Unit-II

<u>Solubility</u> :— It is defined in quantitative terms as the Conc. of solute in a saturated solution at a certain temperature.

* In a qualitative way it can be defined as spontaneous interaction. two or more substance to form homogenous molecular dispersion.

Certain terms related to solubilities:—

(i) <u>Solute</u> :— A Component which dissolve in the solvent and present in less amount in the whole solution.

(ii) <u>Solvent</u>:— A component in which solute is dissolve it is present in more amount than solute.

(iii) <u>Solution</u>:— Mixture of two or more Component that form a homogenous mixture.

(iv) <u>Saturated Solution</u>:— Solution in which the solute in solution is in equilibrium with solvent.

(v) <u>Unsaturated Solution</u>:— Solution Containing dissolved solute in Conc. that is necessary for Complete saturation.

(vi) <u>Super saturated Solution</u>:— Solution Containing more of the dissolved solute than it would normally Contain.

Solubility definition in the U.S.P :-

Solubility

Descriptive Form	Parts of Solvent require for one part of Solute
Very Soluble	< 1
Freely Soluble	1 - 10
Soluble	10 - 30
Sparingly Soluble	30 - 100
Slightly Soluble	100 - 1000
very Slightly Soluble	1000 - 10000
Practically Insoluble	> 10,000

Solubility Expression :-

Normality (N) :- No. of equivalent of solute dissolve in 1 litre of solution.

$$N = \frac{No.\ of\ gram\ equivalent\ of\ solute}{1\ litre\ of\ solution}$$

Molarity (M) :- No. of mole of solute in 1 litre of solution.

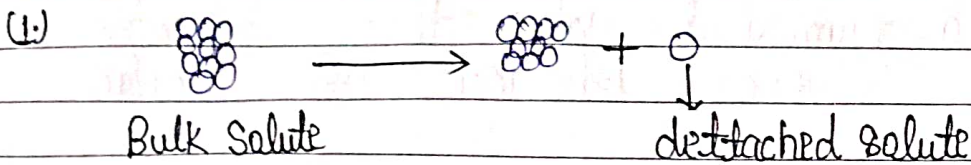$$M = \frac{No.\ of\ mole\ of\ solute}{1\ L\ of\ solution}$$

Molality (m) :- No. of solute of 1000 gm of solvent; It is denoted by 'm'.

% w/w :- Gram of solute in 1000 gm of solution.

% v/v :- ml of solute in 100 ml of solution.

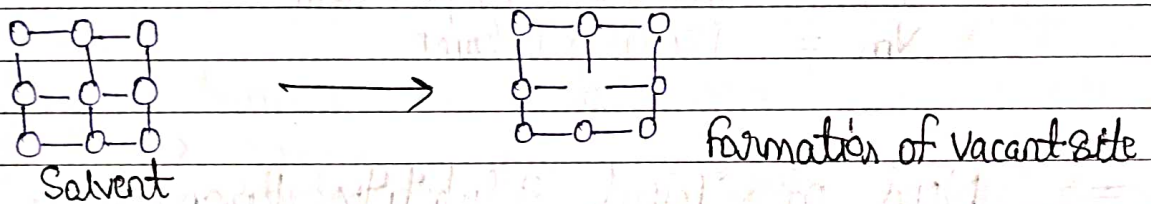% w/v :- Gram of solute in 100 ml of solution.

Mechanism of Solute Solvent Interaction :→

(1.)

Bulk Solute → detached solute
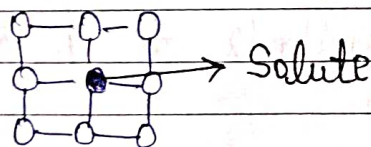
(2) (1.) Detachment of Solute from Bulk form :-

In this step from Solute Bulk 1 mole of Solute gets dettach and this is further used in the interaction of Solute & Solvent.

(2.) Formation of vacant site in Solvent :-

Solvent → formation of vacant site

In this step, 1 molecule from the Solvents gets free and vacant site is formed.

(3.) Inserting of dettach Solute in vacant Site :-

→ Solute

i.) It involves the insertion of dettach solute molecule in site the vacant site of solvent.

ii.) Free solute molecule interact in the vacant site and form solvent embedded solute molecule.

Ideal Solubility Parameter :—

* It is a numerical value that indicates relative solvency behaviour of specific solvent.

* It is derived from Cohesive energy density (C).

$$C = \frac{\Delta H - RT}{V_m}$$

where,

ΔH = Heat of vaporization
R = Gas Constant
T = Constant temperature
V_m = Molar volume

⇒ <u>Need of Ideal Solubility Parameter</u> :—

* It is used for the estimation of whether the substance will dissolve in other material or not.

* It provide numeric methods to predict interaction b/w molecules.

⇒ <u>Types of Ideal Solubility Parameter</u> :—

1. Hildebrand Solubility Parameter (δ) (1936)
2. Hansen Solubility Parameter. (1966)

1. <u>Hildebrand Solubility Parameter (δ)</u> :—

* It is square root of Cohesive energy density.

* It is applicable of non-polar solvent.

* It was proposed in <u>1936</u> by <u>Joel. H. Hildebrand.</u>

$$\sqrt{C} = \sqrt{\frac{\Delta H - RT}{Vm}}$$ or $\sqrt{\delta} = \sqrt{C}$

* Its unit is <u>Cal./cm³</u>.

* Materials with same solubility parameter means that material will be mixible with each other.

2. <u>Hansen Solubility Parameter :-</u>

* It was proposed by <u>Charles Hansen in 1966.</u>

* It is applicable of polar solvent.

* Hansen parameter divided the Hildebrand Solubility parameter into 3 component —

(i) Dispersion force Component
(ii) Hydrogen Bonding Component
(iii) Polar Component

$$St^2 = \delta d^2 + \delta h^2 + \delta p^2$$

Total Hildebrand parameter

Salvation :-

* The interaction b/w solute & solvent molecule leads to stabilization of solute species in the solution is called Salvation.
* In the process of Salvation and an Ion in the solution is surrounding an all Complex. by solvent molecule.
* Salvation of solute with water is called Hydration.
* Salvation is the kinetic process and is quantified by its rate.
* The interaction b/w solute & solvent results in formation of different forces and bond like:-(i) attractive & repulsive forces
  (ii) Hydrogen bonding
  (iii) Vanderwall forces
  (iv) Ion dipole interaction

Association :-

* It is the chemical rean where By Ions of opposite electrical charges comes together in a saln to form different chemical entity.

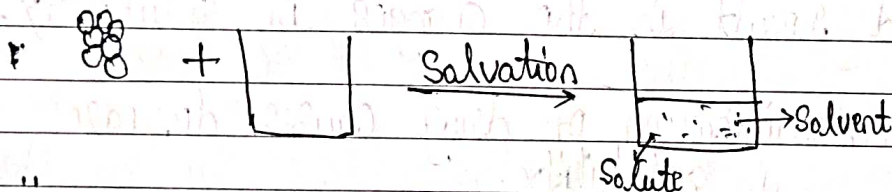* Ion association are classified according to the number of Ion that associate with each other such as —

(a.) Ion Pair

(b.) Ion ~~Effect~~ Triplet

(a) <u>Ion Pair</u> :— Ion pair are formed when a cation and anion come together.

<u>Types of Ion Pair</u> :—

(i) Fully Solvent

(ii) Solvent Shared

(iii.) Contact Ion paired

(i) <u>Fully Solvent</u> :— when both ions have a complete primary solvation sphere then the ion is known as fully solvent.

(ii) <u>Solvent Shared</u> :— when there is about one solvent molecule b/w the anion & cation then the Ion pair is called as solvent shared

(iii) <u>Contact Ion Paired</u> :— when the ions are in contact with each other then ion pair is called as contact ion paired.

(b) <u>Ion Triplet</u> :— The association of three Ions is called Ion triplet.

Factor affecting Solubility of Drugs :-

(i) Particle Size :-
It is ~~directly~~ Inversely proportional to solubility of drug.
when particle size is small than the surface area increases then solubility increases.
Eg:-
Micronized, Griseosulbil.

(ii) Temperature :-
In endothermic reaction solubility increses and in exothermic reaction solubility decreases

(iii) Molecular Structure :-
Modification in the structure of solid result is the changes in solubility.
Eg:-
Esterification of drug causes decrease in solubility.

(iv) Nature of Solvent & Co-solvent :-
Addition of IIIrd substance increases the solubility of drug in solvent which is known as co-solvent.
Eg:-
Poorly soluble drugs are dissolved in a mixture of water & alcohol.

(v) Effect of Complex formation :-
when a complex is formed it results in increase or decrease of solubility.
Eg:-
Addition of I_2 in water result in increased solubility with the addition of KI due to complex formation of KI_3.

(vi) Solubilizing Agent :-
Use of Surface active agent (surfectant) increases the solubility of solid in liquid & also reduces the surface tension.
Eg:-
Poly ethyle glycon when added to a solid form in a liquid medium increases solubility by increasing the contact of solid with the liquid medium.

(vii) Effect of pH :-
Most of the drug are weakly acidic or weakily basic in nature, therefore they are less soluble in water. but there salt form are soluble in water so by formation of salt formation of in drug increase its solubility.

(viii) Effect of Additives / Excipient :-
When large amount of excipient or additives used then solubility increases.

Eg:- Solubility of Caeffin is increases by the large amount of Sodium benzoate.
addition of

(ix) Common Ion Effect :-
The solubility of slightly soluble salt is decreased by the addition of another salt which carry a similar ion to that of earlier. This is known as Common Ion effect.
* when Common Ion is present b/w two salt than solubility decreases.
Eg:- Aluminion hydroxide added to aluminium chloride results decreasing solubility.

(X.) Effect of Electrolyte and Non-electrolyte :-

There is decrease in solubility of slightly soluble salt in water when a non-electrolyte alcohol is added.

Eg :- Precipitation of protein.

Diffusion principle in Biological system :-

· Physical process that refers to the net movement of any molecules of from region of higher Conc. to lower Conc. under the influence of Conc. gradient

⇒ Diffusion Phenomenon application in Pharmaceutical size :-

(i) Estimation of molecular weight of Polymer :-

↑ molecular weight → ↓ Diffusion rate
↓ molecular weight → ↑ Diffusion rate

(ii) Absorption Distribution & Elimination of the drug through biological membrane is determine by diffusion principle :-

(iii) It estimate the release of drug that is sustained release and controlled release

(iv) Permeation Study of drug in living tissue

Diffusion Principle is describe by various Method:

1. Passive ~~Diffu~~ Diffusion
2. Pore Transport
3. Ion Pair Transport
4. Carrier Mediated Transport.

1. Passive Diffusion :-

* It is also known as Non-Ionic diffusion.
* It is the major process for absorption of more than 90% of drug.
* The driving force for this process in conc. gradient.

* Concentration Gradient :- The difference in the conc. of drug on either side of the membrane is called Concentration gradient / Electrochemical gradient.

* Passive Diffusion is described by Fick's law of diffusion :-

$$\frac{dQ}{dt} = \frac{DAK_{m/w}}{h}(C_{GIT} - C)$$

where, $\frac{dQ}{dt}$ = rate of diffusion of drug molecule

D = Diffusion coefficient of the drug through the membrane

A = Surface area of the membrane

$K_{m/w}$ = Partition coefficient of the drug b/w lipiodal membrane and the aqueous phase

$C_{GIT} - C$ = Difference in the conc. of the drug in GIT fluid and Plasma

h = Thickness of the membrane

* Fick's law of Diffusion :-

It is state that drug molecules diffuse from a reason of higher conc. to lower conc. until equilibrium is achieve and rate of diffusion is directly proportional to the conc. gradient across membrane.

2. Pore Transport :-

*   It is also known as Bulk flow / Filteration / Convective Transport.

* This process is important in the absorption of low molecular weight.

* The driving force in pore transport is osmotic pressure across the membrane.

* In this process water soluble drug passes through Narrow or Aqueous filled pores in membrane structure.
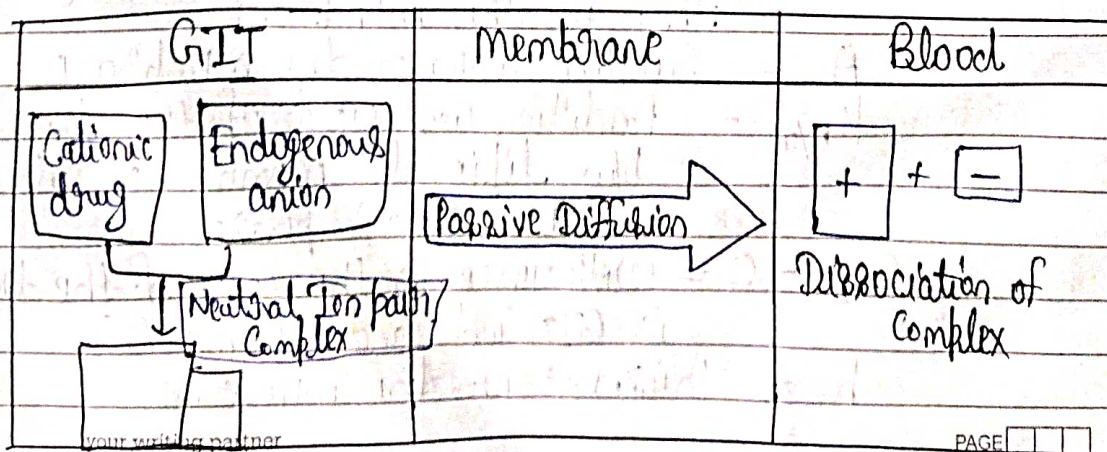
⇒ Significance of Pore Transport :-

(i) Renal Excretion.
(ii) Entry of drug into the Liver.

3. Ion Pair Transport :-

*   They form the reversible neutral complex with endogenous Ion of the GIT like mucil.

GIT	Membrane	Blood
Cationic drug Endogenous anion	Passive Diffusion ⟹	+ + [−]
↓ Neutral Ion pair Complex		Dissociation of Complex

Eg:- Absorption of drugs like Quaternary ammonium compound & Sulphuric Acid.

* Neutral Complex which are formed in Ion pair transport should have required Lipophilicity as well as aqueous solubility.

4. Carrier Mediator Transport:-

* It is movement of Drug molecule across the cell membrane, via special transport carrier that are embeded with in the membrane.
* The carrier may be enzymes or proteins.
* Carrier and Drug Complex transverse across the membrane to the other side where Complex dissociate and release the drug molecule.

Solubility of Gas in Liquid :-

Solubility of gas in liquid is the conc. of dissolved gas in liquid when it is in the equilibrium with the pure gas above the solution.
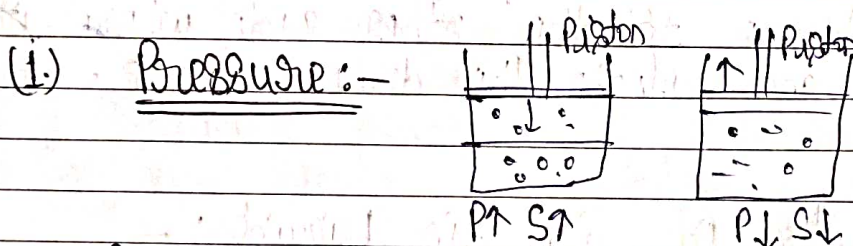Eg:-
(i) Aerosal products containing CO_2 or Nitrogen gas as propellant are considered to be solution of gases in liquid.

(ii) Effervescent preparation containing dissolved CO_2.

(iii) Ammonia water (It is the combination of ammonia gas and water).

(iv) Hydrochloride Gas

* There are many gases that easily dissolve in water, while there are some gases that do not dissolve in water under Normal Condition they required to pressure to dissolve.
                                    maintain

Eg:-

(i) CO_2 is only water soluble gas when pressure is maintained

(ii) Ammonia gas easily dissolve in water.

(iii) Oxygen is sparingly soluble in water.

⇒ <u>Factors affecting Solubility of Gas in Liquid :-</u>

(1) <u>Pressure:-</u>

P↑ S↑   P↓ S↓

* Pressure is directly proportional to the solubility of gas in liquid
                $(P \propto S)$.

* Effect of pressure on the solubility of gas in liquid is given by Henry's law which states that —

                The mass of gas dissolved in solvent is directly proportional to the partial pressure of gas.

                $C \propto P$

                $$\boxed{C = \sigma P}$$

        where,

                C = Conc of gas in liquid
                σ = Henry Constant
                P = Partial Pressure of gas

(2.) Temperature :—

* Temperature is inversely proportional to the solubility of gas in liquid.

$$T \propto \frac{1}{S}$$

* Temp. ↑ $\longrightarrow$ Solubility ↓
  Temp. ↓ $\longrightarrow$ Solubility ↑

(3.) Chemical Reaction :—

* Chemical reaction b/w gas & solvent increases the solubility of gas in liquid.

$$\boxed{Chemical \ rea^n \propto S}$$

Eg :—
    Addition of ammonia in water.

(4.) Electrolyte & Non-Electrolyte :—

Solubility of gases is generally decreased by the addition of electrolyte & Non-electrolyte.

Eg:
        Electrolyte — NaCl
        Non-electrolyte — Sugar.

$$\boxed{Electrolyte \ \& \ Non\text{-}electrolyte \propto \frac{1}{S}}$$

Note:—
    S = Solubility of Gas in liquid.

Solubility of Liquid in Liquid :-

when two or more liquids are frequently mixed together in preparation of pharmaceutical solutions.

E.g:-
(i) Alcohol & water from hydroalcohalic solution.
(ii) Volatile oils and alcohol are mixed to form spirit.

Liquid - Liquid system may be divided into different types on the basis of there solubility.

1. Complete miscible
2. Partial miscible
3. Immiscible

1. __Complete Miscible__ :- In this system liquids are Completely miscible when they are mixed in any proportion.

E.g:-
Polar and Polar solvent (water & Alcohol).

* Similarily Non-polar & Non-polar solvent are miscible.
   E.g:- Carbontetrachloride

2. __Partial Miscible__ :- These liquids are miscible to each other but to a limited extend i.e. partially.
* These liquid mix but forms two layer.
   E.g:-
          Water and ether
          Water and Phenol.

The temperature at which two partial miscible liquids become Completely miscible is known as Critical Solution Temperature (C.ST).

3. **Immiscible / Insoluble / Partially Immiscible :-**
These liquids do not mix in any proportion.

E.g:- Castor Oil and water

⇒ **Factors Affecting Solubility of Liquids in Liquid :-**

1. Nature of solute and solvent — like dissolve like.

2. Temperature, pressure and surface area is directly proportional to the solubility of liquid in liquid.

RAOULT'S LAW

According to Raoult's law of definite temperature the partial pressure of a compound in a liquid mixture is multiplication of vapour pressure of the component and mole fraction.

$$P_A = P_A^0 \cdot X_A$$

where,

P_A = Partial pressure

P_A^0 = Vapour pressure

X_A = Mole fraction.

According to the Dalton law the total pressure of the system is sum of total partial pressure of components.

$$\text{Total Pressure} = P_A + P_B + P_C \text{ ---- eq. } v)$$

According to Raoult's Law —

$$P_A = P_A^0 \cdot X_A$$
$$P_B = P_B^0 \cdot X_B$$
$$P_C = P_C^0 \cdot X_C$$

When we put the value of P_A, P_B and P_C in equ. (i)

$$\text{Total pressure} = P_A^\circ \cdot X_A + P_B^\circ \cdot X_B + P_C^\circ \cdot X_C$$

Deviation of Raoult's Law :-

Non-Ideal Solution
$$\begin{cases} T_P < P_A^\circ \cdot X_A + P_B^\circ \cdot X_B + P_C^\circ \cdot X_C \longrightarrow -ve \text{ deviation} \\ T_P > P_A^\circ \cdot X_A + P_B^\circ \cdot X_B + P_C^\circ \cdot X_C \longrightarrow +ve \text{ deviation} \end{cases}$$

Binary Solution :-

Binary solution are those solution which consist of two components i.e, two solute or two solvent.

Eg:- Salt + water + Sugar.

* In binary solution the component which are present in greater amount is called as solvent while the component in lesser amount is solute.

* In this system each component may be in any state i.e solid, liquid and gas.

Ideal Solution :-

The solution which obey's Raoult's Law is called Ideal solution. In Ideal solution components should be completely miscible. Now heat is evolved or absorbed during the solution formation.

Eg:-
1. mixture of N-hexane and N-heptane
2. mixture of ethyl bromide and ethyl Iodide.

Real Solution :-

The solution which do not obey Raoult's Law is called real solution.

* Heat may be evolved or absorbed.
  E.g:-
    (i) Carbon tetrachloride and acetone mixture
    (ii) Benzene and ethanol.

CRITICAL SOLUTION TEMPERATURE :-

* It is the temperature beyond which two immiscible liquid becomes miscible and form a homogenous solution at all proportion.

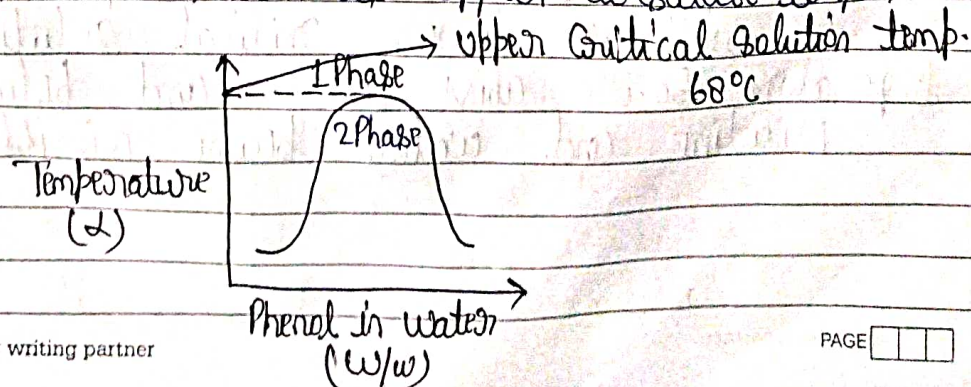* It is also known as Consulute temperature.

⇒ Types of Critical Solution Temperature:-

1. Upper Critical Solution temperature
2. Lower Critical Solution temperature
3. Both upper at lower Critical solution temperature

1: Upper Critical Solution Temperature:-

* It is the Critical temperature above which both partially immiscible liquid becomes Completely miscible in all proportion.
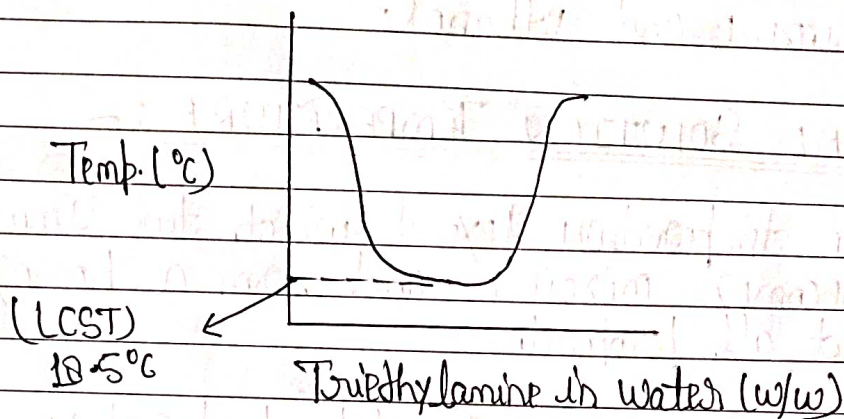
* It is also known as upper Consulute temperature.

→ upper Critical solution temp.
68°C
1 Phase
2 Phase
Temperature (↓)
Phenol in water (w/w)

2. Lower Critical Solution Temperature :-

* It is the critical temperature below which both partially immicible liquid become miscible completely in all preparation.

* It is also known as lower consulate temperature.

Temp. (°C)
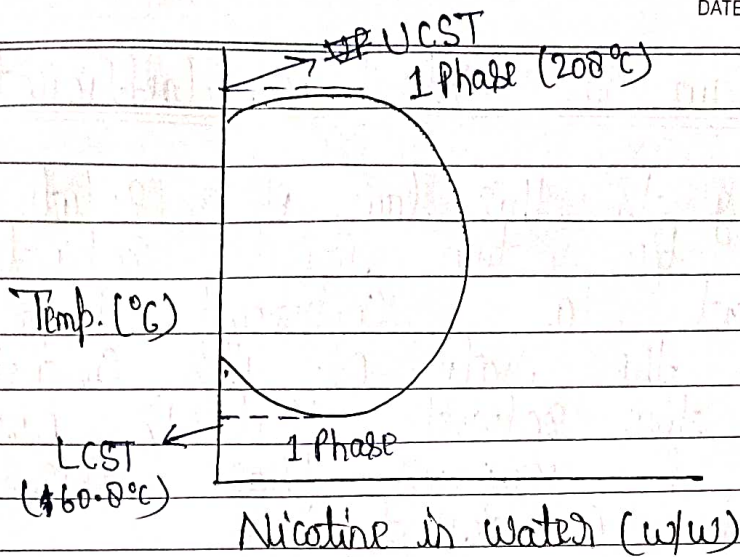
(LCST)
18.5°C   Truethylamine in water (w/w)

* Liquid system of triethylamine and water solubility increases with decrease in temperature and it shows a lower critical solution temperature of 18.5°C.

3. Both upper and Lower Critical Solution Temperature :-

When two immicible liquid become miscible at both high and low temperature is known as upper and lower critical solution temperature.

Eg:-
        Mixture of Nicotine and water exhibit and upper critical solution temperature (208°C) as well as lower critical solution temperature 60.8°c above 208°C and below 60.8 Nicotine and water become miscible.

UCST
1 Phase (208°C)

Temp. (°C)

LCST
(460.0°C)

1 Phase

Nicotine in water (w/w)

→ <u>Application of Critical Solution Temperature:-</u>

* Used in the determination of purity of substance.

* Determine water content in substance.

* It is used in the characterisation of Polymer mixture.

* It is useful for the determination of the % composition of the added substance.

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

* It is used in the extraction of natural drug from a solvent.

Eg:- Ethyl alcohal and cyclo hexane system has Critical solution temperature of 40-50°C and if water is present in small quantity it will rise temperature of 0-15°C in the CST.

Partition Law or Distribution Coefficient :-

According to this law, if a Solute molecule distribute b/w two imisible solvents or liquid at a constant temperature Then the ratio of its concentration in the two solvents that is non-aqueous & aqueous phase this partition coefficient.

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

where,

C_1 = Conc. of drug in non-aqueous phase
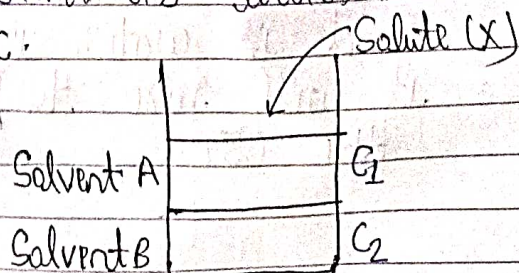
C_2 = Conc. of drug in aqueous phase

K_D = Partition Coefficient or Distribution Coefficient.

* Nernst in 1891 which governs the law distribution of a ~~law~~ b/w two imisible ~~solvent~~ solute solvent this is called Nernst distribution law / Nernst partition law / distribution law / Partition law.

* If the partition coefficient is greater than 1 i.e., Lipophilic.

* If the partition coefficient is lower than 1 then drug is Hydrophilic.

Solute (x) / Solvent A — C_1 / Solvent B — C_2

when distribution of solute reached dynamic equilibrium —

1. The rate at which molecules of solute (x) passes form solvent A to solvent B is directly proportional to its concentration.

$$R_1 \alpha C_1$$

$$R_1 = K_1 C_1 \qquad \text{——} (i)$$

2. The rate (R₂) at which molecules of solute passes from solvent B to solvent A is directly proportional to its concentration.

$$R_2 \alpha C_2$$

$$R_2 = K_2 C_2 \qquad \text{——} (ii)$$

Since at equilibrium —

$$R_1 = R_2$$

$$K_1 C_1 = K_2 C_2$$

$$\frac{C_1}{C_2} = \frac{K_1}{K_2} (K_D)$$

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

where,

$C_1 = $ Conc. of drug in non-aqueous phase

$C_2 = $ Conc. of drug in aqueous phase

$K_D = $ Partition coefficient or Distribution coefficient.

→ Application of Distribution Law :-

(i) Determines the hydrophilicity and Lipophilicity of a drug.

(ii) It helps in the partition chromatography in which it is used in separation, purification & Identification.

(iii) Partition principle is involved in the prolong release of drug.

(iv) It is also involved in the dissolution of insoluble or Sparingaly soluble Substance micellar solubilization.

(v) It helps to understand the absorption pattern of new chemical entity.

(vi) It helps to predict stability of Emulsions.

(vii) It helps to determine the degree of hydrolysis of salt in aqueous medium.

(viii) It helps in determination of association & dissociation of solute in the solvent.

(ix) It helps wide application in pharmaceutical development.

(x) By knowing the value of partition coefficient and the solubility of solute in one solvent, the solubility in the second solvent can be determine.

→ Limitations of Distribution Law :-

(i) Constant Temperature :- Temperature should be kept constant throughout the experiment.

(ii) Dilute Solution :- The conc. of solute must be low in the solvents.

(iii) <u>Equilibrium Concentration</u>:- This is achieved by Shaking the two solvents for longer time.

(iv.) <u>Same molecular State</u>:- Solute must be in same molecular State in both solvents.

(v.) <u>Non-missibility of Solvent</u>:- Solvent must be non-missible so that the Separation can be achieved.