Review Article

Solubility and Distribution Phenomenon

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Abstract

Objective: Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. **Conclusion:** More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. Solubility is a major challenge for formulation scientist. Any drug to be absorbed must be present in the form of solution at the site of absorption. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation, and so forth. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.

Keywords: Solubility, solubility of solid in liquids, factor affecting solubility.

Introduction

Solubility is a phenomenon which involves formation of a uniform homogeneous dispersion upon interaction of two or more substances. It is dependent on many factors such as temperature, nature of solute and solvent under study, pH, pressure etc. A solution is said to be saturated when it contains the maximum amount of solute that a solvent can dissolve at a particular temperature,

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As temperature influences solubility, temperature must be specified when the solubility of a substance is expressed. Under certain conditions, an unsaturated or a supersaturated solution can be obtained. An unsaturated solution is one that contains the dissolved solute in a concentration less than that for required complete saturation at a particular temperature. A supersaturated solution is one that contains more concentration of the solute in the dissolved state than would normally be dissolved at a definite temperature. A supersaturated solution may simply be obtained by cooling a saturated solution carefully to a low temperature (without any precipitation). However, this supersaturated solution is not stable and the excess solute can be precipitated by shaking,

by scratching the sides of the container or by introducing a small crystal of the solute (Lachman et al., 1986; Clugstone and Fleming, 2000; Myrdal and Yalkowsky, 2007; Martin, 2011).

Solubility expression

The solubility of a substance can be expressed in a number of ways. Most pharmacopoeia list the solubility of drugs in terms of the number of parts of solvent required to dissolve one part of the drug. For substances where the exact solubility is not known, the values are expressed by the use of certain general terms as shown in Table 1 (The United States Pharmacopeia, 2007; British Pharmacopoeia, 2009).

Table1. General Terms used for Expressing Solubility

Terms	Parts of Solvent Required to Dissolve 1 Part of Solute
Very Soluble	Less than 1 part
Freely Soluble	1 to 10 parts
Soluble	10 to 30 Parts
Sparingly Soluble	30 to 100 Parts
Slightly Soluble	100 to 1000 Parts
Very Slightly Soluble	1000 to 10000 Parts
Practically Insoluble	More than 10000 Parts

Solubility is also expressed quantitatively in terms of percentage, molarity and molality. In the pharmaceutical field, three concentration terms are often used. These are:

 (i) Percent weight by weight (% w/w) which is the number of grams of salute dissolved in 100 grams of solution.

(ii) Percent volume by volume (% v/v) which is the number of ml of solute dissolved in 100 ml of solution.

(iii) Percent weight by volume (% w/v) which is the number of grams of solute dissolved in 100 ml. of solution.

Molarity is defined as the number of moles (or gram molecular weight) of solute dissolved in 1 litre of solution.

Molality is defined as the number of moles of solute dissolved in 1000 g of solvent.

Detrmination of Solubility (Martin, 2011).

Solubility of a substance is generally determined by first preparing a saturated solution of the substance in the given solvent at a particular temperature followed by analysis of the saturated solution.

For obtaining a saturated solution of the substance at the desired temperature, an excess of the powdered material is added to a solvent and stirred for several hours until equilibrium has been achieved. The temperature of the system is kept constant throughout by immersing the vessel in a constant temperature bath.

A sample of a. saturated solution is taken by separating the solution from the un-dissolved solid by filtration. Filtration is also carried out at the desired temperature for the solubility determination to prevent any change in the equilibrium between dissolved and un-dissolved solid due to change in temperature. Also, loss of volatile components ifany has to be prevented. The solution is then analysed using an appropriate method.

Solvent-Solute Interactions

In general, the solubility of a solute in a solvent may be predicted by the solute-solute, solvent-solvent, and solute-solvent interactions. When the adhesive forces (attraction between unlike molecules i.e., solute-solvent molecules) are more than, the cohesive forces (attraction between like Molecules i.e.," solute-solute or solvent-solvent molecules), the solubility of a solute in a solvent or miscibility of a liquid in some other liquid is generally enhanced.

Water is everywhere in nature. It is considered as universal solvent due to its good solubilizing capacity of various compounds. Before proceeding further one needs to know about the classification of solvents based on its polarity.

(a) Polar solvent

(b) Non Polar solvent

(c) Semi polar solvent

(a) Polar solvent

The polarity of solvent depends up on its dipole moment. For example water has its dielectric constant value 80 and hence it falls under the category of strongly polar solvents. The solubility of compounds in solvents can be generalized under statement like dissolve in like, i.e., polar solvents have strong solubilizing power for polar substances or ionic solutes. Ionic solutes include salts like sodium chloride, potassium chloride etc. the solubility of a compounds also depends on ability to form hydrogen bonds. Compounds having high dipole moment tend to form hydrogen bonds to a greater extend and hence show higher solubility in polar solvents.

E.g. Alcohol, Aldehyde, Ketone

Water dissolves phenols, alcohols, aldehydes ketones that can from hydrogen bonds with water molecules. When polar solvents like alcohol (lower alcohols) are added to water the hydrogen bonds between water molecules are replaced partly by the hydrogen bonds between water molecules are replaced partly by the hydrogen bonds between alcohol and water molecules.

Apart from above mentioned factors the other parameters which play a key role in deciding the solubility include, ratio of polar to non polar groups of the molecule. The solubility is inversely proportional to the carbon chain length. E.g. the solubility of alcohols decreases with increasing carbon chain length. Branching of carbon chain increases the solubility of compound compared to its straight chain compound.

(b) Non Polar solvent

Non-polar solvents have the capacity of dissolving non polar compounds. Generally oils, fats come under this category. They possess a very low dielectric constant value generally ranging from 0-10.

Due to this low dielectric constant value they fail in reducing the attraction between ions of strong and weak electrolytes. These non polar solvents are also called as aprotic solvent (can neither accept nor donate protons) which makes them unable to break covalent bonds or ionize weak electrolytes. Hence non polar solvents dissolve ionic and polar solutes only in negligible quantities.

(c) Semi polar solvent

Ketones and alcohols have the property of inducing certain degree of polarity in non polar solvent molecules. They are used as solvents for increasing solubility of non polar substances in polar substances or polar substances in non polar substances E.g., Propylene glycol has been shown to improve solubility of water in peppermint oil.

Solubility of Gases in Liquids (Myrdal and Yalkowsky, 2007, Martin, 2011)

Examples of pharmaceutical solutions which contain gases dissolved in a liquid include effervescent preparations containing dissolved carbon dioxide, ammonia water and hydrochloric acid (hydrogen chloride gas in water). Pharmaceutical aerosols containing nitrogen or carbon dioxide as the) propellant may also be considered as solutions of gases in liquids.

The solubility of a gas in a liquid represents the concentration of dissolved gas in the liquid when it is in equilibrium with some of the pure gas above the solution.

factors affecting solubility of gases in liquids

The solubility of a gas in a solvent depends on temperature pressure, presence of salts, and chemical reaction if any between the gas and the solvent.

1. **Effect of Pressure**

The pressure of the gas above the solution is important in gaseous solutions since this signifi-cantly changes the solubility of the dissolved gas. The effect of pressure on the solubility of the gas is given by Henry's law which states that in a dilute solution, the mass of a gas which dissolves in a given volume of a liquid at a

constant temperature is directly proportional to the partial pressure of the gas.

According to Henry's Law:

$C \propto P_g$

$C = K. P_g$

Where,

C is the concentration of the dissolved gas in grams perliter of solvent

P_g = Partial pressure in millilitre of H_g

K is Henrys law constant.

P is the partial pressure in mm of Hg of the undissolved gas above the solution and can be obtained by subtracting the vapour pressure of the solvent from the total pressure of the solution s is the proportionality Constant and is referred to as the solubility coefficient.

The solubility of gases generally increases with increase pressure and oh the release of pressure, the solubility decreases and the gases escape.

2. **Effect of Temperature**

Solubility of most gases decreases with a rise in temperature because of the greater tendency of the gases to expand in comparison to the solvent. It is therefore essential that caution, must be,exercised when opening the container containing gaseous solution under elevated temperature. It is, better to reduce the temperature by immersing in ice-cooled water before opening such container.

Henrys law is applicable to the gas that is slightly soluble in the liquid-solvent. H_2 and O_2 which are sparingly soluble in water obey Henrys law. Whereas HCl, SO_2, NH_3 gases do not obey Henrys law. It is because of the interaction between water and these gases.

3. **Effect of Electrolytes and Non-electrolytesor salts**

Solubility of; a gases in a solvent is generally reduced by the addition of electrolytes such as sodium chloride or non-electrolytes such as sugar. This is referred as salting out. This is due to more affinity between the solvent arid the electrolyte or non-electrolyte than between the solvent and the gas.

4. **Effect of Chemical Reaction with the solvent**

Henry's law generally applies to gases that are only slightly soluble in solvent and that do not react in any way with the solvent. Chemical reaction if any between a gas and a solvent greatly increases the solubility of the gas in the solvent. For example hydrogen chloride gas reacts with water by hydrogen bonding when it dissolves in water. This increases the solubility of hydrogen chloride gas in water.

Applications of Solubility of Gases in Liquids

1. For the preparation of reagents such as HCl, H2So4 etc by passing the gases into water.

2. Preparation of carbonated beverages.

3. Solubility of oxygen in blood depends upon the concentration of haemoglobin.

4. Formulations and development of anesthetic gases

Liquids and liquids and solid in liquids (Lachman et al., 1986; Clugstone and Fleming, 2000; Myrdal and Yalkowsky, 2007; Martin, 2011).

Examples of pharmaceutical solutions containing a liquid dissolved in another liquid include hy-dro-alcoholic solutions, aromatic waters such as Chloroform water and Peppermint water, spirits and elixirs. Lotions, sprays, and some medicated oils also contain two or more miscible oils and hence may be considered as a solution of one liquid in another.

As discussed earlier solution can be classified into

(a) **Idealsolutions** in which binary solutions obey raoults law over the whole range of compressions.

(b) **Real Solutions** these are the binary solutions which show either positive or negative deviation from raoults law. If one compound shows positive deviation then other component also tends to show positive deviation. Positive deviations lead to decrease in solubility due to formation of dimers or polymers.

Broadly one can classify liquid-liquid systems into three categories

(a) Complete miscibility

Represents complete solubility of two or more solvents in all proportions.

E.g. Water and Methanol, Glycerin and Alcohol

(c) Partial Immiscibility

Represents systems, which are soluble in all other in definite proportions

E.g. Water and Ether, Nicotine and Water, Phenol and Water

(c) Immiscibility

Represents systems, which are not soluble with other in any in proportions

E.g. Water and Liquid petrolatum

Ideal and Real Solutions

According to the Raoult's law, at a definite temperature, the partial pressure (P_A) of a component (A) in a liquid mixture is equal to vapour pressure in the pure state ($P°_A$) multiplied by the mole fraction of the component (X_A) in the solution. It is expressed as

$$p_A = P°_A X_A$$

Ideal solutions are those which obey Raoult's law over the whole range of composition at all temperatures. Mixtures of nearly adjacent compounds in a homologous series (e.g., benzene-tolu-ene, methanol-ethanol, hexane-heptane etc.) at low temperatures behave as ideal solutions.

However, in practice, there are deviations from Raoult's law. Such solutions showing deviation are called real (or non-ideal) solutions. The deviation may be negative leading to increased solubility because of hydrogen bonding between the polar components. If the deviation is positive, it leads to a decreased solubility because of the association of the molecules of one of the components to form limers or polymers of high order. Positive deviation in most cases is due to the difference in the: cohesive forces or internal pressures of the molecules of each constituent.

Two liquids are either completely miscible or partially miscible. Completely miscible liquids mix in all proportions and hence do hot create any solubility problem. Partially miscible liquids form two miscible liquid layers, each of which is a saturated solution of one liquid in the other. The two liquid phases are called conjugate liquid phases. The mutual solubility of partially miscible liquids is influenced by temperature. For certain systems such as a solution of phenol and water, the mutual solubilities of the two, conjugate liquid phases increase with temperature and at a temperature called critical solution temperature (or consolute temperature) they are miscible. And at this temperature a homogeneous or a single phase results- for any composition.

Ternary Systems

These systems are produced up on the additions of a third component to a pair of partially miscible liquids produce a ternary system. If the added component is soluble in only one of the two components or if its solubility in the two liquids is markedly different, the mutual solubility of the liquid pair is decreased. If the third sub-stance is soluble in both liquids to roughly the same extant, the mutual solubility of the liquid pair is increased.

A turbid or cloudy point was observed at 67% alcohol, 27% oil, and 6% water. This indicates that alcohol which is roughly soluble in oil and water to same extent increase mortal solubility of oil and water i.e., upper critical temperature of solution is lowered and lower critical temperature of solution is raised.

Other factors which influence solubility of liquids in liquids include

(a) Dielectric Constant The solubilityof water and alcohol. Which depicts the solubility (mg/ml) in relation to dielectric constant (ϵ). The dielectric properties of a mixed solvent, such as water and alcohol, can be approximated to the weighted average properties of pure components.

Hence addtive in nature

ϵ mixture = 0.6 (ϵ (ethanol) + 0.4 ϵ (water)

= 0.6 (25) + 0.4 (80)

= 47

Molecular Connectivity

This takes into account structureal features and functional groups of the molecule. It is denoted by χ (chi). The χ represents first order chi term and is obtained by summing the bonds weighted by the reciprocal square root number of each bond.

For e.g.,

Corbon atom 1 is attached to central atom which is inturn joined to other carbons by two bonds.

Propane $H_3C-CH2-CH3$ So the reciprocal square root valance is

$$1/(1.2)^{1/2} = 0.707$$

The same applied to right bond also. The total value of = 1.414

Solubility of Solids in Liquids (Martin, 2011).

Solutions of solids in liquids are the most important types of pharmaceutical solutions encountered. It is de-pendent only on temperature, melting point of the solid and molar heat of fusion (MHF). It is difficult to predict the solubility of solids forming-non-ideal (real) solutions because of a number of factors involved.

A solution can be defined as a defined a homogeneous mixture in which one substance is thought to dissolve in the other. In quantitative terms, solubility is defined as the concentration of solute in a saturated solution at a certain temperature. Qualitatively, solubility is defined as a spontaneous interaction of two or more substances to form a homogenous molecular dispersion.

The solutions are often referred to as molecular dispersion or true solutions, systems in which solute is dispersed as molecules or ions throughout the other solvent. A few examples of solutions are urea in water and sucrose in water.

A saturated solution is the solution in which the dissolved solute is equilibrium with the solute, at a definite temperature.

An unsaturated solution is the solution containing the dissolved solute in concentration below that is necessary for saturation, at a definite temperature.

A supersaturated solution is the one that contains more of the dissolved solute than it would normally contain at a definite temperature.

Applications

1. For the manufacture of liquid orals such as syrups and elixirs etc.
2. For the manufacture of parental formulations such as intravenous, intramuscular and subcutaneous injections etc.
3. The solubility of drugs in gastro-intestinal fluids (dissolutions) is an important step for better absorption of drug.
4. The release rate and absorption of a drug from an ointment or an intramuscular injection depends on the degree of saturation of drug in the solvent.

5. Solubility of a substance is important physical factor under the standard test for purity.
6. Solubility such information is useful for predicating drug receptor interactions, dissociation constant, and solubility parameter.
7. Saturation solution theory is important for the crystallization of drug.
8. Prediction for separating one component from the other and for purification purposes. Examples are extraction and re-crystallization.

The solubility of a solute in a solvent may be considered as occurring in three steps.

(1) The first step involves the elimination of a molecule from the solute phase at a definite temperature.

(2) The second step involves the formation of a hole in the solvent just large enough to accept at solute molecules.

(3) The final step involves placement of the solute molecules in the hole in the solvent.

Determination of concentration of drug in solution

The amount of solute present (concentration) in the saturated solution can be determined by gravimetric, volumetric and modern method.

Gravimetric method if the solvent is volatile and solute is non-volatile; the amount of the latter can be determined by heating the sample to constant weight. Alternatively the solute may be converted to insoluble compound by a chemical reaction. The weight of the substance may be determined after filtration and drying.

Volumetric method acid–base titrations can be used to determine the amount of solute present in a solvent.

Modern method spectrophotometric and HPLC (high performance liquid chromatography) methods provide accurate estimation.

Theories of Solutions

Ideal Solution

In an ideal solution, the heat of solution is equal to the heat of fusion. Ideal solubility is not affected by the nature of the solvent, for such a, solution,

the solubility can be predicted from its heat of fusion. .The equation derived from thermodynamic consideration is:

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

Where,

X_2^i is the ideal solubility of the solute expressed in mole fraction (the superscript i indicates ideal)

T_0 is the melting point in absolute temperature of the solid solute

T is the absolute temperature of the solution.

ΔH_f is the molar heat of fusion of the solid state and can be determined using differential scanning calorimeter.

The equation does not apply when $T > T_0$ and at temperatures considerably below the melting point.

Non-ideal Solution

When the heat of solution has a positive value, the solution is termed as non-ideal. This non-ideality is due to various attractive forces involved between solute, solvent and solute-solvent molecules.

In dealing with non-ideal solutions, activity of the solute must be considered. The activity of a solute in a solution is expressed as its concentration multiplied by the activity coefficient. When concentration is expressed in terms of mole fraction, the activity is expressed as:

$a_2 = X_2 \gamma_2$

Converting to logarithms,

$\log a_2 = \log X_2 + \log \gamma_2$.

Multiplying by minus and rearranging,

$-\log a_2 = -\log X_2 - \log \gamma_2$.

$-\log X_2 = -\log a_2 + \log \gamma_2$.

In an ideal solution $a_2 = X_2^i$ since $\gamma_2 = 1$

Expressing ideal solubility in terms of activity

$$-\log a_2 = -\log X_2^i = \frac{\Delta H_f}{2.303R} \frac{T_0 - T}{T_0 T}$$

Combining the two equations,

$$-\log X_2 = \frac{\Delta H_f}{2.303R} \frac{T_0 - T}{T_0 T} + \log \gamma_2$$

The activity coefficient γ_2 depends on the nature of both the solute and the solvent as well as on the temperature of the solution. All the factors, must be considered before the solubility can be predicted for non-ideal solution. The log y2 appearing in the equations' obtained from the consid-eration of intermolecular forces of attraction involved in the solution process or the work done in the process of solution.

Effects of Temperature

As evident from the above equation the solubility of solid in a liquid depends on the temperature. If heat is absorbed in process of solution then ΔH will be positive and solubility of solute increases with increase with increase in temperature. If a solute gives off heat during the process of solution, ΔH is negative and solubility decreases with increase in temperature.when heat is neither absorbed nor given off, the solubility is not affected by variation of temperature as is nearly the case with sodium chloride.

Solubility of Strong Electrolytes

Whenever a strong electrolyte is dissolved in a solution, we can observe the following

(a) Rise in the temperature of system, or exothermic process.

(b) Decrease in the temperature of system or endothermic process

(c) No change in temperature of system.

According to Lechaterlier principle, any system tends to adjust itself in a manner so as to counteract, any stress. So any change in the temperature of system will proceed in the direction, so as to nullify the change.

Solubility of Weak Electrolytes

Many important drugs belong to the class of weak acids and bases. They react with strong acids bases and, within definite ranges of pH, exist as ions that are ordinarily soluble in water. E.g. many drugs containing carboxylic acid as a functional group are relatively insoluble in water. Upon addition of dilute sodium hydroxide, carbonate they form soluble salts. Sodium citrate is used to solubilize acetyl salicylic acid by the formation of acetyl salicylate ion.

Effects of Ph on Solubility of Weak Electrolytes

Phenobarbital sodium, at below pH 8.3 Phenobarbital sodium starts precipitating from

solution at room temperature. The pH at which the drug precipitates from aqueous solution can be calculated in the following way

Heat of solution ΔH is the sum of heat sublimation of the solid and heat of hydration (salvation) of the ions in the solution.

$$\Delta H_{(solution)} = \Delta H_{(sublimation)} + \Delta H_{(Hydration)}$$

If $\Delta H > 0$ then absorption of heat by system

If $\Delta H < 0$ then evolution of heat by system.

Solubility of Slightly Soluble Electrolyte

The solubility of slightly soluble electrolyte is described by solubility product, Ksp, of the compound. For example, consider silver chloride which when dissolved in excess exists in equilibrium as

$$AgCl_{solid} \rightleftharpoons Ag^+ + Cl^-$$

The equilibrium expression may be written as

$K = [Ag^+][Cl^-]/[AgCl_{solid}]$

The equilibrium expression may be written as

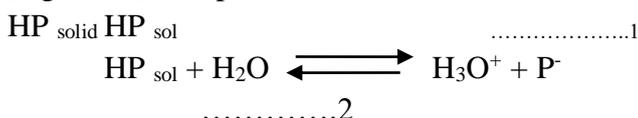$K = [Ag^+][Cl^-]/[AgCl_{solid}]$

As the concentration of $[AgCl_{solid}]$ is constant

$Ksp = [Ag^+][Cl^-]$

Addition of sodium chloride to above silver chloride solution results in common ion effect.

$[Ag^+][Cl^-] > Ksp$

Some of the AgCl precipitates from the solution until equilibrium

$[Ag^+][Cl^-] = Ksp$ is re-established.

HP_{solid} HP_{sol} 1

$$HP_{sol} + H_2O \rightleftharpoons H_3O^+ + P^-$$

.............2

Equilibrium constant for Eq. (2) is

$Ka = [H_3O^+][P^-]/[HP]_{sol}$

Or $[P] = Ka [HP]_{sol}/[H_3O^+]$

And for Eq. (1) equilibrium constant is

$So = [HP_{sol}]$

The total solubility of Phenobarbital consists of the concentration of un-dissociated acid $[HP_{sol}]$ and $[P^-]$

Substituting S_o and K_o, we get

$S = S_o + Ka$, we get,

$S = S_o + Ka S_o/[H_3O^+]$

$S = S_o ([1 + Ka/[H_3O^+])$

or $S-So/So = Ka/[H_3O^+]$

Applying log on both sides

$pH_p = pK_a + Log\ S-S_o/S_o$

Thus we can obtain the pH below which the drug separates from the solution.

The Influence of the Solvent on the Solubility of Drugs

Factors influencing solubility of drugs

Solute related factors

Such as size, shape, and surface area should be less increase the solubility. Physiochemical characters like melting point, heat of fusion, molar volume and pKa. Physical forms-as salt, crystalline state and polymorphism

Solvent related factors

Such as nature of solvent such as polarity, pH of the medium and volume of solvent

Other related factors Temperature and pressure etc.

Some factors are discussed below

Temperature

Most solids dissolve with absorption of heat and the solubility of such solids increases as the temperature is increased. This is in accordance with Le Chatelier's principle since the system tries to neutralize the constraint (increase in temperature) imposed oil it by increasing the solubility of the solid when the extra heat gets absorbed. For solids which dissolve with the evolution of heat an increase in temperature causes a decrease in the solubility. Effect of temperature on the solubility of salts can be represented by the use of solubility curves which are plots of solubility against temperature. Most of the curves are continuous, i.e., the solubility either increases or decreases gradually with a rise in temperature. However, for certain substances such as sodium sulphate, the slope of the curve show an abrupt change. This is because sodium sulphate exists as decahydrate $Na_2SO_4\ 10H_2O$ up to a temperature of $32.5°C$ and its dissolution in water is an endothermic process. Hence, there is an increase in solubility till this temperature is reached. Above this temperature, the material gets converted to the anhydrous form and its dissolution becomes exothermic leading to a decrease in solubility with increase in temperature.

Molecular Structure

Slight modification in the molecular structure of solids can lead to marked changes in their solubility in a given solvent. For example, if a weak acid is converted into its salt, its ionic dissociation in water increases markedly leading to an increase in the interaction between the solute and the solvent which ultimately leads to an increase in the solubility. Solubility can also be decreased by modifications such as esterification. Such a decrease in solubility is sometimes beneficial in pharmaceutical practice since this decrease helps in taste masking of certain drugs such as chloramphenicol (very bitter) versus chloramphenicol palmitate (tasteless) and protects the compound from degradation in the gut as in case of erythromycin and erythromycin propionate.

Particle Size

The particle size of the solid also affects its solubility in a given solvent. Generally, a decrease in the particle size causes an increase in the solubility. This is because a decrease in the particle size results in excess surface free energy due to increase in surface area which increases the solubility.

The increase in solubility with decrease in particle size however, ceases when the particles attain very small radius and any further decrease in the particle size causes a decrease in solubility rather than an increase. This is because of generation of electrical charges on the particles.

Nature of Solvent and Co-solvent

The solubility of a solid depends on the nature of the solvent used, In general, polar solutes dissolve more readily in polar, solvents and non-polar solutes dissolve more readily in non polar solvents (like dissolves like).

Solubility of a solid in a solvent may be altered by the addition of some other solvent which may bring about changes in the properties of the first solvent very often; a mixture of solvents is used to increase the solubility of weak electrolytes as well as non-electrolytes. This phenomenon of increas-ing solubility of poorly soluble substances by the use of more than one solvent is, known as co-solvency. For example, the solubility of weak electrolytes and non-polar molecules in water may be consider-ably increased by the addition of co-solvents such as ethanol, glycerol, propylene glycol or sorbitol. These agents work by decreasing the interfacial tension between the hydrophobic solute arid the aqueous environment or by altering the dielectric constant of the medium.

pH

Most of the drugs are either weak acid or weak bases .and are poorly .soluble in water. The solubility of such drugs is markedly affected by a change in pH. If the pH of a solution of a weakly acidic drug or its salt is reduced, the proportion of the unionized acid molecules in the solution increases. Since the unionized form is generally less soluble than the ionized form, the solubility of such drugs decreases with a decrease in the pH. On the other hand, solubility of weakly basic drugs or their salts increases with a decrease in the pH.

The relationship between the pH, solubility and pKa value of an acidic drug is given by:

$$pH_p = pK_a + \log \frac{S - S_o}{S_o}$$

Where,

pH is the pH below which the drug precipitates from solution.

S is the overall solubility of the drug,

S is the solubility of its unionized form

For basic drugs, the relationship is:

$$pH_p = pK_a + \log \frac{S_o}{S - S_o}$$

The above equations can be used to determine the solubility of a drug at a given pH or to find the pH below which the drug will precipitate from solution. Alternatively, the minimum pH value that is required to maintain the drug in solution can be determined.

Combined Effect of pH and Solvents

The combined effect of a solvent and the pH on the solubility of a weak electrolyte can be determined by studying the solubility changes in a buffered solution. The addition of a solvent such

as alcohol to a buffered aqueous solution may affect the solubility of weak electrolytes in the following two ways:

(I)It increases the solubility of the unionized species of the weak electrolyte by adjusting the polarity of the solvent to a more favorable value.

(II) It decrease's the dissociation of the weak electrolyte thereby increasing the pK_a value and reducing the solubility.

Common Ion Effect

When slightly soluble electrolytes are dissolved to form saturated solutions, the solubility is described by a special constant known as the solubility product, K_{sp}.

For a saturated solution of sparingly soluble electrolyte AB in contact with un-dissolved electro-lyte, the equilibrium may be represented as follows:

AB   λ $A^+ + B^-$
(Solid)   (Ions)

According to Law of Mass action, the equilibrium constant in terms of concentration is given by.

$$K = \frac{[A^+][B^-]}{[AB]}$$

Since the concentration of a solid may be regarded as being constant, the equation may be written as:

$$K_{sp} = [A^+][B^-]$$

WhereK_{sp} is the solubility product of the compound AB

If a compound that carries a common ion (For example A^+) is added to the above system, there is a momentary increase in the ionic product:

$[A^+] [B^-] > K_{sp}$

; In order to re-establish the equilibrium $[A^+] [B^-] = K_{sp}$ some of AB will precipitate out. The same will be the effect if a compound containing the ion $[B^-]$ is added. Thus, the addition of a compound bearing a common ion reduces the solubility of sparingly soluble salt.

Effect of Indifferent Electrolyte on the Solubility Product

An effect opposite to that of common-ioneffectwill be produced if salts carrying no common-ion (indifferent electrolytes) are added to a solution of slightly soluble electrolyte;such

indifferent electrolytes even increase the solubility at moderate Concentrations as they tend to lower the activity coefficient.

Effect of Non-Electrolytes on the Solubility of Electrolytes

The solubility of electrolytes in water primarily depends on the dissociation of the dissolved molecules into ions. The ease with which the electrolytes dissociate depends on the dielectric con-stant of the solvent which is in effect a measure of the polar nature of the solvent.

Addition of a water soluble non-electrolyte such as alcohol to an aqueous solution of a sparingly soluble salt decreases the solubility of sparingly soluble electrolyte. This effect is due to the lowering of dielectric constant and this in turn reduces the dissociation of the dissolved salt.

Effect of Electrolytes on the Solubility of Non-Electrolytes

The solubility of non-electrolytes' depends primarily on the formation of weak intermolecular bonds (hydrogen bonds) between their molecules and those of water. Addition 6f an electrolyte having more affinity towards water reduces the solubility of the non-electrolyte by competing for the aqueous solvent and breaking the intermolecular bonds between the non-electrolyte and water.

Effect of Complex Formation

The apparent solubility of some solutes in a liquid may be increased or decreased; by the addition of a substance that forms a complex which is either more or less soluble. The solubility of the complex determines the apparent change in the solubility of the original solute.

A well known example of complexation is the interaction of Iodine with Povidone to form water soluble Povidone-Iodine complex. A number of compounds, such as nicotinamide and Beta-cyclodextrin, have been used to increase the solubility of poorly water-soluble drugs.

It is also possible that a drug may form an insoluble complex with other ingredients so that the apparent solubility decreases instead of increasing. For example, gentisic acid forms a complex with caffeine that is less soluble than

caffeine alone. Tetracycline forms an insoluble complex with cal-cium ions present in milk or any preparation containing calcium salts.

Effect of Solubilising Agents

Solubility of poorly soluble drugs may be enhanced by a technique known as micellarsolubilisation which involves the use of surfactant for increasing the solubility.

When a surfactant having a hydrophilic and a lipophilic portion is added to a liquid, it first accu-mulates at the air/solvent interface followed by its dispersion throughout the liquid bulk. At a certain concentration known as the critical micelle concentration (CMC), the dispersed surfactant mol-ecules tend to aggregate into groups of molecules known as micelle.

In aqueous medium, the surfactant molecule Orient in such a manner that their hydrophilic por-n; faces the water while the lipophilic portion resides in the micelle interior. An insoluble compound added to the surfactant liquid either enters the micelle interior gets adsorbed onto the micelle surface or sits at some intermediate point depending on its polarity, thus effecting solubilisation. Surfactants that are used as solubilising agents generally have HLB values in excess of 13. Examples include polysorbate-80, polyoxyl 40 stearate, sodium lauryl sulphate and PEG-40-Castor oil remophor). A number of poorly soluble drugs such as fat soluble vitamins A, D, E and K, antibiotics like griseofulvin and chloramphenicol and analgesics such as aspirin and phenacetin have been solubilised by this technique.

Hydrotropic Solubilization

Hydrotropic Solubilization is a solubilization phenomenon whereby addition of large amount of a second results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solution of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium nitate have been observed to enhance the aqueous solubilizaties of many poorly water-soluble drugs.

Mixed Hydro trophy

It is a phenomenon to increase the solubility of poorly, water soluble water soluble drugs in the blends of hydrotropic agents, which may give miraculous synergistic enhancement effect on solubility of poorly water soluble drugs, utilization of dosages from of water insoluble drugs to minimize the side effects. In place of say 5 hydro tropes are used in 1/5th concentration reducing their individual toxicities.

Mechanism of Hydro trope Action Hydro tropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation. They do not have a critical concentration above which self aggregation starts to occur (as found for micelle) instead they aggregation in a stepwise self-aggregation process, gradually increasing aggregation size.

Advantages

1. It is superior to other solubilization methods such as miscibility, micelle solubilization, co-solvency and salting in because the co solvent character is independent of ph, has high selectivity and does not require emulsification.

2. It only requires mixing the drug with the hydro trope in water.

3. It does not require chemical modification of hydrotropic drugs, use of organic solvents, or preparation of emulsification system.

Distribution Phenomenon (Lachman et al., 1986; Martin, 2011).

When we add a solid or liquid to a system of two immiscible liquids .It will distribute itself between the two phases in a definite concentration ratio. The two immiscible liquids may be oil and water system or organic and aqueous phase system.

Let the concentration of solute in organic phase be C_{org} and aqueous phase be C_{aq} at equilibrium. The distribution co-efficient K is the ratio of concentration of solute in organic phase to concentration of solute in aqueous phase.

$K_{o/w} = C_{org}/C_{aq}$ or $K_{w/o} = C_{aq}/C_{org}$ K is also termed as partition coefficient ratio.

Application of Distribution Coefficient

1. Absorption and distribution of drugs in the body

2. Drug action at non-specific sites

3. Preservation of oil-water system etc.

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