Unit - I

Solubility of drugs

Factors influencing the solubility of drugs:

Temperature:

- ✓ Temperature will affect the solubility.
- ✓ Generally, an increase in temperature of solution, increase the solubility of solid solute.
- ✓ If the solution process is endothermic (i.e absorb energy) then solubility will increased as the temperature is increased.
- ✓ Endothermic- Temperature ∝ Solubility
- ✓ With the increase temperature → solubility of KI, NaNO3, KNO3 increases. **Here, the reaction is Endothermic**.
- ✓ If the solution process releases energy (i.e exothermic) then the solubility will decrease with the increasing with the increasing temperature.
- ✓ Exothermic – Temperature ∝ 1/ Solubility.
- ✓ With increase in temperature → Solubility of HCL, NH_3 and SO_2 decreases. **Here the reaction is Exothermic.**

Nature of Solvent:

- ✓ The solubility of solute depends on the nature of solute and solvent.
- ✓ The polarity of solute and the polarity of the solvent affect the solubility.
- ✓ For example – Polar solvents dissolve polar solutes and non- polar solvents dissolves non- polar solutes.

The boiling point of liquid and melting point of solid:

- ✓ Both reflects the strengths of interaction between the molecules in the pure liquid or the solid state.
- ✓ In general, the aqueous solubility decreases with the increasing boiling and melting point.

Crystal properties:

- ✓ Polymorphs have the same chemical structure but different physical properties such as solubility, density, hardness and compression characteristics.
- ✓ A drug that exists as an Amorphous form (non crystalline form) generally dissolve more rapidly that the some drug in crystalline form.

Surface area of Drug particles:

- ✓ ↓ particle size → ↑ surface area → ↑ solubility.
- ✓ But this is valid upto certain extent and beyond which , in the very fine particle static force is developed and club to form agregation.

The influence of substituents in molecular structure:

- ✓ Substituents can be classified either hydrophobic or hydrophillic, depending on their polarity.

  (a) Polar groups such as -OH capable of H-bonding with water molecules impart high solubility.

  (b) Non polar group such as -CH3 and -Cl are hydrophobic and impart low solubility.

  (c) Ionization of the substituents increases solubility.
- ✓ For example : -COOH and -NH2 are slightly hydrollic whereas -COO- and -NH3 are very hydrophillic.

- ✓ The position of the substituents on the molecule can influence its effect on the solubility.
- ✓ For example: The aqueous solubilities of O- , m- and p- dihydroxy benzene is 4 mol.cm^3,9 mol.cm^3 and 0.6 mol.cm^3 respectively. (i.e diffrent).

Molecular size

- ✓ Molecular size will affect the solubility.
- ✓ The larger the number of molecules, higher its molecular weight, the less soluble the substance.
- ✓ Larger molecules are more difficult to surround with molecules in order to solvate the solution.
- ✓ In case of organic compounds the amount of carbon branching will increase the solubility.
- ✓ Since, more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecule with solvent.
- ✓ Example: n – butane and tertiary butyl structure.

pH:

- ✓ pH is one of the primary influence on the solubility of most drug that contains ionizable groups.
- ✓ Large number of drugs are weak acids and weak bases.
- ✓ Solubility depends upon the degree of the Saturation (Ionized/Unionized)
- ✓ Degree of Ionization depends upon the Ph(acid and base)
- ✓ Strong (acidic/basic drugs) —— Ionized at all ph.
- ✓ Weak (acidic/basic drugs) ——-Only Ionized at certion pH
- ✓ Most of the drugs are weak acids or weak bases.

- ✓ Ionized drugs are not very lipid soluble, only non- ionizable form of drug crosses membrane readily.
- ✓ Weak acids become highly Ionized as pH increases.
- ✓ Weak bases become highly Ionized as pH decreases
- ✓ pka is the negative log of the Ionization constant and is equal to the ph at which the drug is 50% ionized and 50% unionized.
- ✓ % Ionization is pH dependent.
- ✓ In case of Ionizable substance, the ph depends upon the Henderson Hasselbalch equation.
- ✓ According to Henderson Hasselbalch – "The difference between the pH of solution and the pka of the drug is the common logarithm of the ratio of Ionized to Un-ionized forms of a drug".

Solute – Solvent Interaction:

- ✓ Relation between solute- solvent interactions is very important in determining solubility.
- ✓ Strong solute-solvent interaction → ↑ Solubility.
- ✓ Weak solute-solvent interaction → ↓ Solubility.

Common ion effect:

- ✓ The process in which solubility of a weak electrolyte is reduced by the addition of a strong electrolyte which has common ion to that of weak electrolyte.
- ✓ Example: On passing HCl gas through aqueous solution of NaCl , concentration of Cl- ions is increased, therefore some of the NaCl is precipitated out to maintain the constant value of the equilibrium constant.
- ✓ This is called as common ion effect which reduces solubility.

Effect of surfactants (solubilising agent):

- ✓ Solubility of poor soluble drugs may be enhanced by a technique known as micellar solubilisation, which involves the use of surfactants for increasing the solubility.
- ✓ When a surfactant having a hydro-philic (water loving) and a lipo-philic (or hydrophobic water hating) portion is added to a liquid, it→ re-arranges itself to from a spherical aggregate known as micelle.

Effect of non-electrolytes on the solubility of electrolytes:

- ✓ The solubility of electrolytes in water primarily depends on the dissociation of the dissolved molecules into ions.
- ✓ The ease with which the electrolyte dissociates depends on the dielectric effect (ability of solvent to produce charge separation between positive and negative ions of an electrolyte and keep them ionized) of the solvent, which depends on the polar nature of the solvent.
- ✓ Addition of a water soluble non-electrolyte such as alcohol to an aqueous solution of a sparingly soluble salt decreases the solubility of sparingly soluble electrolyte i.e. salt.
- ✓ This effect is due to lowering of the dielectric effect (charge separation ability) of the solvent by the non-electrolyte, and this in turn reduces dissociation of the salt.