METHODS FOR ENHANCEMENT OF BIOAVAILABILITY

Presented By

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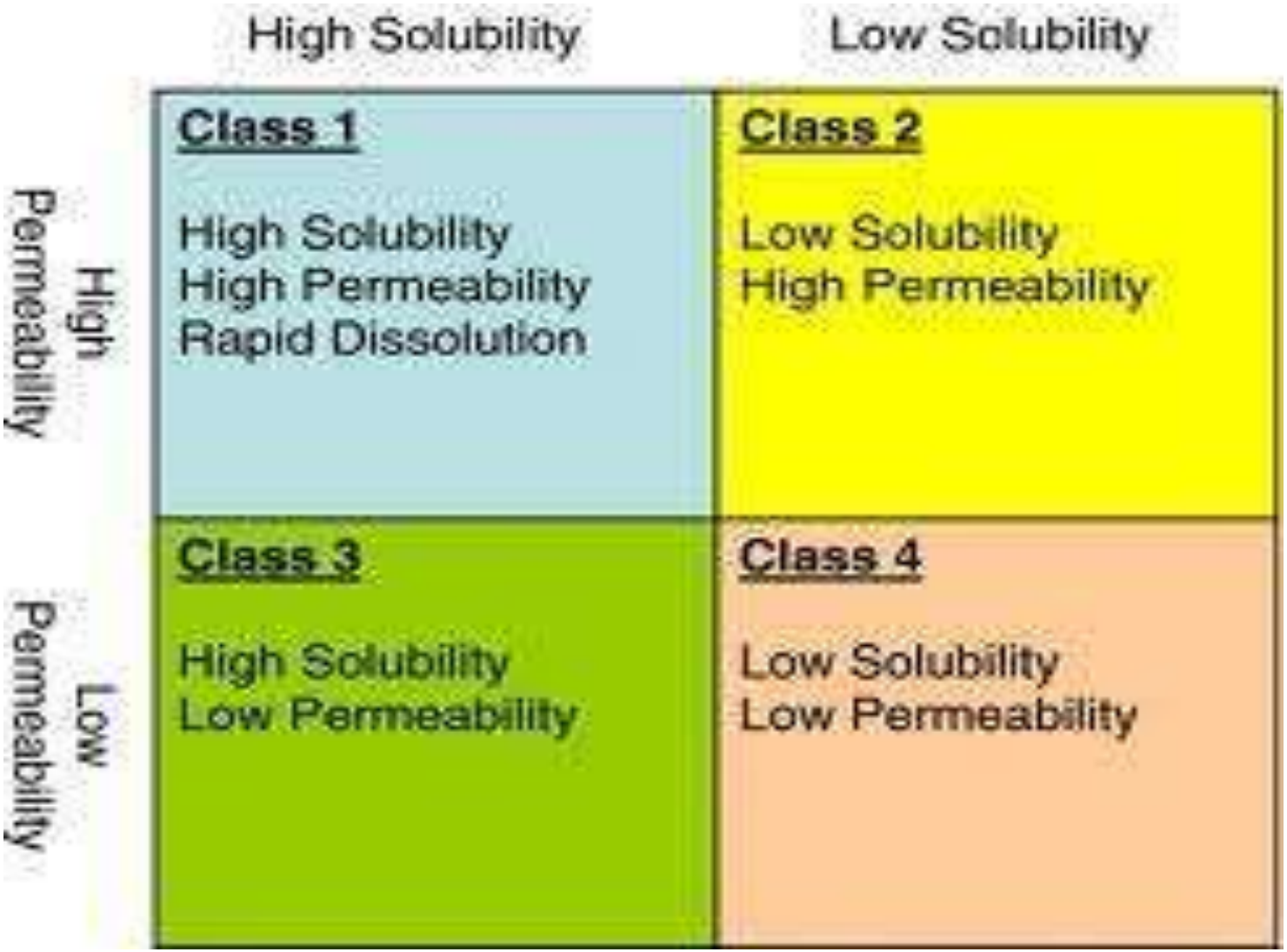
INTRODUCTION :

- Bioavailability means the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action.

- In the oral bioavailability of poorly water soluble compounds, the insufficient dissolution rate is the limiting factor. Some new technologies have been recently developed to improve wet ability and aqueous solubility of APIs.


High Solubility
Low Solubility
High Permeability
Low Permeability
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

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

- **Class I: High Permeability and High Solubility:**

  Formulation independent:- The bioavailability of class I compounds is determined only by delivery of the drug solution to the intestine.

  Examples: Benzapril, Loxoprofen, Sumatriptan etc.

- **Class II: High Permeability but Low solubility:**

  Formulation dependent:- The bioavailability of class II compounds is limited by drug solubility/dissolution.

  Examples: Valsartan, Nimesulide, Loratadine, Aceclofenac etc

- **Class III: Low Permeability but High Solubility:**

  Dependent on barrier properties:- The bioavailability of class III compounds is limited by intestinal permeability.

  Examples: Gabapentine, Topiramate, Atropine etc.

- **Class IV: Low Permeability and Low Solubility:**

  Formulation and barrier properties dependent:- The bioavailability of class IV compounds is limited both by solubility/dissolution and intestinal permeability.

  Examples: Hydrochlorthiazide, Furosemide, Meloxicam etc.

CAUSES OF LOW BIOAVAILABILITY

- First pass metabolism
- Poorly water soluble, slowly absorbing oral drugs
- Insufficient time for absorption in GIT
- Poor dissolution (highly ionized and polar)
- Age, stress, disorders, surgery etc
- Chemical reactions

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

METHODS TO ENHANCE THE DISSOLUTION RATES AND BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

1) Bioavailability enhancement through enhancement of drug solubility or dissolution rate:

a. Micronization

b. Nanonization

c. Sonocrystalisation

d. Supercritical fluid process

e. Use of surfactants

f. Molecular encapsulation with cyclodextrins

2. Enhancement of drug permeability

a. Lipid technologies

b. Ion Pairing

c. Penetration enhancers

3. Enhancement of drug stability

d. Enteric coating

e. Complexation

f. Use of metabolism inhibitors

4. Enhancement of gastrointestinal retention

a. Gastro Retentive Drug Delivery System

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, Fluid energy 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.

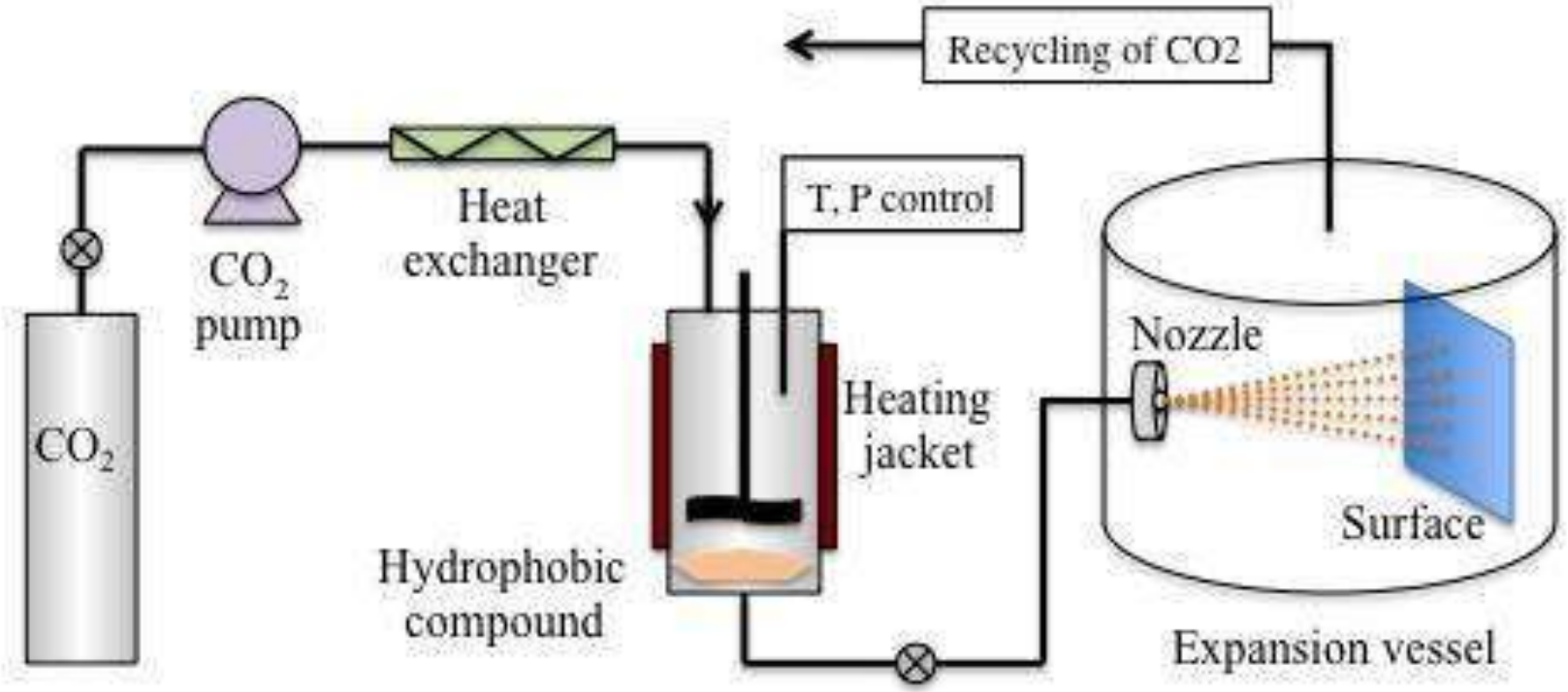
3.Sonocrystallisation :

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.

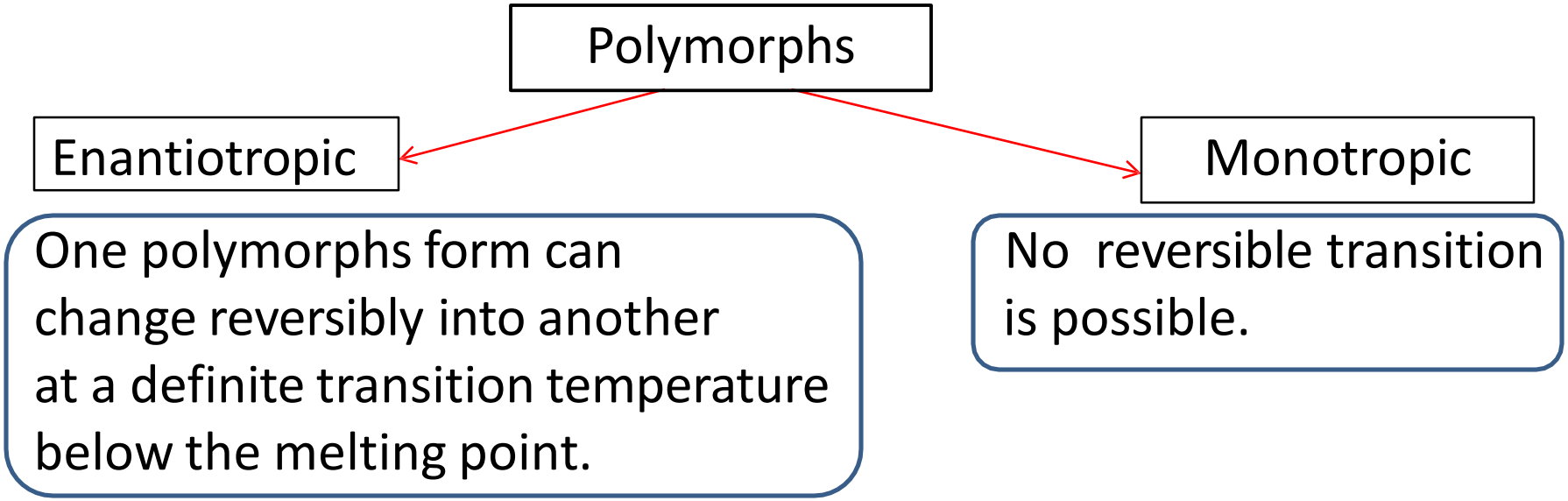
4. Supercritical fluid process :

- 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:



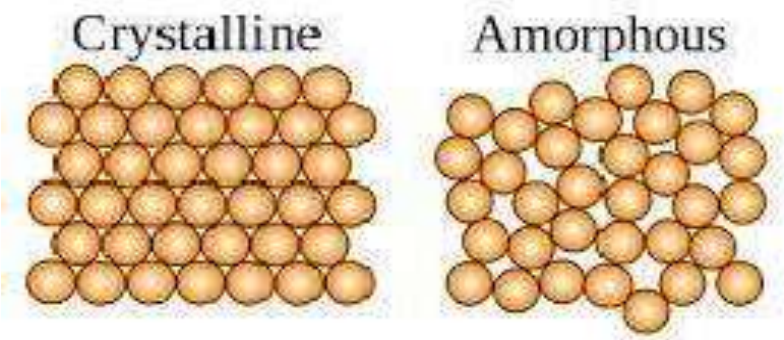
- Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increased surface area.
- The anhydrous form of a drug has greater solubility than the hydrates. This is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

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.

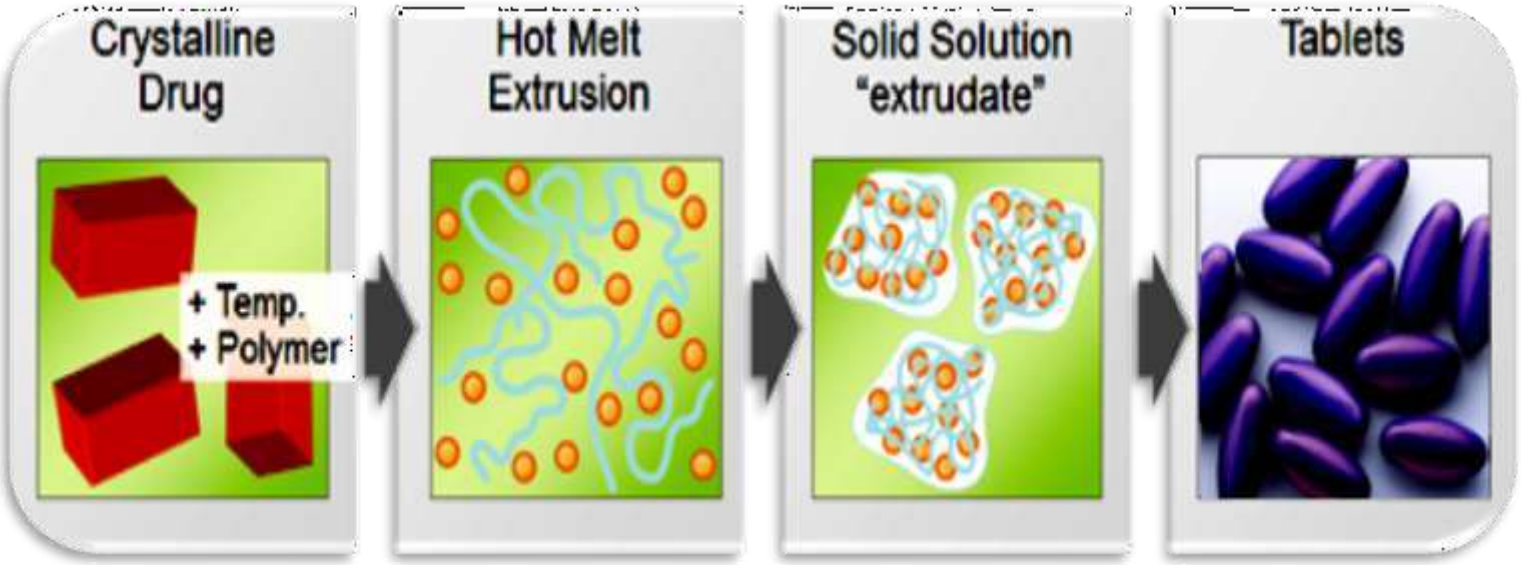
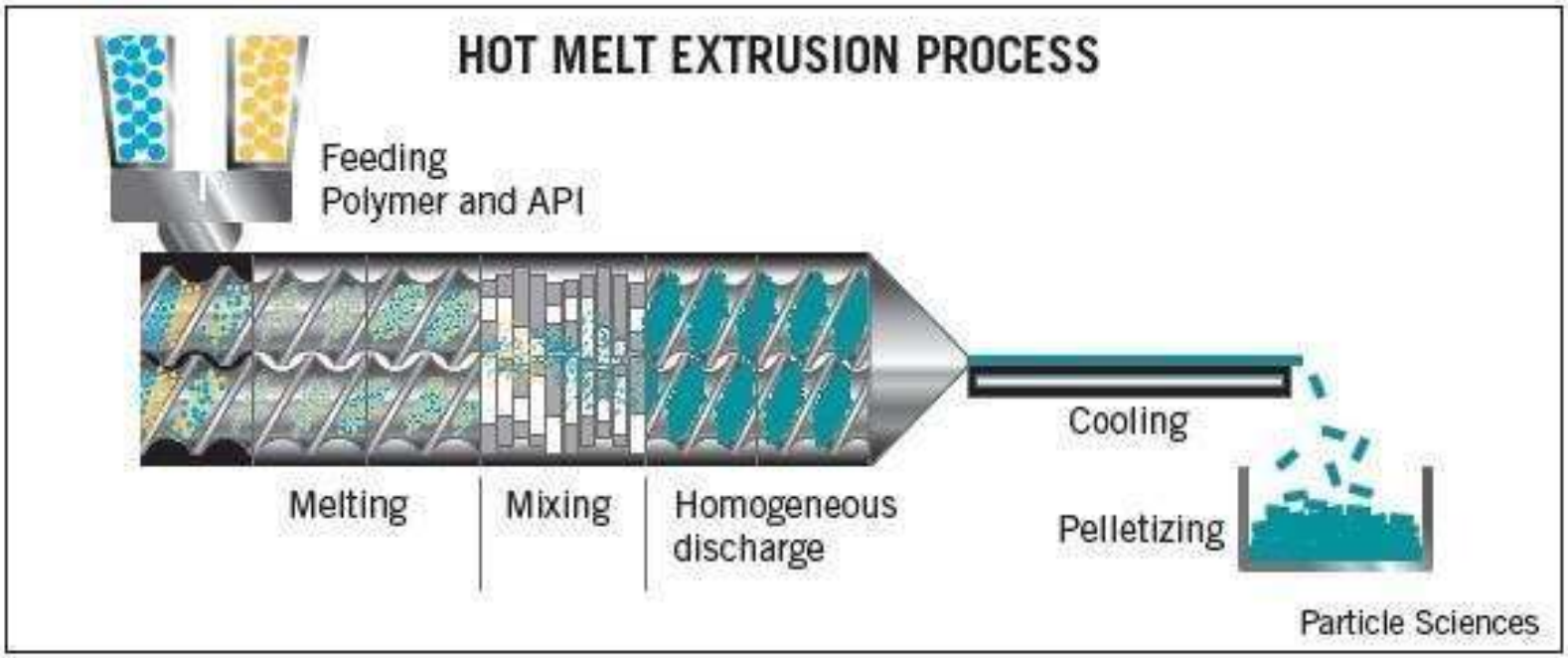


Figure 1

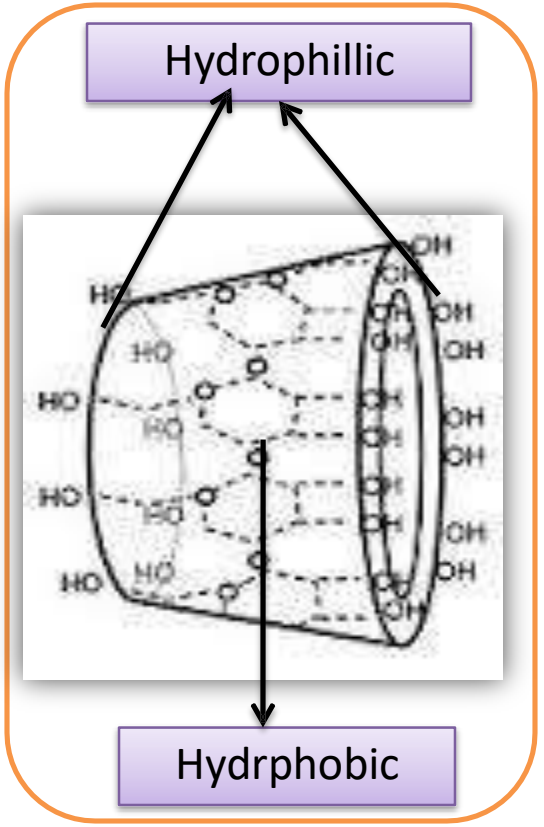

HOT MELT EXTRUSION PROCESS
Feeding
Polymer and API
Cooling
Melting
Mixing
Homogeneous
discharge
Pelletizing
Particle Sciences

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.

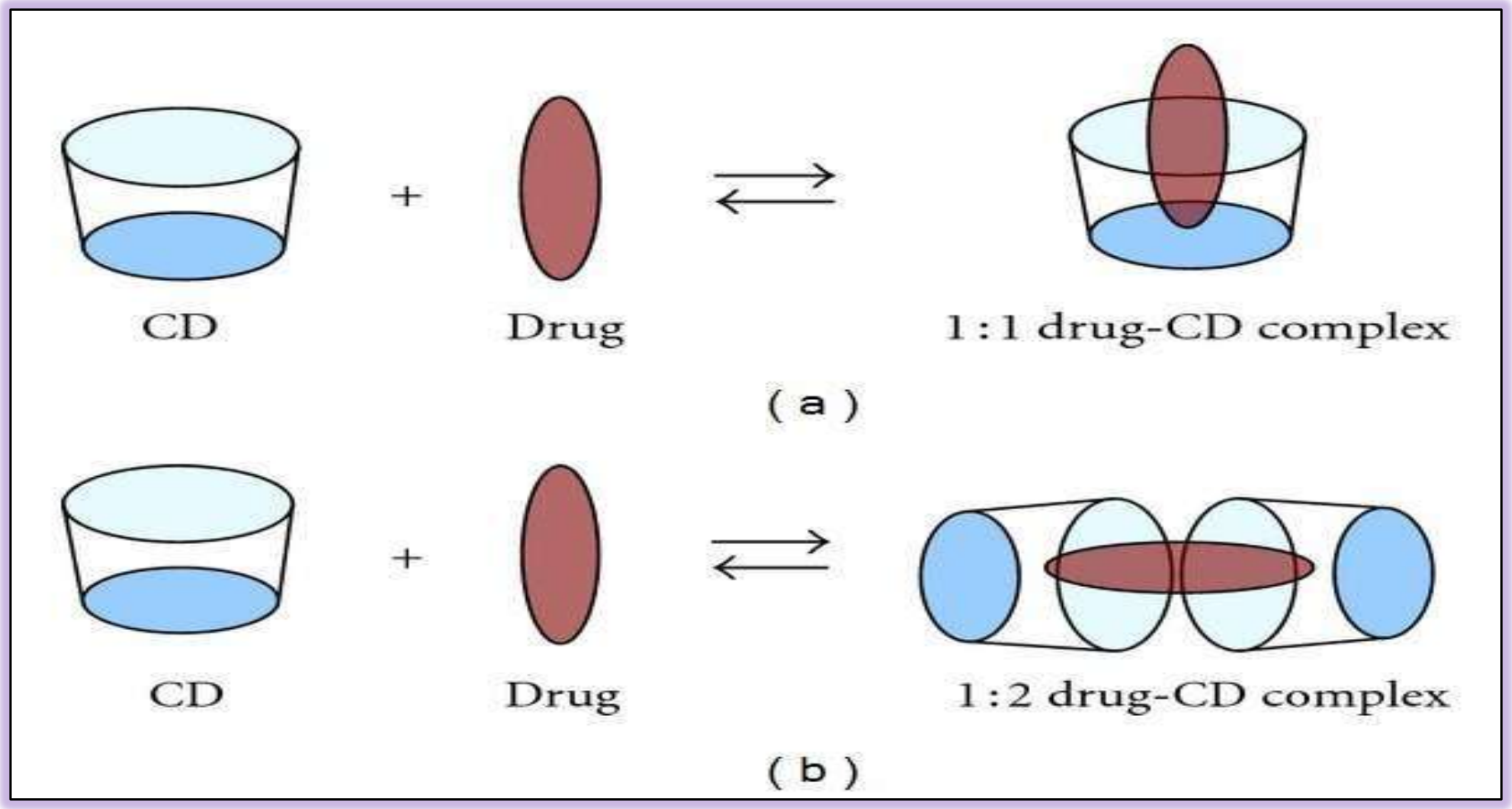
Molecular Encapsulation with Cyclodextrin

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.



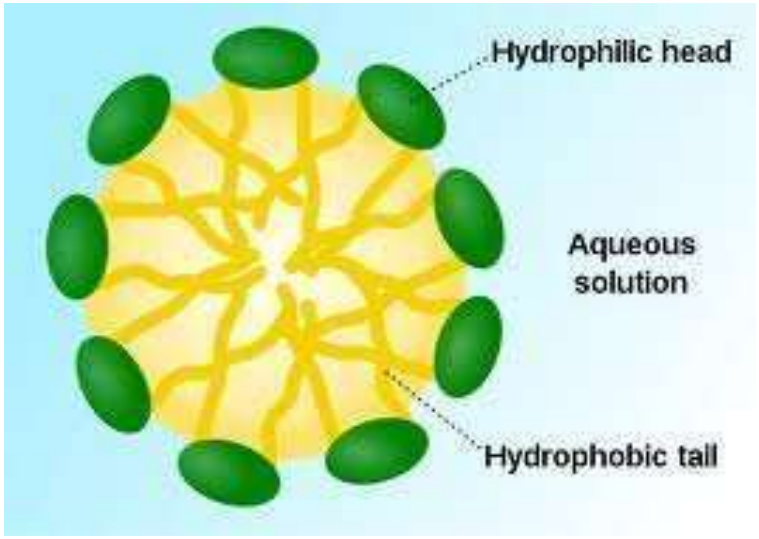
CYCLODEXTRIN

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.



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

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

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

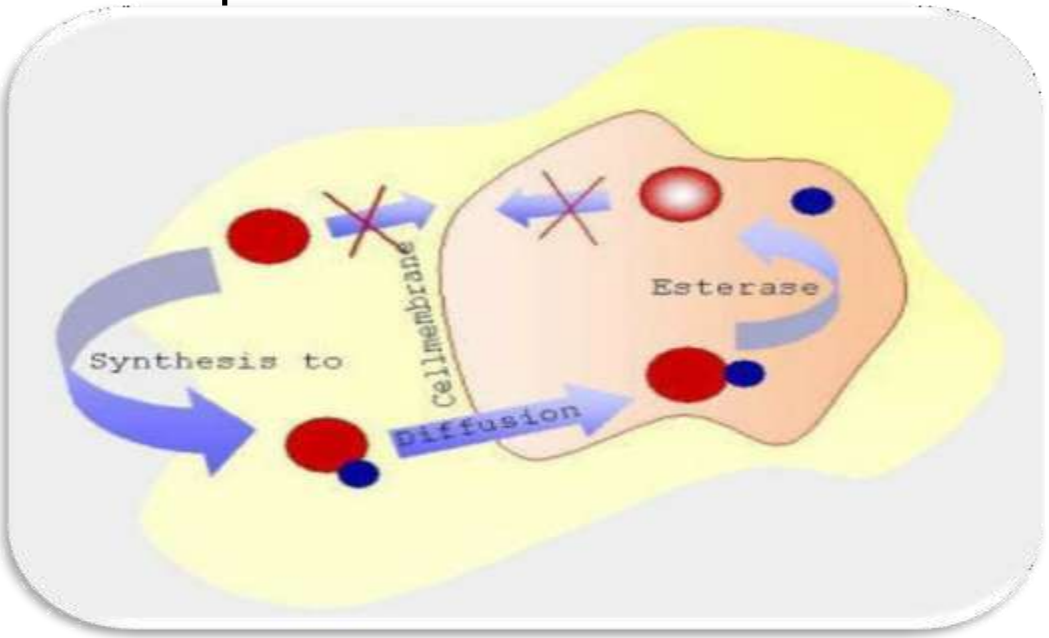
3. **Solubilizing agents:** The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazide85. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly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

4. **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 by evaporation of solvent.

- 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.

GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)

GRDDS are designed on the basis of delayed gastric emptying and controlled release principles, and are intended to restrain and localize the drug delivery device in the stomach or within the upper part of the small intestine until the entire drug is released.

Excipients that are bioadhesive or that swell on hydration when incorporated in an oral dosage form, can promote gastro-retention and absorption by-

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

Cellulose ethers, gums of natural origin, and synthetic acrylic acid polymers have been evaluated for such purposes.

THANK YOU