CHAPTER

1

Solubility and Related Phenomenon

Contents

INTRODUCTION

The solubility of a substance in a particular solvent is defined as the concentration of the substance in a saturated solution at a certain temperature. The solubility of a material is an intrinsic property that can be altered only by the chemical modification of the molecules. A solution is said to be saturated when it contains the maximum amount of solute that a solvent can dissolve at a particular temperature. 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 contains the dissolved solute in a concentration less than that required for complete saturation at a particular temperature. A supersaturated solution contains a higher 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 container's sides or by introducing a small crystal of the solute.

SOLUBILITY EXPRESSIONS

The solubility of a substance can be expressed in several ways. Most pharmacopoeias 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 1.1.

Table 1.1: General terms used for expressing solubility

Term	***Parts of solvent required***
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 10,000 parts
Practically insoluble	More than 10,000 parts
Very insoluble	Less than 1 part

Solubility is also expressed quantitatively in terms of percentage, molarity, molality or mole fraction as shown in Table 1.2.

Table 1.2: Quantitative expressions for solubility

Solubility expression	***Symbol***	***Definition***
Percent weight by weight	% w/w	Number of grams of solute dissolved in 100 grams of solution
Percent volume by volume	% v/v	Number of ml of solute dissolved in 100 ml of solution
Percent weight by volume	% w/v	Number of grams of solute dissolved in 100 ml of solution
Molarity	M	Number of moles (or gram molecular weight) of solute dissolved in 1 litre of solution
Molality	m	Number of moles of solute dissolved in 1000 g of solvent
Normality	N	Gram equivalent weights of solute in 1 litre of solution
Mole fraction	x	The ratio of moles of solute to total moles of solute and solvent

Another recent system for expressing the solubility of drugs as high solubility or low solubility is the biopharmaceutical classification system (BCS) which is a scientific framework to classify drugs into various classes based on their solubility and permeability as shown in Fig. 1.1. As per the BCS, a drug substance is classified as highly soluble if its highest single therapeutic dose is completely soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37 ±1ºC.

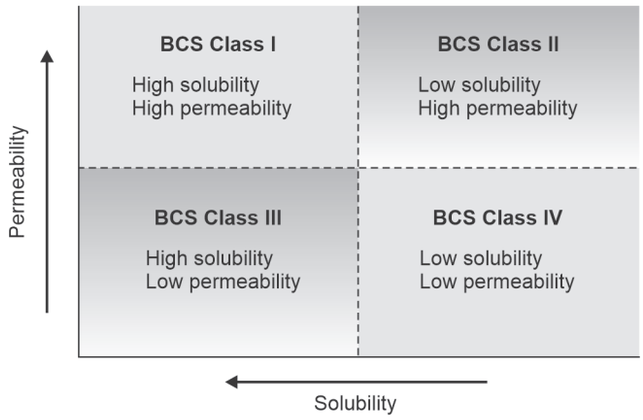

Fig. 1.1: Biopharmaceutical classification system

Determination of Solubility

The thermodynamic solubility or equilibrium saturated solubility of a drug in a solvent is the maximum amount of the most stable crystalline form that remains in solution in a given volume of the solvent at a given temperature and pressure under equilibrium conditions. Thermodynamic equilibrium is achieved when the overall lowest energy state of the system is achieved. This means that only the equilibrium solubility reflects the balance of forces between the solution and the most stable, lowest energy crystalline form of the solid.

The thermodynamic 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 an analysis of the saturated solution.

To obtain 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 undissolved 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 undissolved solids due to temperature changes. Also, the loss of volatile components, if any, has to be prevented, e.g. using sealed containers or minimizing exposure. The solution is then analysed using an appropriate method, e.g. UV spectroscopy, HPLC, etc.

For BCS classification, the equilibrium saturated solubility of the drug substance is also determined using a similar shake-flask technique or an alternative method over a pH range of 1.2–6.8 at 37 ±1°C. Three buffers within this range, specifically at pH 1.2, 4.5, and 6.8, are required to be evaluated. The pH for each test solution is measured after the addition of the drug substance and at the end of the equilibrium solubility study to ensure the solubility measurement is conducted under the specified pH. The pH is adjusted, if necessary. The lowest measured solubility over the pH range of 1.2–6.8 is used to classify the drug substance as high or low solubility as explained above.

MECHANISMS OF SOLUTE–SOLVENT 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 the miscibility of a liquid in some other liquid is generally enhanced. In general, polar solvents dissolve polar solutes and non-polar solvents dissolve non-polar solutes. Semipolar solvents such as acetone and alcohol act as intermediate solvents.

Polar Solvents

The solubility of a drug is primarily influenced by the polarity of the solvent, which is related to its dipole moment. Polar solvents are capable of dissolving ionic solutes and other polar substances. For instance, water can mix with alcohol in any proportion and dissolve sugars and other polyhydroxy compounds. However, considering dipole moments alone is not sufficient to explain the solubility of polar substances in water. The acidic and basic characteristics of the constituents in the Lewis electron donor-acceptor sense also contribute to specific interactions in solutions. The solute's ability to form hydrogen bonds plays a more significant role in solubility than its polarity indicated by a high dipole moment. Water can dissolve alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds that can form hydrogen bonds with water. In addition, the solubility of a substance also relies on structural features, such as the ratio of polar to non-polar groups in the molecule. As the length of a non-polar chain in an aliphatic alcohol increases, its solubility in water decreases.

Non-polar Solvents

The solvent behaviour of non-polar liquids, such as hydrocarbons, is opposite to that of polar substances. Non-polar solvents possess low dielectric constants, which prevents them from reducing the attraction between ions of strong and weak electrolytes. Additionally, they cannot break covalent bonds and ionize weak electrolytes. Moreover, non-polar solvents cannot form hydrogen bridges with non-electrolytes. It is for this reason that ionic and polar solutes show low or no solubility in non-polar solvents.

On the other hand, non-polar compounds can dissolve non-polar solutes through induced dipole interactions, as they share similar internal pressures. The solute molecules are held in solution by weak van der Waals–London forces. Consequently, substances like oils, fats, alkaloidal bases, and fatty acids can dissolve in non-polar solvents such as carbon tetrachloride, benzene and mineral oil.

Semipolar Solvents

Semipolar solvents, such as ketones and alcohols, can induce a certain level of polarity in nonpolar solvent molecules. This means that substances like benzene, which are naturally polarizable, can become soluble in alcohol. Semipolar compounds can serve as intermediary solvents, facilitating the miscibility of polar and non-polar liquids. For instance, when acetone is introduced, it enhances the solubility of ether in water. Crystalline solids have low solubility. The insoluble nature is due to the stable crystalline arrangement and strong intermolecular forces, which resist interaction with the solvent. The melting point can be considered as a measure of intermolecular forces among solute molecules. The higher the melting point of a solute, the less soluble is the solute in a liquid.

Electrolytes have appreciable solubility and their solubility is largely governed by electrostatic forces of attraction and repulsion. They are easily soluble in solvents with

high dielectric constant. For example, water has a high dielectric constant and is a good solvent for polar substances (electrolytes).

IDEAL SOLUBILITY PARAMETERS

A need was felt for a quantitative relationship which could help scientists to predict the solubility of one material in another and to help choose the best solvent for a given material.

Solubility parameters are such numerical parameters or values which can help to predict their relative solubility behaviour. If the value of solubility parameters for two materials is the same or similar, the solubility of one in the other will be good. The solubility parameter values are generally derived from properties of materials which involve molecular or cohesive interactions such as molar heat of vaporization, surface tension, internal pressure, etc.

Hildebrand Solubility Parameter

In the year 1936, Joel Henry Hildebrand proposed a solubility parameter based on the internal pressure to estimate a numeric value for the solubility behaviour of a material which later came to be known as the Hildebrand solubility parameter.

The Hildebrand solubility parameter (δ) is the square root of the cohesive energy density:

$$\delta = \left(\frac{\Delta H_{\mathrm{v}} - RT}{V} \right)^{1/2}$$

where,

ΔH_{v} is the heat of vaporization of a substance.

V_{m} is its molar volume at temperature T.

R is the gas constant.

T is the absolute temperature.

The cohesive energy density is the amount of energy needed to completely remove a unit volume of molecules from their neighbours to achieve an infinite separation. This is equal to the heat of vaporization of the compound divided by its molar volume in the condensed phase. For a material to dissolve, the same interactions are required to be overcome, as the molecules get separated from each other before they can be surrounded and dissolved by the solvent.

For liquids, the overall solubility parameter can be readily estimated by measuring the heat of vaporisation and the molar volume. If the solute is solid at this temperature, its molar volume is required to be determined at an elevated temperature where it is a liquid and extrapolated to the temperature under consideration. The conventional unit for the Hildebrand solubility parameter is $(\mathrm{cal/cm^3})^{1/2}$ while the SI unit is $(\mathrm{MPa})^{1/2}$. Table 1.3 lists the solubility parameters of some commonly used solvents and polymers. From the table, since polyethene has a solubility parameter of 16.7 $\mathrm{MPa}^{1/2}$, it is likely to have good solubility in solvents like diethyl ether and *n*-hexane which have solubility parameters in a similar range. Similarly, polystyrene with a solubility parameter of 18.3 $\mathrm{MPa}^{1/2}$ is likely to dissolve in ethyl acetate with a solubility parameter of 18.2 $\mathrm{MPa}^{1/2}$.

The Hildebrand solubility parameter provides a numerical estimate of the degree of interaction between materials and is a good indication of solubility behaviour, especially for non-polar and slightly polar systems which do not have hydrogen bonding. However, for more complicated systems such as polar molecules, three-dimensional solubility parameters such as Hansen solubility parameters are used.

Table 1.3: Hansen solubility parameters of some common solvents and polymers		
Substance	***Hildebrand solubility parameter***	
	δ *($cal^{1/2}/cm^{3/2}$)*	**δ *($MPa^{1/2}$)***
n-Hexane	7.24	14.9
Diethyl ether	7.62	15.4
Ethyl acetate	9.1	18.2
Chloroform	9.21	18.7
Dichloromethane	9.93	20.2
Acetone	9.77	19.9
2-propanol	11.6	23.8
Ethanol	12.92	26.5
Propylene glycol	14.8	30.3
Water	23.4	27.9
Polyethylene	7.9	16.7
Polypropylene	8.2	16.6
Polystyrene	9.13	18.3
Nylon 66	13.7	28

The quantitative estimate of the solubility parameter takes into account various intermolecular forces, including both polar and non-polar forces. Hildebrand and Scott proposed the below equation to calculate this parameter:

$$\delta^2 = \delta^2 D + \delta^2 P + \delta^2 H$$

where,

$\delta^2 D$ represents the partial solubility parameter arising from non-polar interactions.

$\delta^2 P$ is the partial solubility parameter resulting from polar interactions and $\delta^2 H$ is the partial solubility parameter arising from the hydrogen-bonding tendency among molecules.

The value of $\delta^2 D$ remains relatively constant for all types of molecules, whether they are polar or non-polar, as non-polar forces are present in all these molecules. In contrast, $\delta^2 P$ is influenced by polar forces, which are typically absent in non-polar compounds.

The contribution of $\delta^2 H$ is the highest when hydrogen bonding is present.

For non-polar compounds, such as linear hydrocarbons, the total value of the solubility parameter is primarily composed of $\delta^2 D$ and is close to approximately 7. As a consequence, most hydrocarbons exhibit similar solubility behaviour.

Hansen Solubility Parameters

In 1967, Charles M. Hansen introduced the Hansen solubility parameter as a method for predicting the likelihood of one material dissolving in another to form a solution. Unlike the Hildebrand solubility parameter, the Hansen solubility parameter considers the contributions of dispersion forces, polar forces, and hydrogen bonding forces within the substance. The Hansen solubility parameter is represented as follows:

$$\delta^2 = \delta D^2 + \delta P^2 + \delta H^2$$

where,

δD^2 represents the energy from dispersion forces between molecules.

δP^2 represents the energy from dipolar intermolecular forces between molecules.

δH^2 represents the energy from hydrogen bonds between molecules.

These three parameters can be treated as coordinates in a three-dimensional space known as the Hansen space. When two molecules are close to each other in this three-dimensional space, they are more likely to dissolve into each other. To determine if the parameters of two molecules (usually a solvent and a polymer) are within a specific range, an interaction radius (R_0) is assigned to the substance being dissolved. This value determines the radius of the sphere in Hansen space, with its centre defined by the three Hansen parameters.

To calculate the distance (R_a) between Hansen parameters in Hansen space, the following formula is used:

$$R_a = [(\delta D_1 - \delta D_2)^2 + (\delta P_1 - \delta P_2)^2 + (\delta H_1 - \delta H_2)^2]^{1/2}$$

Combining this with the interaction radius gives the relative energy difference (RED) of the system:

$$RED = R_a / R_0$$

If $RED < 1$, the molecules are similar and will dissolve in each other.

If $RED = 1$, the system will partially dissolve

If $RED > 1$, the system will not dissolve

The Hansen solubility parameter provides a valuable tool for predicting solubility and forming solutions between different substances.

SOLVATION AND ASSOCIATION

Solvation

Solvation, also known as dissolution, refers to the interaction between a solvent and dissolved molecules. Both ionized and uncharged molecules experience significant interactions with the solvent, and the strength and nature of this interaction have a profound impact on various properties of the solute. These properties include solubility, reactivity, colour, as well as the characteristics of the solvent, such as viscosity and density.

During the process of solvation, ions are surrounded by a concentric shell of solvent molecules, forming solvation complexes. This process involves the formation of bonds, hydrogen bonding, ion–dipole interactions, and van der Waals forces between the solvent and solute molecules. When water is the solvent involved in solvation, it is specifically referred to as hydration.

The process of solvation can be conceptualized in three stages (Fig. 1.2):

1. The solute molecule is extracted from its crystal lattice
2. A cavity for the solute molecule is created in the solvent.
3. The solute molecule is inserted into this cavity within the solvent.

The process of solvation involves placing the solute molecule into a solvent cavity, resulting in multiple solute–solvent contacts. Larger solute molecules create more contact. Several factors influence the rate of solvation, including temperature, concentration, surface area of the solute, solvent polarity, and stirring. Increased contact between solute and solvent molecules enhances the rate of solvation.

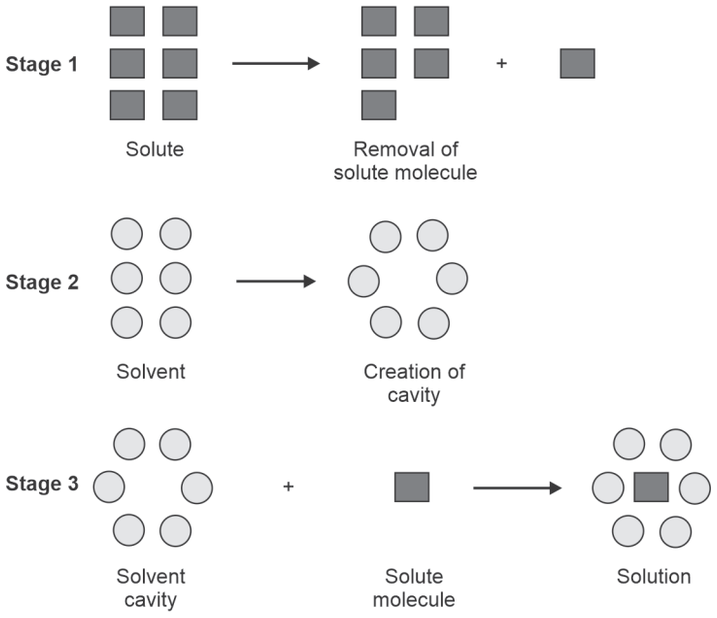

Fig. 1.2: Process of solvation

Association

Association refers to the process of atoms or molecules coming together to form larger units, which are held together by forces that are weaker than the chemical bonds found within molecules. This term typically applies to the formation of aggregates consisting of like molecules or atoms. The resulting molecular aggregate, which forms through association, is commonly known as an association complex.

Due to the relatively weak forces binding the smaller units together, an equilibrium is often observed between the association complex and the corresponding simple molecules. This equilibrium allows the mixture to exhibit chemical behaviour similar to that of the individual small molecules, as the removal of some components through chemical reactions shifts the equilibrium in a way that leads to the dissociation of more of the aggregate, following the law of mass action.

Solubility of Solids in Liquids

Solutions of solids in liquids are the most important types of pharmaceutical solutions encountered. Prediction of the solubility of a solute forming an ideal solution is relatively easy since it is dependent only on temperature, the melting point of the solid and the molar heat of fusion (ΔH_f). It is difficult to predict the solubility of solids forming non-ideal (real) solutions because of several factors involved.

Ideal Solution

In an ideal solution, the heat of the 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 a 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 the 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, the 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 a non-ideal solution. The $\log \gamma_2$ appearing in the equation is obtained from the consideration of intermolecular forces of attraction involved in the solution process or the work done in the process of solution.

FACTORS AFFECTING SOLUBILITY OF SOLIDS IN LIQUIDS

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 on 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.

The effect of temperature on the solubility of salts can be represented by the use of **solubility curves** which are plots of solubility against temperature as shown in Fig. 1.3.

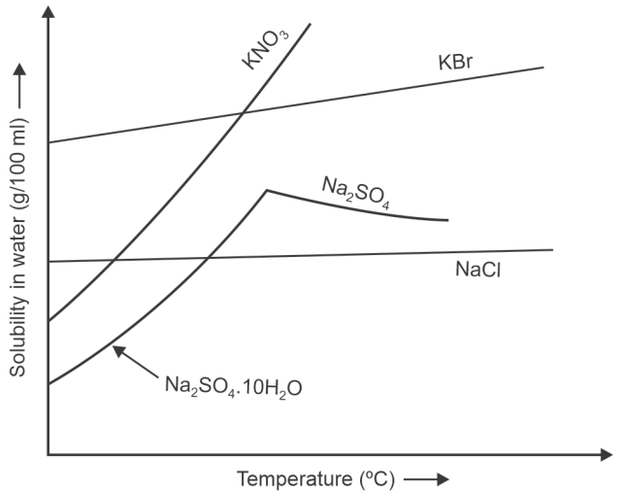

Fig. 1.3: Solubility curves for various substances in water

Most of the curves are continuous, i.e. the solubility either increases or decreases gradually with a temperature rise. However, for certain substances such as sodium sulphate, the slope of the curve shows an abrupt change. This is because sodium sulphate exists as decahydrate $Na_2SO_4 \cdot 10H_2O$ 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 an increase in temperature.

Molecular Structure

A 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 the 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 an increase in surface area which increases the solubility.

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

Nature of Solvent and Cosolvent

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).

The 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 increasing the solubility of poorly soluble substances by the use of more than one solvent is known as cosolvency.* For example, the solubility of weak electrolytes and non-polar molecules in water may be considerably increased by the addition of cosolvents such as ethanol, glycerol, propylene glycol or sorbitol. These agents work by decreasing the interfacial tension between the hydrophobic solute and the aqueous environment or by altering the dielectric constant of the medium.

pH

Most of the drugs are either weak acids 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, the solubility of weakly basic drugs or their salts increases with a decrease in the pH.

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

$$\mathrm{pH_p} = \mathrm{p}K_a + \log \frac{S - S_0}{S_0}$$

where,

$\mathrm{pH_p}$ is the pH below which the drug precipitates from the solution.

S is the overall solubility of the drug.

S_0 is the solubility of its unionized form.

For basic drugs, the relationship is:

$$\mathrm{pH_p} = \mathrm{p}K_a + \log \frac{S_0}{S - S_0}$$

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 the solution. Alternatively, the minimum pH value that is required to maintain the drug in solution can be determined.

Polymorphism

Polymorphism refers to the phenomenon where a substance exists in multiple crystalline forms. Different polymorphs usually exhibit varying solubilities. For instance, chloramphenicol *B* demonstrates higher solubility compared to chloramphenicol *A*.

Amorphism occurs when a substance lacks an ordered structure. In the amorphous form, molecules are randomly arranged, leading to increased solubility compared to the crystalline form. For example, the amorphous form of novobiocin is 10 times more soluble than its crystalline counterpart.

Pseudo-polymorphism arises when solvent molecules become trapped within the crystal lattice of a substance. These trapped molecules are referred to as solvates, and when water is the solvent, they are known as hydrates. Solvates generally exhibit higher solubility than non-solvates. For instance, *n*-pentanol solvates of fludrocortisone demonstrate greater solubility than non-solvated forms.

Combined Effect of Solvent and pH

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:

1. It increases the solubility of the unionized species of the weak electrolyte by adjusting the polarity of the solvent to a more favourable value
2. It decreases the dissociation of the weak electrolyte thereby increasing the pK_a value and reducing the solubility.

Example 1.1: What is the minimum pH required for the complete solubility of the drug in a solution containing 6 g of phenobarbitone sodium (M. wt. 254) in 100 ml of a 30% v/v alcoholic solution (given pK_a of phenobarbitone in 30% v/v alcohol = 7.92 and S_o of phenobarbitone in 30% v/v alcohol = 0.0276 M).

Solution: Molar solubility of phenobarbitone in 30% v/v alcoholic solution (S_o) = 0.0276 mole/liter

Molar concentration of phenobarbitone required in solution (S) = $\frac{60\,g/L}{254}$ = 0.236 mole/liter

pK_a of phenobarbitone = 7.41

pH below which the drug will precipitate from the alcoholic solution,

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

$$= 7.92 + \log\frac{0.236 - 0.0276}{0.0276}$$

$$= 7.92 + \log\frac{0.208}{0.0276}$$

$$= 7.92 + 0.877$$

$$= 8.79$$

Example 1.2: Below what pH will free phenobarbitone begin to precipitate from a solution having 1 g of sodium phenobarbitone (M.wt. 254) per 100 ml at 25°C? The molar solubility of phenobarbitone is 0.0050 and the pK_a = 7.41 at 25°C.

Solution: Molar solubility of phenobarbitone (S_o) = 0.0050 mole/liter

Molar concentration of sodium phenobarbitone initially added (S) = $\frac{10\,g/L}{254}$ = 0.039 mole/liter

pK_a of phenobarbitone = 7.41

Contd.

Contd.

pH below which the drug will precipitate from the alcoholic solution,

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

$$= 7.41 + \log\frac{0.039 - 0.005}{0.005}$$

$$= 7.41 + \log\frac{0.034}{0.005}$$

$$= 7.41 + \log 0.034 - \log 0.005$$
$$= 7.41 + [(-1.468) - (-2.30)]$$
$$= 7.41 - 1.468 + 2.30$$
$$= 8.24$$

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 an undissolved electrolyte, the equilibrium may be represented as follows:

$$\underset{\text{(solid)}}{AB} \rightleftharpoons \underset{\text{(ions)}}{A^+ + B^-}$$

According to the 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:

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

where, K_{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:

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

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*.

Example 1.3: If the solubility product of silver chromate is 2×10^{-12} at 25°C, what is the solubility in mole/litre of silver chromate?

Solution: $$Ag_2CrO_4 \rightleftharpoons \underset{2S}{2Ag^+} + \underset{S}{CrO_4^{2-}}$$

Solubility product of silver chromate

$$K_{sp} = [2S]^2 \times S$$

or $$K_{sp} = 4S^3$$

Contd.

Contd.

or $$S^3 = \frac{K_{sp}}{4}$$

$$S = \sqrt[3]{\frac{K_{sp}}{4}}$$

$$S = \sqrt[3]{\frac{2 \times 20^{12}}{4}}$$ [Given: Solubility product (K_{sp}) of silver chromate = 2×10^{-12}]

or $$S = 0.79 \times 10^{-4} \text{ mole/liter}$$

Hence, solubility of silver chromate = 0.79×10^{-4} mole/liter

Effect of Indifferent Electrolyte on the Solubility Product

An effect opposite to that of the common-ion effect will be produced if salts carrying no common-ion (indifferent electrolytes) are added to a solution of slightly soluble electrolytes. 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 constant of the solvent which is in effect a measure of the polar nature of the solvent.

The addition of a water-soluble non-electrolyte such as alcohol to an aqueous solution of a sparingly soluble salt decreases the solubility of a sparingly soluble electrolyte. This effect is due to the lowering of the 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. The addition of 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 a water-soluble povidone–iodine complex. Several 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 calcium ions present in milk or any preparation containing calcium salts.

Effect of Solubilizing Agents

The solubility of poorly soluble drugs may be enhanced by a technique known as *micellar solubilisation* 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 accumulates 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 molecules tend to aggregate into groups of molecules known as micelle.

In an aqueous medium, the surfactant molecules orient in such a manner that their hydrophilic portion 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 affecting solubilization.

Surfactants that are used as solubilising agents generally have HLB values over 13. Examples include polysorbate-80, polyoxyl-40-stearate, sodium lauryl sulphate and PEG-40-castor oil (cremophor). Several 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 solubilized by this technique.

DISSOLUTION AND DRUG RELEASE

Dissolution

Dissolution may be defined as the process by which a solid solute enters into solution when added to an appropriate solvent. Dissolution rate refers to the rate at which the solid dissolves in a solvent.

When a solid dosage form such as a tablet is introduced into water, the drug contained in the tablet begins to pass into solution. Simultaneously, the solid matrix of the tablet disintegrates into granules and these granules in turn deaggregate into fine particles. Dissolution of the drug takes place both from the disintegrated granules and from the fine particles (Fig. 1.4)

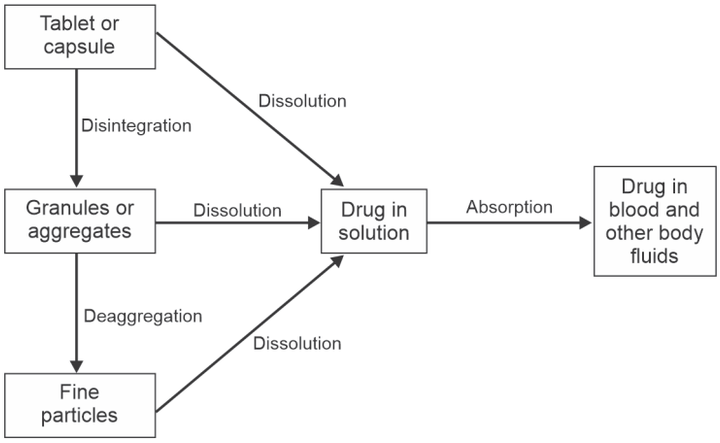

Fig. 1.4: Disintegration, deaggregation and dissolution steps involved in the release of drug from a tablet.

Although the effectiveness of the tablet in releasing the drug is somewhat dependent on the rate of disintegration and deaggregation, of more importance is the rate of dissolution of the solid drug. Most often the dissolution step is the slowest and hence the limiting or rate-controlling step in the bioabsorption of drugs of low solubility.

The rate of dissolution of a solid in a liquid is quantitatively given by the *Noyes-Whitney* equation:

$$\frac{dc}{dt} = \frac{DS}{Vh}(C_s - C)$$

where,

dc/dt is the rate of dissolution, i.e. the rate at which the solid goes into solution
D is the diffusion coefficient
S is the surface area of the exposed solid
V is the volume of the solution
h is the thickness of the diffusion layer
C_s is the solubility of solid drug
C is the solubility of the drug at time t

In dissolution theory, it is assumed that there exists an aqueous diffusion layer or stagnant liquid film surrounding the surface of a solid undergoing dissolution as shown in Fig. 1.5. The thickness of the stationary layer is represented as '*h*'. The solute molecules exist in stationary layer in concentrations from C_s to *C*. Diffusion occurs through this stationary layer and mixes in the bulk solution at a distance *x* greater than '*h*' (or at the far end of '*h*').

At the interface of diffusion layer and the solid surface, the solid solute is in equilibrium with the solute in the diffusion layer. Then the concentration changes with distance across the diffusion layer.

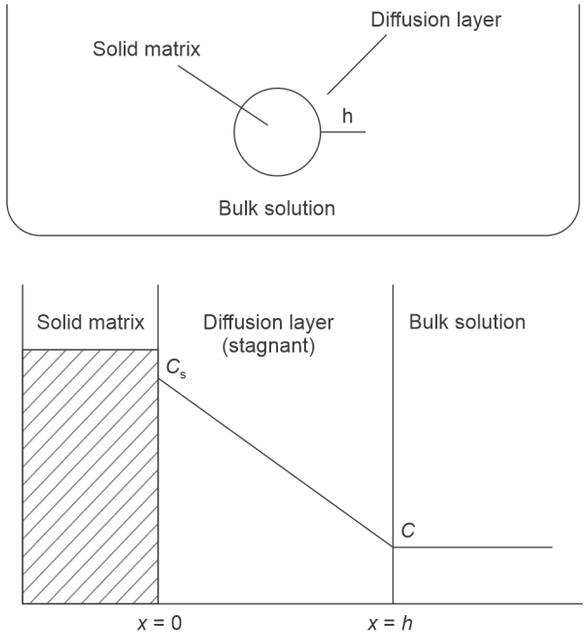

Fig. 1.5: Dissolution of a drug from a solid matrix.

This concentration change (i.e. concentration gradient) is constant and is represented by the downward sloping line (steady state condition).

When C is considerably less than the drug's solubility, C_s, the system is said to exhibit sink conditions. Under these circumstances, the term C may be eliminated from the above equation which now becomes:

$$\frac{dc}{dt} = \frac{DSC_s}{Vh}$$

In the derivation of the Noyes-Whitney equation, it was assumed that h and S are constants but actually S decreases as the particle size decreases when the solid undergoes dissolution and the thickness h of the static diffusion is also altered by agitating. Yet valuable information regarding the dissolution of drug particles, granules or tablets is obtained by the use of above equations.

Dissolution Study

A number of *in vitro* methods have been described to study the rate of dissolution of granules, tablets and capsules. The most widely used apparatus for the study of dissolution rates of active drugs from solid dosage forms such as tablets and capsules are the Basket and Paddle type dissolution apparatus (Fig. 1.6).

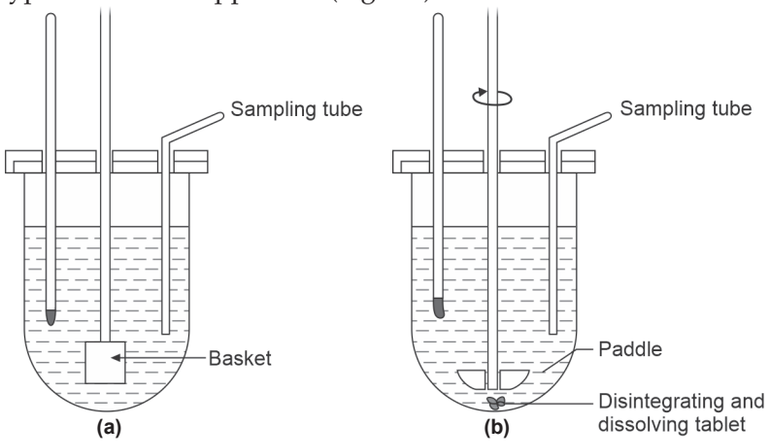

Fig. 1.6: Basket (a) and paddle (b) type dissolution apparatuses

The USP basket type apparatus (Apparatus 1) consists of a 40 mesh stainless steel basket attached to the end of a stirring shaft which in turn is attached to a variable speed motor.

A tablet or a capsule is placed within the basket and immersed in the dissolution fluid contained in a round bottomed container and rotated at a speed specified or desired. The dissolution fluid is either water, buffer solution or dilute hydrochloric acid solution simulating the gastric pH. The dissolution fluid is maintained at a temperature of 37°C. During the run, samples are withdrawn at different times for analysis. The volume of the dissolution fluid is maintained constant by replacing the amount of sample removed with fresh dissolution fluid. The analysis of the sample withdrawn at different specified times is undertaken in order to determine the dissolution rate.

The USP paddle apparatus (Apparatus 2) consists of a paddle attached to the end of a stirring shaft which in turn is attached to a variable speed motor. The paddle is immersed in the dissolution medium contained in a round bottomed l000 ml container which in turn is immersed in a constant temperature bath to maintain the temperature at 37°C. During the operation, the tablet is dropped into the dissolution fluid and the fluid is stirred with the paddle positioned vertically near the bottom of the container at the specified speed (50 to 100 rpm). Samples are withdrawn and analysed as described above.

Under the monograph of dosage forms of drugs, USP generally specifies whether Apparatus 1 or Apparatus 2 is to be used. In general, Apparatus 1 can be used for dosage forms such as capsules which tend to float, whereas Apparatus 2 would be preferred for non-floating dosage forms such as tablets.

Drug Release

The release of a drug from a drug delivery system (dosage form) involves both the processes of dissolution and diffusion. Modern drug delivery systems such as sustained action tablets and capsules generally consist of drugs dispersed in a polymeric matrix where the diffusion predominates.

1. Drug Release from Homogeneous Polymeric Matrices

The drug release from a homogeneous polymer matrix tablet dosage form is assumed to occur by its dissolution within the polymeric matrix followed by its diffusion or leaching into the surrounding medium as shown in Fig. 1.7.

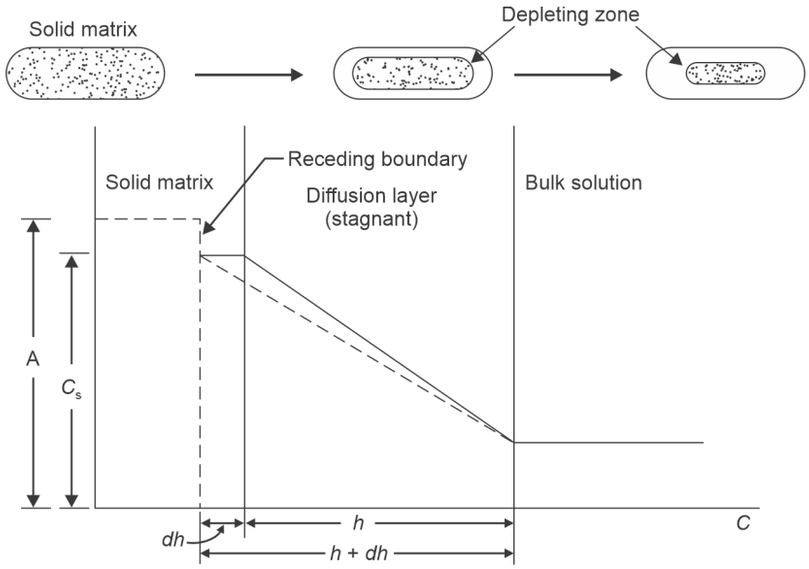

Fig. 1.7: Drug release from homogeneous polymeric matrix

The release of drug from such a matrix can be described by the equation:

$$Q = [D(2A - C_s)C_s t]^{1/2}$$

or

$$\frac{dQ}{dt} = \frac{1}{2}\left[\frac{D(2A - C_s)C_s}{t}\right]^{1/2}$$

where,

Q is the quantity of drug released or depleted at time t

D is the diffusion coefficient

C_s is the solubility or saturation concentration of drug in the matrix.

A is the total concentration of drug in unit volume of the matrix.

If $A >> C_s$, the equation reduces to:

$$Q = (2ADC_s t)^{1/2}$$

and $$\frac{dQ}{dt} = \left[\frac{2ADC_s}{2t}\right]^{1/2}$$

The equation indicates that quantity of drug released is proportional to the square roots of A, D, C_s and t. The rate of release can be altered by increasing or decreasing the drug's solubility, C_s, in the polymeric matrix by complexation. The release rate is also effected by the total concentration of the drug, A, in the matrix.

2. Drug Release from Granular Matrices

Drug release from a granular matrix is assumed to occur by simultaneous penetration of the surrounding liquid into the granular matrix, dissolution of the drug in the liquid and the leaching out of the drug through interstitial channels or pores. Since granules are generally porous rather than homogeneous matrices, the volume and length of the pores or channels in the granules are accounted for in the release equation:

$$Q = [D\varepsilon/\tau\ (2A - EC_s)\ C_s t]^{1/12}$$

where,

ε is the total porosity of the matrix after the drug has been released

τ is the tortuosity of the capillary systems in the granules.

The tortuosity term has been introduced in the equation to account for the increase in path length of diffusion due to branching and bending of the pores in comparison to short straight pores in case of homogeneous matrices.

DIFFUSION PRINCIPLES IN BIOLOGICAL SYSTEMS

Drug molecules pass through living membranes either by passive transport or active transport. Passive transport involves a simple diffusion process from a region of higher concentration to a region of low concentration as seen during drug transport in the gastrointestinal tract. The concentration gradient, i.e. the difference in the concentration of the drug across the membrane is the driving force for passive transport.

In active transport, drug molecules are carried across the membrane by an enzyme or biological carrier. Active transport can also occur against a concentration gradient, i.e. from a region of low concentration to that of high concentration. The net movement of the drug is however towards blood.

The rate of drug transport is influenced by:

1. the physicochemical properties of the drug,
2. the nature of the membrane and
3. the concentration of the drug across the membrane.

The ionic character of weakly acidic or weakly basic drugs also has an important role during the transport process.

Most drugs are either weakly acidic or weakly basic. They exist in aqueous solutions as ionized species. The fraction of the drug that exists as ionized or unionized is determined by the dissociation constant of the drug (pK_a value) and the pH of its aqueous environment per the *Henderson-Hasselbalch* equation for weak acids and bases.

For a weak acid, $$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

For weak base, $$pH = pK_a + \log \frac{[B]}{[BH^+]}$$

where,

$[HA]$ is the concentration of non-ionized weak acid.

$[A^-]$ is the concentration of the conjugate base.

pK_a is the dissociation exponent for the weak acid.

$[B]$ is the concentration of the weak base.

$[BH^+]$ is the concentration of its conjugate acid.

For the weak base,

$$pK_a = pK_w - pK_b$$

Equal amounts of ionized and unionized forms of a drug are present when $pH = pK_a$.

pH Partition Principle

Biological membranes being predominantly lipophilic are permeable to unionized species of a drug in preference to ionized species of the drug. Therefore, *the rate of passive transport of the weak acid or base is related to the concentration of the drug that exists in the unionized form at the site of absorption.* This is known as the *pH partition hypothesis*.

The degree of ionization of a drug in a solution can be calculated using Henderson-Hasselbalch equations for weak acids and bases if the pK_a of the drug and the pH of the solution are known.

However, this principle is only partly applicable in biological systems as evidenced by *in vivo* and *in vitro* studies. That is, both the ionized and unionized forms are significantly transported in contradiction with this simple pH partition hypothesis.

Modification of pH Partition Principle

It has been shown by certain workers that the pH partition principle for the absorption of drugs is also approximate. They proposed that absorption of relatively small ionic and non-ionic species through the aqueous pores within the membrane and aqueous diffusion layer in front of the membrane should also be considered. Other physiological factors such as metabolism of the drug in the biological membrane, absorption in the micellar form and enterohepatic circulatory effects must also be accounted for in the process of absorption.

Percutaneous Absorption of Topically Applied Drugs

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

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

Of the above three steps, the slowest one determines the rate of absorption of the drug through the percutaneous route. Usually the rate-limiting step is the passage of drug molecules through skin layers principally the stratum corneum. Therefore, this step controls the permeation of drugs into the systemic circulation.

In general, the following factors affect the permeation of drug molecules into the skin:

1. The concentration of dissolved drug
2. Partition coefficient between the skin and the vehicle
3. Diffusion coefficients of the drug in the vehicle and the skin barrier.

Diffusion of the drug molecules through skin layers can be influenced by the components of the dosage form (mainly the solvents and the surfactants). Hence, the proper choice of vehicle plays an important role in ensuring the bioavailability of topically applied drugs.

SOLUBILITY OF GASES IN LIQUIDS

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 significantly 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:

$$C = \sigma p$$

where,

C is the concentration of the dissolved gas in grams per litre of solvent.

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.

σ is the proportionality constant and is referred to as the solubility coefficient.

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

2. Effect of Temperature

The 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 a container.

3. Effect of Electrolytes and Non-electrolytes

The solubility of 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 to as salting out. This is due to more affinity between the solvent and the electrolyte or non-electrolyte than between the solvent and the gas.

4. Effect of Chemical Reaction

Henry's law generally applies to gases that are only slightly soluble in the 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.

SOLUBILITY OF LIQUIDS IN LIQUIDS

Examples of pharmaceutical solutions containing a liquid dissolved in another liquid include hydro-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.

Ideal and Real Solutions

According to 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–toluene, 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 dimers 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.

Partially Miscible Liquids

Two liquids are either completely miscible or partially miscible. Completely miscible liquids mix in all proportions and hence do not create any solubility problems. Partially miscible liquids form two immiscible 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 (CST) (or consolute temperature) they are miscible and at this temperature a homogeneous or a single phase results for any composition.

The CST may be of two types:

Lower critical solution temperature (LCST) or lower consolute temperature which is the critical temperature below which partially miscible solvents form a homogenous solution at all compositions. There are some solvent pairs for which mutual solubility increases with a decrease in the temperature and below the LCST they are miscible in all proportions.

For example, the triethylamine–water system has an LCST of 18.5°C (Fig. 1.8) which means both the solvents are miscible below 18.5°C but not above this temperature.

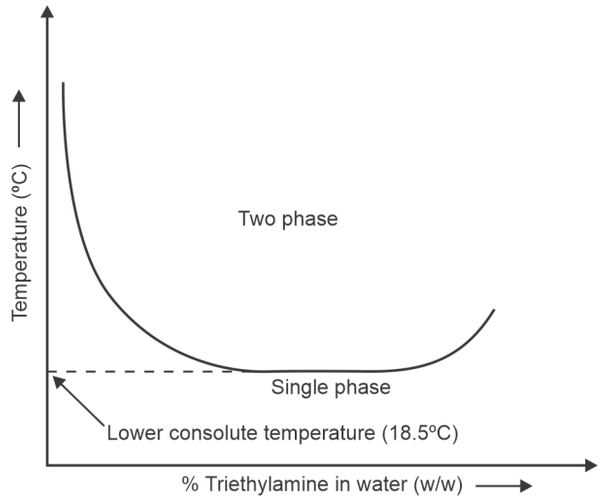

Fig. 1.8: Diagram showing the lower consolute temperature for the triethylamine–water system

Upper critical solution temperature (UCST) or upper consolute temperature which is the critical temperature above which the partially miscible solvents form a homogenous solution at all compositions. For example, phenol and water show a UCST of 66.8°C (Fig. 1.9) which means both the solvents are miscible at all compositions above 66.8°C but not below this temperature.

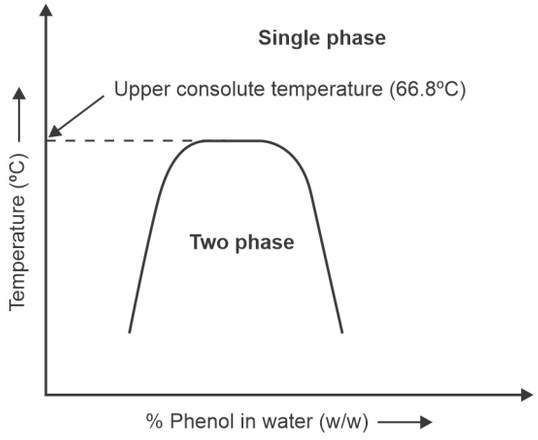

Fig. 1.9: Diagram showing the upper consolute temperature for the phenol–water system

Some solvent pairs show both UCST and LCST which means that the solvents are completely miscible at all compositions above a certain temperature and below a certain temperature. For example, the nicotine-water system has LCST of 60.8°C and UCST of 208°C at a pressure high enough for liquid water to exist at that temperature. It means that these solvents are completely miscible below 60.8°C and above 208°C and partially miscible between them (Fig. 1.10).

Moreover, the presence of impurity in either solvent or both may change the CST. Impurity may raise the UCST and lower the LCST. For example, a 1% solution of NaCl

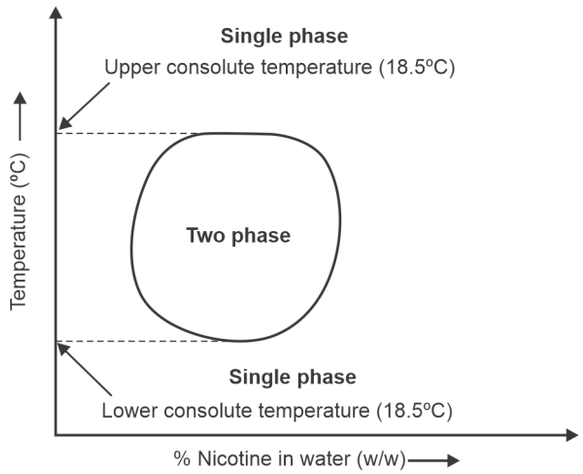

Fig. 1.10: Diagram showing the upper and lower consolute temperatures for the nicotine-water system

raises the UCST of the phenol–water system by 12°C whereas a 1% solution of sodium oleate lowers the LCST by 45°C.

A final type of mixture such as that of ethyl ether and water has neither an upper nor lower critical temperature and the mixture remains partially miscible over the entire temperature range.

208°C and below 60°C, nicotine and water are miscible in all proportions and between these two temperatures, they are partially miscible.

Applications of Critical Solution Temperature

Check the purity of a mixture: As a small amount of impurity changes the critical solution temperature, therefore, its determination can be used to check the purity of a mixture.

The extent of impurity: Change in critical solution temperature value is usually a linear function of the amount of impurities. So, the concentration of impurities can be checked by determining the critical solution temperature. For example, the amount of water in alcohol can be estimated by measuring the critical solution temperature value of the alcohol–cyclohexane system.

Disinfectants: By adding an appropriate amount of sodium oleate to the phenol–water system which makes the phenol completely soluble in the water, disinfectants like Lysol® can be made.

Ternary Systems

Addition of a third component to a pair of partially miscible liquids produces 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 substance is soluble in both liquids to roughly the same extent, the mutual solubility of the liquid pair is increased.

DISTRIBUTION LAW

Nernst studied the distribution pattern of different solutes by taking appropriate solvents and on the basis of his observations, he stated the general distribution law or partition law also known as Nernst's distribution law.

According to his observations, when two immiscible liquids (solvent 1 and solvent 2) are taken in a beaker, they form two separate layers. If a solute X (either solid or liquid), which is soluble in both the liquids is added to the mixture, it is observed that it gets distributed in both the liquids and also molecules of solute move from solvent 1 to 2 and from 2 to 1 to attain a dynamic equilibrium (Fig. 1.11).

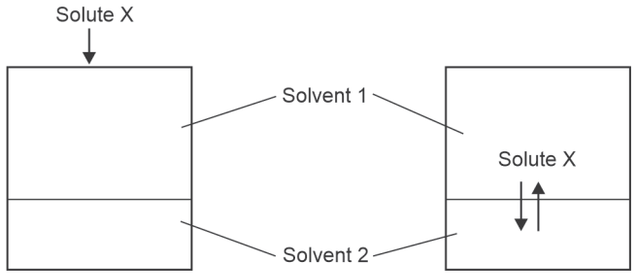

Fig. 1.11: Representation of distribution law

The ratio of the concentrations of the solute in the two solvents is independent of the total amount of solute and has a definite value at equilibrium for a given temperature. This is known as the Nernst's distribution law.

If C_1 and C_2 are the concentrations of the solute in the two solvents at equilibrium, then,

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

where, K_D is the equilibrium constant and is known as the distribution ratio or partition coefficient.

Limitations of Distribution Law

There are various conditions which must be satisfied to apply Nernst's law:

1. The law is applicable only when the solute is present at a low concentration in the two immiscible solvents. If the concentration of solute is very high, the equation for Nernst's distribution law needs to be modified.
2. The law is not applicable if the temperature is changing. Hence, the temperature must be kept constant during the experiment.
3. The law fails if the association or dissociation of solute occurs in either of the solvents. Hence, the solute should remain in the same molecular state in both solvents for the law to be applicable.
4. The two solvents should be immiscible or only slightly miscible with each other. In addition, the mutual solubility of the solvents should remain unchanged after the addition of the solute to the solvents.

Applications of Distribution Law

There are several applications of distribution law in the pharmaceutical and chemical industries. Some of these are as follows:

1. One of the most important applications of the distribution law is to predict or correlate the biological activity of new drugs by determining their partition coefficient in multiple solvents against water. For example, the water–octanol partition coefficient is commonly used to determine the hydrophilicity or hydrophobicity of drugs and to correlate their absorption and distribution in various compartments of the body.

2. The partition coefficient can also be used to arrive at a quantitative structure—the biological activity of a homologous or closely related series of drugs thereby helping in the development of drugs with optimized biological activity.
3. Another important application of the distribution law is the solvent extraction of drugs from their aqueous solutions. Organic solvents such as ether or chloroform are added to the aqueous solution in a separating funnel and shaken. The organic substances pass on from the aqueous layer to the organic layer due to the distribution behaviour and separation.
4. A similar principle also helps in the extraction of drugs from biological fluids such as blood and urine for the purpose of drug analysis.
5. Solvent–solvent extraction is a very common technique devised on the principle of distribution law which is used for the purification of drugs and chemicals which may otherwise get damaged by high temperatures or extremes of pH that may occur in conventional separation processes.
6. Partition chromatography is another important technique which finds wide application in the pharmaceutical and chemical industry for the purpose of separation and analysis of closely related compounds. It works on the principle of differential partitioning of components of a mixture between two phases, a stationary phase and a mobile phase. Examples of partition chromatography include paper chromatography, column chromatography and thin-layer chromatography.
7. The distribution law also finds application in the preservation of creams and emulsions which contain an oily phase and an aqueous phase and the selected preservative has to distribute optimally in both the phases for adequate preservation. Determination of the distribution coefficient helps in the selection of the right preservative as well as the right concentration to be used.

REVISION EXERCISES

I. Long Answer Type Questions

1. What do you understand by solubility and solubility expressions? Describe the factors which can affect the solubility of solids in liquids.
2. What do understand by ideal and real solutions? Describe upper consolute temperature and lower consolute temperature with a suitable example.
3. Discuss the various factors affecting the solubility of gases in liquids.
4. Write notes on:
   a. Cosolvency
   b. Micellar solubilization
   c. Solubility product
   d. Procedure for determination of the solubility of a solid in a liquid solvent
5. With the help of suitable examples, give the importance of diffusion principles in biological systems.
6. Discuss the distribution law and its significance in the partitioning of solutes between immiscible phases. Highlight its limitations, particularly in complex systems, and provide examples of its applications in pharmaceutical formulations
7. What is the critical solution temperature? Write its applications.
8. What do you mean by the term solvation? Explain the process of solvation.

9. Describe the steps by which dissolution of drugs from a dosage form such as tablet takes place.
10. Give the Noyes-Whitney equation, explaining the significance of each term.

II. Short Answer Type Questions

1. State the various expressions used for expressing the solubility of solids in liquids.
2. How do factors like temperature, pressure, and molecular interactions influence the solubility of different substances in a solvent?
3. Describe a suitable method for determining the saturation solubility of a solid in a liquid.
4. What is the solubility curve? Explain continuous and discontinuous solubility curves with suitable examples.
5. What are ideal and non-ideal solutions? Give examples.
6. State the relationship between dielectric constant and solubility.
7. What is the effect of temperature on the solubility of gases in liquids?
8. What do you understand by upper and lower consolute temperature? Explain by giving examples.
9. What is the common ion effect? Explain with examples.
10. What is partition coefficient and what are its applications?
11. What is the importance of diffusion principles in biological systems?
12. Describe the process of drug release from homogeneous polymeric matrices.
13. What are the different types of interactions involved in solvation?
14. Describe the effect of polarity and hydrogen bonding on solvation.
15. What is Raoult's law? Give its limitations.

III. Multiple Choice Questions

1. All of the following physicochemical constants are useful in predicting the solubility of a drug, except:
   a. pH of a solution
   b. pK_a of the drug
   c. Dielectric constant
   d. Valency
2. Which of the following equations is used to represent drug dissolution from a tablet?
   a. Fick's equation
   b. Noyes-Whitney equation
   c. Henderson-Hasselbalch equation
   d. Michaelis-Menten equation
3. Which of the following is the critical step for absorption of drug from a tablet?
   a. Disintegration
   b. Diffusion
   c. Dissolution
   d. Both (a) and (c)
4. Number of moles of solute dissolved in 1 litre of solution is termed as:
   a. Molarity
   b. Molality
   c. Normality
   d. Solubility
5. The phenomenon of increasing the solubility of non-polar drugs by addition of surfactants is known as:
   a. Surface solubilization
   b. Micellar solubilization
   c. Polar solubilization
   d. Non-polar solubilization

6. The general strategies for increasing the aqueous solubility of a relatively non-polar drug of weak ionization tendency include:
   a. Increasing the polarity of the solvent by the addition of cosolvents
   b. Increasing ionization of the drug by adjusting the pH of the solvent
   c. Choosing the amorphous form of the drug
   d. (b) and (c) only
7. Passage of a drug molecule across a cell membrane from a region of high concentration to a region of low concentration is known as:
   a. Active diffusion
   b. Passive diffusion
   c. Carrier mediated diffusion
   d. Efflux
8. When non-polar substances are dissolved in a polar solvent using surfactants, the process is called:
   a. HLB
   b. Solubilization
   c. Emulsification
   d. Gelatinisation
9. The technique of increasing the solubility of poorly soluble drugs by the addition of a miscible solvent in which the drug is soluble is known as:
   a. Cosolvency
   b. Hydrotropism
   c. Complexation
   d. Chemical modification
10. Solubility of most gases usually _____ with an increase in temperature.
   a. Decreases
   b. Increases
   c. Does not change
   d. First increases and then decreases
11. Which law governs the behaviour of ideal solutions in binary mixtures?
   a. Raoult's law
   b. Boyle's law
   c. Charles's law
   d. Nernst's law
12. Ethanol is added to increase the solubility of poorly soluble drugs by acting as a:
   a. Solvent
   b. Co-solvent
   c. Surfactant
   d. Solubilizer
13. According to the biopharmaceutics classification system, class II drugs have:
   a. Low solubility and low permeability
   b. Low solubility and high permeability
   c. High solubility and low permeability
   d. High solubility and high permeability
14. The presence of impurities in a solvent mixture may cause:
   a. Rise in the critical solution temperature
   b. Downfall in the critical solution temperature
   c. Both (a) and (b)
   d. None of the above
15. What are the factors that can influence the solubility of a solute in a solvent?
   a. Temperature
   b. Pressure
   c. The molecular weight of the solute
   d. All of the above

16. What type of intermolecular forces are involved in solvation processes?
    a. Ionic bonds
    b. Covalent bonds
    c. Hydrogen bonding
    d. Metallic bonding
17. Henry's law applies to the solubility of:
    a. Gases in liquids
    b. Liquids in gases
    c. Solids in liquids
    d. Liquids in liquids
18. Real solutions deviate from ideal behaviour due to:
    a. Molecular interactions
    b. High pressure
    c. Low temperature
    d. High solute concentration
19. The critical temperature below which partially miscible solvents form a homogenous solution at all compositions is known as:
    a. Upper critical solution temperature
    b. Lower critical solution temperature
    c. Optimum critical solution temperature
    d. Super critical solution temperature
20. Solvent–solvent extraction of drug components is based on the principle of:
    a. Henry's law
    b. Distribution law
    c. Boyle's law
    d. Raoult's law

ANSWERS

1. (d)	2. (b)	3. (d)	4. (a)	5. (b)	6. (d)	7. (b)	8. (b)	9. (a)	10. (a)	11. (a)	12. (b)
13. (b)	14. (b)	15. (d)	16. (c)	17. (a)	18. (a)	19. (b)	20. (b)				