BIOAVAILABILITY ENHANCEMENT TECHNIQUES

For Class- B.Pharmacy 6th Semester

Subject- BIOPHARMACEUTICS AND PHARMACOKINETICS (BP604T)

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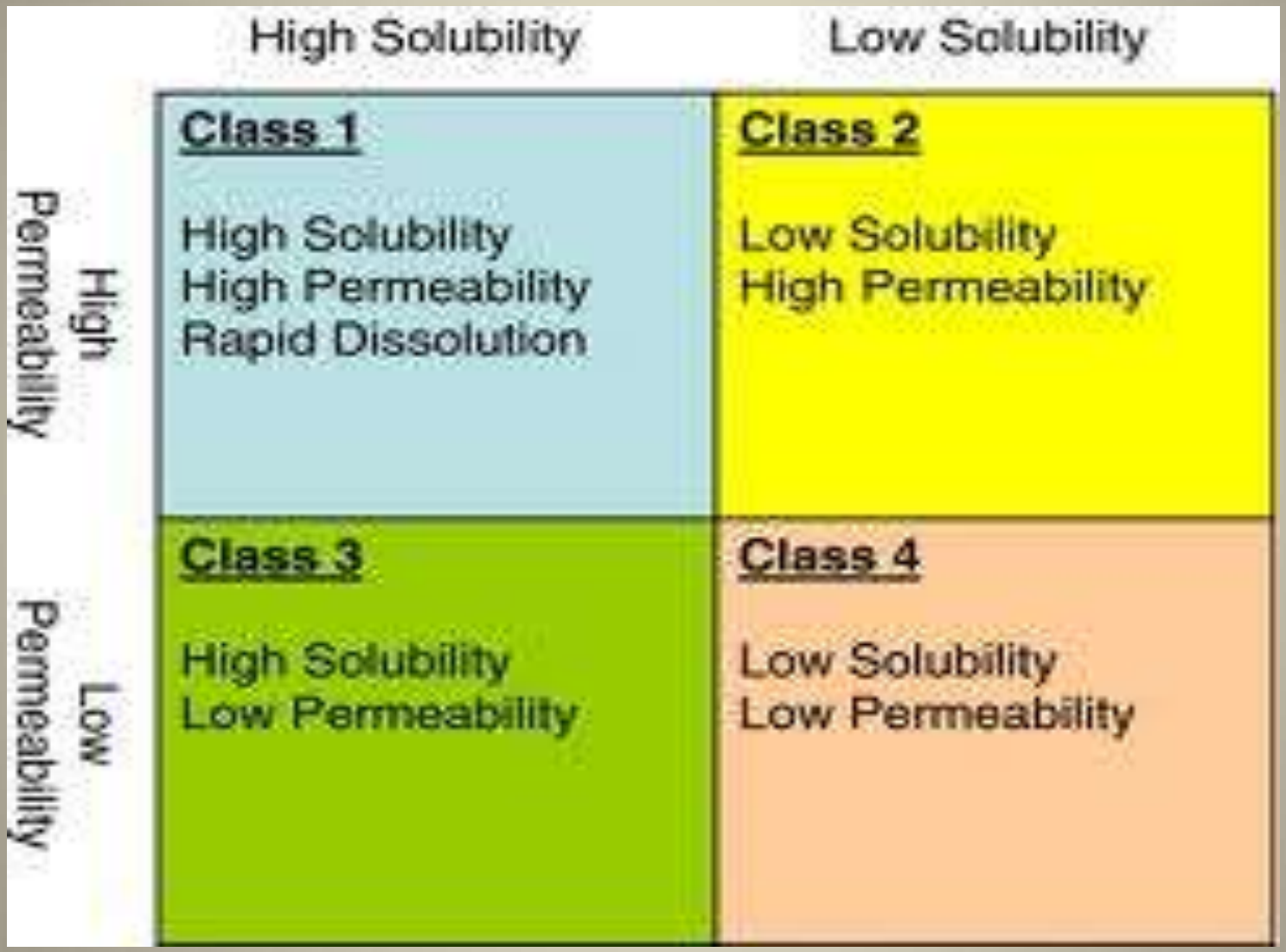
INTRODUCTION :

- DEFINITION : Solubility is defined in quantitative terms as concentration of solute in concentrated solution at a certain temperature, and in qualitative way it can be defined as a spontaneous interaction of two or more substances to form a homogenous molecular dispersion.

- Solubilization can be defined as a preparation of thermodynamically stable isotropic solution of a substance normally insoluble or slightly soluble in a given solvent by introduction of an additional component or components.


High Solubility
Low Solubility
Class 1
High Solubility
High Permeability
Rapid Dissolution
Class 2
Low Solubility
High Permeability
Class 3
High Solubility
Low Permeability
Class 4
Low Solubility
Low Permeability
High Permeability
Low Permeability

The biopharmaceutical classification system (BCS)

CLASS	SOLUBILITY	PERMEABILITY	ABSORPTION PATTERN	RATE LIMITING STEP IN ABSORPTION
I	High	High	Well absorb	Gastric emptying
II	Low	High	variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorb	Case by case

The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. The Indian pharmacopoeia provides general terms to describe a given range. These descriptive terms are given as:

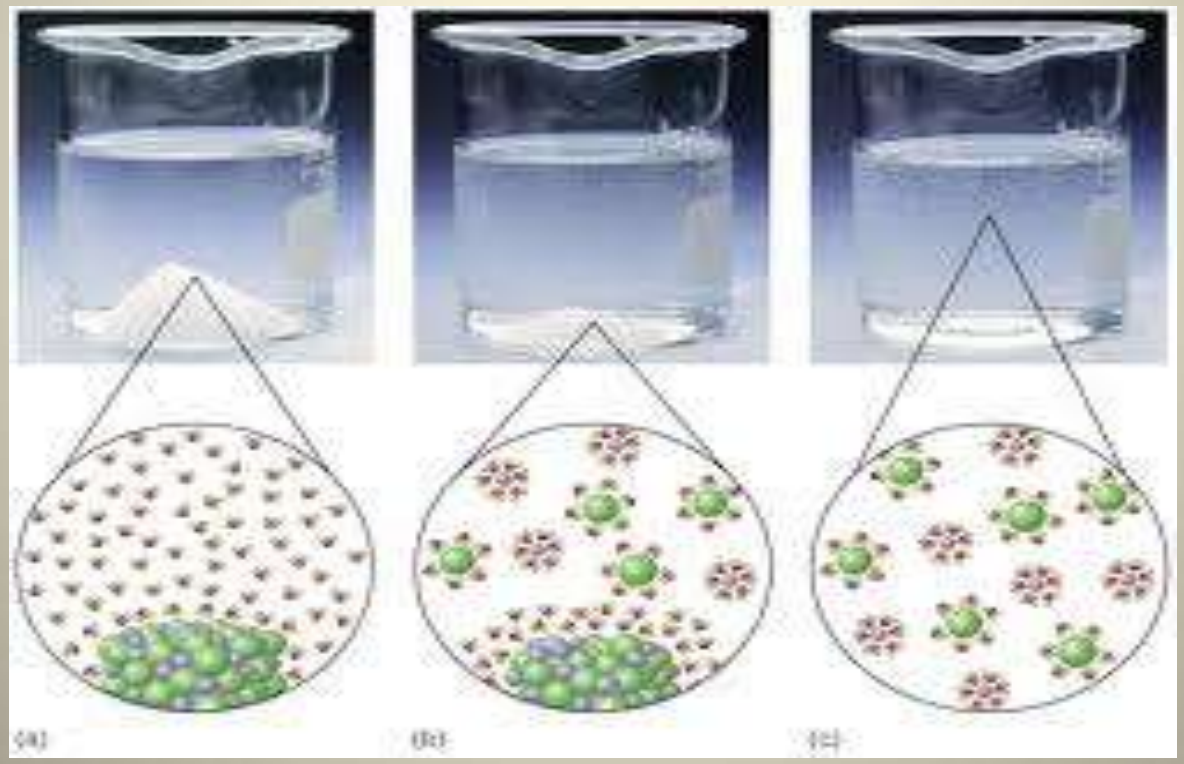
DEFINITION	PARTS OF SOLVENT REQUIRED FOR 1 PART OF SOLUTE
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 – 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 – 10,000
Insoluble	>10,000

IMPORTANCE OF SOLUBILITY:

- Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.
- Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.
- Currently only 8% of new drug candidates have both high solubility and permeability.
- Nearly 40% of the new chemical entities currently being discovered are poorly water soluble.
- More than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories.
- Low aqueous solubility is the major problem encountered with formulation development of new chemical entities.
- Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.

SOLUBILIZATION

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

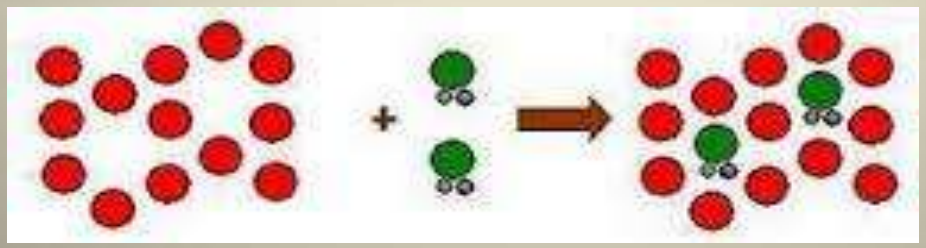


STEPS INVOLVED ARE :

1: Holes opens in the solvent

2. Molecules of the solid breaks away from the bulk.

3. The freed solid molecule is integrated into the hole.



TECHNIQUES OF SOLUBILITY ENHANCEMENT

I. Physical Modifications

A. Particle size reduction

1. Micronization
2. Nanosuspension
3. Sonocrystalisation
4. Supercritical fluid process

B. Modification of the crystal habit

1. Polymorphs
2. Pseudopolymorphs

C. Drug dispersion in carriers

1. Eutectic mixtures
2. Solid dispersions
3. Solid solutions

D. Complexation

Use of complexing agents

E. Solubilization by surfactants

Microemulsions

II. Chemical Modifications

1. Change in the pH
2. Use of buffer
3. Derivatization

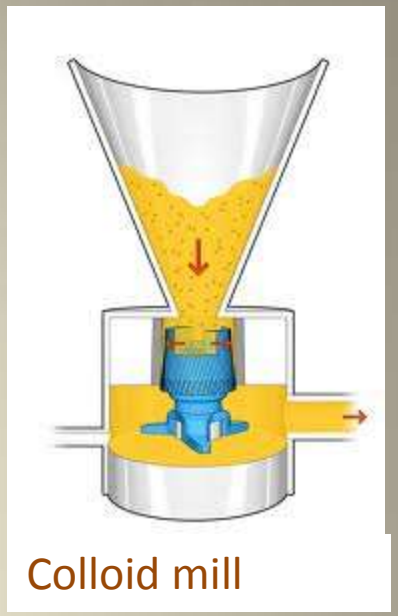
III. Other methods

1.co-crystallisation
2. co-solvency
3.Hydrotrophy
4.Solubilizing agents
5.Selective adsorption on insoluble carrier
6.Solvent deposition
7.Using soluble prodrug
8.Functional polymer technology
9.Precipitation Porous
10.microparticle technology
11.Nanotechnology approaches

A.Particle size reduction:

Particle size reduction can be achieved by

a. Micronization
b. nanosuspension
c. Sonocrystalisation
d.Supercritical fluid process



Colloid mill

1. Micronization:

- Micronization increases the dissolution rate of drugs through increased surface area.
- Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc.
- Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug .
- The process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of attrition methods. The process is also called micro-milling.

2. Nanosuspension :

Nanosuspensions are sub-micron colloidal dispersion of pure particles of the drug, which are stabilized by surfactants. Nanosuspension technology is used for efficient delivery of hydrophobic drugs . The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.

Advantage :

Increased dissolution rate due to larger surface area exposed.

Eg., Nanosuspension approach has been employed drugs like paclitaxel, tarazepide, amphotericin B which are still on research stage.

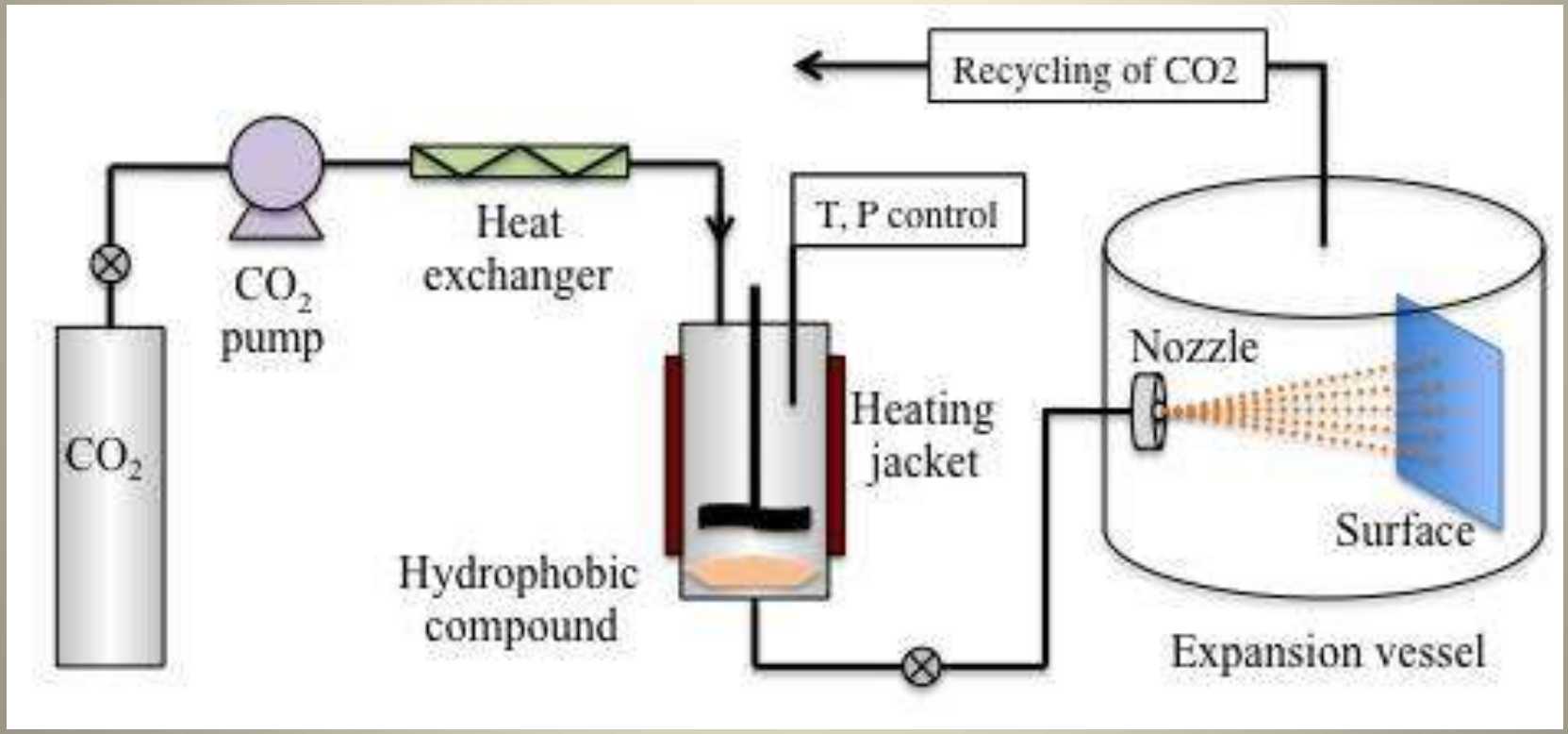
3.Sonocrystallisation :

Particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation . Sonocrystallisation utilizes ultrasound power for inducing crystallisation . It not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz-5 MHz.

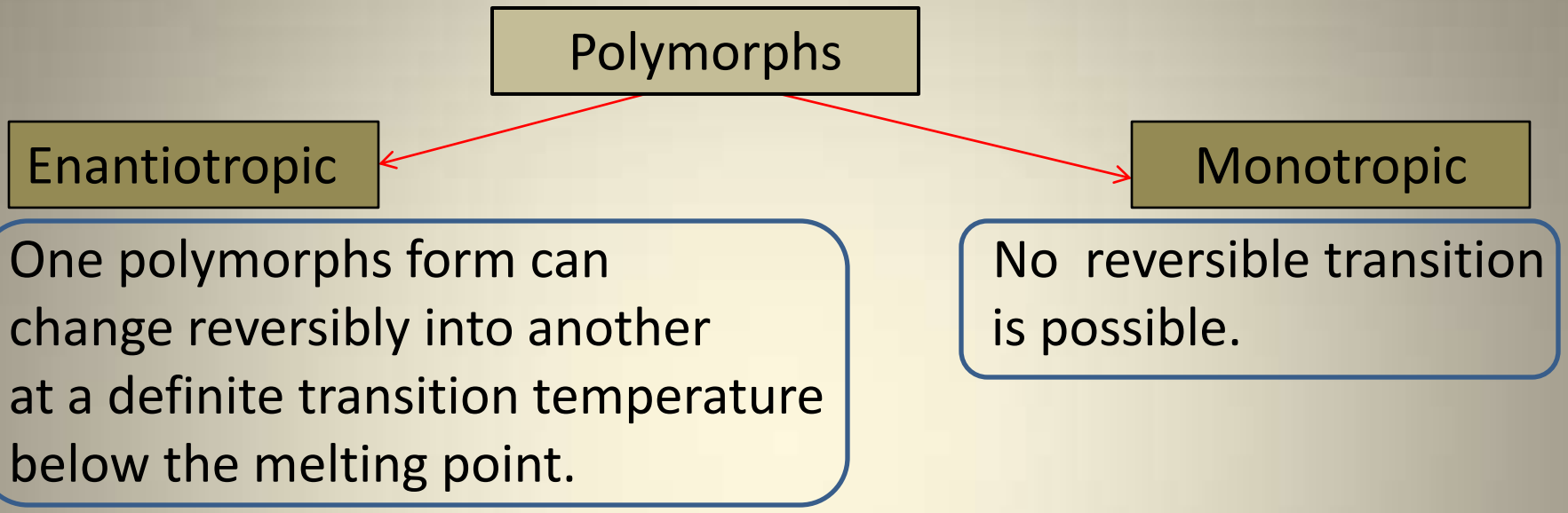
4. Supercritical fluid process :

- A supercritical fluids are dense non-condensable fluid 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.
- Through manipulation of the pressure of SCFs, the favourable characteristics of gases – high diffusivity, low viscosity and low surface tension may be imparted upon the liquids to precisely control the solubilisation of a drug with a supercritical fluid.

- Once the drug particles are solubilised within SCFs, they may be recrystalised at greatly reduced particle sizes.
- A SCF process allows micronisation of drug particles within narrow range of particle size, often to sub-micron levels.



B. Modification of the crystal habit:



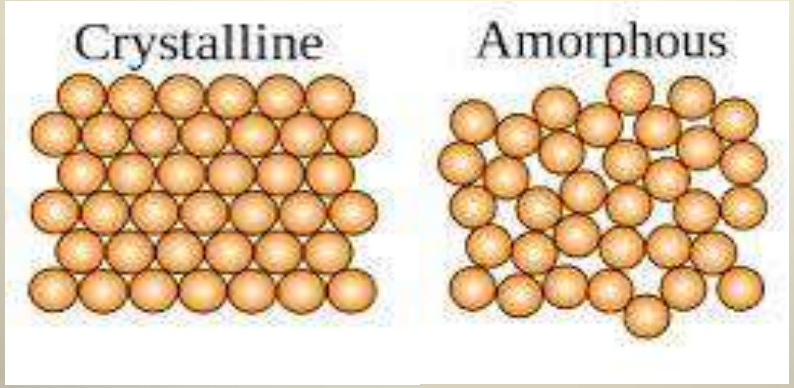
- Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increased surface area.
- The anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction

with water and therefore have less energy for crystal breakup in comparison to the anhydrates.

- They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is

Amorphous > metastable polymorph > stable polymorph

- Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug.



C. Drug dispersion in carriers:

The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the

1. • Hot melt mehod
2. • Solvent evaporation method
3. • Hot melt extrusion method

1. Hot melt method :

Drug + vehicle (m.p low, organic solvent – insoluble)

(heating)

Melting

Freezing quickly

Dosage forms

A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process.

Important requisites :

1. Miscibility of the drug & carrier in the molten form,
2. Thermostability of the drug & carrier.

Suitable to drugs and vehicles with promising heat stability.

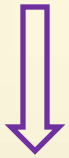
2. Solvent evaporation method:

Drug + vehicle (both soluble in solvent)

organic solvent

solution

evaporate the solvent



coprecipitates

dosage forms

The solvent evaporation can be done by spray drying or freeze drying.

Temperatures used for solvent evaporation generally lie in the range 23-65 C.

suitable to drugs with volatility or poor stability

3.Hot-melt Extrusion:

Hot melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step.

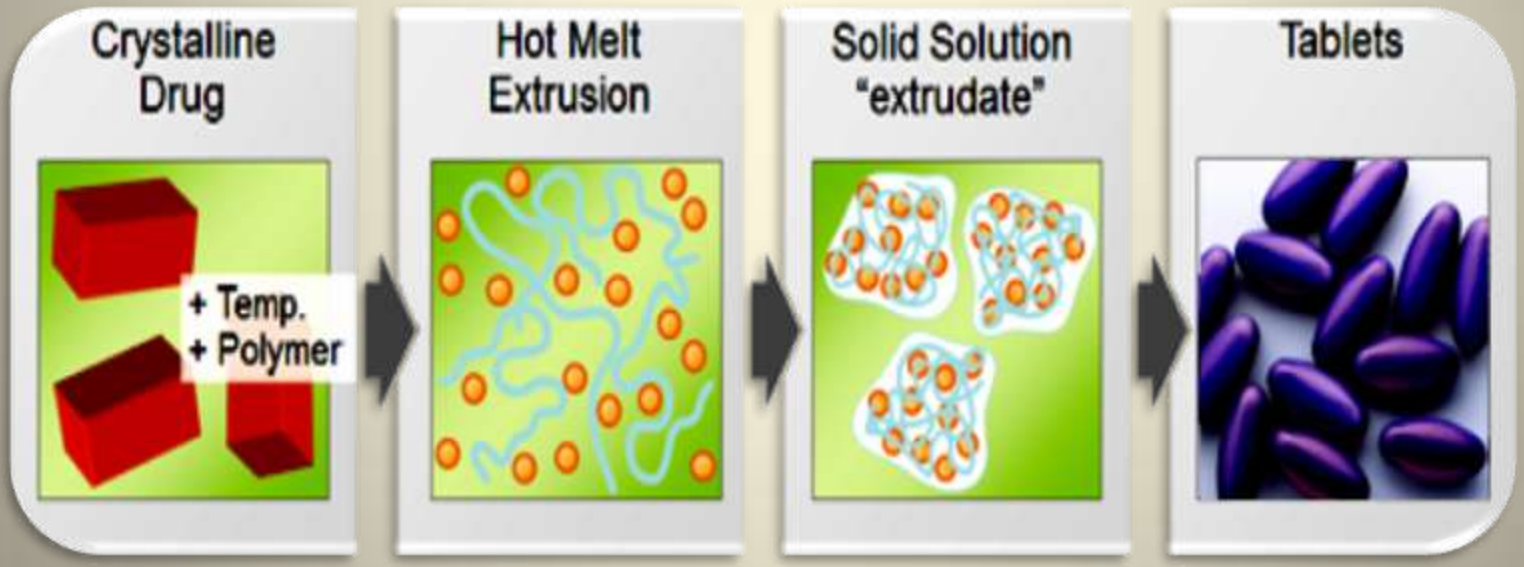
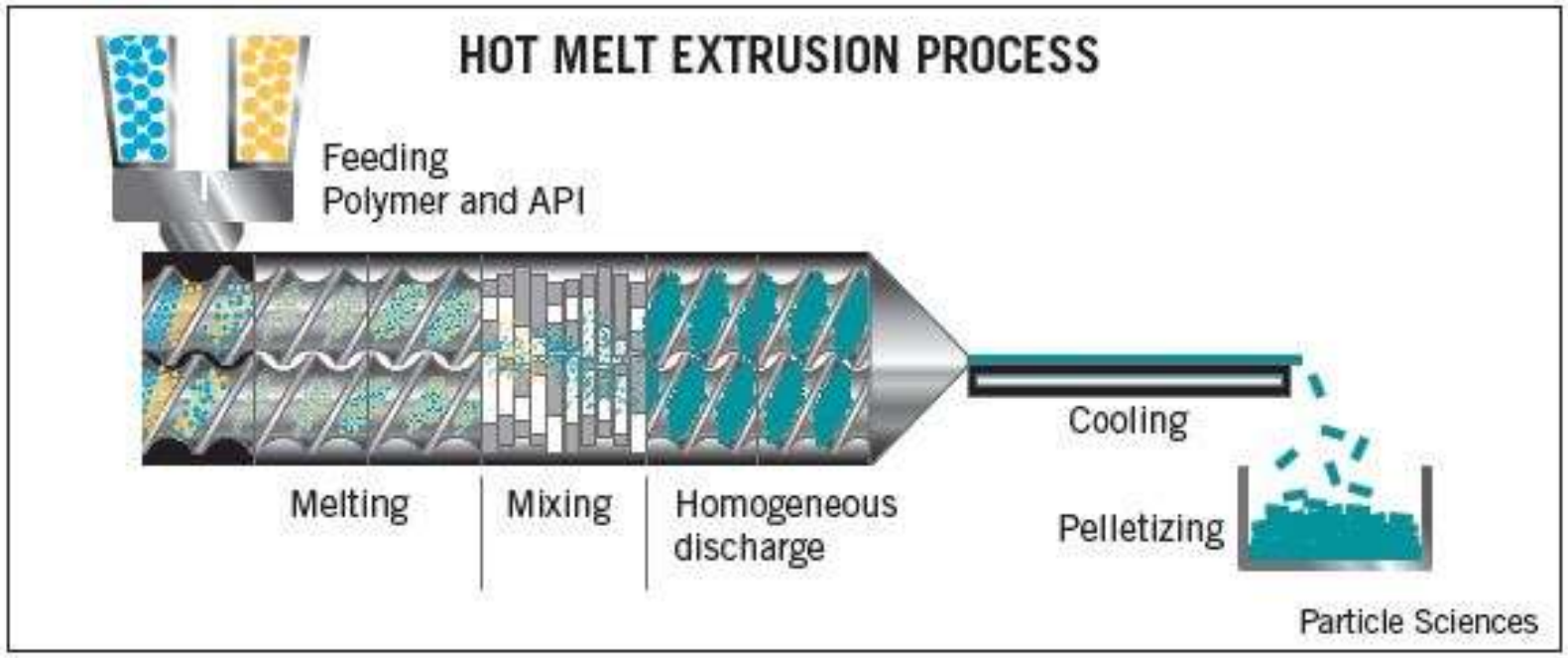


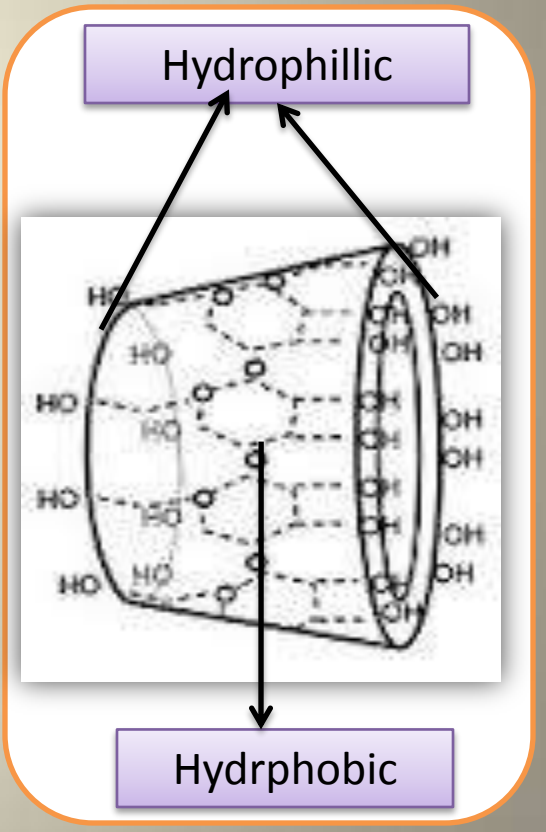
Figure 1


HOT MELT EXTRUSION PROCESS
Feeding
Polymer and API
Cooling
Melting
Mixing
Homogeneous
discharge
Pelletizing
Particle Sciences

D. Complexation :

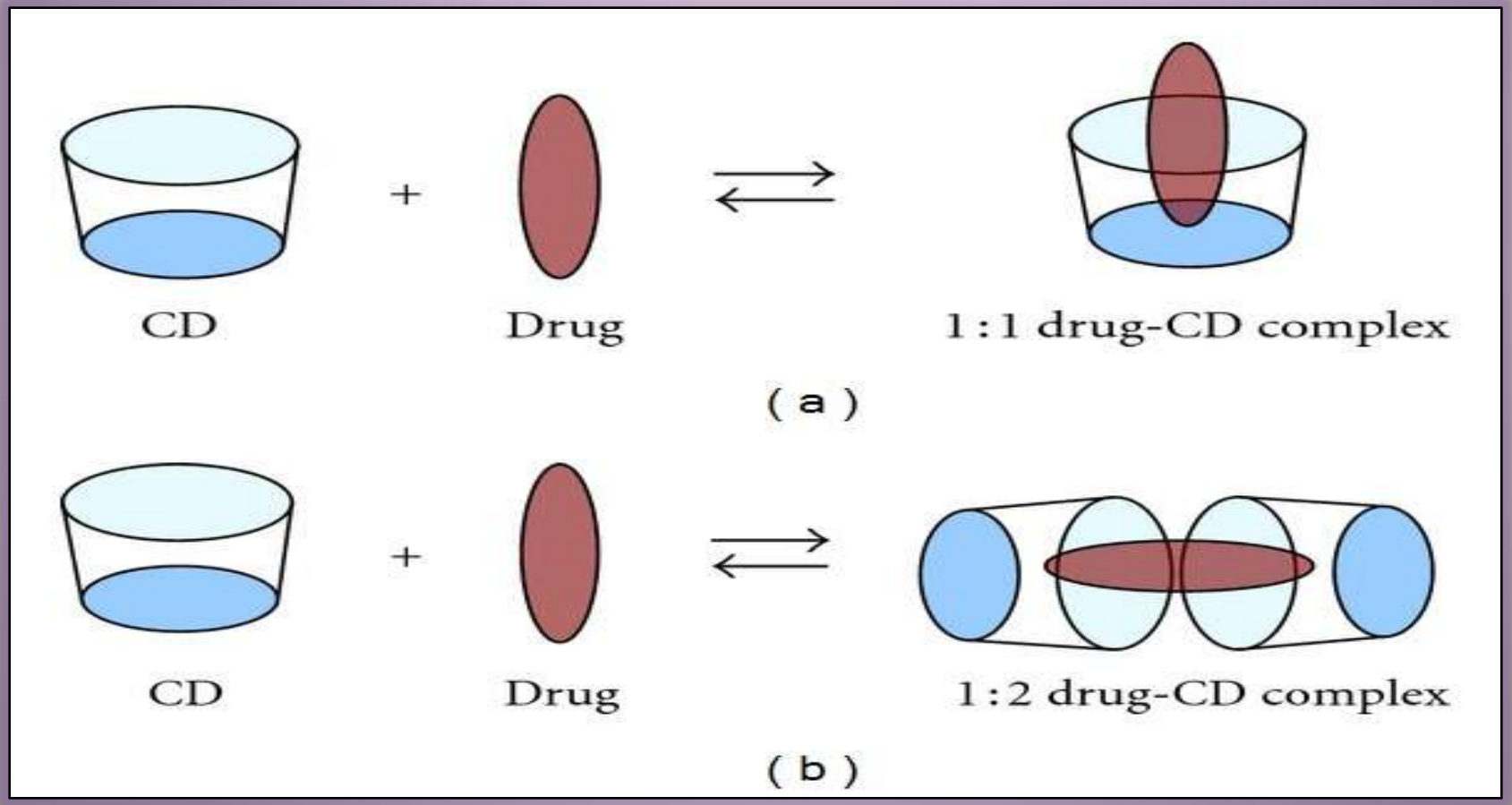
Complexation is the reversible association between two or more molecules to form a nonbonded entity with a well defined stoichiometry . Complexation relies on relatively weak forces such as van-derwaal forces, hydrogen bonding and hydrophobic interactions.

Inclusion complexation: These are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. The most commonly used host molecules are cyclodextrins . Cyclodextrins are non- reducing, crystalline , water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring.



CYCLODEXTRIN

The surface of the cyclodextrin molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non-polar molecules. Based on the structure and properties of drug molecule it can form 1:1 or 1:2 drug cyclodextrin complex. Three naturally occurring CDs are α Cyclodextrin, β Cyclodextrin, and γ Cyclodextrin.



Staching complexation

Organic drug + water → Squeezed out by strong water-water interaction force.

↓

Forms aggregates

↓

Reduces the contact b/w nonpolar hydrocarbon moieties & the polar water molecule

↓

Large nonpolar regions

↓

Opposed by entropy

↓

Random arrangement

↓

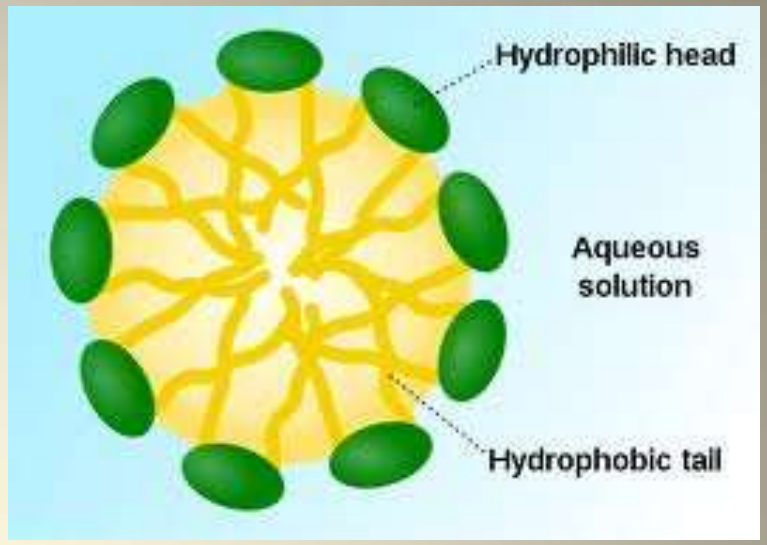
Complexes stached can be homogeneous or mixed

↓

Self association complexation

Eg .,
Nicotinamide,
Anthracene,
Caffeine,
Theobromine.

E. Solubilization by surfactants:



Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitter ionic or nonionic. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent .

Microemulsion : A microemulsion is a four-component system composed of external phase, internal phase, surfactant and co surfactant . The addition of surfactant, which is predominately soluble in the internal phase unlike the co surfactant , results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal phase is <0.1 micron droplet diameter.

The surfactant and the co surfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsion .

Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production.

Advantages :

- Ease of preparation due to spontaneous formation.
- Thermodynamic stability,
- transparent and elegant appearance,
- enhanced penetration through the biological membranes,
- increased bioavailability and
- less inter- and intra-individual variability in drug pharmacokinetics.

II. CHEMICAL MODIFICATIONS

1)By change of pH:

For organic solutes that are ionizable, changing the pH of the system is the simplest and most effective means of increasing aqueous solubility .

For weakly acidic drugs,

LOWER pH → UNIONISED FORM → INSOLUBLE PPT

HIGHER pH → IONISED FORM → MORE SOLUBLE DRUG

For weakly basic drugs,

Lower pH → Ionized form → More soluble drug

Higher pH → UNIONISED FORM → INSOLUBLE PPT

2) Use of buffer: Buffer maintains the pH of the solution overtime and it reduces or eliminate the potential for precipitation upon dilution. On dilution pH alteration occurs that decrease solubility . Change of pH by 1 fold increase solubility by 10 fold If it changes by one pH unit ,that decrease ionization of the drug and solubility decreases by 10 fold.

3) Derivatization : It is a technique used in chemistry which transforms a chemical compound into a product of similar chemical structure, called derivative. Derivatives have different solubility as that of adduct. It is used for quantification of adduct formation of esters and amides via acyl chlorides.

III. OTHER METHODS.

1.Co-crystallization:

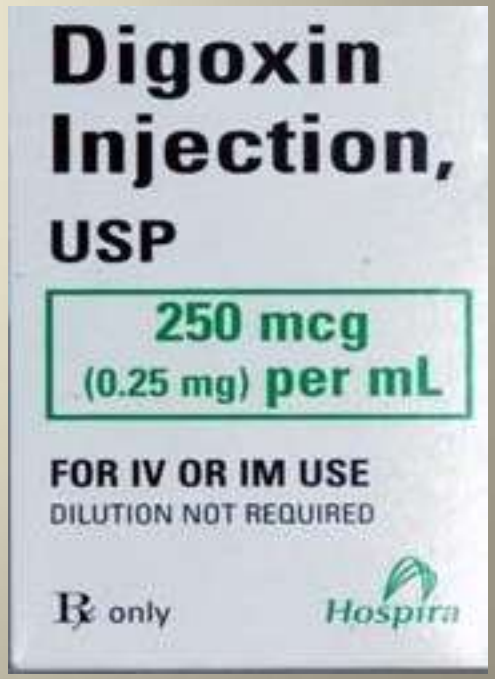
A co-crystal may be defined as a crystalline material that consists of two or more molecular species held together by non-covalent forces.

- Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature.
- Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together.
- Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation.
- Only three of the co-crystallizing agents are classified as generally recognised as safe (GRAS) it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications.

2. Cosolvency : Cosolvents are prepared by mixing miscible or partially miscible solvents. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute.

Aquous solvent - Etahnol, sorbitol, glycerin, propylene glycol.

Non aquous solvent - glycerol dimethyl ketal, glycerol formal, glycofurol, dimethyl acetamide.

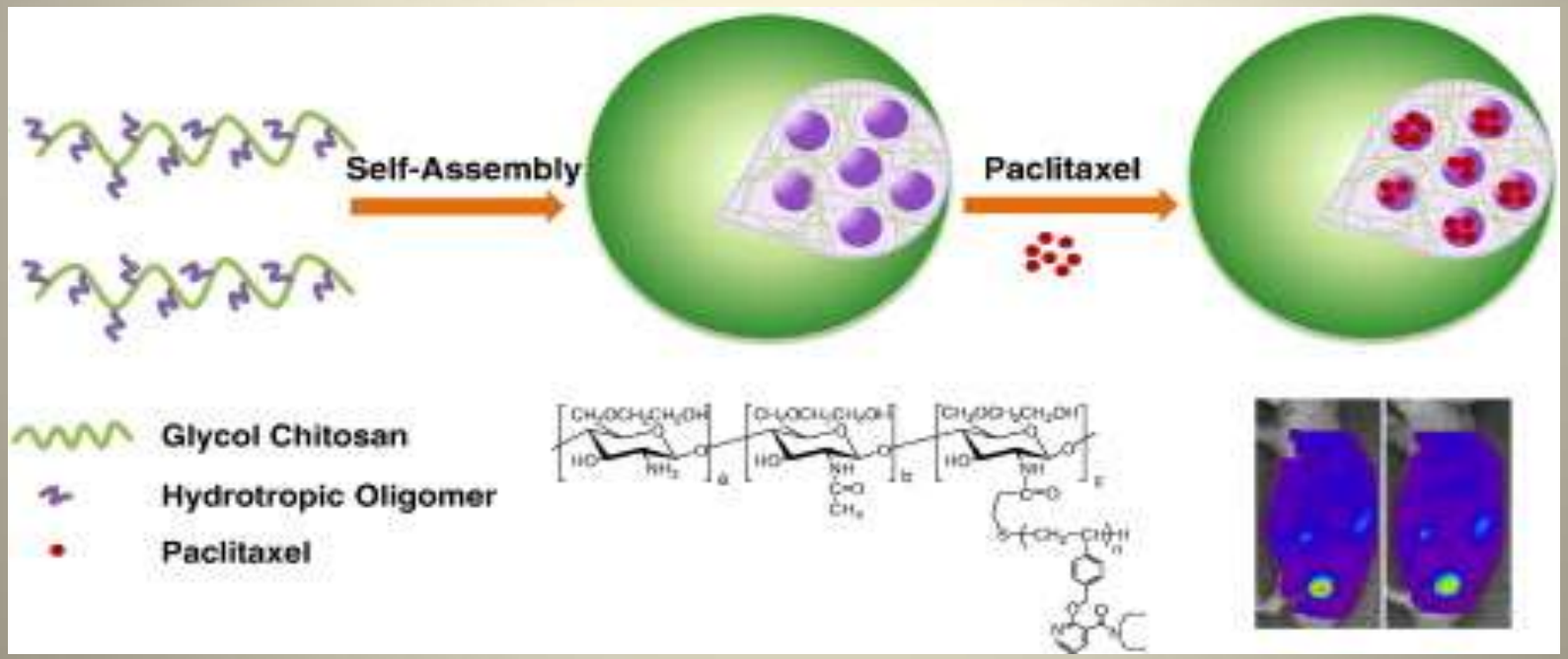


SOME PERANTRALPRODUCT THAT CONTAIN COSOLVENT

1.Diazepam - 10% ethanol + propylene glycol

2.Digoxin - 10% ethanol + propylene glycol

3. Hydrotrophy : Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents (sodium benzoate, sodium acetate, sodium alginate, and urea).



4. Solubilizing agents: The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazide85. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine .

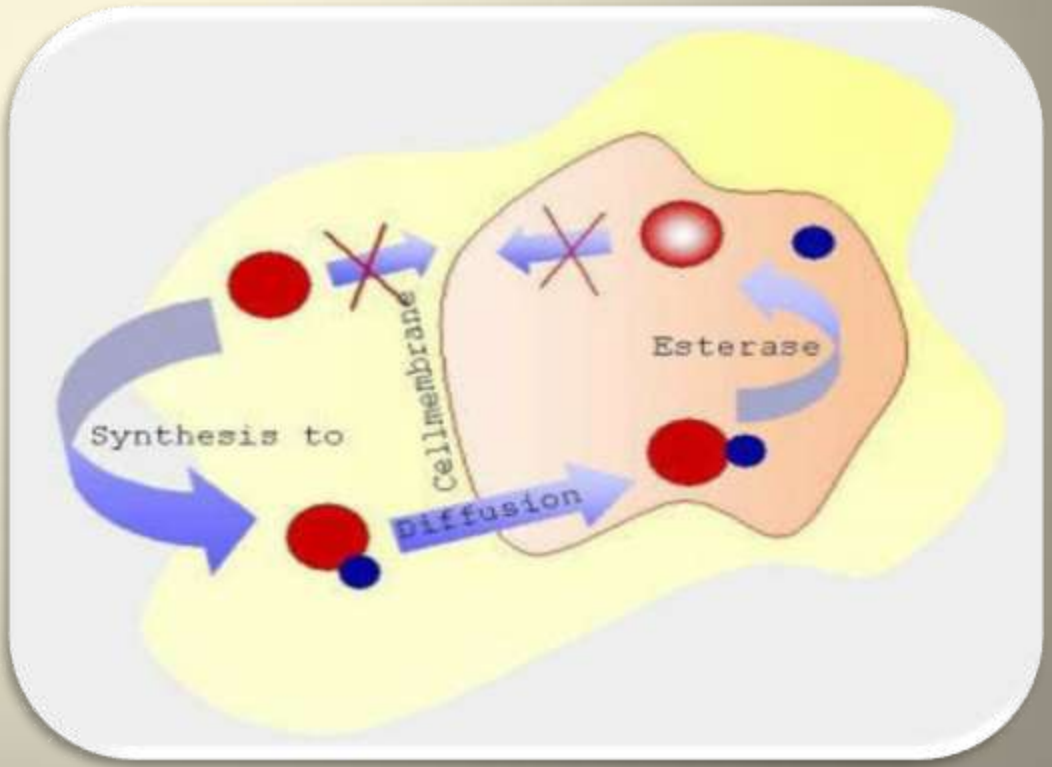
5. Selective adsorption on insoluble carriers: A highly active adsorbent such as inorganic clays like Bentonite can enhance the dissolution rate of poorly water-soluble drugs such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient at its maximum. 2 reasons suggested for rapid release of drugs from the surface of clays :-

1. weak physical bonding between adsorbate and adsorbent.
2. hydration and swelling of the clay in the aqueous media.

6. 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 and evaporation of solvent is done.

7. Use of soluble prodrug :

Prodrug stratergy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility. Example : prodrug of established drugs has been successfully used to improve water solubility of corticosteroids benzodiazepines.



8. Functional Polymer Technology : Functional polymer enhances the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. The dissolution rate of poorly soluble , ionizable drug like cationic, anionic and amphoteric actives can be enhanced by this technology. Applied to heat sensitive materials and oils also.

9. 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 nano size particles. The product so prepared is also called as hydrosol.

10. Porous microparticle technology: The poorly water soluble drug is embedded in a microparticle having a porous, water soluble, sponge like matrix, dissolves wetting the drug and leaving a suspension of rapidly dissolving drug particles. These drug particles provide large surface area for increased dissolution rate . This is the core technology applied as HDDS.

11. Nanotechnology approaches : For many new chemical entities of very low solubility ,oral bioavailability enhancement by micronization is not sufficient because micronized product has a tendency of agglomeration, which leads to decreased effective surface area for dissolution . Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less .

NANOCRYSTAL: Size: 1-1000 nm Crystalline material with dimensions measured in nanometers. There are two distinct methods used for producing nanocrystals . 1 . bottom-up. 2. top-down . The top-down methods (i.e. Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and Cryo -vacuum method), nanoscale materials are chemically composed from atomic and molecular components.

NanoMorph :

• The NanoMorph technology is to convert drug substances with low water-solubility from a coarse crystalline state into amorphous nanoparticles .

•A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous solution of a polymer induces precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth. Using this technology the coarse crystalline drug substances are transformed into a nanodispersed amorphous state, without any physical milling or grinding procedures. It leads to the preparation of amorphous nanoparticles .