9 Solubility and Distribution Phenomena

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Define saturated solution, solubility, and unsaturated solution.
2. Describe and give examples of polar, nonpolar, and semipolar solvents.
3. Define complete and partial miscibility.
4. Understand the factors controlling the solubility of weak electrolytes.
5. Describe the influence of solvents and surfactants on solubility.
6. Define thermodynamic, kinetic, and intrinsic solubility.
7. Measure thermodynamic solubility.
8. Describe what a distribution coefficient and partition coefficient are and their importance in pharmaceutical systems.

General Principles

Introduction[1,2,3,4]

Solubility is defined in quantitative terms as the concentration of solute in a saturated solution 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. Solubility is an *intrinsic* material property that can be altered only by chemical modification of the molecule.[1] In contrast to this, dissolution is an *extrinsic* material property that can be influenced by various chemical, physical, or crystallographic means such as complexation, particle size, surface properties, solid-state modification, or solubilization enhancing formulation strategies.[1]Dissolution is discussed in Chapter 13. Generally speaking, the solubility of a compound depends on the physical and chemical properties of the solute and the solvent as well as on such factors as temperature, pressure, the pH of the solution, and, to a lesser extent, the state of subdivision of the solute. Of the nine possible types of mixtures, based on the three states of matter, only liquids in liquids and solids in liquids are of everyday importance to most pharmaceutical scientists and will be considered in this chapter.

For the most part, this chapter will deal with the *thermodynamic solubility* of drugs (Fig. 9-1). The 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.[4] The equilibrium involves a balance of the energy of three interactions against each other: (1) solvent with solvent, (2) solute with solute, and (3) solvent and solute. Thermodynamic equilibrium is achieved when the overall lowest energy state of the system is achieved. This means that only the equilibrium solubility reflects the balance of forces between the solution and the most stable, lowest energy crystalline form of the solid. In practical terms, this means that one needs to be careful when evaluating a drug's solubility. For example, let us say that you want to determine the solubility of a drug and that you were not aware that it was not in its crystalline form. It is well known that a metastable solid form of a drug will have a higher apparent solubility. Given enough time, the limiting solubility of the most stable form will eventually dominate and since the most stable crystal form has the lowest solubility, this means that there will be excess drug in solution resulting in a precipitate. So, initially you would record a higher solubility but after a period of time the solubility that you measure would be significantly lower. As you can imagine, this could lead to serious problems. This was vividly illustrated by Abbott's antiviral drug ritonavir where the slow precipitation of a new stable polymorph from dosing solutions required the manufacturer to perform an emergency reformulation to ensure consistent drug release characteristics.[2,4]

Key Concept

Solutions and Solubility

A *saturated solution* is one in which the solute in solution is in equilibrium with the solid phase. *Solubility* is defined in quantitative terms as the concentration of solute in a saturated

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

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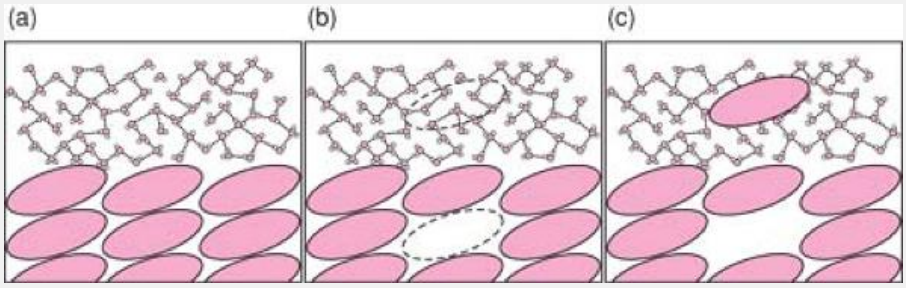


Fig. 9-1. The intermolecular forces that determine thermodynamic solubility. (*a*) Solvent and solute are segregated, each interacts primarily with other molecules of the same type. (*b*) To move a solute molecule into solution, the interactions among solute molecules in the crystal (lattice energy) and among solvent molecules in the space required to accommodate the solute (cavitation energy) must be broken. The system entropy increases slightly because the ordered network of hydrogen bonds among solvent molecules has been disrupted. (*c*) Once the solute molecule is surrounded by solvent, new stabilizing interactions between the solute and solvent are formed (solvation energy), as indicated by the dark purple molecules. The system entropy increases owing to the mingling of solute and solvent (entropy of mixing) but also decreases locally owing to the new short-range order introduced by the presence of the solute, as indicated by the light purple molecules.4 (Adapted from Bhattachar et al. 2006.4)

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 Table 9-1. The European Pharmacopoeia lists six categories (it does not use the *practically insoluble* grouping). For exact solubilities of many substances, the reader is referred to standard reference works such as official compendia (e.g., USP) and the Merck Index.

Solvent–Solute Interactions

The pharmacist knows that water is a good solvent for salts, sugars, and similar compounds, whereas mineral oil is often a solvent for substances that are normally only slightly soluble in water. These

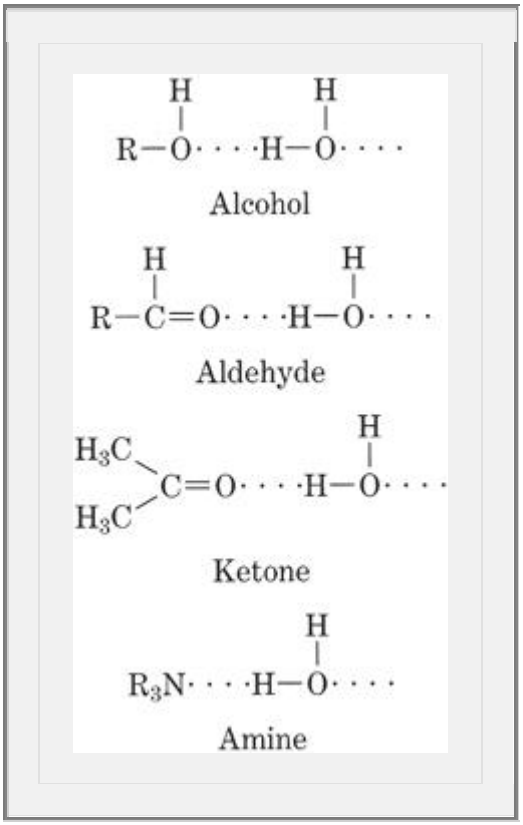
empirical findings are summarized in the statement, “like dissolves like.” Such a maxim is satisfying to most of us, but the inquisitive student may be troubled by this vague idea of “likeness.”

Table 9-1 Solubility Definition in the United States Pharmacopeia

Description Forms (Solubility Definition)	Parts of Solvent Required for One Part of Solute	Solubility Range (mg/mL)	Solubility Assigned (mg/mL)
Very soluble (VS)	<1	>1000	1000
Freely soluble (FS)	From 1 to 10	100–1000	100
Soluble	From 10 to 30	33–100	33
Sparingly soluble (SPS)	From 30 to 100	10–33	10
Slightly soluble (SS)	From 100 to 1000	1–10	1
Very slightly soluble (VSS)	From 1000 to 10,000	0.1–1	0.1
Practically insoluble (PI)	>10,000	<0.1	0.01

Polar Solvents

The solubility of a drug is due in large measure to the polarity of the solvent, that is, to its dipole moment. Polar solvents dissolve ionic solutes and other polar substances. Accordingly, water mixes in all proportions with alcohol and dissolves sugars and other polyhydroxy compounds. Hildebrand showed, however, that a consideration of dipole moments alone is not adequate to explain the solubility of polar substances in water. 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. Water dissolves phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds that can form hydrogen bonds with water:



A difference in acidic and basic character of the constituents in the Lewis electron donor–acceptor sense also contributes to specific interactions in solutions.

In addition to the factors already enumerated, the solubility of a substance also depends on structural features such as the ratio of the polar to the nonpolar groups of the molecule. As 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. When additional polar groups are present in the molecule, as found in propylene glycol, glycerin, and tartaric acid, water solubility increases greatly. Branching of the carbon chain reduces the nonpolar effect and leads to increased water solubility. 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.

Nonpolar Solvents

The solvent action of nonpolar liquids, such as the hydrocarbons, differs from that of polar substances. Nonpolar solvents are unable to reduce the attraction between the ions of strong and weak electrolytes because of the solvents' low dielectric constants. Nor can the solvents break covalent bonds and ionize weak electrolytes, because they belong to the group known as aprotic solvents, and they 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 internal pressures 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.

Key Concept

Solubility

The simple maxim that *like dissolves like* can be rephrased by stating that the solubility of a substance can be predicted only in a qualitative way in most cases and only after considerations of polarity, dielectric constant, association, solvation, internal pressures, acid–

base reactions, and other factors. In short, solubility depends on chemical, electrical, and structural effects that lead to mutual interactions between the solute and the solvent.

Semipolar Solvents

Semipolar solvents, such as ketones and alcohols, can *induce* a certain degree of polarity in nonpolar solvent molecules, so that, for example, benzene, which is readily polarizable, becomes soluble in alcohol. In fact, semipolar compounds can act as *intermediate solvents* to bring about miscibility of polar and nonpolar liquids. Accordingly, acetone increases the solubility of ether in water. Loran and Guth5 studied the intermediate solvent action of alcohol on water–castor oil mixtures. Propylene glycol has been shown to increase the mutual solubility of water and peppermint oil and of water and benzyl benzoate.6

A number of common solvent types are listed in the order of decreasing “polarity” in Table 9-2, together with corresponding solute classes. The term *polarity* is loosely used here to represent not only the dielectric constants of the solvents and solutes but also the other factors enumerated previously.

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 solubilities of the components in liquid–liquid systems.

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. Completely miscible liquid mixtures in general create no solubility problems for the pharmacist and need not be considered further.

Table 9-2 Polarity of some Solvents and the Solutes that Readily Dissolve in each Class of Solvent

	Dielectric Constant of Solvent, ε (Approximately)	Solvent	Solute	
Decreasing Polarity	80	Water	Inorganic salts, organic salts	Decreasing Water Solubility
↓	50	Glycols	Sugars, tannins	↓

	30	Methyl and ethyl alcohols	Caster oil, waxes	
	20	Aldehydes, ketones, and higher alcohols, ethers, esters, and oxides	Resins, volatile oils, weak electrolytes including barbiturates, alkaloids, and phenols	
	5	Hexane, benzene, carbon tetrachloride, ethyl ether, petroleum ether	Fixed oils, fats, petrolatum, paraffin, other hydrocarbons	
	0	Mineral oil and fixed vegetable oils		

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 phenol–water system has been discussed in detail in Chapter 2, and the student at this point should review the section dealing with the phase rule. It is sufficient here to reiterate the following points. (*a*) The mutual solubilities of partially miscible liquids are influenced by temperature. In a system such as phenol and water, the mutual solubilities 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. (*b*) From a knowledge of the phase diagram, more especially the tie lines that cut the binodal curve, it is possible to calculate both the composition of each component in the two conjugate phases and the amount of one phase relative to the other. Example 9-1 gives an illustration of such a calculation.

Example 9-1

Component Weights

A mixture of phenol and water at 20°C has a total composition of 50% phenol. The tie line at this temperature cuts the binodal at points equivalent to 8.4% and 72.2% w/w phenol. What is the weight of the aqueous layer and of the phenol layer in 500 g of the mixture and how many grams of phenol are present in each of the two layers?

Let *Z* be the weight in grams of the aqueous layer. Therefore, 500 - *Z* is the weight in grams of the phenol layer, and the sum of the percentages of phenol in the two layers must equal the overall composition of 50%, or 500 × 0.50 = 250 g. Thus,

$$Z(8.4/100) + (500 - Z)(72.2/100) = 250$$

$$\text{Weight of aqueous layer, } Z = 174 \text{ g}$$

$$\text{Weight of phenol layer, } 500 - Z = 326 \text{ g}$$

$$\text{Weight of phenol in the aqueous layer, } 174 \times 0.084 = 15 \text{ g}$$

$$\text{Weight of phenol in the phenolic layer, } 326 \times 0.722 = 235 \text{ g}$$

In the case of some liquid pairs, the solubility can increase as the temperature is lowered, and the system will exhibit a *lower consolute temperature*, below which the two members are soluble in all proportions and above which two separate layers form. Another type, involving a few mixtures such as nicotine and water, shows both an upper and a lower consolute temperature with an intermediate temperature region in which the two liquids are only partially miscible. A final type exhibits no critical solution temperature; the pair ethyl ether and water, for example, has neither an upper nor a lower consolute temperature and shows partial miscibility over the entire temperature range at which the mixture exists.

Three-Component Systems

The principles underlying systems that can contain one, two, or three partially miscible pairs have been discussed in detail in Chapter 2. Further examples of three-component systems containing one pair of partially miscible liquids are water, CCl_4, and acetic acid; and water, phenol, and acetone. Loran and Guth5 studied the three-component system consisting of water, castor oil, and alcohol and determined the proper proportions for use in certain lotions and hair preparations; a triangular diagram is shown in their report. A similar titration with water of a mixture containing peppermint oil and polyethylene glycol is shown in Figure 9-2.6Ternary diagrams have also found use in cosmetic formulations

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involving three liquid phases.7 Gorman and Hall8 determined the ternary-phase diagram of the system of methyl salicylate, isopropanol, and water (Fig. 9-3).

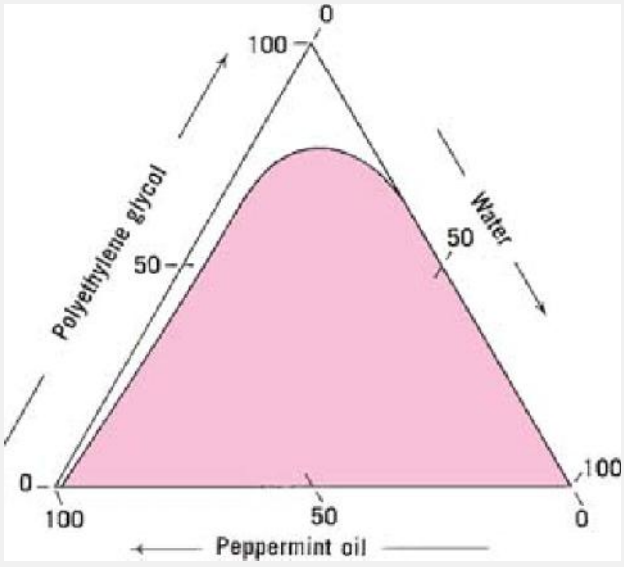

Fig. 9-2. A triangular diagram showing the solubility of peppermint oil in various proportions of water and polyethylene glycol.

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.

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.

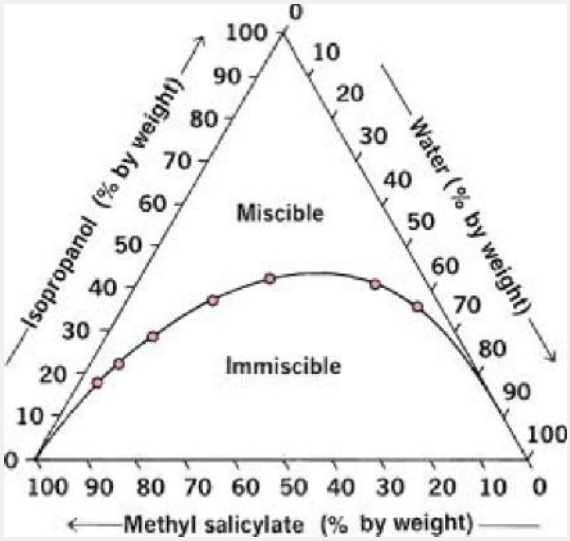

Fig. 9-3. Triangular phase diagram for the three-component system methyl salicylate–isopropanol–water. (From W. G. Gorman and G. D. Hall, J. Pharm. Sci. **53,** 1017, 1964. With permission.)

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, although most alkali metal salts of tartaric acid are soluble. Sodium citrate is used sometimes to dissolve water-insoluble acetylsalicylic acid because the soluble acetylsalicylate ion is formed in the reaction. The citric acid that is produced is also soluble in water, but the practice of dissolving aspirin by this means is questionable because the acetylsalicylate is also hydrolyzed rapidly.

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, alcohol, and fixed oils. 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,

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

Phenol is a weaker acid than H_2CO_3 and is thus displaced and precipitated by CO_2 from its dilute alkali solution. For this reason, carbonates and bicarbonates cannot increase the solubility of phenols in water.

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 oxygens 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.

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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. Butler et al.9 demonstrated that, 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 alkalies, 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

From what has been said about the effects of acids and bases on solutions of weak electrolytes, it becomes evident that 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^-, we write the equilibria in a saturated solution of this slightly soluble weak electrolyte as

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

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

Because the concentration of the un-ionized form in solution, HP_{sol}, is essentially constant, the equilibrium constant for the solution equilibrium, equation (9-1), is

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

where S_o is molar or intrinsic solubility. The constant for the acid–base equilibrium, equation (9-2), is

$$K_a = \frac{[H_3O^+][P^-]}{[HP]} \qquad (9\text{–}4)$$

or

$$[P^-] = K_a \frac{[HP]}{[H_3O^+]} \qquad (9\text{–}5)$$

where the subscript “sol” has been deleted from $[HP]_{sol}$ because no confusion should result from this omission.

The total solubility, S, of phenobarbital consists of the concentration of the undissociated acid, [HP], and that of the conjugate base or ionized form, [P^-]:

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

Substituting S_o for [HP] from equation (9-3) and the expression from equation (9-5) for [P^-] yields

$$S = S_o + K_a \frac{S_o}{[H_3O^+]} \qquad (9\text{–}7)$$

$$S = S_o \left(1 + \frac{K_a}{[H_3O^+]}\right) \qquad (9\text{–}8)$$

When the electrolyte is weak and does not dissociate appreciably, the solubility of the acid in water or acidic solutions is S_o = [HP], which, for phenobarbital is approximately 0.005 mole/liter, in other words, 0.12%.

The solubility equation can be written in logarithmic form, beginning with equation (9-7). By rearrangement, we obtain

$$(S - S_o) = K_a \frac{S_o}{[H_3O^+]}$$

$$\log (S - S_o) = \log K_a + \log S_o - \log [H_3O^+]$$

and finally

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

where 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.[10,11] Solubility and pH data can also be used to obtain the pK_1 and pK_2 values of dibasic acids as suggested by Zimmerman[12] and Blanchard et al.[13]

Example 9-2

Phenobarbital

Below what pH will free phenobarbital begin to separate from a solution having an initial concentration of 1 g of sodium phenobarbital per 100 mL at 25°C? The molar solubility, S_o, of phenobarbital is 0.0050 and the pK_a is 7.41 at 25°C. The secondary dissociation of phenobarbital, referred to previously, can ordinarily be disregarded. The molecular weight of sodium phenobarbital is 254.

The molar concentration of salt initially added is

$$\frac{\text{g/liter}}{\text{mol.wt.}} = \frac{10}{254} = 0.039 \text{ mole/liter}$$

$$pH_p = 7.41 + \log \frac{(0.039 - 0.005)}{0.005} = 8.24$$

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

$$pH_p = pK_w - pK_b + \log \frac{S_o}{S - S_o} \qquad (9\text{–}10)$$

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. In this discussion, we are now interested in the solubility of nonelectrolytes and the undissociated molecules of weak electrolytes. The solubility of undissociated phenobarbital in various solvents is discussed here because it has been studied to some extent by pharmaceutical investigators.

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 chloroform, and in 15 mL of ether at 25°C. The solubility of phenobarbital in water–alcohol–glycerin mixtures is plotted on a semilogarithm grid in Figure 9-4from the data of Krause and Cross.14

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.

Key Concept

Solvents and Weak Electrolytes

The solvent affects the solubility of a weak electrolyte in a buffered solution in two ways: (*a*) The addition of alcohol to a buffered aqueous solution of a weak electrolyte increases the solubility of the un-ionized species by adjusting the polarity of the solvent to a more favorable value. (*b*) Because it is less polar than water, alcohol decreases the dissociation of a weak electrolyte, and the solubility of the drug goes down as the dissociation constant is decreased (pK_a is increased).

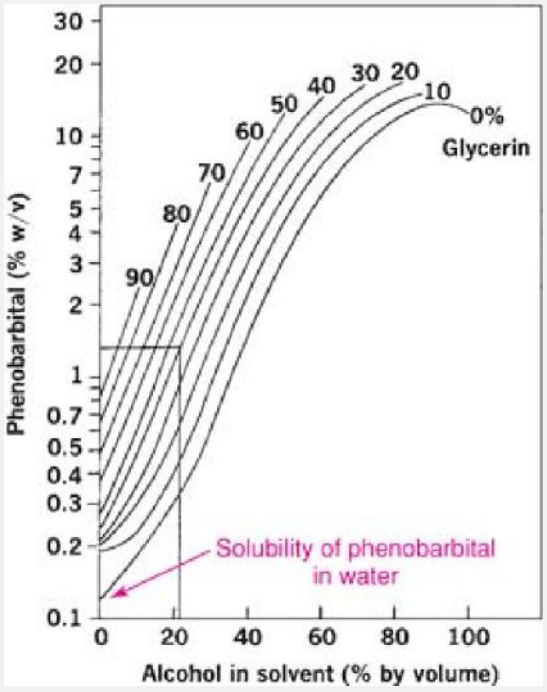

Fig. 9-4. The solubility of phenobarbital in a mixture of water, alcohol, and glycerin at 25°C. The vertical axis is a logarithmic scale representing the solubility of phenobarbital in g/100 mL. (From G. M. Krause and J. M. Cross, J. Am. Pharm. Assoc. Sci. Ed. **40,** 137, 1951. With permission.)

Combined Effect of pH and Solvents

Stockton and Johnson15 and Higuchi et al.16 studied the effect of an increase of alcohol concentration on the dissociation constant of sulfathiazole, and Edmonson and Goyan17 investigated the effect of alcohol on the solubility of phenobarbital.

Schwartz et al.10 determined the solubility of phenytoin as a function of pH and alcohol concentration in various buffer systems and calculated the apparent dissociation constant. Kramer and Flynn18 examined the solubility of hydrochloride salts of organic bases as a function of pH, temperature, and solvent composition. They described the determination of the pK_a of the salt from the solubility profile at various temperatures and in several solvent systems. Chowhan11measured and calculated the solubility of the organic carboxylic acid naproxen and its sodium, potassium, calcium, and magnesium salts. The observed solubilities were in excellent agreement with the pH–solubility profiles based on equation **(**9-9**)**.

The results of Edmonson and Goyan17 are shown in Figure 9-5, where one observes that the pK_a of phenobarbital, 7.41, is raised to 7.92 in a hydroalcoholic solution containing

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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.

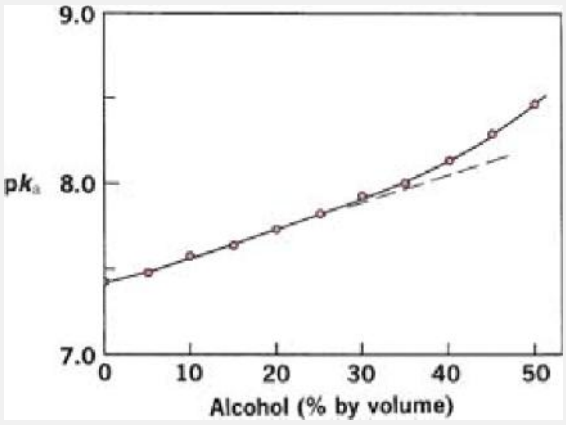

Fig. 9-5. The influence of alcohol concentration on the dissociation constant of phenobarbital. (From T. D. Edmonson and J. E. Goyan, J. Am. Pharm. Assoc. Sci. Ed. **47,** 810, 1958. With permission.)

Example 9-3
Minimum pH for Complete Solubility

What is the minimum pH required for the complete solubility of the drug in a stock solution containing 6 g of phenobarbital sodium in 100 mL of a 30% by volume alcoholic solution?
From equation (9-9),

$$pH_p = 7.92 + \log \frac{0.236 - 0.028}{0.028}$$

$$pH_p = 7.92 + 0.87 = 8.79$$

For comparison, the minimum pH for complete solubility of phenobarbital in an aqueous solution containing no alcohol is computed using equation (9-9):

$$pH_p = 7.41 + \log \frac{0.236 - 0.005}{0.005} = 9.07$$

From the calculations of Example 9-3, it is seen that although the addition of alcohol increases the pK_a, it also increases the solubility of the un-ionized form of the drug over that found in water sufficiently so that the pH can be reduced somewhat before precipitation occurs.
Equations (9-9) and (9-10) can be made more exact if activities are used instead of concentrations to account for interionic attraction effects. This refinement, however, is seldom required for practical work, where the values calculated from the approximate equations just given serve as satisfactory estimates.

Influence of Complexation in Multicomponent Systems

Many liquid pharmaceutical preparations consist of more than a single drug in solution. Fritz et al.19 showed that when several drugs together with pharmaceutical adjuncts interact in solution to form insoluble complexes, 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

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

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 following example is taken from the book by Hildebrand and Scott.20

Example 9-4
Particle Size and Solubility

A solid is to be comminuted so as to increase its solubility by 10%, that is, s/s_o is to become 1.10. What must be the final particle size, assuming that the surface tension of the solid is 100 dynes/cm and the volume per mole is 50 cm^3? The temperature is 27°C.

$$r = \frac{2 \times 100 \times 50}{2.303 \times 8.314 \times 10^7 \times 300 \times 0.0414}$$

$$= 4.2 \times 10^{-6}\text{cm} = 0.042\ \mu\text{m}$$

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.

Key Concept

Poor Aqueous Solubility

"Poor aqueous solubility is caused by two main factors: high lipophilicity and strong intermolecular interactions, which make the solubilization of the solid energetically costly. What is meant by good and poorly soluble depends partly on the expected therapeutic dose and potency of the drug. As a rule of thumb from the delivery perspective, a drug with an average potency of 1 mg/kg should have a solubility of at least 0.1 g/L to be adequately soluble. If a drug with the same potency has a solubility of less than 0.01 g/L it can be considered poorly soluble."3

Determining Thermodynamic and "Kinetic" Solubility

The Phase Rule and Solubility

Solubility can be described in a concise manner by the use of the Gibbs phase rule, which is described using

$$F = C - P + 2 \qquad (9\text{–}12)$$

where *F* is the *number of degrees of freedom*, that is, the number of independent variables (usually temperature, pressure, and concentration) that must be fixed to completely determine the system, *C* is the smallest number of components that are adequate to describe the chemical composition of each phase, and *P* is the number of phases.

The Phase Rule can be used to determine the thermodynamic solubility of a drug substance. This method is based on the thermodynamic principles of heterogeneous equilibria that are among the soundest theoretical concepts in chemistry. It does not depend on any assumptions regarding kinetics or the structure of matter but is applicable to all drugs. The requirements for an analysis are simple, as the equipment needed is basic to most laboratories and the quantities of substances are small. Basically, drug is added in a specific amount of solvent. After equilibrium is achieved, excess drug is removed (usually by filtering) and then the concentration of the dissolved drug is measured using standard analysis techniques such as high-performance liquid chromatography.

A phase-solubility diagram for a pure drug substance is shown in Figure 9-6.21 At concentrations below the saturation concentration there is only one degree of freedom since the studies are performed at constant temperature and pressure. In other words, only the concentration changes. This is represented in Figure 9-6 by the segment A–B of the line. Once the saturation concentration is reached, the addition of more drug to the "system" does not result in higher solution concentrations (segment B–C). Rather, the drug remains in the solid state and the system becomes a two-phase system. Since the temperature, pressure, and solution concentration are constant at drug concentrations above the saturation concentration, the system has zero degree of freedom.

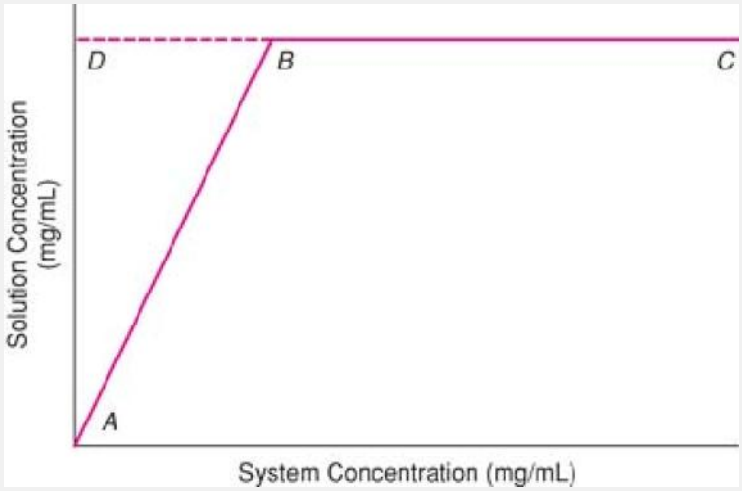

Fig. 9-6. Phase-solubility diagram for a pure drug substance. The line segment A–B represents one phase since the concentration of drug substance is below the saturation concentration. Line segment B–C represents a pure solid in a saturated solution at equilibrium. (From Remington, *The Science and Practice of Pharmacy*, 21st Ed., Lippincott Williams & Wilkins, 2006, p. 216. With permission.)

The situation in Figure 9-6 is valid only for pure drug substances. What if the drug substance is not pure? This situation is described in Figure 9-7.22 If the system has one impurity, the solution becomes saturated with the first component at point B. The situation becomes interesting at this point. In segment B–C of the line, the solution is saturated with component 1 (which is usually the major component such as the drug), so the drug would precipitate out of solution at concentrations greater than this. However, the impurity (the minor component or component 2) does not reach saturation

until it reaches point C on the line. The concentrations of the two components are saturated beyond point C (segment C–D) of the line. Once true equilibrium is achieved, one can extrapolate back to the *Y* axis (solution concentration) to determine the solubility of the two components. Therefore, the thermodynamic solubility of the drug would be equal to the distance A–E and the solubility of the impurity would be equal to the distance represented by E–F. As one can see, this procedure can be used to measure the exact solubility of the pure drug without having a pure form of the drug to start with.

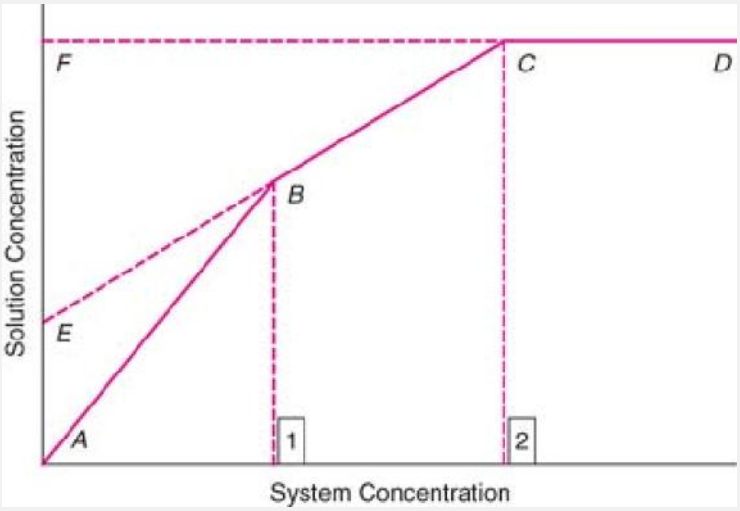

Fig. 9-7. Phase-solubility curve when the drug substance contains one impurity. At point B, the solution becomes saturated with component 1 (the drug). The segment B–C represents two phases—a solution phase saturated with the drug and some of the impurity and a solid phase of the drug. Segment C–D represents two phases—a liquid phase saturated with the drug and impurity and a solid phase containing the drug and the impurity. (From Remington, *The Science and Practice of Pharmacy*, 21st Ed., Lippincott Williams & Wilkins, 2006, p. 217. With permission.)

The practical aspect of measuring thermodynamic solubility is, on the surface, relatively simple but it can be quite time-consuming.4 Some methods have been developed in attempt to reduce the time that it takes to get a result. Starting the experiment with a high purity crystalline form of the substance will give the best chance that the solubility measured after a reasonable incubation period will represent the true equilibrium solubility. However, this may still take several hours to several days. Also, there is still a risk that the incubation period will not be sufficient for metastable crystal forms to convert to the most stable form. This means that the measured concentration may represent the apparent solubility of a different crystal form. This risk must be taken into consideration when running a solubility experiment with material that is not known to be the most stable crystalline form.4

Bhattachar and colleagues4 recently reviewed various aspects of solubility and they are summarized here. In practice, the stable crystalline form of the compound is not available in sufficient purity during early discovery and so the labor-intensive measurement of thermodynamic solubility is not commonly made. The amount of compound required to measure a thermodynamic solubility measurement depends on the volume of solvent used to make the saturated solution and the solubility of the compound in that solvent. Recent reports for miniaturized systems list compound requirements ranging from ~100 mg per measurement for poorly soluble compounds23 to 3 to 10 mg for pharmaceutically relevant compounds.24 Although early-stage solubility information is crucial to drug discovery teams, the number of compounds being assessed, the scarcity of compound, and questionable purity and crystallinity make it nearly impossible to assess thermodynamic solubility.

These challenges have been partially met using a high-throughput kinetic measurement of antisolvent precipitation commonly referred to "*kinetic solubility*."25,26,27,28 "Kinetic solubility is a misnomer, not because it is not kinetic, but because it measures a precipitation rate rather than solubility. Kinetic solubility methods are designed to facilitate high throughput measurements, using submilligram quantities of compound, in a manner that closely mimics the actual solubilization process used in biological laboratories. Typically, the compound is dissolved in dimethyl sulfoxide (because it is a strong organic solvent) to make a stock solution of known concentration. This stock is added gradually to the

aqueous solvent of interest until the anti-solvent properties of the water drive the compound out of solution. The resulting precipitation is detected optically, and the kinetic solubility is defined as the point at which the aqueous component can no longer solvate the drug. Solubility results obtained from kinetic measurements might not match the thermodynamic solubility results perfectly; therefore, caution must be exercised such that the data from the kinetic solubility measurements are used only for their intended application. Since kinetic solubility is determined for compounds that have not been purified to a high degree or crystallized, the impurities and amorphous content in the material lead to a higher solubility than the thermodynamic solubility. Because kinetic solubility experiments begin with the drug in solution, there is a significant risk of achieving supersaturation of the aqueous solvent through precipitation of an amorphous or metastable crystalline form. This supersaturation can lead to a measured value that is significantly higher than the thermodynamic solubility, masking a solubility problem that will become apparent as soon as the compound is crystallized. Owing to the nature of kinetic solubility measurements, there is no time for equilibration of the compound in the aqueous solvent of measurement. Because the compounds tested are in dimethyl sulfoxide solutions, the energy required to break the crystal lattice is not factored into the solubility measurements."4

Key Concept

Effect of pH on Solubility

Solubility must always be considered in the context of pH and pK_a. The relationship between pH and solubility is shown in Figure 9-8. If the measured solubility falls on the steep portion of the pH–solubility profile, small changes to the pH can have a marked effect on the solubility.4

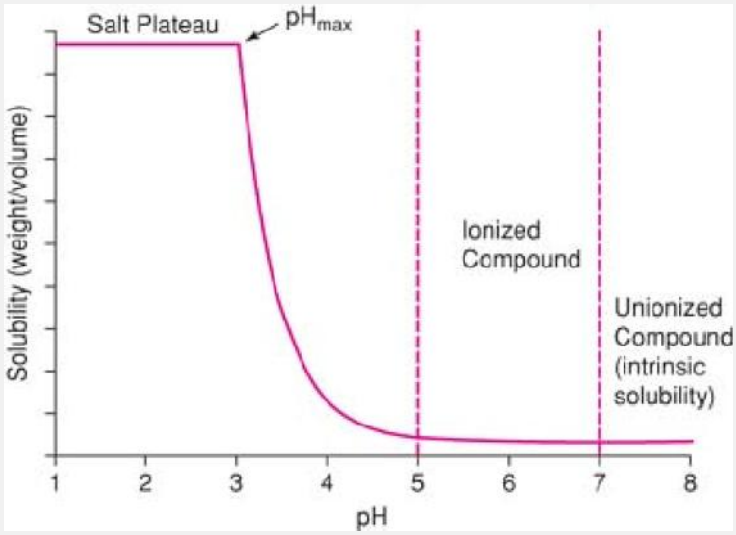

Fig. 9-8. pH–solubility profile for a compound with a single, basic pK_a value of 5. The four regions of pH-dependent solubility are the salt plateau, pH$_{max}$, ionized compound, and un-ionized compound. (Adapted from Bhattachar et al. 2006,4 with permission.)

*Some Limitations of Thermodynamic Solubility*3

In a recent review, Faller and Ertl3 have discussed some of the limitations of traditional methods for determining solubility. For example, if the traditional shake-flask method is used, adsorption to the vial or to the filter, incomplete phase separation, compound instability, and slow dissolution can affect the result. When the potentiometric method is used, inaccurate pK_a determination, compound degradation

during the titration, slow dissolution, or incorrect data analysis can affect the data quality. It is very important to define the experimental conditions well. The intrinsic solubility, S_o, needs to be distinguished from the solubility measured at a given pH value in a defined medium. Intrinsic solubility refers to the solubility of the unionized species. Artursson et al.29 has shown that this parameter is relatively independent of the nature of the medium used. In contrast, solubility measured at a fixed pH value may be highly dependent on the nature and concentration of the counter ions present in the medium.30 This is especially critical for poorly soluble compounds that are strongly ionized at the pH of the measurement. Finally, it is important to note that single pH measurements cannot distinguish between soluble monomers and soluble aggregates of drug molecules, which may range from dimers to micelles unless more sophisticated experiments are performed.30

Computational Approaches

In addition to measuring solubility, computational approaches are widely used and were reviewed recently by Faller and Ertl.3 Briefly, fragment-based models attempt to predict solubility as a sum of substructure contributions—such as contributions of atoms, bonds, or larger substructures. This approach is based on a general assumption that molecule properties are determined completely by molecular structure and may be approximated by the contributions of fragments in the molecule. The inverse relation between solubility and lipophilicity has also been recognized for a long time and empirical relationships between log S_o and log *P*have been reported. Finally, numerous other approaches for predicting water solubility have been reported. The array of possible molecular descriptors that can be used is nearly unlimited. The polar surface area, which characterizes molecule polarity and hydrogen bonding features, is one of the most useful descriptors. Polar surface area, defined as a sum of surfaces of polar atoms, is conceptually easy to understand and seems to encode in an optimal way a combination of hydrogen-bonding features and molecular polarity.

Distribution of Solutes between Immiscible Solvents

If an excess of liquid or solid is added to a mixture of two immiscible liquids, it will distribute itself between the two phases so that each becomes saturated. If the substance is added to the immiscible solvents in an amount insufficient to saturate the solutions, it will still become distributed between the two layers in a definite concentration ratio.

Key Concept

Hydrophobic Parameters

Meyer in 189931 and Overton in 190132 showed that the pharmacologic effect of simple organic compounds was related to their oil/water partition coefficient, *P*. It later became clear that the partition coefficient was of little value for rationalizing specific drug activity (i.e., binding to a receptor) because specificity also relates to steric and electronic effects. However, in the early 1950s, Collander33 showed that the rate of penetration of plant cell membranes by organic compounds was related to *P*. The partition coefficient, *P*, is a commonly used way of defining relative hydrophobicity (also known as lipophilicity) of compounds. For more about partition coefficients, see the text by Hansch and Leo.34

If C_1 and C_2 are the equilibrium concentrations of the substance in $Solvent_1$ and $Solvent_2$, respectively, the equilibrium expression becomes

$$\frac{C_1}{C_2} = K \qquad (9\text{–}13)$$

The equilibrium constant, *K*, is known as the *distribution* ratio, *distribution coefficient*, or *partition coefficient*. Equation (9-13), which is known as the *distribution law*, is strictly applicable only in dilute solutions where activity coefficients can be neglected.

Example 9-5

Distribution Coefficient

When boric acid is distributed between water and amyl alcohol at 25°C, the concentration in water is found to be 0.0510 mole/liter and in amyl alcohol it is found to be 0.0155 mole/liter. What is the distribution coefficient? We have

$$K = \frac{C_{H_2O}}{C_{alc}} = \frac{0.0510}{0.0155} = 3.29$$

No convention has been established with regard to whether the concentration in the water phase or that in the organic phase should be placed in the numerator. Therefore, the result can also be expressed as

$$K = \frac{C_{alc}}{C_{H_2O}} = \frac{0.0155}{0.0510} = 0.304$$

One should always specify, which of these two ways the distribution constant is being expressed.

Knowledge of partition is important to the pharmacist because the principle is involved in several areas of current pharmaceutical interest. These include preservation of oil–water systems, drug action at nonspecific sites, and the absorption and distribution of drugs throughout the body. Certain aspects of these topics are discussed in the following sections.

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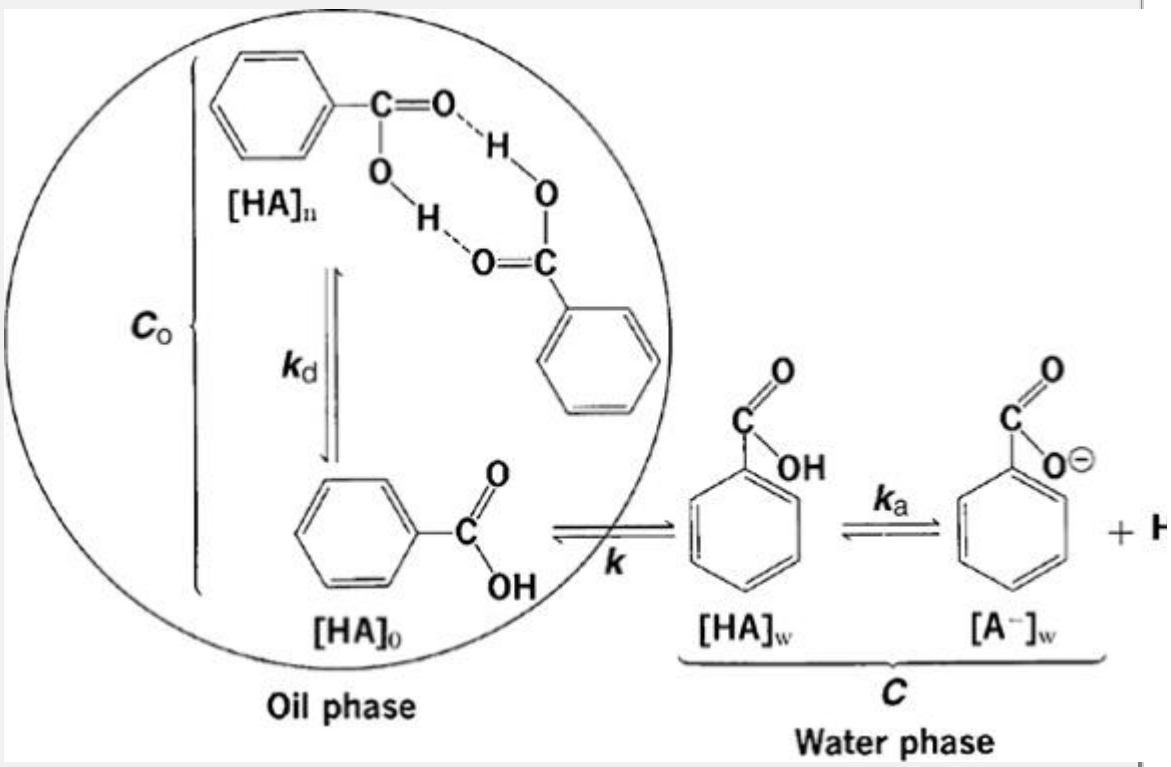

Fig. 9-9. Schematic representation of the distribution of benzoic acid between water and an oil phase. The oil phase is depicted as a magnified oil droplet in an oil-in-water emulsion.

Effect of Ionic Dissociation and Molecular Association on Partition

The solute can exist partly or wholly as associated molecules in one of the phases or it may dissociate into ions in either of the liquid phases. The distribution law applies only to the concentration of the species common to both phases, namely, the *monomer* or simple molecules 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 ions in the water, equation **(**9-13**)** can be used to compute the

distribution constant. When association and dissociation occur, however, the situation becomes more complicated. The general case where benzoic acid associates in the oil phase and dissociates in the aqueous phase is shown schematically in Figure 9-9.

Two cases will be treated. *First*, according to Garrett and Woods,35 benzoic acid is considered to be distributed between the two phases, peanut oil and water. Although benzoic acid undergoes dimerization (association to form two molecules) in many nonpolar 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 Figure 9-9 for the case under consideration, C_o, the total concentration of benzoic acid in the oil phase, is equal to $[HA]_o$, the monomer concentration in the oil phase, because association does not occur in peanut oil.

The species common to both the oil and water phases are the unassociated and undissociated benzoic acid molecules. The distribution is expressed as

$$K = \frac{[HA]_o}{[HA]_w} = \frac{C_o}{[HA]_w} \qquad (9\text{–}14)$$

where K is the *true distribution coefficient*, $[HA]_o = C_o$ is the molar concentration of the simple benzoic acid molecules in the oil phase, and $[HA]_w$ is the molar concentration of the undissociated acid in the water phase.

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

$$C_w = [HA]_w + [A^-]_w \qquad (9\text{–}15)$$

and the experimentally observed or *apparent distribution coefficient* is

$$K' = \frac{[HA]_o}{[HA]_w + [A^-]_w} = \frac{C_o}{C_w} \qquad (9\text{–}16)$$

As seen in Figure 9-9, the observed distribution coefficient depends on two equilibria: the distribution of the undissociated acid between the immiscible phases as expressed in equation (9-14) 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

$$K_a \frac{[H_3O^+][A^-]_w}{[HA]_w} \qquad (9\text{–}17)$$

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 that the concentration, C, of the acid in the aqueous phase before distribution, assuming equal volumes of the two phases, is*

$$C = C_o + C_w \qquad (9\text{–}18)$$

one arrives at the combined result:†

$$\frac{K_a + [H_3O^+]}{C_w} = \frac{K_a}{C} + \frac{K + 1}{C}[H_3O^+] \qquad (9\text{–}19)$$

Expression (9-19) is a linear equation of the form $y = a + bx$, and therefore a plot of $(K_a + [H_3O^+])/C_w$ against $[H_3O^+]$

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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 equation (9-14) by analysis of the oil phase and of the water phase at a sufficiently low pH (2.0) at which the acid would exist completely in the un-ionized form. One of the advantages of equation (9-19), however, is that the oil phase need not be analyzed; only the hydrogen ion concentration and C_w, the total concentration remaining in the aqueous phase at equilibrium, need be determined.

Example 9-6

According to Garrett and Woods,35 the plot of $(K_a + [H_3O^+])/C_w$ against $[H_3O^+]$ for benzoic acid distributed between equal volumes of peanut oil and a buffered aqueous solution yields a slope $b = 4.16$ and an intercept $a = 4.22 \times 10^{-5}$. The K_a of benzoic acid is 6.4×10^{-5}. Compute

the true partition coefficient, K, and compare it with the value $K = 5.33$ obtained by the authors. We have

$$b = (K + 1)/C$$

or

$$K = bC/1$$

Because

$$a = k_a/C \text{ or } c = \frac{K_a}{a}$$

the expression becomes

$$K = \frac{bk_a}{a}1 = \frac{bK_a - a}{a}$$

and

$$K = \frac{(4.16 \times 6.4 \times 10^{-5}) - 4.22 \times 10^{-5}}{4.22 \times 10^{-5}} = 5.31$$

Second, let us now consider the case 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 undissociated molecules in the aqueous layer.

The equilibrium between simple molecules HA and associated molecules $(HA)_n$ in

$$\underset{\text{Associated molecules}}{(HA)_n} \rightleftharpoons \underset{\text{Simple molecules}}{n(HA)}$$

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

$$K_d = \frac{[HA]_o^n}{[(HA)]_n} \qquad (9\text{–}20)$$

or

$$[HA]_o - \sqrt[n]{K_d}\ \sqrt[n]{[(HA)_n]} \qquad (9\text{–}21)$$

Because benzoic acid exists predominantly in the form of double molecules in benzene, C_o can replace $[(HA)_2]$, where C_o is the total molar concentration of the solute in the organic layer. Then equation (9-21) can be written approximately as

$$[HA]_o \cong \text{constant} \times \sqrt{C_o} \qquad (9\text{–}22)$$

In conformity with the distribution law as given in equation (9-14), the true distribution coefficient is always expressed in terms of simple species common to both phases, that is, in terms of $[HA]_w$ and $[HA]_o$. In the benzene–water system, $[HA]_o$ is given by equation (9-22), and the modified distribution constant becomes

$$K'' = \frac{[HA]_o}{[HA]_w} = \frac{\sqrt{C_o}}{[HA]_w} \qquad (9\text{–}23)$$

The results for the distribution of benzoic acid between benzene and water, as given by Glasstone,36 are given in Table 9-3.

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 Glasstone.37 Suppose that w grams of a solute is extracted repeatedly from V_1 mL of one solvent with successive portions of V_2 mL of a second solvent, which is immiscible with the 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

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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 $(w - w_1)/V_2$ g/mL. The distribution coefficient is thus

Table 9-3 Distribution of Benzoic Acid between Benzene and Acidified Water at

6°C*,†

$[HA]_w$	C_o	$K'' - \sqrt{C_o}/HA_w$
0.00329	0.0156	38.0
0.00579	0.0495	38.2
0.00749	0.0835	38.6
0.0114	0.195	38.8

*The concentrations are expressed in mole/liter.

†From S. Glasstone, *Textbook of Physical Chemistry*, Van Nostrand, New York, 1946, p. 738.

$$K = \frac{w_1/V_1}{(w - w_1)V_2} \qquad (9\text{–}24)$$

or

$$w_1 = w\frac{KV_1}{KV_1 + V_2} \qquad (9\text{–}25)$$

The process can be repeated, and after n extractions,37

$$w_n = w\left(\frac{KV_1}{KV_1 + V_2}\right)^n \qquad (9\text{–}26)$$

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. The development just described assumes complete immiscibility of the two liquids. When ether is used to extract organic compounds from water, this is not true; however, the equations provide approximate values that are satisfactory for practical purposes. The presence of other solutes, such as salts, can also affect the results by complexing with the solute or by salting out one of the phases.

Example 9-7

Distribution Coefficient

The distribution coefficient for iodine between water and carbon tetrachloride at 25°C is $K=C_{H2O}/C_{CCl4}$ = 0.012. How many grams of iodine are extracted from a solution in water containing 0.1 g in 50 mL by one extraction with 10 mL of CCl_4? How many grams are extracted by two 5-mL portions of CCl_4? We have

$$w_1 = 0.10 \times \frac{0.012 \times 50}{(0.012 \times 50) + 10}$$
$$= 0.0057 \text{ g remains or } 0.0943 \text{ g is extracted}$$
$$w_2 = 0.10 \times \left(\frac{0.012 \times 50}{(0.012 \times 50) + 5}\right)^2$$
$$= 0.0011 \text{ g of iodine}$$

Thus, 0.0011 g of iodine remains in the water phase, and the two portions of CCl_4 have extracted 0.0989 g.

Solubility and Partition Coefficients

Hansch et al.38 observed a relationship between aqueous solubilities of nonelectrolytes and partitioning. Yalkowsky and Valvani39 obtained an equation for determining the aqueous solubility of liquid or crystalline organic compounds:

$$\log S = -\log K - 1.11\frac{\Delta S_f(\text{mp} - 25)}{1364} + 0.54 \qquad \textbf{(9–27)}$$

where S is aqueous solubility in moles/liter, K is the octanol–water partition coefficient, ΔS_f is the molar entropy of fusion, and mp is the melting point of a 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 equation (9-27) becomes zero.

The entropy of fusion and the partition coefficient can be estimated from the chemical structure of the compound. For rigid molecules, ΔS_f = 13.5 entropy units (eu). For molecules with n greater than five nonhydrogen atoms in a flexible chain,

$$\Delta S_f = 13.5 + 2.5(n - 5)\text{eu} \qquad \textbf{(9–28)}$$

Leo et al.38 provided partition coefficients for a large number of compounds. When experimental values are not available, group contribution methods38,40 are available for estimating partition coefficients.

Example 9-8

Molar Aqueous Solubility

Estimate the molar aqueous solubility of heptyl *p*-aminobenzoate, mp 75°C, at 25°C:

It is first necessary to calculate ΔS_f and log K.

There are nine nonhydrogens in the flexible chain (C, O, and the seven carbons of CH_3). Using equation (9-28), we obtain

$$\Delta S_f = 13.5 + 2.5(9 - 5) = 23.5 \text{ eu}$$

For the partition coefficient, Leo et al.38 give for log K of benzoic acid a value of 1.87, the contribution of NH_2 is -1.16, and that of CH_2 is 0.50, or 7 × 0.50 = 3.50 for the seven carbon atoms of CH_3 in the chain:

$$\log K(\text{heptyl } p\text{-aminobenzoate}) = 1.87 - 1.16 + 3.50 = 4.21$$

We substitute these values into equation (9-27) to obtain

$$\log S = -4.21 - 1.11\left(\frac{23.5(75 - 25)}{1364}\right) + 0.54$$

$$\log S = -4.63$$

$$S_{(\text{calc})} = 2.36 \times 10^{-5}\ \text{M}$$

$$S_{(\text{obs})} = 2.51 \times 10^{-5}\ \text{M}$$

The oil–water partition coefficient is an indication of the lipophilic or hydrophobic character of a drug molecule. Passage of drugs through lipid membranes and interaction with macromolecules at receptor sites sometimes correlate well with the octanol–water partition coefficient of the drug. In the last few sections, the student has been introduced to the distribution of drug molecules between immiscible solvents together with some important applications of partitioning; a number of useful references are available for further study on the subject.41,42,43,44 Three excellent books45,46,47 on solubility in the pharmaceutical sciences will be of interest to the serious student of the subject.

Chapter Summary

The concept of *solubility* was presented in this chapter. As described, solubility is defined in quantitative terms as the concentration of solute in a saturated solution 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. Solubility is an *intrinsic* material property that can be altered only by chemical modification of the molecule. Solubilization was not covered in this chapter. In order to determine the true solubility of a compound, one must measure the

thermodynamic solubility. However, given the constraints that were discussed an alternate method, kinetic solubility determination, was presented that offers a more practical alternative given the realities of the situation. Distribution phenomena were also discussed in some detail. The distribution behavior of drug molecules is important to many pharmaceutical processes including physicochemical (e.g., when formulating drug substances) and biological (e.g., absorption across a biological membrane) processes.

Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

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Recommended Readings

S. N. Bhattachar, L. A. Deschenes, and J. A. Wesley, Drug Discov. Today **11,** 1012–1018, 2006.
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*The meaning of C in equation (9-18) is understood readily by considering a simple illustration. Suppose one begins with 1 liter of oil and 1 liter of water, and after benzoic acid has been distributed between the two phases, the concentration C_o of benzoic acid in the oil is 0.01 mole/liter and the concentration C_w of benzoic acid in the aqueous phase is 0.01 mole/liter. Accordingly, there is 0.02 mole/2 liter or 0.01 mole of benzoic acid per liter of total mixture after distribution equilibrium has been attained. Equation (9-18) gives

$$\begin{aligned} C &= C_o + C_w = 0.01 \text{ mole/liter} + 0.01 \text{ mole/liter} \\ &= 0.02 \text{ mole/liter} \end{aligned}$$

The concentration, C, obviously is not the total concentration of the acid in the mixture at equilibrium but, rather, twice this value. C is therefore seen to be the concentration of benzoic acid in the water phase (or the oil phase) before the distribution is carried out.

†Equation (9-19) is obtained as follows. Substituting for $[A^-]_w$ from equation (9-17) into equation (9-16) gives

$$K' = \frac{[HA]_o}{[HA]_w + \dfrac{K_a[HA]_w}{[H_3O^+]}} = \frac{[HA]_o[H_3O^+]}{[HA]_w(K_a + [H_3O^+])} \qquad (a)$$

Then $[HA]_w$ from equation (9-14) is substituted into (a) to eliminate $[HA]_o$ from the equation:

$$K' = \frac{[HA]_o[H_3O^+]}{[HA]_o/K(K_a + [H_3O^+])} = \frac{K[H_3O^+]}{K_a + [H_3O^+]} \qquad (b)$$

The apparent distribution constant is eliminated by substituting equation (b) into equation (9-16) to give

$$\frac{K[H_3O^+]}{K_a + [H_3O^+]} = \frac{C_o}{C_w} \qquad (c)$$

or

$$C_o = \frac{K[H_3O^+]C_w}{K_a + [H_3O^+]} \qquad (d)$$

C_o is eliminated by substituting equation (c) into equation (9-18):

$$\begin{aligned} C &= \frac{K[H_3O^+]C_w}{K_a + [H_3O^+]} + C_w \\ &= \frac{K[H_3O^+]C_w + (K_a + [H_3O^+]C_w}{K_a + [H_3O^+]} \end{aligned}$$

Rearranging equation (*d*) gives the final result:

$$= \frac{K_a + [H_3O^+]}{C_w} = \frac{[H_3O^+](K + 1) + K_a}{C}$$

Chapter Legacy

Fifth Edition: published as Chapter 10 (Solubility and Distribution Phenomena). Updated by Patrick Sinko.

Sixth Edition: published as Chapter 8 (Solubility and Distribution Phenomena). Updated by Patrick Sinko.