UNIT 1
SOLUBILITY OF DRUGS

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.

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:

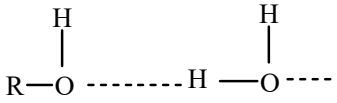
1. Polar solvents
2. Non polar solvents
3. Semi polar solvents

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,

$$P = p_A + p_B \qquad \text{.....(1A.1)}$$

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.

$$p_A = p_A^o X_A \quad \text{.....(1A.2)}$$

$$p_B = p_B^o X_B \quad \text{.....(1A.3)}$$

where p_A, p_B are the partial vapour pressures of the constituents of solution, p_A^o, p_B^o 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.

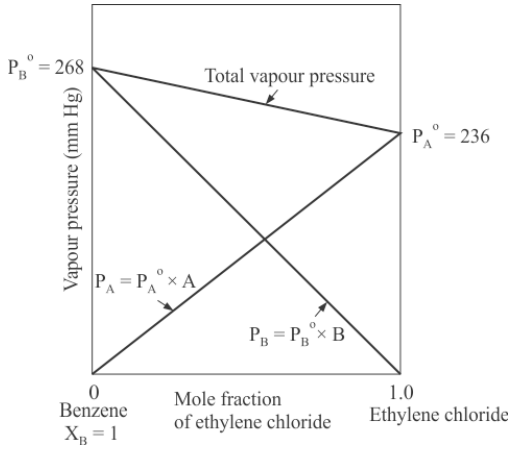


Fig. 1A.1 Vapour pressure composition for an ideal binary system.

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

$$P = p^* a \quad \text{.....(1A.4)}$$

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.

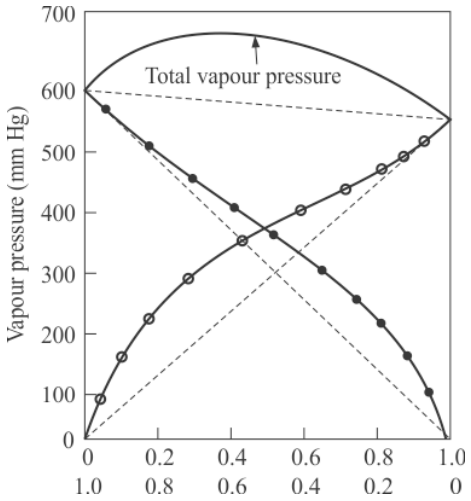


Fig. 1A.2 Vapour pressure of a system showing positive deviation from Raoult's law.

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.

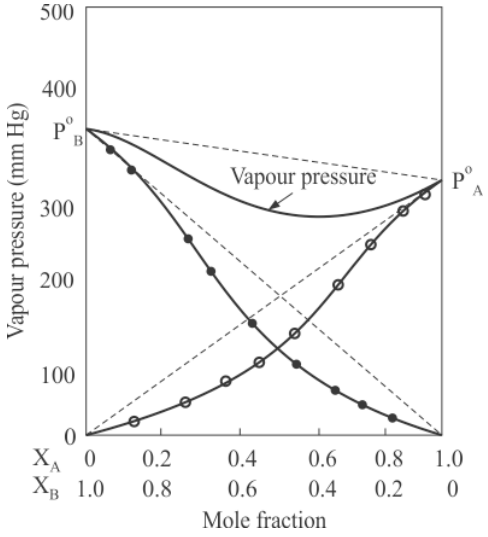


Fig. 1A.3 Vapour pressure of a system showing negative deviation from Raoult's law.

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

$$C = \sigma P \qquad \text{.....(1A.5)}$$

where C refers to the concentration of dissolved gas in grams/litre of solvent, P is partial pressure is 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

$$K = \frac{P}{X} \qquad \text{.....(1A.6)}$$

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

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

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 ^{o}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.

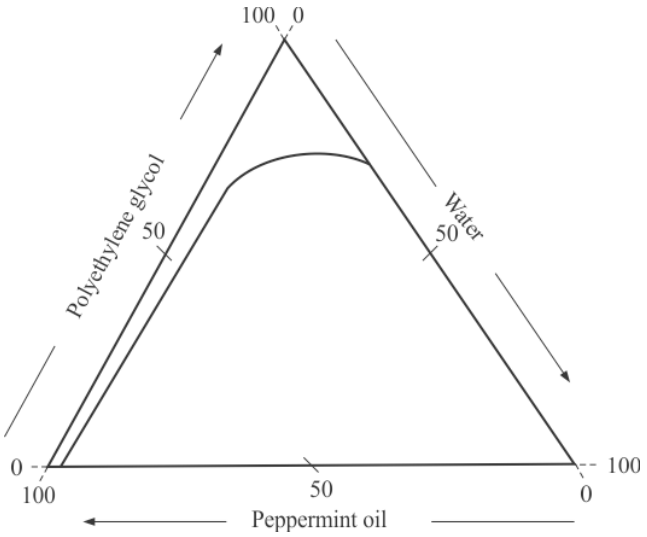


Fig. 1A.4 Triangular diagram showing solubility of peppermint oil in various proportions of water and polyethylene glycol.

Dielectric Constant

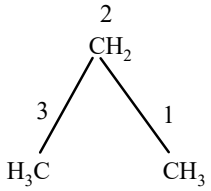
As dielectric constant shows considerable effect on the polarity it is an important factor to be considered in solubility of liquids in liquids. A linear relationship exists when log mole fraction of solute methyl salicylate is plotted against dielectric constant of isopropanol-water mixtures as depicted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

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.

$$\ln S = -1.505 - 2.533\,\chi \qquad \text{.....(1A.8)}$$

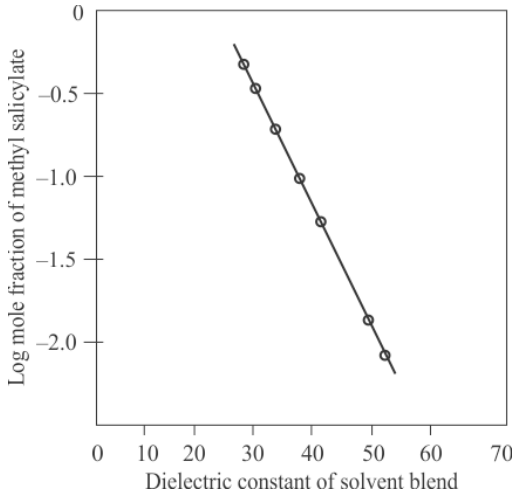


Fig. 1A.5 Solubility of methyl salicylate in isopropanol-water blends of differing dielectric constants.

Molecular Surface Area

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

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

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

Hence above equation is modified as

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

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

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

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

$$a = S\gamma \qquad \text{.....(1A.12)}$$

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

By applying logarithm to eq. 1A.12

$$\log a = \log S + \log \gamma \qquad \text{.....(1A.13)}$$

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

then

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

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

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

log γ 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 $-W_{12}$.

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

Logarithm of activity coefficient is given by

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

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 Walls force and follow geometric mean rule,

$$W_{12} = \sqrt{W_{11}\,W_{12}} \qquad \text{.....(1A.18)}$$

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

$$ln\ \gamma = [W_{11} - 2(W_{11}\ W_{12})^{1/2} + W_{22}]\ \frac{V_2\ \phi_1^2}{RT} \quad .....(1A.19)$$

Above equation is modified as

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

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

Therefore equation (1A.20) becomes

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

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

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

Solubility parameter δ is given by the expression

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

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 they 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 ºC and dissolution is endothermic.

After 32.5 ºC the process is exothermic as it becomes anhydrous.

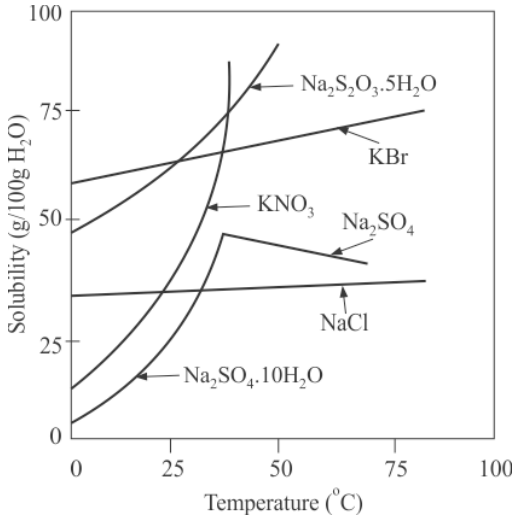


Fig. 1A.6 Influence of temperature on solubility of various salts.

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

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

For weakly basic drug,

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

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

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

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

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

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 $k^1 = \frac{[D]_0}{(D)_0}$ .....(1A.28)

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

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

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

$$k^{11} = \frac{[D^-]\,[1-(M)]}{(D^-)\,(M)}$$ .....(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

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

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

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

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

For ionized drug is aqueous phase

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

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

$$\frac{D_T}{D_T^*} = 1 + (M)\left[\frac{(H^+)\,k^1 + ka\,k^{11}}{ka + (H^+)}\right]$$ …..(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

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

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.

$$NaCl_{solid} \longrightarrow Na^{+}_{gas} + Cl^{-}_{gas}$$

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

$$Na^{+}_{gas} + Cl^{-}_{gas} \xrightarrow{H_2O} Na^{+}_{aq} + Cl^{-}_{aq}$$

In ideal solution $\Delta H_{hyd} = 0$ 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

$$AgCl_{solid} \rightleftharpoons Ag^{+} + Cl^{-} \quad \text{.....(1A.39)}$$

Equilibrium expression for it is,

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

As concentration of solid phase is constant

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

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

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

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.

$$k_{sp} = a_{Ag^+} + a_{Cl} \qquad \text{.....(1A.42)}$$

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

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

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

and

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

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.

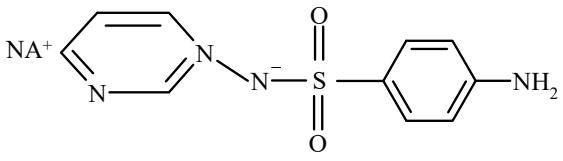
Example is carboxylic acids containing more than five carbons react with dilute carbonates and bicarbonates form soluble salts.

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

$$HP_{solid} \rightleftharpoons HP_{sol} \qquad \text{.....(1A.44)}$$

$$HP_{sol} + H_2O \rightleftharpoons H_3O^+ + P^- \qquad \text{.....(1A.45)}$$

Equilibrium constant for solution equilibrium is

$$S_o = [HP]_{sol} \qquad \text{.....(1A.46)}$$

Constant for acid-base equilibrium is

$$ka = \frac{[H_3O^+][P^-]}{[HP]} \qquad \text{.....(1A.47)}$$

$$[P^-] = \frac{ka\,[HP]}{[H_3O^+]} \qquad \text{.....(1A.48)}$$

Total solubility constitutes both concentration of undissociated and ionised form

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

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

$$S = S_o + ka\frac{S_0}{[H_3O^+]} \qquad \text{.....(1A.50)}$$

$$S = S_0\left(1 + \frac{ka}{[H_3O^+]}\right) \qquad \text{.....(1A.51)}$$

This equation can be modified as

$$(S - S_0) = ka\frac{S_0}{[H_3O^+]} \qquad \text{.....(1A.52)}$$

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

$$\text{Log } (S - S_0) = \log ka + \log S_0 - \log [H_3O^+] \qquad \text{.....(1A.53)}$$

and finally

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

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

1B DISTRIBUTION PHENOMENA

1B.1 Introduction

Distribution is a reversible process. In general distribution is mainly seen in biological fluids. In this case the rate of exchange between plasma and tissue vary widely depending on the type of tissue and drug partition characteristics. When distribution is rapid, the body behaves kinetically as a single homogeneous pool and the plasma concentration time course may be adequately described by a single exponential. On the other hand the kinetics of drug disposition often exhibit multi exponential characteristics. Each additional exponential has been interpreted to represent a group of tissues requiring progressively more time in which to achieve a steady state in drug distribution.

1B.2 Partition Coefficient

If a substance which is soluble in both components of a mixture of immiscible liquids is dissolved in such a mixture, then equilibrium is attained at constant temperature it is found that the solute is distributed between the two liquids in such a way that the ratio of the activities of the substance in each liquid is a constant. This is known as the 'Nernst distribution law", which can be expressed by equation

$$\frac{a_A}{a_B} = \text{constant} \qquad \text{.....(1B.1)}$$

where a_A and a_B are the activities of the solute in the solvent A and B respectively; when the solution is dilute and when the solute behave ideally, the activities may be replaced by concentration (C_A and C_B)

$$\frac{C_A}{C_B} = k \qquad \text{.....(1B.2)}$$

where the constant k is known as "distribution coefficient or partition coefficient".

In case of sparingly soluble substance, k is approximately equal to the ratio of the solubilities (S_A and S_B) of the solute in each liquid i.e.,

$$\frac{S_A}{S_B} = k \qquad \text{.....(1B.3)}$$

In most other systems, however, deviation from ideal behaviour invalidates eq. 1B.3. For example, if the solute exists as monomers in solvent A and as dimer in solvent B, the distribution coefficient is given by eq. 1B.4, in which the square root of the concentration of the dimeric form is used.

$$k = \frac{C_A}{\sqrt{C_B}} \qquad \text{.....(1B.4)}$$

If the dissociation into ions occurs in the aqueous layer, B of a mixture of immiscible liquid, then the degree of dissociation (α) should be taken into account, as indicated by eq. 1B.5.

$$k = \frac{C_A}{C_B(1-\alpha)} \qquad \text{.....(1B.5)}$$

The solvents in which the concentration of the solute is expressed should be indicated when partition coefficient are quoted. For example, a partition coefficient of 2 for a solute distributed between oil and water may also be expressed as a partition coefficient between water and oil at 0.5. This can be represented as

$$k_{water}^{oil} = 2 \text{ and } k_{oil}^{water} = 0.5.$$

The abbreviation k_w^0 is often used for the former.

1B.2.1 Effect of Partition of Ionic Dissociation and Molecular Association

The solute can exist partly or wholly as associated molecules in one of the phases or it may dissociate into ion in either of the liquid phases. The distribution law applies only to the concentration of the species common to both phases, namely, the monomer as simple molecule of the solute.

Consider the distribution of benzoic acid between an oil phase and a water phase. When it is neither associated in the oil nor dissociated into ion in the water. When association and dissociation occurs, however, the situation becomes more complicated. In general case where benzoic acid associated in the oil phase and dissociates in the aqueous phase in shown in Fig. 1B.1.

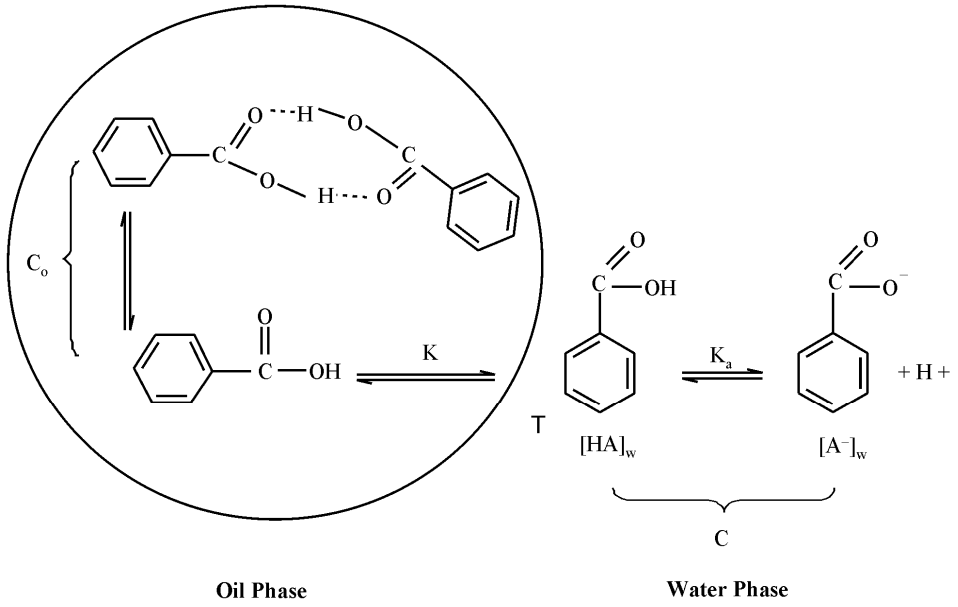


Fig. 1B.1 Schematic representation of distribution of benzoic acid between a water and an oil phase is depicted as a magnified oil droplet in an oil-in water emulsion.

Two cases will be treated. First according to Garrett and Woods benzoic acid is considered to be distributed between the two phases, peanut oil and water. Although benzoic acid undergoes dimerization in many non polar solvents, it does not associate in peanut oil. It ionizes in water to a degree, however, depending on the pH of the solution. Therefore in Fig. 1B.1 for the case under consideration, C_0 the total concentration of benzoic acid in the oil phase is equal to $[HA]_0$, the monomer concentration in the oil phase, because association does not occur in peanut oil.

The species common to both the oil and water phase are the un-associated and un- dissociated benzoic acid molecules. The distribution is expressed as

$$k = \frac{[HA]_0}{[HA]_w} = \frac{C_0}{[HA]_w} \qquad \text{.....(1B.6)}$$

where k is the true distribution coefficient, $[HA]_0 = C_0$ is the molar concentration of the simple benzoic acid molecules in the oil phase and $[HA]_w$ is the molar concentration of the un-dissociated acid in the water phase.

The total acid concentration obtained by analysis of the aqueous phase is

$$C_w = [HA]_w + [A^-]_w \qquad \text{.....(1B.7)}$$

and the experimentally observed or apparent distribution coefficient is

$$k^1 = \frac{[HA]_0}{[HA]_w + [A^-]_w} = \frac{C_0}{C_w} \quad \text{.....(1B.8)}$$

As seen in Fig. 1B.1, the observed distribution coefficient depends on two equilibria; the distribution of the un-dissociated acid between the immiscible phase as expressed in eq. (1B.6) and the species distribution of the acid in the aqueous phase, which depends on the hydrogen ion concentration $[H_3O^+]$ and the dissociation constant k_a of the acid, where

$$k_a = \frac{[H_3O^+]\,[A^-]_w}{[HA]_w} \quad \text{.....(1B.9)}$$

Association of benzoic acid in peanut oil does not occur and k_d (the equilibrium constant for dissociation of associated benzoic acid into monomer in the oil phase) can be neglected in this case.

Given these equations and the fact the concentration of the acid in the aqueous phase before distribution, assuming equal volumes of the two phases,

$$C = C_0 + C_w \quad \text{.....(1B.10)}$$

One arrives at the combine result

$$\frac{k_a + [H_3O^+]}{C_w} = \frac{k_a}{C} = \frac{k+1}{C}\,[H_3O^+] \quad \text{.....(1B.11)}$$

Eq. 1B.11 is a linear equation of the form y = a + bx, and therefore a plot of $[k_a + [H_3O^+]]/C_w$ against $[H_3O^+]$ yields a straight line with a slope b = (k + 1)/C and an intercept a = k_a/C. The true distribution coefficient k can thus be obtained over the range of hydrogen ion concentration considered. Alternatively, the true distribution constant could be obtained according to eq. (1B.6) by analysis of the oil phase and of the water phase, at a sufficiently low pH (2) at which the acid would exist completely in the unionized form. One of the advantage of eq. (1B.11), however is the oil phase need be analyzed; only the hydrogen ion concentration and C_w; the total concentration remaining in the aqueous phase at equilibrium need be determined.

Second, let us consider the cane in which the solute is associated in the organic phase and exists as simple molecules in the aqueous phase. If benzoic acid is distributed between benzene and acidified water, it exists mainly as associated molecules in the benzene layer and as un-dissociated molecules in the aqueous layer.

The equilibrium between simple molecules HA and associated molecules $[HA]_n$ in bezene is

$$(HA)_n \rightleftharpoons n\,(HA)$$

Associated molecules Simple molecules

and the equilibrium constant expressing the dissociation of associated molecules into simple molecules in this solvent is

$$k_d = \frac{[HA]_0^n}{[(HA)_n]} \qquad \text{.....(1B.12)}$$

or

$$[HA]_0 = \sqrt[n]{k_d}\ \sqrt[n]{[(HA)_n]} \qquad \text{.....(1B.13)}$$

Because benzoic acid exists predominantly in the form of double molecules in benzene, C_0 can replace $[(HA)_n]$, where C_0 is the total molar concentration of the solute in the organic layer. The eq. (1B.13) can be written approximately as

$$[HA]_0 \cong \text{constant} \times \sqrt{C_0} \qquad \text{.....(1B.14)}$$

In conformity with distribution law as given in eq. (1B.6), the true distribution coefficient is always expressed in terms of simple species common to both phases, i.e., in terms of $[HA]_n$ and $[HA]_0$. In the benzene-water system, $[HA]_0$ is given by eq. (1B.14) and the modified distribution constant becomes

$$k^{11} = \frac{[HA]_0}{[HA]_w} = \frac{\sqrt{C_0}}{[HA]_w} \qquad \text{.....(1B.15)}$$

1B.2.2 Extraction

To determine the efficiency with which one solvent can extract a compound from a second solvent – an operation commonly employed in analytic chemistry and in organic chemistry – we follow glass tone. Suppose that w gram of a solute is extracted repeatedly from v_1 ml of the one solvent with successive partition of v_2 ml of second solvent, which is immiscible with first.

Let w_1 be the weight of the solute remaining in the original solvent after extracting with the first portion of the other solvent. Then the concentration of solute remaining in the first solvent is (w_1/v_1) g/ml and the concentration of the solute in the extracting solvent is $(w_2 - w_1)$ g/ml. The distribution coefficient is thus.

$$k = \frac{\text{Concentration of solute in original solvent}}{\text{Concentration of solute in extracting solvent}}$$

$$k = \frac{w_1/v_1}{(w_1 - w_2)/v_2} \qquad \text{.....(1B.16)}$$

Or $$w_1 = w \frac{kv_1}{kv_1 + v_2} \quad \text{.....(1B.17)}$$

The process can be repeated and after n extraction

$$w_n = w \left[\frac{kv_1}{kv_1 + v_2} \right]^n \quad \text{.....(1B.18)}$$

By use of this equation, it can be shown that most efficient extraction results when n is large and v_2 is small, in other words, when a large number of extractions are carried out with small portions of extracting liquid.

1B.3 Solubility and Partition Coefficients

Hansch observed a relationship between aqueous solubilities of non electrolytes and partitioning. Yalkowsky and Valvani obtained an equation for determining the aqueous solubility of liquid or crystalline organic compound.

$$\log s = -\log k - 1.11 \frac{\Delta sf\,(mp - 25)}{13\,64} + 0.54 \quad \text{.....(1B.19)}$$

where s is aqueous solubility in moles (lit), k is the octanol water partition coefficient, Δsf is the molar entropy of fusion and mp is the melting point of the solid compound on the centigrade scale. For a liquid compound, mp is assigned a value of 25, so that the second right hand term of eq. (1B.19) becomes zero.

The entropy of fusion and the partition coefficient can be estimated from the chemical structure of the compound. For rigid molecules, $\Delta sf = 13.5$ entropy exists, for molecules with n greater than five non hydrogen atoms in a flexible chain.

$$\Delta sf = 13.5 + 2.5\,(n - 5) \quad \text{.....(1B.20)}$$

Leo *et al.,* provided partition coefficient for a large number of compounds. When experimental values are not available, group contribution methods are available for estimating partition coefficient.

1B.3.1 Preservative Action of Weak Acids in Oil-Water Systems

Solution of foods, drugs and cosmetics are subject to deterioration by the enzymes of micro organisms that act as catalyst in decomposition reaction. These enzymes are produced by yeast, moulds and bacteria and such micro organisms must be destroyed or inhibited to prevent deterioration. Sterilization and the addition of preservatives (chemicals) are common methods used in pharmacy to preserve drug solutions against attack by various micro organisms. Benzoic acid in the form of its soluble salt, sodium benzoate is often used for this purpose because it produces no injurious effect in humans when taken internally in small quantities.

Rahn and Conn showed that the preservative or bacteriostatic action of benzoic acid and similar acids is due almost entirely to the un-dissociated acid and not to the ionic form. These investigators found that the yeast *Saccharomyces ellipsoideus*, which grows normally at a pH of 2.5 to 7.0 in the presence of strong inorganic acids or salts, ceased to grow in the presence of un-dissociated benzoic acid when the concentration of the acid reached 25 mg/100 ml. The preservative action of un-dissociated benzoic acid as compared with the ineffectiveness of the benzoic ion is presumably due to the relative ease with which the unionized molecule penetrated living membrane and conversely, the difficulties with which the ion does so. The undissociated molecule, consisting of a large nonpolar portion is soluble in the lipoidal membrane of the micro organism and penetrates rapidly.

Bacteria in oil-water system are generally located in the aqueous phase and at the oil-water interface. Therefore, the efficacy of a weak acid, such as benzoic acid, as a preservative for these systems is largely a result of the concentration of the undissociated acid in the aqueous phase.

To calculate the total concentration of benzoic acid that must be added to preserve an oil-water mixture, we proceed as follows.

Let us take the peanut oil-water mixture considered by Garrett and woods and begin by writing the expression.

$$C = g\,C_0 + C_w = g\,[HA]_0 + [HA]_w + [A^-]_w \qquad \text{.....(1B.21)}$$

where $g = v_0/v_w$, the volume ratio of the two phases is needed when the volumes are not equal, C is the original concentration of the acid in the water phase before the aqueous solution is equilibrated with peanut oil, C_0 is the molar concentration of the simple dissociated molecules in the oil, because the acid does not dimerize or dissociate in the organic phase, and C_w the molar concentration of benzoic acid in water is equal to the sum of the two terms $[HA]_w$ and $[A^-]_w$ in this ionizing solvent. It is further assumed that concentrations are approximately equal to activities.

The distribution of total benzoic acid among the various species in this system depends upon the distribution coefficient, k, the dissociation constant, ka, of the acid in the aqueous phase, the phase valence ratio and the hydrogen ion concentration of aqueous phase. To account for the first effect, we introduce the term $k = [HA]_0/[HA]_w$ or $[HA]_0 = k[HA]_w$ into eq. (1B.21). We write the dissociation constant $ka = [H_3O^+]\,[A^-]_w/[HA]_w$ or the ionic species, $[A^-]_w = ka\,[HA]_w / [H_3O^+]$ to account for the influence of ka and $[H_3O^+]$ and substitute it also into eq. (1B.21). The expression then become

$$C = kg\,[HA]_w + [HA]_w + ka[HA]_w / [H_3O^+] \qquad \text{.....(1B.22)}$$

Factoring out $[HA]_w$, we have

$$C = \left(\frac{kg + 1 + ka}{\left[H_3O^+ \right]} \right) (HA)_w \qquad \text{.....(1B.23)}$$

or

$$(HA)_w = \frac{C}{\frac{kg + 1 + ka}{\left[H_3O^+ \right]}} \qquad \text{.....(1B.24)}$$

Eq. (1B.23) and (1B.24) can be used to calculate the concentration C of total acid that must be added to the entire two phase system. To obtain a final specified concentration $[HA]_w$ of undissociated acid in the aqueous phase buffered at a definite pH or hydrogen ion concentration.

Kazmi and Mitchell and Bean *et al.,* proposed calculations for presenting solubilized and emulsified system that are slightly different from the Garrett and Woods.

In case where benzoic acid exists as a dimer in the oil phase, the modified distribution coefficient is $k'' = (1/[HA]_w)$ and there from eq. (1B.21) becomes

$$C = k''^2 g [HA]_w^2 + [HA]_w + ka[HA]_w / [H_3O^+] \qquad \text{.....(1B.25)}$$

and finally

$$C = k''^2 g[HA]_w + 1 + \left(\frac{ka}{[H_3O]} \right) [HA]_w \qquad \text{.....(1B.26)}$$

1B.4 Drug Action and Partition Coefficients

More than 100 years ago Meyer and Overton prepared the hypothesis that the narcotic action of a non-specific drug is a function of the distribution coefficient of the compound between a lipoidal medium and water. Later it was concluded that narcosis was a function only of the concentration of the drug in the lipids of the cell. Thus, a wide variety of drugs of different chemical types should produce equal narcotic action at equal concentration in the lipoidal cell substance. Actually, as will be seen shortly, this is a restatement of the theory, first proposed by Ferguson and generally accepted today. The equal degrees of narcotic action should occur at equal thermodynamic activities of the drugs in solution.

The activity of a vapour is obtained approximately by the use of the equation.

$$\frac{p_{nar}}{p^0} = a_{nar} \qquad \text{.....(1B.27)}$$

If p_{nar} is the partial pressure of a narcotic in solution just necessary to bring about narcosis and p^0 is the vapour pressure of the pure liquid, narcosis will occur at a thermodynamic activity of α_{nar}.

1C FICK'S LAWS OF DIFFUSION

1C.1 Introduction

Diffusion is defined as a process of mass transfer of individual molecules of a substance brought about by random molecular motion and associated with a driving force such as a concentration gradient. The mass transfer of solvent or solute forms the basis for many important phenomena in the pharmaceutical sciences. For example, diffusion of a drug across a biological membrane is required for a drug to be absorbed into and eliminated from the body and even for it to get to the site of action within a particular cell on the negative side. The shelf life of a drug product could be significantly reduced if a container or closure does not prevent solvent or drug loss or if it does not prevent the absorption of water vapour into the container. These and many more important phenomena have a basis in diffusion. Drug release from a variety of drug delivery systems, drug absorption and elimination, dialysis, osmosis and ultra filtration are some of the examples.

1C.1.1 Drug Absorption and Elimination

Diffusion through biologic membranes is an essential step for drugs entering or leaving the body. It is also an important component along with concentration for efficient drug distribution throughout the body and into tissues and organs. Diffusion can occur through the lipoidal bilayer of cells. This is termed transcellular diffusion. On the other hand, paracellular diffusion occurs through the spaces between adjacent cells. In addition to diffusion, drugs and nutrients also traverse biologic membranes using membrane transporters and to a lesser extent, cell surface receptors.

Membrane transporters are specialised proteins that facilitate drug transport across biological membranes. The interaction between drugs and transporters can be classified as energy dependent (i.e., active transport) or energy independent (i.e., facilitated diffusion). Membrane transporters are located in every organ responsible for the absorption, distribution, metabolism and excretion of drug substances.

1C.1.2 Drug Release

Elementary drug release is an important process that literally attends nearly every person in everyday life. Drug release is multistep process that includes diffusion, disintegration, deaggregation and dissolution. These processes are important for the release of drug from formulation. Common examples are the release of steroids such as hydrocortisone from topical over-the-counter creams and ointments for the treatment of skin rashes and the release of acetaminophen from a tablet that is taken by mouth.

1C.1.3 Osmosis

Osmosis was originally defined as the passage of the both solute and solvent across a membrane but now refers to an action in which only the solvent is transferred. The solvent passes through a semi permeable membrane to dilute the solution containing solute and solvent. The passage of solute together with solvent now is called diffusion or dialysis. Osmotic drug release system uses osmotic pressure, as a driving force for the controlled delivery of drugs. A simple osmotic pump consists of an osmotic core (containing drug with or without an osmotic agent) and is coated with a semi permeable membrane. The semi permeable membrane has an orifice for drug release from the "pump". The dosage form after coming in contact with aqueous fluids, imbibes water at a rare determined by the fluid permeability of the membrane and osmotic pressure of core formulation. The osmotic imbibition of water results in high hydrostatic pressure inside the pump, which causes the flow of the drug solutions through the delivery orifice.

1C.1.4 Ultra Filtration and Dialysis

Ultra filtration is used to separate colloidal particles and macromolecules by the use of membrane. Hydraulic pressure is used to force the solvent through membrane, where as the micro porous membrane prevents the passage of molecules. Ultra filtration is similar to a process called reverse osmosis.

Dialysis is a separate process based on unequal rates of passage of solutes and solvents through micro porous membranes.

Haemodialysis is used in treating kidney malfunction to rid the blood of metabolic waste product while preserving the high molecular weight components of blood. In ordinary osmosis and as well as in dialysis, separation is spontaneous and does not involve the high applied pressers of ultra filtration and reverse osmosis.

1C.2 Steady-State Diffusion

1C.2.1 Thermodynamic Basis

Mass transfer is the movement of molecules in response to an applied diving force. Convective and diffusive mass transfers are important to many pharmaceutical science applications. Mass transfer is the kinetic process, occurring in the system that is not in equilibrium. To better understand the thermodynamic basis of mass transfer, consider an isolated system consisting of two sections separated by an imaginary membrane (Fig. 1C.1). At equilibrium, the temperature T, pressure P and chemical potentials μ of each two species A and B are equal in the two sections. In this isolated system is unperturbed, it will remain at this thermodynamic equilibrium indefinitely.

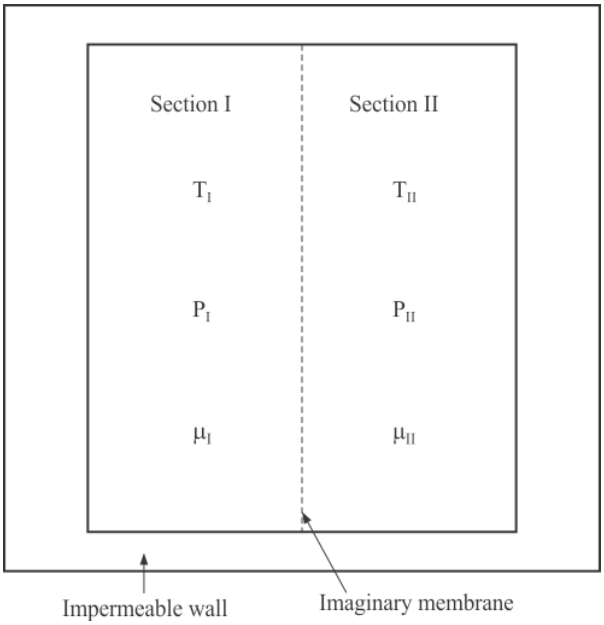


Fig. 1C.1 Isolated system consisting of two sections separated by Imaginary membrane.

Suppose that the chemical potential of one of the species A is now increased in section I so that M_A I > M_A II, because the chemical potential of A is related to its concentration. The ideality of the solution and the temperature, this perturbation of the system can be achieved by increasing the concentration of A in section I. The system will respond to this perturbation by establishing a new thermodynamic equilibrium. Although it could be re establish the equilibrium by altering any of the 3 variables in the system (T, P or μ). Let's assume that it will re equilibrate the chemical potential leaving T and P unaffected. If the membrane separating the two sections will allow for the passage of species A, then equilibrium will be re established by the movement of species A from section I to section II until the chemical potentials of section I and II are once again equal. The movement of mass is response to a spatial gradient in chemical potential as a result of random molecular motion (i.e., Brownian motion) is called diffusion.

1C.3 Fick's Laws of Diffusion

1C.3.1 Fick's First Law

The amount M of material flowing through a unit cross section, δ of a barrier in unit time t is known as the flux J

$$J = \frac{dM}{S.dt} \qquad \text{.....(1C.1)}$$

The flux in turn is proportional to the concentration gradient dc/dx

$$J = -D\frac{dc}{dx} \qquad \text{.....(1C.2)}$$

where D is the diffusion coefficient of diffusant in cm^2 /see. C is the concentration in g/cm^3 and x is the distance in cm of movement perpendicular to the surface of the barrier. In eq. (1C.1). The mass M is usually given in grams or moles, the barrier surface area S in cm^2 and the time t in seconds. The unit of J are g/cm^2 sec. The negative sign of eq. (1C.2) signifies that diffusion occur in a direction opposite to that of increasing concentration. That is diffusion occur in the direction of decreasing concentration of diffusant; thus the flux is always a positive quantity. Diffusion will stop when the concentration gradient no longer exists (i.e., when dc/dx = 0).

Although the diffusion coefficient D or diffusivity as it is often called appear to be proportionality constant; it does not ordinarily remain constant. D is affected by concentration, temperature, pressure, solvent properties and the chemical nature of the diffusant. Therefore D is referred to more correctly as diffusion coefficient rather than as a constant. eq. (1C.2) is known as Fick's first law.

1C.3.2 Fick's Second Law

Fick's second law of diffusion forms the basis for most mathematical models of diffusion process. One often wants to examine the rate of change of diffusant concentration at a point in the system. An equation for mass transport that emphasizes the change in concentration with time at a definite location rather than the mass diffusing across a unit area of barrier in unit time is known as Fick's second law. This diffusion equation is derived as follows.

The concentration C, in a particular volume element (Fig. 1C.2 and 1C.3) changes only as a result of net flow of diffusing molecules into or out of the region. A difference in concentration results from a difference in input and output. The concentration of diffusant in the volume element changes with time, that is $\Delta c/\Delta t$, as the flux or amount diffusing changes with distance $\Delta T/\Delta R$ in the x direction, or

$$\frac{\partial c}{\partial t} = -\frac{\partial j}{\partial x} \qquad \text{.....(1C.3)}$$

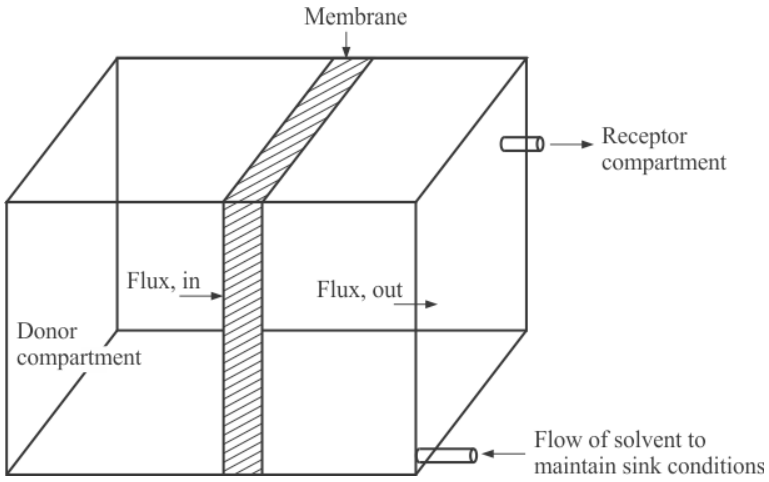


Fig. 1C.2 Diffusion cell. The donor compartment contains diffusant at concentration c.

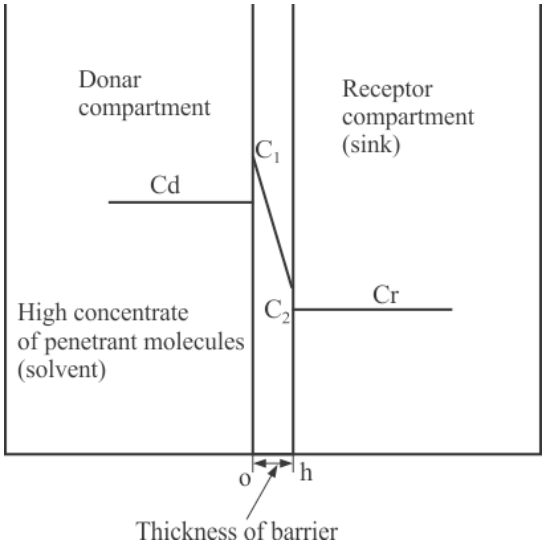


Fig. 1C.3 Concentration gradient of diffusant across the diaphragm of diffusion cell. It is normal for the concentration curve to increase or decrease sharply at the boundaries of barrier because in general, C_1 is different from C_d and C_2 is different from C_r. The concentration C_1 would be equal to C_d for Example, only if $K - C_1/C_d$ had a value of unity.

Differentiating the first law expansion equation (1C.2) with respect to x, one obtain

$$-\frac{\partial j}{\partial x} = D\frac{\partial^2 c}{\partial x^2} \qquad \text{.....(1C.4)}$$

Substituting $\partial c / \partial t$ from eq. (1C.3) into eq. (1C.4) results in Fick's second law, namely

$$\frac{\partial c}{\partial x} = D\frac{\partial^2 c}{\partial x^2} \qquad \text{.....(1C.5)}$$

Eq. (1C.5) represent diffusion only in the x direction. If one wishes to express concentration changes of diffusant in 3 dimensions, Fick's second law is written in the general form.

$$\frac{\partial c}{\partial x} = D\left[\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right] \qquad \text{.....(1C.6)}$$

This expression is not usually needed in pharmaceutical problems of diffusion, however, because movement in one direction is sufficient to describe most cases. Fick's second law states that the change in concentration with time in a particular region is proportional to the change in the concentration gradient at that point in the system.