Solubility and Distribution Phenomena

Solubility is defined the maximum solute concentration in a certain solvent at a certain temperature, and in a qualitative way, it can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.

A ***saturated solution*** is one in which the solute in solution is in equilibrium with the solid Phase.

unsaturated or ***subsaturated*** **solution** is one containing the dissolved solute in a concentration below that necessary for complete saturation at a definite temperature.

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

The solubility of a compound depends on

- the Physical and chemical properties of the solute and the solvent
- temperature.
- Pressure.
- PH of the solution

thermodynamic 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. The equilibrium involves a balance of the energy of three interactions against each other:

(1) solvent with solvent,

(2) solute with solute

(3) solvent and solute

Solubility Expressions

The solubility of a drug may be expressed in a number of ways. The *United States Pharmacopeia (USP)* describes the solubility of drugs as parts of solvent required for one part solute. Solubility is also quantitatively expressed in terms of molality, molarity, and percentage. The USP describes solubility using the seven groups listed in following Table.

Table Solubility Definition in the United States Pharmacopeia

Description Forms (Solubility Definition)	Parts of Solvent Required for One Part of Solute
Very soluble (VS)	<1
Freely soluble (FS)	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble (SPS)	From 30 to 100
Slightly soluble (SS)	From 100 to 1000
Very slightly soluble (VSS)	From 1000 to 10,000
Practically insoluble (PI)	>10,000

Solvent–Solute Interactions

like dissolves like.”

Polar substances tend to dissolve in polar solvents, while nonpolar substances tend to dissolve in nonpolar solvents .

The more similar the intermolecular attractions are the more likely one substance is to be soluble in another.

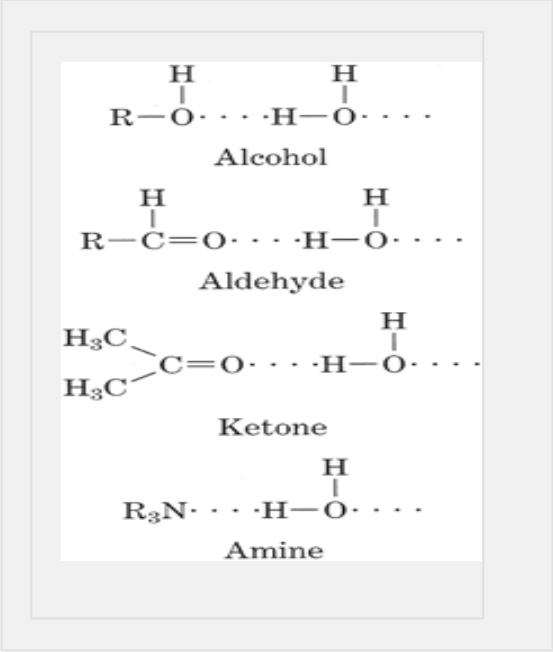
Types of solvents

1-Polar Solvents

Polar solvents dissolve ionic solutes and other polar substances.

The solubility of a drug in polar solvents depend on:

1- The polarity of solute and solvent.
2- The ability of the solute to form hydrogen bonds. Accordingly, water mixes in all proportions with alcohol and dissolves sugars and other poly hydroxy compounds due to the ability of the solute to form hydrogen bonds is a far more significant factor than is the polarity as reflected in a high dipole moment.



3- The ratio of polar and nonpolar groups of the molecule. When additional polar groups are present in the molecule, as found in propylene glycol, glycerin, and tartaric acid, water solubility increases greatly.

When the length of a nonpolar chain of an aliphatic alcohol increases, the solubility of the compound in water decreases. Straight-chain monohydroxy alcohols, aldehydes, ketones, and acids with more than four or five carbons cannot enter into the hydrogen-bonded structure of water and hence are only slightly soluble.

Tertiary butyl alcohol is miscible in all proportions with water, whereas *n*-butyl alcohol dissolves to the extent of about 8 g/100 mL of water at 20°C.

2-Nonpolar Solvents

Ionic and polar solutes are not soluble or are only slightly soluble in nonpolar liquids, such as the hydrocarbons because:-

- Nonpolar solvents are unable to reduce the attraction between the ions of strong and weak electrolytes because of the solvents' low dielectric constants.
- Nonpolar solvents cannot break covalent bonds and ionize weak electrolytes, because they are aprotic .
- Nonpolar solvents cannot form hydrogen bridges with nonelectrolytes. Hence, ionic and polar solutes are not soluble or are only slightly soluble in nonpolar solvents.

Nonpolar compounds, however, can dissolve nonpolar solutes with similar attractive forces through induced dipole interactions. The solute molecules are kept in solution by the weak van der Waals–London type of forces. Thus, oils and fats dissolve in carbon tetrachloride, benzene,

and mineral oil. Alkaloidal bases and fatty acids also dissolve in nonpolar solvents.

3-Semipolar Solvents

Semi polar compounds can act as *intermediate solvents* to bring about miscibility of polar and nonpolar liquids such as ketones and alcohols, can *induce* a certain degree of polarity in nonpolar solvent molecules, so that, for example, acetone increases the solubility of ether in water.

Solubility of Liquids in Liquids

Frequently two or more liquids are mixed together in the preparation of Pharmaceutical solutions. For example, alcohol is added to water to form hydroalcoholic solutions of various concentrations; volatile oils are mixed with water to form dilute solutions known as aromatic waters; volatile oils are added to alcohol to yield spirits and elixirs; ether and alcohol are combined in collodions; and various fixed oils are blended into lotions, sprays, and medicated oils. Liquid–liquid systems can be divided into two categories according to the solubility of the substances in one another: (*a*) ***complete miscibility*** and (*b*) ***partial miscibility***. The term ***miscibility*** refers to the mutual solubility's of the components in liquid–liquid systems.

a) Complete Miscibility

Polar and semipolar solvents, such as water and alcohol, glycerin and alcohol, and alcohol and acetone, are said to be completely miscible because they mix in all proportions. Nonpolar solvents such as benzene and carbon tetrachloride are also completely miscible.

These liquids are miscible because the broken attractive forces in both pure liquids are re-established in the mixture.

b)Partial Miscibility

When certain amounts of water and ether or water and Phenol are mixed, two liquid layers are formed, each containing some of the other liquid in the dissolved state. The mutual solubility of partially miscible liquids are influenced by temperature. In a system such as Phenol and water, the mutual solubility of the two conjugate Phases increase with temperature until, at the critical solution temperature (or upper consolute temperature), the compositions become identical. At this temperature, a homogeneous or single-Phase system is formed.

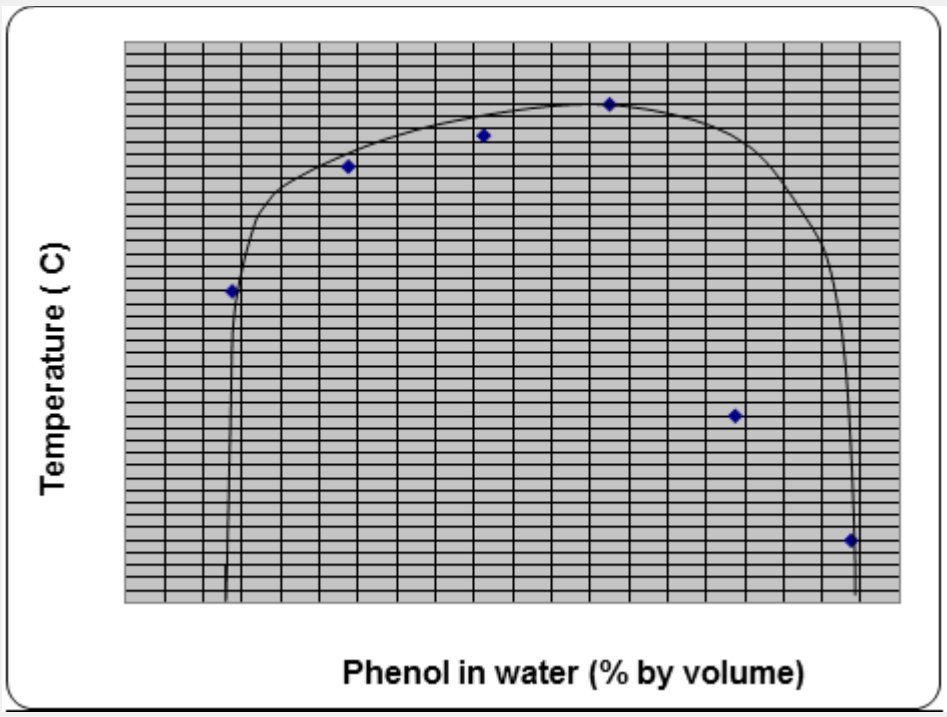


Fig.. Phase diagram for the system phenol–water showing lower consolute temperature.

Three-Component Systems

Three-component systems containing one pair of partially miscible liquids are water, CCl_4, and acetic acid; and water, Phenol, and acetone. Triangular Phase diagram of the system of methyl salicylate, isopropanol, and water was shown in the following Figure.

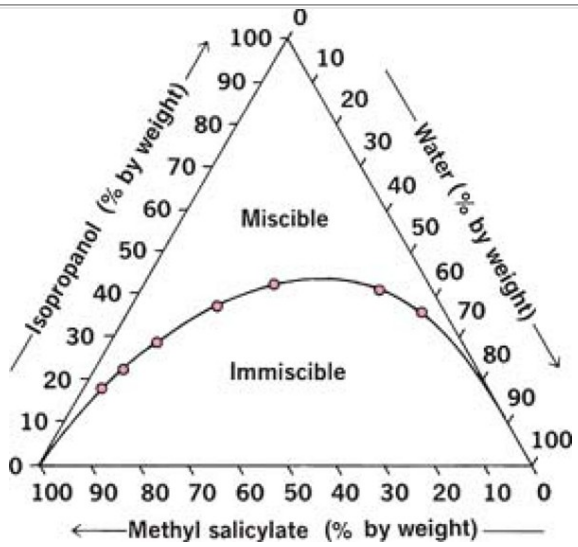


Fig. Triangular Phase diagram for the three-component system methyl salicylate–isopropanol–water.

Solubility of Solids in Liquids

Systems of solids in liquids include the most frequently encountered and probably the most important type of Pharmaceutical solutions.

Many important drugs belong to the class of weak acids and bases. They react with strong acids and bases and, within definite ranges of PH, exist as ions that are ordinarily soluble in water.

Acidic drugs are more soluble in alkaline solutions where the ionized form can be obtained from the following equation.

$$PH - PK_a = \log \frac{[ionized]}{[unionized]}$$

Basic drugs are more soluble in acidic solutions where the ionized form can be obtained from the following equation.

$$PH - PK_a = \log \frac{[unionized]}{[ionized]}$$

Although carboxylic acids containing more than five carbons are relatively insoluble in water, they react with dilute sodium hydroxide, carbonates, and bicarbonates to form soluble salts. The fatty acids containing more than 10 carbon atoms form soluble soaps with the

alkali metals and insoluble soaps with other metal ions. They are soluble in solvents having low dielectric constants; for example, oleic acid ($C_{17}H_{33}COOH$) is insoluble in water but is soluble in alcohol and in ether.

Hydroxy acids, such as tartaric and citric acids, are quite soluble in water because they are solvated through their hydroxyl groups. The potassium and ammonium bitartrates are not very soluble in water.

Aromatic acids react with dilute alkalies to form water-soluble salts, but they can be precipitated as the free acids if stronger acidic substances are added to the solution. They can also be precipitated as heavy metal salts should heavy metal ions be added to the solution. Benzoic acid is soluble in sodium hydroxide solution. Salicylic acid is soluble in alkalies and in alcohol. The OH group of salicyclic acid cannot contribute to the solubility because it is involved in an intramolecular hydrogen bond.

Phenol is weakly acidic and only slightly soluble in water but is quite soluble in dilute sodium hydroxide solution,

$$C_6H_5OH + NaOH \rightarrow C_6H_5O^- + Na^+ + H_2O$$

Many organic compounds containing a basic nitrogen atom in the molecule are important in Pharmacy. These include the alkaloids, sympathomimetic amines, antihistamines, local anesthetics, and others. Most of these weak electrolytes are not very soluble in water but are soluble in dilute solutions of acids; such compounds as atropine sulfate and tetracaine hydrochloride are formed by reacting the basic compounds with acids. Addition of an alkali to a solution of the salt of these compounds precipitates the free base from solution if the solubility of the base in water is low.

The aliphatic nitrogen of the sulfonamides is sufficiently negative so that these drugs act as slightly soluble weak acids rather than as bases. They form water-soluble salts in alkaline solution by the following mechanism. The oxygen of the sulfonyl (—SO_2—) group withdraw electrons, and the resulting electron deficiency of the sulfur atom results in the electrons of the N:H bond being held more closely to the nitrogen atom. The hydrogen therefore is bound less firmly, and, in alkaline solution, the soluble sulfonamide anion is readily formed.

The sodium salts of the sulfonamides are precipitated from solution by the addition of a strong acid or by a salt of a strong acid and a weak base such as ephedrine hydrochloride.

The barbiturates, like the sulfonamides, are weak acids because the electronegative oxygen of each acidic carbonyl group tends to withdraw electrons and to create a positive carbon atom. The carbon in turn attracts electrons from the nitrogen group and causes the hydrogen to be held less firmly. Thus, in sodium hydroxide solution, the hydrogen is readily lost, and the molecule exists as a soluble anion of the weak acid. In highly alkaline solutions, the second hydrogen ionizes. The pK_1 for Phenobarbital is 7.41 and the pK_2 is 11.77. Although the barbiturates are soluble in alkalis, they are precipitated as the free acids when a stronger acid is added and the PH of the solution is lowered.

Calculating the Solubility of Weak Electrolytes as Influenced by PH

The solubility of weak electrolytes is strongly influenced by the PH of the solution. For example, a 1% solution of Phenobarbital sodium is soluble at PH values high in the alkaline range. The soluble ionic form is converted into molecular Phenobarbital as the PH is lowered, and below 9.3 the drug begins to precipitate from solution at room temperature. On the other hand, alkaloidal salts such as atropine sulfate begin to precipitate as the PH is elevated.

To ensure a clear homogeneous solution and maximum therapeutic effectiveness, the preparations should be adjusted to an optimum PH. The PH below which the salt of a weak acid, sodium Phenobarbital, for example, begins to precipitate from aqueous solution is readily calculated in the following manner.

Representing the free acid form of Phenobarbital as HP and the soluble ionized form as P^-, the equilibria in a saturated solution of this slightly soluble weak electrolyte can be written as

$$HP_{solid} \rightleftharpoons HP_{sol} \qquad (9\text{–}1)$$

$$HP_{sol} + H_2O \rightleftharpoons H_3O^+ + P^- \qquad (9\text{–}2)$$

$$pH_p = pK_a + \log \frac{S - S_o}{S_o} \qquad (9\text{–}9)$$

Where S_o is molar or intrinsic solubility

$$S_o = [HP]_{sol} \qquad (9\text{–}3)$$

K_a is the constant for the acid–base equilibrium. *S* is the total solubility, of Phenobarbital consists of the concentration of the undissociated acid, [HP], and that of the conjugate base or ionized form, $[P^-]$:

$$S = [HP] + [P^-] \qquad (9\text{–}6)$$

PH_p is the PH below which the drug separates from solution as the undissociated acid.

In Pharmaceutical practice, a drug such as Phenobarbital is usually added to an aqueous solution in the soluble salt form. Of the initial quantity of salt, sodium Phenobarbital, that can be added to a solution of a certain PH, some of it is converted into the free acid, HP, and some remains in the ionized form, P^- [equation (9-6)]. The amount of salt that can be added initially before the solubility [HP] is exceeded is therefore equal to *S*. As seen from equation (9-9), PH_p depends on the initial molar concentration, *S*, of salt added, the molar solubility of the

undissociated acid, S_o, also known as the ***intrinsic solubility,*** and the pK_a. Equation (9-9) has been used to determine the pK_a of sulfonamides and other drugs. Solubility and PH data can also be used to obtain the pK_1 and pK_2 values of dibasic acids .

An analogous derivation can be carried out to obtain the equation for the solubility of a weak base as a function of the PH of a solution. The expression is

$$\mathrm{pH_p} = \mathrm{p}K_w - \mathrm{p}K_b + \log \frac{S_o}{S - S_o} \qquad (9\text{–}10)$$

where S is the concentration of the drug initially added as the salt and S_o is the molar solubility of the free base in water. Here PH_p is the PH *above* which the drug begins to precipitate from solution as the free base.

The Influence of Solvents on the Solubility of Drugs

Weak electrolytes can behave like strong electrolytes or like nonelectrolytes in solution.

When the solution is of such a PH that the drug is entirely in the ionic form, it behaves as a solution of a strong electrolyte, and solubility does not constitute a serious problem.

However, when the PH is adjusted to a value at which un-ionized molecules are produced in sufficient concentration to exceed the solubility of this form, precipitation occurs.

Frequently, a solute is more soluble in a mixture of solvents than in one solvent alone. This Phenomenon is known as ***cosolvency,*** and the solvents that, in combination, increase the solubility of the solute are called ***cosolvents.*** Approximately 1 g of Phenobarbital is soluble in 1000 mL of water, in 10 mL of alcohol, in 40 mL of chloroform, and in 15 mL of ether at 25°C. The solubility of Phenobarbital in water–alcohol–glycerin mixtures is plotted in Figure 9-4.By drawing lines

parallel to the abscissa in Figure 9-4 at a height equivalent to the required Phenobarbital concentration, it is a simple matter to obtain the relative amounts of the various combinations of alcohol, glycerin, and water needed to achieve solution. For example, at 22% alcohol, 40% glycerin, and the remainder water (38%),1.5% w/v of Phenobarbital is dissolved, as seen by following the vertical and horizontal lines drawn on Figure 9-4

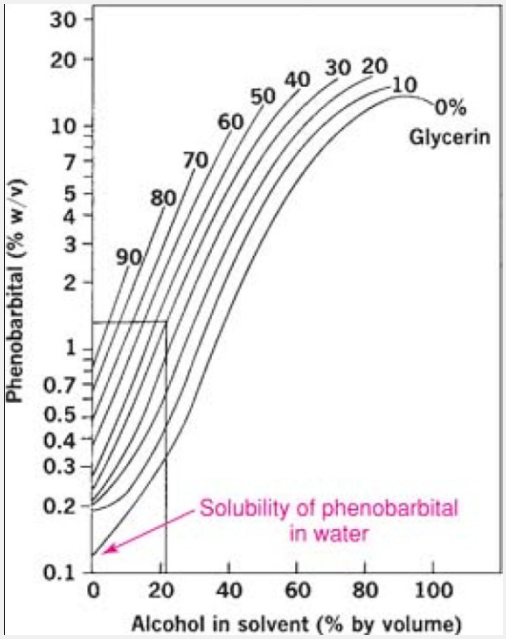


Fig. 9-4. The solubility of Phenobarbital in a mixture of water, alcohol, and glycerin at 25°C. The vertical axis is a logarithmic scale representing the solubility of Phenobarbital in g/100 mL.

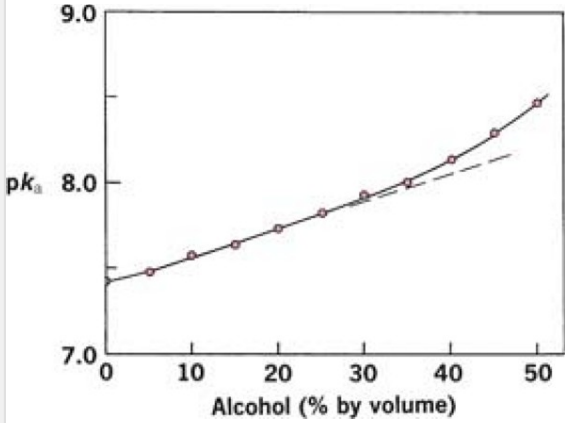


Fig. 9-5. The influence of alcohol concentration on the dissociation constant of Phenobarbital.

Combined Effect of PH and Solvents

The observed solubilities were in excellent agreement with the PH–solubility profiles based on equation **(9-9)**. Figure 9-5, where one observes that the pK_a of Phenobarbital, 7.41, is raised to 7.92 in a hydroalcoholic solution containing 30% by volume of alcohol. Furthermore, as can be seen in Figure 9-4, the solubility, S_o, of un-ionized Phenobarbital is increased from 0.12 g/100 mL or 0.005 M in

water to 0.64% or 0.0276 M in a 30% alcoholic solution. The calculation of solubility as a function of PH involving these results is illustrated in the following example.

Influence of Complexation in Multicomponent Systems

Many liquid Pharmaceutical preparations consist of more than a single drug in solution. simple solubility profiles of individual drugs cannot be used to predict solubilities in mixtures of ingredients. Instead, the specific multicomponent systems must be studied to estimate the complicating effects of species interactions.

Influence of Other Factors on the Solubility of Solids

The size and shape of small particles (those in the micrometer range) also affect solubility. Solubility increases with decreasing particle size according to the approximate equation

$$\log \frac{s}{s_0} = \frac{2\gamma V}{2.303RTr} \qquad (9\text{–}11)$$

where s is the solubility of the fine particles; s_o is the solubility of the solid consisting of relatively large particles; γ is the surface tension of the particles, which, for solids, unfortunately, is extremely difficult to obtain; V is the molar volume (volume in cm^3 per mole of particles); r is the final radius of the particles in cm; R is the gas constant (8.314×10^7 ergs/deg mole); and T is the absolute temperature. The equation can be used for solid or liquid particles such as those in suspensions or emulsions.

The configuration of a molecule and the type of arrangement in the crystal also has some influence on solubility, and a symmetric particle can be less soluble than an unsymmetric one. This is because solubility depends in part on the work required to separate the particles of the crystalline solute. The molecules of the amino acid α-alanine form a

compact crystal with high lattice energy and consequently low solubility. The molecules of α-amino-*n*-butyric acid pack less efficiently in the crystal, partly because of the projecting side chains, and the crystal energy is reduced. Consequently, α-amino-*n*-butyric acid has a solubility of 1.80 moles/liter and α-alanine has a solubility of only 1.66 moles/liter in water at 25°C, although the hydrocarbon chain is longer in α-amino-*n*-butyric acid than in the other compound.