

**Solubility and distribution phenomena**  
**Interfacial phenomena**  
**Complexation and Protein Binding**  
**Colloids**

**Rheology**

**Kinetics**

**Micromeritics**

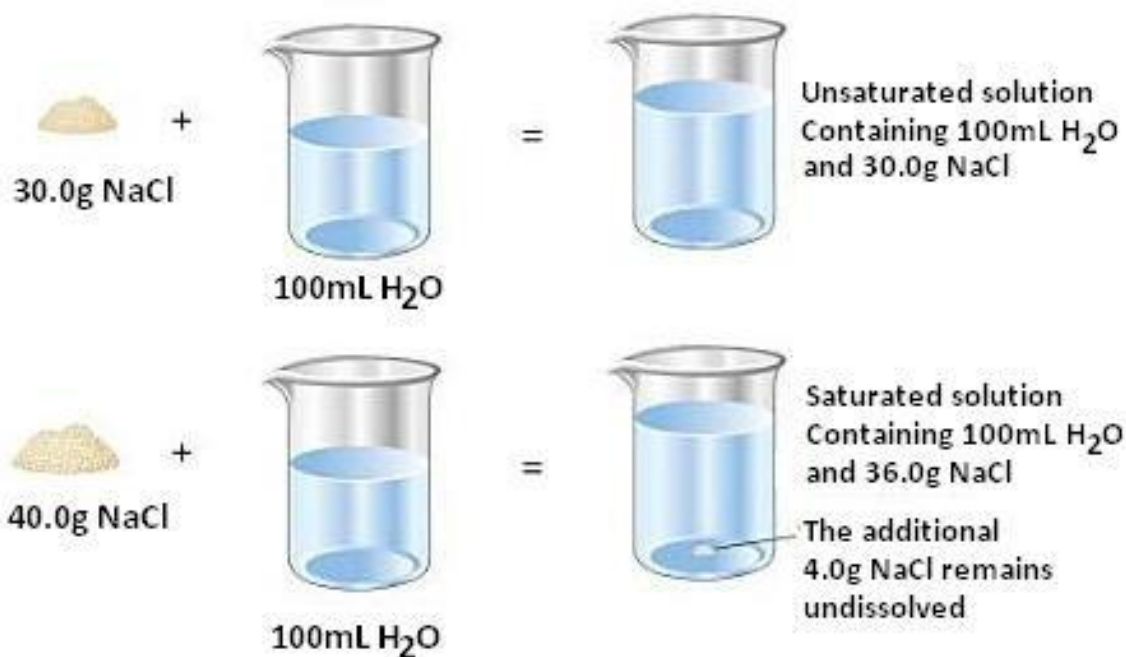
**Pharmaceutical polymers**

# **Solubility and distribution**

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# Solutions and Solubility

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



# SOLUBILITY

## UNSATURATED SOLUTION

more solute  
dissolves



## SATURATED SOLUTION

no more solute  
dissolves



## SUPERSATURATED SOLUTION

becomes unstable,  
crystals form



increasing concentration

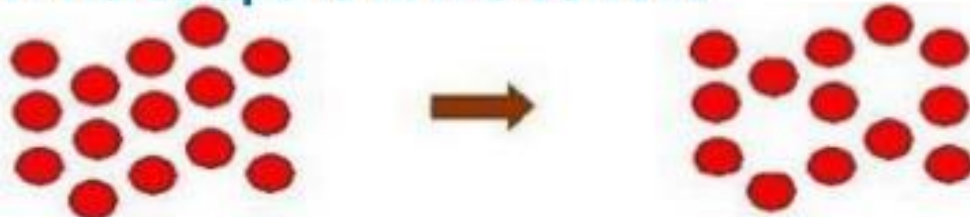


- **Solubility** is defined in **quantitative** terms as the concentration of solute in a saturated solution at a certain temperature, and in a **qualitative way**, it can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.
- **An unsaturated** 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.

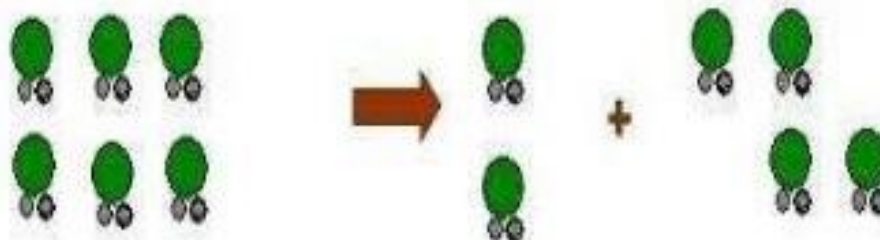
- The solubility of a compound depends on
  1. The physical and chemical properties of the solute
  2. Temperature
  3. Pressure
  4. The pH of the solution.
- **Thermodynamic solubility** of a drug in a solvent is the maximum amount of the most stable crystalline form that remains in solution in a given volume of the solvent at a given temperature and pressure under equilibrium conditions.

# Process of Solubilization

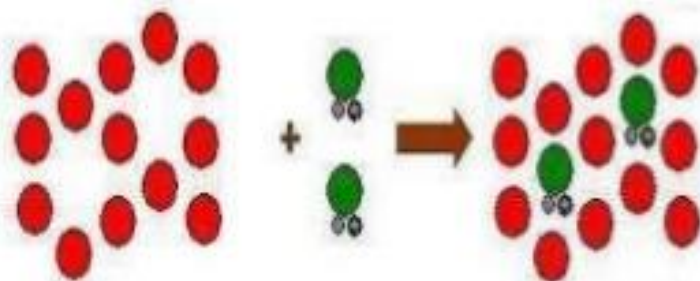
**Step 1: Holes opens in the solvent**



**Step 2: Molecules of the solid break away from the bulk**



**Step 3: The freed solid molecule is integrated into the hole in the solvent**



# ***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.



**Table 9-1 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

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**”.

*H.W : Why water acts as a good solvents?*

# ***Polar Solvents***

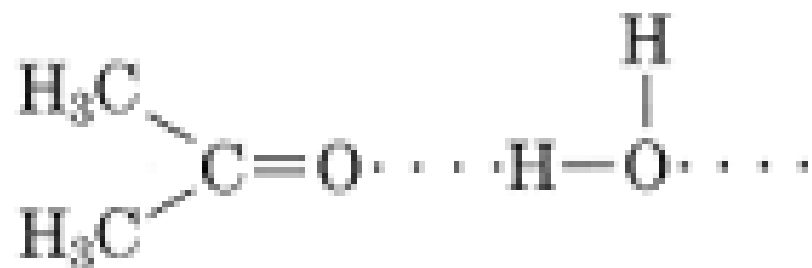
- 1) **Polarity** of the solvent, that is, to its dipole moment. Polar solvents dissolve ionic solutes and other polar substances.
- 2) The ability of the solute to form **hydrogen bonds** is a far more significant factor than is the polarity as reflected in a high dipole moment. Water dissolves phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds.
- 3) Difference in acidic and basic character of the constituents in the **Lewis electron donor–acceptor** sense also contributes to specific interactions in solutions.



Alcohol



Aldehyde



Ketone



Amine

4) 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.

**5) 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.

## *Non-polar 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 .

## *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. The intermediate solvent action of alcohol on water—castor oil mixtures was studied.

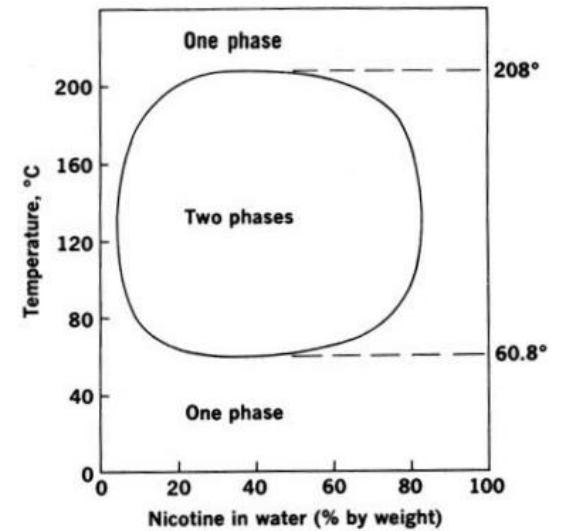
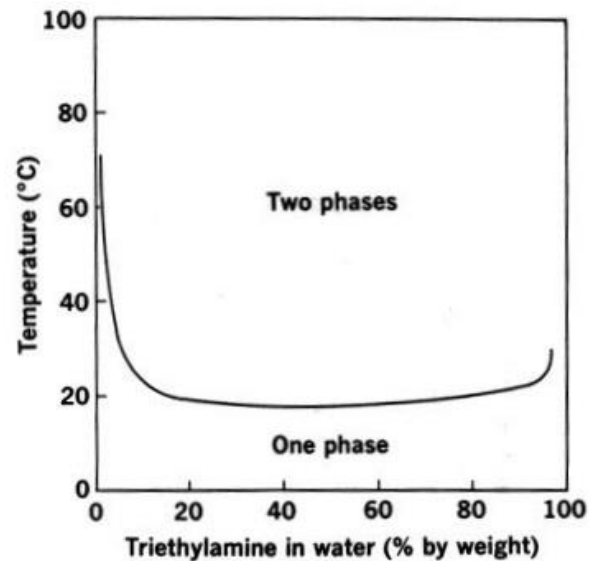
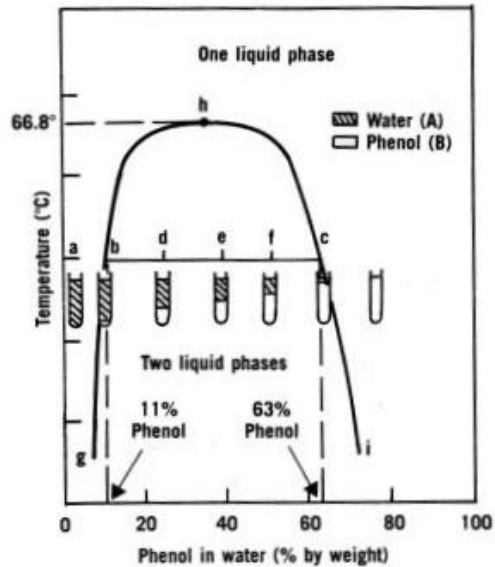
# **Solubility of Liquids in Liquid**

- 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; 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.

# Miscibility



# 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 ( $\text{C}_{17}\text{H}_{33}\text{COOH}$ ) 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.
- 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
- 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 ( $\text{—SO}_2\text{—}$ ) 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.

# 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

- If  $C_1$  and  $C_2$  are the equilibrium concentrations of the substance in Solvent1 and Solvent2, respectively, the equilibrium expression becomes

$$\frac{C_1}{C_2} = K \quad (9-13)$$

- 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

$$K = \frac{C_{\text{H}_2\text{O}}}{C_{\text{alc}}} = \frac{0.0510}{0.0155} = 3.29$$

- 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

$$K = \frac{C_{\text{alc}}}{C_{\text{H}_2\text{O}}} = \frac{0.0155}{0.0510} = 0.304$$

- 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.



# 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<sup>-</sup>, we write the equilibria in a saturated solution of this slightly soluble weak electrolyte as:



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

$$S_0 = [\text{HP}]_{\text{sol}} \quad (9-3)$$

where  $S_0$  is molar or intrinsic solubility. The constant for the acid-base equilibrium, equation (9-2), is

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{P}^-]}{[\text{HP}]} \quad (9-4)$$

or

$$[\text{P}^-] = K_a \frac{[\text{HP}]}{[\text{H}_3\text{O}^+]} \quad (9-5)$$

where the subscript "sol" has been deleted from  $[\text{HP}]_{\text{sol}}$  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,  $[P^-]$ :

$$S = [HP] + [P^-] \quad (9-6)$$

Substituting  $S_0$  for  $[HP]$  from equation (9-3) and the expression from equation (9-5) for  $[P^-]$  yields

$$S = S_0 + K_a \frac{S_0}{[H_3O^+]} \quad (9-7)$$

$$S = S_0 \left( 1 + \frac{K_a}{[H_3O^+]} \right) \quad (9-8)$$

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

$$(S - S_0) = K_a \frac{S_0}{[H_3O^+]}$$
$$\log(S - S_0) = \log K_a + \log S_0 - \log [H_3O^+]$$

and finally

$$pH_p = pK_a + \log \frac{S - S_0}{S_0} \quad (9-9)$$

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<sup>-</sup>.
- **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), **pHp depends on the initial molar concentration, S, of salt added, the molar solubility of the undissociated acid, S<sub>0</sub>, also known as the intrinsic solubility, and the pK<sub>a</sub>.**
- Equation (9-9) has been used to determine the pK<sub>a</sub> of sulfonamides and other drugs.

## 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,  $S_0$ , 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

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

$$\text{pH}_p = 7.41 + \log \frac{(0.039 - 0.005)}{0.005} = 8.24$$

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

$$\text{pH}_p = \text{p}K_w - \text{p}K_b + \log \frac{S_0}{S - S_0} \quad (9-10)$$

where  $S$  is the concentration of the drug initially added as the salt and  $S_0$  is the molar solubility of the free base in water. Here  $\text{pH}_p$  is the pH above which the drug begins to precipitate from solution as the free base.



- **in a solution of a weakly acidic drug:**

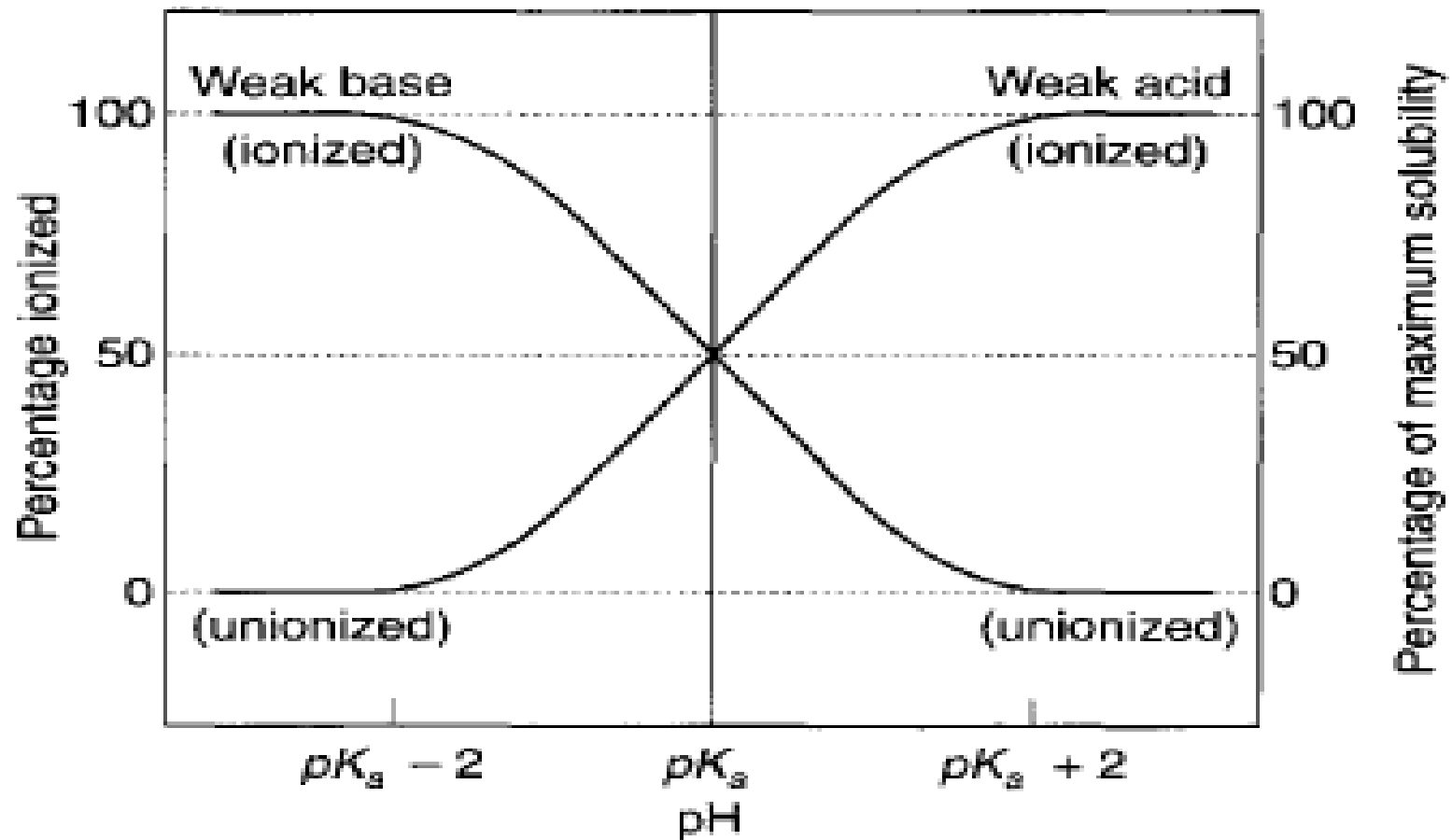
$$pH = pka + \log \frac{A^-}{HA}$$

This is known as the Henderson--Hasselbalch equation.

- For weak bases :

$$pH = pKa + \log \frac{B}{BH^+}$$

- The degree of ionization is controlled by pKa of the molecule and the pH of the surrounding environment.
- When pH is equal to pKa of the drug , that drug is 50% ionized.
- The Henderson –Hasselbach equation also shows that the drug is almost completely ionized or non-ionized when two pH units away from its pKa .



**Fig. 3.1** Change in degree of ionization and relative solubility of weakly acidic and weakly basic drugs as a function of pH.

# Calculation example

1. The  $pK_a$  value of aspirin, which is a weak acid, is about 3.5. If the pH of the gastric contents is 2.0, then from Eqn 3.12:

$$\log \frac{c_u}{c_i} = pK_a - \text{pH} = 3.5 - 2.0 = 1.5$$

so that the ratio of the concentration of unionized acetylsalicylic acid to acetylsalicylate anion is given by:

$$c_u:c_i = \text{antilog } 1.5 = 31.62:1$$

2. The pH of plasma is 7.4, so that the ratio of unionized to ionized aspirin in this medium is given by:

$$\log \frac{c_u}{c_i} = pK_a - \text{pH} = 3.5 - 7.4 = -3.9$$

and

$$c_u:c_i = \text{antilog } -3.9 = 1.259 \times 10^{-4}:1$$

3. The  $pK_a$  of the weakly acidic drug sulphapyridine is about 8.0; if the pH of the intestinal contents is 5.0, then the ratio of unionized to ionized drug is given by:

$$\log \frac{c_u}{c_i} = pK_a - \text{pH} = 8.0 - 5.0 = 3.0$$

and

$$c_u:c_i = \text{antilog } 3.0 = 10^3:1$$

4. The  $pK_a$  of the basic drug amidopyrine is 5.0. In the stomach the ratio of ionized to unionized drug is calculated from Eqn 3.16 as follows:

$$\log \frac{c_i}{c_u} = pK_a - \text{pH} = 5.0 - 2.0 = 3.0$$

and

$$c_i:c_u = \text{antilog } 3.0 = 10^3:1$$

whereas in the intestine the ratio is given by:

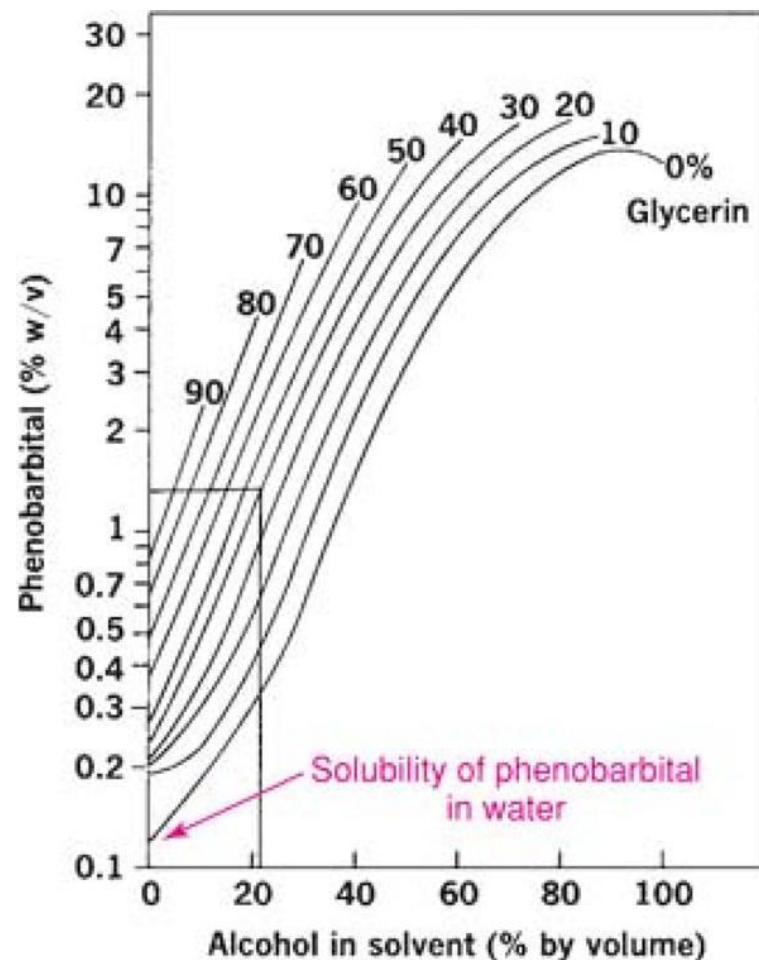
$$\log \frac{c_i}{c_u} = 5.0 - 5.0 = 0$$

and

$$c_i:c_u = \text{antilog } 0 = 1:1$$

## ***The Influence of Solvents on the Solubility of Drugs***

- 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 on a semilogarithm grid in Figure 9-4 from the data of Krause and Cross.

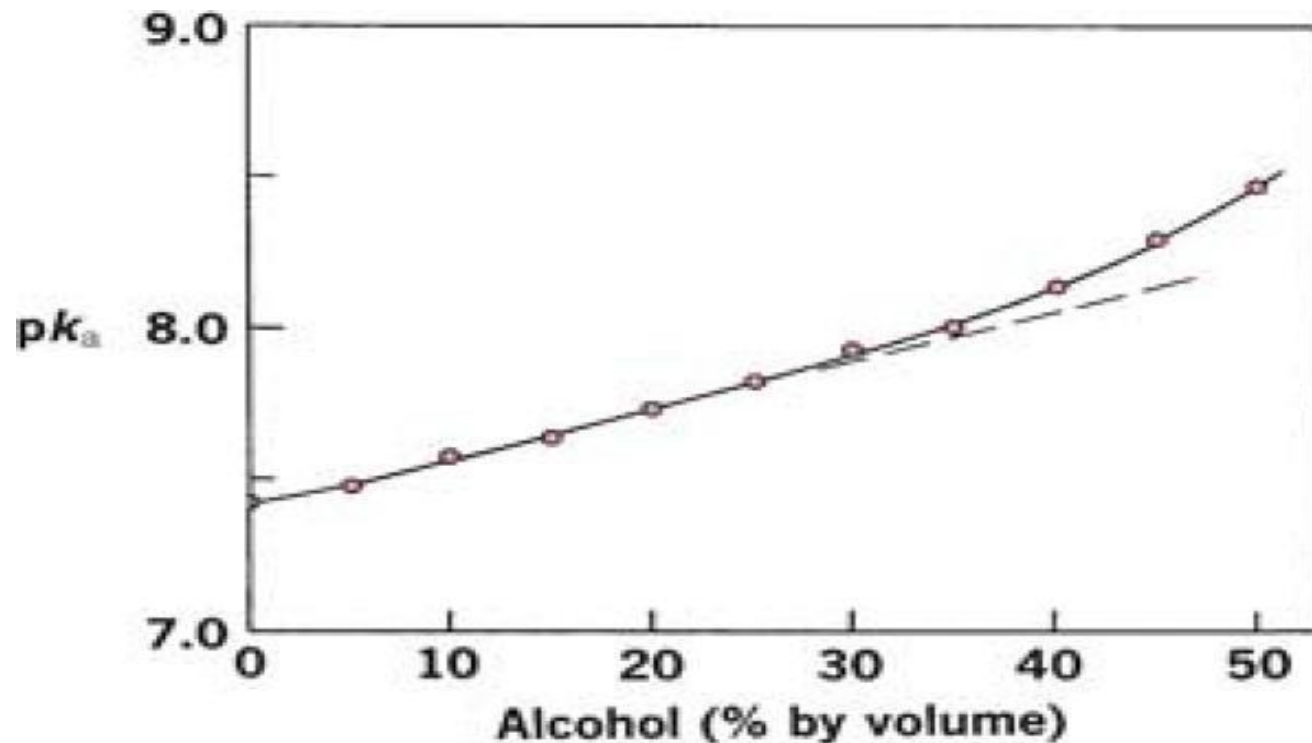


**Fig. 9-4.** The solubility of phenobarbital in a mixture of water, alcohol, and glycerin at 25°C. The vertical axis is a logarithmic scale representing the solubility of phenobarbital in g/100 mL. (From G. M. Krause and J. M. Cross, *J. Am. Pharm. Assoc. Sci. Ed.* **40**, 137, 1951. With permission.)



# ***Combined Effect of pH and Solvents***

- Edmonson and Goyan investigated the effect of alcohol on the solubility of phenobarbital.
- The results of Edmonson and Goyan are shown in Figure 9-5, where one observes that the pKa 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.



**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.)

- The calculation of solubility as a function of pH involving these results is illustrated in the following example.

### 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),

$$\text{pH}_p = 7.92 + \log \frac{0.236 - 0.028}{0.028}$$
$$\text{pH}_p = 7.92 + 0.87 = 8.79$$

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

$$\text{pH}_p = 7.41 + \log \frac{0.236 - 0.005}{0.005} = 9.07$$

- 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.**

## *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  $C_1$  and  $C_2$  are the equilibrium concentrations of the substance in Solvent1 and Solvent2, respectively, the equilibrium expression becomes:

$$\frac{C_1}{C_2} = K \quad (9-13)$$

The equilibrium constant,  $K$ , is known as the distribution ratio, distribution coefficient, or partition coefficient.

## 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

$$K = \frac{C_{\text{H}_2\text{O}}}{C_{\text{alc}}} = \frac{0.0510}{0.0155} = 3.29$$

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

$$K = \frac{C_{\text{alc}}}{C_{\text{H}_2\text{O}}} = \frac{0.0155}{0.0510} = 0.304$$

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.

# *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.
- 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 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

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

or

$$w_1 = w \frac{K V_1}{K V_1 + V_2} \quad (9-25)$$

The process can be repeated, and after  $n$  extractions,<sup>37</sup>

$$w_n = w \left( \frac{K V_1}{K V_1 + V_2} \right)^n \quad (9-26)$$

- 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.

## Example 9-7

### Distribution Coefficient

The distribution coefficient for iodine between water and carbon tetrachloride at 25°C is  $K = C_{\text{H}_2\text{O}}/C_{\text{CCl}_4} = 0.012$ . 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  $\text{CCl}_4$ ? How many grams are extracted by two 5-mL portions of  $\text{CCl}_4$ ? We have

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

Thus, 0.0011 g of iodine remains in the water phase, and the two portions of  $\text{CCl}_4$  have extracted 0.0989 g.