Colligative Properties and Isotonic Solutions

CHAPTER 2

The ingredients information given to consumers by the maker of a sterile eyedrop contains the substances listed in the box below. This information is probably overlooked by most consumers, but perhaps not by students who are learning the principles of physical pharmacy. Why are these substances, excluding the active ingredient tetrahydrozoline HCl, necessary for this formulation? And what are the quantities or concentrations of these added compounds? We shall answer these questions at the end of this chapter.

Formulation of a Sterile Eyedrop

Tetrahydrozoline HCl (0.05%)
Purified water
Sodium chloride
Boric acid
Sodium borate
Benzalkonium chloride (0.01%)
Edetate disodium (0.1%)

Pharmaceutical dosage forms contain nonmedicinally active agents, commonly referred to as *pharmaceutical excipients*. These agents are used for a variety of purposes, including maintaining the tonicity of the body fluids and achieving a desired drug delivery, designed to provide efficacious, nontoxic, and aesthetically appealing medications. This chapter presents an overview of common dosage forms based on drug delivery considerations and the properties of drugs. The focus of discussion is then placed on solutions and the solution properties that allow the dosage form to be compatible with the biological system.

There are four properties of solutions that depend on the nature and the mole fraction of the solvent, but not on any of the properties of the solutes. They are known as the *colligative properties*. As we shall see, these properties play an important role in pharmaceutical solution preparations because, by the dependence on the number of particles of the solutes, they provide a method for determining this number from a measured value of one of the colligative properties. This datum then allows the quantity of each solute (or ingredient) to be determined for the preparation of an isotonic solution.

CHAPTER OUTLINE

OBJECTIVES

1. Understand the various types of pharmaceutical dosage forms.
2. Demonstrate an understanding of colligative properties of solutions and their application in the determination of the molecular weights of drugs.
3. Predict colligative property change based on the amount of drug present and its type (electrolytes, nonelectrolyte, or weak electrolyte).
4. Perform accurate calculations for the preparation of isotonic solutions, using methods derived from the principles of colligative properties of solutions.

I. Pharmaceutical Dosage Forms and Drug Delivery Considerations

A *pharmaceutical dosage form* is a preparation that functions as a vehicle for the administration of medication in a measured amount. Dosage forms contain various agents that are medicinally inactive, often referred to as the pharmaceutical excipients. It is these agents and the choice of dosage form that result in the development of efficacious and safe pharmaceutical products, and it is through these agents and forms that a desired drug delivery is achieved to improve the drug's therapeutic effect. Thus, it is clear that the dosage form is a determining factor of drug efficacy, and that generically or chemically equivalent drugs may not necessarily be bioequivalent because of dosage form variations. The most commonly used method of drug delivery is through either a solid or a liquid formulation. The principles involved in such a formulation closely parallel the chemical properties of drugs in solutions. Thus, as an introduction to pharmaceutical formulation, a brief discussion of the solid and solution dosage forms is provided below; more detailed discussion is given in later chapters.

Solid Dosage Forms

It is as effective as it is natural that most drugs can be delivered using oral dosage forms that include solutions, coarse dispersions (suspensions and emulsions), and solid forms. The basic strategy in dosage form design is to achieve the desired drug absorption pattern through the control of drug release from the dosage form to the biological fluid at the site of absorption. Solid dosage forms including tablets and capsules can be made for *immediate release* or *controlled release* of the drug. In the conventional immediate-release dosage forms, tablets or granules containing the drug are prepared with a wetting agent to allow rapid contact with water. The rate of drug dissolution from the dosage form in the gastrointestinal (GI) tract usually follows Fick's law of diffusion, a kinetic process that predicts the rate of drug release based on the solubility of the drug and the particle size of the drug material. It is well established that drug release from the dosage form in the GI tract gives a positive correlation with the drug's bioavailability, as indicated by the plasma concentration–time curve, and its measurable biological activity. The aqueous solubility of a drug is thus a key factor in formulation considerations, regardless of the state (liquid, solid, etc.) of the dosage form. Also note that the absorption of drugs in various segments of the GI tract is taken up by the hepatic portal vein that perfuses the liver. Oral delivery of drug is thus subjected to the first-pass hepatic metabolic effect. There are, however, small tablets designed for sublingual absorption, which bypass the GI tract for fast action. These tablets, such as those of nitroglycerin, are flat and oval shaped, and they dissolve rapidly when placed beneath the tongue.

The term *controlled release* represents a broad concept of dosage form design, with the intention to bring a more specific drug delivery when compared to conventional approaches. In solid dosage forms, both the *delayed-release* and the *extended-release* products have been met with great

preference for their use as therapeutic products. The enteric coated aspirin tablet, e.g., is a delayed-release product which has an acid-resistant coating that prevents drug release in the gastric fluid, so that the drug release is delayed until it reaches the intestinal fluid, which has an alkaline pH. In comparison, the omeprazole delayed-release capsules consist of enteric coated granules that are acid-labile, allowing the drug to be released in the stomach for the treatment of duodenal ulcer. The extended-release dosage form is a system that can be used to reduce the dosing frequency of a drug compared to the use of a conventional (immediate-release) dosage form. Many drugs with relatively high solubility in water are short-acting and require multiple daily dosing to achieve the desired therapeutic results. When the dosing schedule is not followed, the resulting plasma–concentration curve may reflect a less than optimum drug therapy, as indicated by concentrations that either exceed the minimum toxic level or fall below the minimum therapeutic level. As illustrated in **Figure 2-1,** for an immediate-release dosage form, multiple doses at prescribed time intervals are usually required to achieve a steady-state plasma concentration. If a dose is missed, there will be a delay in achieving the desired plasma level. The extended-release product typically provides an immediate release of drug, which promptly produces the desired therapeutic effect, followed by a gradual and continual release of additional amounts of drug to maintain the effect over a predetermined time. Such a dosage form enhances patient compliance and is especially applicable to drugs used for the treatment of chronic conditions. The proprietary extended-release dosage forms have been developed using a number of pharmaceutical techniques including particle coating, as in the formulation of metoprolol, and the hydrophilic eroding matrix, as in the formulation of quinidine sulfate and morphine sulfate products. It is worth noting that a hydrophilic matrix made from the use of a hydrophilic polymer, such as hydroxypropyl methylcellulose, works as a barrier for drug release in two ways. In gastric fluid, upon wetting, the hydrophilic matrix forms a gel layer around the surface of the tablet, which increases in thickness with time as water permeates. Drug is released from tablet via diffusion through the gel layer. As the polymer becomes fully hydrated, it is eroded from the tablet core, allowing more drug release from the tablet. In this design, the rate of drug release is controlled by the processes of diffusion and tablet erosion.

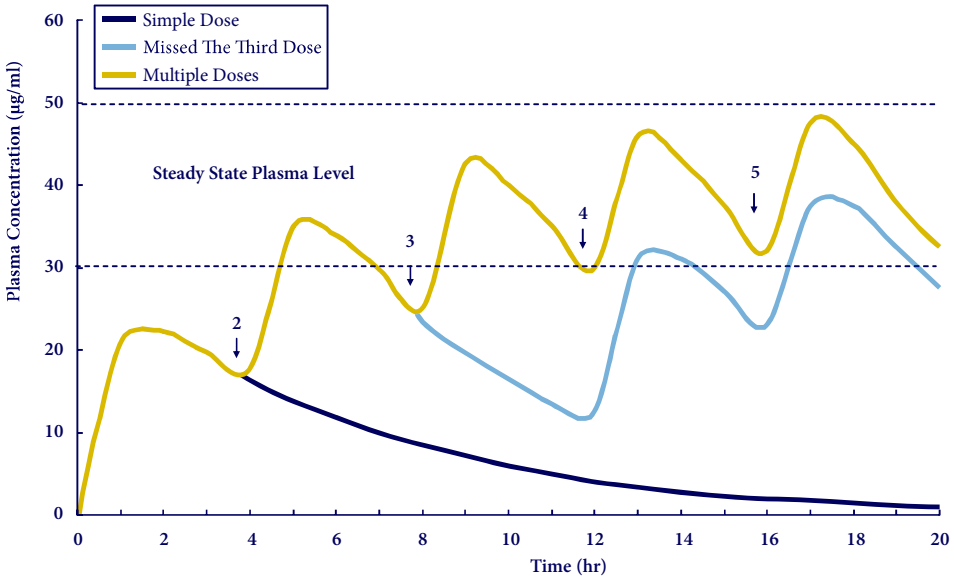

Figure 2-1 Plasma drug concentration versus time profiles: (*A*) a single oral dose, (*B*) multiple oral doses, and (*C*) the result of missing third dose in the multidosing regimen.

Solution Dosage Forms

The term *solution* is usually used to indicate a true solution, which is defined as a mixture of two or more components that form a homogeneous system in which the components are dispersed at the molecular level. In comparison, coarse dispersions, such as pharmaceutical suspensions and emulsions, show distinct separation of phases due to the presence of particles or liquid droplets with diameters greater than 500 nm. These are known as the *polyphasic systems*. Between true solution and the polyphasic system lies the colloidal dispersion, which contains particles in sizes of 1–500 nm. Certain colloidal dispersions may be classified as a true solution or a heterogeneous system depending on the concentrations and molecular aggregations of the dispersed phase. For example, many amphiphilic compounds, which are of pharmaceutical importance, form aggregates of molecules or ions of relatively small size and mass in an aqueous medium. At low concentrations they exist in true solutions, but at sufficiently high concentration, these molecules or ions associate to form micelles, known as *micellar colloids*.

The aqueous solution, which is applicable to nearly all routes of drug delivery except the intrapulmonary system, is much more versatile than the solids as a drug delivery system. There are, however, serious challenges in the development of a solution dosage form due to the poor solubility and chemical instability of many drugs in the aqueous system and the sterility requirement of solutions used for parenteral drug delivery. The solubility property of a drug affects not only the quantity of the drug that can be incorporated into a dosage form, but also the drug's bioavailability and biological activity (detailed discussion of drug solubility is given later). For oral drug delivery, the solubility concern may be partially overcome by using mixed solvent systems containing ethanol and/or propylene glycol in water, or pharmaceutical emulsions that enhance the solubility of water-insoluble drugs. As a historical note, the Sumerian clay tablets of the third millennium BC (University Museum, University of Pennsylvania) have shown us that *beer* was frequently used for the dispersion of pulverized seeds, herbs, and roots of medicinal plants. One suspects that the use of small alcohols to enhance the solubility of organic compounds was well known then, and that the mixed solvent system is, perhaps, the oldest known dosage form for the delivery of medicinal agents.

The most common reactions leading to drug degradation in solutions is the hydrolysis of organic acid derivatives. Hydrolysis is further subjected to specific acid and/or base catalysis, thus making pH an important factor in understanding the stability issue when formulating a solution dosage form. For example, procaine, an ester of *p*-amino benzoic acid and diethylaminoethanol, is notoriously unstable in alkaline pH due to the specific base-catalyzed hydrolysis. The maximum stability of the drug occurs in the pH range of 3.5–4.5. Hence, for the formulation of a solution, procaine hydrochloride, which is soluble in an acidic environment, is usually used. Many oral liquids are also made as reconstituted suspensions to circumvent problems associated with drug stability in solutions.

An important consideration for the preparation of pharmaceutical solutions intended for delivery of drugs through the ocular and parenteral routes is the compatibility of the solution with the biological fluids. The nature of blood serum and interstitial fluids reveals that the environment in which cells and tissue are bathed is an electrolyte solution made up largely of sodium chloride. The normal functioning of the cells demands that the composition and the total number of molecules and ions of these fluids be relatively constant. Although regulatory mechanisms exist to maintain this constancy, it can be disrupted by disease states or by the administration of solution that is incompatible with the biological fluid. Some solution properties, such as the osmotic pressure, depend only on the total number of molecules and ions, but not on the chemical nature of the constituents. It is these properties that are seen to provide a balance between intracellular and extracellular fluids and hence are the focus of discussion for this chapter.

II. Colligative Properties of Solutions

In the discussion of the colligative properties of solutions, it is important to realize that these properties depend on the chemical nature of the solvent and its mole fraction in the solution, but not on any of the properties of the solute. The solvent-specific properties for the liquid solution system include the liquid–vapor phase equilibrium, commonly indicated by vapor pressure, and osmosis, a phenomenon of solvent migration across a semipermeable membrane that allows only the solvent but not the solute molecules to pass through. The latter is measured as the osmotic pressure. To provide clarity to the description of these phenomena, the colligative properties are discussed first in nonelectrolyte solutions and then in electrolyte solutions, using a two-component system.

Vapor Pressures of Solutions

The liquid–vapor equilibrium of a solution can be best understood using the concept of *ideal* solution. It is known from *Dalton's law* for ideal gases that the total pressure of a gaseous solution is equal to the sum of the pressures of the components based on the kinetic molecular theory of noninteracting molecules. As liquids exist only because of molecular interactions, no such "ideal" liquid solutions can be expected in the same sense as an ideal gas solution. Some solutions, however, behave in a simple way and may be considered as ideal solutions. The classical example of a nearly ideal solution is the benzene–toluene system **(Figure 2-2),** which shows that, in equilibrium, the total vapor pressure and the partial vapor pressure for each component are linearly related to the composition of the components expressed in mole fractions.[1] This linear relationship for each component, which is the primary characteristic of an ideal solution, can be written as

$$P_a = X_a P_a^o \qquad P_b = X_b P_b^o \qquad \text{(Raoult's law)}$$

$$\text{and} \quad P = P_a + P_b \qquad \text{(Dalton's law)} \tag{2-1}$$

where P_a and P_b are the partial vapor pressures of components *a* and *b* above a solution, X_a and X_b are the mole fractions of *a* and *b*, P_a^o and P_b^o are the original vapor pressures of the pure components *a* and *b*, and *P* is the total vapor pressure of the solution. Solutions that obey Equations (2-1) and have vapor pressure diagrams similar to Figure 2-2 are said to conform to *Raoult's law*. Other systems such as carbon tetrachloride–silicon tetrachloride and chlorobenzene–bromobenzene also show similar and simple behavior. This has led to the generalization that *simplicity* (or ideality) of solution behavior can be expected from components that are similar in *molecular size* and in *intermolecular interactions*. These stipulations imply that the energy required to break the *a*–*a*, *b*–*b*, and *a*–*b* interactions is the same or similar, therefore resulting in zero heat of mixing, and the solution volume is the sum of the component volumes.

The vapor pressure–composition diagrams for nonideal solutions are usually classified as having either a minimum or a maximum in the total vapor pressure–composition curve, compared to the predicted total vapor pressure curve using Raoult's law **(Figure 2-3).** The chloroform–acetone system, e.g., exhibits lowered total vapor pressure compared to the sum of the vapor pressures of the two components.[2] A simple explanation of this phenomenon is that the intermolecular interaction, through hydrogen bonding between the carbonyl group of acetone and the slightly acidic hydrogen of chloroform,

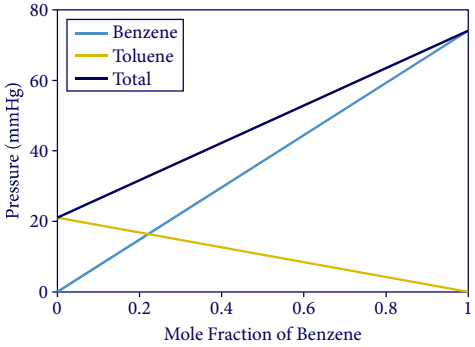

Figure 2-2 The partial and total vapor pressures for the nearly ideal solution of benzene and toluene at 20°C. Data from: B. Bell and T. Wright, *J. Phys. Chem.* 35:129, 1900.

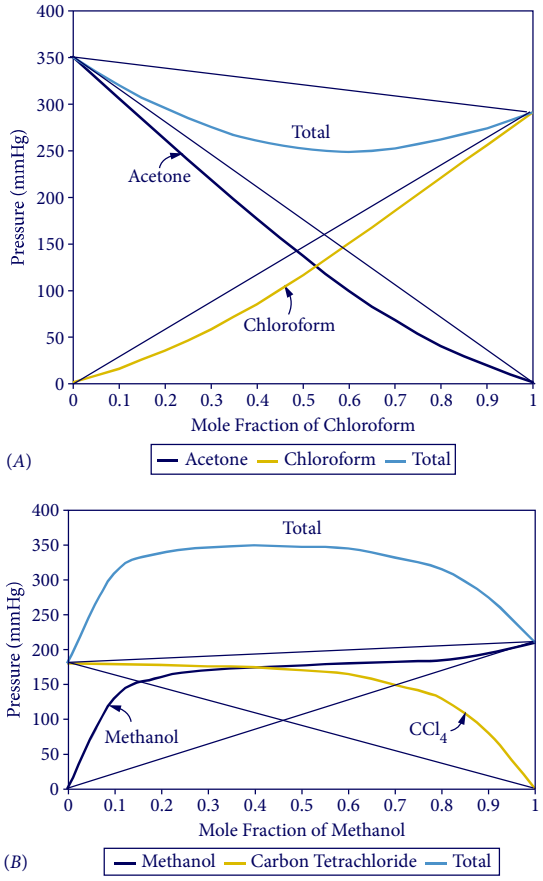

Figure 2-3 Total vapor pressure curves of nonideal solutions: (*A*) the chloroform–acetone system and (*B*) the carbon tetrachloride–methanol system at 35°C.
(*A*) Adapted from: J. von Zawidzki, *Z. Physik. Chem.* 35:129, 1900. (*B*) Adapted from: J. Timmermans, *Physico-chemical Constants of Binary Systems*, vol. 2, Interscience, New York, 1959.

$(CH_3)_2C{=}O\cdots H{-}C(Cl)_3$, is stronger than the interactions between acetone or chloroform molecules in their pure states. In such cases, heat is evolved from the solution upon mixing and thus results in a negative heat (enthalpy) of mixing. Qualitatively, one might also expect that the intermolecular interaction in solution would tend to restrict the motion of the molecules, thus giving the system less entropy than in the ideal case. Solutions that show a maximum in their total vapor pressure, such as in the carbon tetrachloride–methanol system,[3] are frequently those containing a component that is itself associated, as are small alcohols and water. In the carbon tetrachloride–methanol system, e.g., energy is required to break up some the self-association of methanol molecules, thus resulting in a positive heat of mixing. Because heat is added to the system, this enthalpy produces a free energy effect that leads to a higher total vapor pressure than in the ideal situation. These qualitative interpretations have been well tested by thermodynamic principles.

Studies of the vapor pressure–composition relationships of nonelectrolyte solutions have shown that both the concentration and the volatility of the solute contribute to solution nonideality. However, even for volatile solutes, the vapor pressure of the solvent near the two composition limits, i.e., in dilute solutions, tends to follow ideal solution behavior. In summary,

an *ideal solution* is characterized by a zero heat of mixing, a solution volume that is the sum of the component volumes, and a vapor pressure–composition curve that obeys Raoult's law. Thus, in general, a solution of a nonvolatile solute in dilute concentrations may be taken as an ideal solution.

Vapor Pressure Lowering

According to Raoult's law, the partial vapor pressure of the solvent of an ideal solution is equal to the product of the mole fraction of the solvent and its vapor pressure in the pure state. For dilute solution containing a nonvolatile solute, by which the solution is deemed ideal, the partial vapor pressure of the solute P_b approaches zero. Equation (2-1) then becomes

$$P = P_a = X_a P_a^o$$

When the mole fraction of the solvent is expressed in terms of the mole fraction of the solute ($X_a = 1 - X_b$), the above equation gives

$$P = P_a^o (1 - X_b)$$

or $$P_a^o - P_a = \Delta P = P_a^o X_b \qquad (2\text{-}2)$$

The lowering of the vapor pressure, expressed as $P_a^o - P_a$, or ΔP, is thus seen, for dilute solutions, to depend only on the mole fraction of the solute and is, therefore, one of the colligative properties. It will be recalled that the mole fraction of the solute is related to the molality of solute by the equation $X_2 = m/(m + 55.5)$. Hence, for aqueous solution the vapor pressure lowering can be calculated directly using the molal concentration (m) according to the following equation:

$$\Delta P = mP_a^o/(m + 55.5) \qquad (2\text{-}3)$$

For dilute solutions where $m << 55.5$, Equation (2-3) becomes $\Delta P = mP_a^o / 55.5$.

Example 2-1: In an ideal solution containing two liquid components *a* and *b*, the mole fraction of component *a* (X_a) is 0.7. Calculate the total vapor pressure of the solution and the partial vapor pressure of the two components. The vapor pressures of pure components *a* and *b* are 22.3 and 74.7 mmHg at 20°C, respectively.

Solution: From Raoult's law (Equations (2-1)),

$P_b = 74.7[0.3] = 22.41$ mmHg

$P_a = 22.3[0.7] = 15.61$ mmHg

$P = P_a + P_b = 22.41 + 15.61 = 38.02$ mmHg

Example 2-2: Calculate the vapor pressure lowering of a solution containing 50 g of dextrose (mol wt = 180) in 1000 g of water. The vapor pressure of water is 23.77 mmHg at 25°C.

Solution: Molality = 50 × 1000/180 × 1000 = 0.2778 mol/kg

Using Equation (2-3),

$\Delta P = mP_a^o/(m + 55.5)$

$= 0.2778 \times 23.77 / (0.2778 + 55.5)$

$= 0.12$ mmHg

Boiling Point Elevation

The boiling point of a liquid is the temperature at which the vapor pressure of the liquid is equal to the external, usually atmospheric, pressure. Consider a solvent with a temperature at or near its boiling point. The addition of a nonvolatile solute, which according to Raoult's law must lower the vapor pressure of the pure solvent, thus will prevent the solution from boiling until the solution is heated to a higher temperature, at which the vapor pressure lowering by the solute is compensated by an increase in vapor pressure due to the increase in temperature. This results in a boiling point elevation. A thermodynamic explanation of the effect of solute concentration on the boiling point change may be derived from the consideration of the vapor pressure–temperature relationship coupled with the vapor pressure lowering phenomenon. The vapor pressure lowering equation $P_a^o - P_a = P_a^o X_b$ or $(P_a^o - P_a) / P_a^o = X_b$ indicates that at or near the boiling point, the addition of an infinitesimal amount of solute dX_b will result in an infinitesimal drop of vapor pressure expressed as dP/P, that is,

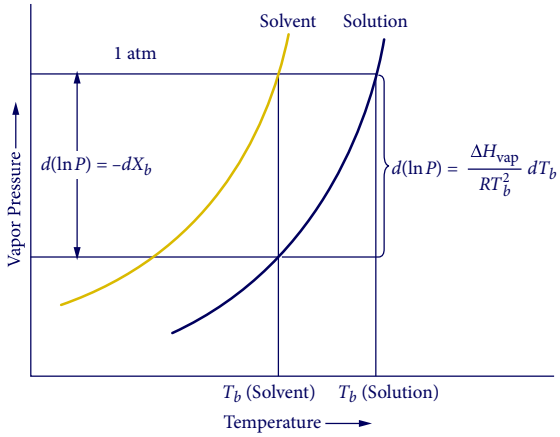

Figure 2-4 Thermodynamic expressions of vapor pressure and temperature changes in the region of the boiling point.
Adapted from: G. Barrow, *Physical Chemistry*, 2nd ed., McGraw-Hill Inc., New York, 1966.

$$dP/P = d(\ln P) = -dX_b \tag{2-4}$$

This relationship is illustrated in **Figure 2-4**. To reach the external pressure and boiling point for a solution, the decrease in the logarithm of the vapor pressure due to the solute shown in Equation (2-4) must be counterbalanced by an increase of the same quantity through a temperature increase. Hence,

$$d(\ln P)_{solute} = -d(\ln P)_{temp} \tag{2-5}$$

The thermodynamic expression of the temperature dependence of vapor pressure is known as the *Clausius–Clapeyron relationship*, which shows that the change of vapor pressure as a function of temperature dP/dT is equal to the molar heat of vaporization ΔH_{vap} of the solution divided by the volume of the vapor V_{vap} and temperature:

$$dP/dT = \Delta H_{vap}/V_{vap}T \qquad \text{for ideal gas:} \qquad V_{vap} = RT/P$$

Assuming ideal gas conditions for the vapor, the term $d\ (\ln P)_{temp}$ can then be written as

$$d(\ln P)_{temp} = \frac{\Delta H_{vap}}{RT^2} dT \tag{2-6}$$

For our discussion, T is the boiling point (T_b); therefore, the combination of Equations (2-4), (2-5), and (2-6) gives the following relation:

$$dT_b = \frac{RT_b^2}{\Delta H_{vap}} dX_b \tag{2-7}$$

In Equation (2-7), dT_b is the boiling point elevation caused by dX_b solute, and R is the gas constant. For diluted solutions, the heat of vaporization for the solution is nearly identical to that of the pure solvent and is a *constant*. The boiling point elevation is therefore independent of all properties of the

solute except its mole fraction in the solution. Thus, the boiling point elevation is another colligative property. The derivation of Equation (2-7) can also be achieved using a well-established thermodynamic concept that at equilibrium between two phases, such as the liquid–vapor system, the *chemical potential* μ, or partial molar free energy, of the solvent in the solution is equal to the partial molar free energy of the vapor.

For dilute solutions, the relationship between mole fraction and molality shows that

X_b = (molality of solute) (mol wt of solvent) / 1000

The common form of Equation (2-7) can thus be written as

$$\Delta T_b = \frac{RT_b^2}{\Delta H_{vap}} X_b = \left(\frac{RT_b^2 \text{ (mol wt of solvent)}}{\Delta H_{vap} (1000)} \right) m \tag{2-8}$$

Here ΔT_b is the boiling point elevation; the expression in parentheses is known as the boiling point elevation or the ebullioscopic constant, generally noted as K_b. Thus,

$$\Delta T_b = K_b m \tag{2-9}$$

The calculated and observed values of K_b for a number of solvents are given in **Table 2-1**. Using Equation (2-8), Example 2-3 will show that for aqueous solutions, K_b has a calculated value of 0.513 deg-kg/mol.

Example 2-3: For water, T_b = 100°C, and ΔH_{vap} = 9720 cal/mol, what is the ebullioscopic constant for this solvent (mol wt = 18.02; R = 1.987 cal/mol-deg)?

Solution: Based on Equation (2-8),

$K_b = 1.987 \times (373.2)^2 \times 18.02 / 9720 \times 1000$

$= 0.513$ deg-kg/mol

Example 2-4: What is the boiling point elevation of a solution containing 50 g of dextrose (mol wt = 180.16) in 1000 g of water?

Solution: Using the value of K_b calculated above and Equation (2-9),

$\Delta T_b = 0.513 \times 50/180.16 = 0.142$°C

Table 2-1 Molal Boiling Point Elevation and Freezing Point Depression Constants at 1 atm Pressure

Solvent	T_b, °C	K_b, deg-kg/mL	T_f, °C	K_f, deg-kg/mol
Water	100.0	0.51	0.00	1.86
Benzene	80.1	2.53	5.50	5.12
Acetic acid	118.0	2.93	16.60	3.90
Ethanol	78.4	1.22		
Cyclohexane			6.50	20.00

Example 2-5: Calculate the concentration of dextrose (mol wt = 180.16), in % wt/wt expression, in a solution that produces a boiling point elevation of 0.222°C. The K_b of water is 0.513 deg-kg/mol.

Solution:

Molality of dextrose = $\Delta T_b / K_b$ = 0.222/0.513 = 0.433 mol/kg

Wt of dextrose = molality × mol wt = 0.433 × 180.16 = 78.01 g

% of dextrose in solution = 78.01 /1078 = 0.0724, or 7.24% wt/wt†

†% wt/wt = $wt_2 \times 100 / (wt_1 + wt_2)$, where 1 and 2 denote solvent and solute, respectively. For the current question, wt_1 = 1000 g; wt_2 =78.01 g.

Freezing Point Depression

The normal freezing point is the temperature at which the solid and liquid have equal vapor pressures when they are subjected to an open pressure of 1 atm. An important fact in freezing point depression is that the solid phase can also exert vapor pressure, which decreases with decreasing temperature, and this vapor pressure is unaffected by the solute in the solution, implying that the cooling of the solution will lead to the formation of the pure solid solvent rather than a solid solution. One may view the lowering of the vapor pressure of the solvent by the presence of solute as an extension of the ranges of pressure and temperature for which the liquid phase can exist. At the freezing point temperature of the pure solvent, the vapor pressure of the solution is obviously lower than that of the solid phase; i.e., the solid and liquid vapor pressures are not in equilibrium, and the system exhibits free energy that favors the liquid phase. At a temperature lower than the freezing point of the pure solvent, however, the vapor pressure of the solution will be lowered, in addition to the solute effect, by the lowering of temperature to that of the solid phase, thus reestablishing the equilibrium between solid and liquid, at which the solution freezes to yield the solid solvent.[4] This vapor pressure diagram for a solvent and solution near the freezing point at a total pressure of 1 atm is illustrated in **Figure 2-5**.

Consider points *A* and *B* in Figure 2-5, which represent the freezing points of the pure solvent and solution, respectively. The change of vapor pressure of the solid, based on the previously mentioned Clausius–Clapeyron equation, occurs via the heat of sublimation, that is, $d(\ln P)_{\text{sublimation}} = (\Delta H_{\text{sub}}/RT_f^2)\, dT_f$, with T_f being the freezing point of the pure solvent. The change of vapor pressure for the solution consists of first the lowering of vapor pressure by the solute, that is, $d(\ln P)_{\text{solute}} = -dX_b$, and then a temperature-dependent change as described in the previous section, that is, $d(\ln P)_{\text{temp}} = (\Delta H_{\text{vap}}/RT_f^2)\, dT_f$. Thus, at equilibrium,

$$d(\ln P)_{\text{sublimation}} = d(\ln P)_{\text{solute}} + d(\ln P)_{\text{temp}}$$

Together, these terms give

$$\frac{\Delta H_{\text{sub}} - \Delta H_{\text{vap}}}{RT_f^2}\, dT_f = -dX_b$$

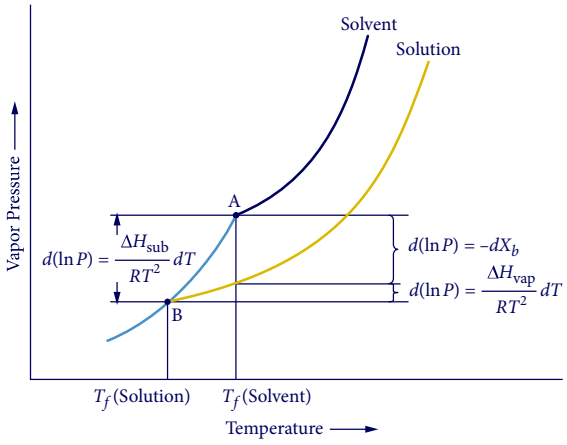

Figure 2-5 Vapor pressure diagram for a solvent and solution near the freezing point at a total pressure of 1 atm.
Adapted from: G. Barrow, *Physical Chemistry*, 2nd ed., McGraw-Hill Inc., New York, 1966.

The terms ΔH_{sub} and ΔH_{vap} can be combined to give the heat of fusion (ΔH_f) in that

$$\Delta H_f = \Delta H_{sub} - \Delta H_{vap}$$

Thus,

$$\frac{\Delta H_f}{RT_f^2}\, dT_f = -dX_b$$

or
$$dT_f = -\frac{RT_f^2}{\Delta H_f} dX_b \qquad (2\text{-}10)$$

Because the freezing point depression dT_f depends only on the properties of the solvent and the mole fraction of the solute, Equation (2-10) attests to the fact that the freezing point depression is a colligative property. The negative sign in Equation (2-10) indicates a lowering of the freezing point. The common form of Equation (2-10) is

$$\Delta T_f = \left(\frac{RT_f^2\ (\text{mol wt of solvent})}{1000\ \Delta H_f}\right) m = K_f m \qquad (2\text{-}11)$$

where ΔT_f is a positive value. The expression in parentheses is called the *freezing point depression* or *cryoscopic constant* (K_f), which can be calculated based on the molecular weight, heat of fusion, and freezing point of the pure solvent (see Example 2-6). For aqueous solutions, K_f = 1.86 deg-kg/mol.

Example 2-6: What is the K_f value for water?

Solution: From the *Handbook of Chemistry and Physics*, T_f = 0°C or 273.2 K and ΔH_f = 1437 cal/mol. Using R = 1.987 cal/mol-deg and mol wt of 18.02,

$$K_{f,water} = 1.987 \times (273.2)^2 \times 18.02 \,/\, 1000 \times 1437$$
$$= 1.860 \text{ deg-kg/mol}$$

Example 2-7: Calculate the freezing point depression of a solution containing 50 g dextrose (mol wt = 180.16) in 1000 g of water.

Solution: $\Delta T_f = K_f m = 1.86(50/180.16) = 0.516$°C

Osmotic Pressure

The phenomenon of osmosis depends on the existence of semipermeable membranes characterized by the fact that only one of the components of a solution is allowed to pass through the membrane. Cellophane and a number of animal and protein membranes, e.g., are permeable to water but not higher-molecular-weight compounds. The mechanism by which a semipermeable membrane may operate varies. In some cases the membrane seems to act simply as a mechanical sieve, letting small molecules such as water through but preventing the passage of larger molecules. Other membranes do not pass or reject molecules based on size, but exhibit chemical properties that lead to the passage of one component but not others. An example of such a semipermeable membrane is the palladium foil, which is permeable to hydrogen but not to nitrogen and other gases based on the fact that hydrogen, but not other gases, dissolves and dissociates at the palladium surface and reunites into molecules after passage through the solid lattice. In any

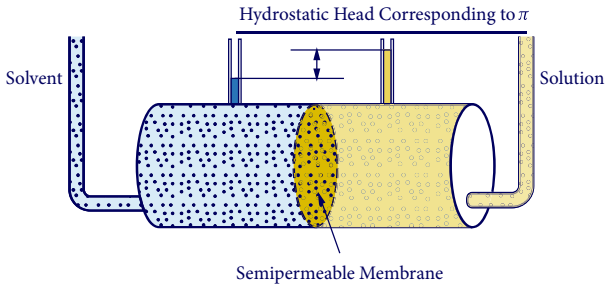

Figure 2-6 The schematic osmotic pressure apparatus.
Adapted from: R. M. Fuoss and D. J. Mead, *J. Phys. Chem.* 47:59, 1943.

case, it is important to point out that as long as a membrane is available that will pass the solvent but not the solute, osmosis can be studied, and the process by which osmosis is accomplished is immaterial.

In a two-chamber system containing the solvent and a solution separated by a semipermeable membrane, there is a natural tendency for the solvent to flow from the pure solvent chamber through the membrane into the solution chamber, and this tendency can be opposed by applying pressure to the solution chamber. As shown in the schematic osmotic pressure apparatus (**Figure 2-6**) of Fuoss and Mead,[5] this balancing pressure is indicated by the hydrostatic head that corresponds to the pressure at equilibrium, and it is called the *osmotic pressure* π.

Is osmotic pressure a colligative property? Before this question is answered, there is, perhaps, a need for a small digression to introduce an important thermodynamic concept on chemical equilibrium. The term *free energy change* (ΔG) is a measure of the useful work that might be obtained from a process at constant temperature and pressure, in that a decrease in free energy of this process (that is, ΔG is negative) indicates a tendency of the process to proceed spontaneously. When the free energy change reaches zero, the system is at equilibrium. If ΔG is positive, the process tends to proceed spontaneously in the opposite direction. The relation of free energy to equilibrium can be seen from the following examples. Consider an ideal gas undergoing change from state 1 with a pressure of P_1 to state 2 with a pressure P_2 at constant temperature. The partial differentiation of free energy G with respect to P at constant temperature is equal to the volume V of the gas based on the gas law. One can write $dG = V\,dP$, as the temperature is constant.

For an ideal gas, P and V are related by the ideal gas law, and the integration of the equation $dG = V\,dP$ gives

$$G_2 - G_1 = nRT \ln(P_2/P_1)$$

If we define state 1 as a standard state, that is, $G_1 = G^o$ at 25°C and 1 atm, then $P_1 = 1$ atm, and subscript 2 can be dropped from P_2. The molar free energy for this gas at any state is then

$$G = G^o + RT \ln P \qquad (2\text{-}12)$$

Now, we further consider a reaction involving gases A, B, C, and D according to the following reaction

$$A + B \rightarrow C + D$$

The equilibrium constant K for this reaction can be obtained by measuring the pressure of each reactant and product at equilibrium, using the equation

$$K = (P_C P_D / P_A P_B)_{\text{equilibrium}}$$

Based on Equation (2-12), one can write the free energy for each gas as

$$G_A = G_A^{\circ} + RT \ln P_A \qquad G_B = G_B^{o} + RT \ln P_B$$
$$G_C = G_C^{o} + RT \ln P_C \qquad G_D = G_D^{o} + RT \ln P_D$$

The free energy change for the reaction can now be calculated as

$$\Delta G = G_{\text{products}} - G_{\text{reactants}} = \Delta G^{o} + RT \ln(P_C P_D / P_A P_B)$$

At equilibrium, $\Delta G = 0$, thus,

$$\Delta G^{o} = -RT \ln K \tag{2-13}$$

Equation (2-13), which relates the standard free energy change to the logarithm of the equilibrium constant, represents one of the *most important results of thermodynamics*. The obvious value of the equation is that it allows the calculation of not only the direction in which a reaction will proceed but also the equilibrium state that the reacting system will finally attain.

With the discussion given above, we can now ascertain the thermodynamic basis of the osmotic pressure. The free energy of the solvent in the solution is less than the free energy of the solvent in pure solvent because of solute-induced vapor pressure lowering. Therefore, there is a spontaneous tendency for the solvent to move from the relatively high free energy state of pure solvent to the relatively low free energy state of solution. This tendency is balanced by increasing the free energy of the solution by subjecting it to an externally applied pressure. The free energy lowering that results from the addition of solute is given in terms of vapor pressure lowering from P^o to P; hence

$$\Delta G = -RT \ln(P/P^o)$$

It is this free energy decrease that is balanced by the effect of the applied pressure. As has been mentioned, the dependency of free energy on pressure at constant temperature is the volume, that is, $dG/dP = V$, or $dG = V\,dP$. Because liquids are quite incompressible, the volume of solvent in the solution can be assumed to be a constant. Thus, the free energy per mole of solvent due to the applied osmotic pressure is πv (π is the osmotic pressure; v is the volume of 1 mol of solvent, or molar volume); the above equation can then be written as

$$\pi v = -RT \ln(P/P^o) \tag{2-14}$$

From Raoult's law, $P/P^o = X_a$, and for a two-component system, $X_a = 1 - X_b$. Thus,

$$\pi v = -RT \ln X_a = -RT \ln(1 - X_b) \tag{2-15}$$

This important thermodynamic result shows that the osmotic pressure is a function of the molar volume of the solvent, the temperature, and the concentration of the solution. It is therefore a colligative property.

Mathematically, one recalls that

$$-\ln(1 - X_b) = X_b + \tfrac{1}{2}X_b^2 + \cdots \approx X_b$$

The limiting value of $-\ln(1 - X_b)$ for a dilute solution is X_b. Also for dilute solutions, X_b approaches the value of the mole ratio of the solute over the solvent, i.e.,

$$X_b = n_b / (n_a + n_b) \approx n_b/n_a$$

With these relations, Equation (2-15) may be rewritten as

$$\pi v = RTX_b \qquad \text{or} \qquad \pi v n_a = RTn_b$$

The product of v and n_a gives the volume of the solvent V; hence,

$$\pi V_{\text{solvent}} = RTn_b$$

Two approximations can be made for the above expression. For aqueous solutions, water has a density of 1 g/mL. If the density of the solution is not significantly different from that of water, that is, V = kilograms of solvent, the above equation can be written as

$$\pi = n_b RT/V = mRT \tag{2-16}$$

The second approximation is that for dilute solutions; the contribution to the solution volume by the solute is negligible. In this case, the volume of the solvent is equal to the volume of the solution, thus

$$\pi = MRT \tag{2-17}$$

Equation (2-17) was first derived by van't Hoff in 1887.[6] The similarity of this expression to the ideal gas law led van't Hoff and others to the idea that the nature of the osmotic pressure may arise from a particle bombardment process. For osmotic pressure calculations, T is in kelvins (K), V is in liters, and R has a value of 0.082 L-atm/deg.

Example 2-8: Calculate the osmotic pressure of a 0.2 *m* solution of sucrose (mol wt = 342) at 20°C using Equations (2-14), (2-16), and (2-17). The solution has a vapor pressure of 17.475 mmHg and a density of 1.029 g/mL. The molar volume for water is 18.04 mL/mol (0.01804 L/mol), and the vapor pressure of pure water at 20°C is 17.542 mmHg.

Solution: (*a*) Using Equation (2-14), $\pi v = -RT \ln(P/P^o)$.

$\pi = -0.082 \times 293.2 \ln(17.475/17.542) / 0.01804 = 5.10$ atm

(*b*) Using Equation (2-16),

$\pi = mRT = 0.2 \times 0.082 \times 293.2 = 4.81$ atm†

(*c*) Using Equation (2-17), the solution contains 68.4 g of sucrose in 1000 g of water; thus the total wt of the solution is 1068.4 g. The density of the solution is 1.029 g/mL. Hence the volume of the solution is $V = 1068.4 / 1.029 = 1038$ mL.

$\pi = MRT = 68.4 \times 1000 \times 0.082 \times 293.2 / 342 \times 1038$

$= 4.63$ atm†

†*Note*: The observed osmotic pressure for this solution is 5.06 atm, indicating that both approximations [Equations (2-16) and (2-17)] underestimate the osmotic pressure of the solution.

Colligative Properties of Electrolytes

It was recognized by Jacobus van't Hoff that the electrolyte colligative behavior could conveniently be obtained by modifying the colligative property equations for nonelectrolytes with a factor, known as the van't Hoff *i* factor. As discussed earlier, this factor derives from the dissociation of

Table 2-2 Degree of Dissociation for Hydrochloric Acid at 25°C

Concentration N	Λ, mho-cm^2/Eq	α	i [= 1 + α(2 – 1)]
0	(426.16)	1.0	
0.001	421.36	0.99	1.99
0.005	415.80	0.98	1.98
0.01	412.00	0.97	1.97
0.05	399.09	0.94	1.94
0.10	391.32	0.92	1.92

Table 2-3 Expressions of Colligative Properties

Colligative Property	Equation (Unit)	Constant for Aqueous System
Vapor pressure lowering	$\Delta P = imP^o / (m + 55.5)^\dagger$	P^o: constant at a given temperature
Boiling point elevation	$\Delta T_b = imK_b$ (°C)	K_b = 0.513 deg-kg/mol
Freezing point depression	$\Delta T_f = imK_f$ (°C)	K_f = 1.860 deg-kg/mol
Osmotic pressure	$\pi = imRT$ (atm)	R = 0.082 L-atm/mol-deg

† If $m << 55.5$, $\Delta P = imP^o/55.5$; the unit of vapor pressure is mmHg (torr).

electrolytes into ions, with i equal to the number of ions generated per molecule. Experimentally, i values can be determined via measurement of the solution equivalent conductance Λ, which, when compared to the equivalent conductance of solution at infinite dilution Λ_o, gives the degree of dissociation α, $\alpha = \Lambda/\Lambda_o$. With the value of α, i can then be determined. An example of this determination is shown in **Table 2-2**. These data indicate that for strong electrolytes, such as hydrochloric acid, in dilute solutions, there is a nearly complete ionization.

In summary, the colligative behavior of solutes applies to both nonelectrolyte and electrolyte solutions. **Table 2-3** summarizes the equations for the determination of the colligative properties. The concentration dependency of the colligative properties can now be attributed to the osmolality rather than the molality of the solution. Osmolality is equal to the value of i times molality. For electrolytes, i is the number of ions generated per molecule, and for nonelectrolytes i may be taken as 1. For weak electrolytes, i may be calculated via determination of the degree of ionization, when necessary. It should be mentioned that osmolality is a solution property, which, in solutions containing more than one solute, is equal to the sum of osmolalities of all solutes.

Example 2-9: The osmotic pressure of a dilute solution of KNO_3 in water is 357 mmHg when measured against water at 25°C. What would be the vapor pressure at 25°C (the vapor pressure of pure water is 23.756 mmHg at this temperature), the boiling point, and freezing point of the solution?

Solution: The common factor for all colligative properties is the osmolality of the solution. From the information of the osmotic pressure†

$im = \pi/RT = 357 / 760 \times 0.082 \times 298.2 = 0.0192$ osmol/L

Thus,

$\Delta P = imP^o / (im + 55.5) = 0.0192 \times 23.756 / 55.5 = 0.008$ mmHg

$P_{solution} = P^o - \Delta P = 23.756 - 0.008 = 23.748$ mmHg

$\Delta T_b = imK_b = 0.0192 \times 0.513 = 0.01°C$

The boiling point of the solution will be 100.01°C.

$\Delta T_f = imK_f = 0.0192 \times 1.86 = 0.036°C$

The freezing point of this solution will be –0.036°C.

[†]The osmotic pressure has a unit of atm; 1 atm = 760 mmHg.

Application of Colligative Properties

The colligative behavior of solutes in solution is an important concept that must be recognized in the preparation of pharmaceutical solutions for parenteral use or for delivery of drugs to soft tissues. This application is discussed in the next section. The principal use of the colligative concept in chemistry is to determine the molecular weights, based on the fact that for a nonelectrolyte

m = wt of drug × 1000 / (mol wt of drug) (wt of solvent)

The determination of the concentration, molality, depends on not only the accuracy of measurement of the colligative property but also the sensitivity that the method provides for such a determination. This is especially true in the determination of compounds with large molecular weights. To maintain dilute solution conditions, the solutions that can be prepared may exhibit insufficient molalities to produce a measurable effect, as can be seen from the calculations shown in Example 2-10.

Example 2-10: A new peptide drug has an estimated molecular weight of about 10,000 daltons. For accurate determination of the molecular weight, which one of the colligative properties would provide the best sensitivity for such a measurement using a solution containing 1 g of the drug in 100 g of water at 25°C? The density of the solution is 1.01 g/mL. The vapor pressure of pure water at 25°C is 23.77 mmHg. The density of mercury is 13.5462 g/mL.

Solution: Estimated molality for this drug = 1 × 1000 / 10,000 × 100
= 0.001 m

$\Delta P = imP^o / 55.5 = 0.001 \times 23.77 / 55.5 = 0.0004$ mmHg

$\Delta T_b = imK_b = 0.001 \times 0.513 = 0.0005°C$

$\Delta T_f = imK_f = 0.001 \times 1.860 = 0.0019°C$

$\pi = imRT = 0.001 \times 0.082 \times 298.2 = 0.0245$ atm[†]

The results show that the osmotic pressure measurement is most sensitive for the determination of molecular weights of macromolecules.

[†]0.0245 atm is equal to 18.58 mmHg or 249.2 mm solution based on the following conversion factors: 1 atm = 760 mmHg (or torr) and mm solution = mmHg × $d_{Hg} / d_{solution}$.

Although several devices exist, the determination of the boiling point elevation remains unpopular. The principal difficulty in accurately determining the boiling point elevation stems from the fact that it is the temperature of the boiling liquid and not the temperature of the refluxing vapor that must be measured. It is, therefore, necessary to arrange the apparatus so that the thermometer is drenched with representative samples of the solution and is not at the condensing vapor. As a result, it is difficult to obtain high precision with the measurement of boiling point elevation. The freezing point depression can usually be measured much more easily and accurately than can the boiling point elevation. The fact that the value of K_f, in the aqueous system, is more than 3 times that of K_b indicates that the freezing point depression method has a greater sensitivity than boiling point elevation for the determination of concentrations and molecular weights. Since the introduction of the Beckmann method, where the freezing point is determined by immersing the solution in a bath fixed at temperature several degrees below the expected freezing point of the solution, followed by temperature measurement of the cooling solution at the solid–solution equilibrium, new temperature-sensing devices have been introduced for freezing point determinations with great precision. Modern osmometers using the freezing point depression concept allow determination of the concentration as low as a few milliosmoles per kilogram of water using microliter-size samples. These instruments are ideal for molecular weight determinations, clinical use involving measurements of biological fluids, and formulations of pharmaceutical products.

The advancement of membrane technology has also led to the development of membrane osmometers for precise measurement of osmotic pressure. The principal use of osmotic pressure measurements is in the determination of the molecular weight of macromolecules such as pharmaceutical polymers and proteins. Solutions of high-molecular-weight compounds will have low-molecular concentrations even though they may be quite concentrated in terms of the weight of the solute. That the osmotic pressure produced by these solutions can be accurately measured makes it the most suitable of the colligative properties for the study of these compounds. It is recalled that Equation (2-16) is an approximation, which, for convenience, can be easily converted to the following expression using the definition of molality:

$$\pi / C = RT / \text{mol wt of solute}$$

where C is the concentration of solute in grams per milliliter. This approximation is only valid and accurate when the solution is at infinite dilution. One can achieve this by measuring π/C as a function of C and extrapolating the results to infinite dilution, so that the value of π/C at zero concentration C can be determined for the calculation of the molecular weight.[7] This application is shown in Example 2–11.

Example 2-11: The following table shows the osmotic pressure of polyisobutylene solutions in cyclohexane and benzene at 25°C.[7] What is the molecular weight of this compound?

Concentration (g/mL)	π/C (atm-mL/g)†	
	In Benzene	In Cyclohexane
0.0200	0.104	0.585
0.0150	0.101	0.440
0.0100	0.099	0.30
0.0050	0.098	0.18

† Calculated from the data of P. J. Flory, *J. Am. Chem. Soc.* 65:373, 1943.

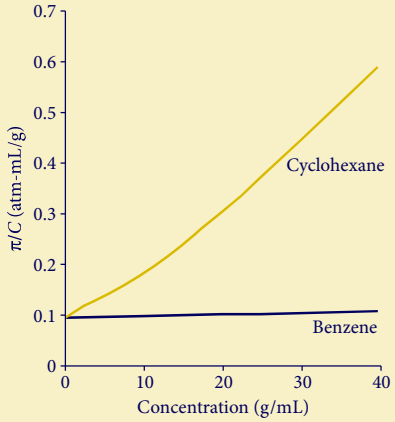

Figure 2-7 Determination of the limiting value of $RT/(\pi/C)$ for the molecular weight calculation in (*A*) benzene and (*B*) cyclohexane.

Solution: The plots of π/C versus C for both systems should yield the same limiting value when extrapolated to zero concentration (see **Figure 2-7**). From these plots, π/C at zero concentration is determined to be 0.097 atm-mL/g.

$$\begin{aligned}\text{Mol wt of polyisobutylene} &= \lim_{C \to 0} RT/(\pi/C) \\ &= 82.06 \times 298.2/0.097^{\dagger} \\ &= 252{,}270\end{aligned}$$

[†] Because C is expressed in grams per millimeter, $R = 82.06$ atm-mL/deg

III. Isotonic Solutions

Across the animal kingdom, the body fluids of all creatures are remarkably constant in their total osmolality, and the major component of the extracellular fluids is sodium chloride (NaCl). The body fluids have an osmotic pressure identical to that of an 0.9% solution of sodium chloride. This solution, being iso-osmotic with the biological fluids, is often referred to as an *isotonic solution*. However, the term *isotonic* implies that the solution does not produce a change in cellular constituents in the physiological system. Iso-osmoticity, in contrast, is a term used for any two liquids that have identical osmotic pressure (or other colligative properties). For instance, a solution of boric acid that is iso-osmotic with blood is not isotonic because it produces hemolysis of erythrocytes due to the ability of boric acid, regardless of its concentration, to cross the red blood cell membranes. Thus, isotonicity relates to the physiological compatibility of a solution, whereas iso-osmoticity only partially does so. Nevertheless, in pharmaceutical preparations, one can minimize cell damage by making the solutions iso-osmotic to body fluids, and thus they are referred to as isotonic solutions. Solutions with an osmotic pressure less than that of biological fluids are called *hypotonic solutions*, and those with a larger osmotic pressure are called *hypertonic solutions*.

It is well established that solutions for parenteral use or for ophthalmic and nasal applications should have the same osmoticity with that of body fluid to prevent cell or tissue damage.

Experiments have shown that when erythrocytes were introduced into a hypertonic solution (for example, 5% NaCl solution), osmosis occurred in which water from intracellular space passed through the cell membrane into the saline solution, resulting in a shrinkage of the red blood cells. This process is called *crenation*. In contrast, when erythrocytes were suspended in water, a hypotonic liquid, the extracellular water penetrated the cell membranes into the erythrocytes, producing a swelling effect and cell leakage of hemoglobin. This process is called *hemolysis*. In comparison, solutions such as normal saline solution (0.9% sodium chloride) and the solution of 5% dextrose (D5W), which are iso-osmotic to the body fluids, do not result in cell damage as described above. Hence, they are termed isotonic solutions.

Preparation of Isotonic Solutions

As a liquid drug delivery system, drugs must be prepared in a solution that is isotonic to the body fluid. This requires that a certain tonicity agent be added so that the total osmotic pressure is the same as the body fluid. Sodium chloride and dextrose are typical agents for the formulation of injectable, ophthalmic, and nasal solutions. Other compounds such as sodium acetate and boric acid have also been used as a tonicity agent. As mentioned before, boric acid can cause erythrocyte damage and is therefore not a choice for systemic drug delivery. But in ophthalmic preparations, it has been found that a buffer of alkaline pH is desirable, as most drugs used in ophthalmic preparations are weak acids, and the eye, through flow of tears, can tolerate a greater deviation from physiological pH toward alkalinity (i.e., with less irritation) than toward the acidic range. For these reasons, boric acid and its salt, sodium borate, have been used as tonicity agents for isotonic ophthalmic solutions.

For convenience, rather than actively measuring the colligative properties, a number of isotonic parameters have been defined and measured for various drugs based on the colligative concept. Because these are experimental values, which have already taken account of the solution nonideality, they can be used to calculate the amount of each ingredient needed for isotonic preparations with accuracy. These parameters include the sodium chloride equivalent (E), *freezing point depression of a 1% drug solution* ($D_{1\%}$ or $\Delta T_{f,\,1\%}$), and the *modified freezing point depression constant* L_{iso} at isotonic condition. Still, there are other expressions that aid in the calculation of isotonic requirement. For example, a *volume factor* V, defined as the milliliters of water required per gram of drug used, can also be used to make an isotonic solution. A list of these values for drugs that are included in this chapter is shown in **Table 2-4**. More extensive lists of these values may be found in standard pharmaceutical reference books.[8]

Sodium Chloride Equivalent (E) Method

The most basic guideline for the preparation of an isotonic solution is that an 0.9%, or 9 mg/mL, solution of NaCl is isotonic with body fluids. Both the body fluid and this 0.9% NaCl solution (known as normal saline) produce a freezing point depression of 0.52°C. Thus, in an isotonic preparation using sodium chloride to adjust the tonicity, one can calculate the amount A of NaCl needed in an equal volume of normal saline without the drug and convert the weight of a drug to an equivalent weight of sodium chloride B using the sodium chloride equivalent E value of the drug. The amount of NaCl needed for this preparation can then be determined to be the difference between A and B. The sodium chloride equivalent E is defined as the equivalent weight to sodium chloride from a unit weight of the drug. For example, if a drug has an E value of 0.12, then 1 g of the drug in a solution will contribute to the same osmolality as that of 0.12 g of NaCl. Based on the colligative property, E can be defined as

$$E_{drug} = \frac{(i_{drug})\ (\text{mol wt}_{NaCl})}{(i_{NaCl})\ (\text{mol wt}_{drug})} \qquad (2\text{-}18)$$

Table 2-4 Parameters for Isotonic Preparations[†]

Compound	Mol Wt	E	$D_{1\%}$	L_{iso}
Antipyrine	188.2	0.17	0.10	1.9
Atropine sulfate	694.8	0.13	0.07	5.3
Boric acid	61.8	0.50	0.29	3.5
Calcium chloride ($2H_2O$)	147.0	0.51	0.30	4.4
Chlorobutanol	177.5	0.24	0.14	2.5
Cocaine HCl	339.8	0.16	0.09	3.2
Dextrose anhydrous	180.2	0.18	0.10	
Dextrose ($1H_2O$)	198.2	0.16	0.09	1.9
Ephedrine HCl	201.7	0.30	0.18	3.6
Ephedrine sulfate	428.5	0.23	0.14	5.8
Epinephrine HCl	219.7	0.29	0.17	3.7
Homatropine HBr	356.3	0.17	0.10	3.6
Magnesium sulfate ($7H_2O$)	246.5	0.17	0.10	2.5
Metycaine HCl	292.8	0.20	0.12	3.4
Morphine HCl	375.8	0.15	0.09	3.3
Morphine sulfate	758.8	0.14	0.08	6.2
Naphazoline HCl	246.7	0.27	0.16	3.3
Neostigmine bromide	303.2	0.22	0.11	3.2
Penicillin G potassium	372.5	0.18	0.11	3.9
Phenacaine HCl	352.9	0.20	0.11	3.3
Physostigmine sulfate	648.5	0.13	0.08	5.0
Pilocarpine HCl	244.8	0.24	0.14	
Potassium chloride	74.5	0.76	0.45	3.3
Potassium iodide	166.0	0.34	0.20	3.3
Procaine HCl	272.8	0.21	0.12	3.3
Silver nitrate	169.9	0.33	0.19	3.3
Sodium borate ($10H_2O$)	381.4	0.42	0.25	9.4
Sodium chloride	58.5	1	0.58	3.4
Sodium nitrate	85.0	0.68	0.39	3.4
Tetracaine HCl	300.8	0.18	0.11	3.2
Zinc sulfate ($7H_2O$)	287.6	0.15	0.09	2.5

[†] Data represent values for 1% drug solution, taken from *Remington's Pharmaceutical Sciences*, 15th ed., Easton, PA, Mack Publishing Co., 1975, pp. 1408–1412.

Equation (2-18) is useful for the calculation of the E value based on the molecular weight of the drug and its ionization characteristic. For example, atropine sulfate has a molecular weight of 694.8 and an i value of 3, whereas NaCl has a molecular weight of 58.5 and an i value of 2; the calculated E value for atropine sulfate is thus $3 \times 58.5 / 2 \times 694.8 = 0.13$, which is identical to the observed value.

The calculations involved in the sodium chloride equivalent method can be summarized in simple steps as follows:

1. Determine the amount of NaCl in normal saline in a volume equal to that of the prescription order.

   $A = 9\,\text{mg/mL} \times \text{volume of Rx}$

2. Calculate the equivalent weights to NaCl *B* for all drug ingredients.

B = mg of drug × E_{drug}

Repeat the calculation for all drugs and express the values as B_1, B_2, ...

3. Calculate amount of NaCl needed for the prescription order *C*.

$C = A - B_1 - B_2 - \ldots .$

Example 2-12: Calculate the amount of NaCl needed to fill the following Rx.

Rx Zinc sulfate 120 mg (E = 0.16)
Antipyrine 650 mg (E = 0.17)
NaCl qs
Distilled water qsad 60 mL
Sig: Isotonic solution for right eye, bid

Solution: The total volume of Rx is 60 mL. Thus,

$A = 9.0 \times 60 = 540.0$ mg
For zinc sulfate: $B_1 = 120 \times 0.16 = 19.2$ mg
For antipyrine: $B_2 = 650 \times 0.17 = 110.5$ mg

Amount of NaCl needed:

$C = A - B_1 - B_2 = 540.0 - 19.2 - 110.5 = 410.3$ mg

Answer: The amount of NaCl needed for this prescription is 410.3 mg.

As an important reminder, because the amount of NaCl in *A* is expressed in milligrams, all weights in subsequent calculations must also be in milligrams. A prescription may be written in different ways so that additional calculations may be required to arrive at the correct answer. Calculations involved in the use of an alternative tonicity agent based on the sodium chloride equivalent method are illustrated in Example 2-13. Here, the amount of the alternative agent *D* is calculated as the value of the amount of NaCl that would be needed, divided by the *E* value of the alternative tonicity agent.

Example 2-13: Show how you would prepare the following prescription.

Rx	Chlorobutanol	0.5%†	(E = 0.18)
	Ephedrine HCl	1.0%	(E = 0.29)
	Dextrose qs		(E = 0.16)
	Distilled water qs	50 mL	
	Mft: Isotonic solution		
	Sig: As nose drops, u.d.		

Solution: Amount of NaCl in equal volume of normal saline is

$A = 9\,\text{mg/mL} \times 50\,\text{mL} = 450\,\text{mg}$

Equivalent weight from drugs:

$B_1 = 250\,\text{mg} \times 0.18 = 45\,\text{mg}$

$B_2 = 500\,\text{mg} \times 0.29 = 145\,\text{mg}$

Amount of NaCl that would be needed:

$C = 450 - 45 - 145 = 260\,\text{mg}$

Amount of dextrose (alternative tonicity agent) needed:

$D = 260\,\text{mg} / 0.16 = 1625\,\text{mg}$

Answer: Weigh out 250 mg of chlorobutanol, 500 mg of ephedrine HCl, and 1625 mg of dextrose; dissolve the ingredients in distilled water, and qs to 50 mL.

[†]0.5% or 1% in 50 mL gives a drug weight of 0.25 or 0.5 g, or 250 or 500 mg, respectively.

Often the preparation of an isotonic solution is made by using an isotonic (may be buffered) vehicle. Calculations involved in the use of an isotonic vehicle are shown in Example 2-14.

Example 2-14: How would you prepare the following prescriptions?

Rx 1	Procaine hydrochloride	0.25 g	($E = 0.22$)
	Purified water qs	50 mL	
	Mft: Isotonic with sodium chloride		
Rx 2	Procaine hydrochloride	0.25 g	($E = 0.22$)
	Sterile saline (0.9%) qs		
	Purified water qsad	50 mL	
	Mft: Isotonic solution		

Solution: For Rx 1,

Amount of NaCl needed $= 9 \times 50 - 250 \times 0.22$

$= 395\,\text{mg}$

For Rx 2, the amount of NaCl needed is the same as in Rx 1, but must be supplied by the normal saline solution. The volume of normal saline (NS) that contains 395 mg of NaCl is

$V_{NS} = 395\,\text{mg} / (9\,\text{mg/mL}) = 43.89\,\text{mL}$

Thus, to prepare Rx 2, dissolve 0.25 g of procaine HCl in 43.89 mL of normal saline and add purified water to 50 mL.

The $D_{1\%}$ Method

$D_{1\%}$ is the same expression as $\Delta T_{f,\,1\%}$ in other textbooks, which represents the freezing point depression caused by a drug when the solution strength is 1% wt/v. This value, when divided by K_f, gives the osmolality or osmolarity of a 1% drug solution. It will be recalled that for dilute solutions, the difference between osmolality and osmolarity is small, and they may be used interchangeably for isotonic

preparations. The requirement for an isotonic solution is to exhibit a freezing point depression of 0.52°C. Thus, using D to express the freezing point depression, one can see that in the final prepared solution

$$D_{\text{tonicity agent}} = 0.52°\text{C} - D_{\text{drug1}} - D_{\text{drug2}} - \cdots$$

The freezing point depression of a drug at a prescribed strength can be determined from the $D_{1\%}$ value using the following relationship:

$$D_{\text{drug}} = \frac{D_{1\%} \times \text{wt of drug (g)} \times 100}{V_{\text{Rx}}}$$

If more than one drug is present in the solution, repeat calculations are needed for all drugs. With these values, the freezing point depression to be made up by the tonicity agent can then be determined. Using sodium chloride as the tonicity agent, it can be seen that the amount of NaCl needed is

$$\text{Wt}_{\text{NaCl}} = \frac{D_{\text{tonicity agent}}}{0.52} \times 9\,\text{mg/mL} \times V_{\text{Rx}} \qquad (2\text{-}19)$$

In Equation (2-19), the calculated weight of NaCl has a unit of milligrams. The use of the $D_{1\%}$ value in isotonic preparation is shown in Example 2-15.

Example 2-15: Calculate the amount of sodium chloride needed to make 60 mL of an isotonic solution containing 0.3 g of atropine sulfate ($D_{1\%} = 0.075°$C).

Solution: $D_{\text{drug}} = 0.075 \times 0.3 \times 100 / 60 = 0.0375°$

$D_{\text{NaCl}} = 0.52 - 0.0375 = 0.4825°$

$\text{Wt}_{\text{NaCl}} = 0.4825 \times 9 \times 60 / 0.52 = 501.1\,\text{mg}$

The $D_{1\%}$ value can also be used to determine the volume of water needed to make an isotonic solution containing a given weight of the drug, when an isotonic vehicle is used. It is readily seen from the definition of $D_{1\%}$ that the percentage strength of a drug that is isotonic is equal to the value of $0.52°/D_{1\%}$. The volume of water required to make this percentage strength can thus be calculated using the following relationship:

$$V_{\text{water}} = \frac{D_{1\%} \times \text{wt of drug (g)}}{0.52} \times 100$$

The above equation is very useful in the preparation of solutions using a buffered isotonic vehicle, as Example 2-16 indicates.

Example 2-16: How would you prepare the following prescription?

Rx	Atropine sulfate	0.3 g	($D_{1\%} = 0.075°$)
	Sterile preserved water qs	60 mL	
	Mft: Isotonic with Sørensen's isotonic buffer (pH 6.8)		
	Sig: u.d.		

Solution: % of drug solution that is isotonic = (0.52 / 0.075)%

= 6.93%

Sterile preserved water needed: $V_{water} = 0.3 \times 100 / 6.93 = 4.33$ mL

Answer: Weigh out 0.3 g of atropine sulfate, dissolve the drug in 4.33 mL of sterile preserved water, and qs to 60 mL with buffered isotonic vehicle.

The L_{iso} Method

The quantity of L_{iso} is defined as the value of iK_f when the molar or molal concentration of a drug produces a freezing point depression of 0.52°C. For example, the 0.9% solution of NaCl is isotonic with body fluids and has a molar concentration of 0.154 *M*. Using the freezing point depression equation shown in Table 2-3,

$$L_{iso} = 0.52 / 0.154 = 3.38$$

Because L_{iso} is an experimental value, it measures the nonideality or the effective *i* value of a strong electrolyte or the partial ionization of a weak electrolyte at a concentration that is isotonic with the body fluid. For nonelectrolytes, L_{iso} is approximately the same as K_f. In isotonic preparations, the L_{iso} value is used to determine the freezing point depression of the drug using Equation (2-20). As can be seen, this equation allows the determination of freezing point depression based on the molal concentration of the drug, without having to consider the van't Hoff *i* factor.

$$\Delta T_f = L_{iso}\, m \qquad (2\text{-}20)$$

The adjustment of tonicity using a tonicity agent can then be calculated using the same equation for the tonicity agent, or using the method described in the $D_{1\%}$ method, as illustrated in Example 2-17.

Example 2-17: Calculate the amount of NaCl needed to prepare the following order.

		L_{iso}	mol wt
Procaine hydrochloride	1%	3.4	272.8
Make isotonic with NaCl		3.4	58.5
Sterile water qs	500 mL		

Solution: The freezing point depression of the 1% procaine HCl is

$$\Delta T_{f,\,drug} = 3.4 \times 1 \times 1000 / 272.8 \times 100 = 0.125°C$$

$$D_{NaCl} = 0.52 - 0.125 = 0.395°C$$

Equation (2-20) can also be used to determine the concentration of NaCl needed by letting

$$\Delta T_{f,\,NaCl} = L_{iso} M_{NaCl}$$

Thus, $M = 0.395 / 3.4 = 0.1162\,M$.

$$Wt_{NaCl} = 0.1162 \times 58.5 \times 500 / 1000 = 3.40\,g$$

Alternatively, the amount of NaCl needed can be determined using Equation (2-19):

$$Wt_{NaCl} = \frac{D_{NaCl}}{0.52} \times 9\,mg/mL \times V_{Rx}$$

$$= 0.395 \times 9 \times 500 / 0.52 = 3418\,mg \text{ or } 3.42\,g$$

Now we can answer the questions posed at the beginning of this chapter. The active ingredient of the sterile eyedrops, tetrahydrozoline HCl, is a topical ocular vasoconstrictor used to alleviate local swelling and congestion. Ophthalmic solutions contain preservatives (such as benzalkonium chloride and edetate disodium) to prevent contaminations from microorganisms, and they are buffered isotonic solutions. The boric acid–sodium borate system is to provide a buffered solution with alkaline pH, which has been shown to cause little or no pain or damage to the ocular system. Studies have shown that the strength of a buffer solution, i.e., the buffer capacity, plays an important role in the preparation of ophthalmic solutions. Although the pH and buffer phenomena will be discussed later, it is clear that at relatively low buffer capacity, the eyedrops can be easily neutralized to physiological pH by the lacrimal fluid and are therefore more compatible with the ocular system. A possible formulation of the eyedrop is given in Example 2-18. Here, the quantities of boric acid and sodium borate are chosen to yield a pH 9 solution with a buffer capacity of about 0.01, which is well below the buffer capacity of the physiological fluids (~0.028 – 0.031) such as the lacrimal fluid. This solution is made isotonic using sodium chloride as the tonicity agent.

Example 2-18: Determine the amount of sodium chloride needed for the preparation of the following isotonic solution.

Tetrahydrozoline HCl	0.05%	$E = 0.22$
Benzalkonium chloride	0.01%	$E = 0.16$
Edetate disodium	0.1%	$E = 0.23$
Boric acid	0.05 g	$E = 0.50$
Sodium borate ($Na_2B_4O_7 \cdot 10H_2O$)	0.40 g	$E = 0.42$
NaCl gs		
Purified water qsad	100 mL	

Solution: Based on the sodium chloride equivalent method,
Sodium chloride equivalent weight from drugs

$$= 50 \times 0.22 + 10 \times 0.16 + 100 \times 0.23 + 50 \times 0.50 + 400 \times 0.42$$

$$= 228.6\,mg$$

Amount of NaCl needed = $9 \times 100 - 228.6 = 671.4$ mg

IV. Chapter Summary

This chapter presents the concept of using iso-osmoticity in pharmaceutical preparations to prevent cell and tissue damage caused by drug delivery alone. However, not all pharmaceutical solutions are iso-osmotic with the biological fluid, as many solutions for infusion are, out of necessity, hypertonic. Such solutions must be delivered via alternative routes to overcome the

adverse osmotic effects. Osmoticity may also play a role in oral drug delivery. Oral medicines that exhibit high osmolalities due to mixed use of drugs or undiluted calcium lactate solution have been shown to cause necrotizing enterocolitis in neonatal patients. This chapter has also provided an overview of the pharmaceutical dosage forms with emphasis on solutions. The expected learning outcomes for this chapter are to understand the physical chemical theories of the colligative properties from which the iso-osmoticity concept is derived and to use the methods of the colligative properties to determine accurately the contents of an isotonic solution.

V. References

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VI. Homework Problems

1. What is the concentration in milliosmoles per liter of $MgSO_4 \cdot 7H_2O$ (mol wt = 246.47) in a solution containing 65 g of the drug per liter of solution?
2. What is the vapor pressure at 100°C of a solution containing 1.68 g of sucrose (mol wt = 342.30) and 15.6 g of water (mol wt = 18.02)?
3. The freezing point lowering of a solution containing 1.00 g of an unknown drug and 100 g of water is 0.573°C at 25°C. (*a*) What is the molecular weight of this drug? (*b*) What is the boiling point of the solution? (*c*) What is the osmotic pressure of the solution?
4. A solution containing 0.2223 g of benzanthine penicillin G in 1000 g of benzene has a freezing point of 0.00124° below that of the pure solvent (5.5°C). What is the molecular weight of this drug? The K_f of benzene = 5.10 deg-kg/mol.
5. (*a*) Calculate the freezing point depression of 1 g of methylcellulose (mol wt of 26,000 g/mol) dissolved in 100 g of water. (*b*) Compute the osmotic pressure of this solution at 20°C. Express the result in millimeters of solution. The density of mercury at 20°C is 13.5462 g/mL; the density of the solution is 1 g/mL.
6. Compute the freezing point depression of a solution containing 0.20% wt/v glucose (mol wt of 180) and 0.5% NaCl (mol wt of 58.5).
7. The freezing point of blood is –0.52°C. (*a*) What is the osmotic pressure of blood at 25°C? (*b*) What is the vapor pressure lowering of blood at this temperature? The vapor pressure of pure water at 25°C is 23.82 mmHg.
8. A solution of sucrose with a concentration of 1.0 *m* (molality) has a measured osmotic pressure of 24.8 atm at 0°C. What is the van't Hoff *i* factor for sucrose at this concentration?
9. The ΔT_f of a solution containing 4.00 g of methapyrilene HCl (mol wt = 297.85) in 100 mL of solution was 0.423. What is the van't Hoff *i* factor?
10. The vapor pressure of water at 25°C is 23.8 torr (mmHg). Compute the lowering of the vapor pressure of water when 25 g of $CaCl_2$ (mol wt = 111 g/mol) is added to 100 g of water.

11. The *E* value for $MgSO_4 \cdot 7H_2O$ is 0.17. What is the *E* value for the anhydrous salt?
For Problems 12–15, use the *E* values from Table 2-4.

12. How many milligrams of NaCl are needed to fill the following prescriptions?

Rx 1: Ephedrine sulfate 260 mg
NaCl qs
Distilled water qsad 30 mL
Mft: Isotonic
Sig: Use as directed

Rx 2: Procaine HCl 1%
NaCl qs
Distilled water qsad 100 mL
Mft: Isotonic

13. How many grams of boric acid are needed to fill the following prescription?

Rx Atropine sulfate 1%
Distilled water qsad 30 mL
Mft: Isotonic with boric acid
Sig: gtts. iv o.d.

14. Calculate the amount of dextrose anhydrous needed to fill the following prescription.

Rx Tetracaine HCl 1%
Dextrose anhydrous qs
Distilled water qsad 60 mL
Mft: Isotonic solution
Sig: gtts iv in each nostril qid

15. How would you prepare the following prescription?

Rx Ephedrine HCl 1.0%
Chlorobutanol 0.5%
D50W qs
Distilled water qsad 30 mL
Mft: Isotonic
Sig: Use as nose drops, u.d.

16. Calculate the amount of distilled water needed and explain how you would fill this prescription. (The 1.9% boric acid is an isotonic vehicle.)

Rx Epinephrine HCl 0.5% ($D_{1\%} = 0.16°$)
$ZnSO_4$ 0.3% ($D_{1\%} = 0.0086°$)
Distilled water qs
Boric acid, 1.9% qsad 30 mL
Mft: Isotonic solution

17. How many grams of sodium nitrate are needed to make 100 mL of an isotonic solution of silver nitrate with a strength of 1:1000?

18. The 1% boric acid has a freezing point depression of 0.29°C. How many milligrams of NaCl are needed to make 100 mL of a 1% boric acid isotonic solution?

19. (*a*) Using the L_{iso}, *E*, and the $D_{1\%}$ methods, calculate the amount of sodium chloride or boric acid needed to fill the following prescriptions.

(*a*)

Rx 1	L_{iso}	**Mol Wt**	***E***	$D_{1\%}$, °C
Ephedrine HCl 0.5 g	3.4	201.7	0.30	0.17
Purified water qs 100 mL				
NaCl qs to make isotonic	3.4	58.5		0.58

(*b*)

Rx 2	L_{iso}	**Mol Wt**	***E***	$D_{1\%}$, °C
Ephedrine sulfate 0.5 g	4.3	428.5	0.23	0.11
NaCl qs	3.4	58.5		0.58
Purified water qsad 50 mL				
Make isotonic solution				

(c)

Rx 3	L_{iso}	**Mol Wt**	***E***	$D_{1\%}$, °C
Epinephrine HCl 1%	3.4	219.7	0.29	0.17
Scopolamine HBr 0.5%	3.4	438.3	0.12	0.07
NaCl qs	3.4	58.5	0.58	
Purified water qsad 60 mL				
Make isotonic				

(*d*)

Rx 4	***E***	$D_{1\%}$, C
Tetracaine HCl 0.1 g	0.18	0.11
Zinc sulfate 0.05 g	0.15	0.086
Boric acid qs	0.52	0.29
Purified water qsad 30 mL		