

Remington: The Science and Practice of Pharmacy

Nineteenth Edition

Volume I

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Library of Congress Catalog Card No. 60-53334

ISBN 0-912734-04-3

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Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

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Solutions and Phase Equilibria

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Solutions and Solubility

A solution is a chemically and physically homogeneous mixture of two or more substances. The term solution generally denotes a homogeneous mixture that is liquid even though it is possible to have homogeneous mixtures which are solid or gaseous. Thus, it is possible to have solutions of solids in liquids, liquids in liquids, gases in liquids, gases in gases and solids in solids. The first three of these are most important in pharmacy and ensuing discussions will be concerned primarily with them.

In pharmacy different kinds of liquid dosage forms are used and all consist of the dispersion of some substance or substances in a liquid phase. Depending on the size of the dispersed particle they are classified as *true solutions*, *colloidal solutions* or *suspensions*. If sugar is dissolved in water, it is supposed that the ultimate sugar particle is of molecular dimensions and that a *true solution* is formed. On the other hand, if very fine sand is mixed with water, a *suspension* of comparatively large particles, each consisting of many molecules, is obtained. Between these two extremes lie *colloidal solutions*, the dispersed particles of which are larger than those of true solutions but smaller than the particles present in suspensions. In this chapter only true solutions will be discussed.

It is possible to classify broadly all solutions as one of two types.

In the first type, although there may be lesser or greater interaction between the dispersed substance (the solute) and the dispersing medium (the solvent), the solution phase contains the same chemical entity as found in the solid phase and, thus, upon removal of the solvent, the solute is recovered unchanged. One example would be sugar dissolved in water where, in the presence of sugar in excess of its solubility, there is an equilibrium between sugar molecules in the solid phase with sugar molecules in the solution phase. A second example would be dissolving silver chloride in water. Admittedly, the solubility of this salt in water is low, but it is finite. In this case the solvent contains silver and chloride ions and the solid phase contains the same material. The removal of the solvent yields initial solute.

In the second type the solvent contains a compound which is different from that in the solid phase. The difference between the compound in the solid phase and solution is due generally to some chemical reaction that has occurred in the solvent. An example would be dissolving aspirin in an aqueous solvent containing some basic material capable of reacting with the acid aspirin. Now the species in solution would not only be undissociated aspirin, but aspirin also as its anion, whereas the species in the solid phase is aspirin in only its undissociated acid form. In this situation, if the solvent were removed, part of the substance obtained (the salt of aspirin) would be different from what was present initially in the solid.

Solutions of Solids in Liquids

Reversible Solubility without Chemical Reaction—From a pharmaceutical standpoint solutions of solids in liquids, with or without accompanying chemical reaction in the solvent, are of the greatest importance, and many quantitative

data on the behavior and properties of such solutions are available. This discussion will be concerned with definitions of solubility, the rate at which substances go into solution and with temperature and other factors which control solubility.

Solubility—When an excess of a solid is brought into contact with a liquid, molecules of the former are removed from its surface until equilibrium is established between the molecules leaving the solid and those returning to it. The resulting solution is said to be saturated at the temperature of the experiment, and the extent to which the solute dissolves is referred to as its *solubility*. The extent of solubility of different substances varies from almost imperceptible amounts to relatively large quantities, but for any given solute the solubility has a constant value at constant temperature.

Under certain conditions it is possible to prepare a solution containing a larger amount of solute than is necessary to form a saturated solution. This may occur when a solution is saturated at one temperature, the excess of solid solute removed and the solution cooled. The solute present in solution, even though it may be less soluble at the lower temperature, does not always separate from the solution and there is produced a *supersaturated solution*. Such solutions, formed by sodium thiosulfate or potassium acetate, for example, may be made to deposit their excess of solute by vigorous shaking, scratching the side of the vessel in contact with the solution or introducing into the solution a small crystal of the solute.

Methods of Expressing Solubility—When quantitative data are available, solubilities may be expressed in many ways. For example, the solubility of sodium chloride in water at 25° may be stated as

- 1 g of sodium chloride dissolves in 2.786 mL of water. (An approximation of this method is used by the USP.)
- 35.89 g of sodium chloride dissolves in 100 mL of water.
- 100 mL of a saturated solution of sodium chloride in water contains 31.71 g of solute.
- 100 g of a saturated solution of sodium chloride in water contains 26.47 g of solute.
- 1 L of a saturated solution of sodium chloride in water contains 5.425 moles of solute. This also may be stated as a saturated solution of sodium chloride in water is 5.425 molar with respect to the solute.

In order to calculate 3 from 1 or 2 it is necessary to know the density of the solution, in this case 1.198 g/mL. To calculate 5, the number of grams of solute in 1000 mL of solution (obtained by multiplying the data in (3) by ten) is divided by the molecular weight of sodium chloride, namely, 58.45.

Several other concentration expressions are used. Molality is the number of moles of solute in 1000 g of solvent and could be calculated from the data in 4 by subtracting grams of solute from grams of solution to obtain grams of solvent, relating this to 1000 g of solvent and dividing by molecular weight to obtain mols.

Mol fraction is the fraction of the total number of mols present which are mole of one component. Mol % may be obtained by multiplying mol fraction by 100. Normality refers to the number of gram equivalent weights of solute dissolved in 1000 mL of solution.

In pharmacy, use also is made of three other concentration expressions. Percent by weight (% w/w) is the number of

The author acknowledges the kind assistance of Dr Sarma Duddu, SmithKline Beecham Pharmaceuticals, in the revision of parts of this chapter.

Table 1—Descriptive Terms for Solubility

Descriptive terms	Parts of solvent for 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparsely soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or insoluble	More than 10,000

grams of solute per 100 g of solution and is exemplified by 4 above. Percent weight in volume (% w/v) is the number of grams of solute per 100 mL of solution and is exemplified by 3 above. Percent by volume (% v/v) is the number of milliliters of solute in 100 mL of solution, referring to solutions of liquids in liquids. The USP indicates that the term "percent," when unqualified, means percent weight in volume for solutions of solids in liquids and percent by volume for solutions of liquids in liquids.

When, in pharmacopeial texts, it has not been possible, or in some instances not desirable, to indicate exact solubility, a descriptive term has been used. Table 1 indicates the meaning of such terms.

Rate of Solution—It is possible to define quantitatively the rate at which a solute goes into solution. The simplest treatment is based on a model depicted in Fig 1. A solid particle dispersed in a solvent is surrounded by a thin layer of solvent having a finite thickness, l in cm. The layer is an integral part of the solid and, thus, is referred to characteristically as the "stagnant layer." This means that regardless of how fast the bulk solution is stirred the stagnant layer remains a part of the surface of the solid, moving wherever the particles moves. The thickness of this layer may get smaller as the stirring of the bulk solution increases, but it is important to recognize that this layer will always have a finite thickness however small it may get.

Using Fick's First Law of Diffusion the rate of solution of the solid can be explained, in the simplest case, as the rate at which a dissolved solute particle diffuses through the stagnant layer to the bulk solution. The driving force behind the movement of the solute molecule through the stagnant layer is the difference in concentration that exists between the concentration of the solute, C_1 , in the stagnant layer at the surface of the solid and its concentration, C_2 , on the farthest side of the stagnant layer (see *Diffusion in Liquids*, page 206). The greater this difference in concentration ($C_1 - C_2$), the faster the rate of solution.

According to Fick's Law, the rate of solution also is directly proportional to the area of the solid, A in cm^2 , exposed to solvent and inversely proportional to the length of the path through which the dissolved solute molecule must diffuse. Mathematically, then, the rate of solution of the solid is given by

$$\text{Rate of solution} = \frac{DA}{l} (C_1 - C_2) \quad (1)$$

where D is a proportionality constant called the diffusion coefficient in cm^2/sec . In measuring the rate of solution experimentally, the concentration C_2 is maintained at a low

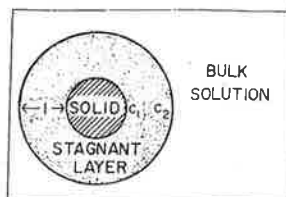


Fig 1. Physical model representing the dissolution process.

value compared to C_1 and hence considered to have a negligible effect on the rate. Furthermore, C_1 most often is the saturation solubility of the solute. Hence Eq 1 is simplified to

$$\text{Rate of solution} = \frac{DA}{l} (\text{saturation solubility}) \quad (2)$$

Equation 2 quantitatively explains many of the phenomena commonly observed that affect the rate at which materials dissolve.

1. Small particles go into solution faster than large particles. For a given mass of solute, as the particle size becomes smaller, the surface area per unit of mass of solid increases; Eq 2 shows that as area increases, the rate must increase proportionately. Hence, if a pharmacist wishes to increase the rate of solution of a drug, its particle size should be decreased.

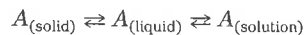
2. Stirring a solution increases the rate at which a solid dissolves. This is because the thickness of the stagnant layer depends on how fast the bulk solution is stirred; as stirring rate increases, the length of the diffusional path decreases. Since the rate of solution is proportional inversely to the length of the diffusional path, the faster the solution is stirred, the faster the solute will go into solution.

3. The more soluble the solute, the faster is its rate of solution. Again, Eq 2 predicts that the larger the saturation solubility, the faster the rate.

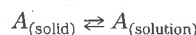
4. With a viscous liquid the rate of solution is decreased. This is because the diffusion coefficient is proportional inversely to the viscosity of the medium; the more viscous the solvent, the slower the rate of solution.

Heat of Solution and Temperature Dependency—Turning from the kinetic aspects of dissolution, this discussion will be concerned with the situation where there is thermodynamic equilibrium between solute in its solid phase and the solute in solution. (It is assumed that there is an amount of solid material in excess of the amount that can go into solution; hence, a solid phase is always present.) As defined earlier, the concentration of solute in solution at equilibrium is the saturation solubility of the substance.

When a solid (Solute A) dissolves in some solvent two steps may be considered as occurring: The solid absorbs energy to become a liquid and then the liquid dissolves.



For the overall dissolution the equilibrium existing between solute molecules in the solid and solute molecules in solution may be treated as any equilibrium. Thus, for Solute A in equilibrium with its solution



Using the Law of Mass Action an equilibrium constant for this system can be defined, just as any equilibrium constant may be written as

$$K_{\text{eq}} = \frac{\alpha_{(\text{solution})}}{\alpha_{(\text{solid})}}$$

where α denotes the activity of the solute in each phase. Since the activity of a solid is defined as unity

$$K_{\text{eq}} = \alpha_{(\text{solution})}$$

Because the activity of a compound in dilute solution is approximated by its concentration and, because this concentration is the saturation solubility, K_s , the van't Hoff Equation (for a more complete treatment, see Ref 1, page 113) may be used, which defines the relationship between an equilibrium constant (here, solubility) and absolute temperature.

$$\frac{d \log K_s}{dT} = \frac{\Delta H}{2.3RT^2} \quad (3)$$

where $d \log K_s/dT$ is the change of $\log K_s$ with a unit change of absolute temperature, T ; ΔH is a constant which in this situation is the heat of solution for the overall process (solid $\rightleftharpoons$ liquid $\rightleftharpoons$ solution); and R is the gas constant, 1.99

cal/mole/deg. Equation 3, a differential, may be solved to give

$$\log K_S = -\frac{\Delta H}{2.3RT} + J \quad (4)$$

where J is a constant. A more useful form of this equation is

$$\log \frac{K_{S,T_2}}{K_{S,T_1}} = \frac{\Delta H(T_2 - T_1)}{2.3RT_1T_2} \quad (5)$$

where K_{S,T_1} is the saturation solubility at absolute temperature T_1 and K_{S,T_2} is the solubility at temperature T_2 . Through the use of Eq 5, if ΔH and the solubility at one temperature are known, the solubility at any other temperature can be calculated.

Effect of Temperature—As is evident from Eq 4, the solubility of a solid in a liquid depends on the temperature. If, in the process of solution, heat is absorbed (as evidenced by a reduction in temperature), ΔH is by convention positive and the solubility of the solute will increase with increasing temperature. Such is the case for most salts, as is shown in Fig 2, in which the solubility of the solute is plotted as the ordinate and the temperature as the abscissa, and the line joining the experimental points represents the solubility curve for that solute.

If a solute gives off heat during the process of solution (as evidenced by an increase in temperature), ΔH is, by convention, negative and solubility decreases with an increase in temperature. This is the case with calcium hydroxide and, at higher temperatures, with calcium sulfate. (Because of the slight solubility of these substances their solubility curves are not included.) When heat is neither absorbed nor given off, the solubility is not affected by variation of temperature as is nearly the case with sodium chloride.

Solubility curves usually are continuous as long as the chemical composition of the solid phase in contact with the solution remains unchanged, but if there is a transition of the solid phase from one form to another, a break will be found in the curve. Such is the case with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$, which dissolves with absorption of heat up to a temperature of 32.4° , at which point there is a transition of the solid phase to anhydrous sodium sulfate, Na_2SO_4 , which dissolves with evolution of heat. This change is evidenced by increased solubility of the hydrated salt up to 32.4° , but above this temperature the solubility decreases.

These temperature effects are what would be predicted from Eq 4. When the heat of solution is negative, signifying that energy is released during dissolution, the relation between $\log K_S$ and $1/T$ is typified in Fig 3 (Curve A), where as

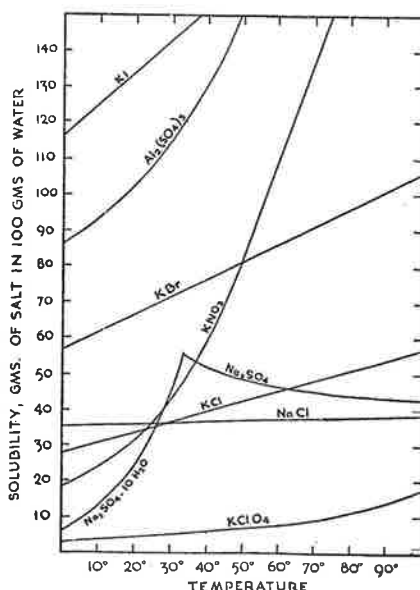


Fig 2. Effect of heat on solubility.

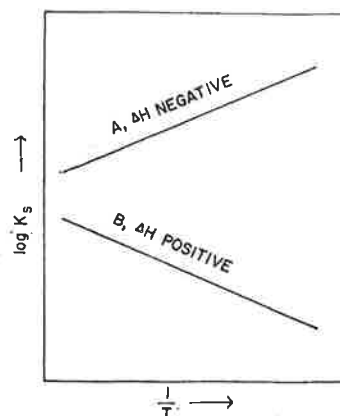


Fig 3. Typified relationship between the logarithm of the saturation solubility and the reciprocal of the absolute temperature.

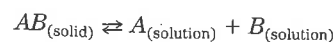
$1/T$ increases, $\log K_S$ increases. It can be seen that with increasing temperature (T itself actually increases proceeding left in Fig 3, A) there is a decrease in solubility. On the other hand, when the heat of solution is positive—that is, when heat is absorbed in the solution process—the relation between $\log K_S$ and $1/T$ is typified in Fig 3, B. Hence, as temperature increases ($1/T$ decreases), the solubility increases.

Effect of Salts—The solubility of a nonelectrolyte, in water, either is decreased or increased generally by the addition of an electrolyte; it is only rarely that the solubility is not altered. When the solubility of a nonelectrolyte is decreased, the effect is referred to as *salting-out*; if it is increased, it is described as *salting-in*. Inorganic electrolytes commonly decrease solubility, though there are some exceptions to the generalization.

Salting-out occurs because the ions of the added electrolyte interact with water molecules and, thus, in a sense reduce the amount of water available for solution of the nonelectrolyte. (Refer to the section on *Thermodynamics of the Solution Process*, page 202, for another view.) The greater the degree of hydration of the ions, the more the solubility of the nonelectrolyte is decreased. If, for example, one compares the effect of equivalent amounts of lithium chloride, sodium chloride, potassium chloride, rubidium chloride and cesium chloride (all of which belong to the family of alkali metals and are of the same valence type), it is observed that lithium chloride decreases the solubility of a nonelectrolyte to the greatest extent and that the salting-out effect decreases in the order given. This is also the order of the degree of hydration of the cations; lithium ion, being the smallest ion and, therefore, having the greatest density of positive charge per unit of surface area (see also Chapter 13 under *Electronegativity Values*), is the most extensively hydrated of the cations while cesium ion is hydrated the least. Salting-out is encountered frequently in pharmaceutical operations.

Salting-in, commonly occurs when either the salts of various organic acids or organic-substituted ammonium salts are added to aqueous solutions of nonelectrolytes. In the first case the solubilizing effect is associated with the anion and in the second, with the cation. In both cases the solubility increases as the concentration of added salt is increased. The solubility increase may be relatively great, sometimes amounting to several times the solubility of the nonelectrolyte in water.

Solubility of Solutes Containing Two or More Species—In cases where the solute phase consists of two or more species (as in an ionizable inorganic salt), when the solute goes into solution, the solution phase often contains each of these species as discrete entities. For some such substance, AB , the following relationship for the solution process may be written.



Since there is an equilibrium between the solute and saturated solution phases, the Law of Mass Action defines an equilibrium constant, K_{eq}

$$K_{eq} = \frac{\alpha_{A(\text{solution})} \cdot \alpha_{B(\text{solution})}}{\alpha_{AB(\text{solid})}} \quad (6)$$

where $\alpha_{A(\text{solution})}$, $\alpha_{B(\text{solution})}$ and $\alpha_{AB(\text{solid})}$ are the activities of A and B in solution and of AB in the solid phase. Recall from the earlier discussion that the activity of a solid is defined as unity; and that in a very dilute solution (eg, for a slightly soluble salt), concentrations may be substituted for activities and Eq 6 then becomes

$$K_{eq} = C_A C_B$$

where C_A and C_B are the concentrations of A and B in solution. In this situation K_{eq} has a special name, the *solubility product*, K_{SP} . Thus

$$K_{SP} = C_A C_B \quad (7)$$

This equation will hold true theoretically only for slightly soluble salts.

As an example of this type of solution, consider the solubility of silver chloride

$$K_{SP} = [Ag^+][Cl^-]$$

where the brackets [] designate concentrations.

At 25° the solubility product has a value of 1.56×10^{-10} , the concentration of silver and chloride ions being expressed in mol/liter. The same numerical value applies also to solutions of silver chloride containing an excess of either silver or chloride ions. If the silver-ion concentration is increased by the addition of a soluble silver salt, the chloride-ion concentration must decrease until the product of the two concentrations again is equal numerically to the solubility product. In order to effect the decrease in chloride-ion concentration, silver chloride is precipitated and, hence, its solubility is decreased. In a similar manner an increase in chloride-ion concentration by the addition of a soluble chloride effects a decrease in the silver-ion concentration until the numerical value of the solubility product is attained. Again, this decrease in silver-ion concentration is brought about by the precipitation of silver chloride.

The solubility of silver chloride in a saturated aqueous solution of the salt may be calculated by assuming that the concentration of silver ion is the same as the concentration of chloride ion, both expressed in mol/liter, and that the concentration of dissolved silver chloride is numerically the same since each silver chloride molecule gives rise to one silver ion and one chloride ion. Since

$$[\text{dissolved AgCl}] = [Ag^+] = [Cl^-]$$

the solubility of AgCl is equal to $\sqrt{1.56 \times 10^{-10}}$, which is 1.25×10^{-5} mole/liter. Multiplying this by the molecular weight of silver chloride (143), we obtain a solubility of approximately 1.8 mg/liter.

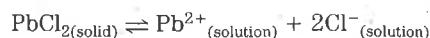
For a salt of the type $PbCl_2$ the solubility product expression takes the form

$$[Pb^{2+}][Cl^-]^2 = K_{SP}$$

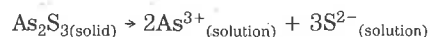
while for As_2S_3 it would be

$$[As^{3+}]^2[S^{2-}]^3 = K_{SP}$$

because from the Law of Mass Action



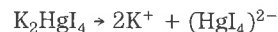
and



For further details of methods of using solubility-product calculations, the reader is referred to books on qualitative or quantitative analyses or physical chemistry.

Recall that the solubility-product principle is valid for aque-

ous solutions of slightly soluble salts, provided the concentration of added salt is not too great. Where the concentrations are high, deviations from the theory occur and these have been explained by assuming that in such solutions the nature of the solvent has been changed. Frequently, deviations also may occur as the result of the formation of complexes between the two salts. An example of increased solubility, by virtue of complex-ion formation, is seen in the effect of solutions of soluble iodides on mercuric iodide. According to the solubility-product principle, it might be expected that soluble iodides would decrease the solubility of mercuric iodide, but because of the formation of the more soluble complex salt K_2HgI_4 which dissociates as



the iodide ion no longer functions as a common ion.

Practical applications of the solubility-product principle are found in qualitative and quantitative analysis whenever an excess of a precipitant is added in order to diminish, by common-ion effect, the solubility of the precipitate.

It is possible to formulate some general rules regarding the effect of the addition of soluble salts to slightly soluble salts where the added salt does not have an ion common to the slightly soluble salt. If the ions of the added soluble salt are not highly hydrated (see *Effects of Salts*, page 196), the solubility product of the slightly soluble salt will increase because the ions of the added salt tend to decrease the interionic attraction between the ions of the slightly soluble salt. On the other hand, if the ions of the added soluble salt are hydrated, water molecules become less available and the interionic attraction between the ions of the slightly soluble salt increases with a resultant decrease in solubility product. Another way of considering this effect is discussed later (*Thermodynamics of the Solution Process*, page 202).

The effect of temperature is, in general, what would be expected; increasing the temperature of the solution results in an increase of the solubility product.

Solubility Following a Chemical Reaction—Thus far in this chapter the discussion has been concerned with solubility that comes about because of interplay of entirely physical forces. The dissolution of some substance resulted from overcoming the physical interactions between solute molecules and solvent molecules by the energy produced when a solute molecule interacted physically with a solvent molecule. The solution process, however, can be facilitated also by a chemical reaction. Almost always the chemical enhancement of solubility in aqueous systems is due to the formation of a salt following an acid-base reaction.

An alkaloidal base, or any other nitrogenous base of relatively high molecular weight, generally is slightly soluble in water, but if the pH of the medium is reduced by addition of acid, the solubility of the base is increased, considerably so, as the pH continues to be reduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water. Conversely, the solubility of a salt of an alkaloid or other nitrogenous base is reduced as pH is increased by addition of alkali.

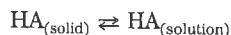
The solubility of slightly soluble acid substances is, on the other hand, increased as the pH is increased by addition of alkali, the reason again being that a salt, relatively soluble in water, is formed. Examples of acid substances whose solubility is thus increased are aspirin, theophylline and the penicillins, cephalosporins and barbiturates. Conversely, the solubility of salts of the same substances is decreased as the pH decreases.

Among some inorganic compounds a somewhat similar behavior is observed. Tribasic calcium phosphate, $Ca_3(PO_4)_2$, for example, is almost insoluble in water, but if an acid is added its solubility increases rapidly with a decrease in pH. This is because hydrogen ions have such a strong affinity for phosphate ions forming nonionized phosphoric acid, that the calcium phosphate is dissolved in order to release phosphate ions. Or, stated in another way, the solubilization is an ex-

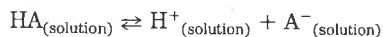
ample of a reaction in which a strong acid (the source of the hydrogen ions) displaces a weak acid.

In all of these examples solubilization occurs as the result of an interaction of the solute with an acid or a base and thus the species in solution is *not* the same as the undissolved solute. Compounds which do not react with either acids or bases are slightly, or not at all, influenced in their aqueous solubility by variations of pH. Such effects as may be observed are generally due to ionic *salt effects*.

It is possible to analyze quantitatively the solubility following an acid-base reaction by considering it as a two-step process. The first example is an organic acid, designated as *HA*, that is relatively insoluble in water. Its two-step dissolution can be represented as



followed by



The equilibrium constant for the first step is the solubility of *HA* ($K_S = [HA]_{(solution)}$), just as was developed earlier when no chemical reaction took place, and the equilibrium constant for the second step is the dissociation constant of the acid is

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

Since the total amount of compound *in solution* is the sum of nonionized and ionized forms of the acid, the total solubility may be designated as $S_{i(HA)}$, or

$$S_{i(HA)} = [HA] + [A^-] = [HA] + K_a \frac{[HA]}{[H^+]} \quad (8)$$

Since $K_S = [HA]$, Eq 8 becomes

$$S_{i(HA)} = K_S \left(1 + \frac{K_a}{[H^+]} \right) \quad (9)$$

Equation 9 is very useful since it equates the total solubility of an acid drug with the hydrogen-ion concentration of the solvent. If the water solubility, K_S , and the dissociation constant, K_a , are known, the total solubility of the acid can be calculated at various hydrogen-ion concentrations. Equation 9 demonstrates quantitatively how the total solubility of the acid increases as the hydrogen-ion concentration decreases (that is, as the pH increases).

It is possible to develop an equation similar to Eq 9 for the solubility of a basic drug, *B*, such as a relatively insoluble nitrogenous base (an alkaloid, for example), at various hydrogen-ion concentrations. The solubility of the base in water may be represented in two steps, as



Again, if K_S is the solubility of the free base in water and K_b is its dissociation constant

$$K_b = \frac{[BH^+][OH^-]}{[B]}$$

the total solubility of the base in water $S_{i(B)}$ is given by

$$\begin{aligned} S_{i(B)} &= [B] + [BH^+] = [B] + \frac{K_b[B]}{[OH^-]} \\ &= K_S \left(1 + \frac{K_b}{[OH^-]} \right) \quad (10) \end{aligned}$$

It is convenient to rewrite Eq 10 in terms of hydrogen-ion concentration by making use of the dissociation constant for water

$$K_W = [H^+][OH^-] = 1 \times 10^{-14}$$

Equation 10 then becomes

$$S_{i(B)} = K_S \left(1 + \frac{K_b}{K_W/[H^+]} \right) = K_S \left(1 + \frac{K_b[H^+]}{K_W} \right) \quad (11)$$

Equation 11 quantitatively shows how the total solubility of the base increases as the hydrogen-ion concentration of the solvent increases. If K_S and K_b are known, it is possible to calculate the total solubility of a basic drug at various hydrogen-ion concentrations using this equation.

Equations 9 and 11 have assumed that the salt formed following a chemical reaction is infinitely soluble. This, of course, is not an acceptable assumption as suggested and demonstrated by Kramer and Flynn.² Rather, for an acidic or basic drug there should be a pH at which *maximum solubility* occurs where this solubility remains the sum of the solution concentrations of the free and salt forms of the drug at that pH. Using a basic drug, *B*, as the example, this would mean that a solution of *B*, at pH values greater than the pH of maximum solubility, would be saturated with free-base form but not with the salt form and the use of Eq 11 would be valid for the prediction of solubility. On the other hand, at pH values less than the pH of maximum solubility, the solution would be saturated with salt form and Eq 11 is no longer really valid. Since in this situation the total solubility of the base, $S_{i(B)}$, is

$$S_{i(B)} = [B] + [BH^+]_s$$

where the subscript, *s*, designates a solution saturated with salt, the correct equation to use at pH values less than the pH maximum would be

$$S_{i(B)} = [BH^+]_s \left(1 + \frac{[OH^-]}{K_b} \right) = [BH^+]_s \left(1 + \frac{K_W}{K_b[H^+]} \right) \quad (12)$$

A relationship similar to Eq 12 likewise can be developed for an acidic drug at pH *s* greater than its pH of maximum solubility.

Effecting Solution of Solids in the Prescription Laboratory—The method usually employed by the pharmacist when soluble compounds are to be dissolved in water in compounding a prescription requires the use of the mortar and pestle. The ordinary practice is to crush the substance into fragments in the mortar with the pestle and pour the solvent on it, meanwhile stirring with the pestle until solution is effected. If definite quantities are used, and the whole of the solvent is required to dissolve the given weight of the salt, only a portion of the solvent should be added first and, when this is saturated, the solution is poured off and a fresh portion of solvent added. This operation is repeated until the solid is dissolved entirely and all the portions combined. Other methods of affecting solution are to shake the solid with the liquid in a bottle or flask or to apply heat to the substances in a suitable vessel. Substances vary greatly in the rate at which they dissolve; some are capable of producing a saturated solution quickly, others require several hours to attain saturation. All too often, in their haste to prepare a saturated solution, pharmacists fail to obtain the required degree of solution of solute.

With hygroscopic substances like pepsin, silver protein compounds and some others, the best method of effecting solution in water is to place the substance directly upon the surface of the water and then stir vigorously with a glass rod. If the ordinary procedure, such as using a mortar and pestle, is employed with these substances, gummy lumps are formed which are exceedingly difficult to dissolve.

The *solubility* of chemicals and the *miscibility* of liquids are important physical factors for the pharmacist to know, as they often have a bearing on intelligently and properly filling prescriptions. Mainly for the information of the pharmacist, the USP provides tabular data indicating the degree of solubility or miscibility of many official substances.

Determination of Solubility—For the pharmacist and pharmaceutical chemist the question of solubility is of paramount importance. Not only is it necessary to know solubili-

ties when preparing and dispensing medicines, but such information is necessary to effect separation of substances in qualitative and quantitative analysis. Furthermore, the accurate determination of the solubility of a substance is one of the best methods for determining its purity.

The details of the determination of the solubility are affected markedly by the physical and chemical characteristics of the solute and solvent and also by the temperature at which the solubility is to be determined. Accordingly, it is not possible to describe a universally applicable method but, in general, the following rules must be observed in solubility determinations.

1. The purity of both the dissolved substance and the solvent is essential, since impurities in either affect the solubility.
2. A constancy of temperature must be maintained accurately during the course of the determination.
3. Complete saturation must be attained.
4. Accurate analysis of the saturated solution and correct expression of the results are imperative.

Consideration should be given also to the varying rates of solution of different compounds and to the marked effect of the degrees of fineness of the particles on the time required for the saturation of the solution.

Many of the solubility data of USP have been determined with regard to the exacting requirements mentioned above.

The Phase Rule and Phase-Solubility Analysis—Phase-solubility analysis is one of the most useful and accurate methods for the determination of the purity of a substance. It involves the application of precise solubility methods to the principle that constancy of solubility, in the same manner as constancy of melting point, indicates that a material is pure or free from foreign admixture. It is important to recognize that the technique can be used to obtain the exact solubility of the pure substance without the necessity of the experimental material itself being pure.

The method is based on the thermodynamic principles of heterogeneous equilibria which are among the soundest of theoretical concepts of chemistry. Thus, it does not depend on any assumptions regarding kinetics or structure of matter, but is applicable to all species of molecules, and is sufficiently sensitive to distinguish between optical isomers. The requirements for an analysis are simple, since the equipment needed is basic to most laboratories and the quantities of substances required are small.

The standard solubility method consists of five steps:

1. Mixing, in separate systems, increasing amounts of a substance with measured amounts of a solvent.
2. Establishment of equilibrium for each system at identical constant temperature and pressure.
3. Separation of the solid phase from the solutions.
4. Determination of the concentration of the material dissolved in the various solutions.
5. Plotting the concentration of the dissolved material per unit of solvent (y -axis, or solution concentration) against the mass of material per unit of solvent (x -axis or system concentration).

The solubility method has been established on the sound theoretical principles of the Gibbs phase rule: $F = C - P - 2$, which relates C , the number of components, F , the degrees of freedom (pressure, temperature and concentration) and P , the number of phases for a heterogeneous equilibrium. Since solubility analyses are carried out at constant temperature and pressure, a pure solid in solution would show only one degree of freedom, because only one phase is present at concentrations below saturation. This is represented by section AB in Fig 4. For a pure solid in a saturated solution at equilibrium (Fig 4, BC), two phases are present, solid and solution; there is no variation in concentration and thus, at constant temperature and pressure, no degrees of freedom.

The curve ABC of Fig 4 represents the type of solubility diagram obtained for: (1) a pure material, (2) equal amounts of two or more materials having identical solubilities or (3) a mixture of two or more materials present in the unique ratio of their solubilities. These latter two cases are rare and often may be detected by a change in solvent system.

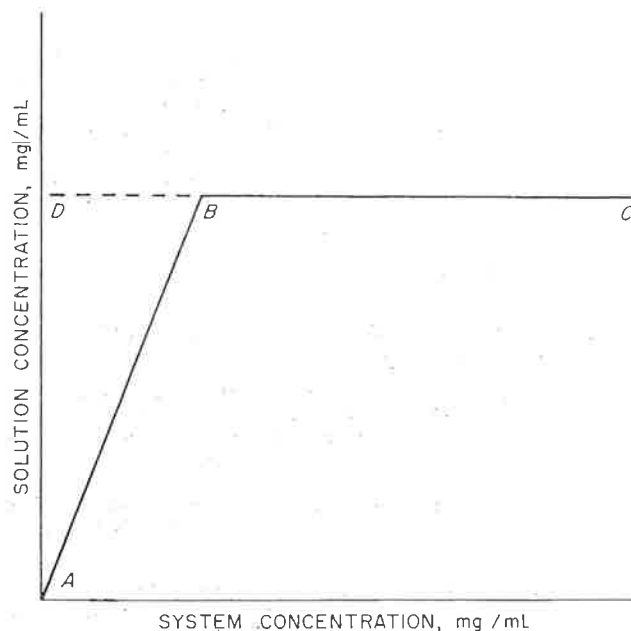


Fig 4. Phase-solubility diagram for a pure substance.

Line segment BC of Fig 4, since it has no slope, usually indicates purity. If, however, this section *does* exhibit a slope, its numerical value indicates the fraction of impurity present. Line segment BC , extrapolated to the y axis at D , is the actual solubility of the pure substance.

A representative type of solubility curve, which is obtained when a substance contains one impurity, is illustrated in Fig 5. Here, at B , the solution becomes saturated with one component. From B to C there are two phases present: a solution saturated with Component I (usually the major component) containing also some Component II (usually the minor component), and a solid phase of Component I. The one degree of freedom revealed by the slope of the line segment BC is the concentration of Component II, which is the impurity (usually the minor component). A mixture of d and l isomers could have such a curve, as would any simple mixtures in which the solubilities are independent of each other.

The section CD indicates that the solvent is saturated with both components of the two-component mixture. Here, three phases are present: a solution saturated with both components and the two solid phases. No variation of concentration is possible, hence, no degree of freedom is possible (indicated by the lack of slope of section CD). The distance AE on the ordinate represents the solubility of the major component, and the distance EF , the solubility of the minor component.

The fact that the equilibration process is time-consuming, requiring as long as 3 weeks in certain cases, is offset by the

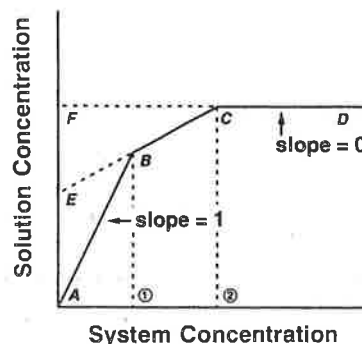


Fig 5. Type of solubility curve obtained when a substance contains one impurity.

fact that all of the sample can be recovered after a determination. This adds to the general usefulness of the method, particularly in cases where the substance is expensive or difficult to obtain. A use for the method other than the determination of purity or of solubility is to obtain especially pure samples by recovering the solid residues at system concentration, corresponding to points on section *BC* in Fig 5. Thus, the method is useful not only as a quantitative analytical tool, but also for purification.

Solutions of Liquids in Liquids

Binary Systems—Under this title the following types of liquid-pairs may be recognized.

1. Those which are soluble completely in each other in all proportions. Examples: alcohol and water; glycerin and water; alcohol and glycerin.
2. Those which are soluble in each other in definite proportions. Examples: phenol and water; ether and water; nicotine and water.
3. Those which are imperceptibly soluble in each other in any proportion. Examples: castor oil and water; liquid petrolatum and water.

The mutual solubility of liquid pairs of Type 2 has been studied extensively and found to show interesting regularities. If a series of tubes containing varying, but known, percentages of phenol and water are heated (or cooled, if necessary) just to the point of formation of a homogeneous solution, and the temperatures at such points noted, there will be obtained, upon plotting the results, a curve similar to that in Fig 6.³ On this graph the area inside the curve represents the region where mixtures of phenol and water will separate into two layers, while in the region outside of the curve homogeneous solutions will be obtained. The maximum temperature on this curve is called the *critical solution temperature*, that is, the temperature above which a homogeneous solution occurs regardless of the composition of the mixture. For phenol and water the critical solution temperature occurs at a composition of 34.5% phenol in water.

Temperature versus composition curves, as depicted in Fig 6, provide much useful information in the preparation of homogeneous mixtures of substances showing mutual-solubility behavior. At room temperature (here assumed to be 25°), by drawing a line parallel to the abscissa at 25°, we find that we actually can prepare two sets of homogeneous solutions, one containing from 0 to about 7.5% phenol and the other containing phenol from 72 to about 95% (its limit of solubility). At compositions between 7.5 and 72% phenol at 25° two liquid layers or phases will separate. In sample tubes containing a concentration of phenol in this two-layer region at 25° one

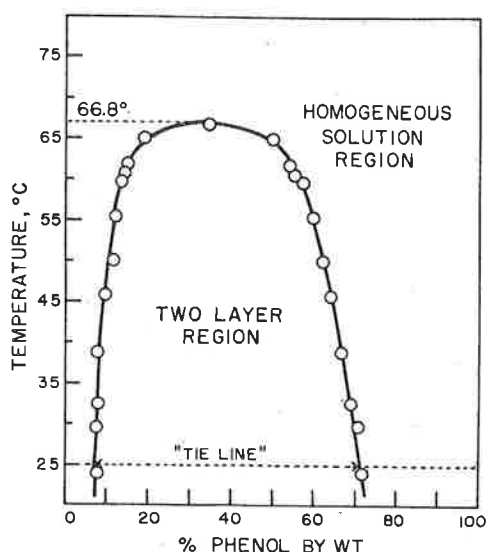


Fig 6. Phenol-water solubility.³

layer always will be phenol-rich and always contain 72% phenol while the other layer will be water-rich and always contain 7.5% phenol. These values are obtained by interpolation of the two points of intersection of the line drawn at 25° with the experimental curve. As it may be deduced, at other temperatures, the composition of the two layers in the two-layer region is determined by the points of intersection of the curve with a line (called the "tie line") drawn parallel to the abscissa at that temperature. The relative amounts of the two layers or phases, phenol-rich and water-rich in this example, will depend on the concentration of phenol added. As expected, the proportion of phenol-rich layer relative to the water-rich layer increases as the concentration of phenol added increases. For example, at 20% phenol in water at 25° there would be more of the water-rich layer than of the phenol-rich layer, while at 50% phenol in water there would be more of the phenol-rich layer. The relative portion of each layer may be calculated from such tie lines at any temperature and compositions as well as the amount of phenol present in each of the two phases. To determine how these calculations are made and for further discussion of this topic the student should consult Ref 1, page 79.

A simple and practical advantage in the use of phase diagrams is pointed out in Ref 1. Based on diagrams such as Fig 6, they point out that the most concentrated stock solution of phenol that perhaps should be used by pharmacists is one containing 76% w/w phenol in water (equivalent to 80% w/v). At room temperature this mixture is a homogeneous solution and will remain homogeneous to around 3.5°, at which temperature freezing occurs. It should be noted that Liquefied Phenol USP contains 90% w/w phenol and freezes at 17°C. This means that if the storage area in the pharmacy falls to about 63°F, the preparation will freeze, resulting in a stock solution no longer convenient to use.

In the case of phenol and water the mutual solubility increases with increase in temperature and the critical solution temperature occurs at a relatively high point. In a certain number of cases, however, the mutual solubility increases with decrease in temperature and the critical solution temperature occurs at a relatively low value. Most of the substances which show lower critical solution temperatures are amines as, for example, triethylamine with water.

In addition to pairs of liquids which show *either* upper or lower critical solution temperatures, there are other pairs which show *both* upper and lower critical solution temperatures and the mutual solubility curve is of the closed type. An example of this type of liquid pair is found in the case of nicotine and water (Fig 7). Mixtures of nicotine and water

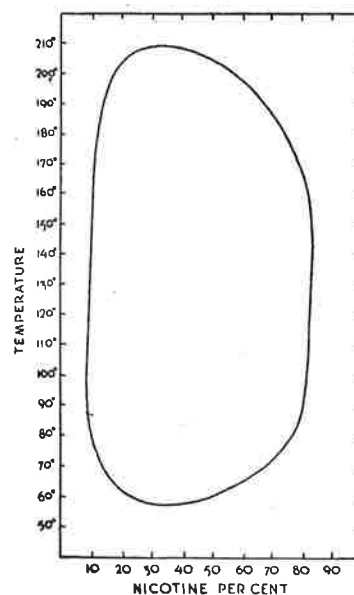


Fig 7. Nicotine-water solubility.

represented by points within the curve will separate into two layers, but mixtures represented by points outside of the curve are perfectly miscible with each other.

In a discussion of solutions of liquids in liquids it is evident that the distinction between the terms solute and solvent loses its significance. For example, in a solution of water and glycerin, which shall be considered to be the soluble and which the solvent? Again, when two liquids are soluble only partially in each other the distinction between solute and solvent might be reversed easily. In such cases the term solvent usually is given to the constituent present in larger quantity.

Ternary Systems—The addition of a third liquid to a binary liquid system to produce a ternary or three-component system can result in several possible combinations.

If the third liquid is soluble in only one of the two original liquids or if its solubility in the two original liquids is markedly different, the mutual solubility of the original pair will be decreased. An upper critical solution temperature will be elevated and a lower critical solution temperature lowered. On the other hand, the addition of a liquid having roughly the same solubility in both components of the original pair will result in an increase in their mutual solubility. An upper critical solution temperature then will be lowered and a lower critical solution temperature elevated.

An equilateral-triangle graph may be used to represent ternary systems. In this type of graph, each side of the triangle represents 0% of one of the components and the apex opposite that side represents 100% of that component. This is illustrated using a particularly common ternary system involving two solvents that are completely miscible and a third that is miscible with only one of the two. In Fig 8,⁴ water and alcohol are the miscible solvents and castor oil is the third solvent that is soluble in alcohol but not in water. Such diagrams could be applied, for example, to surfactant/oil/water systems, flavor/water/alcohol systems, drug/propellant mixture systems, drug/water/propylene glycol systems or any other such system you might think of that would fit into this category. The data in Fig 8 were obtained by determining the amount of water needed to just cloud solutions of oil in alcohol at different concentrations and at room temperature. The percentage of each solvent just clouding the system was

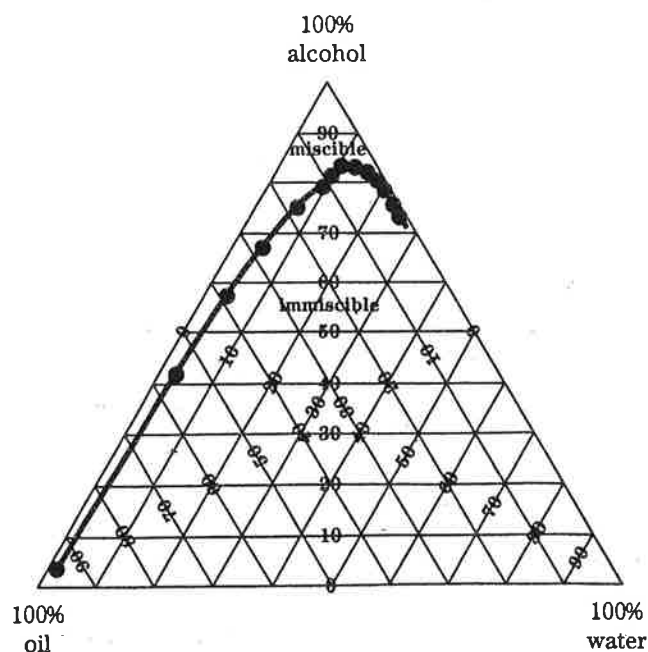


Fig 8. Phase diagram at constant temperature for a ternary system: two liquids completely miscible in one another with a third liquid soluble in only one of the two (courtesy, constructed from data in Loran and Guth⁴).

then calculated and plotted as shown in the figure. For example, a cloudy solution developed at a mixture of about 67% alcohol, 27% oil and 6% water. Note that the percentages of the three components must always equal 100%. In the region labeled "miscible," any combination of the three components will result in a solution. The pharmacist can pick any combination in this region for reasons of taste, safety, stability or cost. Figure 8 is constructed for room temperature; any other temperature would have its own phase diagram. Including temperature as a variable would create a three-dimensional relationship with ternary diagrams such as Fig 8 stacked in the x - y plane as a function of temperature on the z -axis.

Other possibilities exist in ternary liquid systems: e.g. those in which two components are completely miscible and the third is partially miscible with each, and that in which all combinations of two of the three components are only partially miscible.

Solutions of Gases in Liquids

Nearly all gases are more or less soluble in liquids. One has but to recall the solubility of carbon dioxide, hydrogen sulfide or air in water as common examples.

The amount of gas dissolved in a liquid in general follows *Henry's law*, which states that *the weight of gas dissolved by a given amount of a liquid at a given temperature is proportional to its pressure*. Thus, if the pressure is doubled, twice as much gas will dissolve as at the initial pressure. The extent to which a gas is dissolved in a liquid, at a given temperature, may be expressed in terms of the *solubility coefficient*, which is the volume of gas measured under the conditions of the experiment that is absorbed by one volume of the liquid. The degree of solubility also is expressed sometimes in terms of the *absorption coefficient*, which is the volume of gas, reduced to standard conditions, dissolved by one volume of liquid under a pressure of one atmosphere.

Although Henry's law expresses fairly accurately the solubility of slightly soluble gases, it deviates considerably in the case of very soluble gases such as hydrogen chloride and ammonia. Such deviations most frequently are due to chemical interaction of solute and solvent.

The solubility of gases in liquids *decreases* with a *rise* in *temperature* and, in general, also when salts are added to the solvent, the latter effect being referred to as the *salting-out* of the gas.

Solutions of gases potentially are dangerous when exposed to warm temperatures because of the liberation and expansion of the dissolved gas which may cause the container to burst. Bottles containing such solutions (eg, strong ammonia solution) should be cooled before opening, if practical, and the stopper should be covered with a cloth before attempting its removal.

Solutions of Solids in Solids

Various mixtures of one solid in another are being considered in the pharmaceutical sciences primarily as a means to increase bioavailability. For example, melts of solid mixtures of drugs with excipients and eutectic mixtures are being investigated (see Chapter 13). It is possible to have a true solution of one solid in another to give rise to a continuum of one solid dispersed in another as depicted in Fig 9.⁶ Such a system is referred to as a "continuous" dispersion; it is very rarely found. To achieve this would mean that two materials would have to be of similar size, structure and interaction energy so that they might enter and occupy a mutual crystalline structure at the molecular level. Hence, such solid solutions may occur only among racemic mixtures of chiral compounds. If it were possible to form a solid solution of a drug in a water-soluble excipient, bioavailability could increase dramatically because the drug would transfer into water as individual molecules.

There are three types of continuous dispersions depicted in Fig 9: [1] shows an "ideal" dispersion of constant melting

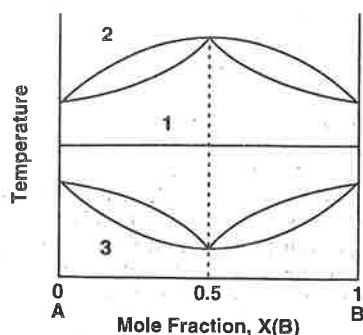


Fig 9. Phase diagram for a "continuous" solution of a Solid A in a Solid B (or of B in A): [1] is an ideal solution, [2] and [3], nonideal solutions (courtesy, adapted from Duddu⁶).

point, while [2] and [3] ("nonideal" solutions) show dispersions having a maximum or minimum respectively. Each of the latter dispersions show an upper or "liquidus line" and a lower or "solidus line" that might be viewed as representing the direction (cooling or heating) used to arrive at the temperature of melting or solidification in each mixture. The composition of the liquid and solid phases in the region between the two lines can be quantified in a way that is related to the "tie-line" treatment for phenol-water systems, although more complicated.

More common are the "discontinuous" solid dispersions illustrated in Fig 10⁷ where two true solid solutions α and β are separated by a eutectic phase. Such a system is found for urea/acetaminophen; which exists as solid solutions in very small regions at very high urea concentration and very high acetaminophen concentration.

At this point it is worthwhile briefly to consider solid complexes. The interaction of a drug with an excipient to form a new solid phase through strong hydrogen-bond formation can give a solid phase that is not precisely a solid solution, but none the less potentially important in its effects on bioavailability—both in a positive and negative sense. The phase diagram in Fig 11⁷ was obtained by fusing and cooling mixtures of griseofulvin (G) and phenobarbital (P). When a complex is stable up to its melting point, the liquidus curve shows a peak referred to as a "congruent melting point." Two congruently melting complexes, PG_3 and P_3G (at $x = 0.25$ and 0.75 in Fig 11), are found for the griseofulvin-phenobarbital system.

Thermodynamics of the Solution Process

In the discussions under this heading the solute is assumed to be in the liquid state, hence, the heat of solution ($\Delta H'$) is a

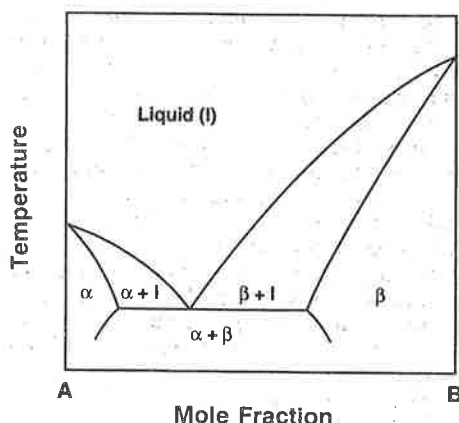


Fig 10. Phase diagram for a "discontinuous" solid solution for Solids A and Solid B: true solid solutions α and β are separated by a eutectic phase (courtesy, adapted from Grant and Abougela⁷).

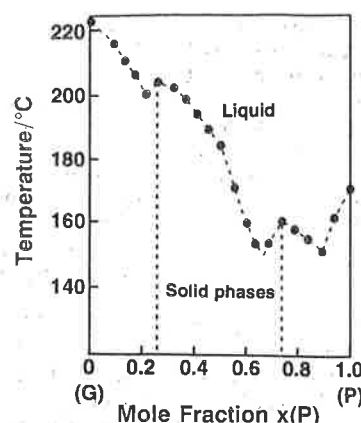


Fig 11. Temperature-concentration relationship for fused mixtures of griseofulvin (G) and phenobarbital (P) (courtesy, adapted from Grant and Abougela⁷).

term different from that in Eq 3 (ΔH). The heat of solution for a solid solute going into solution as defined in Eq 3 is the net heat effect for the overall dissolution

$$A_{(\text{solid})} \rightleftharpoons A_{(\text{liquid})} \rightleftharpoons A_{(\text{solution})}$$

Considering only the process

$$A_{(\text{liquid})} \rightleftharpoons A_{(\text{solution})}$$

and assuming that the solute is a liquid (or a supercooled liquid in the case of a solid) at a temperature close to room temperature, where the energy needed for melting (heat of fusion) is not being considered.

For a physical or chemical reaction to occur spontaneously at a constant temperature and pressure, the net free-energy change, ΔG , for the reaction should be negative (see *Thermodynamics*, Chapter 15). Furthermore, it is known that the free-energy change depends on heat-related enthalpy ($\Delta H'$) and order-related entropy (ΔS) factors as seen in

$$\Delta G = \Delta H' - T\Delta S \quad (13)$$

where T is the temperature. Recall, also, that the relation between free energy and the equilibrium constant, K , for a reaction is given by

$$\Delta G = RT \ln K \quad (14)$$

Equations 13 and 14 certainly apply to the solution of a drug. Since the solubility is, in reality, an equilibrium constant, Eq 14 indicates that the greater the negative value of ΔG , the greater the solubility.

The interplay of these two factors, $\Delta H'$ and ΔS in Eq 13, determines the free-energy change and, hence, whether or not dissolution of a drug will occur spontaneously. Thus, if in the solution process $\Delta H'$ is negative and ΔS positive, dissolution is favored since ΔG will be negative.

As the heat of solution is quite significant in the dissolution process one must look at its origin. (For an excellent and more complete discussion of the interactions and driving forces underlying the dissolution process, see Higuchi.⁵) The mechanism of solubility involves severing of the bonds that hold together the ions or molecules of a solute, the separation of molecules of solvent to create a space in the solvent into which the solute can be fitted and the ultimate response of solute and solvent to whatever forces of interaction may exist between them. In order to sever the bonds between molecules or ions of solute in the liquid state, energy must be supplied, as is the case also when molecules of solvent are to be separated. If heat is the source of energy it is apparent that both processes require the absorption of heat.

Solute-solvent interaction, on the other hand, generally is accompanied by the evolution of heat since the process occurs spontaneously. In effecting solution there is, accordingly, a heat-absorbing effect and a heat-releasing effect to be considered beyond those required to melt a solid. If there is

no, or very little, interaction between solute and solvent, the only effect will be that of absorption of heat to produce the necessary separations of solute and solvent molecules or ions. If there is a significant interaction between solute and solvent, the amount of heat in excess of that required to overcome the solute-solute and the solvent-solvent forces is liberated. If the opposing heat effects are equal, there will be no change of temperature.

When $\Delta H'$ is zero, and there is no volume change, an *ideal solution* is said to exist since the solute-solute, solvent-solvent and solute-solvent interactions are the same. For such an ideal solution, the solubility of a solid can be predicted from its heat of fusion (the energy needed to melt the solid) at temperatures below its melting point. The student is referred to Ref 1, page 281 to see how this calculation is made.

When the heat of solution has a positive (energy absorbed) or negative (energy liberated) value, the solution is said to be a *nonideal solution*. A negative heat of solution favors solubility while a positive heat works against dissolution.

The magnitude of the various attractive forces involved between solute, solvent and solute-solvent molecules may vary greatly and thus could lead to varying degrees of positive or negative enthalpy changes in the solution process. The reason for this is that the molecular structure of the various solutes and solvents determining the interactions can themselves vary greatly. (For a discussion of these effects, see Ref 1, page 41.)

The solute-solute interaction that must be overcome can vary from the strong ion-ion interaction (as in a salt), to the weaker dipole-dipole interaction (as in nearly all organic medicinals that are not salts), to the weakest induced dipole-induced dipole interaction (as with naphthalene).

The attractive forces in the solvent that must be overcome are, most frequently, the dipole-dipole interaction (as found in water or acetone) and the induced dipole-induced dipole interaction (as in liquid petrolatum).

The energy-releasing solute-solvent interactions that must be taken into account may be one of four types. In decreasing energy of interaction these are ion-dipole interactions (eg, a sodium ion interacting with water), dipole-dipole interactions (eg, an organic acid dissolved in water), dipole-induced dipole interaction, to be discussed later (eg, an organic acid dissolved in carbon tetrachloride) and induced dipole-induced dipole interactions (eg, naphthalene dissolved in benzene).

Since the energy-releasing solute-solvent interaction should approximate the energy needed to overcome the solute-solute and solvent-solvent interactions, it should be apparent why it is not possible to dissolve a salt like sodium chloride in benzene. The interaction between the ions and benzene does not supply enough energy to overcome the interaction between the ions in the solute and therefore gives rise to a positive heat of solution. On the other hand, the interaction of sodium and chloride ions with water molecules does provide an amount of energy approximating the energy needed to separate the ions in the solute and the molecules in the solvent.

Consideration must next be given to entropy effects in dissolution processes. Entropy is an indicator of the disorder or randomness of a system. The more positive the entropy change (ΔS) is, the greater the degree of randomness or disorder of the reaction system and the more favorably disposed is the reaction. Unlike $\Delta H'$, the entropy change (an entropy of mixing) in an ideal solution, is not zero, but has some positive value since there is an increase in the disorderliness or entropy of the system upon dissolution. Thus, in an ideal solution with $\Delta H'$ zero and ΔS positive, ΔG would have a negative value and the process, therefore, would be spontaneous.

In a nonideal solution, on the other hand, where $\Delta H'$ is not zero, ΔS can be equal to, greater than or less than the entropy of mixing found for the ideal solution. A nonideal solution with an entropy of mixing equal to that of the ideal solution is called a "regular solution." These solutions usually occur with nonpolar or weakly polar solutes and solvents. Such solutions are accompanied by a positive enthalpy change,

implying that the solute-solvent molecular interaction is less than the solute-solute and solvent-solvent molecular interactions. Regular solutions are amenable to rigorous physical chemical analysis which will not be covered in this chapter but which can be found in outline form in Ref 1, page 282.

The possibility exists in a nonideal solution that the entropy change is greater than for an ideal solution. Such a solution occurs when there is an association among solute or solvent molecules. In essence, then, the dissolution process occurs when one begins at a relatively ordered (low entropy) state and progresses to a disorderly (high entropy) state. The overall entropy change is positive, greater than that of the ideal case, and favorable to dissolution. As may be expected, the enthalpy change in such a solution is positive since association in a solute or solvent must be overcome. The facilitated solubility of citric acid (an unsymmetrical molecule), as compared to inositol (a symmetrical molecule), may be explained on the basis of such a favorable entropy change.⁵

The solubility of citric acid is greater than that of inositol, yet, on the basis of their heats of solution, inositol should be more soluble. One may regard this phenomenon in another way. The reason for the higher solubility of citric acid is that although there is no hindrance in the transfer of a citric acid molecule as it goes from the solute to the solution phase, when the structurally unsymmetrical citric acid attempts to return to the solute phase from solution, it must assume an orientation that will allow ready interaction with polar groups already oriented. If it does not have the required orientation, it will not return readily to the solute, but it will remain in solution, thus bringing about a solubility larger than expected on the basis of heat of solution.

On the other hand, the structurally symmetrical inositol, as it leaves the solution phase, can interact with the solute phase without requiring a definite orientation; all orientations are equivalent. Hence, inositol can enter the solute phase without hindrance and, therefore, no facilitation of its solubility is observed.

In general, unsymmetrical molecules tend to be more soluble than symmetrical molecules.

Another type of nonideal solution occurs when there is an entropy change less than that expected of an ideal solution. Such nonideal behavior can occur with polar solutes and solvents. In a nonideal solution of this type there is significant interaction between solute and solvent. As may be expected, the enthalpy change ($\Delta H'$) in such a solution is negative and favors dissolution, but this effect is tempered by the unfavorable entropy change occurring at the same time. The reason for the lower-than-ideal entropy change can be visualized where the equilibrium system is more orderly and has a lower entropy than that expected for an ideal solution. The overall entropy change of solution, thus, would be less and not favorable to dissolution. One may rationalize the lower-than-expected solubility of lithium fluoride on the basis of this phenomenon. Compared with other alkali halides, it has a solubility lower than would be expected based solely on enthalpy changes. Because of the small size of ions in this salt there may be considerable ordering of water molecules in the solution. This effect must, of course, lead to a lowered entropy and an unfavorable effect on solubility. The effect of soluble salts on the solubility of nonelectrolytes (page 196 or slightly soluble salts (page 197) may be considered as a result of an unfavorable entropy effect.

Pharmaceutical Solvents

The discussion will focus now on solvents available to pharmacists and on the properties of these solvents. It is most important that the pharmacist obtain an understanding of the possible differences in solubility of a given solute in various solvents since he most often is called on to select a solvent which will dissolve the solute. A knowledge of the properties

of solvents will allow the intelligent selection of suitable solvents.

On the basis of the forces of interaction occurring in solvents one may broadly classify solvents as one of three types:

1. *Polar solvents*—those made up of strong dipolar molecules having hydrogen bonding (water or hydrogen peroxide).
2. *Semipolar solvents*—those also made up of strong dipolar molecules but which do not form hydrogen bonds (acetone or pentyl alcohol).
3. *Nonpolar solvents*—those made up of molecules having a small or no dipolar character (benzene, vegetable oil or mineral oil).

Naturally, there are many solvents that may fit into more than one of these broad classes; for example, chloroform is a weak dipolar compound but generally is considered nonpolar in character, and glycerin could be considered a polar or semipolar solvent even though it is capable of forming hydrogen bonds.

Types

Water—Water is a unique solvent. Besides being a highly associated liquid, giving rise to its high boiling point, it has another very important property, a high dielectric constant. The dielectric constant (ϵ) indicates the effect that a substance has, when it acts as a medium, on the ease with which two oppositely charged ions may be separated. The ease of solubilizing salts in solvents like water and glycerin can be explained on the basis of their high dielectric constant. In general, also, the more polar the solvent, the greater its dielectric constant.

There is an important concept that should be considered which has been introduced to pharmaceutical systems.⁸ It must be recognized that pharmacists frequently are concerned with dissolving relatively nonpolar drugs in aqueous or mixed polar aqueous solvents. To understand what may be happening in such cases, factors concerned with the entropic effects arising from interactions originating with the nonpolar solutes must be considered. Previously it had been noted that the favorable entropic effect on dissolution was due to the disruption of associations occurring among solute or solvent molecules. Now, consider the effects on solubility due to solute interactions in the solution phase. Since the solutes under discussion are relatively nonpolar, the interactions are of the London Force type or a *hydrophobic association*. This hydrophobic association in aqueous solutions may cause significant structuring of water with a resultant ordered or low-entropy system, unfavorable to solution. As is known, the solution of an essentially nonpolar molecular in water is not a favorable process. It should be stressed that this is due to not only an unfavorable enthalpy change but also an unfavorable entropy change generated by water structuring. Such an unfavorable entropy change is quite significant in the solution process. As an example of this effect, the aqueous solubility of a series of alkyl *p*-aminobenzoates shows a ten million-fold decrease in solubility in going from the 1-carbon analog to the 12-carbon analog. These findings demonstrate clearly the considerable effect that hydrophobic associations can have.

Alcohols—*Ethanol*, as a solvent, is next in importance to water. An advantage is that growth of microorganisms does not occur in solutions containing alcohol in a reasonable concentration.

Resins, volatile oils, alkaloids, glycosides, etc are dissolved by alcohol, while many therapeutically inert principles, such as gums, albumin and starch, are insoluble, which makes it more useful as a "selective" solvent. Mixtures of water and alcohol, in proportions varying to suit specific cases, are used extensively. They are often referred to as *hydroalcoholic* solvents.

Glycerin is an excellent solvent, although its range is not as extensive as that of water or alcohol. In higher concentrations it has preservative action. It dissolves the fixed alkalis, a large number of salts, vegetable acids, pepsin, tannin, some active principles of plants, etc, but it also dissolves

gums, soluble carbohydrates, starch, etc. It also is of special value as a simple solvent, as in phenol glycerite, or where the major portion of the glycerin simply is added as a preservative and stabilizer of solutions that have been prepared with other solvents (see *Glycerines*, Chapter 87).

Propylene glycol, which has been used widely as a substitute for glycerin, is miscible with water, acetone or chloroform in all proportions. It is soluble in ether and will dissolve many essential oils but is immiscible with fixed oils. It is claimed to be as effective as ethyl alcohol in its power of inhibiting mold growth and fermentation.

Isopropyl alcohol possesses solvent properties similar to those of ethyl alcohol and is used instead of the latter in a number of pharmaceutical manufacturing operations. It has the advantage in that the commonly available product contains not over 1% of water, while ethyl alcohol contains about 5% water, often a disadvantage. Isopropyl alcohol is employed in some liniment and lotion formulations. It cannot be taken internally.

General Properties—Low-molecule-weight and polyhydroxy alcohol forms associated structures through hydrogen bonds just as in water. When the carbon-atom content of an alcohol rises above five, generally only monomers then are present in the pure solvent. Although alcohols have high dielectric constants, compared to other types of solvents, they are small compared to water. As has been discussed, the solubility of salts in a solvent should be paralleled by its dielectric constant. That is, as the dielectric constant of a series of solvents increases, the probability of dissolving a salt in the solvent increases. This behavior is observed for the alcohols. Table 2, taken from Higuchi,⁵ shows how the solubility of salts follows the dielectric constant of the alcohols.

As mentioned earlier, absolute alcohol rarely is used pharmaceutically. However, hydroalcoholic mixtures such as elixirs and spirits frequently are encountered. A very useful generalization is that the dielectric properties of a mixed solvent, such as water and alcohol, can be approximated as the weighted average of the properties of the pure components. Thus, a mixture of 60% alcohol (by weight) in water should have a dielectric constant approximated by

$$\epsilon_{(\text{mixture})} = 0.6(\epsilon_{(\text{alcohol})}) + 0.4(\epsilon_{(\text{water})})$$

$$\epsilon_{(\text{mixture})} = 0.6(25) + 0.4(80) = 47$$

The dielectric constant of 60% alcohol in water is found experimentally to be 43, which is in close agreement with that just calculated. The dielectric constant of glycerin is 46, close to the 60% alcohol mixture. One would, therefore, expect a salt like sodium chloride to have about the same solubility in glycerin as in 60% alcohol. The solubility of sodium chloride in glycerin is 8.3 g/100 g of solvent and in 60% alcohol about 6.3 g/100 g of solvent. This agreement would be even closer if comparisons were made on a volume rather than weight basis. At least qualitatively it can be said that the solubility of a salt in a solvent or a mixed solvent very closely follows the dielectric constant of the medium or, conversely, that the

Table 2—Solubilities of Potassium Iodide and Sodium Chloride in Several Alcohols and Acetone^{a,5}

Solvent	g KI/ 100 g solvent	g NaCl/ 100 g solvent
Water	148	35.9
Glycerin	...	8.3 (20°)
Propylene glycol	50	7.1 (30°)
Methanol	17	1.4
Acetone	2.9	...
Ethanol	1.88	0.065
1-Propanol	0.44	0.0124
2-Propanol	0.18	0.003
1-Butanol	0.20	0.005
1-Pentanol	0.089	0.0018

^a All measurements are at 25° unless otherwise indicated.

polarity of mixed solvents is paralleled by their dielectric constant, based on salt solubility.

Although the dielectric constant is useful in interpreting the effect of mixed solvents on salt solubility, it cannot be applied properly to the effect of mixed solvents on the solubility of nonelectrolytes. It was seen earlier that unfavorable entropic effects can occur upon dissolution of relatively nonpolar nonelectrolytes in water. Such an effect due to hydrophobic association considerably affects solubility. Yalkowsky⁵ studied the ability of cosolvent systems to increase the solubility of nonelectrolytes in polar solvents where the cosolvent system essentially brings about a reduction in structuring of solvent. Thus, by increasing, in a positive sense, the entropy of solution by using cosolvents, it was possible to increase the solubility of the nonpolar molecule. Using as an example the solubility of alkyl *p*-aminobenzoates in propylene glycol-water systems, Yalkowsky⁸ reported that it is possible to increase the solubility of the nonelectrolyte by several orders of magnitude by increasing the fraction of propylene glycol in the aqueous system. Sometimes, it is found that, as a good first approximation, the logarithm of the solubility is related linearly to the fraction of propylene glycol added by

$$\log S_f = \log S_{f=0} + \epsilon f$$

where S_f is the solubility in the mixed aqueous system containing the volume fraction f of nonaqueous cosolvent, $S_{f=0}$ is the solubility in water and ϵ is a constant (not dielectric constant) characteristic of the system under study. Specifically, when a 50% solution of propylene glycol in water is used, there is a 1000-fold increase in solubility of dodecyl *p*-aminobenzoate, in comparison to pure water.

In a series of studies, Martin et al.⁹ have made attempts to predict solubility in mixed solvent systems through an extension of the "regular solution" theory. The equations are logarithmic in nature and can reduce in form to the equations of Yalkowsky.⁸

Acetone and Related Semipolar Materials—Even though acetone has a very high dipole moment (2.8×10^{-18} esu), as a pure solvent it does not form associated structures. This is evidenced by its low boiling point (57°) in comparison with the boiling point of the lower-molecular-weight water (100°) and ethanol (79°). The reason why it does not associate is because the positive charge in its dipole does not reside in a hydrogen atom precluding the possibility of its forming a hydrogen bond. However, if some substance which is capable of forming hydrogen bonds, such as water or alcohol, is added to acetone, a very strong interaction through hydrogen bonding will occur (see *Mechanism of Solvent Action* below). Some substances which are semipolar and similar to acetone are aldehydes, low-molecular-weight esters, other ketones and nitro-containing compounds.

Nonpolar Solvents—This class of solvents includes fixed oils such as vegetable oil, petroleum ether (ligroin), carbon tetrachloride, benzene and chloroform. On a relative basis there is a wide range of polarity among these solvents; for example, benzene has no dipole moment while that of chloroform is 1.05×10^{-18} esu.

It should be emphasized that when a solvent (such as chloroform) has highly electronegative halogen atoms attached to a carbon atom also containing at least one hydrogen atom, such a solvent will be capable of forming strong hydrogen bonds with solutes which are polar in character. Thus, through the formation of hydrogen bonds such solvents will dissolve polar solutes. For example, it is possible to dissolve alkaloids in chloroform.

Mechanism of Solvent Action

A solvent may function in one, or more, of several ways. When an ionic salt is dissolved, eg, by water, the process of solution involves separation of the cations and anions of the salt with attendant orientation of molecules of the solvent about the ions. Such orientation of solvent molecules about the ions of the solute—a process called *solvation* (*hydra-*

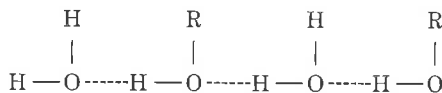
tion, if the solvent is water)—is possible only when the solvent is highly polar, whereby, the dipoles of the solvent are attracted to and held by the ions of the solute. The solvent also must possess the ability to keep the solvated, charged ions apart with minimal energy.

A polar liquid such as water may exhibit solvent action also by virtue of its ability to break a covalent bond in the solute and bring about ionization of the latter. For example, hydrogen chloride dissolves in water and functions as an acid as a result of



The ions formed by this preliminary reaction of breaking the covalent bond subsequently are maintained in solution by the same mechanism as ionic salts.

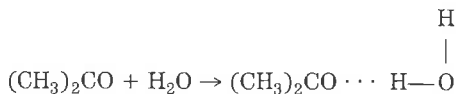
Still another mechanism by which a polar liquid may act as a solvent is that involved when the solvent and solute are capable of being coupled through hydrogen-bond formation. The solubility of the low-molecular-weight alcohols in water, for example, is attributed to the ability of the alcohol molecules to become part of a water-alcohol association complex.



As the molecular weight of the alcohol increases, it becomes progressively less polar and less able to compete with water molecules for a place in the lattice-like arrangement formed through hydrogen bonding; high-molecular-weight alcohols are, therefore, poorly soluble or insoluble in water. When the number of carbon atoms in a normal alcohol reaches five, its solubility in water is reduced materially.

When the number of hydroxyl groups in the alcohol is increased, its solubility in water generally is increased greatly; it is principally, if not entirely, for this reason that such high-molecular-weight compounds as sugars, gums, many glycosides and synthetic compounds, such as the polyethylene glycols, are very soluble in water.

The solubility of ethers, aldehydes, ketones, acids and anhydrides in water, and in other polar solvents, also is attributable largely to the formation of an association complex between solute and solvent by means of the hydrogen bond. The molecules of ethers, aldehydes and ketones, unlike those of alcohols, are not associated themselves, because of the absence of a hydrogen atom which is capable of forming the characteristic hydrogen bond. Notwithstanding, these substances are more or less polar because of the presence of a strongly electronegative oxygen atom, which is capable of association with water through hydrogen-bond formation. Acetone, for example, dissolves in water, in all likelihood, principally because of the following type of association:



The maximum number of carbon atoms which may be present per molecule possessing a hydrogen-bondable group, while still retaining water solubility, is approximately the same as for the alcohols.

Although nitrogen is less electronegative than oxygen and, thus, tends to form weaker hydrogen bonds, it is observed that amines are at least as soluble as alcohols containing an equivalent chain length. The reason for this is that alcohols form two hydrogen bonds with a net interaction of 12 kcal/mole. Primary amines can form three hydrogen bonds; two amine protons are shared with the oxygens of two water molecules, and the nitrogen accepts one water proton. The net interaction for the primary amine is between 12 and 13 kcal/mole and, hence, it shows an equal or greater solubility compared with corresponding alcohols.

The solvent action of nonpolar liquids involves a somewhat different mechanism. Because they are unable to form di-

poles with which to overcome the attractions between ions of an ionic salt, or to break a covalent bond to produce an ionic compound or form association complexes with a solute, nonpolar liquids are incapable of dissolving polar compounds. They only can dissolve, in general, other nonpolar substances in which the bonds between molecules are weak. The forces involved usually are of the induced dipole-induced dipole type. Such is the case when one hydrocarbon is dissolved in another, or an oil or a fat is dissolved in petroleum ether. Sometimes it is observed that a polar substance, such as alcohol, will dissolve in a nonpolar liquid, such as benzene. This apparent exception to the preceding generalization may be explained by the assumption that the alcohol molecule induces a temporary dipole in the benzene molecule which forms an association complex with the solvent molecules. A binding force of this kind is referred to as a *permanent dipole-induced dipole force*.

Some Useful Generalizations—The preceding discussion indicates that enough is known about the mechanism of solubility to be able to formulate some generalizations concerning this important physical property of substances. Because of the greater importance of organic substances in the field of medicinal chemistry, certain of the more useful generalizations with respect to organic chemicals are presented here in summary form. It should be remembered, however, that the phenomenon of solubility usually involves several variables, and there may be exceptions to general rules.

One general maxim which holds true in most instances is: *the greater the structural similarity between solute and solvent, the greater the solubility*. As often stated to the student, "like dissolves like." Thus, phenol is almost insoluble in petroleum ether but is very soluble in glycerin.

Organic compounds containing polar groups capable of forming hydrogen bonds with water are soluble in water, providing that the molecular weight of the compound is not too great. It is demonstrated easily that the polar groups OH, CHO, COH, CHOH, CH₂OH, COOH, NO₂, CO, NH₂ and SO₃H tend to increase the solubility of an organic compound in water. On the other hand, nonpolar or very weak polar groups, such as the various hydrocarbon radicals, reduce solubility; the greater the number of carbon atoms in the radical, the greater the decrease in solubility. Introduction of halogen atoms into a molecule in general tends to decrease solubility because of an increased molecular weight without a proportionate increase in polarity.

The greater the number of polar groups contained per molecule, the greater the solubility of a compound, provided that the size of the rest of the molecule is not altered; thus, pyrogallol is much more soluble in water than phenol. The *relative positions* of the groups in the molecule also influence solubility; thus, in water, resorcinol (*m*-dihydroxybenzene) is more soluble than catechol (*o*-dihydroxybenzene), and the latter is more soluble than hydroquinone (*p*-dihydroxybenzene).

Polymers and compounds of high molecular weight generally are insoluble or only very slightly soluble.

High melting points frequently are indicative of low solubility for organic compounds. One reason for high melting points is the *association* of molecules and this cohesive force tends to prevent dispersion of the solute in the solvent.

The *cis* form of an isomer is more soluble than the *trans* form. See Table 3.

Table 3—Demonstration of Solubility Rules

Chemical compound	Solubility ^a
Aniline, C ₆ H ₅ NH ₂	28.6
Benzene, C ₆ H ₆	1430
Benzoic acid, C ₆ H ₅ COOH	275
Benzyl alcohol C ₆ H ₅ CH ₂ OH	25
1-Butanol, C ₄ H ₉ OH	12
<i>t</i> -Butyl alcohol, (CH ₃) ₃ COH	Miscible
Carbon tetrachloride, CCl ₄	2000
Chloroform, CHCl ₃	200
Fumaric acid (<i>trans</i> -butenedioic acid)	150
Hydroquinone, C ₆ H ₄ (OH) ₂	14
Maleic acid, <i>cis</i> -butenedioic acid	5
Phenol, C ₆ H ₅ OH	15
Pyrocatechol, C ₆ H ₄ (OH) ₂	2.3
Pyrogallol, C ₆ H ₃ (OH) ₃	1.7
Resorcinol, C ₆ H ₄ (OH) ₂	0.9

^a The number of mL of water required to dissolve 1 g of solute.

Solvation, which is evidence of the existence of a strong attractive force between solute and solvent, enhances the solubility of the solute, provided there is not a marked ordering of the solvent molecules in the solution phase.

Acids, especially strong acids, usually produce water-soluble salts when reacted with nitrogen-containing organic bases.

Colligative Properties of Solutions

Up to this point concern has been with dissolving a solute in a solvent. Having brought about the dissolution, the solution, quite naturally, has a number of properties which are different from that of the pure solvent. Of very great importance are the *colligative properties* which a solution possesses.

The colligative properties of a solution are those that depend on the *number* of solute particles in solution, irrespective of whether these are molecules or ions, large or small. Ideally, the effect of a solute particle of one species is considered to be the same as that of an entirely different kind of particle, at least in dilute solution. Practically, there may be differences which may become substantial as the concentration of the solution is increased.

The colligative properties which will be considered are:

1. Osmotic pressure.
2. Vapor-pressure lowering.
3. Boiling-point elevation.
4. Freezing-point depression.

Of these four, all of which are related, osmotic pressure has the greatest direct importance in the pharmaceutical sciences. It is the property that largely determines the physiological acceptability of a variety of solutions used for therapeutic purposes.

Osmotic-Pressure Elevation

Diffusion in Liquids—Although the property of diffusion is rapid in gaseous systems, it is not limited to such systems. That molecules or ions in liquid systems possess this same freedom of movement may be demonstrated by placing carefully a layer of water on a concentrated aqueous solution of any salt. In time it will be observed that the boundary between solvent and solution widens gradually since salt moves into the water layer and water migrates from its layer into the salt solution below. Eventually, the composition of the new solution will become uniform throughout. This experiment indicates that *substances tend to move or diffuse from regions of higher concentration to regions of lower concentrations* so that differences in concentration eventually disappear.

Osmosis—In carrying out the experiment just described, it is impossible to distinguish between the diffusion of the solute and that of the solvent. However, by separating the solution and the solvent by means of a membrane that is permeable to the solvent, but not to the solute (such a membrane is referred to as a *semipermeable* membrane), it is possible to demonstrate visibly the diffusion of solvent into the concentrated solution, since volume changes will occur. In a similar manner, if two solutions of different concentration are separated by a membrane, the solvent will move from the solution of lower solute concentration to the solution of higher solute concentration. This diffusion of solvent through a membrane is called *osmosis*.

There is a difference between the activity or escaping tendency of the water molecules found in the solvent and salt solution separated by the semipermeable membrane. Since *activity*, which is related to water concentration, is higher on the pure solvent side, water moves from solvent to solution in order to equalize escaping-tendency differences. The difference in *escaping-tendency* gives rise to what is referred to as the *osmotic pressure* of the solution, which might be visualized as follows. A semipermeable membrane is placed over the end of a tube and a small amount of salt solution placed over the membrane in the tube. The tube then is immersed in a trough of pure water so that the upper level of the salt

solution initially is at the same level as the water in the trough. With time, solvent molecules will move from solvent into the tube. The height of the solution will rise until the *hydrostatic pressure* exerted by the column of solution is equal to the *osmotic pressure*.

Osmotic Pressure of Nonelectrolytes—From quantitative studies with solutions of varying concentration of a solute that does not ionize, it has been demonstrated that *osmotic pressure is proportional to the concentration of the solute*; ie, twice the concentration of a given nonelectrolyte will produce twice the osmotic pressure in a given solvent. (This is not strictly true in solutions of fairly high solute concentration, but does hold quite well for dilute solutions.)

Furthermore, the osmotic pressures of solutions of different nonelectrolytes are proportional to the number of molecules in each solution. Stated in another manner, the osmotic pressures of two nonelectrolyte solutions of the same molal concentration are identical. Thus, a solution containing 34.2 g of sucrose (mol wt 342) in 1000 g of water has the same osmotic pressure as a solution containing 18.0 g of anhydrous dextrose (mol wt 180) in 1000 g of water. These solutions are said to be *iso-osmotic* (*isomotic*) with each other because they have identical osmotic pressures.

A study of the results of osmotic-pressure measurements on different substances led the Dutch chemist Jacobus Henricus van't Hoff, in 1885, to suggest that the solute in a solution may be considered as being analogous to the molecules of a gas and by the osmotic pressure as being produced by the bombardment of the semipermeable membrane by the molecules of solute. According to van't Hoff's theory the osmotic pressure of a solution is equal to the pressure which the dissolved substance would exert in the gaseous state if it occupied a volume equal to the volume of the solution. From this it follows that, just as in the case of a gas, there is a proportionality between pressure and concentration of dissolved substance. This proportionality is illustrated well by the values of the osmotic pressure of solutions of sucrose at 0° as determined by the Earl of Berkeley and EGJ Hartley and shown in Table 4.

In column *PV* of Table 4 a quantitative confirmation, at least for fairly dilute solutions, of van't Hoff's oversimplified though useful generalization is shown by the constancy of the values of the product *PV*. Recall that the product of the pressure and the volume of a gas, at constant temperature, is likewise constant (Boyle's law).

Van't Hoff also deduced that the osmotic pressure must be proportional to the absolute temperature, just as in Charles' law for gases, which deduction was confirmed by the experiments of several workers. From this it follows that the equation $PV = nRT$ is valid for dilute solutions of nonelectrolytes just as a similar equation is valid for gases. However, even as Boyle's law does not apply to gases under high pressures and at low temperatures, so van't Hoff's equation for osmotic pressure does not apply in concentrated solutions.

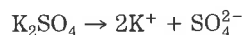
Osmotic Pressure of Electrolytes—In discussing the generalizations concerning the osmotic pressure of solutions of nonelectrolytes it was stated that the osmotic pressures of two solutions of the same molal concentration are identical. This generalization, however, cannot be made for solutions of electrolytes, ie, acids, alkalies and salts (see Chapter 17).

For example, sodium chloride is assumed to ionize as



It is evident that each molecule of sodium chloride that ionizes produces two ions and, if sodium chloride is completely ionized, there will be twice as many particles as would be the case if it were not ionized at all. Furthermore, if each ion has the same effect on osmotic pressure as a molecule, it might be expected that the osmotic pressure of the solution would be twice that of a solution containing the same molal concentration of nonionizing substance.

For solutions which yield more than two ions as, for example



it is expected that the complete dissociation of the molecules would give rise to osmotic pressures that are three and four times, respectively, the pressure of solutions containing an equivalent quantity of a nonionized solute. Accordingly, the equation $PV = nRT$, which may be employed to calculate the osmotic pressure of a *dilute* solution of a nonelectrolyte, also may be applied to *dilute* solutions of electrolytes if it is changed to $PV = inRT$, where the value of *i* approaches the number of ions produced by the ionization of the stronger electrolytes cited in the preceding examples. For weak electrolytes *i* represents the total number of particles, ions and molecules together, in the solution, divided by the number of molecules that would be present if the solute did not ionize. The experimental evidence indicates that in dilute solutions, at least, the osmotic pressures approach the predicted values. It should be emphasized, however, that in more concentrated solutions of electrolytes the deviations from this simple theory are considerable, due to interionic attraction, solvation and other factors.

Biological Aspects of Osmotic Pressure—Osmotic-pressure experiments were made as early as 1884 by the Dutch botanist Hugo de Vries in his study of plasmolysis, which term is applied to the contraction of the contents of plant cells placed in solutions of comparatively high osmotic pressure. The phenomenon is caused by the osmosis of water out of the cell through the practically semipermeable membrane surrounding the protoplasm. If suitable cells (eg, the epidermal cells of the leaf of *Tradescantia discolor*) are placed in a solution of higher osmotic pressure than that of the cell contents, water flows out of the cell, causing the contents to draw away from the cell wall. On the other hand, if the cells are placed in solutions of lower osmotic pressure, water enters the cell, producing an expansion which is limited by the rigid cell wall. By immersing cells in a series of solutions of varying solute concentration, a solution may be found in which plasmolysis is barely detectable or absent. The osmotic pressure of such a solution is then the same, or very nearly the same, as that of the cell contents, and it is then said that the solution is *isotonic* with the cell contents. Solutions of greater concentration than this are said to be *hypertonic* and solutions of lower concentration, *hypotonic*.

Red blood cells, or erythrocytes, have been studied similarly by immersion into solutions of varying concentration of different solutes. When introduced into water or into sodium chloride solutions containing less than 0.90 g of solute per 100 mL, human erythrocytes swell, and often burst, because of the diffusion of water into the cell and the fact that the cell wall is not sufficiently strong to resist the pressure. This phenomenon is referred to as *hemolysis*. If the cells are placed in solutions containing more than 0.90 g of sodium chloride per 100 mL, they lose water and shrink. By immersing the cells in a solution containing exactly 0.90 g of sodium chloride in 100 mL, no change in the size of the cells is observed; since in this solution the cells maintain their "tone," the solution is said to be *isotonic* with human erythrocytes. For the reasons indicated it is desirable that solutions to be injected into the blood should be made isotonic with

Table 4—Osmotic Pressure of Sucrose Solutions

Conc. (g/L), C	Vol in L in which 1 g mol is dissolved, V ^a	Pressure in atmos P	P/C	PV
10.00	34.2	0.65	0.065	22.2
20.00	17.1	1.27	0.064	21.7
45.00	7.60	2.91	0.065	22.1
93.75	3.65	6.23	0.067	22.7

^a These figures were obtained by calculating the volume of solution in which 342 (mol wt) g of sucrose would be dissolved.

erythrocytes. The manner in which this may be done is described in Chapter 36.

Distinction between Iso-osmotic (Isosmotic) and Iso-tonic—The terms isosmotic and isotonic are not to be considered as equivalent, although a solution often may be described as being both isosmotic and isotonic. If a plant or animal cell is in contact with a solution that has the same osmotic pressure as the cell contents, there will be no net gain or loss of water by either solution *provided* the cell membrane is impermeable to all the solutes present. Since the volume of the cell contents remains unchanged, the "tone," or normal state, of the cell is maintained, and the solution in contact with the cell may be described not only as being isosmotic with the solution in the cell, but also as being isotonic with it. If, however, one or more of the solutes in contact with the membrane can pass through the latter, it is evident that the volume of the cell contents will change, thus altering the "tone" of the cell; in this case the two solutions may be isosmotic, yet not be isotonic.

It is possible that some substances used in an injection dosage form can cause hemolysis of red blood cells, even when their concentrations are such as to produce solutions theoretically isosmotic with the cells, because the solutes diffuse through the membrane of the cells. For example, a 1.8% solution of urea has the same osmotic pressure as a 0.9% solution of sodium chloride, but the former solution produces hemolysis of red blood cells; obviously the urea solution is not isotonic with the cells. To determine if a solution is isotonic with erythrocytes, it is necessary to determine the concentration of solute at which the cells retain their normal size and shape. A simple method for doing this was devised by Setnikar and Temelcou,¹⁰ who determined the concentration of a solution at which red blood cells maintained a volume equal to that occupied in an isotonic solution of sodium chloride. The red cell volumes were determined by centrifuging suspensions of them in different solutions, using a hematocrit tube.

Vapor-Pressure Lowering

When a nonvolatile solute is dissolved in a liquid solvent the vapor pressure of the solvent is lowered. This easily can be described qualitatively by visualizing solvent molecules on the surface of the solvent, which normally could escape into the vapor, being replaced by solute molecules which have little if any vapor pressure of their own. For ideal solutions of nonelectrolytes the vapor pressure of the solution follows Raoult's law

$$P_A = X_A P_A^\circ \quad (15)$$

where P_A is the vapor pressure of the solution, P_A° is the vapor pressure of the pure solvent and X_A is the mole fraction of solvent. This relationship states that the vapor pressure of the solution is proportional to the number of molecules of solvent in the solution. Rearranging Eq 15 gives

$$\frac{P_A^\circ - P_A}{P_A^\circ} = (1 - X_A)X_B \quad (16)$$

where X_B is the mole fraction of the solute. This equation states that the lowering of vapor pressure in the solution relative to the vapor pressure of the pure solvent—called simply the *relative vapor-pressure lowering*—is equal to the mole fraction of the solute. The *absolute* lowering of vapor pressure of the solution is defined by

$$P_A^\circ - P_A = X_B P_A^\circ \quad (17)$$

Example—Calculate the lowering of vapor pressure and the vapor pressure at 20°, of a solution containing 50 g of anhydrous dextrose (mol wt 180.16) in 1000 g of water (mol wt 18.02). The vapor pressure of water at 20°, in absence of air, is 17.535 mm.

First calculate the lowering of vapor pressure, using Eq 17 in which X_B is the mol fraction of dextrose, defined by

$$X_B = \frac{n_B}{n_A + n_B}$$

where n_A is the number of moles of solvent and n_B is the number of mols of solute. Substituting numerical values

$$n_B = \frac{50}{180.2} = 0.278$$

$$n_A = \frac{1000}{18.02} = 55.5$$

$$X_B = \frac{0.278}{55.5 + 0.278} = 0.00498$$

the lowering of vapor pressure is

$$\begin{aligned} P_A^\circ - P_A &= 0.00498 \times 17,535 \\ &= 0.0873 \text{ mm} \end{aligned}$$

The vapor pressure of the solution is

$$\begin{aligned} P_A &= 17.535 - 0.0873 \\ &= 17.448 \text{ mm} \end{aligned}$$

Boiling-Point Elevation

In consequence of the fact that the vapor pressure of any solution of a nonvolatile solute is less than that of the solvent, the boiling point of the solution—the temperature at which the vapor pressure is equal to the applied pressure (commonly 760 mm)—must be higher than that of the solvent. This is clearly evident in Fig 12.

The relationship between the elevation of boiling point and the concentration of nonvolatile, nonelectrolyte solute may be derived from the Clausius–Clapeyron equation (see Chapter 15), which is

$$\frac{dP}{dT} = \frac{P \cdot \Delta H_{\text{vap}}}{DT^2} \quad (18)$$

Replacing the differential expression of dP/dT by $\Delta P/\Delta T_b$, where ΔP is the lowering of vapor pressure and ΔT_b is the elevation of boiling point, and introducing P_A° , the vapor pressure of the solvent at its boiling point T_0 , results in

$$\frac{\Delta P}{\Delta T_b} = \frac{P_A^\circ \cdot \Delta H_{\text{vap}}}{RT_0^2} \quad (19)$$

Since the lowering of vapor pressure in an ideal solution is

$$\Delta P = X_B P_A^\circ \quad (20)$$

substitution of this equation into Eq 19, with rearrangement to provide a solution for ΔT_b , gives

$$\Delta T_b = \frac{RT_0^2}{\Delta H_{\text{vap}}} X_B \quad (21)$$

This equation may be used to calculate the elevation of the

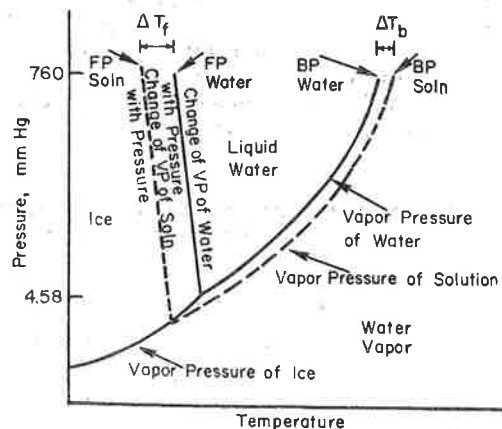


Fig 12. Vapor-pressure-temperature diagram for water and an aqueous solution, illustrating elevation of boiling point and lowering of freezing point of the latter.

boiling point if the concentration of solute is expressed as the mole fraction. A more common expression, however, is in terms of the molality m (the number of gram-mols of solute per 1000 g of solvent), which relationship is derived as

$$X_B = \frac{n_B}{n_A + n_B} = \frac{m}{1000/M_A + m} \approx \frac{m}{1000/M_A} \quad (22)$$

In these equations M_A is the molecular weight of the solvent. When the solutions are dilute, so that m is small, it may be neglected in the denominator (*but not in the numerator!*) to give the approximate equivalent in Eq. 22. Substituting this equivalent into Eq 21 gives

$$\Delta T_b = \frac{RT_0^2 M_A m}{1000 \Delta H_{\text{vap}}} \quad (23)$$

Grouping the constants into a single term results in

$$\Delta T_b = K_b m \quad (24)$$

where

$$K_b = \frac{RT_0^2 M_A}{1000 \Delta H_{\text{vap}}} \quad (25)$$

and is called the molal boiling-point elevation constant.

The value of this constant for water, which boils at 373.1°K, has a heat of vaporization of 539.7 cal/g and a molecular weight of 18.02, is

$$K_b = \frac{1.987 \times 373.1^2 \times 18.02}{1000 \times 18.02 \times 539.7} = 0.513^\circ \quad (26)$$

Notwithstanding that K_b is called a molal boiling-point elevation constant, it should not be interpreted as the actual rise of boiling point for a 1-molal solution. Such solutions are generally too concentrated to exhibit the ideal behavior assumed in deriving the equation for calculating the theoretical value of the constant. In dilute solutions, however, the actual boiling-point elevation, *calculated to a 1-molal basis*, approaches the theoretical value, the closer the more dilute the solution.

The elevation of boiling point of a dilute solution of a nonelectrolyte solute may be used to calculate the mol wt of the latter. In a solution containing w_B g of solute of M_B in w_A of solvent the molality m is

$$m = \frac{1000 w_B}{w_A M_B} \quad (27)$$

substituting this into Eq 24 and rearranging gives

$$M_B = \frac{K_b 1000 w_B}{w_A \Delta T_b} \quad (28)$$

Freezing-Point Depression

The freezing point of a solvent is defined as the temperature at which the solid and liquid forms of the solvent coexist in equilibrium at a fixed external pressure, commonly 1 atm (760 mm of mercury). At this temperature the solid and liquid forms of the solvent must have the same vapor pressure, for if this were not so, the form having the higher vapor pressure would change into that having the lower vapor pressure.

The freezing point of a solution is the temperature at which the solid form of the pure solvent coexists in equilibrium with the solution at a fixed external pressure, again commonly 1 atm. Since the vapor pressure of a solution is lower than that of its solvent, it is obvious that solid solvent and solution cannot coexist at the same temperature as solid solvent and liquid solvent; only at some lower temperature, where solid solvent and solution do have the same vapor pressure, is equilibrium established. A schematic pressure-temperature diagram for water and an aqueous solution, not drawn to scale and exaggerated for the purpose of more effective illustration,

shows the equilibrium conditions involved in both freezing-point depression and boiling-point elevation (Fig 12).

The freezing-point lowering of a solution may be quantitatively predicted for ideal solutions, or *dilute solutions* which obey Raoult's law, by mathematical operations similar to (though somewhat more complex than) those used in deriving the boiling-point elevation constant. The equation for the freezing point lowering, ΔT_f , is

$$\Delta T_f = \frac{RT_0^2 M_A m}{1000 \Delta H_{\text{fus}}} = K_f m \quad (29)$$

where

$$K_f = \frac{RT_0^2 M_A}{1000 \Delta H_{\text{fus}}} \quad (30)$$

The value of K_f for water, which freezes at 273.1°K and has a heat of fusion of 79.7 cal/g, is

$$K_f = \frac{1.987 \times 273.1^2 \times 18.02}{1000 \times 18.02 \times 79.7} = 1.86^\circ \quad (31)$$

The molal freezing-point depression constant is not intended to represent the freezing-point depression for a 1-molal solution, which is too concentrated for the premise of ideal behavior to be applicable. In dilute solutions the freezing-point depression, calculated to a 1-molal basis, approaches the theoretical value, the agreement between experiment and theory being the better the more dilute the solution.

The freezing point of a dilute solution of a nonelectrolyte solute may be used, as was the boiling point, to calculate the molecular weight of the solute. The applicable equation is

$$M_B = \frac{K_f 1000 w_B}{w_A \Delta T_f} \quad (32)$$

The molecular weight of organic substances soluble in molten camphor may be determined by observing the freezing point of a mixture of the substance with camphor. This procedure, called the *Rast method*, uses camphor because it has a very large molal freezing-point-depression constant, about 40°. Since the "constant" may vary with different lots of camphor and with variations of technique, the method should be standardized using a solute of known molecular weight.

Freezing-point determinations of molecular weights have the advantage over boiling-point determinations of greater accuracy and precision by virtue of the larger magnitude of the freezing-point depression compared to boiling-point elevation. Thus, in the case of water the molal freezing-point depression is approximately 3.5 times greater than the molal boiling-point elevation.

Relationship between Osmotic Pressure and Vapor-Pressure Depression

The lowering of vapor pressure and the development of osmotic pressure in a solution are both manifestations of the basic condition that the free energy of solvent molecules in the pure solvent is greater than the free energy of solvent molecules in the solution. Consequently, solvent molecules will transfer spontaneously, if given an opportunity, from solvent to solution until equilibrium conditions are established. The transfer can take place either through a membrane permeable only to solvent molecules or, if such contact between solvent and solution is not available, by distillation of solvent from pure solvent to solution, if access through a vapor phase is provided.

If an experiment is performed with two sets of vessels containing solution and solvent, as illustrated in Fig 13 differing only in that the long tube of one set has a semipermeable membrane attached to its lower end, while in the other a hypothetical membrane separates the vapor phases, in time

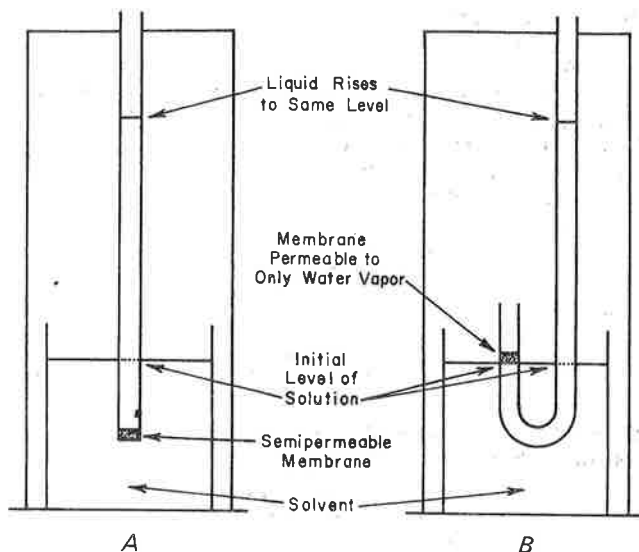


Fig 13. Transfer of solvent to equal volumes of solution. A: Osmotically, through a semipermeable membrane separating solution and solvent. B: By distillation, through a membrane separating solution and solvent vapor.

the same hydrostatic pressure should develop in both cases. For a definite volume, eg, a mol, of solvent transferred to the solution by distillation the change of free energy, ΔG , in the process is

$$\Delta G = RT \ln \frac{P_A}{P_A^\circ} \quad (33)$$

where P_A is the vapor pressure of the solution and P_A° is the vapor pressure of the solvent.

For the transfer of the same volume of solvent by osmosis the free-energy change is

$$\Delta G = -\bar{V}_A \pi \quad (34)$$

where $\bar{V}_A$ is the partial molal volume of solvent (the volume of 1 mole of solvent in the solution) and π is the osmotic pressure of the solution. Since the free-energy change is the same in both processes

$$-\bar{V}_A \pi = RT \ln \frac{P_A}{P_A^\circ} \quad (35)$$

rearranging the equation yields

$$\pi = \frac{RT}{\bar{V}_A} \ln \frac{P_A^\circ}{P_A} \quad (36)$$

With this equation the osmotic pressure of a solution may be calculated if its vapor pressure and the partial molal volume of the solvent are known, not only when the solution is sufficiently dilute that Raoult's law is obeyed but also when the concentration is so high as to introduce substantial deviation from the law.

From Eq 36, which has some resemblance to van't Hoff's empirical equation ($\pi V = nRT$) for dilute solutions, the latter equation may be derived as follows. If a solution is sufficiently dilute to correspond to Raoult's law, then

$$P_A = A_A P_A^\circ = (1 - X_B) P_A^\circ \quad (37)$$

and then Eq 36 may be written

$$\pi = -\frac{RT}{\bar{V}_A} \ln (1 - X_B) \quad (38)$$

When X_B is small (as in a dilute solution), the term $-\ln$

$(1 - X_B)$ can be shown to be approximately equal to X_B , so that

$$\pi = \frac{RT}{\bar{V}_A} X_B \quad (39)$$

In dilute solutions the approximations $X_B = n_B/n_A$ (where n_B and n_A are the moles of solute and solvent, respectively) and $\bar{V}_A = V/n_A$ (where V is the volume of solution) may be introduced, yielding

$$\pi V = n_B RT \quad (40)$$

which is van't Hoff's equation.

Ideal Behavior and Deviations

In setting out to derive mathematical expressions for colligative properties, such phrases as "for ideal solutions" or "for dilute solutions" were used to indicate the limitations of the expressions. Samuel Glasstone defines an ideal solution as "one which obeys Raoult's law over the whole range of concentration and at all temperatures" and gives as specific characteristics of such solutions their formation only from constituents which mix in the liquid state without heat change and without volume change. These characteristics reflect the fact that addition of a solute to a solvent produces no change in the forces between molecules of the solvent. Thus, the molecules have the same *escaping-tendency* in the solution as in the pure solvent and the vapor pressure above the solution is proportional to the ratio of the number of solvent molecules in the surface of the solution to the number of the molecules in the surface of the solvent—which is the basis for Raoult's law.

Any change in intermolecular forces produced by mixing the components of a solution may result in deviation from ideality; such a deviation may be expected particularly in solutions containing both a polar and a nonpolar substance. Solutions of electrolytes, except at high dilution, are especially prone to depart from ideal behavior, even though allowance is made for the additional particles, that result from ionization. When solute and solvent combine to form solvates, the escaping-tendency of the solvent may be reduced in consequence of the reduction in the number of free molecules of solvent; thus, a negative deviation from Raoult's law is introduced. On the other hand, the escaping-tendency of the solvent, in a solution of nonvolatile solute, may be increased because the cohesive forces between molecules of solvent are reduced by the solute; this results in a positive deviation from Raoult's law. Chapter 17 considers deviations from ideality in more detail.

While few solutions exhibit ideal behavior over a wide range of concentration, most solutions behave ideally at least in high dilution, where deviations from Raoult's law are negligible.

Comparison of Colligative Properties—In view of the established interrelationships of the colligative properties of ideal solutions or very dilute real solutions, it is possible to predict, by calculation, the magnitude of all these properties of such solutions if the concentration of the nonelectrolyte solute is given. Also, if the magnitude of one of the properties, eg, the freezing point, is known for a solution of unspecified concentration, it is possible to calculate the vapor pressure, boiling point and osmotic pressure, provided the solution is ideal or sufficiently dilute to show negligible deviation from ideality. To what upper limit of concentration a non-ideal solution remains "sufficiently dilute" to show ideal behavior is difficult to specify. The answer depends at least in part on the degree of agreement expected between experimental and theoretical values. Certainly, a 1-molal concentration is much too concentrated for a nonideal solution to show conformance with ideal behavior and even in 0.1 molal concentration, deviations are significant and for some purposes may be excessive.

In dealing with colligative properties of solutions which do not behave ideally, caution should be exercised in attempting

to predict the magnitude of other colligative properties from one that has been determined experimentally. Earlier, an equation was derived for calculating the vapor pressure of a solution from its osmotic pressure, or *vice versa*, this equation being valid even with solutions showing substantial departures from ideal behavior. The equation is limited, however, to a comparison of these colligative properties at the same temperature. The degree of deviation from ideal behavior for one colligative property will be exactly the same for another only when the temperature is the same for both. It does not follow that the degree of deviation of the colligative properties of a given nonideal solution will be the same for all the properties since at least two of these (freezing point and boiling point) must be determined at quite different temperatures. While in dilute solutions the intermolecular (and/or interionic) forces and interactions *may* change little over the temperature interval between freezing and boiling, in concentrated solutions the change *may* be marked. In the absence of adequate knowledge about the forces and interactions involved, only by experiment can one establish the magnitude of the colligative properties of other than very dilute nonideal solutions. It is important to keep this in mind in estimating the osmotic pressure of a nonideal solution at body temperature from a freezing point determined some 37° lower. While in many cases—possibly the majority of them—such an estimate is warranted by virtue of essential constancy of the various forces and interactions over a wide range of temperature, that is not always the case and the estimate may be significantly inaccurate.

Colligative Properties of Electrolyte Solutions (see Chapter 17)—Earlier in this chapter attention was directed to the increased osmotic pressure observed in solutions of electrolytes, the enhanced effect being attributed to the presence of ions, each of which acts, in general, in the same way as a molecule in developing osmotic pressure. Similar magnification of vapor-pressure lowering, boiling-point elevation and freezing-point depression occurs in solutions of electrolytes. Thus, at a given constant temperature the abnormal effect of an electrolyte on osmotic pressure is paralleled by abnormal lowering of vapor pressure; the other colligative properties are, subject to variation of effect with temperature, comparable intensified. In general the magnitude of each colligative property is proportional to the total number of particles (molecules and/or ions) in solution.

While in *very* dilute solutions the osmotic pressure, vapor-pressure lowering, boiling-point increase and freezing-point depression of solutions of electrolytes would approach values 2, 3, 4, etc times greater for NaCl, Na₂SO₄ and Na₃PO₄ than in solutions of the same molality of a nonelectrolyte, two other effects are observed as the concentration of electrolyte is increased. The first effect results in *less* than 2-, 3- or 4-fold intensification of a colligative property. This reduction is ascribed to interionic attraction between the positively and negatively charged ions, in consequence of which the ions are not completely dissociated from each other and do not exert their full effect in lowering vapor pressure, etc. This deviation generally increases with increasing concentration of electrolyte. The second effect intensifies the colligative properties and is attributed to the attraction of ions for solvent molecules, which holds the solvent in solution and reduces its escaping-tendency, with consequent enhancement of the vapor-pressure lowering. Solvation also may reduce interionic attraction and thereby further lower the vapor pressure. These factors (and possibly others) combine to effect a progressive reduction in the molal values of colligative properties as the concentration of electrolyte is increased to 0.5 to 1 molal, beyond which the molal quantities either increase, sometimes quite abruptly, or remain almost constant.

Activity and Activity Coefficient

Various mathematical expressions are employed to relate properties of chemical systems (equilibrium constants, colligative properties, pH, etc) to the stoichiometric concentration

of one or more molecular, atomic or ionic species. In deriving such expressions it either is stated or implied that they are valid only so long as intermolecular, interatomic and/or interionic forces may be ignored or remain constant, under which restriction the system may be expected to behave ideally. But intermolecular, interatomic and/or interionic forces do exist, and not only do they change as a result of chemical reaction but also with variation in the concentration or pressure of the molecules, atoms or ions under observation. In consequence, mathematical expressions involving stoichiometric concentrations or pressures generally have limited applicability. The conventional concentration terms, while providing a count of molecules, atoms or ions per unit volume, afford no indication of the physical or chemical activity of the species measured, and it is this activity which determines the physical and chemical properties of the system.

In recognition of this, GN Lewis introduced both the quantitative concept and methods for evaluation of activity as a true measure of the physical or chemical activity of molecular, atomic or ionic species, whether in the state of gas, liquid or solid, or whether present as a single species or in a mixture. Activity may be considered loosely as a corrected concentration or pressure which takes into account not only the stoichiometric concentration or pressure but also any intermolecular attractions, repulsions or interactions between solute and solvent in solution, association and ionization. Thus, activity measures the net effectiveness of a chemical species. Because only relative values of activity may be determined, a *standard state* must be chosen for quantitative comparisons to be made. Indeed, because activity measurements are needed for many different types of systems, several standard states must be selected. Since this discussion is concerned mainly with solutions, the standard state for the solvent is pure solvent, while for the solute it is a hypothetical solution with free energy corresponding to unit molality under conditions of ideal behavior of the solution. The relationship of activity to concentration is measured in terms of an activity coefficient which is discussed in Chapter 17.

Practical Applications of Colligative Properties

One of the most important pharmaceutical applications of colligative properties is in the preparation of isotonic intravenous and isotonic lacrimal solutions, the details of which are discussed in Chapter 36.

Other applications of the colligative properties are found in experimental physiology. One such application is in the immersion of tissues in salt solutions, which are isotonic with the fluids of the tissue, in order to prevent changes or injuries that may arise from osmosis.

The colligative properties of solutions also may be used in determining the molecular weight of solutes or, in the case of electrolytes, the extent of ionization. The method of determining molecular weight depends on the fact that each of the colligative properties is altered by a constant value when a definite number of molecules of solute is added to a solvent (See Chapter 17). For example, in dilute solutions the freezing point of water is lowered at the rate of 1.855° for each mol of a nonelectrolyte dissolved in 1000 g of water.*

The constant 1.855° is commonly called the *molal freezing-point depression* of water. To find the molecular weight of a nonelectrolyte, therefore, all that is necessary is to determine the freezing point of a dilute aqueous solution of known concentration of the nonelectrolyte and, by proportion, to calculate the quantity that would produce, theoretically, a depression of 1.855° when 1000 g of water is used as the solvent. If the substance is insoluble in water, it may be dissolved in another solvent, in which case, however, the freezing-point depression of a solution corresponding to a gram-molecular weight of the solute in 1000 g of solvent will be some value

other than 1.855°. In the case of benzene, for example, this value is 5.12°; carbon tetrachloride, 2.98°; phenol, 7.27° and camphor, about 40° (see *Freezing-Point Depression*, page 209).

The boiling-point elevation may be used similarly for determining molecular weights. The boiling point of water is raised at the rate of 0.52° for each mol of solute dissolved in 1000 g of water,* the corresponding values for benzene, carbon tetrachloride and phenol being 2.57°, 4.88° and 3.60°, respectively. The observation of vapor-pressure lowering and osmotic pressure likewise may be used to calculate molecular weights.

To determine the extent to which an electrolyte is ionized, it is necessary to know its molecular weight, as determined by some other method, and then to measure one of the four

colligative properties. The deviation of the results from similar values for nonelectrolytes then is used in calculating the extent of ionization.

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*These constants apply only to solutions that are considerably more dilute than 1 molal; a substantial deviation would be observed if a 1 molal solution were to be used.

Tonicity, Osmoticity, Osmolality and Osmolarity

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Basic Definitions

If a solution is placed in contact with a membrane that is permeable to molecules of the solvent, but not to molecules of the solute, the movement of solvent through the membrane is called osmosis. Such a membrane often is called *semi-permeable*. As the several types of membranes of the body vary in their permeability, it is well to note that they are *selectively* permeable. Most normal living-cell membranes maintain various solute concentration gradients. A *selectively permeable membrane* may be defined either as one that does not permit free, unhampered diffusion of all the solutes present, or as one that maintains at least one solute concentration gradient across itself. Osmosis, then, is the diffusion of water through a membrane that maintains at least one solute concentration gradient across itself.

Assume Solution A is on one side of the membrane, and Solution B of the same solute but of a higher concentration is on the other side; the solvent will tend to pass into the more concentrated solution until equilibrium has been established. The pressure required to prevent this movement is the osmotic pressure. It is defined as the excess pressure, or pressure greater than that above the pure solvent, which must be applied to Solution B to prevent passage of solvent through a perfect semipermeable membrane from A to B. The concentration of a solution with respect to effect on osmotic pressure is related to the number of particles (unionized molecules, ions, macromolecules, aggregates) of solute(s) in solution and thus is affected by the degree of ionization or aggregation of the solute. See Chapter 16 for review of colligative properties of solutions.

Body fluids, including blood and lacrimal fluid, normally have an osmotic pressure which often is described as corresponding to that of a 0.9% solution of sodium chloride. The body also attempts to keep the osmotic pressure of the contents of the gastrointestinal tract at about this level, but there the normal range is much wider than that of most body fluids. The 0.9% sodium chloride solution is said to be *iso-osmotic* with physiological fluids. The term *isotonic*, meaning equal tone, is in medical usage commonly used interchangeably with *isoosmotic*. However, terms such as *isotonic* and *tonicity* should be used *only* with reference to a physiologic fluid. *Isoosmotic* actually is a physical term which compares the osmotic pressure (or another colligative property, such as freezing-point depression) of two liquids, neither of which may be a physiological fluid, or which may be a physiological fluid only under certain circumstances. For example, a solution of boric acid that is *isoosmotic* with both blood and lacrimal fluid is *isotonic* only with the lacrimal fluid. This solution causes hemolysis of red blood cells because molecules of boric acid pass freely through the erythrocyte membrane regardless of concentration. Thus, *isotonicity* infers a sense of physiological compatibility where *isoosmoticity* need

not. As another example, a "chemically defined elemental diet" or enteral nutritional fluid can be *iso-osmotic* with the contents of the gastrointestinal tract, but would not be considered a physiological fluid, or suitable for parenteral use.

A solution is *isotonic* with a living cell if there is no net gain or loss of water by the cell, or other change in the cell when it is in contact with that solution. Physiological solutions with an osmotic pressure lower than that of body fluids, or of 0.9% sodium chloride solution, are referred to commonly as being *hypotonic*. Physiological solutions having a greater osmotic pressure are termed *hypertonic*.

Such qualitative terms are of limited value, and it has become necessary to state osmotic properties in quantitative terms. To do so, a term must be used that will represent all the particles which may be present in a given system. The term used is *osmol*. An *osmol* is defined as the weight, in grams, of a solute, existing in a solution as molecules (and/or ions, macromolecules, aggregates, etc), which is osmotically equivalent to a mole of an ideally behaving nonelectrolyte. Thus, the *osmol-weight* of a nonelectrolyte, in a dilute solution, generally is equal to its gram-molecular-weight. A milliosmol, abbreviated *mOsm*, is the weight stated in milligrams.

If one extrapolates this concept of relating an *osmol* and a mole of a nonelectrolyte as being equivalent, then one also may define an *osmol* in the following ways. It is the amount of solute which will provide one Avogadro's number (6.02×10^{23}) of particles in solution and it is the amount of solute which, on dissolution in 1 kg of water, will result in an osmotic pressure increase of 17,000 torr at 0° or 19,300 torr at 37°. One *mOsmol* is one-thousandth of an *osmol*. For example, 1 mole of anhydrous dextrose is equal to 180 g. One *osmol* of this nonelectrolyte is also 180 g. One *mOsmol* would be 180 mg. Thus 180 mg of this solute dissolved in 1 kg of water will produce an increase in osmotic pressure of 19.3 torr at body temperature.

For a solution of an electrolyte such as sodium chloride, one molecule of sodium chloride represents one sodium and one chloride ion. Hence, one mol will represent 2 *osmols* of sodium chloride theoretically. Accordingly, 1 *osmol* NaCl = 58.5 g/2 or 29.25 g. This quantity represents the sum total of 6.02×10^{23} ions as the total number of particles. Ideal solutions infer very dilute solutions or infinite dilution. However, as the concentration is increased, other factors enter. With strong electrolytes, interionic attraction causes a decrease in their effect on colligative properties. In addition, and in opposition, for all solutes, including nonelectrolytes, solvation and possibly other factors operate to intensify their colligative effect. Therefore, it is very difficult and often impossible to predict accurately the osmoticity of a solution. It may be possible to do so for a dilute solution of a single, pure and well-characterized solute, but not for most parenteral and enteral medicinal and/or nutritional fluids; experimental determination likely is required.

Therapeutic Considerations

It generally is accepted that osmotic effects have a major place in the maintenance of homeostasis (the state of equilibrium in the living body with respect to various functions and to the chemical composition of the fluids and tissues, eg, temperature, heart rate, blood pressure, water content or blood sugar). To a great extent these effects occur within or between cells and tissues where they cannot be measured. One of the most troublesome problems in clinical medicine is the maintenance of adequate body fluids and proper balance between extracellular and intracellular fluid volumes in seriously ill patients. It should be kept in mind, however, that fluid and electrolyte abnormalities are not diseases, but are the manifestations of disease.

The physiological mechanisms which control water intake and output appear to respond primarily to serum osmoticity. Renal regulation of output is influenced by variation in rate of release of pituitary antidiuretic hormone (ADH) and other factors in response to changes in serum osmoticity. Osmotic changes also serve as a stimulus to moderate thirst. This mechanism is sufficiently sensitive to limit variations in osmoticity in the normal individual to less than about 1%. Body fluid continually oscillates within this narrow range. An increase of plasma osmoticity of 1% will stimulate ADH release, result in reduction of urine flow and, at the same time, stimulate thirst that results in increased water intake. Both the increased renal reabsorption of water (without solute) stimulated by circulating ADH and the increased water intake tend to lower serum osmoticity.

The transfer of water through the cell membrane occurs so rapidly that any lack of osmotic equilibrium between the two fluid compartments in any given tissue usually is corrected within a few seconds and, at most, within a minute or so. However, this rapid transfer of water does not mean that complete equilibration occurs between the extracellular and intracellular compartments throughout the entire body within this same short period of time. The reason is that fluid usually enters the body through the gut and then must be transported by the circulatory system to all tissues before complete equilibration can occur. In the normal person it may require 30 to 60 min to achieve reasonably good equilibration throughout the body after drinking water. Osmoticity is the property that largely determines the physiologic acceptability of a variety of solutions used for therapeutic and nutritional purposes.

Pharmaceutical and therapeutic consideration of osmotic effects has been, to a great extent, directed toward the side effects of ophthalmic and parenteral medicinals due to abnormal osmoticity, and to either formulating to avoid the side effects or finding methods of administration to minimize them. More recently this consideration has been extended to total (central) parenteral nutrition, to enteral hyperalimentation ("tube" feeding) and to concentrated-fluid infant formulas.¹ Also, in recent years, the importance of osmometry of serum and urine in the diagnosis of many pathological conditions has been recognized.

There are a number of examples of the direct therapeutic effect of osmotic action, such as the intravenous use of mannitol as a diuretic which is filtered at the glomeruli and thus increases the osmotic pressure of tubular urine. Water must then be reabsorbed against a higher osmotic gradient than otherwise, so reabsorption is slower and diuresis is observed. The same fundamental principle applies to the intravenous administration of 30% urea used to affect intracranial pressure in the control of cerebral edema. Peritoneal dialysis fluids tend to be somewhat hyperosmotic to withdraw water and nitrogenous metabolites. Two to five percent sodium chloride solutions or dispersions in an oleaginous base (Muro, *Bausch & Lomb*) and a 40% glucose ointment are used topically for corneal edema. Ophthalgan (*Wyeth-Ayerst*) is ophthalmic glycerin employed for its osmotic effect to clear edematous cornea to facilitate an ophthalmoscopic or gonioscopic examination. Glycerin solutions in 50% concentration [*Os-moglyn (Alcon)*] and isosorbide solution [*Ismotic (Alcon)*]

are oral osmotic agents for reducing intraocular pressure. The osmotic principle also applies to plasma extenders such as polyvinylpyrrolidone and to saline laxatives such as magnesium sulfate, magnesium citrate solution, magnesium hydroxide (via gastric neutralization), sodium sulfate, sodium phosphate and sodium biphosphate oral solution and enema (*Fleet*).

An interesting osmotic laxative which is a nonelectrolyte is a lactulose solution. Lactulose is a nonabsorbable disaccharide which is colon-specific, wherein colonic bacteria degrade some of the disaccharide to lactic and other simple organic acids. These, *in toto*, lead to an osmotic effect and laxation. An extension of this therapy is illustrated by Cephulac (*Marion Merrell Dow*) solution, which uses the acidification of the colon via lactulose degradation to serve as a trap for ammonia migrating from the blood to the colon. The conversion of ammonia of blood to the ammonium ion in the colon ultimately is coupled with the osmotic effect and laxation, thus expelling undesirable levels of blood ammonia. This product is employed to prevent and treat frontal systemic encephalopathy.

Osmotic laxation is observed with the oral or rectal use of glycerin and sorbitol. Epsom salt has been used in baths and compresses to reduce edema associated with sprains. Another approach is the indirect application of the osmotic effect in therapy via osmotic pump drug delivery systems.²

Osmolality and Osmolarity

It is necessary to use several additional terms to define expressions of concentration in reflecting the osmoticity of solutions. The terms include osmolality, the expression of osmolal concentration and osmolarity, the expression of osmolar concentration.

Osmolality—A solution has an osmolal concentration of one when it contains 1 osmol of solute/kg of water. A solution has an osmolality of n when it contains n osmoles/kg of water. Osmolal solutions, like their counterpart molal solutions, reflect a weight-to-weight relationship between the solute and the solvent. Since an osmol of any nonelectrolyte is equivalent to 1 mol of that compound, then a 1 osmolal solution is synonymous to a 1 molal solution for a typical nonelectrolyte.

With a typical electrolyte like sodium chloride, 1 osmol is approximately 0.5 mol of sodium chloride. Thus, it follows that a 1 osmolal solution of sodium chloride essentially is equivalent to a 0.5 molal solution. Recall that a 1 osmolal solution of dextrose or sodium chloride each will contain the same particle concentration. In the dextrose solution there will be 6.02×10^{23} molecules/kg of water and in the sodium chloride solution one will have 6.02×10^{23} total ions/kg of water, one-half of which are Na^+ ions and the other half Cl^- ions.

As in molal solutions, osmolar solutions usually are employed where quantitative precision is required, as in the measurement of physical and chemical properties of solutions (ie, colligative properties). The advantage of the w/w relationship is that the concentration of the system is not influenced by temperature.

Osmolarity—The relationship observed between molality and osmolality is shared similarly between molarity and osmolarity. A solution has an osmolar concentration of 1 when it contains 1 osmol of solute/L of solution. Likewise, a solution has an osmolarity of n when it contains n osmoles/L of solution. Osmolar solutions, unlike osmolal solution, reflect a weight in volume relationship between the solute and final solution. A 1 molar and 1 osmolar solution would be identical for nonelectrolytes. For sodium chloride a 1 osmolar solution would contain 1 osmol of sodium chloride per liter which approximates a 0.5 molar solution. The advantage of employing osmolar concentrations over osmolal concentrations is the ability to relate a specific number of osmoles or milliosmoles to a volume, such as a liter or mL. Thus, the osmolar concept is simpler and more practical. Volumes of

solution, rather than weights of solution, are more practical in the delivery of liquid dosage forms.

Many health professionals do not have a clear understanding of the difference between osmolality and osmolality. In fact, the terms have been used interchangeably. A 1 osmolar solution of a solute always will be more concentrated than a 1 osmolal solution. With dilute solutions the difference may be acceptably small. For example, a 0.9% *w/v* solution of sodium chloride in water contains 9 g of sodium chloride/L of solution, equivalent to 0.308 osmolal; or 9 g of sodium chloride/996.5 g of water, equivalent to 0.309 osmolal, less than a 1% error. For concentrated solutions the % difference between osmolality and osmolality is much greater and may be highly significant; 3.5% for 5% *w/v* dextrose solution and 25% for 25% *w/v* dextrose solution. One should be alerted to the sizable errors which may occur with concentrated solutions or fluids, such as those employed in total parenteral nutrition, enteral hyperalimentation and oral nutritional fluids for infants.

Reference has been made to the terms hypertonic and hypotonic. Analogous terms are hyperosmotic and hypoosmotic. Assuming normal serum osmolality to be 285 mOsmol/kg, as serum osmolality increases due to water deficit, the following signs and symptoms usually are found to accumulate progressively at approximately these values: 294 to 298—thirst (if the patient is alert and communicative); 299 to 313—dry mucous membranes; 314 to 329—weakness, doughy skin; above 330—disorientation, postural hypotension, severe weakness, fainting, CNS changes, stupor and coma. As serum osmolality decreases due to water excess the following may occur: 275 to 261—headache; 262 to 251—drowsiness, weakness; 250 to 233—disorientation, cramps; below 233—seizures, stupor and coma.

As indicated previously, the mechanisms of the body actively combat such major changes by limiting the variation in osmolality for normal individuals to less than about 1% (approximately in the range 282 to 288 mOsmol/kg, based on the above assumption).

The value given for normal serum osmolality above was described as an assumption because of the variety of values found in the literature. Serum osmolality often is stated loosely to be about 300 mOsmol/L. Various references report 280 to 295 mOsmol/L, 275 to 300 mOsmol/L, 290 mOsmol/L, 306 mOsmol/L and 275 to 295 mOsmol/kg.

Reference has been made to confusion in the use of the terms osmolality and osmolality, a distinction of special importance for nutritional fluids. Awareness of high concentrations of infant-formula should give warning as to possible risks. Unfortunately, the osmoticity of infant formulas, tube feedings and total parenteral nutrition solutions has not been described adequately either in textbooks or in the literature,³ and the labels of many commercial nutritional fluids do not, in any way, state their osmoticity. Only recently have enteral fluids been characterized in terms of osmoticity. Some product lines now are accenting isoosmotic enteral nutritional supplements. Often, when the term osmolality is used, one cannot discern whether this simply is incorrect terminology, or if osmolality actually has been calculated from osmolality.

Another current practice which can cause confusion, is the use of the terms *normal* and/or *physiological* for isotonic sodium chloride solution (0.9%). The solution surely is isoosmotic. However, as to being physiological, the concentration of ions are each of 154 mEq/L while serum contains about 140 mEq of sodium and about 103 mEq of chloride.

The range of mOsmol values found for serum raises the question as to what really is meant by the terms hypotonic and hypertonic for medicinal and nutritional fluids. One can find the statement that fluids with an osmolality of 50 mOsmol or more above normal are hypertonic and, if 50 mOsmol or more below normal, are hypotonic. One also can find the statement that peripheral infusions should not have an osmolality exceeding 700 to 800 mOsmol/L.⁴ Examples of osmolal concentrations of solutions used in peripheral infusions are: (D5W) 5% dextrose solution—252 mOsmol/L; (D10W) 10%

dextrose solution—505 mOsmol/L; Lactated Ringer's 5% Dextrose—525 mOsmol/L. When a fluid is hypertonic, undesirable effects often can be decreased by using relatively slow rates of infusion, and/or relatively short periods of infusion. 25% dextrose solution (D25W)—4.25% Amino Acids is a representative example of a highly osmotic hyperalimentation solution. It has been stated that when osmolal loading is needed, a maximum safe tolerance for a normally hydrated subject would be an approximate increase of 25 mOsmol/kg of water over 4 hours.³

Computation of Osmolality

Several methods are used to obtain numerical values of osmolality. The osmolar concentration, sometimes referred to as the "theoretical osmolality," is calculated from the *w/v* concentration using the following equation:

$$\frac{\text{g}}{\text{L}} \times \frac{\text{mols}}{\text{g}} \times \frac{\text{osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = \frac{\text{mOsmol}}{\text{L}} \quad (1)$$

The number of osmols/mol is equal to 1 for nonelectrolytes and is equal to the number of ions per molecule for strong electrolytes.

This calculation, omits consideration of factors such as solvation and interionic forces. By this method of calculation 0.9% sodium chloride has an osmolar concentration of 308 mOsmol/L and a concentration of 154 mOsmol/L in either sodium or chloride ion.

Two other methods compute osmolality from values of osmolality. The determination of osmolality will be discussed later. One method has a strong theoretical basis of physical-chemical principles⁵ using values of the partial molal volume(s) of the solute(s). A 0.9% sodium chloride solution, found experimentally to have an osmolality of 286 mOsmol/kg, was calculated to have an osmolality of 280 mOsmol/L, rather different from the value of 308 mOsmol/L calculated as above. The method, using partial molal volumes, is relatively rigorous, but many systems appear to be too complex and/or too poorly defined to be dealt with by this method.

The other method is based on calculating the weight of water from the solution density and concentration

$$\frac{\text{g water}}{\text{mL solution}} = \frac{\text{g solution}}{\text{mL solution}} - \frac{\text{g solute}}{\text{mL solution}}$$

then

$$\text{osmolality} \left(\frac{\text{mOsmol}}{\text{L solution}} \right) = \text{osmolality} \left(\frac{\text{mOsmol}}{1000 \text{ g water}} \right) \times \frac{\text{g water}}{\text{mL solution}}$$

The experimental value for the osmolality of 0.9% sodium chloride solution was 292.7 mOsmol/kg; the value computed for osmolality was 291.4 mOsmol/L. This method uses easily obtained values of density of the solution and of its solute content and can be used with all systems. For example, the osmolality of a nutritional product was determined by the freezing-point depression method to be 625 mOsmol/kg;⁷ its osmolality was calculated as $625 \times 0.839 = 524 \text{ mOsmol/L}$.

Monographs in the USP for solutions which provide intravenous replenishment of fluid, nutrient(s) or electrolyte(s), and for osmotic diuretics such as Mannitol Injection, require the osmolar concentration be stated on the label in osmols/L, except that where the contents are less than 100 mL, or where the label states the article is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolar concentration in mOsmol/ mL.

An example of the use of the first method described above is the computation of the approximate osmolar concentration ("theoretical osmolality") of a Lactated Ringer's 5% Dextrose Solution (Abbott), which is labeled to contain, per L, dextrose (hydrous) 50 g, sodium chloride 6 g, potassium chloride 300 mg, calcium chloride 200 mg and sodium lactate

3.1 g. Also stated is that the total osmolar concentration of the solution is approximately 524 mOsmol per L, in part contributed by 130 mEq of Na^+ , 109 mEq of Cl^- , 4 mEq of K^+ , 3 mEq of Ca^{2+} and 28 mEq of lactate ion.

The derivation of the osmolar concentrations from the stated composition of the solution may be verified by calculations using Eq 1.

Dextrose

$$\frac{50 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{198 \text{ g}} \times \frac{1 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{Osmol}} = 252 \text{ mOsmol/L}$$

Sodium Chloride

$$\frac{6 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{58.4 \text{ g}} \times \frac{2 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = 205 \frac{\text{mOsmol}}{\text{L}} \left\{ \begin{array}{l} (102.7 \text{ mOsmol Na}^+) \\ (102.7 \text{ mOsmol Cl}^-) \end{array} \right.$$

Potassium Chloride

$$\frac{0.3 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{74.6 \text{ g}} \times \frac{2 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = \frac{8.04 \text{ mOsmol}}{\text{L}} \left\{ \begin{array}{l} (4.02 \text{ mOsmol K}^+) \\ (4.02 \text{ mOsmol Cl}^-) \end{array} \right.$$

Calcium Chloride

$$\frac{0.2 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{111 \text{ g}} \times \frac{3 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = \frac{5.41 \text{ mOsmol}}{\text{L}} \left\{ \begin{array}{l} (1.80 \text{ mOsmol Ca}^{2+}) \\ (3.61 \text{ mOsmol Cl}^-) \end{array} \right.$$

Sodium Lactate

$$\frac{3.1 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{112 \text{ g}} \times \frac{2 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = \frac{55.4 \text{ mOsmol}}{\text{L}} \left\{ \begin{array}{l} (27.7 \text{ mOsmol Na}^+) \\ (27.7 \text{ mOsmol lactate}) \end{array} \right.$$

The total osmolar concentration of the five solutes in the solution is 526, in good agreement with the labeled total osmolar concentration of approximately 524 mOsmol/L.

The mOsmol of sodium in 1 L of the solution is the sum of the mOsmol of the ion from sodium chloride and sodium lactate, ie, $102 + 27.6 = 129.6$ mOsmol. Chloride ions come from the sodium chloride, potassium chloride and calcium chloride, the total osmolar concentration being $102 + 4.02 + 3.61 = 109.6$ mOsmol. The mOsmol values of potassium, calcium and lactate are calculated to be 4.02, 1.80 and 27.6, respectively.

The osmolality of a mixture of complex composition, such as an enteral hyperalimentation fluid, cannot be calculated with any acceptable degree of certainty and, therefore, the osmolality of such preparations should be determined experimentally.

Undesirable Effects of Abnormal Osmoticity

Ophthalmic Medication—It is generally accepted that ophthalmic preparations intended for instillation into the cul-de-sac of the eye should, if possible, be approximately isotonic to avoid irritation (see Chapter 89). It also has been stated that the abnormal tonicity of contact lens solutions can cause the lens to adhere to the eye and/or cause burning or dryness and photophobia.

Parenteral Medication—Osmoticity is of great importance in parenteral injections, its effects depending on the degree of deviation from tonicity, the concentration, the location of the injection, the volume injected, the speed of the injection, the rapidity of dilution and diffusion, etc. When formulating parenterals, solutions otherwise hypotonic usually have their tonicity adjusted by the addition of dextrose or sodium chloride. Hypertonic parenteral drug solutions cannot be adjusted. Hypotonic and hypertonic solutions usually are administered slowly in small volumes, or into a large vein such as the subclavian, where dilution and distribution occur rapidly. Solutions that differ from the serum in tonicity gen-

erally are stated to cause tissue irritation, pain on injection and electrolyte shifts, the effect depending on the degree of deviation from tonicity.

Excessive infusion of *hypotonic* fluids may cause swelling of red blood cells, hemolysis and water invasion of the body's cells in general. When this is beyond the body's tolerance for water, water intoxication results, with convulsions and edema, such as pulmonary edema.

Excessive infusion of *isotonic* fluids can cause an increase in extracellular fluid volume, which can result in circulatory overload.

Excessive infusion of *hypertonic* fluids leads to a wide variety of complications. For example, the sequence of events when the body is presented with a large intravenous load of hypertonic fluid, rich in dextrose, is as follows: hyperglycemia, glycosuria and intracellular dehydration, osmotic diuresis, loss of water and electrolytes, dehydration and coma.

One cause of osmotic diuresis is the infusion of dextrose at a rate faster than the ability of the patient to metabolize it (as greater than perhaps 400 to 500 mg/kg/hr for an adult on total parenteral nutrition). A heavy load of unmetabolizable dextrose increases the osmoticity of blood and acts as a diuretic; the increased solute load requires more fluid for excretion, 10 to 20 mL of water being required to excrete each gram of dextrose. Solutions, such as those for total parenteral nutrition, should be administered by means of a metered constant-infusion apparatus over a lengthy period (usually more than 24 hours) to avoid sudden hyperosmotic dextrose loads. Such solutions may cause osmotic diuresis; if this occurs, water balance is likely to become negative because of the increased urinary volume, and electrolyte depletion may occur because of excretion of sodium and potassium secondary to the osmotic diuresis. If such diuresis is marked, body weight falls abruptly and signs of dehydration appear. Urine should be monitored for signs of osmotic diuresis, such as glycosuria and increased urine volume.

If the intravenous injection rate of hypertonic solution is too rapid, there may be catastrophic effects on the circulatory and respiratory systems. Blood pressure may fall to dangerous levels, cardiac irregularities or arrest may ensue, respiration may become shallow and irregular and there may be heart failure and pulmonary edema. Probably the precipitating factor is a bolus of concentrated solute suddenly reaching the myocardium and the chemoreceptors in the aortic arch and carotid sinus.³

Abrupt changes in serum osmoticity can lead to cerebral hemorrhage. It has been shown experimentally that rapid infusions of therapeutic doses of hypertonic saline with osmotic loads produce a sudden rise in cerebrospinal fluid (CSF) pressure and venous pressure (VP) followed by a precipitous fall in CSF pressure. This particularly may be conducive to intracranial hemorrhage, as the rapid infusion produces an increase in plasma volume and venous pressure at the same time the CSF pressure is falling. During the CSF pressure rise, there is a drop in hemoglobin and hematocrit, reflecting a marked increase in blood volume.

Hyperosmotic medications, such as sodium bicarbonate (osmolality of 1560 at 1 mEq/mL), which are administered intravenously, should be diluted prior to use and should be injected slowly to allow dilution by the circulating blood. Rapid "push" injections may cause a significant increase in blood osmoticity.⁵

As to other possibilities, there may be crenation of red blood cells and general cellular dehydration. Hypertonic dextrose or saline, etc, infused through a peripheral vein with small blood volume may traumatize the vein and cause thrombophlebitis. Infiltration can cause trauma and necrosis of tissues. Safety, therefore, demands that all intravenous injections, especially highly osmotic solutions, be performed slowly, usually being given preferably over a period not less than that required for a complete circulation of the blood, eg, 1 minute. The exact danger point varies with the

state of the patient, the concentration of the solution, the nature of the solute and the rate of administration.

Hyperosmotic solutions also should not be discontinued suddenly. In dogs, marked increase in levels of intracranial pressure occur when hyperglycemia produced by dextrose infusions is reversed suddenly by stopping the infusion and administering saline. It also has been shown that the CSF pressure in humans rises during treatment of diabetic ketoacidosis in association with a fall in the plasma concentration of dextrose and a fall in plasma osmolality. These observations may be explained by the different rates of decline in dextrose content of the brain and of plasma. The concentration of dextrose in the brain may fall more slowly than in the plasma, causing a shift of fluid from the extracellular fluid space to the intracellular compartment of the CNS, resulting in increased intracranial pressure.

Osmometry and the Clinical Laboratory

Serum and urine osmometry may assist in the diagnosis of certain fluid and electrolyte problems. However, osmometry values have little meaning unless the clinical situation is known. Osmometry is used in renal dialysis as a check on the electrolyte composition of the fluid. In the clinical laboratory, as stated above, the term "osmolality" is used generally, but usually is reported as mOsmol/L. It may seem unnecessary to mention that osmolality depends not only on the number of solute particles, but also on the quantity of water in which they are dissolved. However, it may help one to understand the statement that the normal range of urine osmolality is 50 to 1400 mOsmol/L, and for a random specimen is 500 to 800 mOsmol/L.

Serum Osmoticity

Sodium is by far the principal solute involved in serum osmoticity. Therefore, abnormal serum osmoticity is most likely to be associated with conditions that cause abnormal sodium concentration and/or abnormal water volume.

Thus, hyperosmotic serum is likely to be caused by an increase in serum sodium and/or loss of water. It may be associated with diabetes insipidus, hypercalcemia, diuresis during severe hyperglycemia or with early recovery from renal shutdown. Alcohol ingestion is said to be the most common cause of the hyperosmotic state and of coexisting coma and the hyperosmotic state. An example of hyperosmoticity is a comatose diabetic with a serum osmoticity of 365 mOsmol/L.

In a somewhat analogous fashion, hypoosmotic serum is likely to be due to decrease in serum sodium and/or excess of water. It may be associated with the postoperative state (especially with excessive water replacement therapy), treatment with diuretic drugs and low-salt diet (as with patients with heart failure, cirrhosis, etc), adrenal disease (eg, Addison's disease, adrenogenital syndrome) or SIADH (syndrome of inappropriate ADH secretion). There are many diseases which cause ADH to be released inappropriately (ie, in spite of the fact that serum osmoticity and volume may have been normal initially). These include oat-cell carcinoma of the lung, bronchogenic carcinoma, congestive heart failure, inflammatory pulmonary lesions, porphyria, severe hypothyroidism or cerebral disease (such as tumor, trauma, infection, vascular abnormalities, etc). It also may be found with some patients with excessive diuretic use. Serum and urine osmoticity are measured when SIADH is suspected. In SIADH there is hypoosmoticity of the blood in association with a relative hyperosmoticity of urine. The usual cause is a malfunction of the normal osmotic response of osmoreceptors, an excess of exogenous vasopressin, or a production of a vasopressin-like hormone that is not under the regular control of serum osmoticity. The diagnosis is made by simultaneous measurement of urine and serum osmolality. The serum osmolality will be lower than normal and much lower than the urine osmolality, indicating inappropriate secretion of a concentrated urine in the presence of a dilute serum.

Cardiac, renal and hepatic disease characteristically reduce the sodium/osmolality ratio, this being partially attributed to the effects of increased blood sugar, urea or unknown metabolic products. Patients in shock may develop disproportionately elevated measured osmolality compared to calculated osmolality, which points toward the presence of circulating metabolic products.

There are several approximate methods for estimating serum osmolality from clinical laboratory values for sodium ion, etc. They may be of considerable value in an emergency situation.

1. Serum osmolality may be estimated from

$$\text{mOsmol} = (1.86 \times \text{sodium}) + \frac{\text{blood sugar}}{18} + \frac{\text{BUN}}{2.8} + 5$$

(Na in mEq/L, blood sugar and BUN in mg/100 mL)

2. A quick approximation is

$$\text{mOsmol} = 2 \text{ Na} + \frac{\text{BS}}{20} + \frac{\text{BUN}}{3}$$

3. The osmolality is usually, *but not always*, very close to two times the sodium reading plus 10.

Urine Osmoticity

The two main functions of the kidney are glomerular filtration and tubular reabsorption. Clinically, tubular function is measured best by tests that determine the ability of the tubules to concentrate and dilute the urine. Tests of urinary dilution are not as sensitive in the detection of disease, as are tests of urinary concentration. As concentration of urine occurs in the renal medulla (interstitial fluids, loops of Henle, capillaries of the medulla and collecting tubules), the disease processes that disturb the function or structure of the medulla produce early impairment of the concentrating power of the kidney. Such diseases include acute tubular necrosis, obstructive uropathy, pyelonephritis, papillary necrosis, medullary cysts, hypokalemic and hypercalcemic nephropathy and sickle-cell disease.

Measurement of urine osmolality is an accurate test for the diluting and concentrating ability of the kidneys. In the absence of ADH, the daily urinary output is likely to be 6 to 8 L, or more. The normal urine osmolality depends on the clinical setting; normally, with maximum ADH stimulation, it can be as much as 1200 mOsmol/kg, and with maximum ADH suppression as little as 50 mOsmol/kg. Simultaneous determination of serum and urine osmolality often is valuable in assessing the distal tubular response to circulating ADH. For example, if the patient's serum is hyperosmotic, or in the upper limits of normal ranges, and the patient's urine osmolality measured at the same time is much lower, a decreased responsiveness of the distal tubules to circulating ADH is suggested.

Measurement of urine osmolality during water restriction is an accurate, sensitive test of decreased renal function. For example, under the conditions of one test, normal osmolality would be greater than 800 mOsmol/kg. With severe impairment the value would be less than 400 mOsmol/kg. Knowledge of urine osmolality may point to a problem even though other tests are normal (eg, the Fishberg concentration test, BUN, PSP excretion, creatinine clearance or IV pyelogram). Knowledge of its value may be useful especially in diabetes mellitus, essential hypertension and silent pyelonephritis. The urine/serum osmolality ratio should be calculated and should be equal to or greater than 3.

Osmoticity and Enteral Hydration

Some aspects of nutrition are discussed briefly here because of the potential major side effects due to abnormal osmoticity of nutritional fluids, and because there exists in-

creasing dialogue on nutrition among pharmacists, dietitians, nurses and physicians. An example is the professional organization, ASPEN (The American Society for Parenteral and Enteral Nutrition), with membership open to all of the above health practitioners. It is desirable, therefore, that pharmacists be able to discuss these matters with these other health professionals in terms of nutrition as well as medicine.

Osmoticity has been of special importance in the intravenous infusion of large volumes of highly concentrated nutritional solutions. Their hyperosmoticity has been a major factor in the requirement that they be injected centrally into a large volume of rapidly moving blood, instead of using peripheral infusion. Use of such solutions and knowledge of their value have led, more recently, to the use of similar formulations administered, not parenterally, but by instillation into some part of the gastrointestinal tract, orally, by nasogastric tube, feeding gastrostomy or by needle-catheter jejunostomy. This method has given excellent total nutrition, for a period of time, to many patients and obviously avoids some of the problems associated with injections.

Enteral nutritional formulas can be modular allowing individual supplementation of protein, carbohydrate or fat. Other formulas are called "defined formula diets" and contain protein, carbohydrate, fat, minerals and vitamins. These nutritionally complete formulations can be monomeric (or oligomeric), based on amino acids, short peptides and simple carbohydrates or polymeric, based on complex protein and carbohydrates.

These diets are necessarily relatively high in osmoticity because their smaller molecules result in more particles per gram than in normal foods. An example is a fluid consisting of: L-amino acids, dextrose oligosaccharides, vitamins (including fat-soluble vitamins), fat as a highly purified safflower oil or soybean oil, electrolytes, trace minerals and water. As it contains fat, that component is not in solution and therefore should have no direct effect on osmoticity. However, the potential for interactions can cause some significant changes in total particle concentration and indirectly affect the osmoticity.⁸

Although easily digested, dextrose contributes more particles than most other carbohydrate sources, such as starch, and is more likely to cause osmotic diarrhea, especially with bolus feeding. Osmoticity is improved (decreased) by replacing dextrose with dextrose oligosaccharides (carbohydrates that yield on hydrolysis 2 to 10 monosaccharides). Flavoring also increases the osmoticity of a product, different flavors causing varying increases.

Commercial diets are packaged as fluids or as powders for reconstitution. Reconstitution is usually with water. These products are categorized on caloric density, (calories/mL), protein content or osmolality (mOsm/kg of H₂O). Parenteral nutritional products, on the other hand, are labeled in terms of osmolality (mOsm/L).

The enteric route for hyperalimentation frequently is overlooked in many diseases or post-trauma states, if the patient is not readily responsive to traditional oral feedings. Poor appetite, chronic nausea, general apathy and a degree of somnolence or sedation are common concomitants of serious disease. This frequently prevents adequate oral alimentation and results in progressive energy and nutrient deficits. Often, supplementary feedings of a highly nutritious formula are taken poorly or refused entirely. However, the digestive and absorptive capabilities of the gastrointestinal tract are frequently intact and, when challenged with appropriate nutrient fluids, can be used effectively. By using an intact GI tract for proper alimentation, the major problems of sepsis and metabolic derangement which relate to intravenous hyperalimentation largely are obviated, and adequate nutritional support is simplified greatly. Because of this increased safety and ease of administration, the enteric route for hyperalimentation should be used whenever possible.⁹

When ingested in large amounts or concentrated fluids, the osmotic characteristics of certain foods can cause an upset in the normal water balance within the body. For a given weight

of solute the osmolality of the solution is inversely proportional to the size of the particles. Nutritional components can be listed in an approximate order of decreasing osmotic effect per gram, as¹⁰

1. Electrolytes such as sodium chloride
2. Relatively small organic molecules such as dextrose (glucose) and amino acids
3. Dextrose oligosaccharides
4. Starches
5. Proteins
6. Fats (as fats are not water-soluble they have no osmotic effect)

Thus, in foods, high proportions of electrolytes, amino acids and simple sugars have the greatest effect on osmolality, and as a result, on tolerance. The approximate osmolality of a few common foods and beverages is

	mOsm/kg
Whole milk	295
Tomato juice	595
Orange juice	935
Ice cream	1150

When nutrition of high osmoticity is ingested, large amounts of water will transfer to the stomach and intestines from the fluid surrounding those organs in an attempt to lower the osmoticity. The higher the osmoticity, the larger the amount of water required; a large amount of water in the GI tract can cause distention, cramps, nausea, vomiting, hypermotility and shock. The food may move through the tract too rapidly for the water to be reabsorbed, and result in diarrhea; severe diarrhea can cause dehydration. The hyperosmotic enteral effects have been observed by the administration of undiluted hypertonic oral medication;¹¹ Table I from this work lists average osmolality values of some commercially available drug solutions and suspensions. Thus, there is some analogy to the effect of hyperosmotic intravenous infusions.

Hyperosmotic feedings may result in mucosal damage in the GI tract. Rats given hyperosmotic feeding showed transient decrease in disaccharidase activity, and an increase in alkaline phosphatase activity. They also showed morphologic alterations in the microvilli of the small intestines. After a period of severe gastroenteritis, the bowel may be unusually susceptible to highly osmotic formulas, and their use may increase the frequency of diarrhea. Infant formulas that are hyperosmotic may affect preterm infants adversely during the early neonatal period, and they may produce or predispose neonates to necrotizing enterocolitis when delivered to the jejunum through a nasogastric tube.

The body attempts to keep the osmoticity of the contents of the stomach and intestines at approximately the same level as that of the fluid surrounding them. As a fluid of lower osmoticity requires the transfer of less water to dilute it, it should be tolerated better than one of higher osmoticity. As to tolerance, there is a great variation from one individual to another in sensitivity to the osmoticity of foods. The majority of patients receiving nutritional formulas, either orally or by tube, are able to tolerate feedings with a wide range of osmoticities if administered slowly and if adequate additional fluids are given. However, certain patients are more likely to develop symptoms of intolerance when receiving fluids of high osmoticity. These include debilitated patients, patients with GI disorders, pre- and postoperative patients, gastrostomy- and jejunostomy-fed patients and patients whose GI tracts have not been challenged for an extended period of time. Thus, osmoticity always should be considered in the selection of the formula for each individual patient. With all products, additional fluid intake may be indicated for individuals with certain clinical conditions. Frequent feedings of small volume or a continual instillation (pumped) may be of benefit initially in establishing tolerance to a formula. For other than isoosmotic formulas, feedings of reduced concentration (osmolality less than 400 mOsm/kg) also may be helpful initially if tolerance problems arise in sensitive individuals. Concentration and size of feeding then can be increased gradually to normal as tolerance is established.

A common disturbance of intake encountered in elderly individuals relates to excess solid intake rather than to reduced water intake. For example, an elderly victim of a cerebral vascular accident who is being fed by nasogastric tube may be given a formula whose solute load requires a greatly increased water intake. Thus, tube feeding containing 120 g of protein and 10 g of salt will result in the excretion of more than 1000 mOsmol of solute. This requires the obligatory excretion of a volume of urine between 1200 and 1500 mL when the kidneys are capable of normal concentration ability. As elderly individuals often have significant impairment in renal function, water loss as urine may exceed 2000 to 2500 mL per day. Such an individual would require 3 to 4 L of water/day simply to meet the increased demand created by this high solute intake. Failure of the physician to provide such a patient with the increased water intake needed will result in a progressive water deficit which rapidly may become critical. The importance of knowing the complete composition of the tube feeding formulas used for incapacitated patients cannot be overemphasized.

Osmolality Determination

The need for experimental determination of osmolality has been established. In regard to this there are four properties of solutions that depend only on the number of "particles" in the solution. They are osmotic pressure elevation, boiling point elevation, vapor pressure depression and freezing point depression. These are called colligative properties and if one of them is known, the others can be calculated from its value. Osmotic pressure elevation is the most difficult to measure satisfactorily. The boiling-point elevation may be determined but the values are rather sensitive to changes in barometric pressure. Also, for an aqueous solution the molal boiling-point elevation is considerably less than the freezing-point depression. Thus, it is less accurate than the freezing-point method. Determinations of vapor-pressure lowering are quite easy, rapid and convenient. A vapor-pressure osmometer with a precision of <2 mOsmol/kg is reported by Dickerson, *et al.*¹¹ Another commonly used method is that of freezing-point depression, which can be determined quite readily with a fair degree of accuracy (see *Freezing-Point Depression*, Chapter 16). It should be noted that the data in Appendix A can be converted readily to vapor pressure lowering if desired.

The results of investigations by Lund *et al.*¹² indicate that the freezing point of normal, healthy human blood is -0.52° . Inasmuch as water is the medium in which the various constituents of blood are either suspended or dissolved in this method, it is assumed that *any aqueous solution* freezing at -0.52° is *isotonic with blood*. Now it is rare that a simple aqueous solution of the therapeutic agent to be injected parenterally has a freezing point of -0.52° , and to obtain this freezing point it is necessary either to add some other therapeutically inactive solute if the solution is hypotonic (freezing point above -0.52°) or to dilute the solution if it is hypertonic (freezing point below -0.52°). The usual practice is to add either sodium chloride or dextrose to adjust hypotonic parenteral solutions to isotonicity. Certain solutes, including ammonium chloride, boric acid, urea, glycerin and propylene glycol, cause hemolysis even when they are present in a concentration that is isoosmotic and such solutions obviously are not isotonic. See Appendix A.

In a similar manner solutions intended for ophthalmic use may be adjusted to have a freezing point identical to that of lacrimal fluid, namely, -0.52° . Ophthalmic solutions with higher freezing points usually are made isotonic by the addition of boric acid or sodium chloride.

In laboratories where the necessary equipment is available, the method usually followed for adjusting hypotonic solutions is to determine the freezing-point depression produced by the ingredients of a given prescription or formula, and then to add a quantity of a suitable inert solute calculated to lower the freezing point to -0.52° , whether the solution is for paren-

teral injection or ophthalmic application. A final determination of the freezing-point depression may be made to verify the accuracy of the calculation. If the solution is hypertonic, it must be diluted if an isotonic solution is to be prepared, but it must be remembered that some solutions cannot be diluted without impairing their therapeutic activity. For example, solutions to be used for treating varicose veins require a high concentration of the active ingredient (solute) to make the solution effective. Dilution to isotonic concentration is not indicated in such cases.

Freezing-Point Calculations

As explained in the preceding section, freezing-point data often may be employed in solving problems of isotonicity adjustment. Obviously, the utility of such data is limited to those solutions where the solute does not penetrate the membrane of the tissue, eg, red blood cells, with which it is in contact. In such cases, Appendix A, giving the freezing-point depression of solutions of different concentrations of various substances, provides information essential for solving the problem.

For most substances listed in the table the concentration of an isotonic solution, ie, one that has a freezing point of -0.52° , is given. If this is not listed in the table, it may be determined with sufficient accuracy by simple proportion using, as the basis for calculation, that figure which most nearly produces an isotonic solution. Actually the depression of the freezing point of a solution of an electrolyte is not absolutely proportional to the concentration but varies according to dilution; for example, a solution containing 1 g of procaine hydrochloride in 100 mL has a freezing-point depression of 0.12° , whereas a solution containing 3 g of the same salt in 100 mL has a freezing-point depression of 0.33° , not 0.36° ($3 \times 0.12^{\circ}$). Since the adjustment to isotonicity need not be absolutely exact, approximations may be made. Nevertheless, adjustments to isotonicity should be as exact as practicable.

Effect of Solvents—Besides water, certain other solvents frequently are employed in nose drops, ear drops and other preparations to be used in various parts of the body. Liquids such as glycerin, propylene glycol or alcohol may compose part of the solvent. In solving isotonicity adjustment problems for such solutions it should be kept in mind that while these solvent components contribute to the freezing-point depression they may or may not have an effect on the "tone" of the tissue to which they are applied, ie, an *isoosmotic* solution may not be *isotonic*. It is apparent that, in such cases, the utility of the methods described above or, for that matter, of any other method of evaluating "tonicity" is questionable.

Tonicity Testing by Observing Erythrocyte Changes

Observation of the behavior of human erythrocytes when suspended in a solution is the ultimate and direct procedure for determining whether the solution is isotonic, hypotonic or hypertonic. If hemolysis or marked change in the appearance of the erythrocytes occurs, the solution is not isotonic with the cells. If the cells retain their normal characteristics, the solution is isotonic.

Hemolysis may occur when the osmotic pressure of the fluid in the erythrocytes is greater than that of the solution in which the cells are suspended, but the specific chemical reactivity of the solute in the solution often is far more important in producing hemolysis than is the osmotic effect. There is no certain evidence that any single mechanism of action causes hemolysis. The process appears to involve such factors as pH, lipid solubility, molecular and ionic sizes of solute particles and possibly inhibition of cholinesterase in cell membranes and denaturing action on plasma membrane protein.

Some investigators test the tonicity of injectable solutions by observing variations of red-blood-cell volume produced by

these solutions. This method appears to be more sensitive to small differences in tonicity than those based on observation of a hemolytic effect. Much useful information concerning the effect of various solutes on erythrocytes has been obtained by this procedure and a summary of many of these data is given in RPS-14, page 1562.

Methods of Adjusting Tonicity

There are several methods for adjusting the tonicity of an aqueous solution provided, of course, that the solution is hypotonic when the drug and additives are dissolved. The most prominent of these methods are the freezing point depression method, the sodium chloride equivalent method and the isotonic solution V-value method. The first two of these methods can be used with a three step problem solving process based on sodium chloride.

1. Identify a reference solution and the associated tonicity parameter.
2. Determine the contribution of the drug(s) and additive(s) to the total tonicity.
3. Determine the amount of sodium chloride needed by subtracting the contribution of the actual solution from the reference solution.

The result of Step 3 also indicates whether the actual solution is hypotonic, isotonic or hypertonic. If the actual solution contributes less to the total tonicity than the reference solution, then the actual solution is hypotonic. If, however, the actual solution contributes a greater amount to tonicity than the reference solution, the actual solution is hypertonic and can be adjusted to isotonicity only by dilution. This may not be possible on therapeutic grounds.

The amount of sodium chloride resulting in Step 3 also can be converted into an amount of other materials, such as dextrose, to render the actual solution isotonic.

Freezing Point Depression Method—The freezing point method makes use of a “D value” (found in Appendix A) which has the units of °C/(x% drug). For example, in Appendix A, dexamethasone sodium phosphate has D values of 0.050°C/(0.5% drug), 0.180°C/(2.0% drug), 0.52°C/(6.75% drug), etc. It is apparent that the D value is nearly proportional to concentration. If a D value is needed for a concentration of drug not listed in Appendix A, a D value can be calculated from the Appendix by direct proportion, using a D value closest to the concentration of drug in the actual solution.

The reference solution for the freezing point depression method is 0.9% sodium chloride which has a freezing point depression of $\Delta T_f = 0.52^\circ\text{C}$.

Using the three steps described above, the dexamethasone sodium phosphate solution in Example 1 can be rendered isotonic as follows:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water	qs
Mft Isotonic Solution	30 mL

Step 1—Reference solution: 0.9% sodium chloride.

$$\Delta T_f = 0.52^\circ\text{C}$$

$$D = 0.050^\circ\text{C}/0.5\% \text{ dexamethasone sod phosphate}$$

Step 2—Contribution of drug.

$$\frac{0.050^\circ\text{C}}{0.5\% \text{ drug}} \times 0.1\% \text{ drug} = 0.010^\circ$$

Step 3—Reference solution – actual solution.

$$0.52^\circ - 0.01^\circ = 0.51^\circ$$

Sodium chloride needed.

$$\frac{0.9\% \text{ NaCl}}{0.52^\circ} \times 0.51^\circ = 0.883\% \text{ NaCl}$$

$$\frac{0.883 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.265 \text{ g NaCl}$$

The above solution could be made isotonic with any appropriate material other than sodium chloride by using the D value for that material. For example, to make the solution isotonic with dextrose with a D value; $D =$

$$0.091^\circ/1\%;$$

$$\frac{1\% \text{ Dextrose}}{0.091^\circ} \times 0.51^\circ = 5.60\% \text{ Dextrose}$$

$$\frac{5.60 \text{ g Dextrose}}{100 \text{ mL}} \times 30 \text{ mL} = 1.68 \text{ g Dextrose}$$

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water	qs
Mft Isotonic solution	30 mL

Step 1—Reference solution: 0.9% sodium chloride.

$$\Delta T_f = 0.52^\circ$$

$$D = 0.14^\circ/1\% \text{ (naphazoline HCl)}$$

$$D = 0.086^\circ/1\% \text{ (zinc sulfate)}$$

Step 2—Contribution of drugs.

$$\frac{0.14^\circ\text{C}}{1\% \text{ N.HCl}} \times 0.02\% \text{ N.HCl} = 0.003^\circ$$

$$\frac{0.086^\circ\text{C}}{1\% \text{ ZnSO}_4} \times 0.25\% \text{ ZnSO}_4 = 0.022^\circ$$

$$0.003^\circ + 0.022^\circ = 0.025^\circ$$

Step 3—Reference solution – actual solution.

$$0.52^\circ - 0.025^\circ = 0.495^\circ$$

Sodium chloride needed.

$$\frac{0.9\% \text{ NaCl}}{0.52^\circ} \times 0.495^\circ = 0.857\% \text{ NaCl}$$

$$\frac{0.857 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.257 \text{ g NaCl}$$

The above solution could be made isotonic with any appropriate material other than sodium chloride by utilizing the D value for that material. For example, to make the solution isotonic with dextrose with a D value, $D = 0.091^\circ/1\%$;

$$\frac{1\% \text{ Dextrose}}{0.091^\circ} \times 0.495^\circ = 5.44\% \text{ Dextrose}$$

$$\frac{5.44 \text{ g Dextrose}}{100 \text{ mL}} \times 30 \text{ mL} = 1.63 \text{ g Dextrose}$$

Sodium Chloride Equivalent Method—A sodium chloride equivalent, “E value,” is defined as the weight of sodium chloride which will produce the same osmotic effect as 1 g of the drug. For example, in Appendix A, dexamethasone sodium phosphate has an E value of 0.18 g NaCl/g drug at 0.5% drug concentration, 0.17 g NaCl/g drug at 1% drug concentration and a value of 0.16 g NaCl/g drug at 2% drug. This slight variation in the sodium chloride equivalent with concentration is due to changes in interionic attraction at different concentration of drug; the E value is not directly proportional to concentration as was the freezing-point depression.

The reference solution for the sodium chloride equivalent method is 0.9% sodium chloride as it was for the freezing-point depression method.

The dexamethasone sodium phosphate solution in Example 1 can be rendered isotonic using the sodium chloride equivalent method as follows:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water	qs
Mft Isotonic Solution	30 mL

Step 1—Reference solution: 0.9% sodium chloride.

$$\frac{0.9 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.270 \text{ g NaCl}$$

$$E = 0.18 \text{ g NaCl/g drug}$$

Step 2—Contribution of drug.

$$\frac{0.18 \text{ g NaCl}}{1 \text{ g drug}} \times \frac{0.1 \text{ g drug}}{100 \text{ mL}} \times 30 \text{ mL} = 0.0054 \text{ g NaCl}$$

Step 3—Reference solution – actual solution.

$$0.270 \text{ g NaCl} - 0.0054 \text{ g NaCl} = 0.265 \text{ g NaCl}$$

The above solution can be made isotonic with a material other than sodium chloride, such as dextrose, by using the *E* value of that material. For example, to make the solution isotonic with dextrose, *E* = 0.16 g NaCl/g dextrose, the amount of sodium chloride needed in Step 3, can be converted to dextrose as follows:

$$\frac{1 \text{ g Dextrose}}{0.16 \text{ g NaCl}} \times 0.265 \text{ g NaCl} = 1.66 \text{ g Dextrose}$$

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—Reference solution: 0.9% sodium chloride.

$$\frac{0.9 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.270 \text{ g NaCl}$$

$$E = 0.27 \text{ g NaCl/g N.HCl}$$

$$E = 0.15 \text{ g NaCl/g ZnSO}_4$$

Step 2—Contribution of drugs.

$$\frac{0.27 \text{ g NaCl}}{1 \text{ g N.HCl}} \times \frac{0.02 \text{ g N.HCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.002 \text{ g NaCl}$$

$$\frac{0.15 \text{ g NaCl}}{1 \text{ g ZnSO}_4} \times \frac{0.25 \text{ g ZnSO}_4}{100 \text{ mL}} \times 30 \text{ mL} = 0.011 \text{ g NaCl}$$

$$0.002 \text{ g NaCl} + 0.011 \text{ g NaCl} = 0.013 \text{ g NaCl}$$

Step 3—Reference solution – actual solution.

$$0.270 \text{ g NaCl} - 0.013 \text{ g NaCl} = 0.257 \text{ g NaCl}$$

The above solution can be made isotonic with a material other than sodium chloride, such as dextrose, by using the *E* value of that material. For example, to make the solution isotonic with dextrose, *E* = 0.16 g NaCl/g dextrose, the amount of sodium chloride needed in Step 3 can be converted to dextrose as follows:

$$\frac{1 \text{ g Dextrose}}{0.16 \text{ g NaCl}} \times 0.257 \text{ g NaCl} = 1.61 \text{ g Dextrose}$$

Isotonic Solution V-Values—The “*V* value” of a drug is the volume of water to be added to a specified weight of drug (0.3 g or 1.0 g depending on the table used) to prepare an isotonic solution. Appendix B gives such values for some commonly used drugs. The reason for providing data for 0.3 g of drug is for convenience in preparing 30 mL (approximately 1 fluidounce) of solution, a commonly prescribed volume. The basic principle underlying the use of *V* values is to prepare an isotonic solution of the prescribed drug and then dilute this solution to final volume with a suitable isotonic vehicle.

The two solutions in the previous examples can be prepared as follows using the *V* value method:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—The *V* value for dexamethasone sodium phosphate can be calculated from the sodium chloride equivalent, *E*, as outlined in the footnote in Appendix B.

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.17 \text{ g NaCl}}{1 \text{ g drug}} \times 0.3 \text{ g drug} = 5.67 \text{ mL Soln}$$

for a dilute solution: 5.67 mL Soln $\approx$ 5.67 mL H₂O

$$\therefore V = (5.67 \text{ mL H}_2\text{O}) / (0.3 \text{ g drug})$$

Step 2—Amount of drug needed.

$$\frac{0.1 \text{ g drug}}{100 \text{ mL}} \times 30 \text{ mL} = 0.030 \text{ g drug}$$

Volume of water needed to prepare an isotonic solution.

$$\frac{5.67 \text{ mL H}_2\text{O}}{0.3 \text{ g drug}} \times 0.030 \text{ g drug} = 0.57 \text{ mL H}_2\text{O}$$

Step 3—To prepare the solution, dissolve 0.030 g of drug in 0.57 mL water, and qs to volume with a suitable isotonic vehicle such as 0.9% sodium chloride solution, 5.51% dextrose or an isotonic phosphate buffer.

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—The *V* value for naphazoline HCl can be calculated from the sodium chloride equivalent, *E*, as outlined in the footnote in Appendix B; the *V* value for zinc sulfate is taken directly from Appendix B.

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.27 \text{ g NaCl}}{1 \text{ g N.HCl}} \times 0.3 \text{ g N.HCl} = 9.00 \text{ mL Soln}$$

for a dilute solution: 9.00 mL Soln $\approx$ 9.00 mL H₂O

$$\therefore V = (9.00 \text{ mL H}_2\text{O}) / (0.3 \text{ g N.HCl})$$

$$V = 5.00 \text{ mL H}_2\text{O} / 0.3 \text{ g ZnSO}_4$$

Step 2—Amount of drugs needed.

$$\frac{0.02 \text{ g N.HCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.006 \text{ g N.HCl}$$

$$\frac{0.25 \text{ g ZnSO}_4}{100 \text{ mL}} \times 30 \text{ mL} = 0.075 \text{ g ZnSO}_4$$

Volume of water needed to prepare an isotonic solution.

$$\frac{9.00 \text{ mL H}_2\text{O}}{0.3 \text{ g N.HCl}} \times 0.006 \text{ g drug} = 0.18 \text{ mL H}_2\text{O}$$

$$\frac{5.00 \text{ mL H}_2\text{O}}{0.3 \text{ g ZnSO}_4} \times 0.075 \text{ g ZnSO}_4 = 1.25 \text{ mL H}_2\text{O}$$

$$0.18 \text{ mL H}_2\text{O} + 1.25 \text{ mL H}_2\text{O} = 1.43 \text{ mL H}_2\text{O}$$

Step 3—To prepare the solution, dissolve 0.006 g of naphazoline HCl and 0.075 g zinc sulfate in 1.43 mL water, and qs to volume with a suitable isotonic vehicle such as 0.9% sodium chloride solution, 5.51% dextrose or an isotonic phosphate buffer.

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Appendix A—Sodium Chloride Equivalents, Freezing-Point Depressions and Hemolytic Effects of Certain Medicinals in Aqueous Solution

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Acetrizolate methylglucamine	0.09		0.08		0.08		0.08		0.08		12.12	0.07		0	7.1
Acetrizolate sodium	0.10	0.027	0.10	0.055	0.10	0.109	0.10	0.163	0.10	0.273	9.64	0.09	0.52	0	6.9†
Acetylcysteine	0.20	0.055	0.20	0.113	0.20	0.227	0.20	0.341			4.58	0.20	0.52	100*	2.0
Adrenaline HCl											4.24			68	4.5
Alphaprodine HCl	0.19	0.053	0.19	0.105	0.18	0.212	0.18	0.315			4.98	0.18	0.52	100	5.3
Alum (potassium)			0.18				0.15		0.15		6.35	0.14		24*	3.4
Amantadine HCl	0.31	0.090	0.31	0.180	0.31	0.354					2.95	0.31	0.52	91	5.7
Aminoacetic acid	0.42	0.119	0.41	0.235	0.41	0.470					2.20	0.41	0.52	0*	6.2
Aminohippuric acid	0.13	0.035	0.13	0.075											
Aminophylline				0.098 ^c											
Ammonium carbonate	0.70	0.202	0.70	0.405							1.29	0.70	0.52	97	7.7
Ammonium chloride			1.12								0.8	1.12	0.52	93	5.0
Ammonium lactate	0.33	0.093	0.33	0.185	0.33	0.370					2.76	0.33	0.52	98	5.9
Ammonium nitrate	0.69	0.200	0.69	0.400							1.30	0.69	0.52	91	5.3
Ammonium phosphate, dibasic	0.58	0.165	0.55	0.315							1.76	0.51	0.52	0	7.9
Ammonium sulfate	0.55	0.158	0.55	0.315							1.68	0.54	0.52	0	5.3
Amobarbital sodium			0.25	0.143 ^c			0.25				3.6	0.25	0.52	0	9.3
d-Amphetamine HCl											2.64			98	5.7
Amphetamine phosphate			0.34	0.20			0.27	0.47			3.47	0.26	0.52	0	4.5
Amphetamine sulfate			0.22	0.129 ^c			0.21	0.36			4.23	0.21	0.52	0	5.9
Amprotropine phosphate											5.90			0	4.2
Amylcaine HCl			0.22				0.19				4.98	0.18		100	5.6
Anileridine HCl	0.19	0.052	0.19	0.104	0.19	0.212	0.18	0.316	0.18	0.509	5.13	0.18	0.52	12	2.6
Antazoline phosphate											6.05			90	4.0
Antimony potassium tartrate			0.18				0.13		0.10						
Antipyrine			0.17	0.10			0.14	0.24	0.14	0.40	6.81	0.13	0.52	100	6.1
Apomorphine HCl			0.14	0.080 ^c											
Arginine glutamate	0.17	0.048	0.17	0.097	0.17	0.195	0.17	0.292	0.17	0.487	5.37	0.17	0.52	0	6.9
Ascorbic acid				0.105 ^c							5.05		0.52 ^b	100*	2.2
Atropine methylbromide			0.14				0.13		0.13		7.03	0.13			
Atropine methylnitrate											6.52			0	5.2
Atropine sulfate			0.13	0.075			0.11	0.19	0.11	0.32	8.85	0.10	0.52	0	5.0
Bacitracin			0.05	0.03			0.04	0.07	0.04	0.12					
Barbital sodium			0.30	0.171 ^c			0.29	0.50			3.12	0.29	0.52	0	9.8
Benzalkonium chloride			0.16				0.14		0.13						
Benzotropine mesylate	0.26	0.073	0.21	0.115	0.15	0.170	0.12	0.203	0.09	0.242					
Benzyl alcohol			0.17	0.09 ^c			0.15								
Bethanechol chloride	0.50	0.140	0.39	0.225	0.32	0.368	0.30	0.512			3.05	0.30		0	6.0
Bismuth potassium tartrate			0.09				0.06		0.05						
Bismuth sodium tartrate			0.13				0.12		0.11		8.91	0.10		0	6.1
Boric acid			0.50	0.288 ^c							1.9	0.47	0.52	100	4.6
Brompheniramine maleate	0.10	0.026	0.09	0.050	0.08	0.084									
Bupivacaine HCl	0.17	0.048	0.17	0.096	0.17	0.193	0.17	0.290	0.17	0.484	5.38	0.17	0.52	83	6.8
Butabarbital sodium	0.27	0.078	0.27	0.155	0.27	0.313	0.27	0.470			3.33	0.27	0.52	0	6.8
Butacaine sulfate			0.20	0.12			0.13	0.23	0.10	0.29					
Caffeine and sodium benzoate			0.26	0.15			0.23	0.40			3.92	0.23	0.52	0	7.0
Caffeine and sodium salicylate			0.12	0.12			0.17	0.295	0.16	0.46	5.77	0.16	0.52	0	6.8
Calcium aminosaliclate											4.80			0	6.0
Calcium chloride			0.51	0.298 ^c							1.70	0.53	0.52	0	5.6
Calcium chloride (6 H ₂ O)			0.35	0.20							2.5	0.36	0.52	0	5.7
Calcium chloride, anhydrous			0.68	0.39							1.3	0.69	0.52	0	5.6
Calcium disodium edetate	0.21	0.061	0.21	0.120	0.21	0.240	0.20	0.357			4.50	0.20	0.52	0	6.1
Calcium gluconate			0.16	0.091 ^c			0.14	0.24							
Calcium lactate			0.23	0.13			0.12	0.36			4.5	0.20	0.52	0	6.7
Calcium lactobionate	0.08	0.022	0.08	0.043	0.08	0.085	0.07	0.126	0.07	0.197					
Calcium levulinate			0.27	0.16			0.25	0.43			3.58			0	7.2
Calcium pantothenate											5.50			0	7.4
Camphor				0.12 ^d											
Capreomycin sulfate	0.04	0.011	0.04	0.020	0.04	0.042	0.04	0.063	0.04	0.106					
Carbachol				0.205 ^c							2.82			0	5.9
Carbenicillin sodium	0.20	0.059	0.20	0.118	0.20	0.236	0.20	0.355			4.40	0.20	0.52	0	6.6
Carboxymethylcellulose sodium	0.03	0.007	0.03	0.017	0.145										

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Cephaloridine	0.09	0.023	0.07	0.041	0.06	0.074	0.06	0.106	0.05						
Chloramine-T											4.10			100*	9.1
Chloramphenicol															
Chloramphenicol sodium succinate			0.06 ^d												
Chlordiazepoxide HCl	0.14	0.038	0.14	0.078	0.14	0.154	0.13	0.230	0.13	0.382	6.83	0.13	0.52	partial	6.1
Chlorobutanol (hydrated)	0.24	0.068	0.22	0.125	0.19	0.220	0.18	0.315	0.17	0.487	5.50	0.16	0.52	66	2.7
Chloroprocaine HCl			0.24	0.14											
Chloroquine phosphate	0.20	0.054	0.20	0.108	0.18	0.210									
Chloroquine sulfate	0.14	0.039	0.14	0.082	0.14	0.162	0.14	0.242	0.13	0.379	7.15	0.13	0.52	0	4.3
Chlorpheniramine maleate	0.10	0.028	0.09	0.050	0.08	0.090	0.07	0.127	0.07	0.195					
Chlortetracycline HCl	0.17	0.048	0.15	0.085	0.14	0.165	0.13	0.220	0.09	0.265					
Chlortetracycline sulfate	0.10	0.030	0.10	0.061	0.10	0.121									
Citric acid			0.13	0.08			0.10	0.17							
Clindamycin phosphate			0.18	0.10			0.17	0.295	0.16	0.46	5.52	0.16	0.52	100*	1.8
Cocaine HCl	0.08	0.022	0.08	0.046	0.08	0.095	0.08	0.144	0.08	0.242	10.73	0.08	0.52	58*	6.8
Codeine phosphate			0.16	0.090 ^c			0.15	0.26	0.14	0.40	6.33	0.14	0.52	47	4.4
Colistimethate sodium			0.14	0.080 ^c			0.13	0.23	0.13	0.38	7.29	0.12	0.52	0	4.4
Cupric sulfate	0.15	0.045	0.15	0.085	0.15	0.170	0.15	0.253	0.14	0.411	6.73	0.13	0.52	0	7.6
Cyclizine HCl			0.18	0.100 ^c			0.15		0.14		6.85	0.13		trace*	3.9
Cyclophosphamide	0.20	0.060													
Cytarabine	0.10	0.031	0.10	0.061	0.10	0.125									
Deferoxamine mesylate	0.11	0.034	0.11	0.066	0.11	0.134	0.11	0.198	0.11	0.317	8.92	0.10	0.52	0	8.0
Demecarium bromide	0.09	0.023	0.09	0.047	0.09	0.093	0.09	0.142	0.09	0.241					
Dexamethasone sodium phosphate	0.14	0.038	0.12	0.069	0.10	0.108	0.08	0.139	0.07	0.192					
Dextroamphetamine HCl	0.18	0.050	0.17	0.095	0.16	0.180	0.15	0.260	0.14	0.410	6.75	0.13	0.52	0	8.9
Dextroamphetamine phosphate	0.34	0.097	0.34	0.196	0.34	0.392					2.64	0.34	0.52		
Dextroamphetamine sulfate			0.25	0.14			0.25	0.44			3.62	0.25	0.52	0	4.7
Dextrose	0.24	0.069	0.23	0.134	0.22	0.259	0.22	0.380			4.16	0.22	0.52	0	5.9
Dextrose (anhydrous)			0.16	0.091 ^c			0.16	0.28	0.16	0.46	5.51	0.16	0.52	0	5.9
Diatrizoate sodium			0.18	0.101 ^c			0.18	0.31			5.05	0.18	0.52	0	6.0
Dibucaine HCl	0.10	0.025	0.09	0.049	0.09	0.098	0.09	0.149	0.09	0.248	10.55	0.09	0.52	0	7.9
Dicloxacillin sodium (1 H ₂ O)			0.074 ^c												
Diethanolamine	0.10	0.030	0.10	0.061	0.10	0.122	0.10	0.182							
Dihydrostreptomycin sulfate	0.31	0.089	0.31	0.177	0.31	0.358					2.90	0.31	0.52	100	11.3
Dimethylpyrindene maleate			0.06	0.03			0.05	0.09	0.05	0.14	19.4	0.05	0.52	0	6.1
Dimethyl sulfoxide	0.13	0.039	0.12	0.070	0.11	0.120									
Diperodon HCl	0.42	0.122	0.42	0.245	0.42	0.480					2.16	0.42	0.52	100	7.6
Diphenhydramine HCl	0.15	0.045	0.14	0.079	0.13	0.141									
Diphenidol HCl			0.161 ^c								5.70			88*	5.5
Doxapram HCl	0.16	0.045	0.16	0.09	0.16	0.180									
Doxycycline hyclate	0.12	0.035	0.12	0.070	0.12	0.140	0.12	0.210							
Dyphylline	0.12	0.035	0.12	0.072	0.12	0.134	0.11	0.186	0.09	0.264					
Echothiophate iodide	0.10	0.025	0.10	0.052	0.09	0.104	0.09	0.155	0.08	0.245					
Edetate disodium	0.16	0.045	0.16	0.090	0.16	0.179									
Edetate trisodium monohydrate	0.24	0.070	0.23	0.132	0.22	0.248	0.21	0.360			4.44	0.20	0.52	0	4.7
Emetine HCl	0.29	0.079	0.29	0.158	0.28	0.316	0.27	0.472			3.31	0.27	0.52	0	8.0
Ephedrine HCl			0.058 ^c				0.17		0.29						
Ephedrine sulfate			0.30	0.165 ^c			0.28				3.2	0.28		96	5.9
Epinephrine bitartrate			0.23	0.13			0.20	0.35			4.54	0.20	0.52	0	5.7
Epinephrine hydrochloride			0.18	0.104			0.16	0.28	0.16	0.462	5.7	0.16	0.52	100*	3.4
Ergonovine maleate			0.29	0.16 ^b			0.26				3.47	0.26			
Erythromycin lactobionate			0.089 ^c												
Ethyl alcohol	0.08	0.020	0.07	0.040	0.07	0.078	0.07	0.115	0.06	0.187					
Ethylenediamine			0.253 ^c								1.39			100	6.0
Ethylmorphine HCl			0.16	0.088 ^c			0.15	0.26	0.15	0.43	2.08	0.15	0.52	100*	11.4
Eucatropine HCl			0.11 ^d								6.18	0.15	0.52	38	4.7
Ferric ammonium citrate (green)															
Floxuridine											6.83			0	5.2
Fluorescein sodium	0.14	0.040	0.13	0.076	0.13	0.147	0.12	0.213	0.12	0.335	8.47	0.12	0.52	3*	4.5
Fluphenazine 2-HCl			0.31	0.181 ^c			0.27	0.47			3.34	0.27	0.52	0	8.7
d-Fructose	0.14	0.041	0.14	0.082	0.12	0.145	0.09	0.155							
Furtrethonium iodide											5.05			0*	5.9
Galactose	0.24	0.070	0.24	0.133	0.22	0.250	0.21	0.360			4.44	0.20	0.52	0	5.4
Gentamicin sulfate											4.92			0	5.9
D-Glucuronic acid	0.05	0.015	0.05	0.030	0.05	0.060	0.05	0.093	0.05	0.153					
Glycerin			0.203 ^c								5.02			48*	1.6
Glycopyrrolate											2.6			100	5.9
Gold sodium thiomalate	0.15	0.042	0.15	0.084	0.15	0.166	0.14	0.242	0.13	0.381	7.22	0.12	0.52	92*	4.0
Hetacillin potassium	0.10	0.032	0.10	0.061	0.10	0.111	0.09	0.159	0.09	0.250					
Hexafluorenum bromide	0.17	0.048	0.17	0.095	0.17	0.190	0.17	0.284	0.17	0.474	5.50	0.17	0.52	0	6.3
Hexamethonium tartrate	0.12	0.033	0.11	0.065											
Hexamethylene sodium acetaminosalicylate	0.16	0.045	0.16	0.089	0.16	0.181	0.16	0.271	0.16	0.456	5.68	0.16	0.52		
	0.18	0.049	0.18	0.099	0.17	0.199	0.17	0.297	0.16	0.485	5.48	0.16	0.52	0*	4.0

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Hexobarbital sodium				0.15 ^c											
Hexylcaine HCl											4.30			100	4.8
Histamine 2HCl	0.40	0.115	0.40	0.233	0.40	0.466					2.24	0.40	0.52	79 *	3.7
Histamine phosphate				0.149 ^c							4.10			0	4.6
Histidine HCl											3.45			40	3.9
Holocaine HCl			0.20	0.12											
Homatropine hydrobromide			0.17	0.097 ^c			0.16	0.28	0.16	0.46	5.67	0.16	0.52	92	5.0
Homatropine methylbromide			0.19	0.11			0.15	0.26	0.13	0.38					
4-Homosulfanilamide HCl											3.69			0	4.9
Hyaluronidase	0.01	0.004	0.01	0.007	0.01	0.013	0.01	0.020	0.01	0.033					
Hydromorphone HCl											6.39			64	5.6
Hydroxyamphetamine HBr				0.15 ^d							3.71			92	5.0
8-Hydroxyquinoline sulfate											9.75			59 *	2.5
Hydroxystilbamidine isethionate	0.20	0.060	0.16	0.090	0.12	0.137	0.10	0.170	0.07	0.216					
Hyoscyamine hydrobromide											6.53			68	5.9
Imipramine HCl	0.20	0.058	0.20	0.110	0.13	0.143									
Indigotindisulfonate sodium	0.30	0.085	0.30	0.172											
Intracaine HCl											4.97			85	5.0
Iodophthalein sodium				0.07 ^c							9.58			100	9.4
Isometheptene mucate	0.18	0.048	0.18	0.095	0.18	0.196	0.18	0.302			4.95	0.18	0.52	0	6.2
Isoproterenol sulfate	0.14	0.039	0.14	0.078	0.14	0.156	0.14	0.234	0.14	0.389	6.65	0.14	0.52	trace	4.5
Kanamycin sulfate	0.08	0.021	0.07	0.041	0.07	0.083	0.07	0.125	0.07	0.210					
Lactic acid				0.239 ^c							2.30			100*	2.1
Lactose			0.07	0.040 ^c			0.08		0.09		9.75	0.09		0*	5.8
Levallorphan tartrate	0.13	0.036	0.13	0.073	0.13	0.143	0.12	0.210	0.12	0.329	9.40	0.10	0.52	59*	6.9
Levorphanol tartrate	0.12	0.033	0.12	0.067	0.12	0.136	0.12	0.203							
Lidocaine HCl				0.13 ^c							4.42			85	4.3
Lincormycin HCl	0.16	0.045	0.16	0.090	0.15	0.170	0.14	0.247	0.14	0.400	6.60	0.14	0.52	0	4.5
Lobeline HCl				0.09 ^a											
Lyapolate sodium	0.10	0.025	0.09	0.051	0.09	0.103	0.09	0.157	0.09	0.263	9.96	0.09	0.52	0	6.5†
Magnesium chloride				0.45							2.02	0.45		0	6.3
Magnesium sulfate			0.17	0.094 ^c			0.15	0.26	0.15	0.43	6.3	0.14	0.52	0	6.2
Magnesium sulfate, anhydrous	0.34	0.093	0.32	0.184	0.30	0.345	0.29	0.495			3.18	0.28	0.52	0	7.0
Mannitol				0.098 ^c					5.07					0*	6.2
Maphenide HCl	0.27	0.075	0.27	0.153	0.27	0.303	0.26	0.448			3.55	0.25	0.52		
Menadiol sodium diphosphate											4.36			0	8.2
Menadione sodium bisulfite											5.07			0	5.3
Menthol				0.12 ^d											
Meperidine HCl				0.125 ^c							4.80			98	5.0
Mepivacaine HCl	0.21	0.060	0.21	0.116	0.20	0.230	0.20	0.342			4.60	0.20	0.52	45	4.5
Merbromin				0.08 ^b											
Mercuric cyanide			0.15				0.14		0.13						
Mersalyl				0.06 ^b											
Mesoridazine besylate	0.10	0.024	0.07	0.040	0.05	0.058	0.04	0.071	0.03	0.087					
Metaraminol bitartrate	0.20	0.060	0.20	0.112	0.19	0.210	0.18	0.308	0.17	0.505	5.17	0.17	0.52	59	3.8
Methacholine chloride				0.184 ^c							3.21			0	4.5
Methadone HCl				0.101 ^c							8.59			100*	5.0
Methamphetamine HCl				0.213 ^c							2.75			97	5.9
Methdilazine HCl	0.12	0.035	0.10	0.056	0.08	0.080	0.06	0.093	0.04	0.112					
Methenamine			0.23				0.24				3.68	0.25		100	8.4
Methiodal sodium	0.24	0.068	0.24	0.136	0.24	0.274	0.24	0.410			3.81	0.24	0.52	0	5.9
Methitural sodium	0.26	0.074	0.25	0.142	0.24	0.275	0.23	0.407			3.85	0.23	0.52	78	9.8
Methocarbamol	0.10	0.030	0.10	0.060											
Methotrimeprazine HCl	0.12	0.034	0.10	0.060	0.07	0.077	0.06	0.094	0.04	0.125					
Methoxyphenamine HCl	0.26	0.075	0.26	0.150	0.26	0.300	0.26	0.450			3.47	0.26	0.52	96	5.4
p-Methylaminoethanolphenol tartrate	0.18	0.048	0.17	0.095	0.16	0.190	0.16	0.282	0.16	0.453	5.83	0.16	0.52	0	6.2
Methyldopate HCl	0.21	0.063	0.21	0.122	0.21	0.244	0.21	0.365			4.28	0.21	0.52	partial	3.0
Methylergonovine maleate	0.10	0.028	0.10	0.056											
N-Methylglucamine	0.20	0.057	0.20	0.111	0.18	0.214	0.18	0.315	0.18	0.517	5.02	0.18	0.52	4	11.3
Methylphenidate HCl	0.22	0.065	0.22	0.127	0.22	0.258	0.22	0.388			4.07	0.22	0.52	66	4.3
Methylprednisolone Na succinate	0.10	0.025	0.09	0.051	0.09	0.102	0.08	0.143	0.07	0.200					
Minocycline HCl	0.10	0.030	0.10	0.058	0.09	0.107	0.08	0.146							
Monoethanolamine	0.53	0.154	0.53	0.306							1.70	0.53	0.52	100	11.4
Morphine HCl			0.15	0.086 ^c			0.14								
Morphine sulfate			0.14	0.079 ^c			0.11	0.19	0.09	0.26					
Nalorphine HCl	0.24	0.070	0.21	0.121	0.18	0.210	0.17	0.288	0.15	0.434	6.36	0.14	0.52	63	4.1
Naloxone HCl	0.14	0.042	0.14	0.083	0.14	0.158	0.13	0.230	0.13	0.367	8.07	0.11	0.52	35	5.2
Naphazoline HCl			0.27	0.14 ^d			0.24				3.99	0.22		100	5.3
Neosarsphenamine											2.32			17	7.8
Neomycin sulfate			0.11	0.063 ^c			0.09	0.16	0.08	0.232					
Neostigmine bromide			0.22	0.127 ^c			0.19				4.98			0	4.6
Neostigmine methylsulfate			0.20	0.115 ^c			0.18		0.17		5.22	0.17			

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Nicotinamide			0.26	0.148 ^c			0.21	0.36			4.49	0.20	0.52	100	7.0
Nicotinic acid			0.25	0.144 ^c											
Nikethamide				0.100 ^c							5.94			100	6.9
Novobiocin sodium	0.12	0.033	0.10	0.057	0.07	0.073									
Oleandomycin phosphate	0.08	0.017	0.08	0.038	0.08	0.084	0.08	0.129	0.08	0.255	10.82	0.08	0.52	0	5.0
Orphenadrine citrate	0.13	0.037	0.13	0.074	0.13	0.144	0.12	0.204	0.10	0.285					
Oxophenarsine HCl											3.67			trace*	2.3
Oxymetazoline HCl	0.22	0.063	0.22	0.124	0.20	0.232	0.19	0.335			4.92	0.18	0.52	86	5.7
Oxyquinoline sulfate	0.24	0.068	0.21	0.113	0.16	0.182	0.14	0.236	0.11	0.315					
<i>d</i> -Pantothenyl alcohol	0.20	0.053	0.18	0.100	0.17	0.193	0.17	0.283	0.16	0.468	5.60	0.16	0.52	92	6.8
Papaverine HCl			0.10	0.061 ^c											
Paraldehyde	0.25	0.071	0.25	0.142	0.25	0.288	0.25	0.430			3.65	0.25	0.52	97	5.3
Pargyline HCl	0.30	0.083	0.29	0.165	0.29	0.327	0.28	0.491			3.18	0.28	0.52	91	3.8
Penicillin G, potassium			0.18	0.102 ^c			0.17	0.29	0.16	0.46	5.48	0.16	0.52	0	6.2
Penicillin G, procaine				0.06 ^d											
Penicillin G, sodium			0.18	0.100 ^c			0.16	0.28	0.16	0.46	5.90			18	5.2
Pentazocine lactate	0.15	0.042	0.15	0.085	0.15	0.169	0.15	0.253	0.15	0.420					
Pentobarbital sodium				0.145 ^c							4.07			0	9.9
Pentolinium tartrate											5.95			55*	3.4
Phenacaine HCl				0.09 ^d											
Pheniramine maleate				0.09 ^d											
Phenobarbital sodium			0.24	0.135 ^c			0.23	0.40			3.95	0.23	0.52	0	9.2
Phenol			0.35	0.20							2.8	0.32	0.52	0*	5.6
Phentolamine mesylate	0.18	0.052	0.17	0.096	0.16	0.173	0.14	0.244	0.13	0.364	8.23	0.11	0.52	83	3.5
Phenylephrine HCl			0.32	0.184 ^c			0.30				3.0	0.30		0	4.5
Phenylephrine tartrate											5.90			58*	5.4
Phenylethyl alcohol	0.25	0.070	0.25	0.141	0.25	0.283									
Phenylpropanolamine HCl			0.38	0.219 ^c							2.6	0.35		95	5.3
Physostigmine salicylate			0.16	0.090 ^c											
Physostigmine sulfate				0.074 ^c											
Pilocarpine HCl			0.24	0.138 ^c			0.22	0.38			4.08	0.22	0.52	89	4.0
Pilocarpine nitrate			0.23	0.132 ^c			0.20	0.35			4.84	0.20	0.52	88	3.9
Piperocaine HCl				0.12 ^d							5.22			65	5.7
Polyethylene glycol 300	0.12	0.034	0.12	0.069	0.12	0.141	0.12	0.216	0.13	0.378	6.73	0.13	0.52	53	3.8
Polyethylene glycol 400	0.08	0.022	0.08	0.047	0.09	0.098	0.09	0.153	0.09	0.272	8.50	0.11	0.52	0	4.4
Polyethylene glycol 1500	0.06	0.015	0.06	0.036	0.07	0.078	0.07	0.120	0.07	0.215	10.00	0.09	0.52	4	4.1
Polyethylene glycol 1540	0.02	0.005	0.02	0.012	0.02	0.028	0.03	0.047	0.03	0.094					
Polyethylene glycol 4000	0.02	0.004	0.02	0.008	0.02	0.020	0.02	0.033	0.02	0.067					
Polymyxin B sulfate			0.09	0.052			0.06	0.10	0.04	0.12					
Polysorbate 80	0.02	0.005	0.02	0.010	0.02	0.020	0.02	0.032	0.02	0.055					
Polyvinyl alcohol (99% hydrol)	0.02	0.004	0.02	0.008	0.02	0.020	0.02	0.035	0.03	0.075					
Polyvinylpyrrolidone	0.01	0.003	0.01	0.006	0.01	0.010	0.01	0.017	0.01	0.035					
Potassium acetate	0.59	0.172	0.59	0.342							1.53	0.59	0.52	0	7.6
Potassium chlorate											1.88			0	6.9
Potassium chloride			0.76	0.439 ^c							1.19	0.76	0.52	0	5.9
Potassium iodide			0.34	0.196 ^c							2.59	0.34	0.52	0	7.0
Potassium nitrate			0.56	0.324 ^c							1.62	0.56		0	5.9
Potassium phosphate			0.46	0.27							2.08	0.43	0.52	0	8.4
Potassium phosphate, monobasic			0.44	0.25							2.18	0.41	0.52	0	4.4
Potassium sulfate			0.44								2.11	0.43		0	6.6
Pralidoxime chloride	0.32	0.092	0.32	0.183	0.32	0.364					2.87	0.32	0.52	0	4.6
Prilocaine HCl	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.375			4.18	0.22	0.52	45	4.6
Procainamide HCl			0.22	0.13			0.19	0.33	0.17	0.49					
Procaine HCl			0.21	0.122 ^c			0.19	0.33	0.18		5.05	0.18	0.52	91	5.6
Prochlorperazine edisylate	0.08	0.020	0.06	0.033	0.05	0.048	0.03	0.056	0.02	0.065					
Promazine HCl	0.18	0.050	0.13	0.077	0.09	0.102	0.07	0.112	0.05	0.137					
Proparacaine HCl	0.16	0.044	0.15	0.086	0.15	0.169	0.14	0.247	0.13	0.380	7.46	0.12	0.52		
Propiomazine HCl	0.18	0.050	0.15	0.084	0.12	0.133	0.10	0.165	0.08	0.215					
Propoxycaine HCl											6.40			16	5.3
Propylene glycol											2.00			100	5.5
Pyrithiazine HCl	0.22	0.065	0.17	0.095	0.11	0.123	0.08	0.140	0.06	0.170					
Pyridostigmine bromide	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.377			4.13	0.22	0.52	0	7.2
Pyridoxine HCl											3.05			31*	3.2
Quinacrine methanesulfonate				0.06 ^c											
Quinine bisulfate			0.09	0.05			0.09	0.16							
Quinine dihydrochloride			0.23	0.130 ^c			0.19	0.33	0.18		5.07	0.18	0.52	trace*	2.5
Quinine hydrochloride			0.14	0.077 ^c			0.11	0.19							
Quinine and urea HCl			0.23	0.13			0.21	0.36			4.5	0.20	0.52	64	2.9
Resorcinol				0.161 ^c							3.30			96	5.0
Rolitetracycline	0.11	0.032	0.11	0.064	0.10	0.113	0.09	0.158	0.07	0.204					
Rose Bengal	0.08	0.020	0.07	0.040	0.07	0.083	0.07	0.124	0.07	0.198	14.9	0.06	0.52		
Rose Bengal B	0.08	0.022	0.08	0.044	0.08	0.087	0.08	0.131	0.08	0.218					
Scopolamine HBr			0.12	0.07			0.12	0.21	0.12	0.35	7.85	0.11	0.52	8	4.8
Scopolamine methylnitrate			0.16				0.14		0.13		6.95	0.13		0	6.0

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Secobarbital sodium			0.24	0.14			0.23	0.40			3.9	0.23	0.52	trace	9.8
Silver nitrate			0.33	0.190 ^c							2.74	0.33	0.52	0*	5.0
Silver protein, mild			0.17	0.10			0.17	0.29	0.16	0.46	5.51	0.16	0.52	0	9.0
Silver protein, strong				0.06 ^d											
Sodium acetate			0.46	0.267							2.0	0.45	0.52		
Sodium acetazolamide	0.24	0.068	0.23	0.135	0.23	0.271	0.23	0.406			3.85	0.23	0.52		
Sodium aminosalicylate				0.170 ^c							3.27			0	7.3
Sodium ampicillin	0.16	0.045	0.16	0.090	0.16	0.181	0.16	0.072	0.16	0.451	5.78	0.16	0.52	0	8.5
Sodium ascorbate											3.00			0	6.9
Sodium benzoate			0.40	0.230 ^c							2.25	0.40	0.52	0	7.5
Sodium bicarbonate			0.65	0.375							1.39	0.65	0.52	0	8.3
Sodium biphosphate (H ₂ O)			0.40	0.23							2.45	0.37	0.52	0	4.1
Sodium biphosphate (2 H ₂ O)			0.36								2.77	0.32		0	4.0
Sodium bismuth thioglycollate	0.20	0.055	0.19	0.107	0.18	0.208	0.18	0.303	0.17	0.493	5.29			0	8.3
Sodium bisulfite			0.61	0.35							1.5	0.61	0.52	0*	3.0
Sodium borate			0.42	0.241 ^c							2.6	0.35	0.52	0	9.2
Sodium bromide											1.60			0	6.1
Sodium cacodylate			0.32				0.28				3.3	0.27		0	8.0
Sodium carbonate, monohydrated			0.60	0.346							1.56	0.58	0.52	100	11.1
Sodium cephalothin	0.18	0.050	0.17	0.095	0.16	0.179	0.15	0.259	0.14	0.400	6.80	0.13	0.52	partial	8.5
Sodium chloride			1.00	0.576 ^c			1.00	1.73	1.00	2.88	0.9	1.00	0.52	0	6.7
Sodium citrate			0.31	0.178 ^c			0.30	0.52			3.02	0.30		0	7.8
Sodium colistimethate	0.16	0.045	0.15	0.087	0.14	0.161	0.14	0.235	0.13	0.383	6.85	0.13	0.52	0	8.4
Sodium hypophosphite											1.60			0	7.3
Sodium iodide			0.39	0.222 ^c							2.37	0.38	0.52	0	6.9
Sodium iodohippurate											5.92			0	7.3
Sodium lactate											1.72			0	6.5
Sodium lauryl sulfate	0.10	0.029	0.08	0.046	0.07	0.068	0.05	0.086			5.30			0	8.4
Sodium mercaptomerin											1.38	0.65	0.52	5*	4.5
Sodium metabisulfite			0.67	0.386 ^c							6.00	0.15	0.52	0	5.8
Sodium methicillin	0.18	0.050	0.18	0.099	0.17	0.192	0.16	0.281	0.15	0.445					
Sodium nafcillin	0.14	0.039	0.14	0.078	0.14	0.158	0.13	0.219	0.10	0.285	1.36	0.66		0	6.0
Sodium nitrate			0.68								1.08	0.83		0*	8.5
Sodium nitrite			0.84	0.480 ^c							6.64	0.14	0.52	0	6.0
Sodium oxacillin	0.18	0.050	0.17	0.095	0.16	0.177	0.15	0.257	0.14	0.408	5.34	0.17	0.52		
Sodium phenylbutazone	0.19	0.054	0.18	0.104	0.17	0.202	0.17	0.298	0.17	0.488	3.33	0.27	0.52	0	9.2
Sodium phosphate			0.29	0.168			0.27	0.47							
Sodium phosphate, dibasic (2 H ₂ O)			0.42	0.24							2.23	0.40	0.52	0	9.2
Sodium phosphate, dibasic (12 H ₂ O)			0.22				0.21				4.45	0.20		0	9.2
Sodium propionate			0.61	0.35							1.47	0.61	0.52	0	7.8
Sodium salicylate			0.36	0.210 ^c							2.53	0.36	0.52	0	6.7
Sodium succinate	0.32	0.092	0.32	0.184	0.31	0.361					2.90	0.31	0.52	0	8.5
Sodium sulfate, anhydrous			0.58	0.34							1.61	0.56	0.52	0	6.2
Sodium sulfite, exsiccated			0.65	0.38							1.45			0	9.6
Sodium sulfobromophthalein	0.07	0.019	0.06	0.034	0.05	0.060	0.05	0.084	0.04	0.123	2.72	0.33	0.52	0	7.3
Sodium tartrate	0.33	0.098	0.33	0.193	0.33	0.385					2.98	0.30	0.52	0	7.4
Sodium thiosulfate			0.31	0.181 ^c							6.10	0.15	0.52	0	8.1
Sodium warfarin	0.18	0.049	0.17	0.095	0.16	0.181	0.15	0.264	0.15	0.430	5.48			0	5.9
Sorbitol (½ H ₂ O)											9.46	0.10	0.52	19*	3.5
Sparteine sulfate	0.10	0.030	0.10	0.056	0.10	0.111	0.10	0.167	0.10	0.277	5.66	0.16	0.52	3	4.4
Spectinomycin HCl	0.16	0.045	0.16	0.092	0.16	0.185	0.16	0.280	0.16	0.460					
Streptomycin HCl			0.17	0.10 ^c			0.16	0.16							
Streptomycin sulfate			0.07	0.036 ^c			0.06	0.10	0.06	0.17					
Sucrose			0.08	0.047 ^c			0.09	0.16	0.09	0.26	9.25	0.10	0.52	0	6.4
Sulfacetamide sodium			0.23	0.132 ^c			0.23	0.40			3.85	0.23	0.52	0	8.7
Sulfadiazine sodium			0.24	0.14			0.24	0.38			4.24	0.21	0.52	0	9.5
Sulfamerazine sodium			0.23	0.13			0.21	0.36			4.53	0.20	0.52	0	9.8
Sulfapyridine sodium			0.23	0.13			0.21	0.36			4.55	0.20	0.52	5	10.4
Sulfathiazole sodium			0.22	0.13			0.20	0.35			4.82	0.19	0.52	0	9.9
Tartaric acid				0.143 ^c							3.90			75*	1.7
Tetracaine HCl			0.18	0.109 ^c			0.15	0.26	0.12	0.35					
Tetracycline HCl			0.14	0.081 ^c			0.10								
Tetrahydrozoline HCl											4.10			60*	6.7
Theophylline			0.02 ^b												
Theophylline sodium glycinate											2.94			0	8.9
Thiamine HCl				0.139 ^c							4.24			87*	3.0
Thiethylperazine maleate	0.10	0.030	0.09	0.050	0.08	0.089	0.07	0.119	0.05	0.153					
Thiopental sodium				0.155 ^c							3.50			74	10.3
Thiopropazate diHCl	0.20	0.053	0.16	0.090	0.12	0.137	0.10	0.170	0.08	0.222					
Thioridazine HCl	0.06	0.015	0.05	0.025	0.04	0.042	0.03	0.055	0.03	0.075					
Thiotepa	0.16	0.045	0.16	0.090	0.16	0.182	0.16	0.278	0.16	0.460	5.67	0.16	0.52	10*	8.2
Tridihexethyl chloride	0.16	0.047	0.16	0.096	0.16	0.191	0.16	0.280	0.16	0.463	5.62	0.16	0.52	97	5.4
Triethanolamine	0.20	0.058	0.21	0.121	0.22	0.252	0.22	0.383			4.05	0.22	0.52	100	10.7
Trifluoperazine 2HCl	0.18	0.052	0.18	0.100	0.13	0.144									
Triflupromazine HCl	0.10	0.031	0.09	0.051	0.05	0.061	0.04	0.073	0.03	0.092					

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Trimeprazine tartrate	0.10	0.023	0.06	0.035	0.04	0.045	0.03	0.052	0.02	0.061					
Trimethadione	0.23	0.069	0.23	0.133	0.22	0.257	0.22	0.378			4.22	0.21	0.52	100	6.0
Trimethobenzamide HCl	0.12	0.033	0.10	0.062	0.10	0.108	0.09	0.153	0.08	0.232					
Tripeleennamine HCl				0.13 ^d							5.50			100	6.3
Tromethamine	0.26	0.074	0.26	0.150	0.26	0.300	0.26	0.450			3.45	0.26	0.52	0	10.2
Tropicamide	0.10	0.030	0.09	0.050											
Trypan blue	0.26	0.075	0.26	0.150											
Tryparsamide				0.11 ^c											
Tubocurarine chloride				0.076 ^c											
Urea			0.59	0.34							1.63	0.55	0.52	100	6.6
Urethan				0.18 ^b							2.93			100	6.3
Uridine	0.12	0.035	0.12	0.069	0.12	0.138	0.12	0.208	0.12	0.333	8.18	0.11	0.52	0*	6.1
Valethamate bromide	0.16	0.044	0.15	0.085	0.15	0.168	0.14	0.238	0.11	0.324					
Vancomycin sulfate	0.06	0.015	0.05	0.028	0.04	0.049	0.04	0.066	0.04	0.098					
Viomycin sulfate			0.08	0.05			0.07	0.12	0.07	0.20					
Xylometazoline HCl	0.22	0.065	0.21	0.121	0.20	0.232	0.20	0.342			4.68	0.19	0.52	88	5.0
Zinc phenolsulfonate											5.40			0*	5.4
Zinc sulfate			0.15	0.086 ^c			0.13	0.23	0.12	0.35	7.65	0.12	0.52		

^a The unmarked values were taken from Hammarlund et al.¹³⁻¹⁶ and Sapp et al.¹⁷

^b Adapted from Lund et al.¹²

^c Adapted from BPC.¹⁸

^d Obtained from several sources.

^e E: sodium chloride equivalents. D: freezing-point depression, °C. H: hemolysis, %, at the concentration which is iso-osmotic with 0.9% NaCl, based on freezing-point determination or equivalent test. pH: approximate pH of solution studied for hemolytic action. *: change in appearance of erythrocytes and/or solution.^{17-19†} pH determined after addition of blood.

NB—See also, Budavari S, ed: *Merck Index*, 11th ed, Merck & Co, Rahway NJ, 1988; pp MISC 79-103.

Appendix B—Isotonic Solution V-Values^{20a,b}

Drug (0.3 g)	Water needed for isotonicity, mL	Drug (0.3 g)	Water needed for isotonicity, mL	Drug (0.3 g)	Water needed for isotonicity, mL
Alcohol	21.7	Epinephrine hydrochloride	9.7		
Ammonium chloride	37.3	Ethylmorphine hydrochloride	5.3	Silver nitrate	11.0
Amobarbital sodium	8.3	Fluorescein sodium	10.3	Silver protein, mild	5.7
Amphetamine phosphate	11.3	Glycerin	11.7	Sodium acetate	15.3
Amphetamine sulfate	7.3	Holocaine hydrochloride	6.7	Sodium bicarbonate	21.7
Antipyrine	5.7	Homatropine hydrobromide	5.7	Sodium biphosphate, anhydrous	15.3
Apomorphine hydrochloride	4.7	Homatropine methylbromide	6.3	Sodium biphosphate	13.3
Ascorbic acid	6.0	Hyoscyamine sulfate	4.7	Sodium bisulfite	20.3
Atropine methylbromide	4.7	Neomycin sulfate	3.7	Sodium borate	14.0
Atropine sulfate	4.3	Oxytetracycline hydrochloride	4.3	Sodium iodide	13.0
Bacitracin	1.7	Penicillin G, potassium	6.0	Sodium metabisulfite	22.3
Barbital sodium	10.0	Penicillin G, sodium	6.0	Sodium nitrate	22.7
Bismuth potassium tartrate	3.0	Pentobarbital sodium	8.3	Sodium phosphate	9.7
Boric acid	16.7	Phenobarbital sodium	8.0	Sodium propionate	20.3
Butacaine sulfate	6.7	Physostigmine salicylate	5.3	Sodium sulfite, exsiccated	21.7
Caffeine and sodium benzoate	8.7	Pilocarpine hydrochloride	8.0	Sodium thiosulfate	10.3
Calcium chloride	17.0	Pilocarpine nitrate	7.7	Streptomycin sulfate	2.3
Calcium chloride (6 H ₂ O)	11.7	Piperocaine hydrochloride	7.0	Sulfacetamide sodium	7.7
Chlorobutanol (hydrated)	8.0	Polymyxin B sulfate	3.0	Sulfadiazine sodium	8.0
Chlortetracycline sulfate	4.3	Potassium chloride	25.3	Sulfamerazine sodium	7.7
Cocaine hydrochloride	5.3	Potassium nitrate	18.7	Sulfapyridine sodium	7.7
Cupric sulfate	6.0	Potassium phosphate, monobasic	14.7	Sulfathiazole sodium	7.3
Dextrose, anhydrous	6.0	Procainamide hydrochloride	7.3	Tetracaine hydrochloride	6.0
Dibucaine hydrochloride	4.3	Procaine hydrochloride	7.0	Tetracycline hydrochloride	4.7
Dihydrostreptomycin sulfate	2.0	Scopolamine hydrobromide	4.0	Viomycin sulfate	2.7
Ephedrine hydrochloride	10.0	Scopolamine methylnitrate	5.3	Zinc chloride	20.3
Ephedrine sulfate	7.7	Secobarbital sodium	8.0	Zinc sulfate	5.0

^a Table of "Isotonic Solution Values" showing volumes in mL of water to be added to 300 mg of the specified drug in sterile water to produce an isotonic solution. The addition of an isotonic vehicle (commonly referred to as diluting solution) to make 30 mL yields a 1% solution. Solutions prepared as directed above are isoosmotic with 0.9% sodium chloride solution but may not be isotonic with blood (see Appendix A for hemolysis data).

^b V-values for drugs which do not appear in Appendix B, but are listed in Appendix A can be calculated from the sodium chloride equivalent for 1% drug.

Example—Calculate the V-value for anileridine HCl (Appendix A defines E = 0.19).

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.19 \text{ g NaCl}}{1 \text{ g drug}} \times 0.3 \text{ g drug} = 6.33 \text{ mL Soln}$$

for dilute solution 6.33 mL soln $\approx$ 6.33 mL water

$$\therefore V = 6.33 \text{ mL water}/0.3 \text{ g drug.}$$