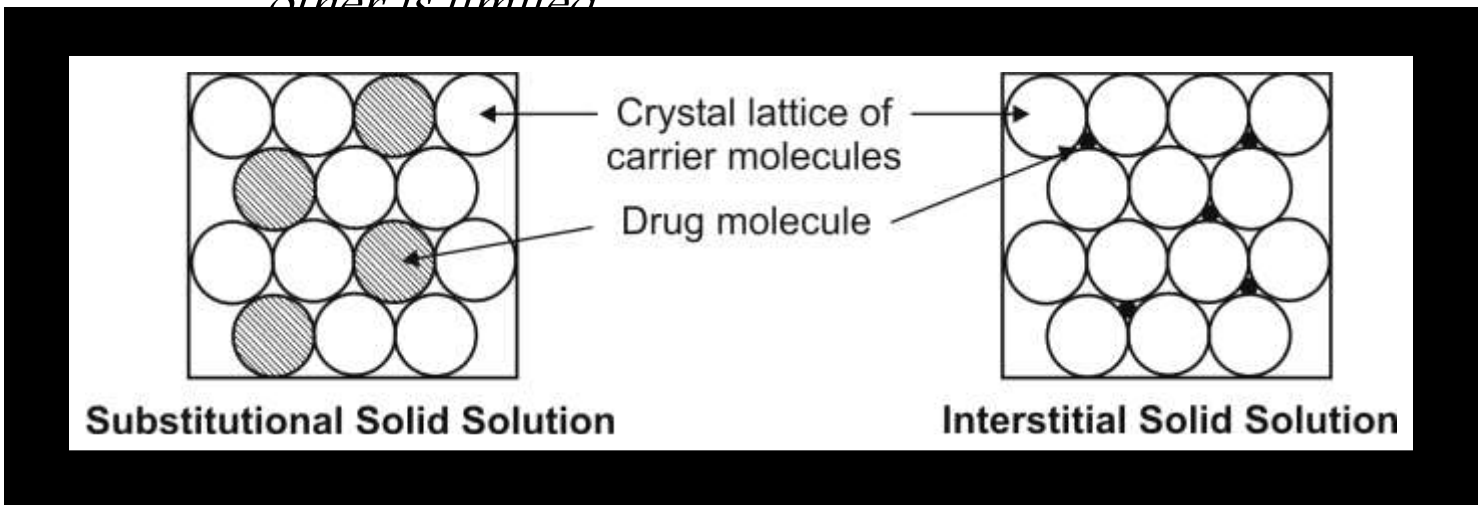
•on this basis the solid solutions are divided into two categories –

✓ ***Continuous solid solution***

In which both the drug and the carrier are miscible in all proportions. Such a solid solution is not reported in pharmaceutical literature.

✓ ***Discontinuous solid solution***

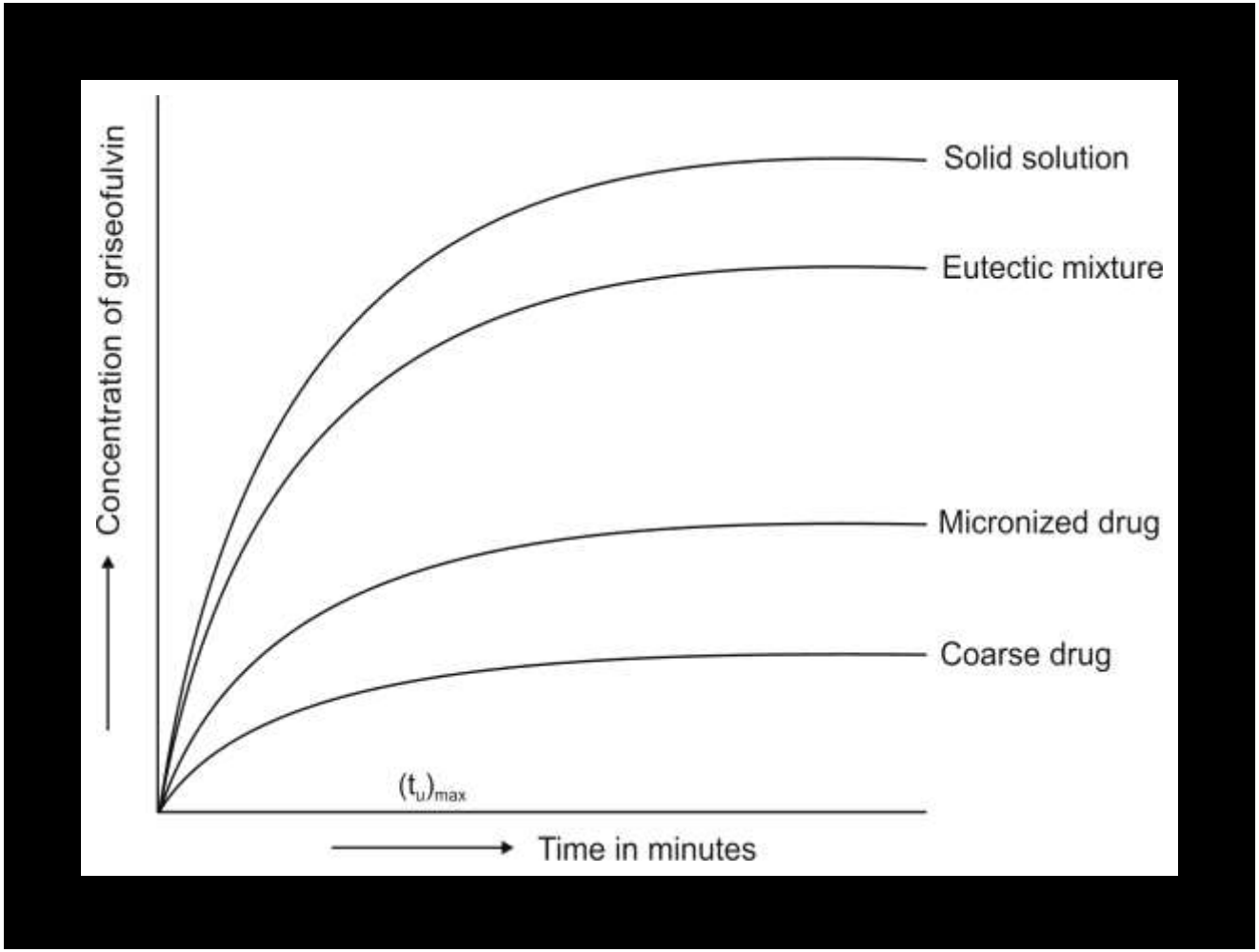
where solubility of each of the component in the other is limited



MECHANISMS FOR ENHANCED SOLUBILITY AND RAPID DISSOLUTION OF MOLECULAR DISPERSIONS

1. When the binary mixture is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles, and

2. When the solid solution, which is said to be in a state of randomly arranged solute and solvent molecules in the crystal lattice, is exposed to the dissolution fluid, the soluble carrier dissolves rapidly leaving the insoluble drug stranded at almost molecular level.



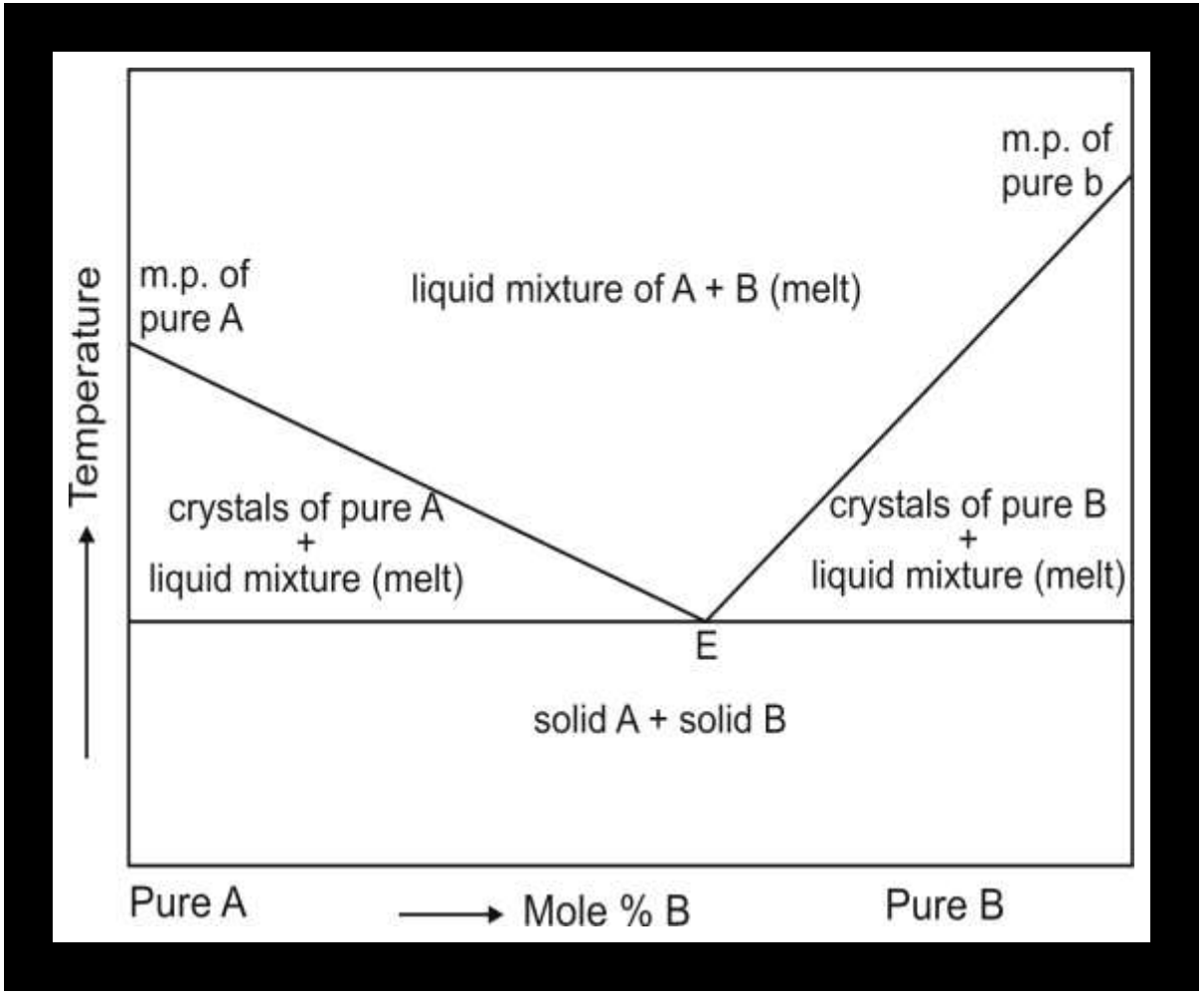
Dissolution rates of griseofulvin as coarse particles, as micronized particles and as eutectic and solid solution with succinic acid.

EUTECTIC MIXTURES

- These systems are also prepared by fusion method.

- Eutectic melts differ from solid solutions in that the fused melt of solute-solvent show complete miscibility but negligible solid-solid solubility i.e. *such systems are basically intimately blended physical mixture of two crystalline components*.

- When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in a microcrystalline state which solubilises rapidly.



Simple binary phase diagram showing eutectic point E.
The eutectic composition at point E of substances A and B represents the one having lowest melting point.

- Examples of eutectics include paracetamol-urea, griseofulvin-urea, griseofulvin-succinic acid, etc.

- Solid solutions and eutectics, which are basically melts, are easy to prepare and economical with no solvents involved.

- The method cannot be applied to:

  - Drugs which fail to crystallize from the mixed melt.
  - Drugs which are thermolabile.
  - Carriers such as succinic acid that decompose at their melting point. The eutectic product is often tacky, intractable or irregular crystal.

SOLID DISPERSIONS

- These are generally prepared by solvent or co-precipitation method whereby both the guest solute and the solid carrier solvent are dissolved in a common volatile liquid solvent such as alcohol.

- The liquid solvent is removed by evaporation under reduced pressure or by freeze-drying which results in amorphous precipitation of guest in a crystalline carrier.

- The basic difference between solid dispersions and solid solutions/ eutectics is that the drug is precipitated out in an amorphous form in the former as opposed to crystalline form in the latter

  e.g. amorphous sulphathiazole in crystalline urea.

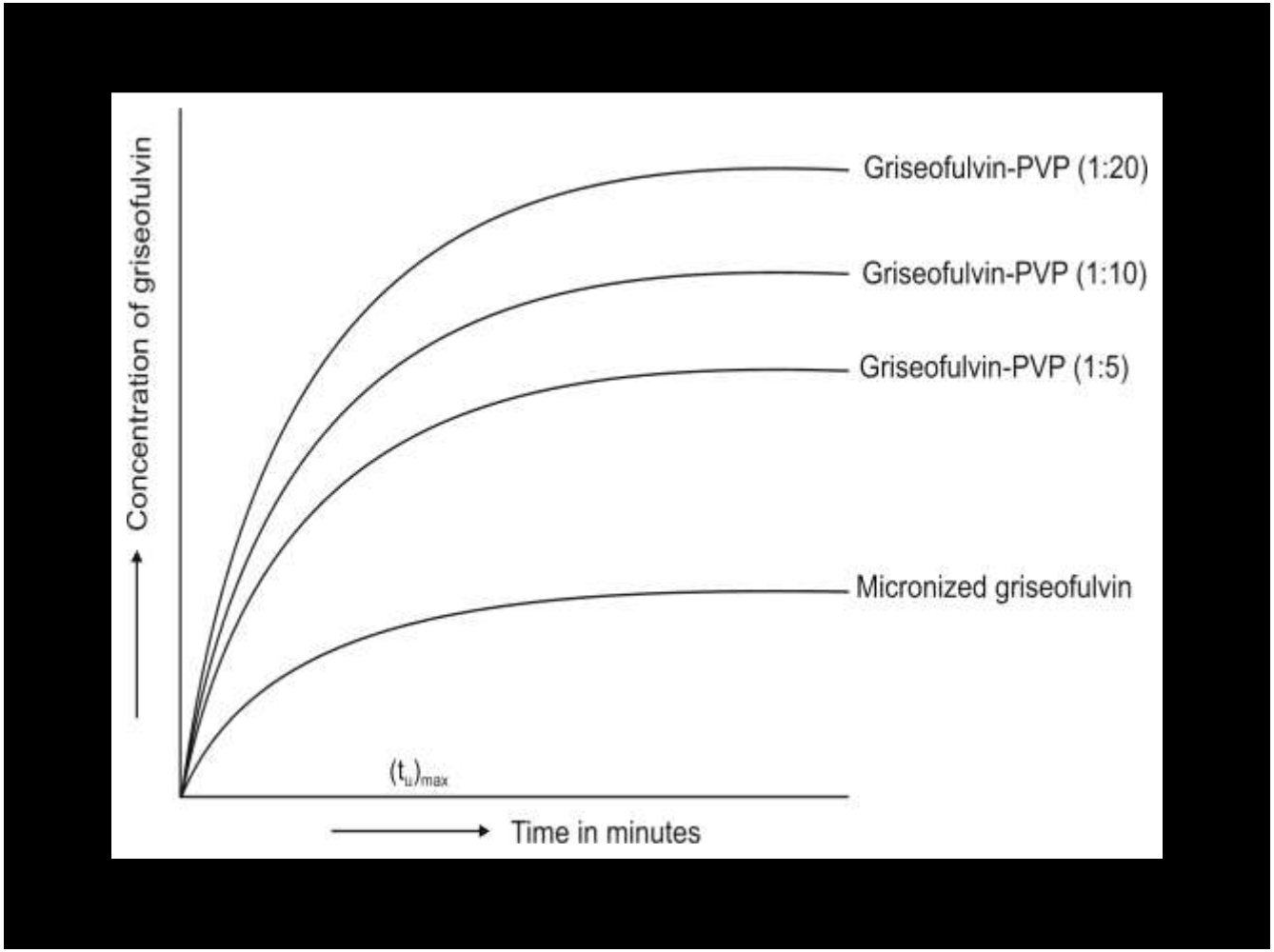
- Such dispersions are often called as co-evaporates or co-precipitates.

- The method is suitable for thermolabile substances but has a number of disadvantages like higher cost of processing, use of large quantities of solvent, difficulty in complete removal of solvent, etc.

- The carriers used are same as for eutectics or solid solutions.

- With glassy materials, the dispersions formed are called as glass dispersions or glass suspensions.

- Other polymers such as PEG and HPMC are also employed to prepare solid dispersions of poorly water-soluble drugs such as Nifedipine and Itraconazole.



DISSOLUTION RATE ENHANCEMENT OF GRISEOFULVIN BY SOLID DISPERSION TECHNIQUE.

LIMITATIONS OF PREPARATION OF SOLID DISPERSIONS

- Since the carrier is hydrophilic and the drug is hydrophobic, it is difficult to find a common solvent to dissolve both components.
- The product is often soft, waxy and possesses poor compressibility and flowability.
- Physical instability of the solid dispersion.
- Difficulty in preparation of a reproducible product.

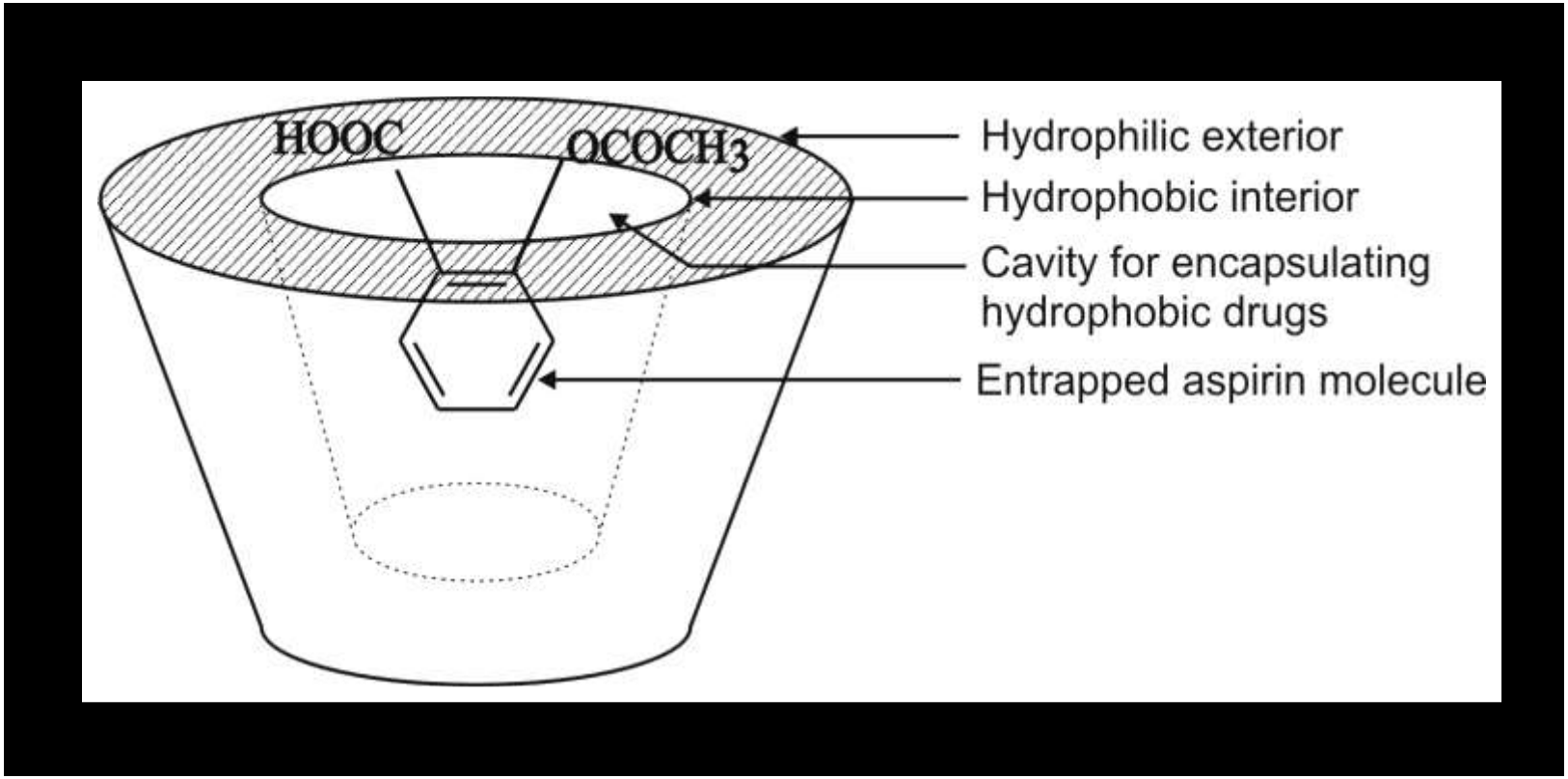
MOLECULAR ENCAPSULATION WITH CYCLODEXTRINS

- The beta- and gamma-cyclodextrins and several of their derivatives are unique in having the ability to form *molecular inclusion complexes* with hydrophobic drugs having poor aqueous solubility.

- These bucket-shaped oligosaccharides produced from starch are versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophilic drugs as guests; the outside of the host molecule is relatively hydrophilic

- Thus, the molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate.

- There are several examples of drugs with improved bioavailability due to such a phenomenon — Thiazide Diuretics, Barbiturates, Benzodiazepines and a number of NSAIDs.



FUNCTIONAL AND STRUCTURAL FEATURE OF A CYCLODEXTRIN MOLECULE

BIOAVAILABILITY ENHANCEMENT THROUGH ENHANCEMENT OF DRUG PERMEABILITY ACROSS BIOMEMBRANE

1. Lipid Technologies::

Lipid solutions and suspensions, micelle solubilization, coarse emulsions, microemulsions, multiple emulsions, self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS), nanoparticles and liposomes.

2. Ion Pairing:

3. Penetration Enhancers

BIOAVAILABILITY ENHANCEMENT THROUGH ENHANCEMENT OF DRUG STABILITY

1.Enteric Coating:

2. Complexation:

3. Use of Metabolism Inhibitors:

- *Bioadhesive delivery systems*
- *Controlled-release microencapsulated systems*
- *Immobilization of enzyme inhibitors*

BIOAVAILABILITY ENHANCEMENT THROUGH GASTROINTESTINAL RETENTION

GRDDS

- Increased contact with epithelial surfaces
- Prolonging residence time in the stomach
- Delaying intestinal transit.