**Solubility and the Solution Process:**

 The solid dissolves rapidly at first, but as the solution approaches saturation the net rate of dissolution decreases since the process is in dynamic equilibrium.

 Once at equilibrium, the amount of solute does not change with time.

 At equilibrium- rate of dissolution = rate of solution.

**Solubility Thermodynamics:**

 The Gibbs Free Energy of Mixing- ΔG = ΔH – T.ΔS

Where ΔG= Gibbs Free Energy of Mixing, ΔH = enthalpy (energy, heat), ΔS = entropy (disorder), T = temperature.

 The entropy of mixing favours complete miscibility of all components.

 Enthalpy- balance of the:

o Drug-drug interactions (D-D) (cohesive forces).

o Solvent-solvent interactions (S-S) (cohesive forces).

o Drug-solvent interactions D-S (adhesive forces).



 ΔH is sometimes negative, and sometimes positive, as it is a sum of the following:

o S-S – energy required to break weak bonds between solvent molecules.

o D-D – energy required to break intermolecular bonds between the solute molecules.

o D-S – ΔH is negative since bonds are formed between the species.

 Intermolecular forces are important in determining the solubility of a substance as ‘like’ intermolecules forces for solute and solvent will make the solute soluble in the solvent.

 ΔG must be negative for a solution to form. (ΔG - = stable system, + = unstable system)

ΔH should be minimal.

 ΔS should be maximal (increases stability)

**Clinical Relevance of Solubility:**

 Solubility can affect bioavailability and therapeutic response.

 Need enough drug in solution to reach concentrations that are therapeutically meaningful.

 Stability of drug.

 Formulated drug product disintegrates into dispersed drug particles, which undergo dissolution into solubilised drug which passes a membrane (must be permeable to drug) and is absorbed.

Increasing no. drugs BCS Class II and IV (poorly soluble drugs). 90% and higher = high permeability. Below

90% - low permeability.

API = Active Pharmaceutical Ingredient, NCE= New Chemical Entity (still in developmental stages).



**Measurement of Solubility:**

N.B. –

 The solvent and solute must be pure.

 A saturated solution must be obtained before any solution is removed for analysis.

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