NameofUnit:	Solubility of Drugs
Subject/Coursename:	B Pharmacy/ Physical Pharmaceutics- I
Course/ Subject Code:	BP302T
Module no.	1
Class:B.Pharm.Semester:	3rd
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Learning Outcome of Module-1

LO	LearningOutcome	Course Outcome Code
LO1	Students will able to learn solubility expressions, solubility parameters and solvation and association phenomenon.	CO1
LO2	They will able to learn the factors influencing the solubility of drugs, various laws and diffusion principles in biological system.	CO1
LO3	Students will also able to know the binary, ideal, and real solutions.	CO1
LO4	They will also learn distribution law including its applications and limitations	CO1

Module Contents

No.	Topic
1	Solubility expressions, mechanisms of solute solvent interactions, ideal solubility parameters, solvation and association.
2	Quantitative approach to the factors influencing solubility of drugs, diffusion principles in biological systems.
3	Solubility of gas in liquids, solubility of liquids in liquids, (Binary solutions, ideal solutions) Raoult's law, real solutions.
4	Partially miscible liquids, Critical solution temperature and applications.
5	Distribution law, its limitations and applications.

Solubility

The solubility of a drug may be expressed in a number of ways. The United States Pharmacopeia (USP) describes the solubility of drugs as parts of solvent required for one part solute. Solubility is also quantitatively expressed in terms of molality, molarity, and percentage. Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g. precipitation of solids). The solubility equilibrium occurs when the two processes proceed at a constant rate.

Term	**required to dissolve 1mass part of solute**
Very soluble	<1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10,000
Practically insoluble	≥ 10,000

Mechanism of solute solvent interactions

When a solute is dissolved in a solvent, there takes place few changes in solute and solvent. The intermolecular bonding between the solute particles and solvent particles like, Vander Waals forces, dipole-dipole interaction, etc. are disturbed and broken and a new bond between a solute and a solvent particle is formed.

The intermolecular interaction between the solvent and the solute molecules determines the mutual solubility of the components in a mixture rather than the rule ‘‘like dissolves like’’. A compound A dissolves in a solvent B only when the intermolecular forces of attraction KAA and KBB for the pure compounds can be overcome by the forces KAB in solution. The sum of the interaction forces between the molecules of solvent and solute can be related to the polarity of A and B.

Ideal Solubility Parameters

Ideal solubility parameters may refer to parameters of solubility:

1. Hildebrand solubility parameters: It is a numerical estimate of degree of interaction between materials, and can be good indication of solubility.
2. Hansen solubility parameters: It is one of the way to predict if one material will dissolve in another and form of solution.

Hildebrand Solubility Parameters: The Hildebrand solubility parameter is the square root of the cohesive energy density. The cohesive energy density is the amount of energy needed to completely remove unit volume of molecules from their neighbors to infinite separation (an idealgas). This is equal to the heat of vaporization of the compound divided by its molar volume in the condensed phase. In order for a material to dissolve, these same interactions need to be overcome, as the molecules are separated from each other and surrounded by the solvent. In 1936 Joel Henry Hildebrand suggested the square root of the cohesive energy density as a numerical value indicating solvency behavior. This later became known as the "Hildebrand solubility parameter". Materials with similar solubility parameters will be able to interact with each other, resulting in solvation, miscibility or swelling.

Hansen Solubility Parameters: The Hansen solubility parameter (Hansen, 2007) accounts individually for all the molecular interactions in a mole of material, namely dispersion forces, polar interactions (dipole–dipole), and specific interactions such as hydrogen bonding. The cohesive energy, expressed as

$E = \Delta H - RT$ (ΔH refers to the latent heat of vaporization, T is the absolute temperature, and R is the universal gas constant), is expressed as a sum of each contribution (Hansen, 2007).

E=ED+EP+EH

Solvation and Association

Solvation refers to the surrounding of each dissolved molecule or ion by a shell of more or less tightly bound solvent molecules. This solvent shell is the result of intermolecular forces between solute and solvent. During the dissolution process, when a relatively small amount of solute dissolves in relatively large amount of solvent to form a homogeneous phase, a variety of intermolecular forces play a role such as solvent-solvent interaction, solute-solvent interaction and solute-solute interaction. The forces holding together the solute molecules gradually disappear during the dissolving process and to same extend an analogous process takes place in a portion ofthe

solvent. These disappearing intermolecular forces are to be replaced by the new intermolecularforces that will be operative between solute and solvent molecules. The solute molecules will disturb the structure of the solvent when they enter into solution, and they create some more or less ordered solvation shell around themselves.

Association

It is a chemical reaction whereby ions of opposite electrical charge come together in solution to form a distinct chemical entity. The most important factor to determine the extent of ion association is the dielectric constant of the solvent.

It can also be defined as process in which large number of ions and molecules associate or linked together to form an association complex.

$$F = q1q2 / r$$

F is Force of attaraction. q magnitude of electric charge.r is distance between ions.

Quantitative Factors influencing Solubility of Drugs

1. **Temperature:** Basically, solubility increases with temperature. It is the case for most of the solvents. The situation is though different for gases. With increase of the temperature they became less soluble in each other and in water, but more soluble in organic solvents.

2. **Polarity:** In most cases solutes dissolve in solvents that have a similar polarity. Chemists use a popular aphorism to describe this feature of solutes and solvents: **"Like dissolves like"**. Non-polar solutes do not dissolve in polar solvents and the other.

3. **Gas Solutes:** As for gasses the Henry's law states that solubility of gas is directly proportional to the pressure of this gas. This is mathematically presented as: p = kc, wherek is a temperature dependent constant for a gas. A good proof of Henry's law can be observed when opening a bottle of carbonated drink. When we decrease the pressure in a bottle, the gas that was dissolved in the drink bubbles out of it.

4. **Molecular size:** The larger the molecules of the solute are, the larger is their molecular weight and their size. It is more difficult it is for solvent molecules to surround bigger molecules. If all of the above mentioned factors are excluded, a general rule can be found that larger particles are generally less soluble. If the pressure, and temperature are the same than out of two solutes of the same polarity, the one with smaller particles is usually more soluble.

5. **Stirring:** Stirring does not have an effect on solubility of a substance, but everyone knows that if he puts sugar in his tea and does not stir, it will not dissolve. Actually, if we left the tea to stand for a long enough time, the sugar would dissolve. Stirring only increases the speed of the process - it increases move of the solvent what exposes solute to fresh portionsof it, thus enabling solubility. As molecules in liquid substances are in constant move, the process would take place anyway, but it would take more time.

Diffusion principles in biological systems

Diffusion: It is defined as a mass transfer of individual molecules of a substance caused by random molecular motion. The movement is based on the kinetic energy (velocity), the charge and the mass of molecules. A number of drugs are absorbed by passive diffusion process.

The diffusion phenomenon is applied in pharmaceutical sciences includes:

1. Release of drug from dosage form is diffusion dependent.
2. Estimation of molecular weight of the polymers.
3. Prediction of absorption and elimination of drug molecules in living system.

The rate of drug transport in biological system is influenced by:

1. By physiochemical properties of drug.
2. By the nature of membrane.
3. By the concentration of drug across the membrane.

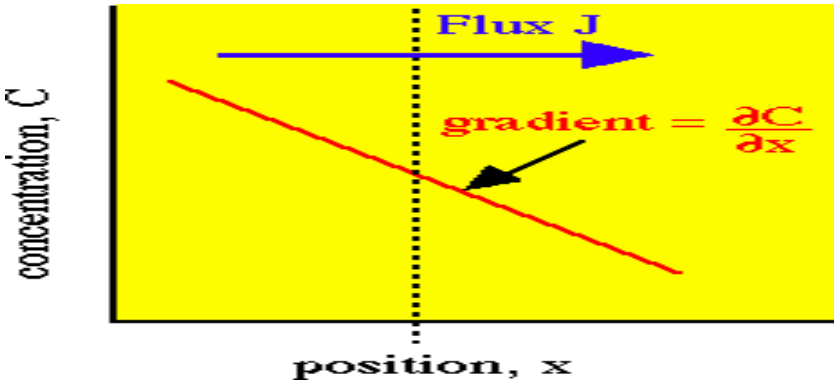
Diffusivity

Diffusivity, mass diffusivity or diffusion coefficient is proportionality constant betweenthe molar flux due to molecular diffusion and the gradient in the concentration of the species (or the driving force for diffusion). Diffusivity is encountered in Fick's law and numerous other equations of physical chemistry.

Laws of Diffusion

Fick's First law of Diffusion

Diffusion occurs in response to a concentration gradient expressed as the change in concentration due to a change in position, the local rule for movement or flux J is given by Fick's 1st law



in which the flux J [cm-2 s-1] is proportional to the diffusivity [cm2/s] and the negative gradientof concentration, [cm-3 cm-1] or [cm-4]. The negative sign indicates that J is positive when movement is down the gradient, i.e., the negative sign cancels the negative gradient along the direction of positive flux.

For optical diffusion, Fick's 1st law is expressed as the energy flux J [W cm-2] proportional to the diffusion constant D [cm] and the negative fluence gradient dF/dx:

$$J = -D\frac{\partial F}{\partial x}$$

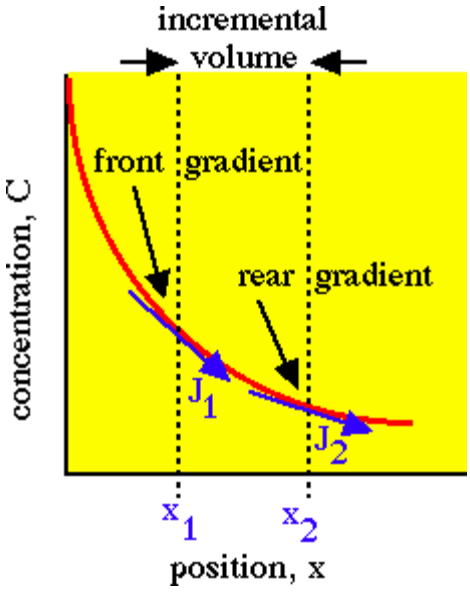
which was obtained by substituting cD for and substituting F/c for C. The factors c and 1/c cancelto yield the above equation.

Fick's Second Law of Diffusion

Fick's 2nd law of diffusion describes the rate of accumulation (or depletion) of concentration within the volume as proportional to the local curvature of the concentration gradient. The local rule for accumulation is given by Fick's 2nd law of diffusion:

$$\frac{\partial C}{\partial t} = \chi\frac{\partial^2 C}{\partial x^2}$$

in which the accumulation, dC/dt [cm-3 s-1], is proportional to the diffusivity [cm2/s] and the 2nd derivative (or curvature) of the concentration, [cm-3 cm-2] or [cm-5]. The accumulation is positive when the curvature is positive, i.e., when the concentration gradient is more negative on the front end of the planar volume and less negative on the rear end so that more flux is driven into the volume at the front end than is driven out of the volume at the rear end.



The differential equation for optical diffusion is simply Fick's 2nd law with the substitution of the product cD for the diffusivity and substitution of F/c for concentration C, although the 1/c factors introduced on both sides of the equation cancel:

$$\frac{\partial F}{\partial t} = cD\frac{\partial^2 F}{\partial x^2}$$

Steady State Diffusion

The concentration around which the drug concentration consistently stays is known as the steady-state concentration.

A system is said to be steady state, if mass transfer dC/dt remains constant with time.

Percutaneous absorption of topically applied drugs

Percutaneous absorption is the term that is most often used in reference to the passage of drugs through the skin, however many other terms may be encountered throughout literature, which include: sorption, per sorption, permeation and penetration.

Percutaneous absorption of drugs through skin generally involves the following 3 steps:

1. Dissolution of drug in the vehicle.
2. Diffusion of dissolved drug from the vehicle to the surface of skin.
3. Penetration of drug molecules through the skin layer.

From the above three steps the slowest one determines the rate of absorption of the drug through percutaneous route. The following factors affect the permeation of drug molecule into the skin.

1. Concentration of dissolves drug.

2. Partition coefficient between skin and vehicle.
3. Diffusion coefficient of drug in the vehicle and skin barrier.

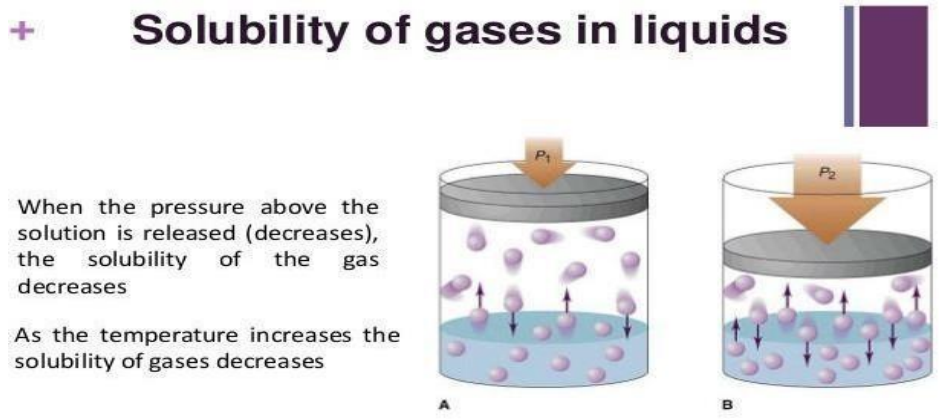
Solubility of gas in liquid

Gases as might be expected increase in solubility with an increase in pressure. Henry's Law states that: The solubility of a gas in a liquid is directly proportional to the pressure of that gas above the surface of the solution.

There are two direct factors that affect solubility: temperature and pressure. Temperature affects the solubility of both solids and gases, but pressure only affects the solubility of gases.

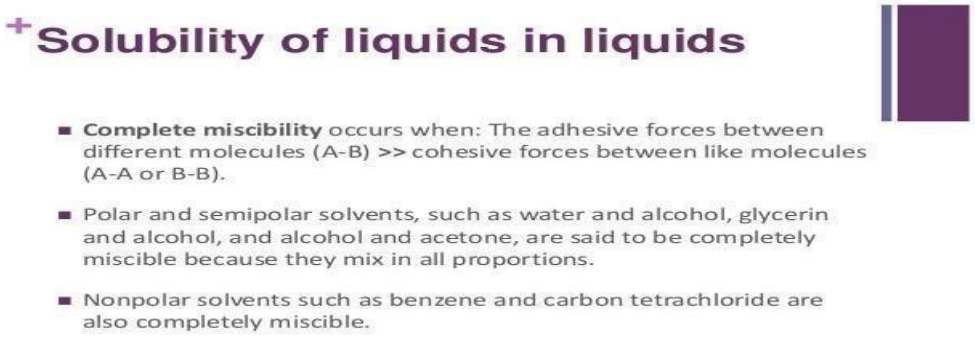
For Gases, solubility decreases as temperature increases. The physical reason for this is that when most gases dissolve in solution, the process is exothermic. This means that heat is released as the gas dissolves. This is very similar to the reason that vapour pressure increases with temperature.

Increased temperature causes an increase in kinetic energy.



Solubility of Liquids in Liquid

Solubility of Liquids in Liquids: Water is known as a universal solvent as it dissolves almost every solute except for a few. Certain factors can influence the solubility of a substance.



Binary Solutions

Binary solution is a mixture of two liquids that are completely miscible one with another. The boiling point of binary solution depends upon the solution composition and there can be three cases:

1. The boiling points of solutions of all compositions lie between the boiling points of clean liquids.
2. The boiling points of solutions of any composition lie above the boiling points of clean liquids.
3. The boiling points of solutions of some compositions lie below the boiling points of clean liquids.

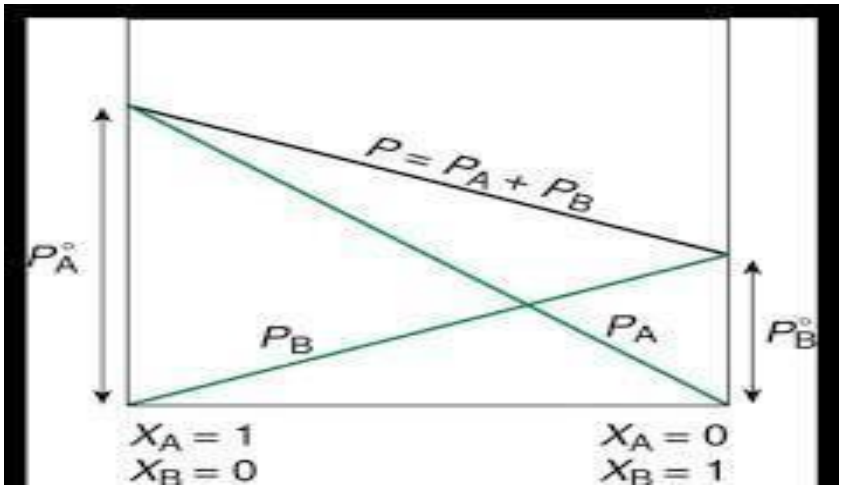
Binary solutions are the solutions that have two components one is called solute(generally present in less quantity) and other is solvent (generally present in large quantity). For example salt + water and sugar + water.

Ideal Solutions

An ideal solution or ideal mixture is a solution in which the gas phase exhibits thermodynamic properties analogous to those of a mixture of ideal gases. The enthalpy of mixing is zero, as is the volume change on mixing by definition; the closer to zero the enthalpy of mixing is the more "ideal" the behaviour of the solution becomes. The vapour pressure of the solution obeys either Raoult's law or Henry's law (or both), and the activity coefficient of each component (which measures deviation from ideality) is equal to one.

Raoult's Law

It is a law of thermodynamics established by French chemist François-Marie Raoult in 1887. It states that the partial pressure of each component of an ideal mixture of liquids is equal to the vapour pressure of the pure component multiplied by its mole fraction in the mixture. In consequence, the relative lowering of vapour pressure of a dilute solution of non-volatile solute is equal to the mole fraction of solute in the solution. P= PA + PB



Real Solutions

Many pairs of liquids are present in which there is no uniformity of attractive forces, i.e., the adhesive and cohesive forces of attraction are not uniform between the two liquids, so that they deviate from the Raoult's law applied only to ideal solutions.

1. Negative Deviation

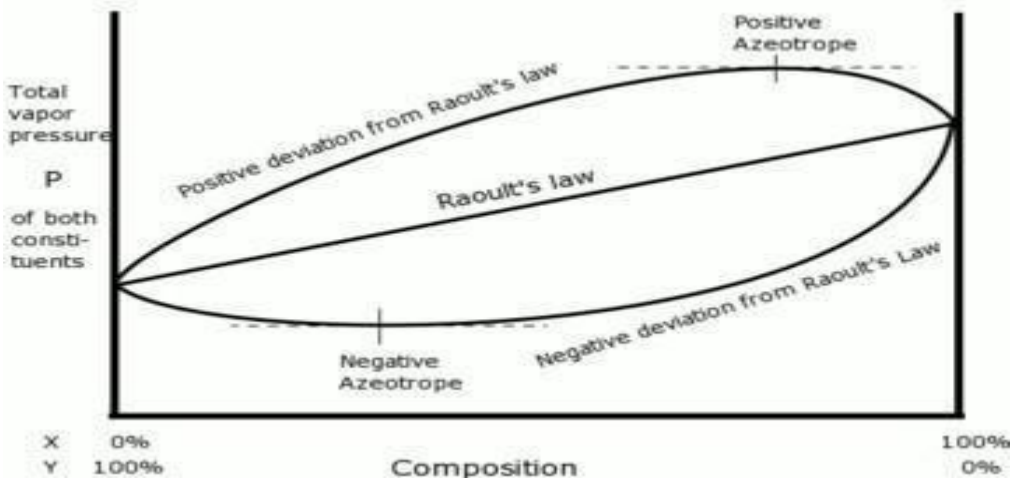
If the vapour pressure of a mixture is lower than expected from Raoult's law, there is said to be a negative deviation.

Negative deviations from Raoult's law arise when the forces between the particles in the mixture are stronger than the mean of the forces between the particles in the pure liquids. This is evidence that the adhesive forces between different components are stronger than the average cohesive forces between like components. In consequence each component is retained in the liquid phase by attractive forces that are stronger than in the pure liquid so that its partial vapour pressure is lower.

2. Positive Deviation

When the cohesive forces between like molecules are greater than the adhesive forces between dissimilar molecules, the dissimilarities of polarity leads both components to escape solution more easily. Therefore, the vapor pressure is greater than expected from the Raoult's law, showing positive deviation. If the deviation is large, then the vapor pressure curve shows a maximum at a particular composition and form a positive azeotrope. Some mixtures in which this happens are

1. Benzene and methanol, (2) carbon disulfide and acetone, and (3) chloroform and ethanol. When these pairs of components are mixed, the process is endothermic reaction as weaker intermolecular forces are formed.



Partially Miscible Liquids

A pair of liquids is considered partially miscible if there is a set of compositions over which the liquids will form a two-phase liquid system. This is a common situation and is the general case for a pair of liquids where one is polar and the other non-polar (such as water and vegetable oil.)

A liquid is partially miscible in another liquid if, when mixed, the two liquids make two (liquid) phases that contain some fraction of each liquid in each phase.

Critical Solution Temperature

The temperature at which complete miscibility is reached as the temperature is raised or in some cases lowered —used of two liquids that are partially miscible under ordinary conditions.

The critical solution temperature (upper con solute temperature): It is the maximum temperature at which the two phase region exists. In the case of the phenol-water system this is 66.8°.

Distribution Law

Distribution law or the Nernst's distribution law gives a generalization which governs the distribution of a solute between two non miscible solvents. This law was first given by Nernst who studied the distribution of several solutes between different appropriate pairs of solvents.

Applications of Distribution Law

There are numerous applications of distribution law in the laboratory as well as in industry solvent extraction- This is the process used for the separation of organic substances from aqueous solutions.

Limitations of Distribution Law

The solute that is being distributed shall not on ant condition reactive towards the solvents being used. The molecular state of the solute must remain constant when in contact with the solvent. It should not undergo dissociation or association.

Important key points of Module

1. Solubility: It is defined as the solubility of drugs as parts of solvent required for one part solute.
2. Hildebrand and Hansen solubility parameters are two ideal solubility parameters.
3. Solvation refers to the surrounding of each dissolved molecule or ion by a shell of more or less tightly bound solvent molecules.
4.

5. Association: It is a chemical reaction whereby ions of opposite electrical charge come together in solution to form a distinct chemical entity.
6. Diffusion: It is defined as a mass transfer of individual molecules of a substance caused by random molecular motion.
7. Binary solution is a mixture of two liquids that are completely miscible one with another.
8. An ideal solution or ideal mixture is a solution in which the gas phase exhibits thermodynamic properties analogous to those of a mixture of ideal gases.
9. Distribution law or the Nernst's distribution law gives a generalization which governs the distribution of a solute between two non miscible solvents.

Important questions

2 Marks

1. Define solubility.
2. What is raoults's law?
3. Differentiate between ideal, real and binary solutions.
4. What is diffusivity?
5. Give solubility expressions.
6. What is critical solution temperature?

5 Marks

1. Write a note on factors affecting solubility of drugs.
2. Explain the process of solvation and association.
3. Explain distribution law along with its applications and limitations.
4. Write a detail note on ideal solubility parameters.

10 Marks

1. Explain diffusion principles in biological system.
2. Explain solubility of gases in liquids and solubility of liquids in liquids.
3. Explain fick's laws of diffusion.
4. What is percutaneous absorption?
5. Explain Hildebrand and Hansen ideal solubility parameters.