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Importance of studying the phenomenon of solubility-

Understanding the phenomenon of solubility helps the pharmacist to:

1.Select the best solvent for a drug or a mixture of drugs.

2.Overcome problems arising during preparation of pharmaceutical solutions.

3.Have information about the structure and intermolecular forces of the drug.

4.Many drugs are formulated as solutions, or added as powder or solution forms to liquids.

5.Drugs with low aqueous solubility often present problems related to their formulation and bioavailability.

Definitions

- **Solution:** is a mixture of two or more components that form a homogenous mixture. The components are referred to the **solute and/or solutes** & the **solvent and/or solvents** .
- **Solute:** is the dissolved agent . (less abundant part of the solution)
- **Solvent** : is the component in which the solute is dissolved (more abundant part of the solution).
- **A saturated solution:** is one in which an equilibrium is established between dissolved and undissolved solute at a definite temperature. Or A solution that contains the maximum amount of solute at a definite temperature

- **An unsaturated solution:** or subsaturated solution is one containing the dissolved solute in a concentration below that necessary for complete saturation at a definite temperature.
- **A supersaturated solution:** contains more of the dissolved solute than it would normally contain in a saturated state at a definite temperature.

- **In a quantitative way:** it is the concentration of solute in a saturated solution at a certain temperature
- **In a qualitative way:** it is the spontaneous interaction of two or more substances (solute & solvent) to form a homogeneous molecular dispersion

Thermodynamic solubility of drugs

- The thermodynamic solubility of a drug in a solvent is the maximum amount of the most stable crystalline form that remains in solution in a given volume of the solvent at a given temperature and pressure under equilibrium conditions.
- The equilibrium involves a balance of the energy of three interactions against each other:

(1) solvent with solvent

(2) solute with solute

(3) solvent and solute

Solubility expressions

- The USP lists the solubility of drugs as: the number of ml of solvent in which 1g of solute will dissolve.
- E.g. 1g of boric acid dissolves in 18 mL of water, and in 4 mL of
- glycerin.
- Substances whose solubility values are not known are described by the following terms:

Sr. No.	Description forms (Solubility)	Parts of solvent required for one part of solute
1	Very soluble (VS)	<1
2	Poorly soluble (PS)	1-10
3	Soluble	10-30
4	Sparingly soluble (SPS)	30-100
5	Slightly soluble (SS)	100-1000
6	Very slightly soluble (VSS	1000-10000
7	Practically insoluble (PI)	>10000

Mechanism of solute solvent interactions

Sr. No	Nature of Solvent	Mechanism of solubility	Example
1	Polar	a. High dielectric constant b. H- bond formation c. dipole interactions	Water+ ethanol
2	Non-polar	weak van der waal's forces	Fats, oils, alkaloidal bases + CCL4, benzene
3	Semi-polar	induce certain degree of polarity	Acetone increase solubility of ether in water

Solvent - Solute Interactions

- In pre - or early formulation, selection of the most suitable **solvent** is based on the principle of **"like dissolves like"**
- That is, a solute dissolves best in a solvent with similar chemical properties. Or two substances with similar intermolecular forces are likely to be soluble in each others
- Polar solutes dissolve in polar solvents. E.g **salts & sugar dissolve in water.**
- Non polar solutes dissolve in non polar solvents. Eg**. Naphtalene dissolves in benzene.**

Polar solute – polar solvent

Ammonia Dissolves in Water:

- Polar ammonia molecules dissolve in polar water molecules.
- These molecules mix readily because both types of molecules
- engage in hydrogen bonding.
- Since the intermolecular attractions are roughly equal, the molecules can break away from each other and form new solute (NH3), solvent (H2O) hydrogen bonds.

Alcohol Dissolves in Water:

- The -OH group on alcohol is polar and mixes with the polar water through the formation of hydrogen bonds.
- A wide variety of solutions are in this category such as sugar in water, alcohol in water, acetic and hydrochloric acids.

Solute-Solvent interactions

- If the solvent is **A** & the solute is **B**, and the forces of attraction are represented by **A-A**, **B-B** and **A-B**, **One of the following conditions will occur:**

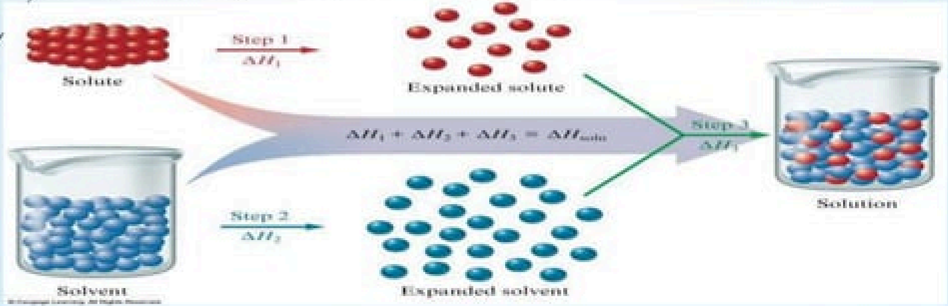
1. If **A-A >> A-B** The solvent molecules will be attracted to each other & the solute will be excluded. Example: Benzene & water, where benzene molecules are unable to penetrate the closely bound water aggregates.
2. If **B-B >> A-A** The solvent will not be able to break the binding forces between solute molecules. Example NaCl in benzene, where the NaCl crystal is held by strong electrovalent forces which cannot be broken by benzene.
3. If **A-B >> A-A** or **B-B**, or the three forces are equal The solute will Form a solution. Example: NaCl in water.

Solvation / Dissolution

" Interaction of a solute with the solvent, which leads to stabilization of solute species in the solution"

+ve solvation energy= endothermic dissolution

-ve solvation energy= exothermic dissolution

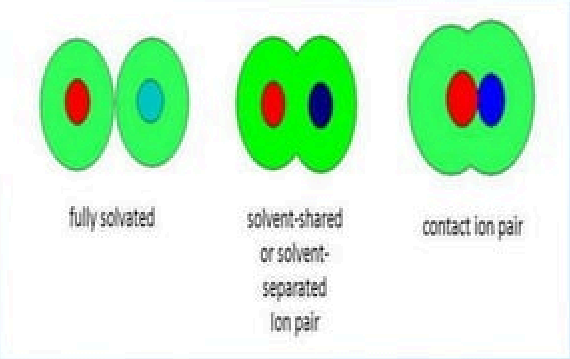


Association

" Chemical reaction in which the opposite electric charge ions come together in solution & form a distinct chemical entity"

Classification according to nature of interaction:

1. Contact
2. Solvent shared
3. Solvent separated

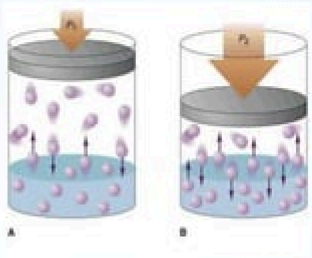


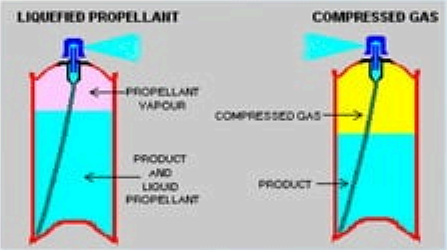
Factors influencing solubility

- Temperature
- Nature of solvent (like dissolves like)
- Pressure
- pH
- Particle size
- Crystal structure
- Solubilizing agents

Solubility of gases in liquids

- When the pressure above the solution is released (decreases), the solubility of the gas decreases
- As the temperature increases the solubility of gases decreases.
- Ex: Carbonated water: is exothermic process.
- Ex: Pharmaceutical aerosols: Liquefied gas under pressure "Propellant"





Solubility of liquids in liquids

- Preparation of pharmaceutical solutions involves mixing of 2 or more liquids
- Alcohol & water to form hydroalcoholic solutions
- volatile oils & water to form aromatic waters
- volatile oils & alcohols to form spirits , elixirs

Liquid-liquid systems may be divided into 2 categories:

- 1. Systems showing *complete miscibility* such as alcohol & water, glycerin & alcohol, benzene & carbon tetrachloride.
- 2. Systems showing *Partial miscibility* as phenol and water; two liquid layers are formed each containing some of the other liquid in the dissolved state.
- **The term miscibility refers to the mutual solubility of the components in liquid-liquid systems.**

- **Complete miscibility** occurs when: The adhesive forces between different molecules (A-B) >> cohesive forces between like molecules (A-A or B-B).
- Polar and semipolar solvents, such as water and alcohol, glycerin and alcohol, and alcohol and acetone, are said to be completely miscible because they mix in all proportions.
- Nonpolar solvents such as benzene and carbon tetrachloride are also completely miscible.
- Ex: Polar and semipolar solvents: water-alcohol, glycerin-alcohol, alcohol--acetone
- Ex: Nonpolar solvents: benzene and CCl_4

- **Partial miscibility** results when: Cohesive forces of the constituents of a mixture are quite different, e.g. water (A) and hexane (B). A-A » B-B.
- When certain amounts of water and ether or water and phenol are mixed, two liquid layers are formed, each containing some of the other liquid in the dissolved state.
- The effect of temperature on the miscibility of two-component liquids is expressed by phase diagrams.
- In the phase diagrams of two-component liquids, the mixture will have an upper critical solution temperature, a lower critical solution temperature or both.

Raoult's law

- "The partial pressure (Pi) of each component in a solution is equal to the mole fraction of the component & the vapour pressure of the pure component"

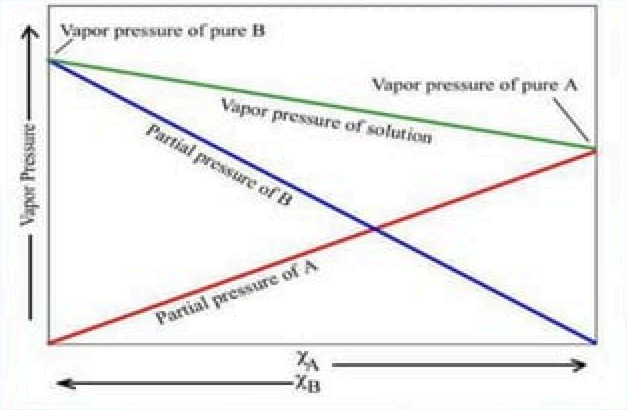
$$Pi = xP$$

Or

$$P = pAxA + pBxB$$

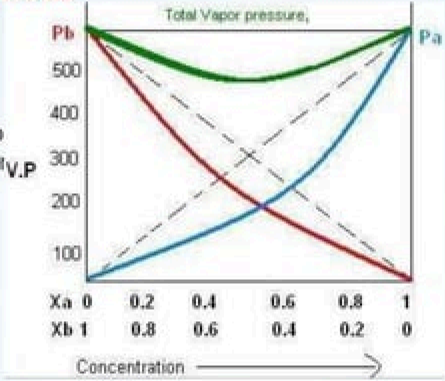
Ideal solutions

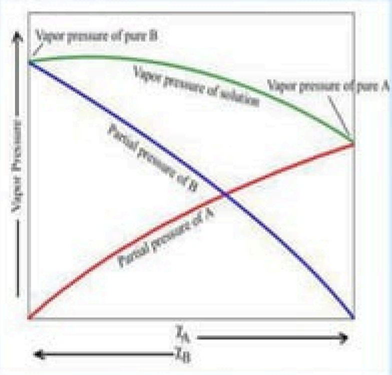
- " Solutions which obey Raoult's law in all the solute composition in a solvent"



Real/ non ideal solutions

- "Solutions which do not ob
Raoult's law over entire ra
of composition"





Negative deviation

PA < Xa P

ΔH < 0

ΔV < 0

Positive deviation

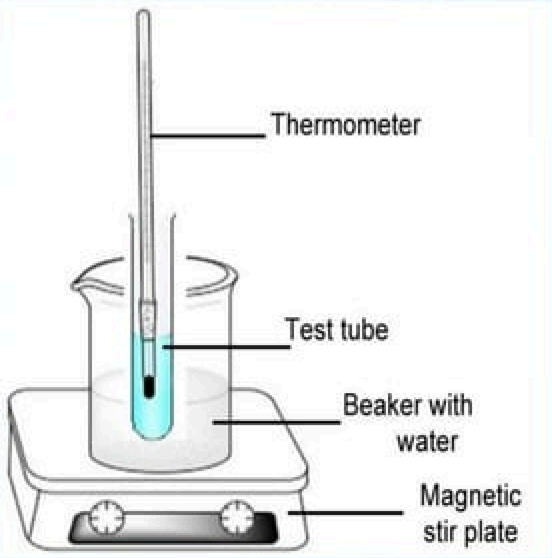
PA > Xa P

ΔH > 0

ΔV > 0

Critical Solution Temperature

- When two partialy miscible liquids mixed together , some liquid A is dissolved into B and some liquid B is dissoved into B both of these layer are known as conjugate solution.
- If such a mixture is heated the two layers disappear and form one layer. The tem at Which two partially miscible liquids become completely miscible is called " Critical Solution Temparature" or "Upper Consulate temperature"



Example

- Water and Phenol System
- Upper layer contams- 95% water and 5% Phenol
- Lower layer contains- 70% Phenol and 30% water
- At 68.4˚C (CST), two layer disappears.

Distribution Law

- The movement of molecules from one phase to another is called partitioning.
- If two immiscible phases are placed adjacent to each other, the solute will distribute itself between two immiscible phases until equilibrium is attained; therefore no further transfer of solute occurs.
- When a substance is added in excess quantity in two immiscible solvents, it distributes itself between two liquid phases so that each becomes saturated.
- The distribution or partition of a solute between immiscible liquids is known as Nernst's distribution law or simply distribution law or partition law.

- Nernst's distribution law states that when the added substance is insufficient to saturate the immiscible liquids, the solute distributes between the liquids in such a way that at equilibrium the ratio of concentrations of the solute in the two liquids is constant, at constant temperature.
- Partition(P) or distribution coefficient(D) is the ratio of concentration of a compound in the two phases of a mixture of two immiscible solvents at equilibrium.
- Hence these coefficients are a measure of differential solubility of the compound between two solvents. • One of the solvents is water and the second one is hydrophobic such as octanol. It is useful in estimating the distribution of drugs within the body.


Thank you!
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