



UNIT - I



SOLUBILITY

Points to be covered in this topic

1. INTRODUCTION

2. SOLUBILITY EXPRESSION

3. IDEAL SOLUBILITY PARAMETERS

4. APPLICATION OF SOLUBILITY
PARAMETERS

5. FACTOR AFFECTING SOLUBILITY

6. DIFFUSION PRINCIPLE

7. SOLUBILITY OF GAS IN LIQUIDS

8. SOLUBILITY OF LIQUIDS IN LIQUIDS

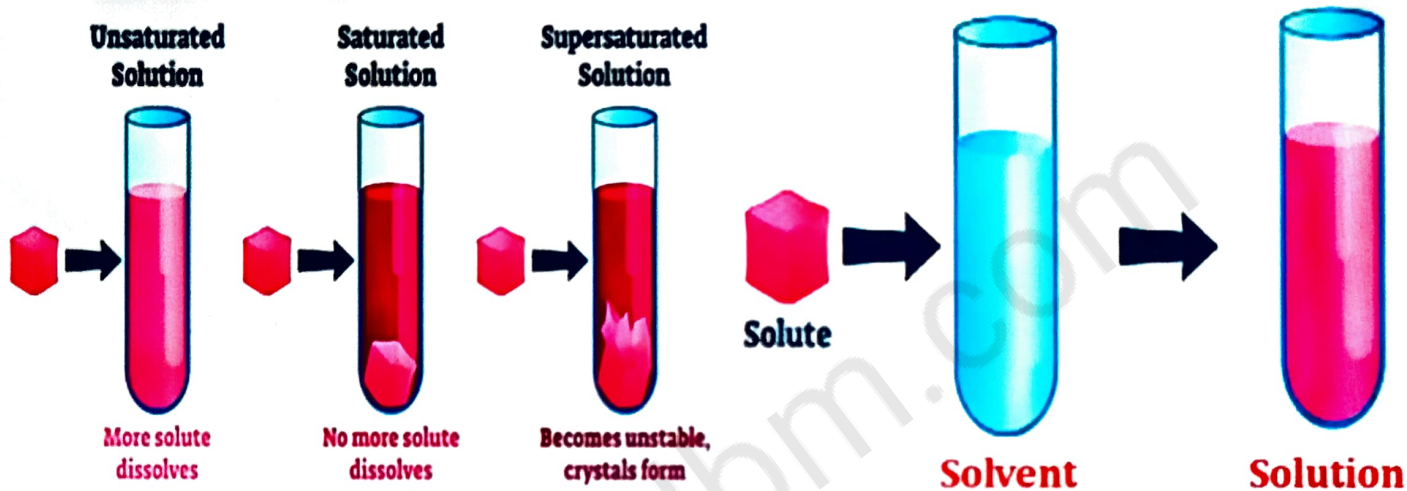
9. DISTRIBUTION LAW



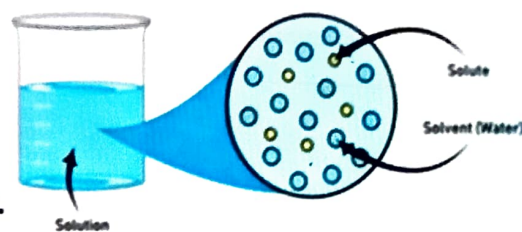
❑ INTRODUCTION

❖ SOLUBILITY :-

- The **concentration of a substance (solute)** that dissolves in a given **volume of solvent** at a certain temperature to form **homogenous solution**.
- The spontaneous interaction of two or more substances to form a **homogenous molecular dispersion**.



- ✓ **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 EXPRESSION

- The solubility of a drug or other substance in a solvent can be expressed quantitatively in numerous terms viz. **percent by mass, percent by volume, molality (m), molarity (M), mole fraction (x), and parts per million (ppm)**, etc.

S. No.	Description forms (solubility)	Parts of solvent required of 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

(I) Normality (N) :-

It is defined as no of equivalents of solute dissolve in one liter of solution.

$$N = \frac{\text{No. of gram equivalent. of solute}}{\text{Litre of solution}}$$

$$\text{Gram equivalent} = \frac{\text{Gram of Solute}}{\text{Equivalent weight}}$$

(II) Molarity :-

- Molarity (M) is **the amount of a substance in a certain volume of solution.**
- Molarity is defined as the moles of a solute per liters of a solution.
- Molarity is also known as the molar concentration of a solution.**

(III) Molality :-

- Molality (m), or molal concentration, is the **amount of a substance dissolved in a certain mass of solvent**.
- It is defined as the **moles of a solute per kilograms of a solvent**.

(IV) Mole fraction :-

The ratio of the **number of moles of one component** of a solution or other mixture to the **total number of moles** representing all of the components.

(V) Percentage by weight :-

- **Percent by mass (percent by weight) is the percent of the total mass of the solution that is one component.**
- **Percent by mass = Mass fraction \times 100.**

(VI) Percentage by volume :-

- **Volume/Volume percentage (V/V percent) is a measure of concentration of a substance in a solution.**
- It is expressed as the ratio of the **volume of the solute** to total volume of the **solution multiplied by 100 ml**

(VII) Percentage weight in volume (%w/v) :-

- **The grams of solute in 100 milliliters of solution.**

❖ MECHANISM OF SOLUTE-SOLVENT INTERACTION

- A **solute dissolves in a solvent** when it **forms favourable interactions** with the solvent.
- This **dissolving process all depends upon the free energy changes of both solute and solvent.**
- The free energy of **solvation is a combination of several factors**

"LIKE DISSOLVES LIKE"

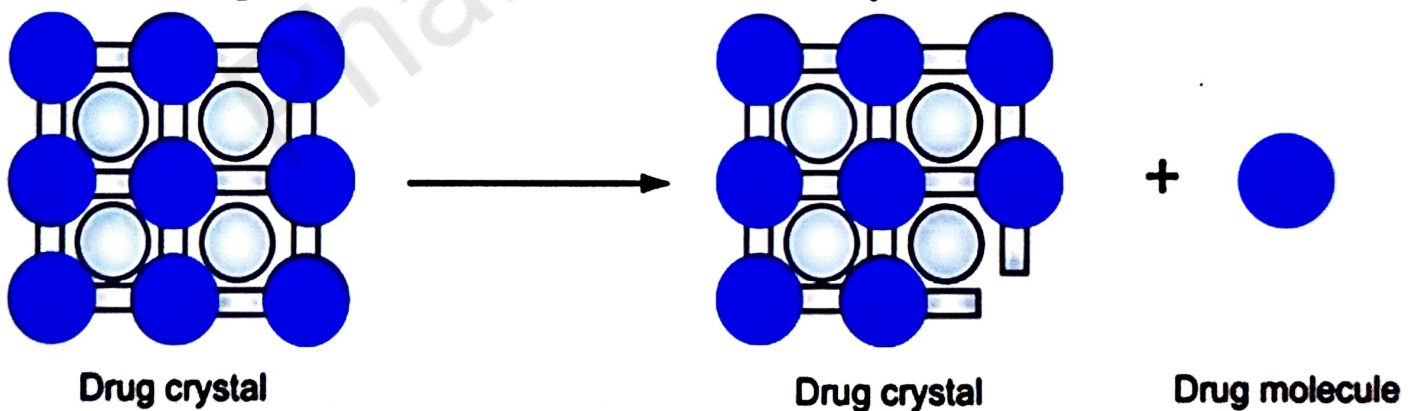
S. No.	Nature of solvent	Mechanism of solubility	Example
1	Polar	<ul style="list-style-type: none">▪ High dielectric Constant▪ H-bond formation▪ Dipole interactions	Water + Ethanol
2	Non-polar	Weak van der waals forces	Fats, Oils, Alkaloidal bases + CCL ₄ , Benzene
3	Semi-polar	Induce certain degree of polarity	Acetone increase solubility of ether in water

➤ Mechanism involves in 3 steps

- i. Detachment of Solute from bulk form
- ii. Formation of vacant site in solvent
- iii. The solute (drug) molecule is inserted into this cavity

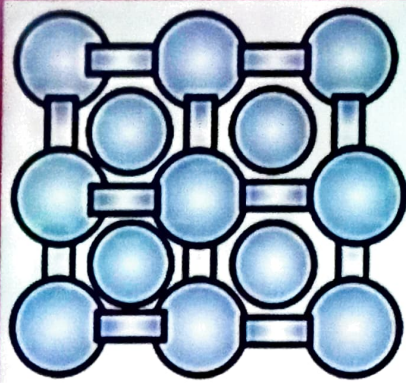
(I) Detachment of Solute from bulk form

- In this step, from solute **gets bulk one mole of solute** get detach and this is further used in the **Solute-solvent interaction**.
- A solute (drug) molecule is '**removed**' from its crystal.

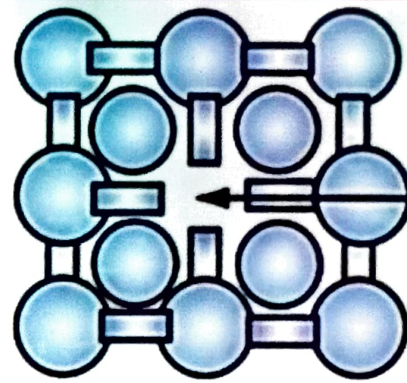


(II) Formation of vacant site in solvent

- In this step, from the **solvent one molecule gets free** and **created a vacant site**.
- This vacant site is further used in **solute solvent interaction** in the third step. A cavity for the **drug molecule is created in the solvent**.



Solvent



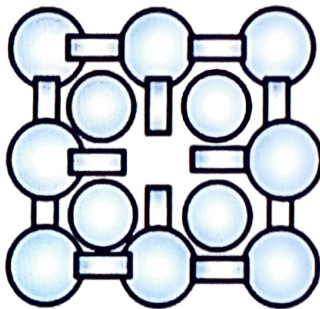
Cavity

Cavity in solvent

(III) Insertion of detached solute molecule in vacant site of solvent

$$\text{Solute - Solvent Interaction} \propto \text{Solubility}$$

- This step involve the **insertion detached solute**.
- Molecule, inside the created **vacant site of Solvent**.
- The **solute (drug) molecule** is inserted into this cavity.

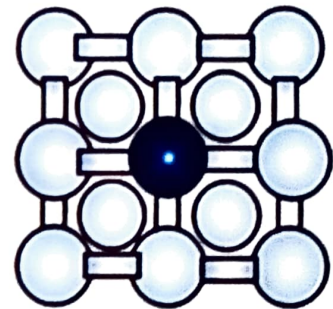


Solvent with cavity

+



Drug molecule



Drug in solvent

In this **3 step vacant site** created in the Solvent & the free solute molecule both of them interacted and we get solvent with **embedded solute molecule**.

☐ IDEAL SOLUBILITY PARAMETERS

- Ideal solubility," defined as **the amount of a solute that can dissolve in the perfect solvent without incurring any energy penalty**.
- The **solubility parameter** is thus a measure of the intermolecular forces on the ability of the **liquid to act as a solvent**.
- To estimate **Solubility as a result solute-solvent interaction** some ideal solubility are very well parameters are, explained by **Regular Solution Theory**.

$$\delta_1 = \left(\frac{\Delta H_v - RT}{V_1} \right)^{1/2}$$

The difference b/w δ and δ_1 & δ_2 ($\delta_1 - \delta_2$) gives the numerical value for solubility.

- ΔH_v is heat of vaporization
- V_1 is the molar volume of solute as a liquid
- R is the gas constant
- T is absolute temperature
- SI unit $\rightarrow J^{1/2} m^{-3/2}$ i.e., equivalent to $Pa^{1/2}$

❖ Hildebrand solubility parameter :-

Hildebrand solubility parameter (δ) provides a **numerical estimate** of the degree of interaction between materials and can be a good indication of solubility, particularly for nonpolar materials such as many polymers. Materials with similar values of δ are likely to be miscible.

Hildebrand solubility parameter :

(δ) "square root of cohesive energy density"

$$\delta = \sqrt{\Delta H_v - RT / V_m}$$

❖ Hansen solubility parameter (δ_t) :-

This parameter is a **way of predicting** if one **material will dissolve** in another and form a solution. They are based on the **idea that like dissolves like** where one molecule is defined as being 'like' another if it bonds to itself in a similar way.

'Hansen solubility parameter (δ_t)'

$$\delta_t = \delta_d + \delta_p + \delta_h$$

δ_d = The energy from dispersion forces between molecules

δ_p = The energy from dipolar intermolecular force between molecules

δ_h = The energy from hydrogen bonds between molecules

SOLUBILITY PARAMETERS

COMPOUNDS	SOLUBILITY PARAMETERS (δ)
n-Butane	7.1
n-Hexane	7.3
n-Heptane	7.5
n-Hexadecane	8.0
Cyclohexane	8.2
Carbon tetrachloride	8.6
Toluene	8.9
Ethyl acetate	9.2
Benzene	9.3
Chloroform	9.3
Aniline	9.8
Phenanthrene	9.8
Acetaldehyde	9.9
Naphthalene	9.9
Anthracene	9.9

➤ Predict the solubility of compounds:

- (a) More similarity in the structure of solute and solvent enhances the solubility of solute in that solvent.
- (b) Polar solutes dissolve in polar solvents while nonpolar solutes dissolve in non polar solvents.
- (c) Addition of polar groups like **-OH, CHO, -CHOH, -CH₂OH, -COOH, NH₂** etc, tend to increase the solubility of organic compounds in water.
- (d) **Addition of non polar groups** tends to decrease the solubility of compounds in water.
- (e) **Introduction of halogen groups** tend to decrease the solubility while **branching of chains** increase **the solubility in water**.
- (f) **Solid compounds of high molecular weights** are generally more difficult to dissolve in water.
- (g) **Solute-Solvent interactions** - If **solvent is X** & **solute is Y**, and the **forces of attraction** are represented by **X-X, Y-Y** and **X-Y**. **Following will occur :-**
- ✓ **X-X >> X-Y** → 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.
 - ✓ **Y-Y >> X-X** → The solvent will not be **able to break the binding forces** between solute molecules. Example NaCl in benzene, where NaCl crystal is held by strong electrovalent forces which cannot be broken by benzene.
 - ✓ **X-Y >> X-X / Y-Y, OR X-Y = X-X = Y-Y** the three forces are equal. Then the **solute will form a solution**. Example :- NaCl in water.

APPLICATION OF SOLUBILITY PARAMETERS

- ✓ Selection of solvent, **Preparation of polarity scales**
- ✓ Determination of Cosolvency power & Chemical kinetics
- ✓ **Determining mechanism involved in drug action**
- ✓ **Structural activity relationship (SAR)**
- ✓ **Drug transport through model, Lipid-based delivery**
- ✓ **To guide organic solvent selection, Cocrystals and salt screening**
- ✓ **Solid dispersions and nano- or microparticulate drug delivery systems**

➤ Advantages Regular solution Theory

- To predict excess free energy of mixing .

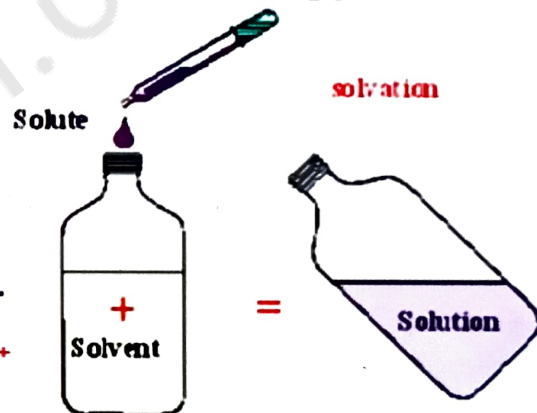
➤ Limitation of Regular solution Theory

- Not able to predict thermodynamic properties Like –
 - i) Heat of solution
 - ii) Volume after mixing

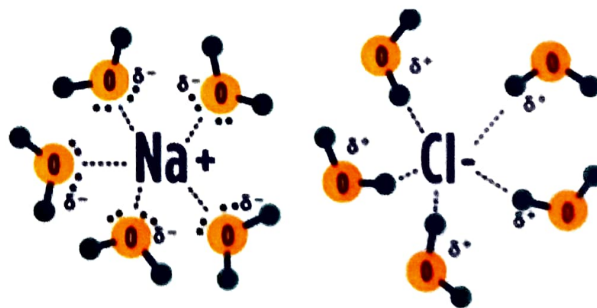
❖ SOLVATION AND ASSOCIATION

➤ Solvation

- **Solvation is an interaction** of a solute with the solvent it which leads to stabilization of the **solute species in the solution**.
- **Solvation is the phenomenon** in which solvent interacts strongly with the molecules or ions of solute which leads to stabilization of **solute species in the solution**.
- **In the solvated state**, an ion in a solution is surrounded or complexed by solvent molecules.
- For example, in order to **dissolve NaCl , the Na⁺ & Cl⁻ ions** must break free from the crystal-lattice structure of solid.
- **When the ions are in solution** they are surrounded by water molecules, and the ions are said to be solvated, or **dissolved in aqueous solution** denoted (Aq).



- **The following chemical equation describes the phenomenon :-**



NaCl

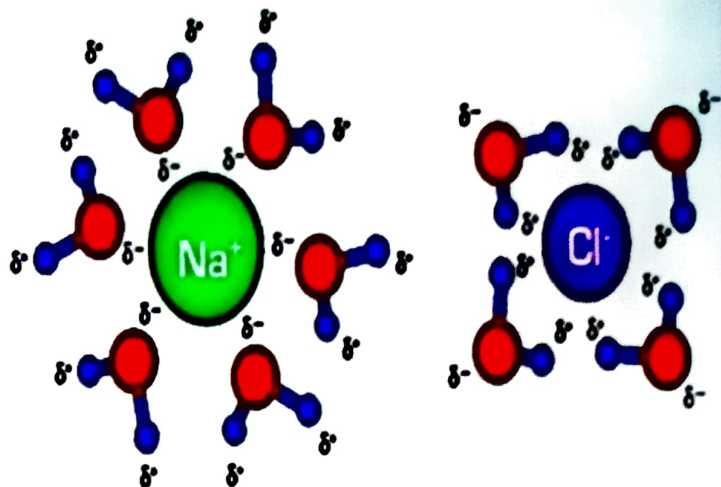
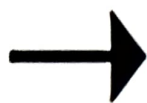
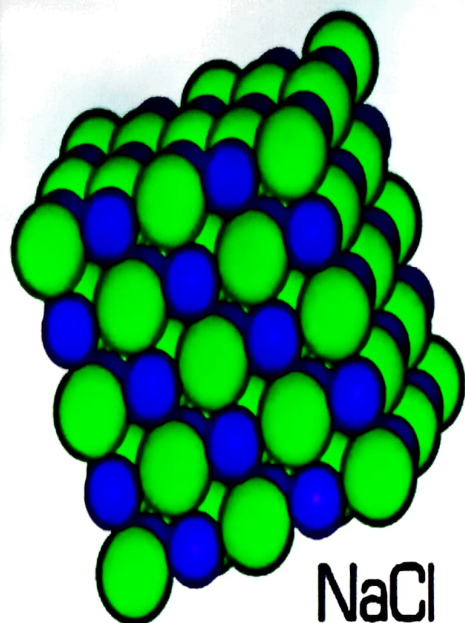
H₂O

Na⁺(Aq) + Cl⁻(Aq)

Sodium chloride

Sodium ion

Chloride ion



- **H₂O is a polar solvent** which has negatively and positively charged regions.
- **The charged regions are attracted to ions with the opposite charge.**
- Hence, the positively charged regions of water molecules are attracted to Cl⁻ ions, and **negatively charged regions of water molecules are attracted to Na⁺ ions**.
- When similar water molecules **surround in ions in the crystal**, the sum of the attractive forces between the **water molecules and the ions** may become **strong enough to overcome** the attractive force between cations and the **anions in the crystal**.
- The water molecules forms a shell of solvation around the ions and the **water surrounded ion can** break away from the crystal and the ions have **become solvated by water molecules**.

➤ Association

- **Association Means join/addition.**
- when the same molecules of one of the components in a solution (need → solute-solute association or solvent - solvent Mol.) interact then this **phenomenon is termed as Association**

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

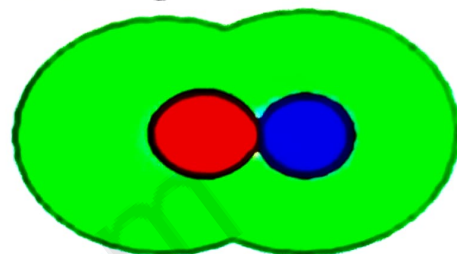
➤ **Classification according to nature of interaction:**

1. Contact
2. Solvent shared
3. Solvent separated

E.G :- Interlinking of water molecules by hydrogen bonding.

1. Contact

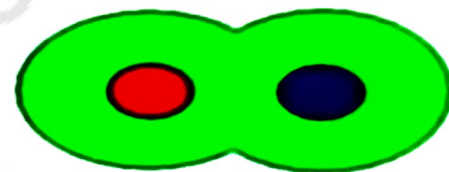
- It works on strong electrolytes.
- On ion contact with each other so firstly solutes contact then solvent cover the solutes.



contact ion pair

2. Solvent shared

When solvent are attached with each other and shared our part and then cover the solute



solvent-shared
or solvent-separated
ion pair

3. Solvent separated

Different particles of solvents cover separately to anionic and cationic particles of solutes.

❑ FACTOR AFFECTING SOLUBILITY

- Solubility is a primary physicochemical factor which is considered in preparing pharmaceutical solutions of various types of drugs.
- There are many factors affecting the solubility of the drugs or solutes which are described as follows.

1. Temperature

2. Nature of solvent (like dissolves like)

3. Pressure

4. pH

5. Particle size

6. Common ion effect

7. Molecular structure

8. Solute-solvent interactions

9. Addition of substituent

10. Solubilizing agents

1. Temperature

- Solubility of solute is a function of temperature.
- Most of the substances are endothermic and hence absorbs heat in the process of dissolution.
- Thus, increase in temperature during the dissolution of such solutes results in increase in the solubility.

2. Nature of solvent (like dissolves like)

- The statement says that "Like dissolves like" means thereby polar solute dissolves in polar solvent and vice-versa.
- The technique of cosolvency is exploited to enhance the aqueous solubility of poorly soluble solute by addition of water miscible cosolvent in which the solute is highly soluble.
- For example ethanol, propylene glycol and other glycols.
- Example :- Metronidazole which is soluble in the quantity of 1000 mg in 10 ml, but if a cosolvent is added its aqueous solubility is enhanced by five fold.

3. Pressure

- In case of solids and liquids solutes there is no effect of pressure on the solubility. But in case of gases decreasing pressure will lead to decrease in solubility.

↓ Pressure → ↓ Solubility

↑ Pressure → ↑ Solubility

4. pH

- Ionizable solute the solubility is the function of pH.
- The solubility of weak acid is increased by increasing pH whereas solubility of weak base is increased by decreasing the pH.
- This can be demonstrated by the following graphs.

5. Particle size

- Particle size of the solids **influences the solubility**.
- It is clear that the greater the surface area of contact between a solute and solvent, the more **rapid is the process of solution**.
- Hence small crystals pass into the **solution more rapidly** than the large crystals.
- This can be demonstrated by the equation :-

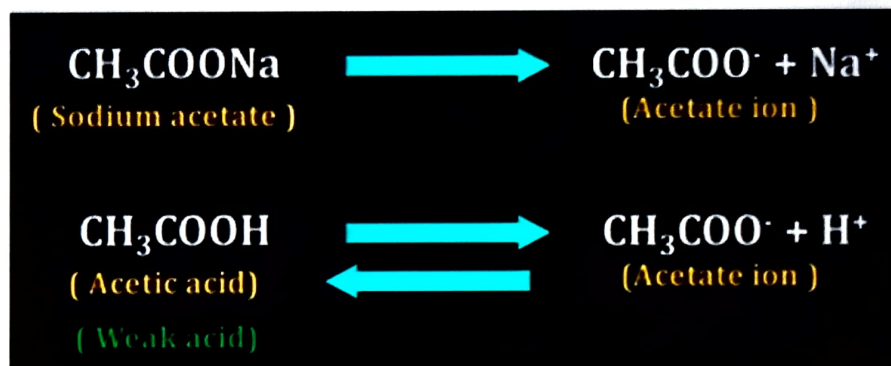
$$\text{Log} \frac{S}{S_0} = \frac{2\gamma V}{2.303 RTr}$$

- ✓ **S is the solubility of the fine particles**
- ✓ **S₀ is the solubility of the solid consisting of relatively large particles**
- ✓ **γ is the surface tension of the particles**
- ✓ **V is the molar volume, r is the final radius of the particle**
- ✓ **R is the gas constant (8.314 × 10⁷ erg/ deg mole)**
- ✓ **T is the absolute temperature**

6. Common ion effect

- The common ion effect is the suppression of **degree of dissociation** of weak **electrolyte containing a common ion**.
- The solubility of sparingly soluble salt is reduced in a solution that contains an **ion in common with that salt**.
- Addition of sodium chloride reduces the **solubility of sodium soap**.
- The soap precipitates due to a combination of **common effect and increased ionic strength**.

Similarly, if a salt of weak acid is **added to the solution of acid itself**, the **dissociation of the acid is diminished**. For example, addition of sodium acetate to the solution of acetic acid **suppresses the dissociation of acetic acid**, which **is already small**.



7) Effect of non-electrolytes on the solubility of electrolytes:

- The electrolyte is dissociated by the **effect of dielectric constant** of the polar solvent.
- The solvent with high **dielectric constant** like water reduces the attractive forces between the oppositely charged ions of an electrolyte resulting in the **dissociation to oppositely**

8) Effect of electrolyte on the solubility of non-electrolyte :-

- The **non-electrolyte is the substance** which does not dissociate in ions in the aqueous solvent.
- The solubility , **non-electrolytes depends** primarily on the formation of weak **intermolecular bonds (Vander waal's forces, hydrogen bonding) between their molecules and the water**.
- Addition of a very soluble electrolyte having high affinity towards water reduces solubility of **non-electrolytes by competing for aqueous solvent** and breaking the **intermolecular bonds between non-electrolyte molecules and the water**.
- **This process is also called salting out.**

9) Effect of complex formation:

- The **apparent solubility of some solute** in liquid may be increased or decreased by the addition of a substance that forms a complex which is **either more or less soluble**.
- For example, solubility of iodine in water is increased addition of potassium iodide **which forms a soluble complex [KI₃]**.

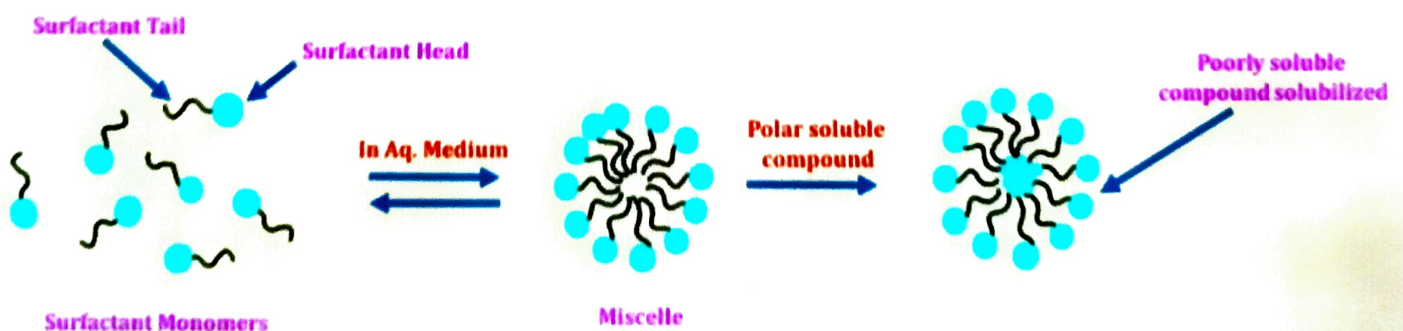


10) Solubilizing agents:

- Solubilization is the increase in solubility of a poorly water- soluble **substance with surface-active agents**.
- The mechanism involves entrapment (adsorbed or dissolved) of molecules in micelles and the tendency of **surfactants to form colloidal aggregations at critical micelle concentration levels**.
- **E.G. :-** Surfactants, SLSM, Span, Tween, Isopropyl alcohol, Propylene glycol.

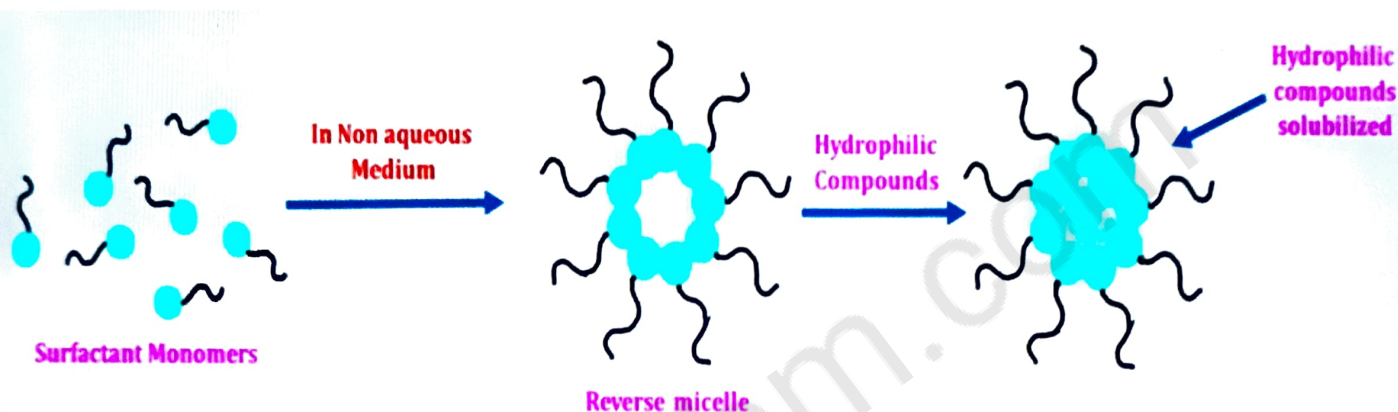
➤ Solubilization of hydrophobic compounds by micelles formation

In the medium the solubilizing agents distributes in such a way that **their polar portion will face the water** & nonpolar portion resides in the micellar interior. When **poorly soluble compound** is added to liquid having micelles which **enters the micelle interior** and get solubilized and resulting in the **enhancement of solubility**.



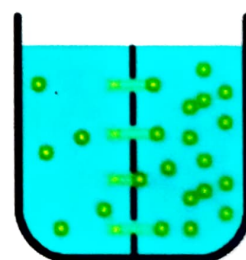
➤ Solubilization of hydrophilic compounds by micelles formation

- In non-aqueous medium (Oil) the **surfactant molecules orient** in such a way that their **hydrophobic portion faces the non-aqueous liquid** and the **hydrophilic portion resides in the micellar interior**.
- Insoluble compounds (Such as water or aqueous solution of drug) added to the surfactant liquid, enters the micelle interior and get solubilized.



❑ DIFFUSION PRINCIPLE IN BIOLOGICAL SYSTEMS

- Diffusion is defined as a **process of mass transfer** of individual molecules of a substance caused by random **molecular motion** and associated with a concentration gradient.
- The rate of diffusion depends on temperature, size of the particles, and the **size of the concentration gradient**.
- Selectively permeable **cell membrane creates two forms** of **diffusion** namely :-
 - **Osmosis for the diffusion of water**
 - **Dialysis for the diffusion of solutes**



Diffusion
(Solvent moves by concentration gradient)

1. **Osmosis** :- It is the passage of solvent across a membrane which is semipermeable in nature.
 2. **Dialysis** :- Separation process based on unequal rates of passage of solutes and solvent through microporous membranes, carried out in batch or continuous mode. **The apparatus used is called dialysis.**
- **Diffusion is one principle method** of movement of substances within cells, as well as for essential small molecules to **cross the cell membrane.**
 - Cell membranes act as barriers to **most, but not all, molecules.**
 - **Cell membrane functions** as a semi-permeable barrier, allowing a very few molecules across it while holding majority of **chemicals inside cell.**
 - Cell membrane is composed of **phospholipids and proteins.**
 - **Transport of drug molecules** through a non-porous membrane occurs by diffusion.
 - **Transport through porous cell membranes** occurs by diffusion and convection.
 - **Rate of diffusion is expressed by equation**

$$\frac{dM}{dt} = DSK \frac{(C_1 - C_2)}{h}$$

Where,

M = Amount of drug dissolved

t = Time

D = Diffusion coefficient of drug

S = Surface area of membrane

K = Oil/water partition coefficient

h = Thickness of the liquid film

C₁ = Conc. of drug at donor side of membrane

C₂ = Conc. of drug at receptor side

C₁ - C₂ = Conc. gradient

- Typically, the gradient is measured as $C_d - C_r$, representing the partition at each phase, namely $K_o/w = C_1/C_d$ and $K_o/w = C_2/C_r$.
- Rate of drug transport into diffusional system is dependent upon the **magnitude of the concentration gradient considering** the other parameters constant.

- Water, carbon dioxide, and oxygen are the few simple molecules that can **cross the cell membrane by diffusion**.
- Metabolic processes in animals and plants **usually require oxygen**, which is in lower concentration inside the cell, have the net flow of oxygen into the cell through diffusion.

❑ SOLUBILITY OF GAS IN LIQUIDS

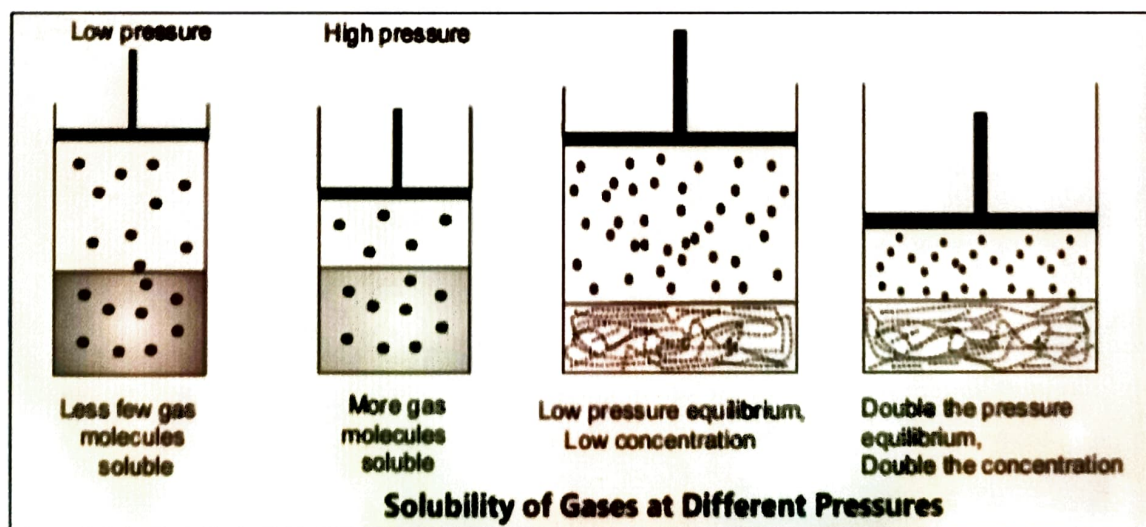
- Concentration of dissolved gas in the liquid when it is in equilibrium with the **pure gas above the solution**.
- Example includes effervescent **preparations containing dissolved** carbon dioxide, **ammonia water and hydrochloride gas**.
- Aerosol products containing nitrogen or carbon dioxide as propellant.

❖ Factors Affecting Solubility of Gas in Liquids :-

- The solubility of gas in liquids depends on pressure, temperature, salt present, chemical reaction and micellar solubilization.

1. Pressure -

- **Liquids and solids** do not show any **change of solubility** with changes in pressure.
- But, solubility of gases in liquids, depends on the **pressure of the gas** in contact with the liquid.
- At higher gas pressure, more gas is **dissolved in liquids** Solubility of Gases **at different Pressures**.



The effect of pressure on the **solubility of gas is given Henry's law** which states that in dilute **solution the mass** of gas which **dissolves in each volume** of liquid solvent at **constant temperature** is directly proportional to partial **pressure of gas**.

2. **Temperature :-**

As the **temperature increases the solubility** of most gases decreases due to **increased tendency of gas to expand**.

3. **Salting out :-**

- **Gases are liberated from** the solution in which they are dissolved by the introduction of an electrolyte such as **sodium chloride** and non electrolyte such as sucrose. **This phenomenon is called as "salting out"**
- The resultant escape of gas is due to attraction of salt ions or highly polar non **electrolytes for water molecules** which decreases the density of aqueous **environment adjacent to gas molecules**.

4. **Effect of chemical reaction :-**

- **Henry's law applies** to gases that are slightly soluble in solution and does not react in anyway with the solvent.
- **Gases such as HCl, ammonia** show deviations from this law due to their chemical interaction with the solvent.

☐ SOLUBILITY OF LIQUIDS IN LIQUIDS

❖ Binary Solutions

- **It is very common** for two or more liquids to be **mixed together** to make a solution. Therefore, we need to know what liquids can be mixed together **without precipitation**.
- **Examples of pharmaceutical solutions** of liquid dissolved in liquids are hydroalcoholic solutions, aromatic **waters, spirits, elixirs**, lotions, sprays and some medicated oils that contain **mixture of two or more miscible oils**

- When two or more liquids mixed together they can be **completely miscible**, **partially miscible** or **practically immiscible**.
- ✓ **Completely miscible** liquids mix uniformly in all proportions and hence do not get separated.
- ✓ **Partially miscible** liquids form two **immiscible liquid layers**, each of which is saturated solution of **one liquid in the other**. Such liquid pairs are called as **conjugated liquid pairs**.
- ✓ **Immiscibility** refers to those systems which do not mix with each other at all such as water and **liquid paraffin** or **water and oil**.

❖ Ideal Solutions

- An ideal solution is one in which there is no change in the properties of the **components other than dilution** when they are mixed to form the solution.
- In another way it can be stated as a solution which shows no shrinkage or expansion **when components are mixed to form solution**.
- **No heat is evolved or absorbed** during the solution formation. The final volume of real solution is an additive **property of the individual component**.
- In another way it can be stated as a solution which shows no shrinkage or expansion **when components are mixed to form solution**.
- Ideal solutions are formed by mixing different substances having similar **properties** and therefore there is complete uniformity of attractive **intermolecular forces**.
- **In ideal solution** there is a complete absence of attractive or repulsive forces and therefore the **solvent does not affect solubility**.
- The solubility in this case depends on temperature, the melting point of **solute and the molar heat of fusion (ΔH_f)**.

❖ Ideal Solutions

- In ideal solution heat of solution is equal to ΔH_f . Therefore solubility in an **ideal solution can be expressed by :-**

$$\log X_2^i = \frac{\Delta H_f}{2.303R} \left(\frac{T_0 - T}{T_0 T} \right)$$

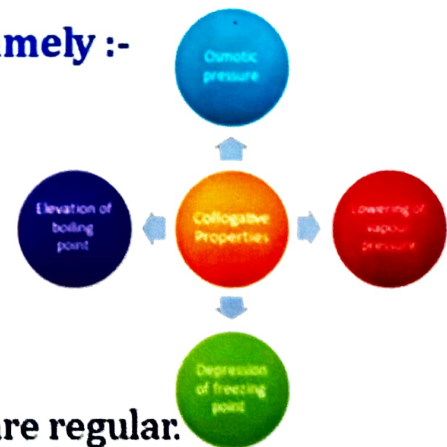
Where, X_2^i is the ideal solubility in terms of mole fraction, R is gas constant; T is the temperature of solution and T_0 is the temperature (Kelvin) of solute. This equation be used to calculate molar heat of fusion by plotting the log solubility versus reciprocal of absolute temperature which results in a slope of $-\Delta H_f/2.303R$.

❖ RAOULT'S LAW

- According to Raoult's law the vapor pressure of a solvent above a solution is equal to the vapor pressure of the pure solvent at the same temperature scaled by the mole fraction of the solvent present.
- **Colligative properties** are properties of a solution that depend mainly on the **relative numbers** of particles of solvent and solute molecules and not on the chemical properties of the molecules themselves.

- **There are four types of colligative properties namely :-**

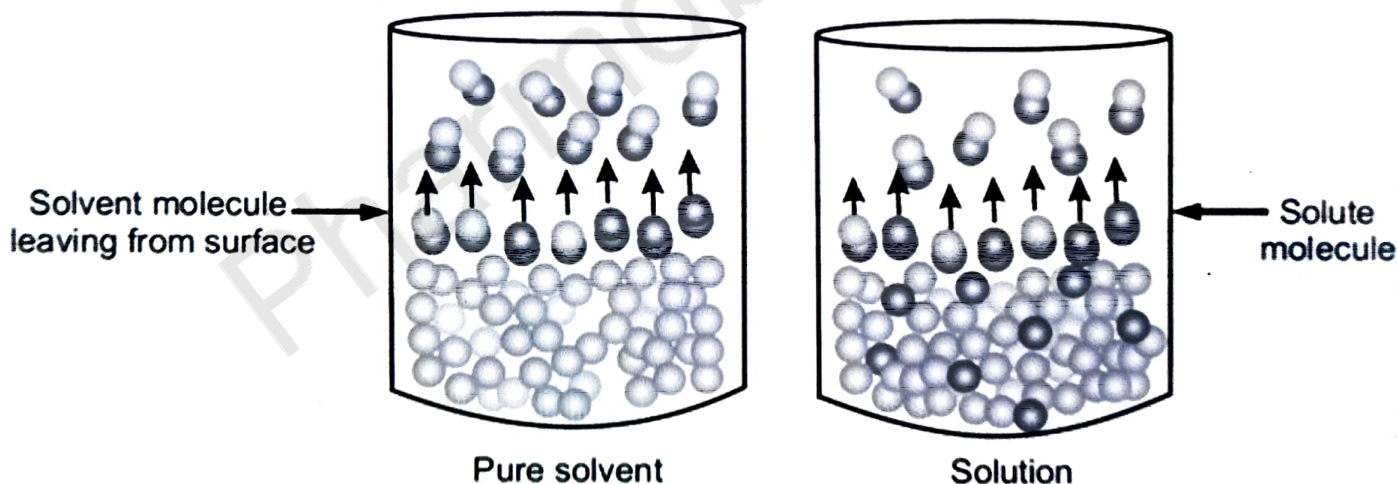
1. Lowering of vapour pressure.
2. Elevation of boiling point.
3. Depression of freezing point.
4. Osmotic pressure.



- Colligative properties of non-electrolyte solutions are regular.
- Colligative properties are equal for equimolar concentration of drugs.
- **Osmotic pressure** is the most important colligative property since it is related with physiological compatibility of **parenteral, ophthalmic and nasal solution**.

❖ Lowering of Vapour Pressure

- **Lowering of vapour pressure** is the simplest of the colligative properties and easiest to understand based on physical model.
- **The pressure brought** by vapour in equilibrium with its liquid at constant **temperature is known as vapour pressure.**
- **It increases with temperature.** The vapour **pressure of solvent** is due to its escaping tendency.
- Temperature at which the vapour pressure of the liquid is equal to the atmospheric pressure is **called as normal boiling point.**
- **The vapour pressure of pure liquid** solvent depends upon the rate of escape of molecule from the surface **known as escaping tendency.**
- **Solvents with greater escaping** tendencies have greater vapour pressure.
- The added solute is generally **non-volatile which does not contribute** directly to the **vapour pressure of the solution.**



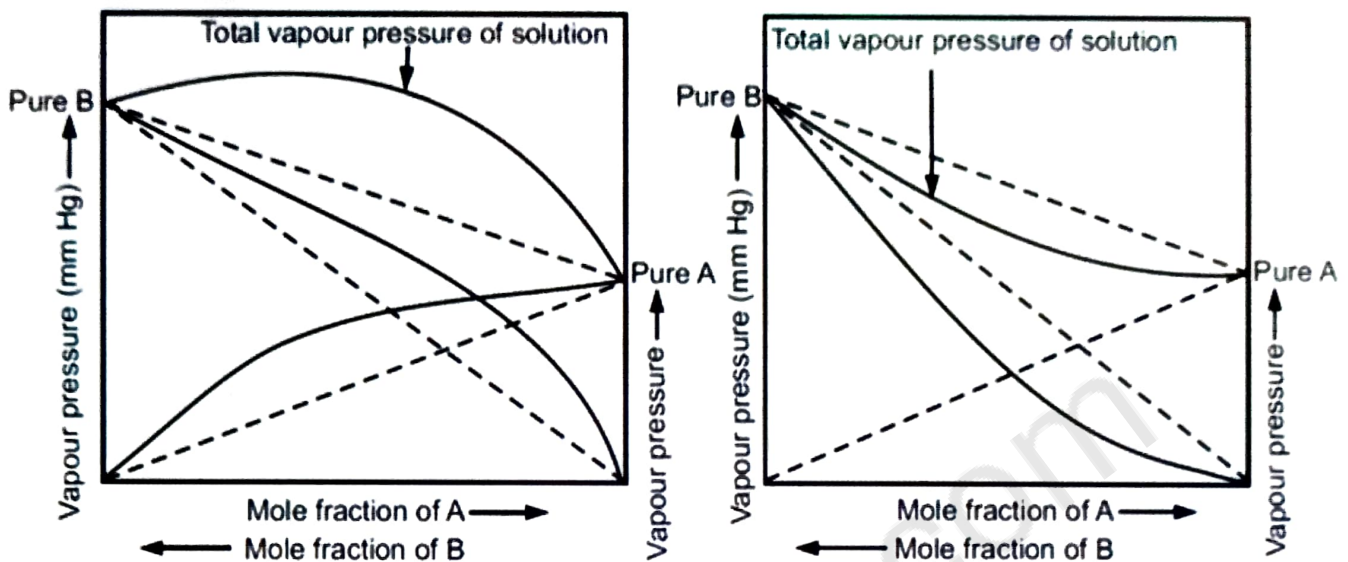
Lowering of Vapour Pressure on Addition of Non-volatile Solute

❖ Deviations from Raoult's Law

In real solutions, there is no **complete uniformity** of intermolecular attractive forces. There are many such liquid pairs that show **greater cohesive forces** than the **attractive forces** and greater attractive forces than the cohesive forces. It can be observed even when liquids are **completely miscible** in all proportion. **Such mixtures of liquid pair** are **real/non-ideal solution.**

❖ Deviations from Raoult's Law

They **do not adhere** to the **Raoult's law** over the **entire range** of concentrations and are **represented** as deviations. This behavior shown by **liquid mixtures** are called as **positive deviation** and **negative deviation**.



❖ Limitations of Raoult's Law

Raoult's law work only for **ideal solutions** over **entire range** of concentrations. An ideal solution obeys Raoult's law. While applying this law to **real solutions** it has following limitations.

✓ Real Solutions :-

In real solution, the **concentration of solute** is high and thus intermolecular **forces between solute-solute** and **solute-solvent** are **predominant** that slows down the escaping of **solvent molecules** from the surface.

✓ Nature of the Solute :-

Raoult's law is **applicable only** for **solutes** which are **non-volatile in nature**. Volatile solutes can contribute for vapour pressure above the solution which may cause the **deviation from Raoult's law**. Raoult's law does not apply if the **added solute associates or dissociates** in solvent. If association takes place the number of particles or **molecules decreases** causing reduction in **lowering of vapour pressure**.

❖ REAL SOLUTIONS

Real solutions show change in the total volume of the solution upon mixing its different components together. **Also, there is absorption or evolution of heat during mixing and solution formation.** For example, at room temperature when **100 ml of sulfuric acid** is mixed with 100 ml of water, the total volume of solution becomes **180 ml rather than 200 ml.** **During mixing of acid** and water considerable **heat is evolved causing reduction** in total volume of the solution.

❖ PARTIALLY MISCIBLE LIQUIDS

- Although three types of **liquid/liquid systems** are commonly encountered **liquid/liquid systems** are mainly divided into two categories depending on the **solubility of one substance in the other.**
- The **categories are complete miscibility** and partial miscibility. Miscibility is the common solubilities of the **components in liquid-liquid systems.**
- **Partial miscibility** is when the **substances only mix partially.**
- When mixed, there are two layers formed each layer containing some of both liquids. **Of these two mixed layers, each layer contains some of both the liquids for example, phenol and water.**
- Some liquids are practically immiscible (**For example, Water and Mercury**), whilst others (**For example, Water and Ethyl alcohol or Acetone**) mix with **one another in all proportions.**
- The mutual solubility or **miscibility of two liquids** is a function of **temperature and composition.**
- When two liquids (**liquid A and liquid B**) are partially soluble in each other, **two liquid phases can be observed.** **At equilibrium,** each phase contains **liquid A & liquid B in amounts** that reflect their mutual solubility.

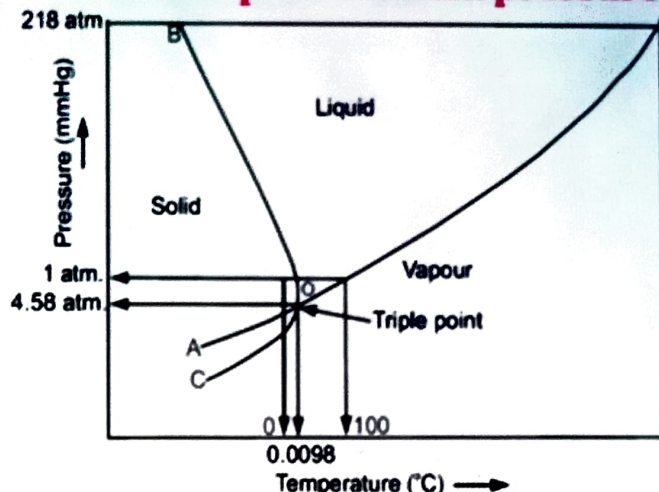
❖ CRITICAL SOLUTION TEMPERATURE

A phase diagram is a plot describing conditions of **temperature and pressure** under which two or more physical **states coexist in dynamic equilibrium**.

It means **phase diagram is a graphical representation of chemical equilibrium**.

This diagram is also called as

Pressure - Temperature graph.



- In phase diagram of water **there are three lines or curves** that separate the area of each phase. Adjacent to each line there **exist a different single phase** of water. At any point on line there exist equilibrium between two phases shown by area i.e. solid/liquid, **liquid/vapour and solid/vapour**.
- The line **OA, OB and OC represents** equilibrium between liquid and vapour, solid and liquid and **solid and vapour phases**, respectively.

❖ Applications of critical solution temperature :-

- Critical solution temperature **allows the temperature limits** for some reactions to be **determined if it requires** that two **liquids are miscible**.
- It is used to determine the **water content in substances** such as methyl and ethyl alcohols. Here the system is usually the alcohol and a hydrocarbon, such as **-hexane or dicyclohexyl**.
- The water is, insoluble in the **hydrocarbon**. Thus, the methyl alcohol-cyclohexane system has a **Critical solution temperature 45 - 50 °C** and even **presence of 0.1 % water** produces a rise of **0-15 °C** in the Critical solution temperature.
- Critical solution temperature may be taken as a **criterion for the purity of a substance**.

□ DISTRIBUTION LAW

According to Distribution Law " if a solute A distributes itself between two immiscible solvents X and Y at constant temperature and A is in the same molecular condition in both solvents."

In pharmaceutical practice, often a single substance is dissolved in two immiscible phases' i.e. two liquid phases in contact that do not mix, such as chloroform and water.

When an excess amount of solute is added to two immiscible liquid phases, it distributes itself between these phases until saturation, if mixed by shaking vigorously. If insufficient amount of solute is added it distributes in a definite ratio.

❖ Limitations of Distribution Law

- The selected solvent liquid pair must be immiscible with each other. Any mutual solubility must not affect distribution of solute if left aside for enough time to separate.
- The experimental temperature must be maintained constant. As temperature has effect on solubility of solute, any change in temperature during determinations may change the findings.
- The solute in question should be in same molecular state in both the solvents. If any chemical change is observed the concentration of species common to both solvents only should be considered.
- Solute must be present in both the solvents at low concentrations. At high concentrations of solutes Nernst's distribution law does not hold good.
- Samples should be withdrawn for analysis only after achievement of equilibrium.
- Early equilibrium attainment can be possible by vigorous shaking.

❖ Applications of Distribution Law

- **Partition coefficient** first finds applications in medicinal chemistry and **drug design**.
- It has proved useful in other related areas such as **drug absorption, bioavailability, toxicity, bioaccumulation and metabolism**.
- Partition coefficient values are helpful in knowing the **hydrophobic drug receptor interactions**.
- Partition coefficient help to **understand the mechanism** of preservative action of weak acids and **determination of its optimum concentration for the effectiveness of action**.
- From the partition coefficient **general idea** about the drugs solubility in solvent can be judged. It can be **further useful in drugs solubility enhancement**.