Unit III

Surface and interfacial phenomenon

Solubilization:

It can be defined as the preparation of a thermodynamically stable isotropic solution of a substance normally insoluble or very slightly soluble in a given solvent by the addition of component or components or by any suitable methods

Process of solubilization

1) Breaking of inter-ionic or inter–molecular bonds in the solute
2) Separation of solute molecules to provide space for the solute
3) Interaction between the solvent and solute molecule or ion

a) Molecules of solids break away from bulk

b) Separation of solvent molecules

c) Freed solid molecules is integrated into the holes of solvent molecule

Solubilization techniques- co- solvency:

- Substances like weak electrolytes and non-polar molecules are poorly soluble in water.
- The solubility of these substances can be enhanced by the addition of water miscible solvents in which the drug has good solubility.
- This process of improving solubility is called as co-solvency and the solvents used are known as co-solvents.
- This technique is mainly used in the formulation of parenterals.

- Commonly used co-solvents are Ethanol, Sorbitol, Glycerin, Polyethylene glycol, propylene glycol etc.
- The solubilizing effect by co-solvency is depends on the polarity of the drug with respect to solvent and co-solvent. That means more non-polar the solute the greater is the solubilization achieved by the added solvents.
- Mechanism responsible for solubility enhancement through co-solvency is by reducing the interfacial tension the predominantly aqueous solution and hydrophobic solutes and reduces the contact angle between the solid and liquid.
- Co-solvents increases the solubility by reducing the difference between the polarity of the drug and water system. Ex. For co-solvency
- The solubility of diazepam can be increased by using 10% ethanol and 40% propylene glycol. Phenobarbitone is relatively insoluble in water but its solubility can be increased by using mixture of solvents like water, alcohol and glycerin.

Addition of surfactants:

- Surfactants are very useful as absorption enhancers and enhance both dissolution rate as well as permeability of the drug.
- Surfactants act by reducing the surface tension and forms colloidal aggregates known as micelles.
- Micelles are formed at CMC
- CMC: The lowest concentration at which micelles first appear is called the critical concentration for micelle formation.
- The critical micelle concentration is the point at which surfactant molecules aggregate together in the liquid to form groups known as micelles.

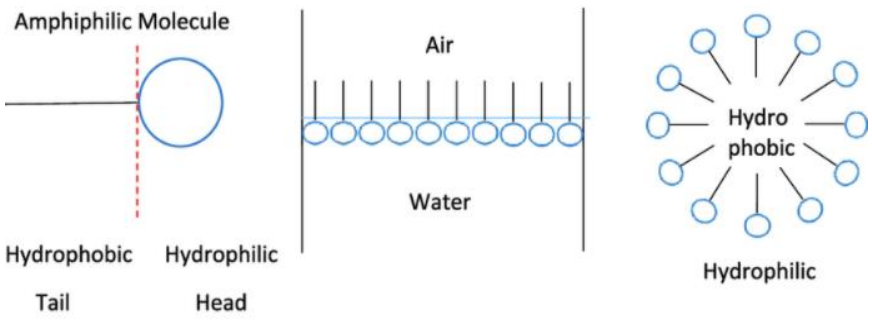

Figure: Micelles formation

- Ability of a surfactant solution to dissolve or solubilise water insoluble materials starts at CMC and increases with increase in conc. of micelles.
- Lipophilic surfactants with HLB value higher than 15 are best solubilising agents Concentration of surfactant must be controlled.
  - very high concentration → Affect on bioavailability
  - very less concentration → Improper solubilization

Complexation:

- It is reversible association of a substrate and ligand molecule.
- The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylene glycol, N methylglucamide.
- Cyclodextrin are unique since they increase the water solubility of poorly soluble drugs by fitting them into the hydrophobic cavity of the cyclodextrin molecule.
- Cyclodextrin are unique since they increase the water solubility of poorly soluble drugs by fitting them into the hydrophobic cavity of the cyclodextrin molecule.
- These cyclodextrins have the ability to form molecular inclusion complexes with hydrophobic drugs having poor aqueous solubility.

Changing temperature:

- The solubility of a solute or solid in a liquid is dependent on temperature, nature of solute and nature of solvent.
- ΔHs(heat of solution) represents the heat released or absorbed when a mole of solute is dissolved in a large amount of solvent.
- If the solution process is endothermic, increase in temperature increases the solubility of the solute.
- And if the solution process is exothermic, increase in temperature decreases the solubility of the solute.

pH Control:

- Majority of the drugs are either weak acids or bases, and therefore their solubilities in water can be influenced by the pH of the system. There is a little or no effect of pH on solubility of non-ionizable substances with few exceptions.
- For ionizable solutes such as carboxylic acid (HA) solubility is function of pH, Fig. The solubility of weak acid is increased by an increasing pH where as solubility of weak base increased by decreasing pH.

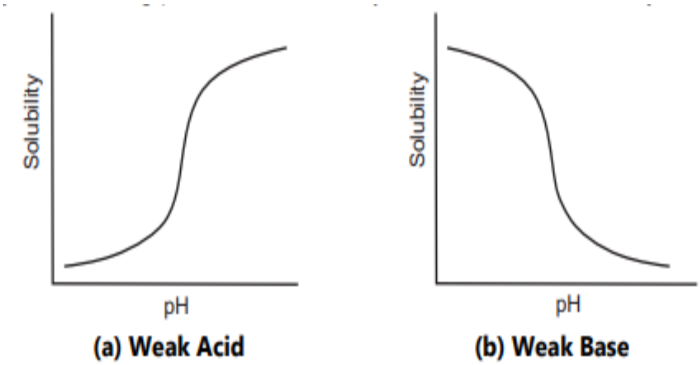

Fig: The Effect of pH on Solubility

- The pH of solute is related to its pKa and concentration of the ionized and unionized form of the solute by equation
  - $pH = pKa + \log [A^-] / [HA]$
- If the solute is brought outside its pKa by changing the pH value where half portion is ionized and half portion remains unionized, then the solubility will be changed. This is due to introduction of intermolecular forces, mainly ionic force of attraction.
- For example, carboxylic acid groups (−COOH) have pKa around pH 4 and if the pH is increased above 4 the −COOH is changed to $-COO^-$.
- The negative charge introduced is free to have introduction with a partial positive charges of the hydrogen of water.
- The effect of the pH on solubility of weak electrolytes is described by equation
  - $pHp = pKa + \log [\frac{S - So}{So}]$

  Where, pHp is the pH below which the drug precipitates from solution as the undissociated acid, S is the total solubility and So is the molar solubility of the undissociated acid. We often consider that ionize form is freely soluble but is not always true.
- For example, carboxylic acids have pKa ~ 4. For the administration of methyl prednesolone hemisuccinate (solubility <1 mg/ml if base such as sodium hydroxide is added the carboxylic acid becomes deprotonated and solubility increases to more than 200 mg/ml. The same can be observed for base, therefore,

$$pHp = pKw + pKb + \log[\frac{S}{S - So}]$$

Where, pKw is dissociation constant of water, pKb is dissociation constant of base and pHp is the pH above which the free base precipitates out of solution.

- Solubility of weak electrolytes in buffer solution can be changed by addition of cosolvents. The undissociated species get dissolved by modifying polarity of solvent to a more favourable value.
- In improving solubility of drugs by pH control it must be ensured that the selected pH does not change the other requirement of the product such as chemical stability that may also depend on pH.
- Non-ionizable, hydrophobic solutes can have improved solubility by changing the dielectric constant of solvent by use of cosolvent. The maximum solubility must be best achieved by appropriate balance between pH and concentration of cosolvent.
- The solubilities of the non-electrolytes are not much affected by the pH changes therefore other methods can be tried for their solubility enhancement.

Solid state manipulations:

- Polymorphic modifications
- Solubility of each form depends upon the ability of the molecules to escape from the crystal to solvent.
- The stable form posses the lower free energy at a particular temperature and therefore has the lower solubility or escaping tendency where as the meta stable forms posses higher free energy hence has higher solubility.
- About fifty to hundred percent increase in the dissolution rate can be achieved through polymorphic modifications.

  Examples: Chloramphenicol palmitate (form B)

Methyl prednisolone (form 2)

Chlor tetracycline (form B)

Prepared by:

Sridevi Murugesan

Department of Pharmaceutics

SNS College of Pharmacy and Health Sciences