

CHAPTER 1A

SOLUBILITY

1A.1 Introduction

Solutions are used in pharmaceutical practice and development frequently either as dosage form or for clinical trials material and also the drugs function in solution form in the body. Hence an understanding of properties of solutions and factors that affect solubility is essential to pharmacists for choosing best solvent medium for a drug or combination of drugs.

1A.1.1 Definition of Terms

Solubility can be defined as the ability of the solute to dissolve in a given solvent.

Solution is a homogenous mixture of one or more substances dispersed molecularly in a sufficient quantity of dissolving media. Solution contains two components – solute and solvent. Solute is the substance that is being dissolved and is usually present in smaller proportion. Solvent is the substance that is capable of dissolving solute and usually constitutes the greater proportion in a solution.

A true solution is a homogenous mixture of two or more components in which solute molecules are dispersed as small molecules or ions throughout the solvent. It thus differs from colloidal dispersion where dispersed state molecules or ions are larger.

A saturated solution refers to a solution in which solute is in equilibrium with solid phase at a definite temperature. An unsaturated solution contains solute proportion in lower amounts that is necessary to maintain saturation at definite temperature. Supersaturated solution contains solute in higher proportion that is necessary to maintain saturation at definite temperature.

1A.1.2 Methods of Expressing Solubility

Substance solubility can be expressed in number of parts of solvent required for dissolving one part of solute.

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S. No.	Solubility Characteristics	Parts of Solvent Required
1.	Very soluble	Less than 1 part
2.	Freely soluble	1 to 10 parts
3.	Soluble	10 to 30 parts
4.	Sparingly soluble	30 to 100 parts
5.	Slightly soluble	100 to 1000 parts
6.	Very slightly soluble	1000 to 10000 parts
7.	Practically insoluble or insoluble	More than 10000 parts

1A.2 Solute-Solvent Interactions

Ideal solubility depends on the crystalline structure of the solute and solvent. Solute molecule undergoes dissociation from crystal lattice before it goes into solution. This dissociation is accompanied by free energy change. The higher the energy required for dissociation lower the solubility.

Polarity of the solvent contributes to the solubility of the solute. Based on the polarity solvents are of three types:

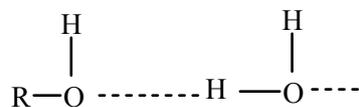
1. Polar solvents
2. Non polar solvents
3. Semi polar solvents

1A.2.1 Polar Solvents

These solvents dissolve ionic solutes and other polar substances. Factors such as dipole moment, ability of solute to form hydrogen bonds contribute to the polarity of solvents.

Example

Water dissolves aldehydes, ketones, alcohols, phenols etc.



Alcohol with water

In addition, ratio of polar to non polar groups of the molecule also determines solubility character. As the length of a non polar chain of an aliphatic alcohol increases, the solubility in water decreases.

Water solubility increases:

1. If compound contains additional polar groups.
E.g.: Glycerine
2. Branching of carbon side chain. This is because as branching occurs non polar character decreases and solubility in water increases.

Reasons for high Solubility Character of Polar Solvents

1. High dielectric constant which reduces the force of attraction between oppositely charged ions in the crystal.
2. Ability to break covalent bonds of potentially strong electrolytes.
3. Capability to solvate molecules and ions through dipole interaction forces, which leads to solubility of the compound.

1A.2.2 Non Polar Solvents

These solvents dissolve non polar solutes having same internal pressures.

These can dissolve solutes through induced dipole attractions.

E.g.: Dissolution of alkaloidal bases in non polar solvents such as benzene, mineral oil.

They have the poor capacity of solubilizing ionic and polar solutes due to following reasons:

1. Have low dielectric constant
2. Do not form hydrogen bonds
3. Do not break covalent bridges

1A.2.3 Semi Polar Solvents

These solvents induce polarity in non polar substances to certain extent.

E.g.: Propylene glycol increases solubility of water and peppermint oil.

These solvents act as intermediates to increase the solubility of polar and non polar substances.

1A.3 Ideal and Real Solutions

In ideal solutions, all the intermolecular forces such as solvent-solvent, solute-solvent and solute-solute are similar in strength. No heat is evolved or absorbed during the mixing process.

Total vapour pressure of binary system can be measured using equation,

$$P = p_A + p_B \quad \dots(1A.1)$$

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where P is total vapour pressure of system and p_A , p_B are the partial vapour pressures exerted by solute and the solvent.

Vapour pressure of solution is an important property that defines escaping tendency.

Raoult's law states that in an ideal solution, the partial vapour pressure of each volatile constituent is equal to the product of vapour pressure of pure constituent and its mole fraction in the solution.

$$p_A = p_A^\circ X_A \quad \dots(1A.2)$$

$$p_B = p_B^\circ X_B \quad \dots(1A.3)$$

where p_A , p_B are the partial vapour pressures of the constituents of solution, p_A° , p_B° are the vapour pressures of pure components and X_A , X_B are the mole fractions of the constituents.

In an ideal solution where two liquids are mixed together, the vapour pressure of one of the component gets reduced by another and it depends on the mole fraction of the constituents.

Vapour pressure - composition curve for binary system benzene and ethylene chloride is given in Fig. 1A.1 at 50 °C.

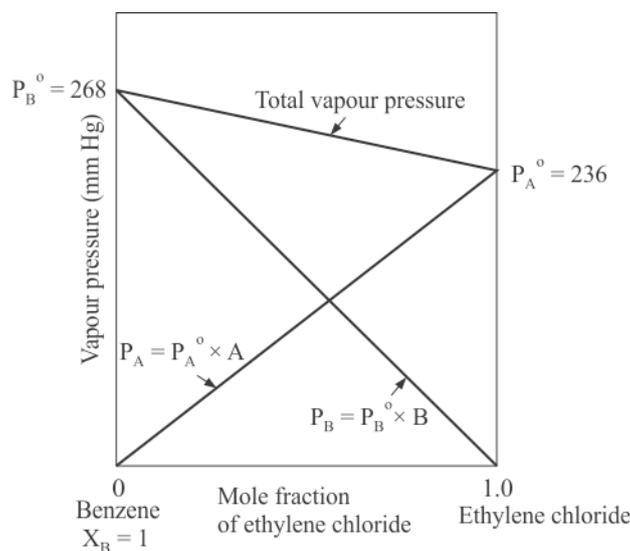


Fig. 1A.1 Vapour pressure composition for an ideal binary system.

Real or non-ideal solutions do not have equal forces of interaction between solute-solute, solute-solvent and solvent-solvent systems.

Heat is either evolved or absorbed when non-ideal solutions are mixed.

These solutions deviate from the Raoult's law. Partial vapour pressure exerted is given by expression

$$P = p^* a \quad \dots(1A.4)$$

where p^* is the partial pressure exerted by pure component and it refers to thermodynamic activity usually referred to as activity.

When adhesive attractions between molecules of different species are less than cohesive attractions then activities are greater than mole fractions and Raoult's law show positive deviation.

Examples are benzene and ethyl alcohol, chloroform and ethyl alcohol.

Vapour pressure of system showing positive deviation is given in Fig. 1A.2.

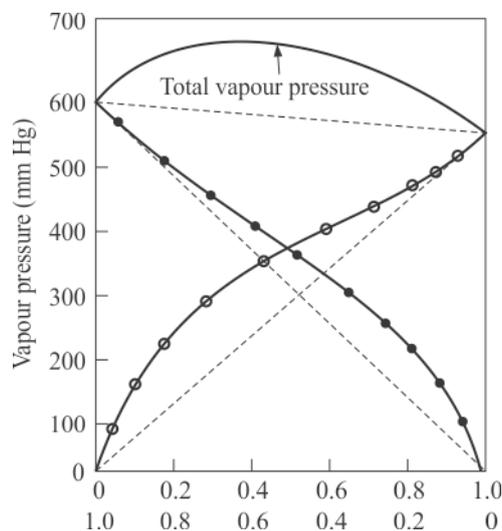


Fig. 1A.2 Vapour pressure of a system showing positive deviation from Raoult's law.

When adhesive forces between different species molecules exceed cohesive forces then Raoult's law shows negative deviation.

Example: Chloroform and acetone.

Vapour pressure of system showing negative deviation is given in Fig. 1A.3.

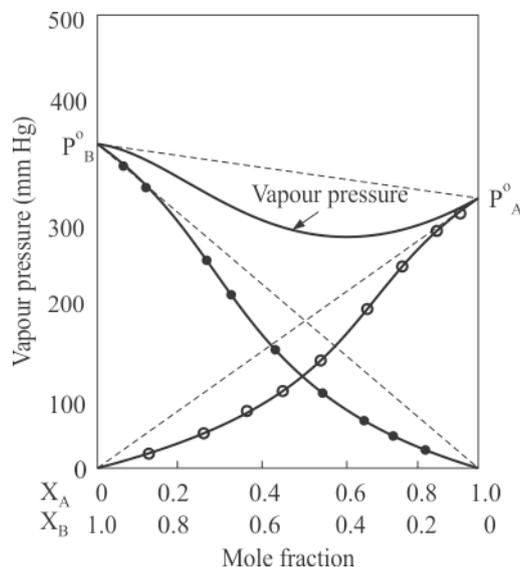


Fig. 1A.3 Vapour pressure of a system showing negative deviation from Raoult's law.

1A.4 Solubility of Gases in Liquids

Solubility of gas in liquid is defined as process of attaining equilibrium between the dissolved gas and the pure gas above the solution.

E.g.: Ammonia water, Hydrochloric acid.

1A.4.1 Factors Affecting Solubility of Gases in Liquids

The following are the factors which affect solubility of gases in liquids:

1. Pressure
2. Temperature
3. Presence of salts
4. Chemical reaction

Pressure

Effect of pressure on solubility of gas in liquids is expressed by Henry's law. This law states that in a very dilute solution at constant temperature the concentration of dissolved gas is proportional to partial pressure of gas above the solution at equilibrium. It is given by expression

$$C = \sigma P \quad \dots(1A.5)$$

where C refers to the concentration of dissolved gas in grams/litre of solvent, P is partial pressure in millilitres, σ is inverse of Henry's law constant, K or solubility coefficient.

Henry's law relays upon the fact that solubility of gas increases directly with pressure on the gas and may also decrease if pressure above solution is released.

Temperature

As temperature increases, ability of gas to expand also increases and this results in the reduction of solubility of gas in liquids. Hence precautions have to be taken while opening containers of gaseous solutions at elevated temperatures.

Presence of Salts

Gases get liberated upon introduction of either electrolytes or rarely non electrolytes. This is because their occurrence increases in attraction of salt ions or highly polar non electrolytes with liquids. This results in decrease of density of solvent molecules around gaseous molecules and gaseous molecules can easily escape out.

Chemical Reaction

Gases, such as ammonia, hydrogen chloride due to their chemical reaction with water show increase in solubility.

E.g.: Hydrogen chloride is more soluble in water than in oxygen.

Solubility of gases in liquids is expressed using Henry's law constant K, Bunsen absorption coefficient, α .

Henry's law constant K is given by

$$K = \frac{P}{X} \quad \dots(1A.6)$$

where P is pressure of gas in torrs or atmospheres and X is mole fraction of gas in solution.

$$K = \frac{P}{C \text{ or } M} \quad \dots(1A.7)$$

where M refers to molality or molarity and C refers to g/l of gas in solution.

1A.5 Solubility of Liquids in Liquids

Frequent mixing of two or more liquids occurs in formulation of many pharmaceutical preparations such as spirits, aromatic waters, elixirs etc. When two liquids are mixed together they exhibit either complete miscibility or partial miscibility.

Complete miscibility is expressed between similar solvents, i.e., in between polar and semi-polar solvents such as water and alcohol, glycerine and alcohol and in between non polar solvents such as benzene and carbon tetrachloride. Partial miscibility is expressed between compounds such as phenol and water, water and ether.

1A.5.1 Factors Affecting Solubility of Liquids in Liquids

The following are the factors affecting solubility of liquids in liquids:

1. Temperature
2. Presence of foreign substances
3. Three component system
4. Dielectric constant
5. Molecular connectivity
6. Molecular surface area

Temperature

Effect of temperature is more on the partially miscible liquids. Mutual solubilities of two conjugate phases may increase when temperature is either increased or decreased.

In case of phenol and water, mutual solubilities of two conjugate systems increases with temperature till a critical solution temperature or upper consolute temperature is attained.

In case of certain liquid pairs, miscibility increased when temperature is lowered and at lower consolute temperature exhibit maximum miscibility.

Mixtures such as nicotine and water exhibit both upper and lower consolute temperature, and ethyl ether and water exhibit neither upper or lower consolute temperature.

Presence of Foreign Substances

The addition of substance to binary system produces ternary system. Its effect on solubility depends on its solubility parameter.

If added substance is soluble in only one of the components of binary system, then the mutual solubility of liquid pair decreases. In this case upper consolute temperature is raised or lower consolute temperature is lowered.

E.g.: If 0.1M naphthalene is added to mixture of phenol and water upper consolute temperature is raised by 20 °C.

If added substance is soluble in both the components of binary system then mutual solubility of liquid pair increase. In this case upper consolute temperature is lowered or lower temperature is raised.

E.g.: Addition of sodium oleate to phenol-water system lowers upper consolute temperature.

This type of increasing mutual solubility is referred to as blending. If added substance is surfactant micellar solubilization phenomenon commences.

Three Component System

Phase equilibria that exist in three component system is usually complex. They are useful in several areas of pharmaceutical processing such as crystallization, salt form selection, etc. A triangular diagram showing solubility of peppermint oil in various proportions of water and polyethylene glycol is given in Fig. 1A.4.

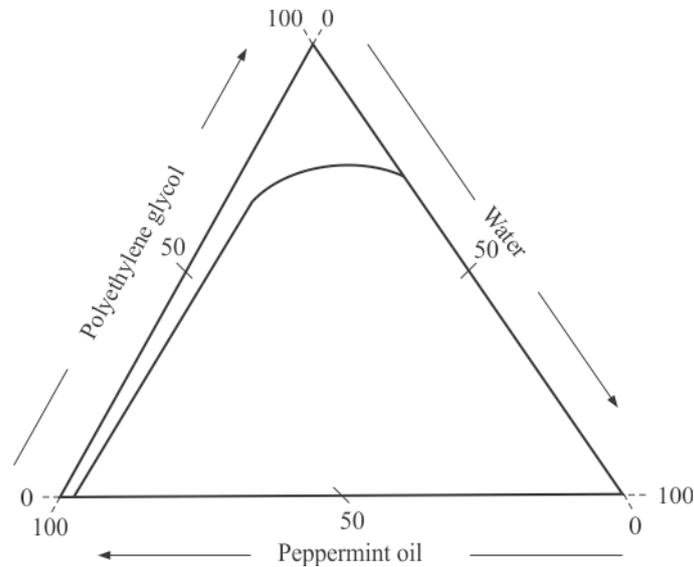


Fig. 1A.4 Triangular diagram showing solubility of peppermint oil in various proportions of water and polyethylene glycol.

Dielectric Constant

As dielectric constant shows considerable effect on the polarity, it is an important factor to be considered in solubility of liquids in liquids. A linear relationship exists when log mole fraction of solute methyl salicylate is plotted against dielectric constant of isopropanol-water mixtures as depicted in Fig. 1A.5.

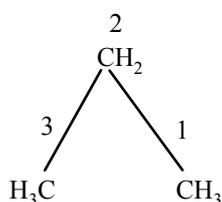
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Molecular Connectivity

Solubility depends on the structural features and functional groups of a particular component. Kier and Hall used molecular connectivity phenomenon to describe solubility. They used structural index χ (chi).

χ term obtained by summing bonds weighted by reciprocal square root number of each bond.

E.g.: Consider propane structure



C_1 connected to C_2 by single bond and

C_2 connected to C_3 and C_1 by 2 bonds.

Reciprocal square root valence = $(1.2)^{-1/2} = 0.707$

$$\chi = 0.707 + 0.707 = 1.414$$

Molal solubilities of alcohol, esters in water is correlated using regression analysis.

$$\ln S = -1.505 - 2.533 \chi \quad \dots(1A.8)$$

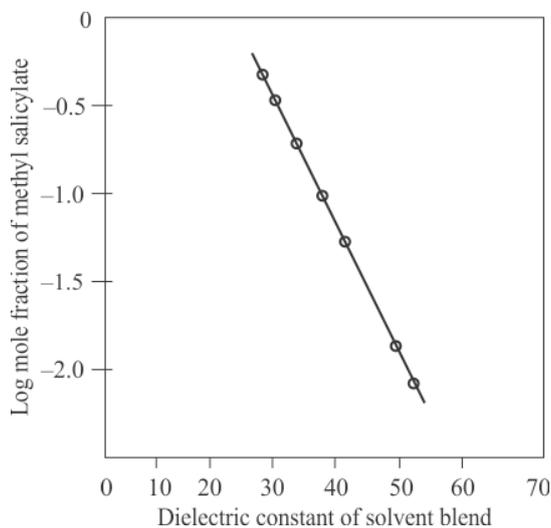


Fig. 1A.5 Solubility of methyl salicylate in isopropanol-water blends of differing dielectric constants.

Molecular Surface Area

Using regression analysis log (solubility) of solute is correlated to its total surface area (TSA)

$$\log (\text{solubility}) = 0.0168 (\text{TSA}) + 4.44 \quad \dots(1A.9)$$

Total surface area includes hydrocarbon (HYSA) and functional surface area (FGSA).

Hence above equation is modified as

$$\ln (\text{solubility}) = -0.0430 (\text{HYSA}) - 0.0586 (\text{FGSA}) + 8.003 I + 4.420 \dots(1A.10)$$

where I is indicator variable, HYSA is hydrocarbon surface area and FGSA is functional group surface area.

1A.6 Solubility of Solids in Liquids

Solutions of solids in liquids are most common type of systems in pharmaceutical practice.

1A.6.1 Solubility of Solids in Liquids Determination

A saturated solution is obtained either by stirring excess powdered solute with solvent for several hours at required temperature until equilibrium has been attained or by warming the solvent with excess of solute and allowing the mixture to cool to the required temperature. A sample of saturated solution is obtained for analysis by separating undissolved solid from solution. Filtration is usually used.

To determine solubility of solid in liquid, the solute and solvent must be pure, temperature must be adequately controlled, method of analysing must be reliable and method of separating a sample of saturated solution from undissolved solute must be satisfactory.

Solubility of solute/solid in a liquid for an ideal solution is given by

$$-\log S_2 = \frac{\Delta H_f}{2.303 R} \left(\frac{T_0 - T}{TT_0} \right) \quad \dots(1A.11)$$

where S refers to ideal solubility of solute, T_0 is melting point in absolute degrees, T is absolute temperature of solution, ΔH_f is heat of fusion, R is gas constant.

For non ideal solutions, the activity of solute in a solution is expressed as product of mole fraction and activity coefficient

$$a = S\gamma \quad \dots(1A.12)$$

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where γ is mole fraction scale known as rational activity coefficient.

By applying logarithm to eq. 1A.12

$$\log a = \log S + \log \gamma \quad \dots(1A.13)$$

For ideal solution $a =$ mole fraction, $\gamma = 1$

then

$$-\log a = -\log S = \frac{\Delta H_f}{2.303 RT} \left(\frac{T_0 - T}{T_0} \right) \quad \dots(1A.14)$$

Therefore by combining equations 1A.13, 1A.14, we get

$$-\log S = \frac{\Delta H_f}{2.303 R} \left(\frac{T_0 - T}{T_0 T} \right) + \log \gamma \quad \dots(1A.15)$$

$\log \gamma$ value refers to the amount of work carried out in removing the solute molecule and placing it in solvent. It involves three steps:

First step involves removal of molecule from solute phase at definite temperature. The gain in potential energy for process is W_{22} .

Second step involves creation of space in the solvent system for the solute molecule. Work required here is W_{11} .

Third step involves placing solute molecule in solvent system. Decrease in potential energy here is $-W_{12}$.

$$\text{Total work} = W_{22} + W_{11} - W_{12} \quad \dots(1A.16)$$

Logarithm of activity coefficient is given by

$$\ln \gamma = (W_{22} + W_{11} - 2W_{12}) \frac{V_2 \phi_1^2}{RT} \quad \dots(1A.17)$$

where V_2 is molar volume or volume per mole of liquid solute and ϕ_1 is volume fraction, R is gas constant, T is absolute temperature.

As Van der Waals force and follow geometric mean rule,

$$W_{12} = \sqrt{W_{11} W_{22}} \quad \dots(1A.18)$$

By substituting eqs. 1A.18 in 1A.17 it becomes

$$\ln \gamma = [W_{11} - 2(W_{11} W_{22})^{1/2} + W_{22}] \frac{V_2 \phi_1^2}{RT} \quad \dots(1A.19)$$

Above equation is modified as

$$\ln \gamma = [(W_{11})^{1/2} - (W_{22})^{1/2}]^2 \frac{V_2 \phi_1^2}{RT} \quad \dots(1A.20)$$

$(W)^{1/2}$ terms are solubility parameters and can be designed as δ .

Therefore equation (1A.20) becomes

$$\ln \gamma = [\delta_1 - \delta_2] \frac{V_2 \phi_1^2}{RT} \quad \dots(1A.21)$$

When equation (1A.21) is substituted in (1A.15) it is modified as

$$-\log S = \frac{\Delta H_f}{2.303 RT} \left(\frac{T_0 - T}{T_0} \right) + \frac{V_2 \phi_1^2}{2.303 RT} [\delta_1 - \delta_2]^2 \dots(1A.22)$$

Solubility parameter δ is given by the expression

$$\delta = \left(\frac{\Delta H_v - RT}{V_L} \right)^{1/2} \quad \dots(1A.23)$$

1A.6.2 Factors Affecting Solubility of Solids in Liquids

The following are the factors affecting solubility of solids in liquids:

1. Temperature
2. Nature of solvent, cosolvents
3. Molecular structure of solute
4. pH
5. Particle size of solid
6. Influence of surfactants
7. Effect of complexation

Temperature

Dissolution process is usually an endothermic process i.e., heat is absorbed when dissolution occurs. However there are exceptions where dissolution process is exothermic.

When solubility is plotted against temperature we obtain solubility curves.

Solubility curve is given in Fig. 1A.6

Sodium sulphate exists as decahydrate up to 32.5 °C and dissolution is endothermic.

After 32.5 °C the process is exothermic as it becomes anhydrous.

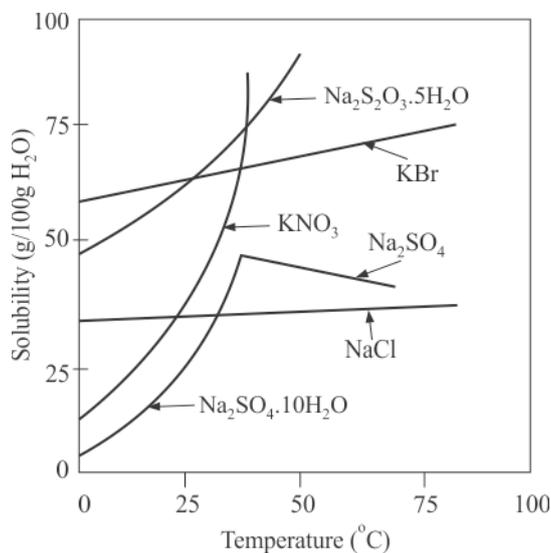


Fig. 1A.6 Influence of temperature on solubility of various salts.

Nature of Solvent, Cosolvents

The importance of statement “Like dissolves Like” applies here. For example polar solvents dissolve polar solutes. In pharmaceutical practice cosolvents such as ethanol or propylene glycol which are miscible with water are used to dissolve solutes in excess of their solubilities.

Molecular Structure of Solute

Even a small change in the molecular structure of compound shows remarkable effect in the solubility.

For example introduction of hydrophilic hydroxyl group can produce a large improvement in water solubility.

pH

Solubility of ionised solutes and pH is extremely important with regard to ionization of weakly acidic and basic drugs as they pass through gastrointestinal track. pH effects degree of ionisation of drug molecule which in turn influences solubility.

Relationship between pH, pKa and solubility is given by Henderson-Hasselbalch equation.

For weakly acidic drug, equation is

$$\text{pH} = \text{pKa} + \log \frac{[\text{Salt}]}{[\text{Acid}]} \quad \dots(1A.24)$$

For weakly basic drug,

$$\text{pH} = \text{pKw} - \text{pKb} + \log \frac{[\text{Base}]}{[\text{Salt}]} \quad \dots(1A.25)$$

Particle Size of Solid

Solubility increases with a decrease in particle size. But too small size causes decrease in solubility.

Changes in interfacial free energy that accompany the dissolution of particles of varying size causes the solubility of a substance to increase with decreasing particle size.

This is indicated by following equation

$$\log \frac{S}{S_0} = \frac{2 \gamma M}{2.303 RT Pr} \quad \dots(1A.26)$$

Influence of Surfactants

Weakly acidic drugs and basic drugs are made solubilised by use of surface active agents. Total solubility of acidic drug is expressed as sum of concentration of species in solution

$$D_T = (D) + (D^-) + [D] + [D^-] \quad \dots(1A.27)$$

where (D), (D⁻) are non ionized and ionized acid, respectively not in the micelles and [D], [D⁻] are non ionized and ionized acid respectively in the micelles.

Partition is express as

For non ionized acid $k^1 = \frac{[D]_0}{(D)_0} \quad \dots(1A.28)$

For ionized acid $k^{11} = \frac{[D^-]_0}{(D^-)_0} \quad \dots(1A.29)$

In terms of total volume, eq. (1A.28), (1A.29) become

$$k^1 = \frac{[D] [1 - (M)]}{(D) (M)} \frac{n!}{r!(n-r)!} \quad \dots(1A.30)$$

$$k^{11} = \frac{[D^-][1-(M)]}{(D^-)(M)} \quad \dots(1A.31)$$

The concentration term, (M) is the volume fraction of surfactant as micelles in solution, amount in true solution is small. Hence (1 - M) is neglected.

Then eq. (1A.30), (1A.31) become

$$[D] = k^1 (D) (M) \quad \dots(1A.32)$$

$$[D^-] = k^{11} (D^-) (M) \quad \dots(1A.33)$$

Total drug solubility, D_T^* in a solution at definite pH in absence of surfactant is given by

$$D_T^* = (D) + (D^-) \quad \dots(1A.34)$$

For ionized drug is aqueous phase

$$\frac{(D)}{D_T^*} = \frac{(H^+)}{ka + (H^+)} \quad \dots(1A.35)$$

or
$$D_T^* = (D) \frac{ka + (H^+)}{(H^+)} \quad \dots(1A.36)$$

$$\frac{D_T}{D_T^*} = 1 + (M) \left[\frac{(H^+) k^1 + ka k^{11}}{ka + (H^+)} \right] \quad \dots(1A.37)$$

Complexation

When several drugs together with additives interact in solution to form insoluble complexes, apparent solubility of the solute may be increased or decreased due to complex formed.

1A.7 Solubility of Strong Electrolytes

Dissolution process can be exothermic or endothermic process. According to Le Chatelier principle, system tends to adjust in a manner so as to counteract a stress such as increase or decrease in temperature.

Sodium sulphate solubility varies with temperature which is explained in Fig. 1A.6.

Solubility can be explained by means of heat of solution, ΔH . ΔH is known as partial or differential heat of solution which is heat absorbed per mole when a small quantity of solute is added to large quantity of solution. Total or Integral heat of solution is heat absorbed when one mole of solute is dissolved in enough solvent to produce solution of specified concentration.

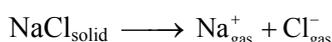
Heat of solution of crystalline substance is the sum of heat of sublimation of solid and heat of hydration of ions in solution

$$\Delta H (\text{solution}) = \Delta H_{\text{subl}} + \Delta H_{\text{hyd}} \quad \dots(1A.38)$$

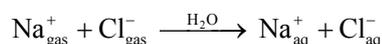
where ΔH_{sub} – Heat of sublimation

ΔH_{hyd} – Heat of hydration

Heat of sublimation is the energy required to separate one mole of crystal into its ions in gaseous state or to vapourise solid.



Heat of hydration is the heat liberated when gaseous ions are hydrated.

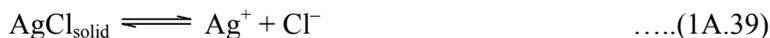


In ideal solution $\Delta H_{\text{hyd}} = 0$ as heat absorbed is only that required to transform crystals to liquid state.

1A.8 Solubility of Slightly Soluble Electrolytes

Solubility product k_{sp} is used to describe the process of dissolution of slightly soluble electrolytes to form saturated solutions.

Example for slightly soluble electrolyte is silver chloride when excess solid in equilibrium with ions in saturated solution at specific temperature is represented as



Equilibrium expression for it is,

$$k = \frac{[\text{Ag}^{+}][\text{Cl}^{-}]}{[\text{AgCl}_{\text{solid}}]} \quad \dots(1A.40)$$

As concentration of solid phase is constant

$$k_{\text{sp}} = [\text{Ag}^{+}][\text{Cl}^{-}] \quad \dots(1A.41)$$

If an ion in common either Ag^{+} or Cl^{-} is added then equilibrium is altered.

For example addition of sodium chloride increases chloride ion concentration and

$$[\text{Ag}^{+}][\text{Cl}^{-}] > k_{\text{sp}}$$

Some of AgCl precipitates until equilibrium is attained. Hence addition of common ion reduces the solubility of slightly soluble electrolytes.

Salts having no ion in common with slightly soluble electrolyte if added at modulate concentration causes increase in the solubility because of reduction of activity coefficient.

$$k_{sp} = a_{Ag^+} + a_{Cl^-} \quad \dots(1A.42)$$

Because activities can be replaced by product of concentration and activity coefficients,

$$k_{sp} = [Ag^+] [Cl^-] \gamma_{Ag^+} + \gamma_{Cl^-} = [Ag^+] [Cl^-] \gamma_{\pm}^2$$

$$\frac{k_{sp}}{\gamma_{\pm}^2} = [Ag^+] [Cl^-]$$

and

$$\text{solubility} = [Ag^+] = [Cl^-] = \frac{\sqrt{k_{sp}}}{\gamma_{\pm}} \quad \dots(1A.43)$$

1A.9 Solubility of Weak Electrolytes

Most of the drugs are either weakly acidic or weakly basic, which react with strong acids and bases at definite pH range and exists as ions that are ordinarily soluble in water.

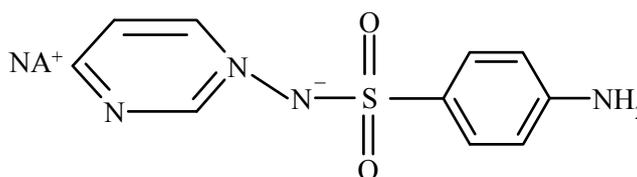
Example is carboxylic acids containing more than five carbons react with dilute carbonates and bicarbonates form soluble salts.

Hydroxy acids such as tartaric acid are soluble in water because they are solvated through hydroxyl groups.

Salicylic acid is soluble in alcohol and alkalies. This is because OH group is involved in intermolecular hydrogen bond.

Many compounds containing basic nitrogen atom in the molecule such as sulphonamides are important in pharmacy. These exist as salts.

E.g.: Sulfadiazine sodium



Oxygen of sulfonyl group withdraw electrons from sulphur atom which results in electrons of N : H bond being held more close to nitrogen atom. Hydrogen is less firmly held and can be easily removed.

Solubility of weak electrolytes is greatly influenced by pH.

Consider acid form of drug, HP with soluble ionised form P⁻.

Equilibria in saturated solution can be expressed as



Equilibrium constant for solution equilibrium is

$$S_0 = [\text{HP}]_{\text{sol}} \quad \dots(1A.46)$$

Constant for acid-base equilibrium is

$$k_a = \frac{[\text{H}_3\text{O}^+][\text{P}^-]}{[\text{HP}]} \quad \dots(1A.47)$$

$$[\text{P}^-] = \frac{k_a [\text{HP}]}{[\text{H}_3\text{O}^+]} \quad \dots(1A.48)$$

Total solubility constitutes both concentration of undissociated and ionised form

$$S = [\text{HP}] + [\text{P}^-] \quad \dots(1A.49)$$

Substituting S_0 from eq. (1A.46) and $[\text{P}^-]$ from eq. (1A.48), the eq. (1A.49) becomes

$$S = S_0 + k_a \frac{S_0}{[\text{H}_3\text{O}^+]} \quad \dots(1A.50)$$

$$S = S_0 \left(1 + \frac{k_a}{[\text{H}_3\text{O}^+]} \right) \quad \dots(1A.51)$$

This equation can be modified as

$$(S - S_0) = k_a \frac{S_0}{[\text{H}_3\text{O}^+]} \quad \dots(1A.52)$$

By applying logarithm to eq. (52), it becomes

$$\text{Log}(S - S_0) = \text{log } k_a + \text{log } S_0 - \text{log } [\text{H}_3\text{O}^+] \quad \dots(1A.53)$$

and finally

$$\text{pHp} = \text{pKa} + \text{log} \frac{S - S_0}{S_0}$$

where pHp is pH below which drug separates from solution as undissociated acid.