PHYSICAL PHARMACEUTICS-I

UNIT 1 NOTES

SOLUBILITY OF DRUGS

- SOLUBILITY EXPRESSION
- MECHANISM OF SOLUTE SOLVENT INTERACTION
- IDEAL SOLUBILITY PARAMETERS
- SOLVATION AND ASSOCIATION
- FACTORS AFFECTING SOLUBILITY
- DIFFUSION PRINCIPLE
- SOLUBILITY OF GAS IN LIQUIDS
- SOLUBILITY OF LIQUIDS IN LIQUIDS
- RAOULT'S LAW
- REAL SOLUTION
- CRITICAL SOLUTION TEMPERATURE
- DISTRIBUTION LAW

IMPERFECT PHARMACY

SOLUBILITY

- The maximum amount of solute that can be dissolved in a fixed volume of solvent at constant temperature is defined as the **Solubility**.
- In other words we can say it is the ability of two or more substances (solute and solvent) to homogenous mixture.

IMPORTANT DEFINITIONS RELATED TO SOLUBILITY

SOLUTE : It is the component which is dissolved in the solvent, present in less amount in the solution

SOLVENT : It is the component in which solute is dissolved, present in more amount than solute in the solution

SOLUTION : It is the mixture of two or more components that forms a homogenous mixture. The components are referred to solute/ solutes & solvent/ solvents.

IMPORTANCE OF SOLUBILITY IN PHARMACY

- To select the best solvent for a Drug or Mixture of Drugs.
- To solve the problems arise during preparation of solutions.
- To know about structure & intermolecular forces of drugs.
- To identify drugs with low aqueous solubility.

Types Of Solutions

There are mainly 3 types of solutions :
Saturated Solution
Unsaturated Solution
Super Saturated Solution

Saturated Solution

The solution which contains maximum amount of solute that can be dissolved by the solvent at a given temperature is known as Saturated Solution.

Unsaturated Solution

A solution which contains less than maximum amount of solute that is capable of being dissolved at a given temperature is known as Unsaturated Solution.

Super Saturated Solution

A solution which contains more than maximum amount of solute that is capable of being dissolved at a given temperature is known as Super Saturated Solution

SOLUBILITY EXPRESSIONS

The solubility of drug substances in a solvent can be expressed in following 2 ways :

① Quantitative Expression
② Qualitative Expression

QUANTITATIVE EXPRESSION

Quantitatively solubility can be expressed by following concentration terms :

- Molarity
- Molality
- Normality
- Mole Fraction
- Percentage Concentration
- Parts Per Million

MOLARITY

It is defined as no. of moles of solute dissolved per litre of the solution. It is denoted by 'M'.

$$M = \frac{\text{No of moles of solute}}{\text{Volume of solution (In Litre)}}$$

MOLALITY

It is defined as no. of moles of solute dissolved per kg of solvent. It is denoted by 'm'

$$m = \frac{\text{No of moles of solute}}{\text{Volume of Solvent (in kg)}}$$

NORMALITY

It is defined as no. of gram equivalent of solute dissolved / present per litre of solution. It is denoted by 'N'

$$N = \frac{\text{No. of Gram Equivalent}}{\text{Volume of Solution (in Litre)}}$$

PERCENTAGE CONCENTRATION

$$\%\ W/W = \frac{\text{Mass of Solute}}{\text{Mass of Solution}} \times 100$$

$$\%\ V/V = \frac{\text{Volume of Solute}}{\text{Volume of Solution}} \times 100$$

$$\%\ W/V = \frac{\text{Mass of Solute}}{\text{Volume of Solution}} \times 100$$

PARTS PER MILLION

It is used to express the concentration of very dilute solutions
It is represented by Cppm

$$C_{ppm} = \frac{\text{Mass of Solute}}{\text{Mass of Solution}} \times 10^6$$

MOLE FRACTION

Mole Fraction is defined as number of moles of a component (either solute or solvent) divided by total number of moles in solution.

$$X_A = \frac{\text{Moles of A}}{\text{Total Moles of Solution}}$$

QUALITATIVE EXPRESSION

Qualitatively Solubility can be expressed as follows:

TERMS	PARTS OF SOLVENT REQ FOR 1 PART SOLUTE
• Very Soluble	Less than 1 part
• Freely Soluble	1 - 10 part
• Soluble	10 - 30 part
• Sparingly Soluble	30 - 100 part
• Slightly Soluble	100 - 1000 part
• Very Slightly Soluble	1000 - 10,000 part
• Practically Insoluble	More than 10,000 part

MECHANISM OF SOLUTE SOLVENT INTERACTION

- Solute - Solvent interaction is a process which results in the stabilisation of solute species in the solvent molecules.
- This interaction influences various properties of solute like reactivity colour, stability & physical properties of solvents like density & viscosity.
- The interaction depends on various factors like attractive & repulsive forces, ion- dipole interaction, H- bonding, Wander- wall forces etc.

CONDITION FOR SOLUBILITY

If A is the solvent & B is the solute then there are mainly 3 types of interaction involved in solute- solvent interaction :

① A - A Interaction
② A - B Interaction
③ B - B Interaction

Now for the formation of solution at normal conditions (A-B) > (A-A, B-B) interactions.

PRINCIPLE OF SOLUTE - SOLVENT INTERACTION

- Solute - Solvent interaction based on principle of "Like dissolves Like"
- Polar Solute dissolves in Polar Solvents
- Non- Polar Solute dissolves in Non- Polar Solvents

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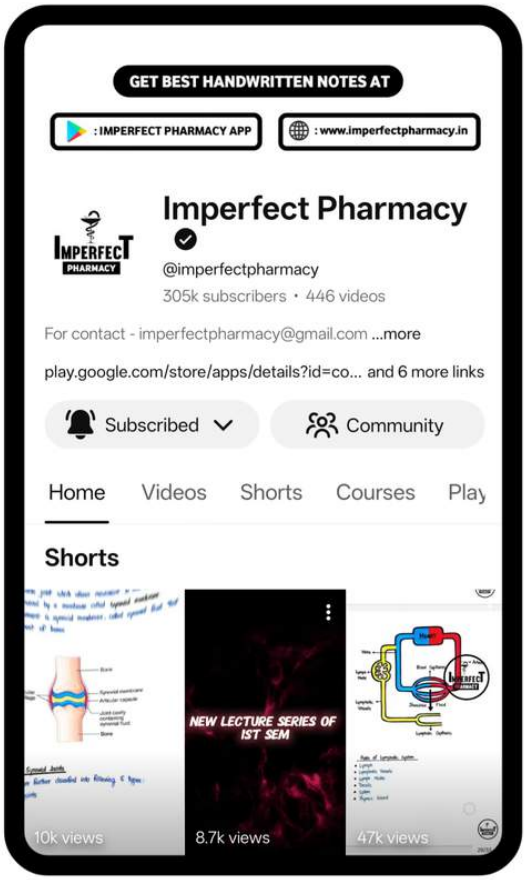

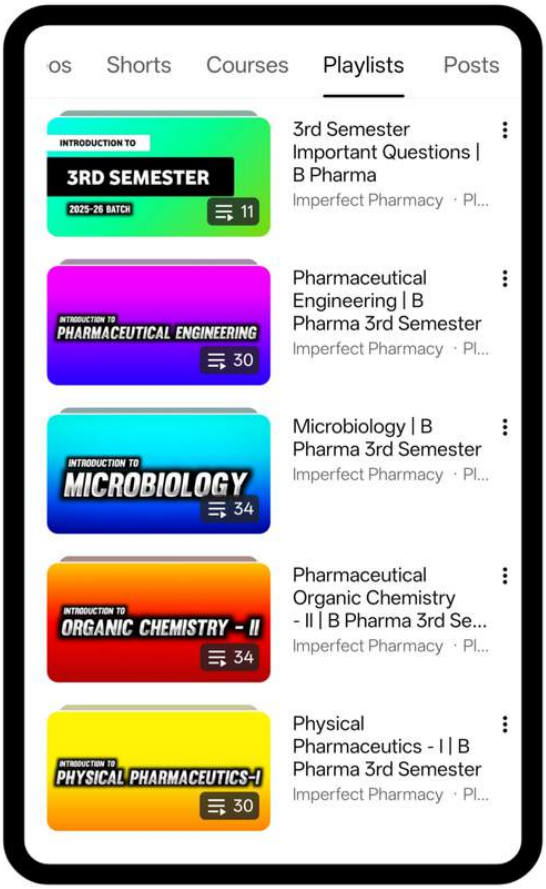

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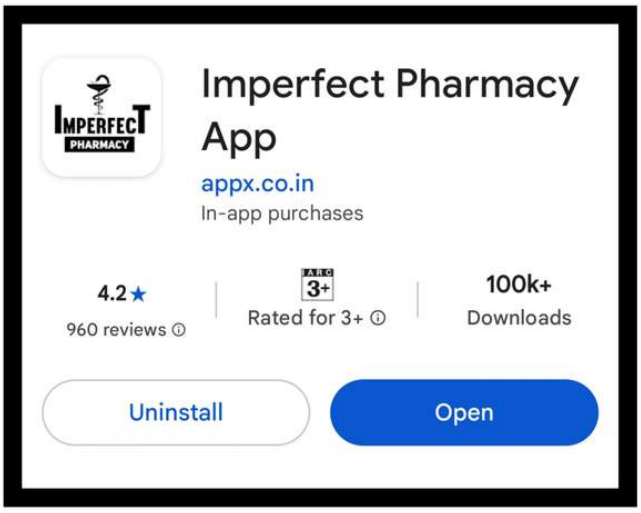


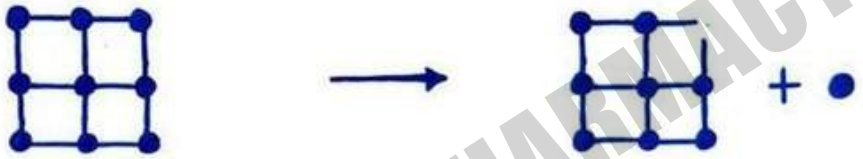
MECHANISM

The mechanism of solute solvent interaction involved 3 steps :

- Detachment of Solute from Bulk form
- Formation of Vacant site in Solvent
- Insertion of Solute molecules in the vacant site of Solvent.

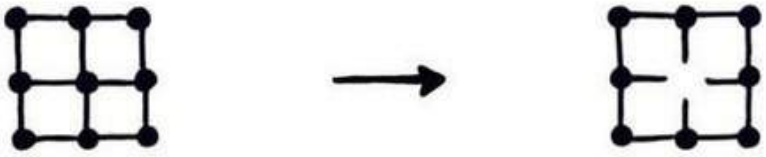
Detachment Of Solute From Bulk Form

In this step one molecule of solute gets detached from solute bulk crystals & this is further used in solute - solvent interactions.



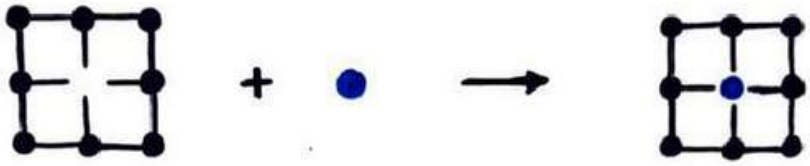
Formation Of Vacant Site In Solvent

In this step from the solvent bulk , one molecule gets free and created a vacant site.
The vacant site is further used in solute solvent interaction .



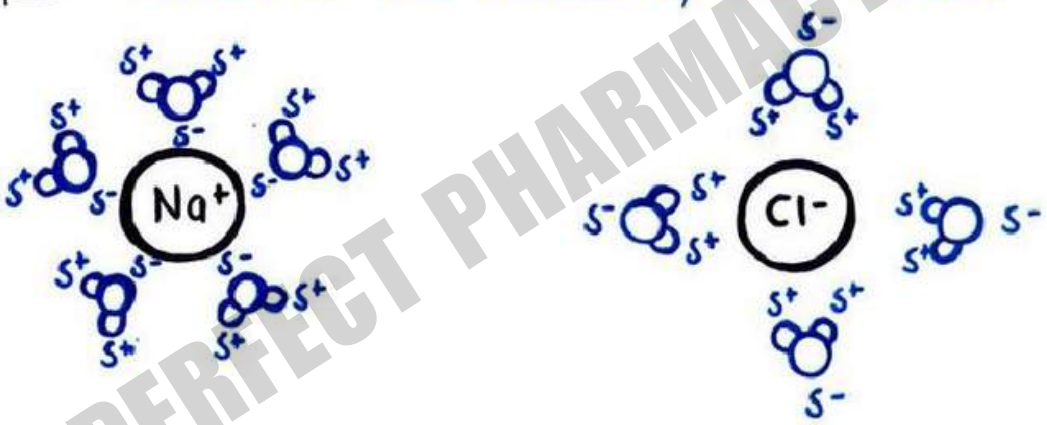
Insertion Of Solute Molecule In The Vacant Site Of Solvent

In the final step the detached solute molecule inserted inside the vacant site of solvent & this is how we get solvent with embedded solute molecule.



SOLVATION

- Solvation is a process of interaction of solute molecules with solvent molecules which leads to stabilization of solute species in the solution.
- In the solvation process ions of solute gets surrounded by solvent molecules that leads to the formation of **Solvation Complex**.
- If the solvent used in solute-solvent interaction is water, then the process of solvation is termed as **Hydration**.
- Example : Solvation of NaCl molecules by water molecules



Factors Affecting Solvation

- Solvation $\propto$ Surface Area
- Solvation $\propto$ Agitation (Stirring)
- Solvation $\propto$ Temperature

ASSOCIATION

- Association is defined as a chemical reaction in which oppasite electric charge ions comes together in solution & form a distinct chemical entity.
- It is simply joining or addition of ions.
- The principle behind association is defined by Coulomb's Law

$$F = \frac{1}{4\pi\varepsilon_0} \frac{q_1 \cdot q_2}{r^2}$$

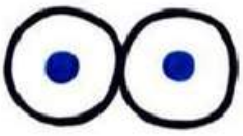
TYPES OF ASSOCIATION

Association can be of 3 types according to nature of interaction.

① Fully Solvated
② Solvent Shared
③ Contact Ion Pairs

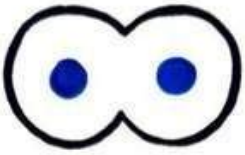
Fully Solvated

In this anionic & cationic particles of solute covered separately by different particles of solvent.



Solvent Shared

In this solvent molecules are attached with each other & share their part & cover the solute molecules



Contact Ion Pair

It works on strong electrolytes.
In this first solute ions contact with each other then it will get covered by solvent molecules.

IDEAL SOLUBILITY PARAMETERS

- Ideal Solubility parameter is a numerical value that indicates relative solvency behaviour of specific solvent.
- Solubility Parameters provides numerical methods to predict interaction b/w material.
- It is used to define whether the solute will dissolve in the solvent or not.
- If values of solubility parameter are same then we can say one substance is soluble in another.
- It is denoted by 'δ'
- There are mainly two types of solubility parameters :

① Hildebrand Solubility Parameter
② Hansen Solubility Parameter

HILDEBRAND SOLUBILITY PARAMETER

- It is given by Joel H. Hildebrand in 1936.
- It provides a numerical estimation of degree of interaction b/w materials & can be a good indication of solubility.
- It is derived by cohesive energy density of molecules.
- Joel H. Hildebrand proposed the value of ideal solubility parameter as square root of cohesive energy density.

$$\delta = \sqrt{C} \quad \text{—— ①}$$

Here δ = Hildebrand solubility parameter
C = Cohesive energy density

Now $C = \frac{\Delta E_v}{V}$ ——— ②

Here, ΔE_v = Energy of Vapourisation
V = Molar Volume

Now, again $\Delta E_v = \Delta H_v - RT$ ——— ③

putting value of ③ in ②

$$C = \frac{\Delta H_v - RT}{V} \quad \text{——— ④}$$

Finally putting the value of ④ in ①, we get

$$\boxed{\delta = \left(\frac{\Delta H_v - RT}{V}\right)^{1/2}}$$

Here δ = Hildebrand Solubility Parameter
ΔH_v = Heat of Vapourization
R = Universal Gas Constant
T = Absolute Temperature
V = Molar Volume

HANSEN SOLUBILITY PARAMETER

- In 1966 Charles M. Hansen developed a three parameter system to define the value of ideal solubility parameter
- Hensen parameter divides the total Hildebrand value into 3 parts :

① Dispersion Force Component
② A Hydrogen Bonding Component
③ A Polar Component

$$\delta = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2}$$

- $\delta^2 d$ = dispersion component
- $\delta^2 p$ = Polar component
- $\delta^2 h$ = H- bonding component
- δ = Hansen Solubility Parameter

APPLICATION OF SOLUBILITY PARAMETERS

- Selection of Solvents
- Preparation of Polarity scales
- Cosolvency Power Determination
- Chemical kinetics Determination
- Structural Activity Relationship (SAR)

FACTORS AFFECTING SOLUBILITY OF DRUGS

There are many factors that affects the solubility of drugs as described as follows :

- Temperature
- Nature of Solvents
- Pressure
- pH
- Crystalline Structure
- Particle Size
- Common Ion Effect
- Molecular Structure
- Solubilizing Agents / Surfactants

TEMPERATURE

There are mainly two types of process / reactions.

① Endothermic Process (Absorbs Heat)
② Exothermic Process (Releases Heat)

- Now For Endothermic process → Solubility increases with increase in temperature.
- For Exothermic process → Solubility decreases with increase in temperature.

NATURE OF SOLVENT

- Solubility follows the principle of 'Like dissolves Like'
- Polar Solute dissolves in Polar Solvents.
- Non- Polar Solute dissolves in Non- Polar Solvents.

PRESSURE

- In case of solids & liquid solutes, there is no effect of pressure on solubility.
- But in the case of gaseous solute, solubility depends on pressure
- Solubility of Gases increases with increase in ~~temperature~~ Pressure.
- Solubility of Gases decreases with decrease in ~~temperature~~ Pressure.

pH

- pH is one of the major factor influences the solubility of drugs that contain ionizable groups
- Solubility of ionic compounds depends upon degree of ionization
- In the case of strong Acidic & strong basic compound, pH doesn't plays a major role as they are ionazable nearly at all pH.
- But, In the case of weak Acid → Solubility increases with increase in pH (Basic pH).
- In the case of weak Base → Solubility ~~decreases~~ increases with decrease in pH (Acidic pH).

CRYSTALLINE STRUCTURE

- Solid drugs generally exist in two crystalline form as follows :

① Crystalline Form
② Amorphous Form

- Now a drug exist in amorphous form generally dissolves more rapidly than crystalline form.

PARTICLE SIZE

- Particle size plays a major role in the solubility of drugs.
- Particle size ↓ → Surface Area ↑ → Solubility ↑.
- Decrease in particle size leads to increase in solubility of drugs.

COMMON ION EFFECT

- Common Ion Effect is defined as suppression in degree of dissociation of weak electrolyte in the presence of a strong electrolyte both having a common ion.
- Common Ion effect decreases the solubility of weak electrolytes.
- For Example : Addition of Sodium Acetate (CH_3COONa) in the solution of Acetic Acid (CH_3COOH) supress the dissociation of acetic acid.

$$CH_3COONa \longrightarrow CH_3COO^- + Na^+$$
$$CH_3COOH \rightleftharpoons CH_3COO^- + H^+$$

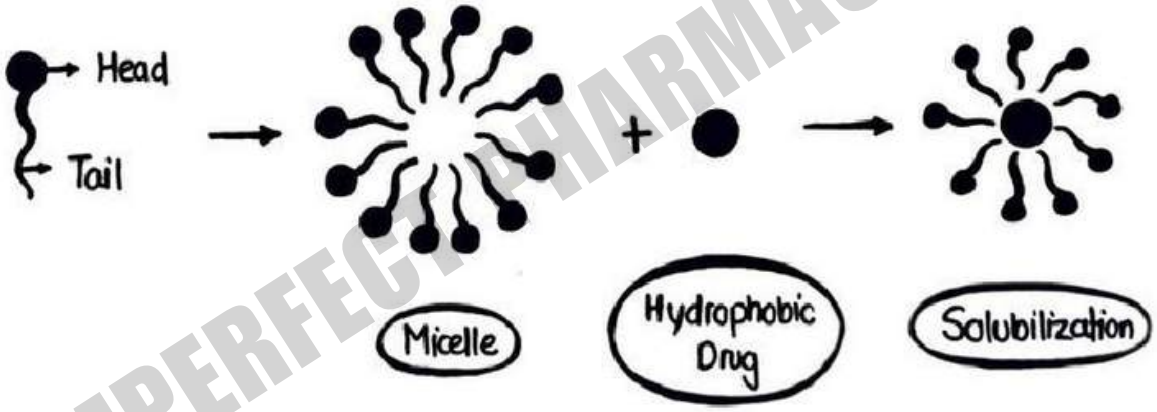
MOLECULAR STRUCTURE

- Molecular size affects the solubility at major extent.
- The larger the molecule or higher its molecular weight, lesser the solubility of substance.
- Large molecules are more difficult to surround by solvent molecules in order to solvate the substance.

SOLUBILIZING AGENTS / SURFECTANTS

- Solubilization is the process of increase in solubility of poorly water soluble substances and the agents used in the process of solubilization is known as Solubilizing Agents or Surfectants or Surface Active Agents.
- Surfectant Molecules contains a Head → Hydrophillic Nature
  & a Tail → Hydrophobic Nature

- The mechanism of solubilization involves entrapment (dissolvation) of solute molecules in Micelles and tendency of surfectant to form this Micelle at 'Critical Micelle Concentration'.



Note: The vacant space inside micelle is known as 'Core'

Diffusion In Biological System

- Diffusion is simply defined as a physical process that refers to the net movement of molecules from a region of high concentrati. to lower concentration under the influence of concentration gradient.
- It can also be defined as Mass transfer of individual molecules of a substance caused by random molecular motion, associated with driving force such as concentration gradient.

Application Of Difussion In Pharmaceutical Study

- Release of drug from dosage form.
- Ultrafiltration, Microfiltration, Dialysis, Hemodialysis.
- Permeation & Distribution of drugs in living tissues.
- Estimation of molecular weight of polymers.
- Prediction of absorbtion & elimination of drug.

Types Of Diffusion

Diffusion is of mainly two types :

① Passive Diffusion
② Facilitated Diffusion

Passive Diffusion

- It is the most important mechanism for transport of drugs through membranes.
- In passive diffusion drug simply diffuse from the region of higher concentration to the region of lower concentration.

Facilitated Diffusion

- It is also known as Carrier Mediated Diffusion
- In facilitated diffusion drug molecules diffuse through cell membrane with the help of carrier proteins embedded within cell membrane.

LAW OF DIFFUSION

- It is given by Adolf Fick in 1856.
- He gives the simplest description of diffusion by Fick's Laws developed by Adolf Fick in 19th century.
- He gives two laws to understand principle of diffusion.

① Fick's First Law Of Diffusion.
② Fick's Second Law Of Diffusion.

Fick's Fist Law Of Diffusion

According to fick's first law the movement of particles (Diffusion Flux) from region of high concentration to low concentration is directly proportional to concentration gradient.

$$J \propto \frac{dc}{dx} \quad \text{or} \quad J = -D\frac{dc}{dx}$$

Here, J = Diffusion Flux
D = Diffusion Coefficient
dc = Change in Concentration
dx = Change in Position
$\frac{dc}{dx}$ = Concentration Gradient

Fick's Second Law Of Diffusion

- Fick's First law applies to steady state systems, where concentration keeps constant, but in many cases, the concentration however changes with time, so in those cases diffusion kinetics is defined by Fick's second Law.
- Fick's second law states that change in concentration with time in a particular region is proportional to the change in concentration gradient at that point.

$$\frac{dC}{dt} = -\frac{dJ}{dx} \quad \text{or} \quad \frac{dC}{dt} = D\frac{d^2C}{dx^2}$$

Here $\frac{dC}{dt}$ = Change in concentration with time

D = Diffusion coefficient

$\frac{d^2C}{dx^2}$ = Second derivative of $\frac{dC}{dx}$

Factors Affecting Rate Of Diffusion

- Concentration gradient
- Temperature
- Surface Area
- Permeability of Membrane

SOLUBILITY OF GAS IN LIQUIDS

- Solubility of Gas in Liquids is defined as the concentration of dissolved gas in the liquid when it is in equillibrium with the pure Gas above the solution.
- The example of Gas in Liquid includes ammonia water, hydrochloride gases and effervescent preparations containing dissolved carbon di oxide.
- Aerosols are also one of the best example for Gas in Liquid preparations.

FACTORS AFFECTING SOLUBILITY OF GAS IN LIQUIDS

The solubility of Gas in Liquids is mainly depends upon following 4 factors :

① Pressure
② Temperature
③ Salting Out
④ Chemical Reactions.

PRESSURE

- Pressure is the major factor that affects the solubility of Gas in Liquid.
- Solubility of Gas in Liquid is directly proportional to pressure
- An Increase in Pressure leads to increase in solubility
- A Decrease in pressure leads to decrease in solubility.

- Effect of Pressure on solubility is basically explained by Henry's Law.

Henry's Law

According to Henry's Law the partial pressure of a gas above a solution is directly proportional to mole fraction of Gas in the solution.

$$P = k_H X$$

Here P = Partial Pressure of Gas
X = Mole fraction of Gas in the solution
k_H = Henry's Constant

TEMPERATURE

- Solubility of Gas decreases with increase in temperature.
- It is because increase in temperature causes an increase in kinetic energy that causes more motion in molecules that breaks intermolecular bonds b/w Gas and Liquids which ultimately leads to escaping of gas molecules and decrease in solubility.

SALTING OUT

- Addition of salts generally lowers the solubility of Gas in Liquids.
- Salts are highly polar electrolytes & have high affinity towards water molecules, as soon as they are added in the solution of Gas in liquid, water molecules surrounds the gas molecules leaves the gases and attracted towards salt & thus the density of aqueous atmosphere around the gas particles decreases & Gases escaped from the solution.

CHEMICAL REACTION

- Effect of chemical reaction on solubility of Gas in Liquids is basically depends on nature of Gaseous substance & their interaction with solvent molecules.
- Generally in most of the cases solubility of Gas in liquids increases with chemical reaction b/w Gas & solvent.
- This is why water solubility of HCl is 10,000 times more compare to oxygen.

SOLUBILITY OF LIQUID IN LIQUID

- Solubility of liquid in liquid is simply defined as mixture of two or more liquids for the preparation of pharmaceutical solution
- Solubility of liquid in liquid is very common phenomenon.
- Examples : Alcohol & water to form Hydro-alcoholic solution.
  Volatile Oils & Alcohols to form spirits.

TYPES OF LIQUID - LIQUID SYSTEM

On the basis of proportion of miscibility of one liquid in another, thre are 3 types of liquid-liquid solubility :

① Completely Miscible Liquids
② Partially Miscible Liquids
③ Immiscible Liquids

Completely Miscible Liquids

In this system liquids are completely miscible with each other at all proportions. example : Alcohol-Water, Glycerin-Alcohol etc.

Partially Miscible Liquids

In this system liquids are miscible with each other but to a particular extent. example : Phenol-water solution.

Immiscible Liquids

In this system liquids are not miscible with each other at any proportion. example : Benzene-Water, Benzene-Alcohol etc.

RAOULT'S LAW

- Raoult's Law states that the partial vapour pressure of a component in a solution is directly proportional to the mole fraction of that component in the solution.
- In other words it can also be defined as the partial vapour pressure of any component in a solution is equal to the vapour pressure of pure component multiplied by mole fraction of that component in the solution.

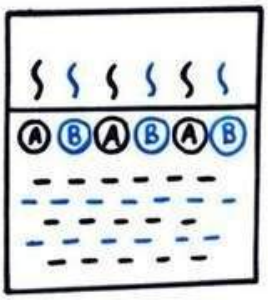
$$P \propto X \quad \text{or} \quad P = P_0 X$$

- Here, P = Partial Vapour Pressure
  P_0 = Pure Vapour Pressure
  X = Mole Fraction

LET US CONSIDER A SOLUTION OF TWO VOLATILE LIQUIDS A & B

- Here, we have a solution of two volatile and completely miscible liquids A & B
- Now according to Raoult's Law :

$$P_A = P^\circ_A X_A$$
$$P_B = P^\circ_B X_B$$



- Now, according to Dalton's Law the total Vapour pressure exerted by the solution is equal to the sum of individual partial pressure exerted by all the components in the solution.

$$P_{TOTAL} = P_A + P_B$$

Now, after combining Raoult's Law & Dalton's Law, Finally we get :

$$P_{TOTAL} = P^{\circ}_{A} X_A + P^{\circ}_{B} X_B$$

Now Here,

- P_{TOTAL} = Total Vapour Pressure of the solution
- P°_{A} = Vapour pressure of Pure A
- X_A = Mole fraction of A
- P°_{B} = Vapour pressure of pure B
- X_B = Mole fraction of B

LIMITATIONS OF RAOULT'S LAW

- It is applicable only to very dilute solutions.
- It is applicable only when solute doesn't dissociate or associate in the solution.
- It is applicable only for ideal solutions.

IDEAL SOLUTIONS

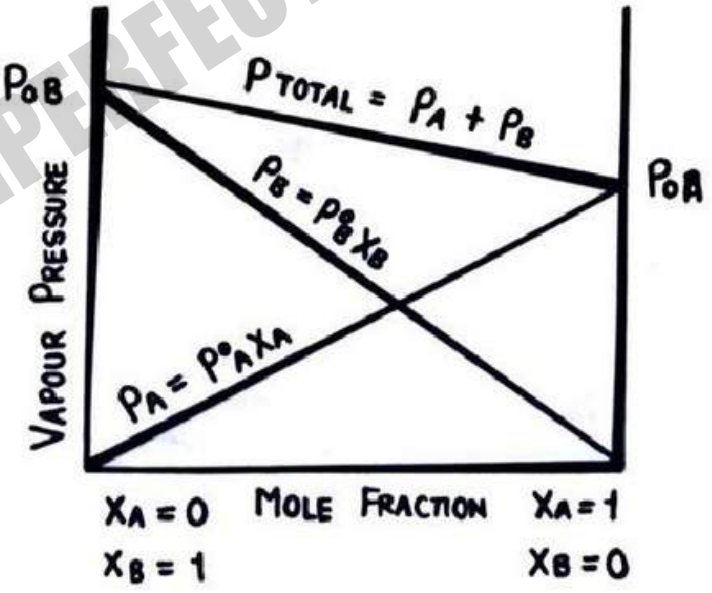
- Ideal Solutions are the ones which follows Raoult's Law at all concentration and all temperature
- In ideal solutions the volume of solution is equal to the sum of volume of all the components of solution.
- The change in enthalpy in ideal solution is zero.
- In an ideal solution of two liquid components A & B, the forces of attraction between :

$$A - A = B - B = A - B$$

- Let us consider, we have an ideal solution of A & B
- Now $P_A = P_{oA} X_A$

  $P_B = P_{oB} X_B$

  & $P_{TOTAL} = P_{oA} X_A + P_{oB} X_B$
- Now if we plot a graph of this solution :



NON - IDEAL SOLUTIONS

- Non - ideal solutions are those which do not obeys Raoult's Law at all concentration & Temperature
- It is also known as Real Solutions.
- In Non ideal solutions, $V_{SOLUTION} \neq V_{COMPONENTS}$
- In these solutions, change in enthalpy $\neq 0$

TYPES OF NON - IDEAL SOLUTION

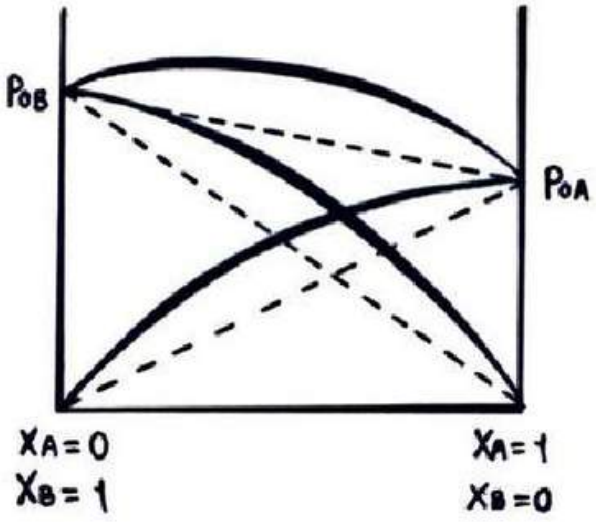
According to the deviation from Raoult's Law, Non - ideal solution can be classified into two categories :

① Non - Ideal Solution showing Positive Deviation
② Non - Ideal Solution showing Negative Deviation

Positive Deviation

In positive deviation the total vapour pressure of the solution is greater than sum of partial pressure of individual components

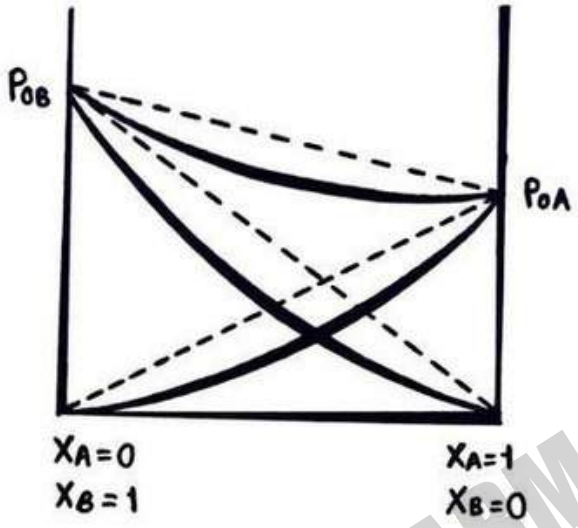
$$P_{TOTAL} > P_{0A}X_A + P_{0B}X_B$$



Negative Deviation

In Negative deviation the total vapour pressure of the solution is less than sum of partial pressure of individual component.

$$P_{TOTAL} < P_{oA}X_A + P_{oB}X_B$$



CRITICAL SOLUTION TEMPERATURE

- The temperature at which two partially miscible liquids are completely mixed at all proportion is known as 'Critical Solution Temperature'.
- It is also known as Consolate Temperature.
- There are two types of Critical Solution Temperature.

UPPER CST : The temperature above which two partially miscible liq. mixed together is known as Upper CST.

LOWER CST : The temperature below which two partially miscible liq. become miscible is known as Lower CST.

DISTRIBUTION LAW

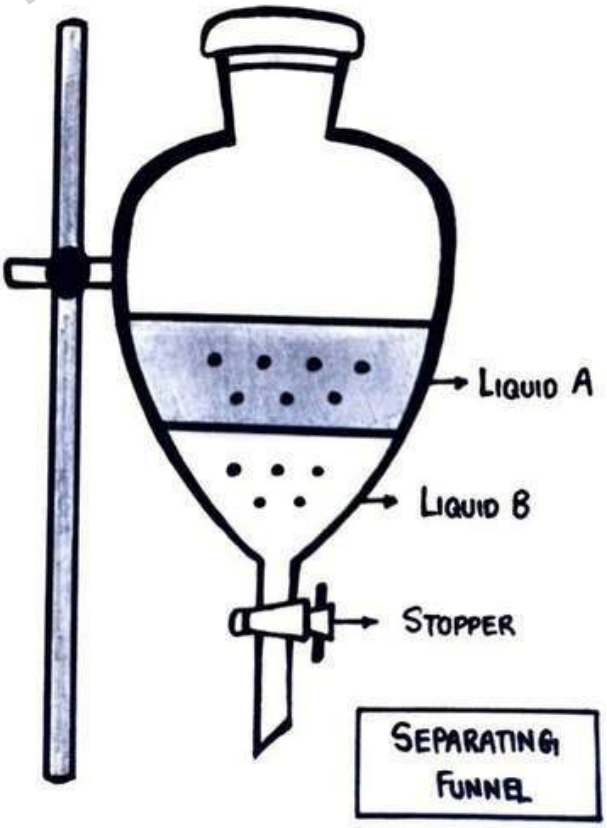
- The distribution law was given by Sir Walther Hermann Nernst, a German chemist, hence it is also known as Nernst Distribution Law or 'Partition Coefficient'.
- The law was given to find out the distribution of solute in two non-miscible (immiscible) solvents.
- According to Nernst Distribution Law : If a solute X distributes itself between two immiscible solvents A & B at constant temper. and same molecular condition then :

$$\frac{\text{Concentration of X in A}}{\text{Concentration of X in B}} = K_D$$

- Here k_D is the constant known as Distribution Coefficient.
- Now if we denote :
  - Conc. of X in A = C_1
  - & Conc. of X in B = C_2
- we can write the above formula as :

$$\frac{C_1}{C_2} = K_D$$

- If $k_D > 1$, then : X is more soluble in A
- & If $k_D < 1$ then : X is more soluble in B



Limitations Of Distribution Law

- Distribution law is applicable only for very dilute solutions.
- Temperature must be constant throughout the experiment.
- Solute must be in same molecular state in both solvents.
- The concentration of solute should be measured after the acheivement of equillibrium.
- Solvents must be immiscible.

Application Of Distribution Law

- Solvent Extraction
- Determination of Degree of Dissociation
- Determination of Degree of Association
- Determination of Solubility

THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER

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