SOLUBILITY OF DRUGS

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SOLUBILITY

" The concentration of a substance (solute) that dissolves in a given volume of solvent at a certain temperature to form a homogenous solution."

OR

" The spontaneous interaction of two or more substances to form a homogenous molecular dispersion."

Definitions

Solute: a component which dissolved in the solvent, present in less amount in the solution.

Solvent: a component in which solute is dissolved, present in more amount than solute.

Solution: A system in which solutes are completely dissolved in solvent & form a homogenous molecular dispersion.

Saturated solution: Solution in which the solute in solution is in equilibrium with solid phase.

Unsaturated solution: Solution containing dissolved solute in concentration below that necessary for complete saturation.

Supersaturated solution: Solution containing more of the dissolved solute than it would normally contain.

SOLUBILITY EXPRESSIONS

Sr.no	Description forms (Solubility)	Parts of solvent required for one part of solute
1)	Very soluble	<1
2)	Poorly soluble	1-10
3)	Soluble	10-30
4)	Sparingly soluble	30-100
5)	Slightly soluble	100-1000
6)	Very slightly soluble	1000-10000
7)	Practically insoluble	>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	Water+ ethanol
2)	Non-polar	weak van der waal's forces	Fats, oils, alkaloidal bases + CCL4, benzene
3)	Semi-polar	Semi-polar induce certain degree of polarity	Acetone increase solubility of ether in water

IDEAL SOLUBILITY PARAMETERS

'Ability of a liquid to act as a solvent'

1) Hildebrand solubility parameter (δ)

2) " square root of cohesive energy density"

$$\delta = \sqrt{\Delta Hv - RT/ Vm\ 2)}$$
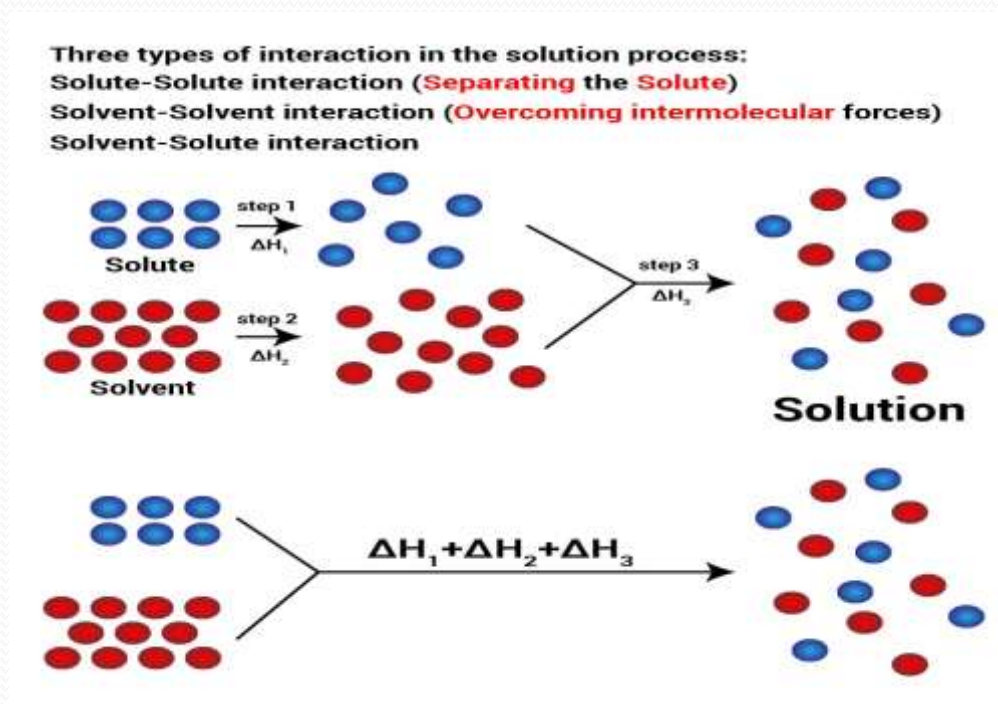
Hansen solubility parameter (δt)

$$\delta t = \delta d + \delta p + \delta h\ 6$$

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

Three types of interaction in the solution process:
Solute-Solute interaction (Separating the Solute)
Solvent-Solvent interaction (Overcoming intermolecular forces)
Solvent-Solute interaction

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 (Fully solvated)

2. Solvent shared (Solvent separated ion pair)

3. Solvent separated (Contact ion pair)

FACTORS INFLUENCING SOLUBILITY

1)Temperature

2) Nature of solvent (like dissolves like)

3) Pressure

4) pH

5) Particle size

6) Crystal structure

7) Molecular structure

8) Solute- solvent interactions

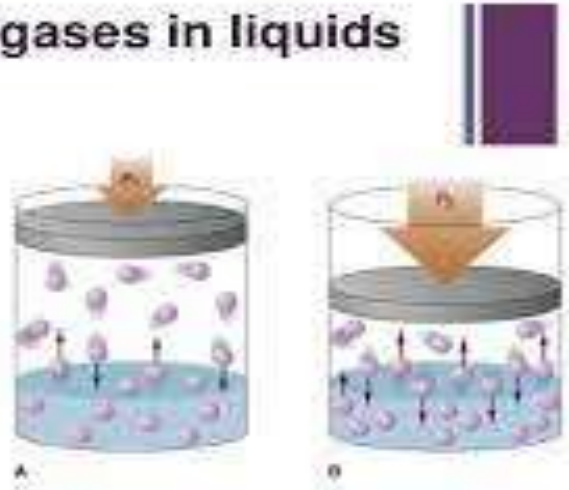9) Addition of substituent

SOLUBILITY OF GASES IN LIQUIDS

Henry's law: 'Solubility is directly proportional to partial pressure of gas at a constant temperature'.

$$S = KP$$

SOLUBILITY OF LIQUIDS IN LIQUIDS

1) Completely miscible liquids:

    e.g. Water+ ethanol, Glycerine+ Alcohol, benzene+ CCL4

2) Partially miscible liquids:

    e.g. Phenol+ water.

3) Completely immiscible liquids:

    e.g. Mercury+ water.

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

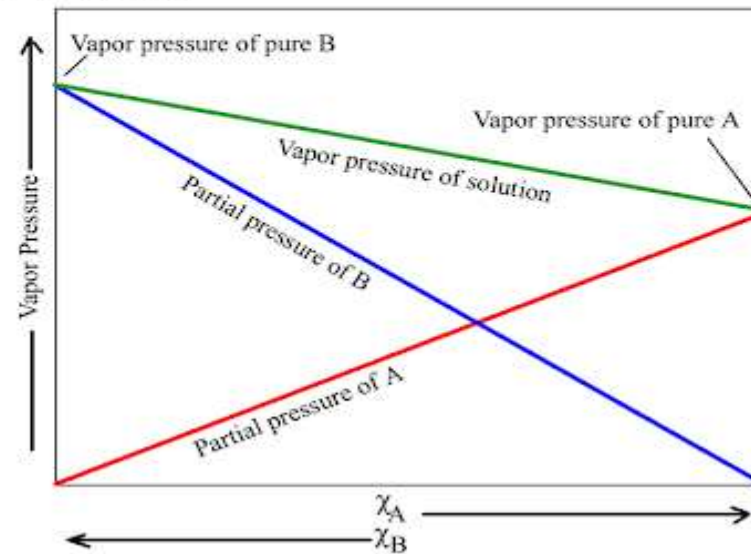P = pAxA + pBxB

IDEAL SOLUTIONS

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

REAL/ NON IDEAL SOLUTIONS

Ideal – solution	Non-ideal solution
1. The interactions between the components are similar to those in the pure components.	The interactions between the components are different to those of the pure components.
2. There is no volume change and enthalpy change on mixing the components. ($\Delta V=0$, $\Delta H=0$)	There is a change on volume and enthalpy on mixing the components. ($\Delta V \neq 0$, $\Delta H \neq 0$)
3. Each component obeys Raoults's law at all temperatures and concentrations, i.e., $p_A = x_A p°_A$ and $p_B = x_B p°_B$	They do not obey Raoult's law. They show positive or negative deviation from Raoult's law, i.e., $p_A \neq x_A p°_A$ and $p_B \neq x_B p°_B$

Partially miscible

These liquids are miscible to each other but to a limited extent i.e. partially. These liquids mix but form two layers. Each layer is a solution of one liquid into the other. Some liquid 'A' is dissolved into 'B' and some liquid 'B' is dissolved into liquid 'A'. Both of these layers (i.e. solutions) are known as conjugate solutions. If such a mixture is heated, the two layers disappear and form one layer. The temperature at which two partially miscible liquids become completely miscible is called "critical solution temperature or upper consulate temperature".

For example, when water and phenol are mixed in equal quantities, they form two layers at 25CO . The upper layer contains solution of 95% water + 5% phenol, and lower layer contains solution of 70% phenol + 30 % water. But at 68.4 CO (critical solution temperature), two layers disappear to form one phenol-water solution.

Other examples of partially miscible liquids include; Aniline – water, nicotine – water, triethylamine – water et

Critical solution temperature

The upper critical solution temperature is the highest temperature at which phase separation occurs.

Above the upper critical temperature the two component are fully miscible.

The temperature exist because the greater thermal motion overcomes any potential energy advantages in molecule of one type being close together.
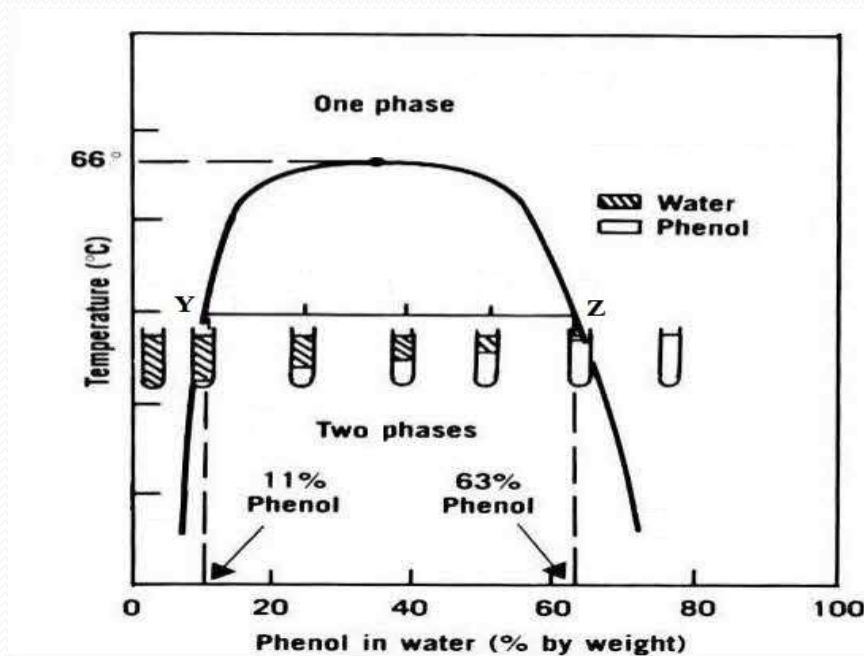
Applications

1) CST provide the temperature limits for some reaction if it occur in two miscible liquids.

2) CST is used to determined the water content in substances such as methyl alcohol.

3) It is used to determine the efficiency with which one solvent can extract a compound from a second solvent.

4) Used in extraction of neutral drugs.

NERNS'T DISTRIBUTION LAW (PARTITION COEFFICIENT)

" If a solute distributes between two immiscible solvents at a constant temperature then the ratio of its concentration in two solvents is a constant value".

K= C1/ C2

When two immiscible solvents A and B taken in a beaker, they form separate layers. Now a solute X which is soluble in both solvents is added, it gets distributed or partitioned between them. Molecules of X pass from solvent A to B and from B to A. finally a dynamic equilibrium is set up. At equilibrium, the rate, at which molecules of X pass from one solvent to the other is balanced.

Concentration of x in A = a constant

Concentration of x in B

Nernst (1891) studied the distribution of several solutes between different appropriate pairs of solvents. He gave a generalization which governs the distribution of a solute between two non-miscible solvents. This is called Nernst's Distribution law or Nernst's Partition law or simply Distribution law or Partition law. It states that, " if a solute X distributes itself between two immiscible solvents A and B at constant temperature and X is in the same molecular condition in both solvents." Concentration of x in A = KD constant

Concentration of x in B

If $C1$ denotes the concentration of the solute in solvent A and $C2$ the concentration in solvent B, Nernst's Distribution law can be expressed as

$$C1/ C2 = KD$$

Limitations of the Nernst Distribution Law

The law is valid when the molecular state of the solute is same in both the solvents.

If the solute undergoes dissociation or association in any one of the solvents, then in such cases the distribution law no longer holds good.

The distribution law can be applied in such cases with some modifications

Application of distribution law

There are numerous applications of distribution law in the laboratory as well as in industry

1) Solvent Extraction-

This is the process used for the separation of organic substances from aqueous solutions. The aqueous solution is shaken with an immiscible organic solvent such as ether (or benzene) in a separatory funnel. The distribution ratio being in favour of ether, most of the organic substance passes into the ethereal layer. The ethereal layer is separated and ether distilled off. Organic substance is left behind

2) Partition Chromatography-

A paste of the mixture is applied at the top of a column of silica soaked in water. Another immiscible solvent (hexane) is allowed to flow down the column. Each component of the mixture is partitioned between the stationary liquid phase (water) and the mobile liquid phase (hexane). The various components of the mixture are extracted by hexane in order of their distribution coefficients.

3) Desilverization of Lead (Parke's Process)

When molten zinc is added to molten lead containing silver (argentiferous lead), zinc and lead form immiscible layers and silver is distributed between them. Since the distribution ratio is about 300 in favour of zinc at 800º C, most of silver passes into the zinc layer. On cooling the zinc layer, an alloy of silver and zinc separates. The Ag-Zn alloy is distilled in a retort when zinc passes over leaving silver behind. The lead layer still contains unextracted silver. This is treated with fresh quantities of molten zinc to recover most of the silver

4) Confirmatory Test for Bromide and Iodide

The salt solution is treated with chlorine water. Small quantity of bromine or iodine is thus liberated. The solution is then shaken with chloroform. On standing chloroform forms the lower layer. The free bromine or iodine being more soluble in chloroform concentrates into the lower layer, making it red for bromine and violet for iodine.

5) Determination of Association

When a substance is associated (or polymerized) in solvent A and exists as simple molecules in solvent B, the Distribution law is modified as

$$n\sqrt{C_a}/C_b = k$$

when n is the number of molecules which combine to form an associated molecule

6) Determination of Dissociation

Suppose a substance X is dissociated in aqueous layer and exists as single molecules in ether.
If x is the degree of dissociation (or ionisation), the distribution law is modified as

$$C_1 /C_2)(1-x) = K$$

where C_1 = concentration of X in benzene C_2 = concentration
of X in aqueous layer

The value of x can be determined from conductivity measurements, while C_1 and C_2 are found experimentally.

Thus the value of K can be calculated. Using this value of K, the value of x for any other concentrations of X can be determined