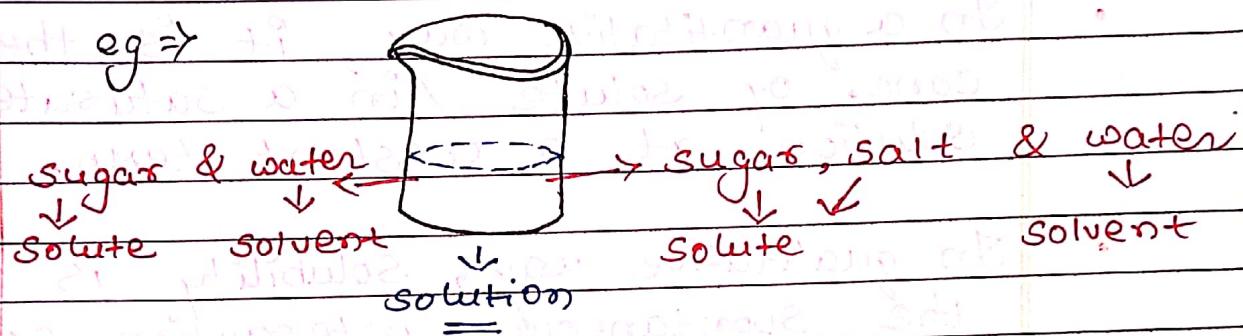


## Solubility Of Drugs

→ **Solution** : is a mixture of two or more components that form a homogenous mixture. The components are referred to as the solute &/or solutes & the solvent and /or solvents.



→ **Solute** : The substance usually present in lesser amount & getting dissolved in the solution.

→ **Solvent** : is the component in which the solute is dissolved.

→ **A saturated solution** : A solution that contains the maximum amount of solute at a definite temperature.

→ **unsaturated solution** : A solution that contains less solute than the saturated solution that completely dissolves at a definite temperature.

→ **Supersaturated solution** : A solution that contains more solute than the saturated solution (undissolved solute) than the saturated solution at a definite temperature.

(X marks)  
~~(X)~~

Solubility = = / =

Solubility is the ability of one substance to fully dissolved in another substance under specified condition.

- In a quantitative way, it is the conc. of solute in a saturated solution at a constant temp.
- In qualitative way, solubility is the spontaneous interaction of two or more substances (solute & solvent) to form a homogenous molecular dispersion.

→ Solubility Expression :

i) Normality - (N.)

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

$$N = \frac{\text{No. of gram Eq. of Solute}}{\text{litre of soln}}$$

~~Eq. wt~~  
~~No. wt~~  
Acidity  
Basicity

$$\text{Gram Eq.} = \frac{\text{Gram of Solute}}{\text{Equivalent wt.}}$$

$$N \Rightarrow \frac{\text{Gram of Solute} \times 1000}{\text{Eq. wt} \times \text{Quantity of soln in ml}}$$

ii) Molarity - (M)

- No. of moles of solute in ~~1lt.~~ 1lt. of solution.

iii) Molality - (m)

- No. of moles of solute in 1000gm of solvent.

iv) Mole fraction - (x)

- Ratio of moles of solute to total mass of soln + solvent.

v) Percentage by weight - (% w/w)

- Gram of solute in 100gm of soln.

vi) Percentage by vol. - (% v/v)

- ml of solute in 100ml of solution.

vii) Percentage weight in vol. - (% w/v)

- gm of solute in 100ml of solution.

Term

Parts of solvent required for 1 part of solute.

- very soluble: less than 1 part
- fairly soluble: 1 to 10 parts
- soluble: 10 to 30 parts
- sparsingly soluble: 30 to 100 parts
- slightly soluble: 100 to 1000 parts
- very slightly soluble: 1000 to 10000 parts
- Insoluble: more than 10000 parts.

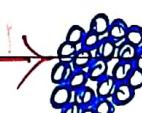
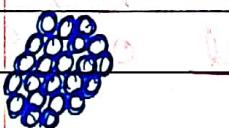
~~X marks~~

## # Mechanism of solute - solvent interaction

- When favourable interaction b/w takes place b/w solute and solvent then solute get dissolved in Solvent.
- This dissolving process depends on free energy change of solute and solvent.
- Mechanism involves in 3 steps:

### 1) Detachment of solute from bulk form:

- In this step, from solute bulk one mole of solute gets detach and this is further used in the solute-solvent interaction.

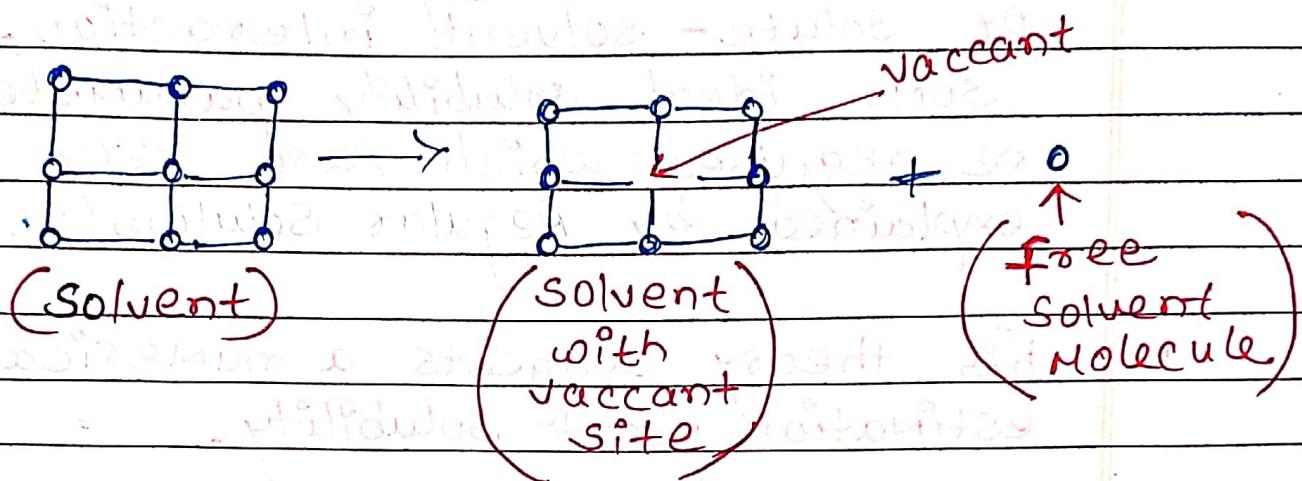


detach solute molecule

### 2) formation of vacant site in solvent:

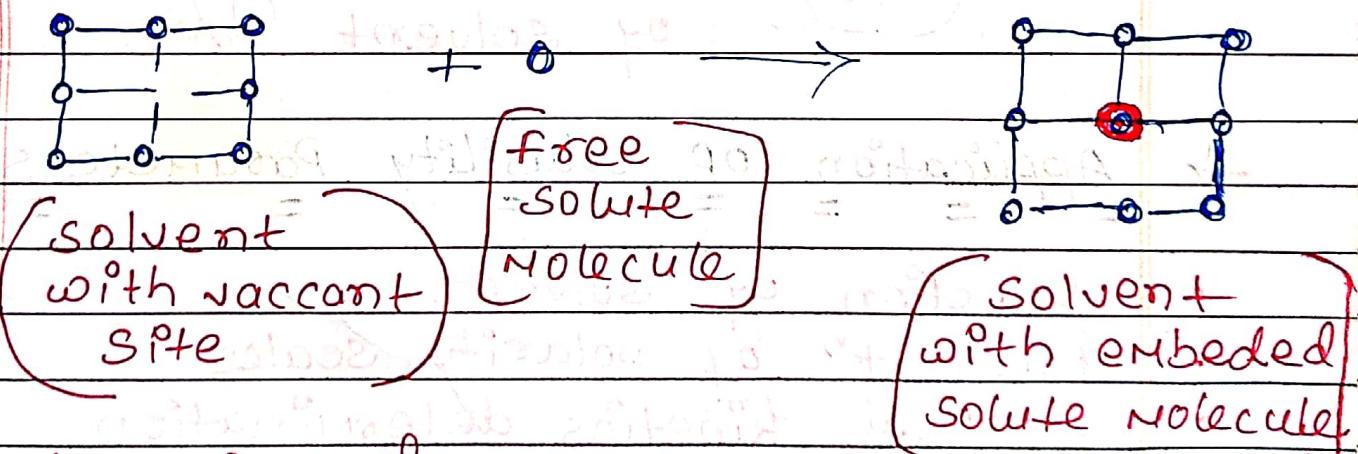
- In this step, From the solvent one molecule of solvent gets free and created a vacant site.

This vacant site is further involved in solute-solvent interaction in the third step.



### 3) Insertion of detached solute molecule in vacant site of solvent :

- This step involves the insertion of detached solute molecule inside the newly created vacant site of solvent.



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

(X marks)

## Ideal solubility Parameters

- To estimate solubility as a result of solute-solvent interaction, some ideal solubility parameters are required which are very well explained by Regular Solution Theory.
- This theory suggests a numerical estimation about solubility.

$$\delta_1 = \left( \frac{\Delta U}{\rho V} \right)^{1/2} = \left( \frac{\Delta H - RT}{V} \right)^{1/2}$$

where,  $\delta_1$  = solubility parameter.

$\Delta U$  = Molar energy

$\rho V$  = Molar volume of solvent

$(\Delta U/V)$  = cohesive energy density of solvent.

$\Delta H$  = Molar heat of vaporization of solvent.

Note :-

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

- SI unit  $\rightarrow J^{1/2} m^{-3/2}$  i.e., equivalent to  $Pa^{1/2}$

## → Application of solubility parameters

- (1) Selection of solvent.
- (2) Preparation of polarity scales
- (3) cosolvency power ↳ d/gt solvent have d/gt solubility value. we make a polarity chart of inc. or dec. order of solubility.  
Cosolvency power is the ability to inc. ag. solubility of drug to enhance its efficacy.
- (4) chemical kinetics → when the solubility product of solute & solvent are more then the rate of rxn. is obviously more.
- (5) Determination of mechanism involved in drug actions.
- (6) structural activity relationship (SAR)
- (7) Drug transport through model membrane.

## → Advantages of Regular soln Theory:

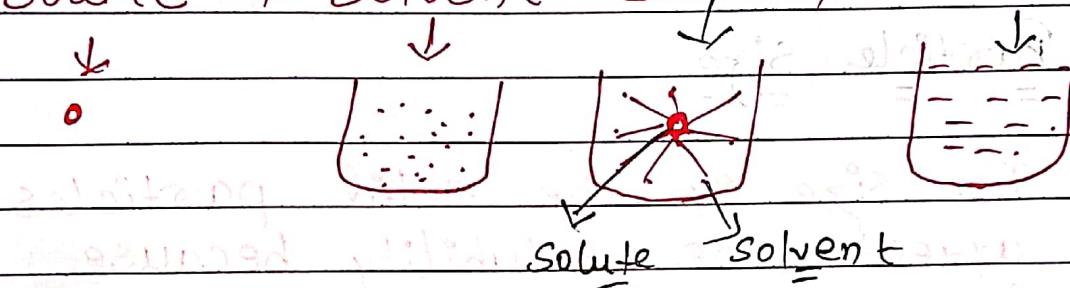
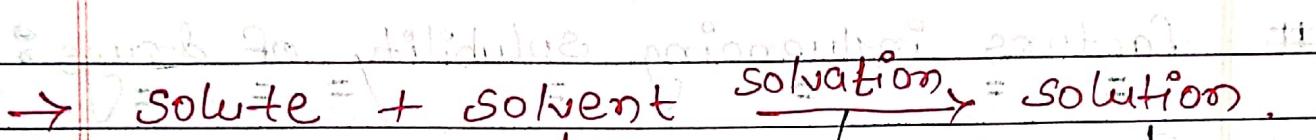
- To predict excess free energy of mixing.
- Limitations of Regular soln Theory:
- Not able to predict thermodynamic properties like - i) Heat of solution ii) volume after mixing.

(2 marks)

## II Solvation and Association

### \* Solvation

- solvation is an interaction of a solute with the solvent ~~part~~ which leads to stabilization of the solute species in the solution.



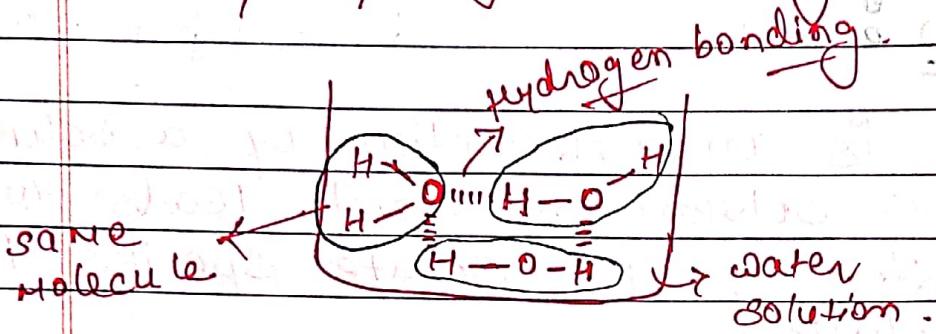
- In solvation state, a solute ion in a soln is surrounded by solvent molecule.
- solvation involves bond formation, hydrogen bonding, van der waals forces, etc.

### \* Association

- Association means joining / addition.

- when the same molecules of one of the components in a soln (need  $\rightarrow$  solute-solute mol. or solvent-solvent mol.) interact then this phenomenon is termed as association.

$\Rightarrow$  e.g. Interlinking of water molecules by hydrogen bonding.



# factors influencing solubility of drugs:

i) Particle size

- The size of the solid particles affects the solubility because with the decrease in particle size, the surface area ↑ & the solubility ↑.

$$\log \frac{S}{S_0} = \frac{2 \gamma v}{R T \sigma}$$

where,

$S_0$  → is the solubility of large particle

$S$  → is the solubility of fine particles

$\gamma$  → is the surface tension of particles

$v$  → is molar mass.

$T$  → is the absolute temp.

$\sigma$  → radius of fine particles

$R$  → gas constant.

### iii) Molecular Size

- The molecular size will affect the solubility of the drug because the larger / the molecules or higher the molecular weight of the drugs, less is the solubility of the substance.

Molecular Size ↑ → Solubility ↓

### iv) Temperature

- With the inc. in temp. the process of sol<sup>n</sup> absorbs the energy & thus the solubility will get inc.
- But if the process of sol<sup>n</sup> release the energy with the inc. in temp. then it will dec. the solubility.

### v) Pressure

- In case of solids and liquids solutes, there is no effect of pressure on the solubility. The dec. in pressure there is a dec. in solubility.

↓ Pressr → ↓ solubility

↑ Pressr → ↑ solubility.

## # Diffusion Principle in biological system :

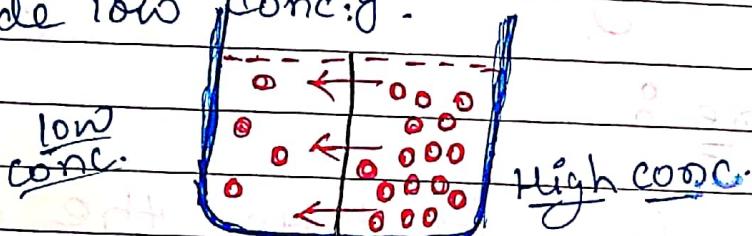
### → Diffusion :

- It is defined as the spontaneous process of mass transfer of solute individual molecules of a substance caused by random molecular motion and conc. gradient.

one side high conc.g.  
one side low conc.g.

→ as though

down  
concentration



### Diffusion

## → Application of diffusion in pharmacy :

- Absorption, distribution and elimination of the drug through biological membranes is by the diffusion.
- Release of drug from the dosage form is diffusion controlled  
e.g., sustained release, controlled release.
- Molecular weight of the polymer can be estimated by diffusion process. → using one end of  
Mol. wt ↑ → Diffusion rate ↓  
Mol. wt ↓ → Diffusion rate ↑.

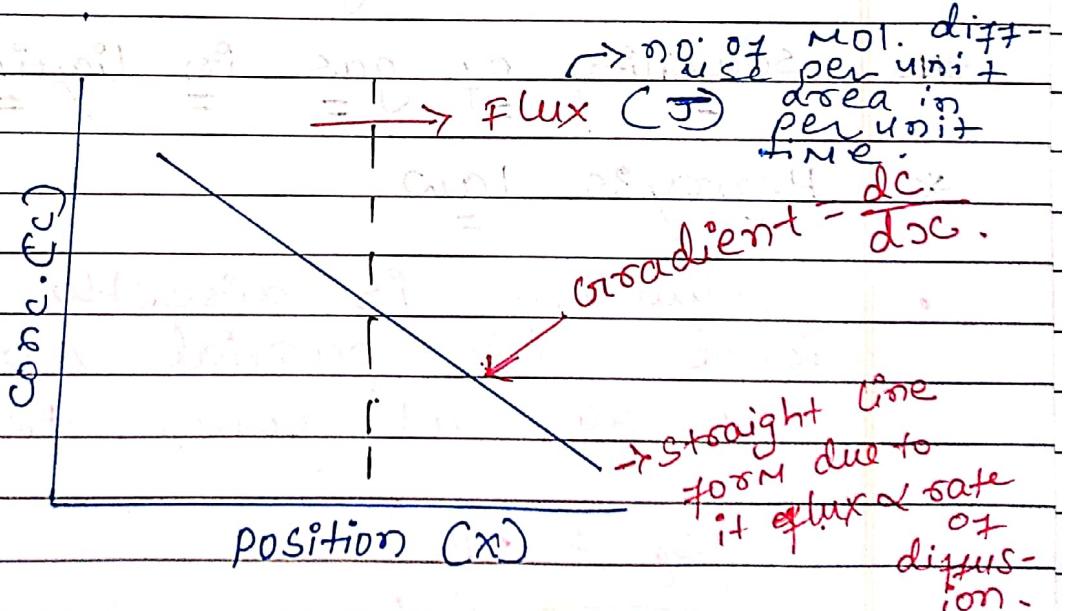
→ Laws of Diffusion :

\* Fick's first law of diffusion :

- It states that rate of diffusion across a surface is proportional to the conc. gradient and area of the surface.

$$J \propto \frac{dc}{dx} \quad , \quad J = -D \left( \frac{dc}{dx} \right)$$

- $J$  = flux
  - $D$  = Diffusion coefficient of drug
  - $\frac{dc}{dx}$  = change in conc. of material.
  - $\frac{dx}{dc}$  = change in distance.
- Rate of diffusion



→ flux : it is defined as no. of atoms diffusing across the unit area per unit time.

by biological membrane.

Date \_\_\_\_\_  
Page No. \_\_\_\_\_

\* Fick's second law:  $\frac{dc}{dt} = -D \frac{d^2c}{dx^2}$

- Predicts how diffusion causes the conc. to change with time.

- It is expressed as

$$\frac{dc}{dt} = - \frac{dJ}{dx} = D \left( \frac{d^2c}{dx^2} \right)$$

$dJ$  = change in flux

$dc$  = change in conc. of material

$dt$  = change in time

$dx$  = change in distance

# Solubility of gas in liquid

\* Henry's law

- Solubility is directly proportional to partial pressure of gas at const. temp.

$$S_g \propto P_g \rightarrow [S_g = k P_g] \rightarrow P_g \propto X_g$$

where,  $S_g$  = solubility of the gas

$k$  = Henry's law const. for that gas in solvent.

$P_g$  = Partial pressure of the gas above the liquid.

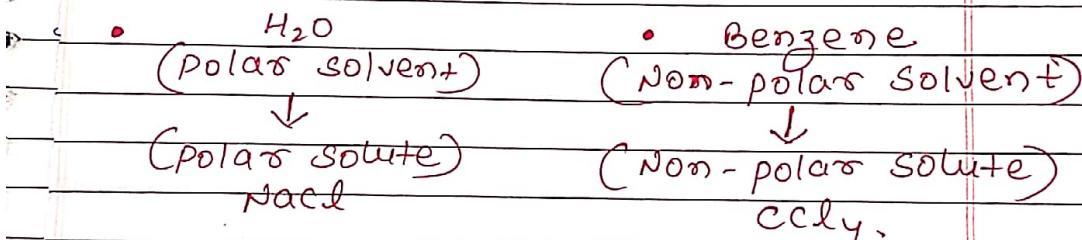
- The solubility of a gas in liquid depends upon:
  - i) Nature of solute and solvent.
  - ii) Effect of temp.
  - iii) Effect of pressure.

ii) Nature of solute & solvent:

$$= \quad = \quad = \quad = \quad =$$

Note: like dissolves like.

- Polar solute dissolve in polar solvent & Non-polar solute dissolve in non-polar solvent.



iii) Temperature:

$$=$$

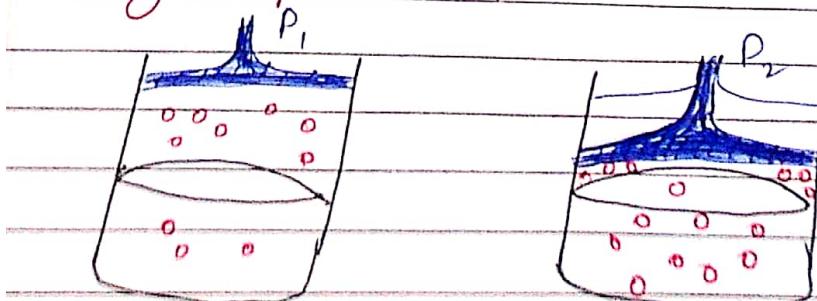
Solute + Solvent  $\longrightarrow$  solution.

- if process  $\Rightarrow$  Temp.  $\uparrow$  solubility  $\uparrow$   
 Endothermic  
 (need heat)  $\xrightarrow{\text{form}}$
- Exothermic  $\Rightarrow$  Temp.  $\uparrow$  solubility  $\downarrow$   
 (release heat)

iii) Pressure:

$$=$$

$S_g \uparrow$  if we  $\uparrow$  pressure.



(tonantes)

## Solubility of liquids in liquids

→ Prepn of pharmaceutical soln involves mixing of two or more liquids.

- Alcohol & water to form hydro-alcoholic soln.
- volatile oils & Alcohols to form spirits, elixirs.

→ Liquids - liquids system may be divided into 2 categories:

- system showing complete miscibility such as alcohol & water, glycerin & alcohol.
- system showing partial miscibility as phenol & water.

→ complete miscibility -

- If the solvent is A & the other solvent is B, & the forces of attraction are represented by A-A, B-B & A-B.

$\downarrow$                $\downarrow$                $\downarrow$   
 Cohesive force    Cohesive force    Adhesive force

- Complete miscibility occurs when, the adhesive forces between different molecule ( $A-B$ )  $\gg$  cohesive forces b/w like molecules ( $A-A, B-B$ ).
- Polar & semi-polar solvents, such as water & alcohol, glycerin & alcohol are said to be completely miscible becoz they mix in all proportions.

### Raolt's Law

- It states that the partial pressure ( $P_A$ ) of each component of an ideal mixture of liquid is equal to the vapour pressure of the pure compound component ( $P_A^\circ$ ) multiplied by its mole fraction ( $x_A$ ) in the mixture.

$$\text{Equation: } P_A = P_A^\circ \times X_A \quad \text{for liquid A}$$

$$P_B = P_B^\circ \times X_B \quad \text{for liquid B}$$

→ Total vapour pressure  $P_T$

$$P_{\text{Total}} = P_A + P_B = (P_A^\circ \times X_A) + (P_B^\circ \times X_B)$$

$$P_T = P_A^\circ \cdot X_A + P_B^\circ \cdot X_B$$

(2 marks)

## Ideal solution :

$$= = =$$

- Ideal soln are the soln which obey Raoult's law at all conc. and temp.

→ Ideal soln should follow the given conditions.

- The components of the soln should obey Raoult's law.

- The component should be completely miscible and volatile in behaviour.

- They should be zero enthalpy change.

→ eg. • mixture of ethyl bromide & ethyl iodide.

(2 marks) (2 marks) • mixture of n-hexane & n-heptane

## Real (Non-ideal) solution :

$$= = =$$

- Non-ideal soln are the soln which don't obey Raoult's law. at all conc. & temp.

→ condition followed by Real soln :

- These soln should not obey Raoult's law

- intermolecular attraction b/w the molecule should not be uniform

- Enthalpy change of these solns may vary.

e.g.  $\text{CCl}_4$  & Acetone mixture.

Benzene & ethanol mixture.

## # Binary Solution

- Binary solns are those solns which consist of two components i.e., solute & solvent.

e.g. salt + water & sugar + water

- In binary soln, the component which is present in greater amount is termed as solvent, while the component in lesser amount is termed as solute.
- In binary soln each component may be solid, liquid or in gaseous state.

## # Partially Miscible liquids :

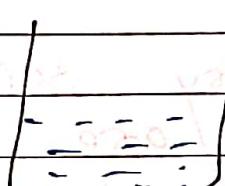
- Two liquids shows limited solubility in each other.

e.g. → i) ether & water

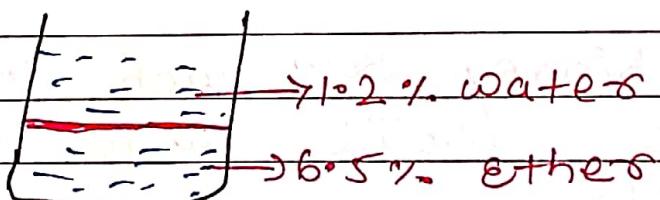
- Ether dissolves around 1.2% of water and water dissolves 6.5% of ether, they are partially miscible due to their limited mutual solubility.



ether  
(100ml)



water  
(100ml)



- On shaking equal vol. of ether and water, one layer of saturated soln of ether in water & a second layer of a saturated soln of water in ether is formed.
- These two soln are conjugate soln.

*(X marks)*

# critical solution Temperature =

or  
Consolute Temp.

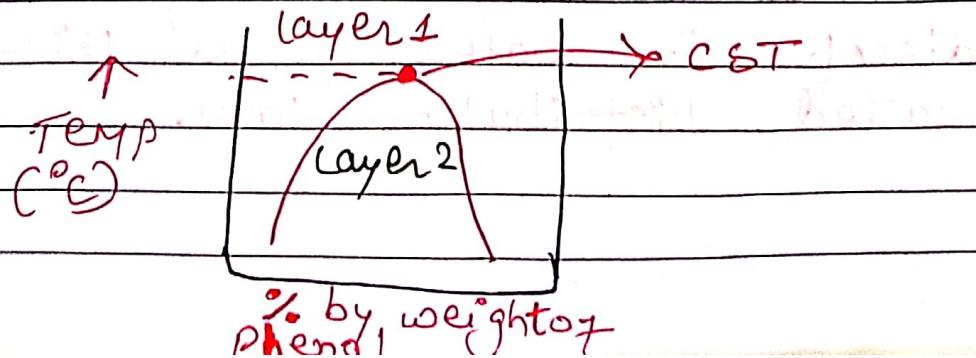
- critical soln temp. is the temp. above or below which the pair of partially miscible liquids becomes completely miscible in all the proportion.
- It is also known as consolute temp.

- e.g. → Phenol + water System

- on shaking equal vol. of phenol and water, we get two layers, the upper layer is a soln. of water in phenol & the lower layer is a soln. of phenol in water.

- At a fix. temp. the composition of each soln is mixed & both the soln are in equilibrium.

- The temp. at which such soln are completely miscible in all proportion is known as critical soln temp.



### i) UCST [Upper critical soln temp.]

- The UCST is the critical temp. above which pair of partially liquid becomes completely miscible in all the proportion.
- e.g. → Hexane & nitrobenzene.

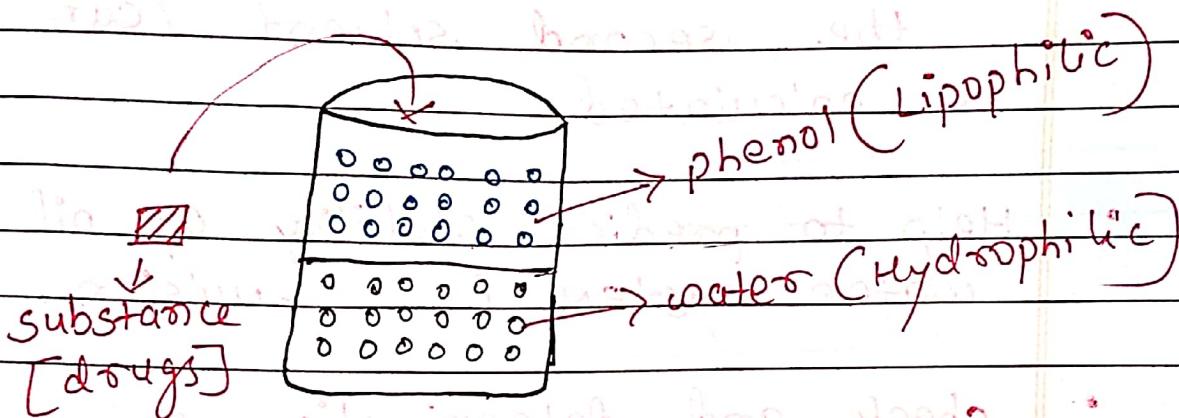
### ii) LCST [lower critical soln temp.]

- The LCST is the critical temp. below which pair of partially liquids becomes completely miscible in all the proportion.
- e.g. → Triethylamine & water.

## III Distribution law → Neost's

- Also known as Partition law.
- In a binary soln of two immiscible liquid when any drug is mixed then some fraction of drug is dissolve in oil phase and some fraction of drug is dissolve in water phase this is called Distribution law.

- The ratio of drug is dissolve in lipophilic medium, the drug dissolve in hydrophilic medium also called Distribution coefficient or partition coefficient.



$\therefore \text{partition coefficient} = \frac{\text{Drug dissolve in oil phase}}{\text{Drug dissolve in water phase}}$

Partition coefficient  $P = \frac{x_o}{x_w}$   $\rightarrow$  fraction of drug dissolve in oil  $\rightarrow$  fraction of drug dissolve in water.

$\rightarrow$  If  $P$  is more than one then substance is lipophilic in nature.

$\rightarrow$  If  $P$  is less than one then substance is hydrophilic in nature.

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

'Distribution coefficient'.

' $K_D$ '

## \* Application of Distribution law:

- Knowing the value of  $K$  and the solubility of solute in one solvent, the solubility in the second solvent can be calculated.
- Help to predict stability of oil water system i.e., emulsion.
- Check and determination of association and dissociation of solute in the solvents.
- In pharmaceutical development.
- It is a measure of a drug's hydrophobicity and an indicator of its ability to cross cell membrane.

## \* Limitation of Distribution law:

- Dilute solution  $\rightarrow$  The conc. of solute must be low in two solvents. This doesn't hold good when the conc. are high.

- Constant Temperature  $\rightarrow$  Temp. should be kept const. throughout the experiment, since solubility is dependent on temperature.
- Same molecular state  $\rightarrow$  Solute must be in the same molecular state in the both solvent.
- Equilibrium concentration  $\rightarrow$  This is achieving by shaking the mixture for longer time!