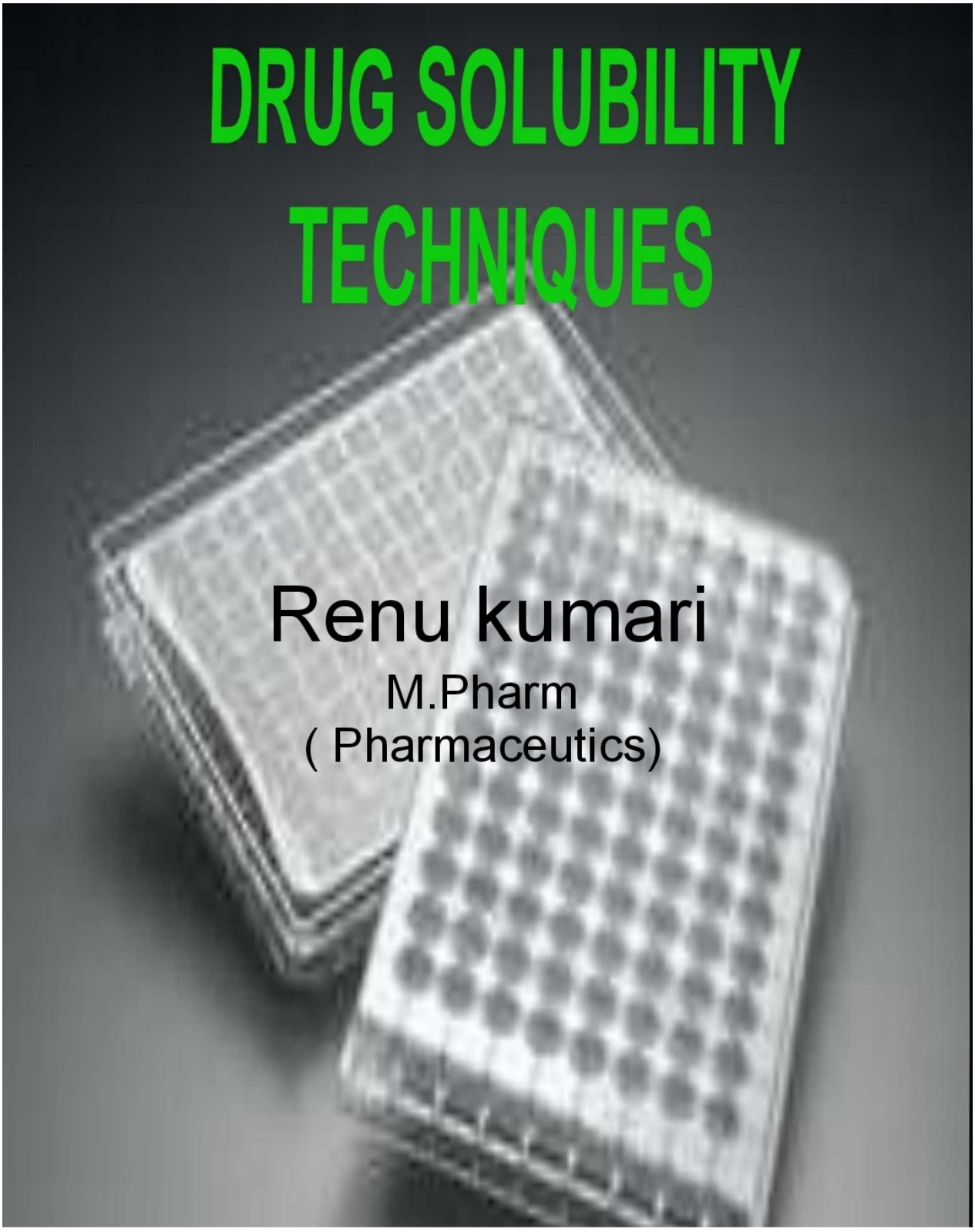
DRUG SOLUBILITY TECHNIQUES



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Introduction

- *According to recent estimates, nearly 40% of new chemical entities are rejected because of poor biopharmaceutical properties.*

- *To counter this problem, pharmaceutical companies are implementing strategies to measure, predict and improve solubility of promising new drug candidates during the preclinical phases of drug development.*

Contents

- Introduction
- Terms related to solubility
- Bio-pharmaceutical classification
- Importance of solubilty
- Theory of solubilisation
- Solubilisation techniques

- **Solution**

  Solution is a homogeneous dispersion of two or more kinds of molecular or ionic substance.

- **Solvent**

  The components of solution present in gratest quantity

- **Solute**

  The component which are dissolved in greatest quantity

- **Solubility**

  The quantity of solute that will dissolve in a specified quantity of aolvent to produce a saturated solution .

- *Saturated*

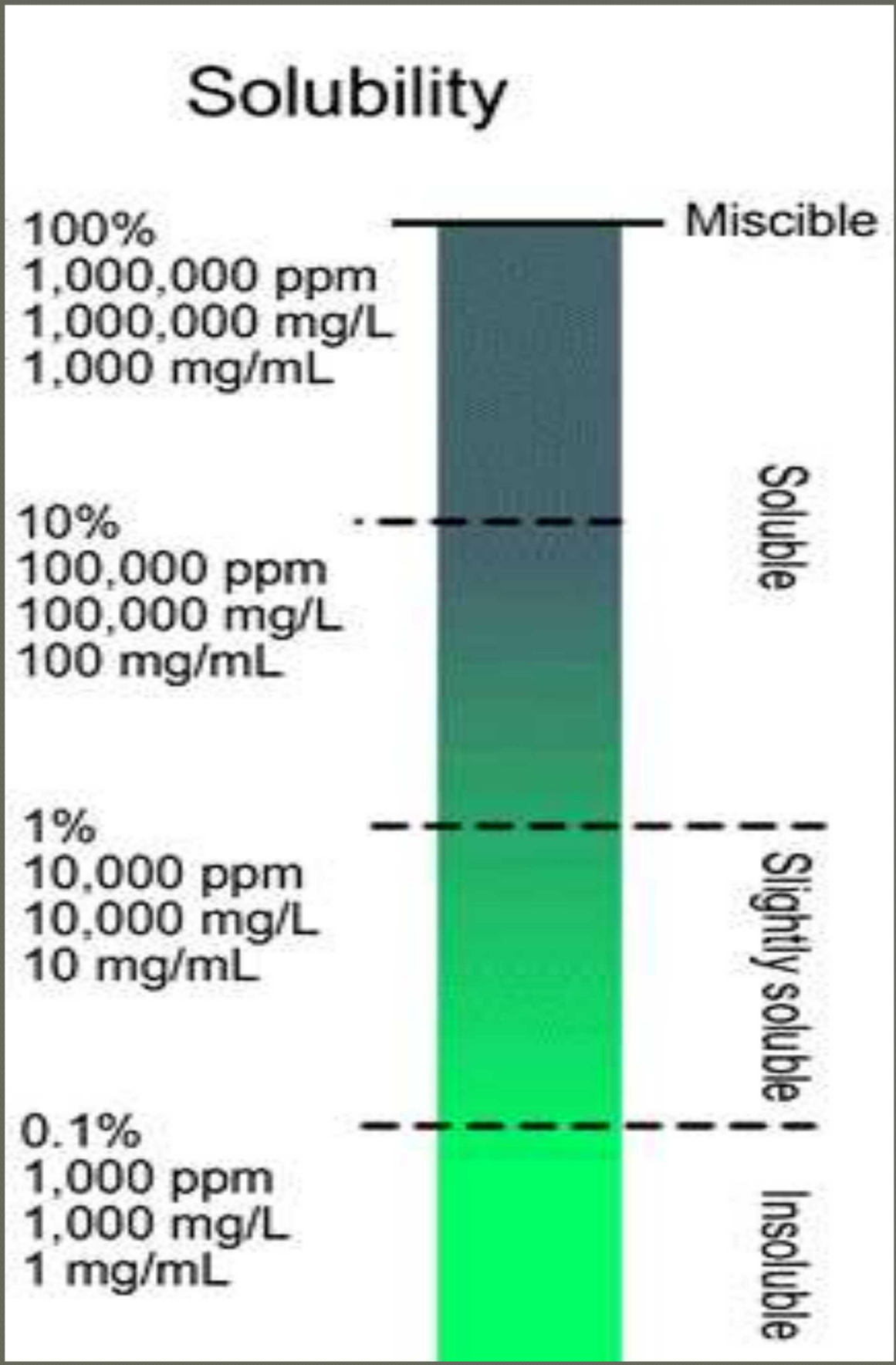
  A condition which exists when no more of a molecular or ionic species will dissolve in a liquid solution

- *Unsaturated solution*

  A condition which exists when more of molecular or ionic species could be dissolved in solutuion.

- *Super saturated solution*

  A condition which exist when a solvent holds more of solute in a solution then is normally possible at a given temperature


Solubility
100%
1,000,000 ppm
1,000,000 mg/L
1,000 mg/mL
Miscible
10%
100,000 ppm
100,000 mg/L
100 mg/mL
Soluble
1%
10,000 ppm
10,000 mg/L
10 mg/mL
Slightly soluble
0.1%
1,000 ppm
1,000 mg/L
1 mg/mL
Insoluble

Definition Required	Parts of solvent for one part of solute
Very soluble	< 1
Freely soluble	1-10
Soluble	10-30
Sparingly	30-100
Slightly	100-1000
Very slightly	1000-10,000
Insoluble	>10,000

Biopharmaceutics Classification

Class I - High Permeability, High Solubility

Example: Metoprolol

Class II - High Permeability, Low Solubility

Example: Glibenclamide

Class III - Low Permeability, High Solubility

Example: Cimetidine

Class IV - Low Permeability, Low Solubility

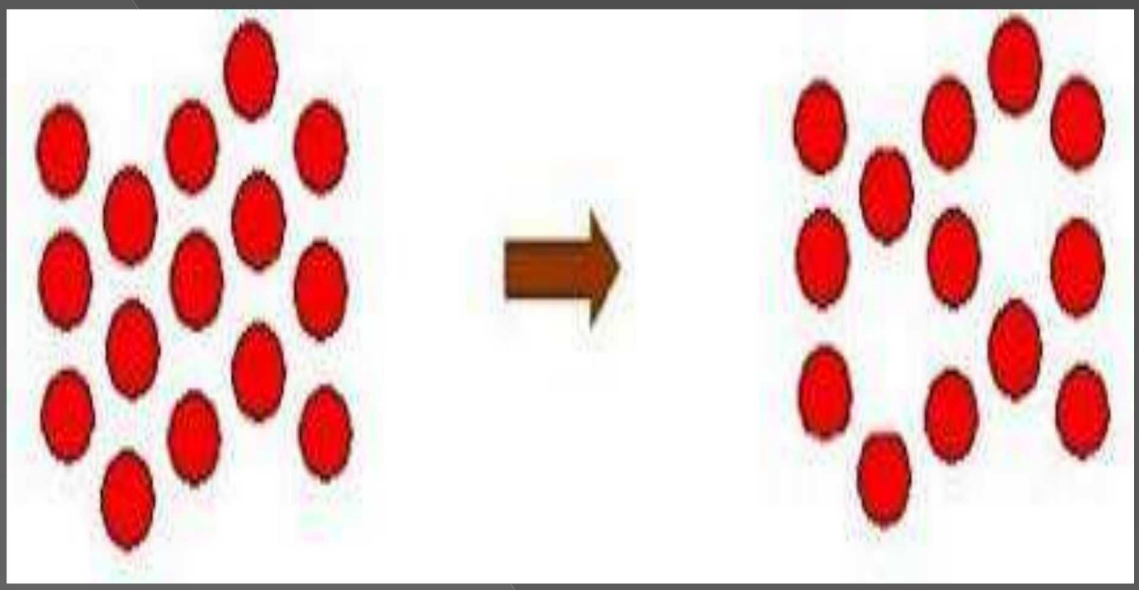
Example: Hydrochlorothiazide

PROCESS OF SOLUBLISATION

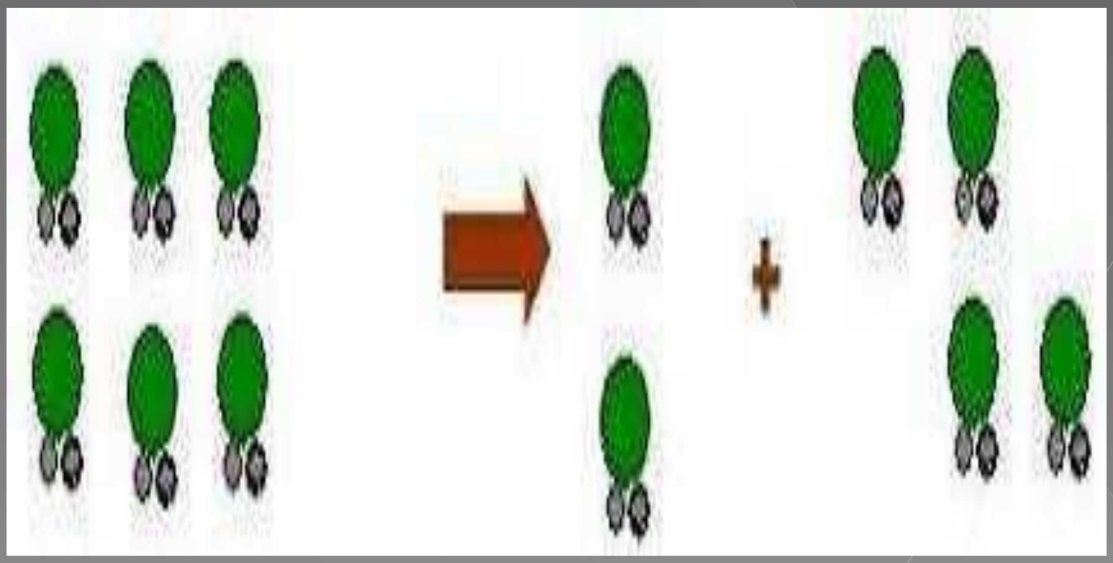
The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute , the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion .

Process is explained in three steps as follows

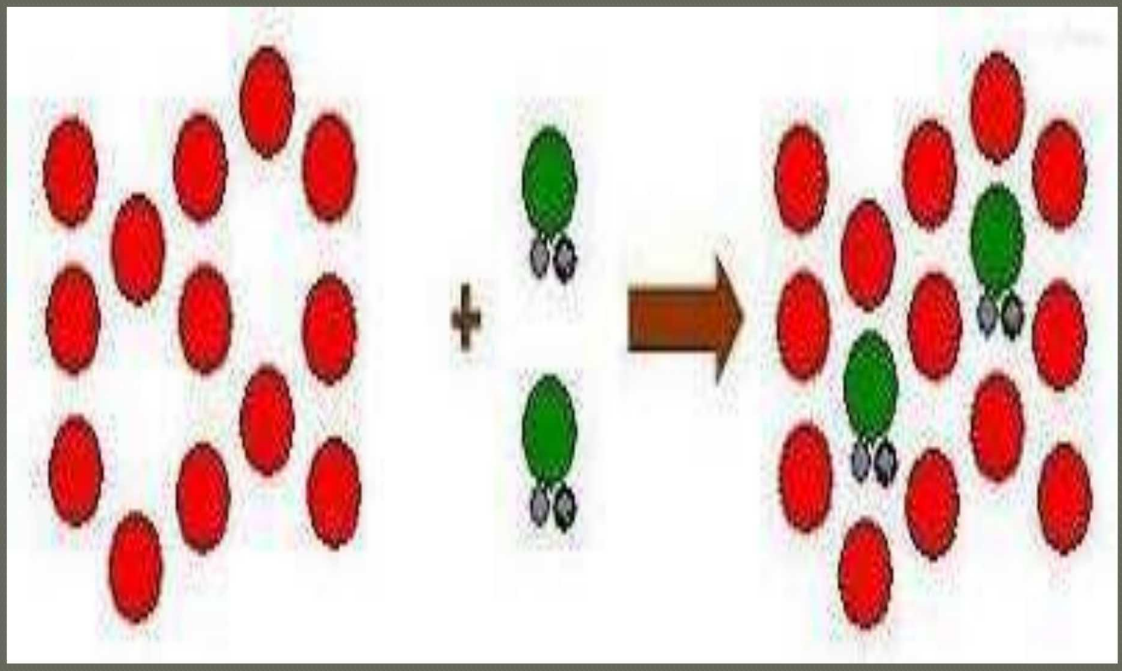
- Step 1: Holes opens in the solvent



- Step2: Molecules of the solid breaks away from the bulk



- **Step 3: The freed solid molecule is integrated into the hole in the solvent**



Solubility Process

A mechanistic perspective of solubilization process for organic solute in water involves the following steps:

a. break up of solute-solute intermolecular bonds
b. break up of solvent-solvent intermolecular bonds
c. formation of cavity in solvent phase large enough to accommodate solute molecule
d. vaporization of solute into cavity of solvent phase
e. formation of solute-solvent intermolecular bonds
f. reformation of solvent-solvent bonds with solvent restructuring

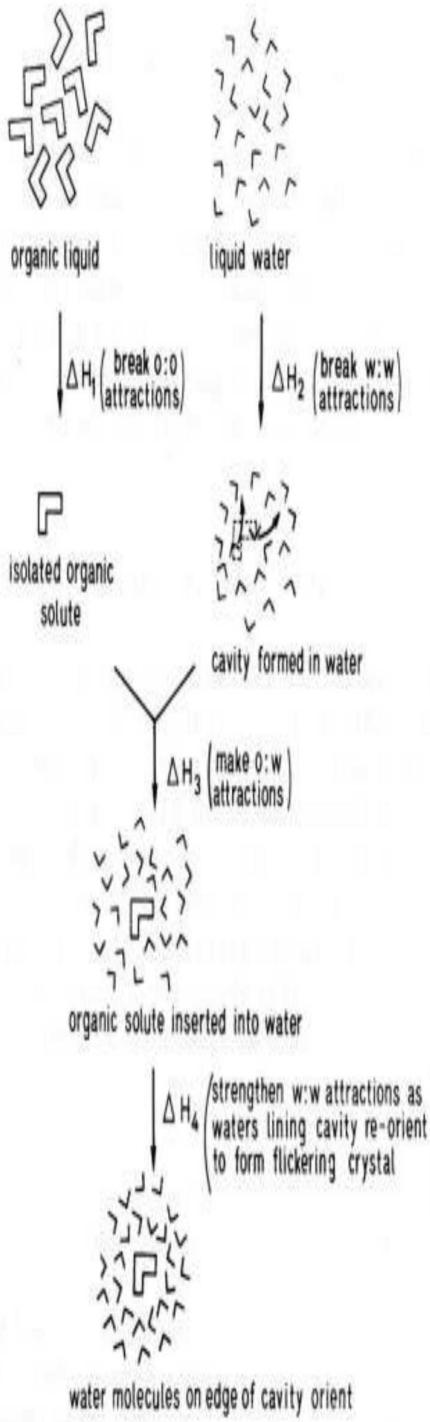


Figure 5.2 Schematic representation of the various enthalpies involved when dissolving a neutral organic molecule in water.

TECHNIQUES

1. Particle Size Reduction
2. Addition of Solubilising Excipients
3. Solid Dispersions
4. Inclusion Complexes
5. Lipid-based Emulsion Systems
6. Manipulation of Solid State
7. Manipulation Novel Nanotechnologies for Solubilisation

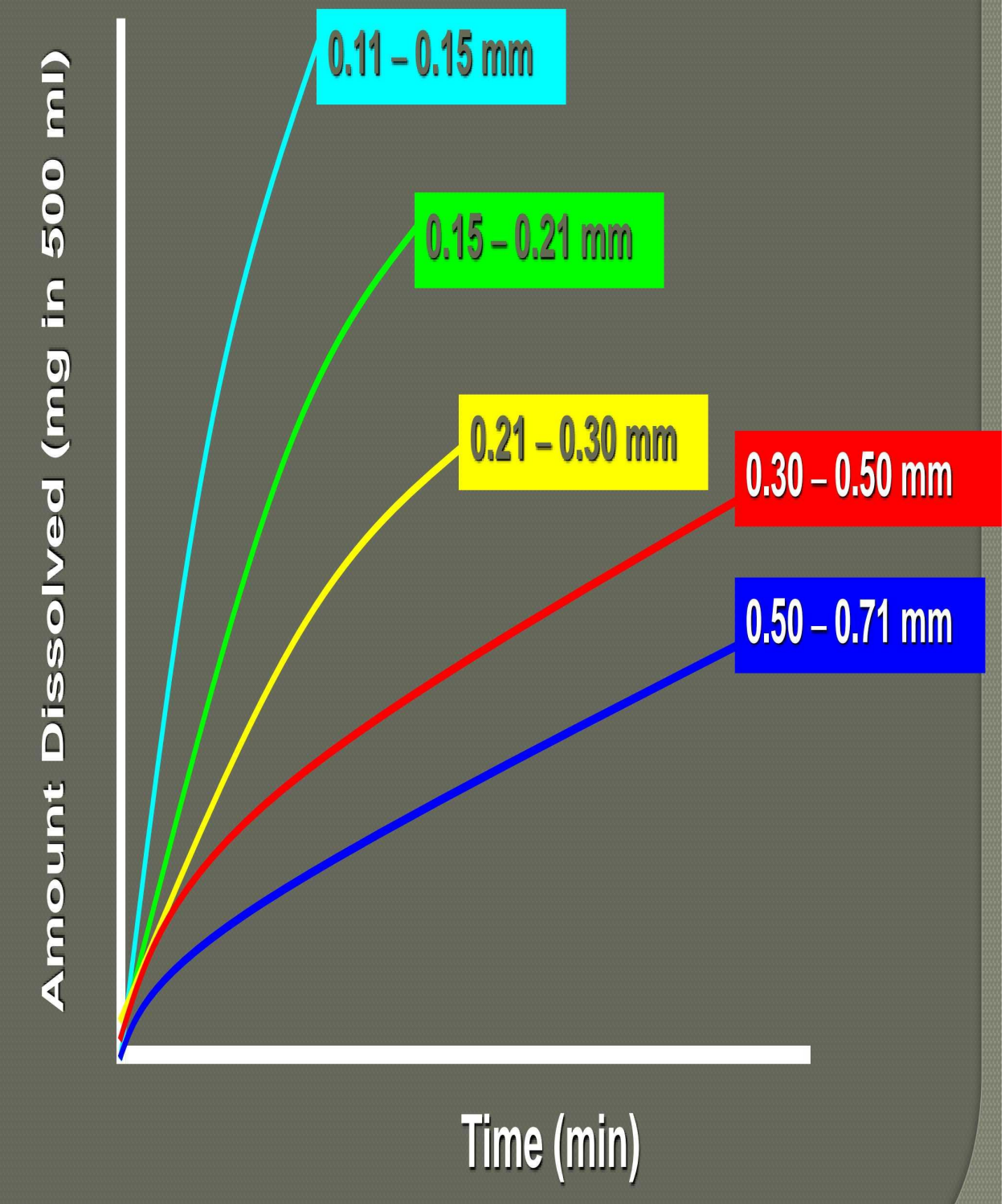
Particle Size Reduction

- *Particle size reduction results in increased surface area that generally improves drug dissolution.*

- *Where by the raw material is subjected to mechanical shear forces resulting in the deaggregation of the solid particles.*

COLLOIDAL MILL:

Effect of particle size of phenacetin on dissolution rate of the drug from granules



(Finholt)

Addition of Solubilising Excipients

Solubilising excipients in the form of

1. P^H adjusters
2. Co- solvents
3. Surfactants

P^H adjustment

- *Depends on the pKa of the drug and Generally Regarded as Safe (GRAS) buffering agents are used as necessary.*
- *PH ranges from 2 to 11 are generally acceptable for oral products, whereas it is desirable to formulate as close to the physiological pH as possible for parenteral products as significant variations can result in painful injections.*

Co-solvent

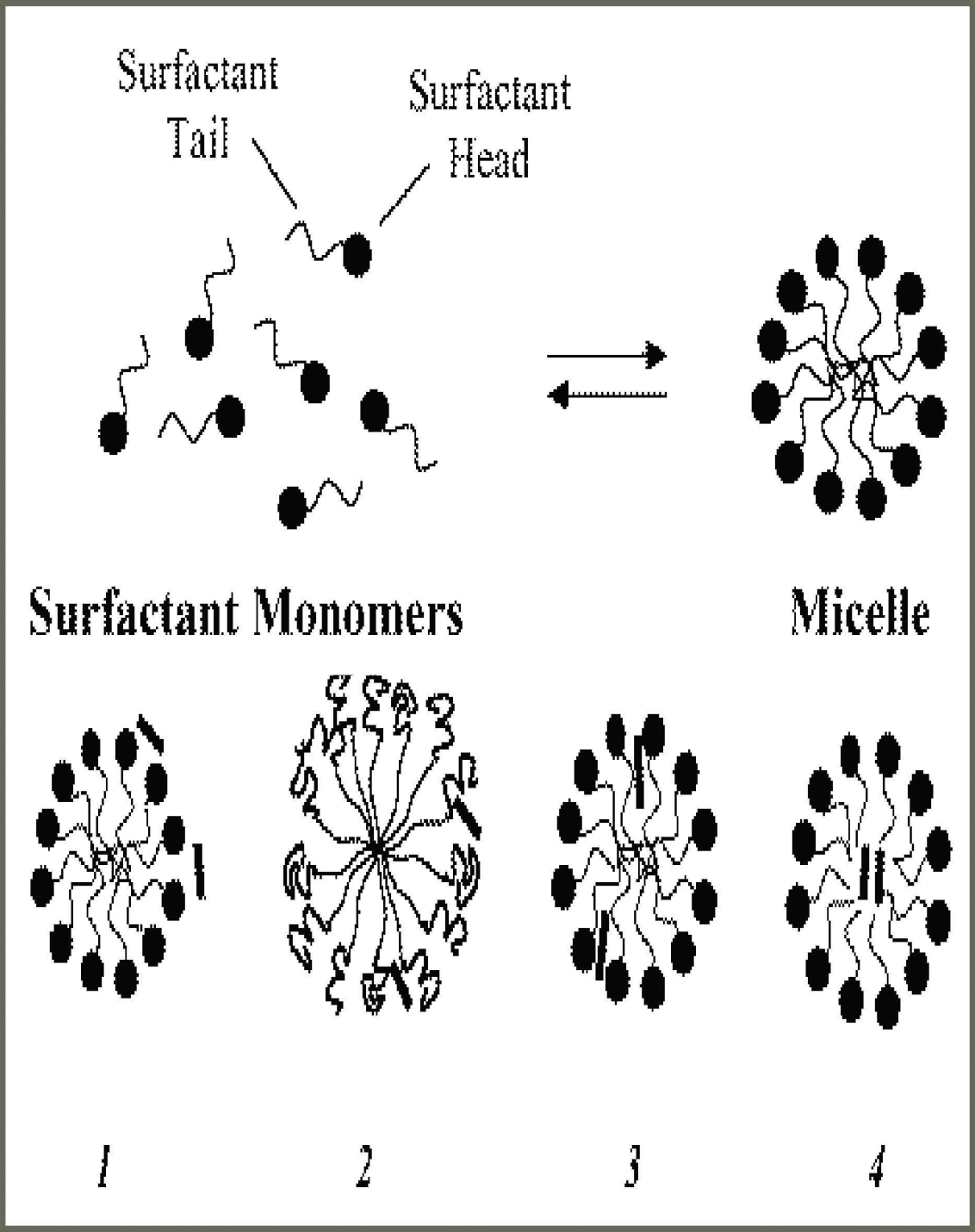
- *A poorly soluble drug is mixed with a water-miscible organic solvent in which the drug has high solubility before addition to an aqueous medium.*
- *The solubility of a non-polar drug has generally been observed to increase in a log-linear fashion with the addition of co-solvents*

Eg: Ethanol, propylene glycol, glycerin & Low molecular weight polyethylene glycols

Surfactants

Surfactants can lower surface tension & improve the dissolution of lipophilic drugs in aqueous medium.

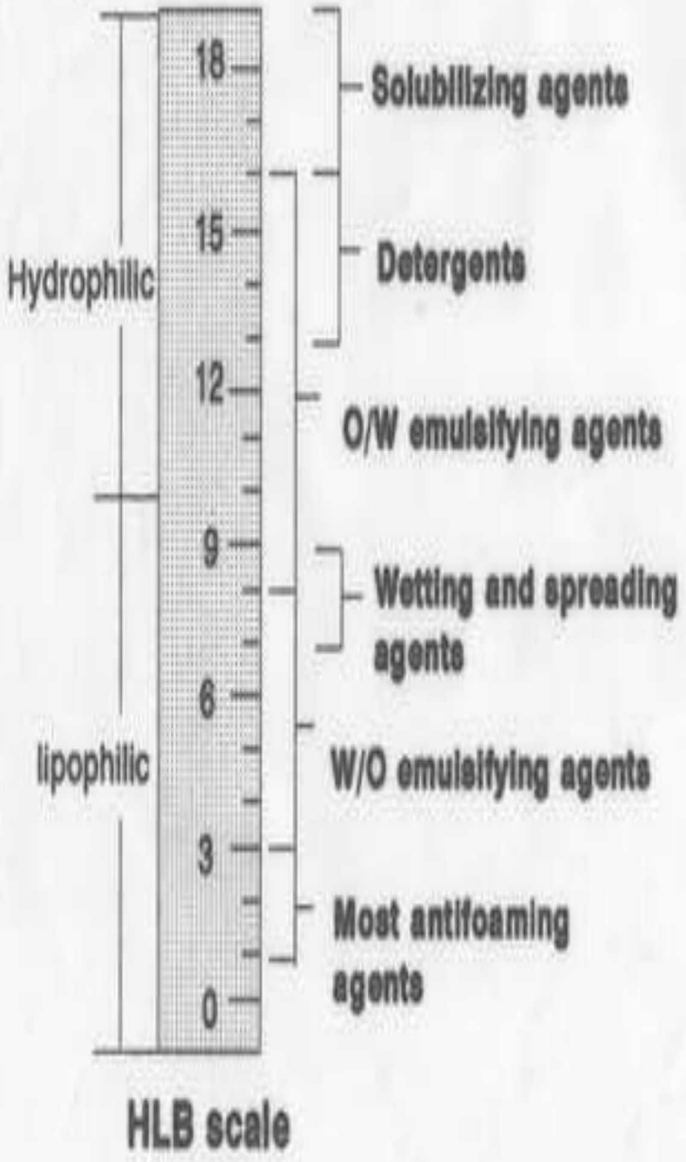
Eg:-Non-ionic surfactants include polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauroyl macroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols



Accordingly, hydrophilic drugs can be adsorbed on the surface of the micelle (1), drugs with intermediate solubility should be located in intermediate positions within the micelle such as between the hydrophilic head groups of PEO micelles (2) and in the palisade layer between the hydrophilic groups and the first few carbon atoms of the hydrophobic group, that is the outer core (3), and completely insoluble hydrophobic drugs may be located in the inner core of the micelle (4)

Relationship between HLB Value and Use of Surfactants

Range of HLB	Use of Surfactant
3 - 6	W/O emulsifier
6 - 9	Wetting agent
8 - 18	O/W emulsifier
13 - 15	Detergent
15 - 18	Solubilizing agent

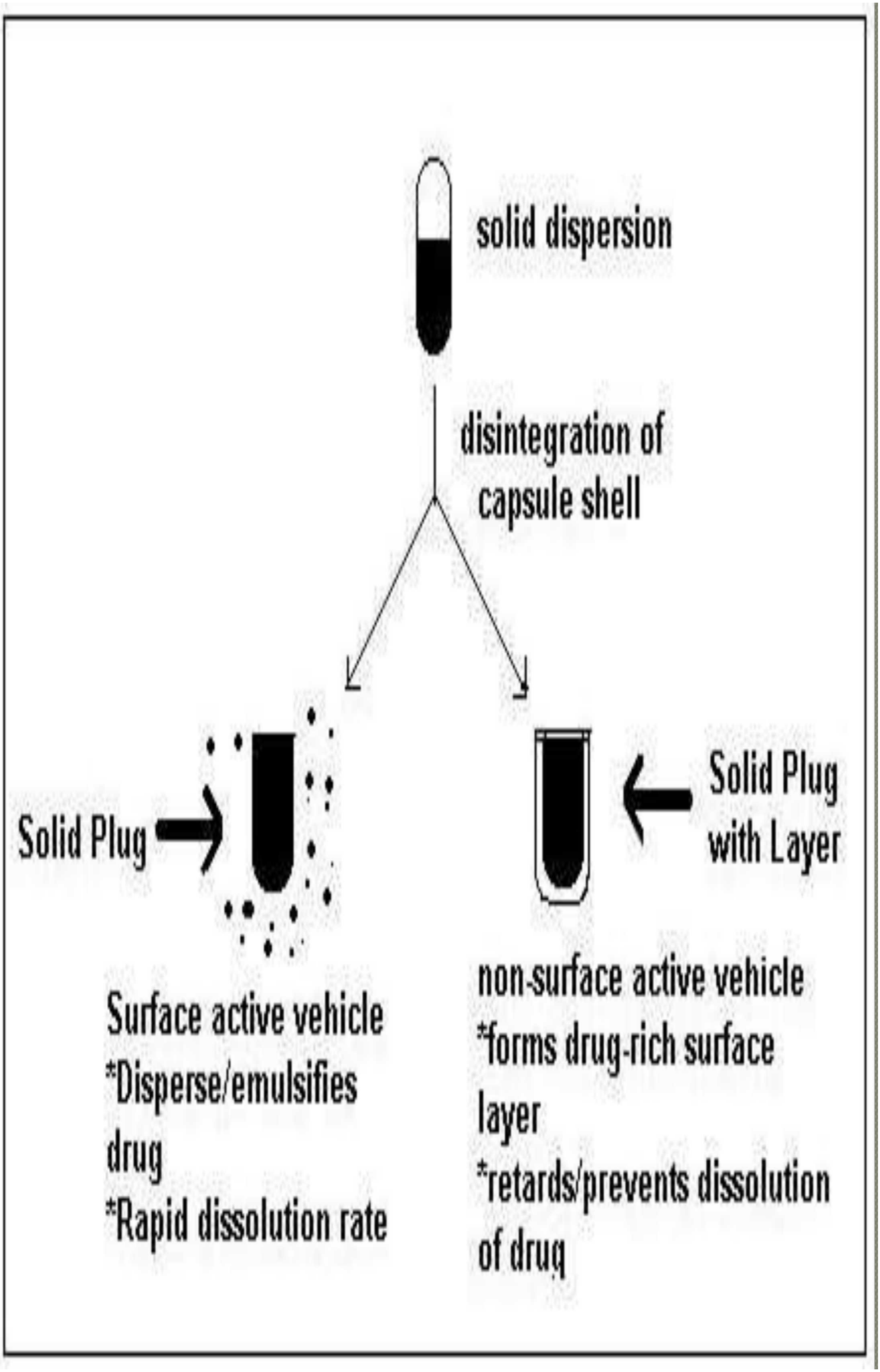


HLB =Σ (hydrophilic group number) - Σ (lipophilic group number + 7

Solid Dispersions

In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug.

- Solid dispersion techniques can yield eutectic (non-molecular level mixing) or solid solution (molecular level mixing) products
- Eutectic dispersions are homogeneous dispersions of crystalline or amorphous drugs in crystalline or amorphous carriers.


solid dispersion
disintegration of capsule shell
Solid Plug
Solid Plug with Layer
Surface active vehicle
*Disperse/emulsifies drug
*Rapid dissolution rate
non-surface active vehicle
*forms drug-rich surface layer
*retards/prevents dissolution of drug

Inclusion Complexes

Lipophilic drug-cyclodextrin complexes, commonly known as inclusion complexes, can be formed simply by adding the drug and excipient together, resulting in enhanced drug solubilisation

Eg:-Hence, methyl, hydroxypropyl, sulfoalkylated and sulfated derivatives of natural cyclodextrins that possess improved aqueous solubility are preferred for pharmaceutical use.

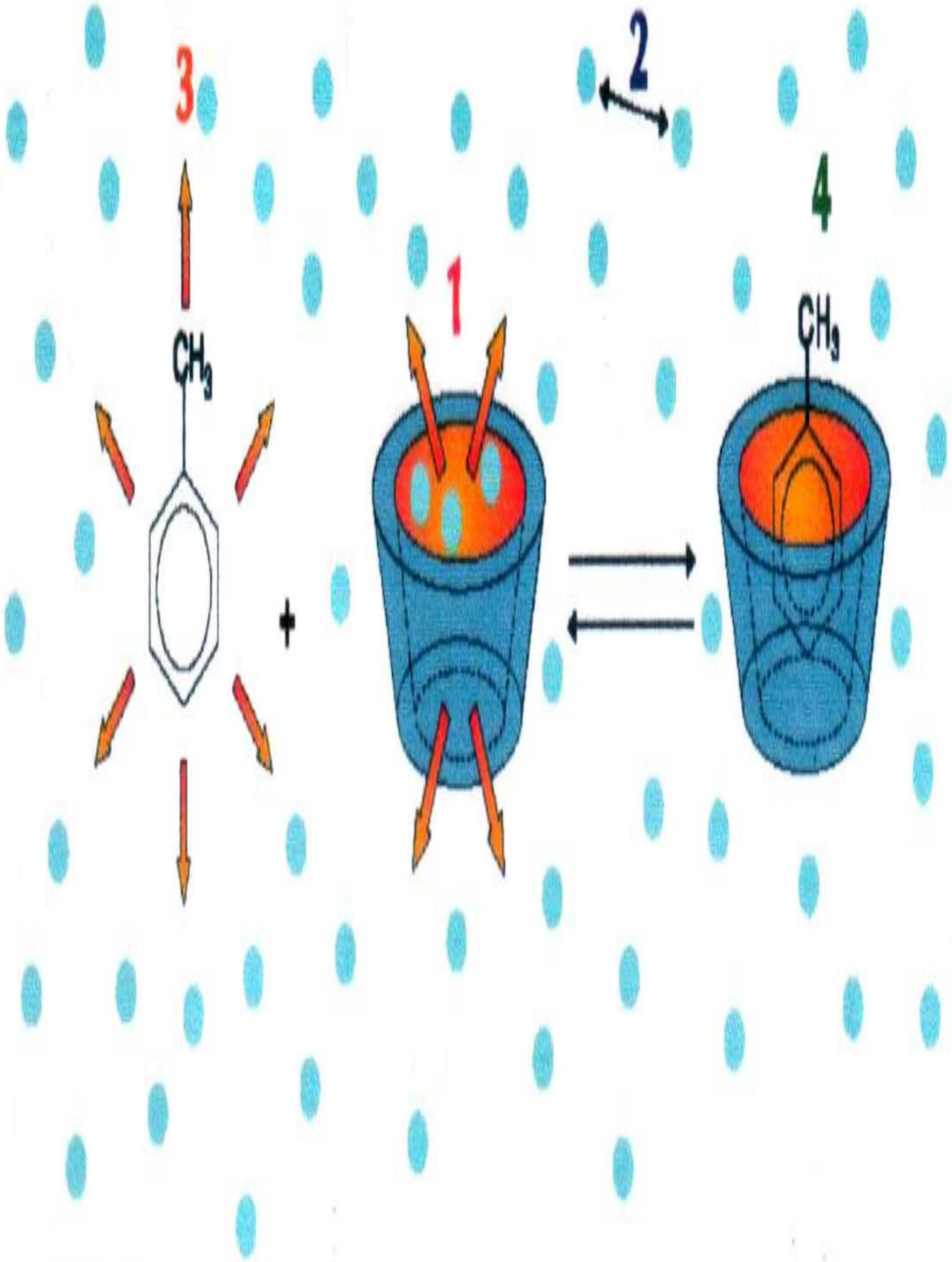


Figure 2.

The driving force for forming cyclodextrin inclusion complex with a guest molecule.

Lipid-based Emulsion Systems

As the drugs are solubilised in the oil phase, emulsions facilitate the absorption of poorly soluble drugs as the micro- or nanosized dispersed oil phase is easily absorbed.

- *Micro emulsions are thermodynamically stable, optically isotropic solutions that form spontaneously*

- Self-emulsifying or self-micro emulsifying systems use the concept of *in situ* formation of emulsion in the gastrointestinal tract.

  Eg: Neoral

- Sub-micron emulsions (droplet size <1000 nm) prepared by high- pressure homogenisation or microfluidisation and with very low levels of surfactants

  Eg:-Emulsions for total parenteral nutrition (TPN) therap Diprivan (propofol) and Diazemuls (diazepam)

Manipulation of Solid State

- *Depend on the escaping tendency of the molecules from a particular crystalline structure.*
- *For a drug that exists in multiple polymorphic forms, the polymorph with the highest order of crystallinity is the most stable form, i.e. with the least amount of free energy, and, consequently, possesses least melting point and the highest solubility.*

THANK YOU