8

Buffered and Isotonic Solutions

Buffers are compounds or mixtures of compounds that, by their presence in solution, resist changes in pH upon the addition of small quantities of acid or alkali. The resistance to a change in pH is known as *buffer action.* According to Roos and Borm,[1] Koppel and Spiro published the first paper on buffer action in 1914 and suggested a number of applications, which were later elaborated by Van Slyke.[2]

If, to water or a solution of sodium chloride, a small amount of a strong acid or base is added, the pH is altered considerably; such systems have no buffer action.

A combination of a weak acid and its conjugate base (i.e., its salt), or a weak base and its conjugate acid act as buffers. If 1 mL of a 0.1-*N* HCl solution is added to 100 mL of pure water, the pH is reduced from 7 to 3. If the strong acid is added to a 0.01-*M* solution containing equal quantities of acetic acid and sodium acetate, the pH is changed only 0.09 pH units, because the base Ac^- ties up the hydrogen ions according to the reaction

$$Ac^- + H_3O^+ \rightleftharpoons HAc + H_2O \tag{8-1}$$

If a strong base, sodium hydroxide, is added to the buffer mixture, acetic acid neutralizes the hydroxyl ions as follows:

$$HAc + OH^- \rightleftharpoons H_2O + Ac^- \tag{8-2}$$

THE BUFFER EQUATION

Common Ion Effect and the Buffer Equation for a Weak Acid and Its Salt. The pH of a buffer solution and the change in pH upon the addition of an acid or base may be calculated by use of the *buffer equation.* This expression is developed by considering the effect of a salt on the ionization of a weak acid when the salt and the acid have an ion in common.

For example, when sodium acetate is added to acetic acid, the dissociation constant for the weak acid,

$$K_a = \frac{[H_3O^+][Ac^-]}{[HAc]} = 1.75 \times 10^{-5} \tag{8-3}$$

is momentarily disturbed since the acetate ion supplied by the salt increases the $[Ac^-]$ term in the numerator. To reestablish the constant K_a at 1.75×10^{-5}, the hydrogen ion term in the numerator $[H_3O^+]$ is instantaneously decreased, with a corresponding increase in [HAc]. Therefore, the constant K_a remains unaltered, and the equilibrium is shifted in the direction of the reactants. Consequently, the ionization of acetic acid,

$$HAc + H_2O \rightleftharpoons H_3O^+ + Ac^- \tag{8-4}$$

is *repressed* upon the addition of the common ion $[Ac^-]$. This is an example of the *common ion effect.* The pH of the final solution is obtained by rearranging the equilibrium expression for acetic acid:

$$[H_3O^+] = K_a \frac{[HAc]}{[Ac^-]} \tag{8-5}$$

If the acid is weak and ionizes only slightly, the expression [HAc] may be considered to represent the total concentration of acid, and it is written simply as [acid]. In the slightly ionized acidic solution, the acetate concentration $[Ac^-]$ may be considered as having come entirely from the salt, sodium acetate. Since 1 mole of sodium acetate yields 1 mole of acetate ion, $[Ac^-]$ is equal to the total salt concentration and is replaced by the term [salt]. Hence, equation (8-5) is written,

$$[H_3O^+] = K_a \frac{[acid]}{[salt]} \tag{8-6}$$

Equation (8–6) may be expressed in logarithmic form, with the signs reversed, as

$$-\log [H_3O^+] = -\log K_a - \log [\text{acid}] + \log [\text{salt}] \quad (8-7)$$

from which is obtained an expression, known as the *buffer equation* or the *Henderson–Hasselbalch equation*, for a weak acid and its salt:

$$pH = pK_a + \log \frac{[\text{salt}]}{[\text{acid}]} \quad (8-8)$$

The ratio [acid]/[salt] in equation (8–6) has been inverted by undergoing the logarithmic operations in (8–7) and it appears in (8–8) as [salt]/[acid]. pK_a, the negative logarithm of K_a, is called the *dissociation exponent* (p. 152).

The buffer equation is important in the preparation of buffered pharmaceutical solutions; it is satisfactory for calculations within the pH range of 4 to 10.

Example 8–1. What is the pH of 0.1-*M* acetic acid solution, pK_a = 4.76? What is the pH after enough sodium acetate has been added to make the solution 0.1 *M* with respect to this salt?

The pH of the acetic acid solution is calculated by use of the logarithmic form of equation (7–99) on p. 155.

$$pH = \tfrac{1}{2}pK_a - \tfrac{1}{2}\log c$$

$$pH = 2.38 + 0.50 = 2.88$$

The pH of the buffer solution containing acetic acid and sodium acetate is determined by use of the buffer equation (8–8):

$$pH = 4.76 + \log \frac{0.1}{0.1} = 4.76$$

It is seen from *Example 8–1* that the pH of the acetic acid solution has been *increased* almost 2 pH units; that is, the acidity has been *reduced* to about one hundredth of its original value by the addition of an equal concentration of a salt with a common ion. This example bears out the statement regarding the repression of ionization upon the addition of a common ion.

Sometimes it is desired to know the ratio of salt to acid in order to prepare a buffer of a definite pH. *Example 8–2* demonstrates the calculation involved in such a problem.

Example 8–2. What is the molar ratio, [salt]/[acid], required to prepare an acetate buffer of pH 5.0? Also express the result in mole percent.

$$5.0 = 4.76 + \log \frac{[\text{salt}]}{[\text{acid}]}$$

$$\log \frac{[\text{salt}]}{[\text{acid}]} = 5.0 - 4.76 = 0.24$$

$$\frac{[\text{salt}]}{[\text{acid}]} = \text{antilog } 0.24 = 1.74$$

Therefore, the mole ratio of salt to acid is 1.74/1. Mole percent is mole fraction multiplied by 100. The mole fraction of salt in the salt–acid mixture is 1.74/(1 + 1.74) = 0.635, and in mole percent, the result is 63.5%.

The Buffer Equation for a Weak Base and Its Salt. Buffer solutions are not ordinarily prepared from weak bases and their salts because of the volatility and instability of the bases and because of the dependence of their pH on pK_w, which is often affected by temperature changes. Pharmaceutical solutions—for example, a solution of ephedrine base and ephedrine hydrochloride—however, often contain combinations of weak bases and their salts.

The buffer equation for solutions of weak bases and the corresponding salts may be derived in a manner analogous to that for the weak acid buffers. Accordingly,

$$[OH^-] = K_b \frac{[\text{base}]}{[\text{salt}]} \quad (8-9)$$

and using the relationship, $[OH^-] = K_w/[H_3O^+]$, the buffer equation becomes

$$pH = pK_w - pK_b + \log \frac{[\text{base}]}{[\text{salt}]} \quad (8-10)$$

Example 8–3. What is the pH of a solution containing 0.10 mole of ephedrine and 0.01 mole of ephedrine hydrochloride per liter of solution? The pK_b of ephedrine is 4.64.

$$pH = 14.00 - 4.64 + \log \frac{0.10}{0.01}$$

$$pH = 9.36 + \log 10 = 10.36$$

Activity Coefficients and the Buffer Equation. A more exact treatment of buffers begins with the replacement of concentrations by activities in the equilibrium of a weak acid:

$$K_a = \frac{a_{H_3O^+} a_{Ac^-}}{a_{HAc}} = \frac{(\gamma_{H_3O^+} c_{H_3O^+}) \times (\gamma_{Ac^-} c_{Ac^-})}{\gamma_{HAc} c_{HAc}} \quad (8-11)$$

The activity of each species is written as the activity coefficient multiplied by the molar concentration. The activity coefficient of the undissociated acid γ_{HAc} is essentially 1 and may be dropped. Solving for the hydrogen ion activity and pH, defined as $-\log a_{H_3O^+}$, yields the equations

$$a_{H_3O^+} = \gamma_{H_3O^+} \times c_{H_3O^+} = K_a \frac{c_{HAc}}{\gamma_{Ac^-} c_{Ac^-}} \quad (8-12)$$

$$pH = pK_a + \log \frac{[\text{salt}]}{[\text{acid}]} + \log \gamma_{Ac^-} \quad (8-13)$$

From the Debye–Hückel expression (equation (6–59), p. 136) for an aqueous solution of a univalent ion at 25° C having an ionic strength not greater than about 0.1 or 0.2, we write

$$\log \gamma_{Ac^-} = \frac{-0.5\sqrt{\mu}}{1 + \sqrt{\mu}}$$

and equation (8–13) then becomes

$$pH = pK_a + \log \frac{[\text{salt}]}{[\text{acid}]} - \frac{0.5\sqrt{\mu}}{1 + \sqrt{\mu}} \quad (8-14)$$

The general equation for buffers of polybasic acids is

$$pH = pK_n + \log \frac{[\text{salt}]}{[\text{acid}]} - \frac{A(2n - 1)\sqrt{\mu}}{1 + \sqrt{\mu}} \quad (8-15)$$

in which n is the stage of the ionization. (See *Problem 8–3*, p. 187).

Example 8–4. A buffer contains 0.05 mole per liter of formic acid and 0.10 mole per liter of sodium formate. The pK_a of formic acid is 3.75. The ionic strength of the solution is 0.10. Compute the pH (*a*) with and (*b*) without consideration of the activity coefficient correction.

(*a*)

$$\text{pH} = 3.75 + \log \frac{0.10}{0.05} - \frac{0.5\sqrt{0.10}}{1 + \sqrt{0.10}}$$
$$= 3.93$$

(*b*)

$$\text{pH} = 3.75 + \log \frac{0.10}{0.05} = 4.05$$

Some Factors Influencing the pH of Buffer Solutions. The addition of neutral salts to buffers changes the pH of the solution by altering the ionic strength, as shown in equation (8–13). Changes in ionic strength and hence in the pH of a buffer solution may also be brought about by dilution. The addition of water in moderate amounts, while not changing the pH, may cause a small positive or negative deviation because it alters activity coefficients and because water itself can act as a weak acid or base. Bates[3a] has expressed this quantitatively in terms of a *dilution value*, which is the change in pH on diluting the buffer solution to one half its original strength. Some dilution values for National Bureau of Standards buffers are found in Table 9–2, p. 199. A positive dilution value signifies that the pH rises with dilution, and a negative value signifies that the pH decreases with dilution of the buffer.

Temperature also influences buffers. Kolthoff and Tekelenburg[4] determined the *temperature coefficient of* pH, that is, the change in pH with temperature, for a large number of buffers. The pH of acetate buffers was found to increase with temperature, whereas the pH of boric acid–sodium borate buffers decreased with temperature. Although the temperature coefficient of acid buffers was relatively small, the pH of most basic buffers was found to change more markedly with temperature, owing to K_w, which appears in the equation of basic buffers and which changes significantly with temperature. Bates[3] refers to several basic buffers that show only a small change of pH with temperature and can be used in the pH range of 7 to 9. The temperature coefficients for the calomel electrode are given in Bates,[3b] Table 10–10.

Drugs as Buffers. It is important to recognize that solutions of drugs that are weak electrolytes also manifest buffer action. Salicylic acid solution in a soft glass bottle is influenced by the alkalinity of the glass. It might be thought at first that the reaction would result in an appreciable increase in pH; however, the sodium ions of the soft glass combine with the salicylate ions to form sodium salicylate. Thus, there arises a solution of salicylic acid and sodium salicylate—a buffer solution that resists the change in pH. Similarly, a solution of ephedrine base manifests a natural buffer protection against reductions in pH. Should hydrochloric acid be added to the solution, ephedrine hydrochloride is formed, and the buffer system—ephedrine plus ephedrine hydrochloride—will resist large changes in pH until the ephedrine is depleted by reaction with the acid. Therefore, a drug in solution may often act as its own buffer over a definite pH range. Such buffer action, however, is often too weak to counteract pH changes brought about by the carbon dioxide of the air and the alkalinity of the bottle. Additional buffers are therefore frequently added to drug solutions to maintain the system within a certain pH range. A quantitative measure of the efficiency or capacity of a buffer to resist pH changes will be discussed in a later section.

pH Indicators. Indicators may be considered as weak acids or weak bases that act like buffers and also exhibit color changes as their degree of dissociation varies with pH. For example, methyl red shows its full alkaline color, yellow, at a pH of about 6 and its full acid color, red, at about pH 4. Indicators therefore offer a convenient alternative method to electrometric techniques (Chapter 9) for determining the pH of a solution.

The dissociation of an acid indicator is given here in simplified form:

$$\underset{\substack{\text{Acid}_1 \\ \text{(acid color)}}}{\text{HIn}} + \underset{\text{Base}_2}{H_2O} \rightleftharpoons \underset{\text{Acid}_2}{H_3O^+} + \underset{\substack{\text{Base}_1 \\ \text{(alkaline color)}}}{\text{In}^-} \qquad (8\text{–}16)$$

The equilibrium expression is

$$\frac{[H_3O^+][\text{In}^-]}{[\text{HIn}]} = K_{\text{In}} \qquad (8\text{–}17)$$

HIn is the un-ionized form of the indicator, which gives the acid color, and In^- is the ionized form, which produces the basic color. K_{In} is referred to as the *indicator constant*. If an acid is added to a solution of the indicator, the hydrogen ion concentration term on the right-hand side of equation (8–16) is increased, and the ionization is repressed by the common ion effect. The indicator is then predominantly in the form of HIn, the acid color. If base is added, $[H_3O^+]$ is reduced by reaction of the acid with the base, reaction (8–16) proceeds to the right, yielding more ionized indicator In^-, and the base color predominates. Thus, the color of an indicator is a function of the pH of the solution. A number of indicators with their useful pH ranges are listed in Table 8–1.

The equilibrium expression (8–16) may be treated in a manner similar to that for a buffer consisting of a weak acid and its salt or conjugate base. Hence

$$[H_3O^+] = K_{\text{In}} \frac{[\text{HIn}]}{[\text{In}^-]} \qquad (8\text{–}18)$$

and since [HIn] represents the acid color of the indicator and the conjugate base $[\text{In}^-]$ represents the

TABLE 8–1. *Color, pH and pK_{In}, the Indicator Constant, of Some Common Indicators*

Indicator	Color: Acid	Color: Base	pH Range	pK_{In}
Thymol blue (acid range)	red	yellow	1.2– 2.8	1.5
Methyl violet	blue	violet	1.5– 3.2	—
Methyl orange	red	yellow	3.1– 4.4	3.7
Bromcresol green	yellow	blue	3.8– 5.4	4.7
Methyl red	red	yellow	4.2– 6.2	5.1
Bromcresol purple	yellow	purple	5.2– 6.8	6.3
Bromthymol blue	yellow	blue	6.0– 7.6	7.0
Phenol red	yellow	red	6.8– 8.4	7.9
Cresol red	yellow	red	7.2– 8.8	8.3
Thymol blue (alkaline range)	yellow	blue	8.0– 9.6	8.9
Phenolphthalein	colorless	red	8.3–10.0	9.4
Alizarin yellow	yellow	lilac	10.0–12.0	—
Indigo carmine	blue	yellow	11.6–14	—

basic color, these terms may be replaced by the concentration expressions, [acid] and [base]. The formula for pH as derived from equation (8–18) becomes

$$pH = pK_{In} + \log \frac{[\text{base}]}{[\text{acid}]} \qquad (8\text{–}19)$$

Example 8–5.* An indicator, methyl red, is present in its ionic form In^-, in a concentration of 3.20×10^{-3} M and in its molecular form, *HIn*, in an aqueous solution at 25° C in a concentration of 6.78×10^{-3} M. From Table 8–1 we observe a pK_{In} of 5.1 for methyl red. What is the pH of this solution?

$$pH = 5.1 + \log \frac{3.20 \times 10^{-3}}{6.78 \times 10^{-3}} = 4.77$$

Just as a buffer shows its greatest efficiency when $pH = pK_a$, an indicator exhibits its *middle tint* when [base]/[acid] = 1 and $pH = pK_{In}$. The most efficient indicator range, corresponding to the effective buffer interval, is about 2 pH units, that is, $pK_{In} \pm 1$. The reason for the width of this color range may be explained as follows. It is known from experience that one cannot discern a change from the acid color to the salt or conjugate base color until the ratio of [base] to [acid] is about 1 to 10. That is, there must be at least 1 part of the basic color to 10 parts of the acid color before the eye can discern a change in color from acid to alkaline. The pH value at which this change is perceived is given by the equation

$$pH = pK_{In} + \log \frac{1}{10} = pK_{In} - 1 \qquad (8\text{–}20)$$

Conversely, the eye cannot discern a change from the alkaline to the acid color until the ratio of [base] to [acid] is about 10 to 1, or

$$pH = pK_{In} + \log \frac{10}{1} = pK_{In} + 1 \qquad (8\text{–}21)$$

Therefore, when base is added to a solution of a buffer in its acid form, the eye first visualizes a change in color at $pK_{In} - 1$, and the color ceases to change any further at $pK_{In} + 1$. The effective range of the indicator between its full acid and full basic color may thus be expressed as

$$pH = pK_{In} \pm 1 \qquad (8\text{–}22)$$

As buffers may be mixed to cover a wide pH range, so also can several indicators be combined to yield so-called *universal indicators*. The *Merck Index* suggests one such universal indicator consisting of a mixture of methyl yellow, methyl red, bromthymol blue, thymol blue, and phenolphthalein, which covers the range from pH 1 to 11.

The colorimetric method for the determination of pH is probably less accurate and less convenient but also less expensive than the electrometric method. It may be used in the determination of the pH of aqueous solutions that are not colored or turbid, and it is particularly useful for the study of acid–base reactions in nonaqueous solutions. The details of the method are given in the treatise of Kolthoff and Rosenblum.[5] Wyss[6] has discussed the determination of the pH of solutions in the prescription laboratory. In general, the colorimetric determination of pH involves the following steps.

(*a*) Determine the approximate pH of the solution by the addition of several drops of a universal indicator. Wide-range pH papers, prepared by applying a universal indicator solution to paper strips, may be used.

(*b*) A series of Clark–Lubs buffer solutions as modified by Bower and Bates,[7] differing by 0.2 pH unit and within the pH range of the unknown solution, are chosen. Several drops of an indicator solution, having a pK_{In} approximately equal to the pH of the unknown solution so that it changes color within the pH range

*In dealing with indicators, one is concerned only with the color changes and not with the concentrations of the colored species of the indicator. Example (8–5) simply shows that if the concentrations of the colored species were known, the same equation could be used in principle for indicator solutions as for buffer systems to calculate the pH of a solution.

under consideration, are added to each buffer sample and to the unknown solution contained in suitable test tubes.

(*c*) The colors of the buffers of known pH are matched with the color of the unknown solution; accordingly, the pH of the unknown solution can be determined to within 0.1 pH unit.

Narrow-range pH papers may be used in the same way as the indicator solution by comparing the color when a drop of buffer and a drop of the unknown solution are applied to adjacent strips.

Goyan and Coutsouris[8] concluded that it was possible to cover the pH range from 4 to 8 by the use of only three indicators, bromcresol green, bromthymol blue, and thymol blue. For details of this method, refer to the original article.

A final note of caution should be added regarding the colorimetric method. Since indicators themselves are acids (or bases), their addition to unbuffered solutions whose pH is to be determined will change the pH of the solution. The colorimetric method is therefore not applicable to the determination of the pH of sodium chloride solution or similar unbuffered pharmaceutical preparations unless special precautions are taken in the measurement. Some medicinal solutions and pharmaceutical vehicles, however, to which no buffers have been added, are buffered by the presence of the drug itself (p. 171) and can withstand the addition of an indicator without a significant change in pH. Errors in the result may also be introduced by the presence of salts and proteins, and these errors must be determined for each indicator over the range involved.

BUFFER CAPACITY

Thus far it has been stated that a buffer counteracts the change in pH of a solution upon the addition of a strong acid, a strong base, or other agents that tend to alter the hydrogen ion concentration. Furthermore, it has been shown in a rather qualitative manner how this buffer action is manifested by combinations of weak acids and weak bases together with their salts. The resistance to changes of pH now remains to be discussed in a more quantitative way.

The magnitude of the resistance of a buffer to pH changes is referred to as the buffer capacity β. It is also known as *buffer efficiency*, *buffer index*, and *buffer value*. Koppel and Spiro[1] and Van Slyke[2] introduced the concept of buffer capacity and defined it as the ratio of the increment of strong base (or acid) to the small change in pH brought about by this addition. For the present discussion, the approximate formula,

$$\beta = \frac{\Delta B}{\Delta \text{pH}} \qquad (8\text{–}23)$$

may be used, in which delta, Δ, has its usual meaning, a *finite change*, and ΔB is the small increment in gram equivalents per liter of strong base added to the buffer solution to produce a pH change of ΔpH. According to equation (8–23), the buffer capacity of a solution has a value of 1 when the addition of 1 gram Eq of strong base (or acid) to 1 liter of the buffer solution results in a change of 1 pH unit. The significance of this index will be appreciated better when it is applied to the calculation of the capacity of a buffer solution.

Approximate Calculation of Buffer Capacity. Consider an acetate buffer containing 0.1 mole each of acetic acid and sodium acetate in 1 liter of solution. To this are added 0.01-mole portions of sodium hydroxide. When the first increment of sodium hydroxide is added, the concentration of sodium acetate, the [salt] term in the buffer equation, increases by 0.01 mole/liter, and the acetic acid concentration [acid] decreases proportionately, because each increment of base converts 0.01 mole of acetic acid into 0.01 mole of sodium acetate according to the reaction

$$\underset{(0.1-0.01)}{\text{HAc}} + \underset{(0.01)}{\text{NaOH}} \rightleftharpoons \underset{(0.1+0.01)}{\text{NaAc}} + H_2O \qquad (8\text{–}24)$$

The changes in concentration of the salt and the acid by the addition of a base are represented in the buffer equation (8–8) by using the modified form:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{salt}] + [\text{base}]}{[\text{acid}] - [\text{base}]} \qquad (8\text{–}25)$$

Before the addition of the first portion of sodium hydroxide, the pH of the buffer solution is

$$\text{pH} = 4.76 + \log \frac{(0.1 + 0)}{(0.1 - 0)} = 4.76 \qquad (8\text{–}26)$$

The results of the continual addition of sodium hydroxide are shown in Table 8–2. The student should verify the pH values and buffer capacities by the use of equations (8–25) and (8–23) respectively.

As may be seen from Table 8–2, the buffer capacity is not a fixed value for a given buffer system, but rather depends on the amount of base added. The buffer capacity changes as the ratio log [salt]/[acid] increases with added base. With the addition of more sodium hydroxide, the buffer capacity decreases rapidly, and,

TABLE 8–2. ***Buffer Capacity of Solutions Containing Equimolar Amounts (0.1 M) of Acetic Acid and Sodium Acetate***

Moles of NaOH Added	pH of Solution	Buffer Capacity, β
0	4.76	
0.01	4.85	0.11
0.02	4.94	0.11
0.03	5.03	0.11
0.04	5.13	0.10
0.05	5.24	0.09
0.06	5.36	0.08

when sufficient base has been added to convert the acid completely into sodium ions and acetate ions, the solution no longer possesses an acid reserve. The buffer has its greatest capacity before any base is added where [salt]/[acid] = 1, and, therefore, according to equation (8–8), pH = pK_a. The buffer capacity is also influenced by an increase in the total concentration of the buffer constituents since, obviously, a great concentration of salt and acid provides a greater alkaline and acid reserve. The influence of concentration on buffer capacity is treated following the discussion of Van Slyke's equation.

A More Exact Equation for Buffer Capacity. The buffer capacity calculated from equation (8–23) is only approximate. It gives the average buffer capacity over the increment of base added. Koppel and Spiro[1] and Van Slyke[2] developed a more exact equation,

$$\beta = 2.3C\,\frac{K_a[H_3O^+]}{(K_a + [H_3O^+])^2} \qquad (8\text{–}27)$$

where C is the total buffer concentration, that is, the sum of the molar concentrations of the acid and the salt. Equation (8–27) permits one to compute the buffer capacity at any hydrogen ion concentration—for example, at the point where no acid or base has been added to the buffer.

Example 8–6. At a hydrogen ion concentration of 1.75×10^{-5} (pH = 4.76), what is the capacity of a buffer containing 0.10 mole each of acetic acid and sodium acetate per liter of solution? The total concentration, C = [acid] + [salt], is 0.20 mole per liter, and the dissociation constant is 1.75×10^{-5}.

$$\beta = \frac{2.3 \times 0.20 \times (1.75 \times 10^{-5}) \times (1.75 \times 10^{-5})}{[(1.75 \times 10^{-5}) + (1.75 \times 10^{-5})]^2}$$
$$= 0.115$$

Example 8–7. Prepare a buffer solution of pH 5.00 having a capacity of 0.02. The steps in the solution of the problem are:

(*a*) One chooses a weak acid having a pK_a close to the pH desired. Acetic acid, pK_a = 4.76, is suitable in this case.

(*b*) The ratio of salt and acid required to produce a pH of 5.00 was found in *Example 8–2* to be [salt]/[acid] = 1.74/1.

(*c*) The buffer capacity equation (8–27) is used to obtain the total buffer concentration, C = [salt] + [acid]

$$0.02 = 2.3C\,\frac{(1.75 \times 10^{-5}) \times (1 \times 10^{-5})}{[(1.75 \times 10^{-5}) + (1 \times 10^{-5})]^2}$$
$$C = 3.75 \times 10^{-2}\ \text{mole/liter}$$

(*d*) Finally from (*b*), [salt] = 1.74 × [acid], and from (*c*):

$$C = (1.74 \times [\text{acid}]) + [\text{acid}]$$
$$= 3.75 \times 10^{-2}\ \text{mole/liter}$$

Therefore

$$[\text{acid}] = 1.37 \times 10^{-2}\ \text{mole/liter}$$

and

$$[\text{salt}] = 1.74 \times [\text{acid}]$$
$$= 2.38 \times 10^{-2}\ \text{mole/liter}$$

The Influence of Concentration on Buffer Capacity. The buffer capacity is affected not only by the [salt]/[acid] ratio but also by the total concentrations of acid and salt. As shown in Table 8–2, when 0.01 mole of base was added to a 0.1 molar acetate buffer, the pH increased from 4.76 to 4.85 or a ΔpH of 0.09.

If the concentration of acetic acid and sodium acetate is raised to 1 molar, the pH of the original buffer solution remains at about 4.76, but now, upon the addition of 0.01 mole of base, it becomes 4.77, a ΔpH of only 0.01. The calculation, disregarding activity coefficients, is

$$\text{pH} = 4.76 + \log\frac{(1.0 + 0.01)}{(1.0 - 0.01)} = 4.77 \qquad (8\text{–}28)$$

Therefore, an increase in the concentration of the buffer components results in a greater buffer capacity or efficiency. This conclusion is also evident in equation (8–27), where an increase in the total buffer concentration, C = [salt] + [acid], obviously results in a greater value of β.

In summary, the buffer capacity depends on (*a*) the value of the ratio [salt]/[acid], increasing as the ratio approaches unity; and (*b*) the magnitude of the individual concentrations of the buffer components, the buffer becoming more efficient as the salt and acid concentrations are increased.

Maximum Buffer Capacity. An equation expressing the maximum buffer capacity may be derived from the buffer capacity formula of Koppel and Spiro[1] and Van Slyke[2] (equation (8–27)). The maximum buffer capacity occurs where pH = pK_a, or, in equivalent terms, where $[H_3O^+] = K_a$. Substituting $[H_3O^+]$ for K_a in both the numerator and denominator of equation (8–27) gives

$$\beta_{max} = 2.303C\,\frac{[H_3O^+]^2}{(2[H_3O^+])^2} = \frac{2.303}{4}\,C$$

$$\beta_{max} = 0.576C \qquad (8\text{–}29)$$

in which C is the total buffer concentration.

Example 8–8. What is the maximum buffer capacity of an acetate buffer with a total concentration of 0.020 mole per liter?

$$\beta_{max} = 0.576 \times 0.020$$
$$= 0.01152 \text{ or } 0.012$$

Neutralization Curves and Buffer Capacity. A further understanding of buffer capacity can be obtained by considering the titration curves of strong and weak acids when they are mixed with increasing quantities of alkali. The reaction of an equivalent of an acid with an equivalent of a base is called neutralization; it may be expressed according to the method of Brönsted and Lowry. The neutralization of a strong acid by a strong base and weak acid by a strong base are written, as explained on pp. 143–145, in the form

Acid$_1$	Base$_2$	Acid$_2$	Base$_1$
$H_3O^+(Cl^-)$ +	$(Na^+)OH^-$ =	H_2O +	$H_2O + Na^+ + Cl^-$
HAc +	$(Na^+)OH^-$ =	H_2O +	$(Na^+)Ac^-$

in which $(H_3O^+)(Cl^-)$ is the hydrated form of HCl in water. The neutralization of a strong acid by a strong base simply involves a reaction between hydronium and hydroxyl ions and is usually written

$$H_3O^+ + OH^- = 2H_2O \qquad (8-30)$$

Since (Cl^-) and (Na^+) appear on both sides of the equation just given, they may be disregarded without influencing the result. The reaction between the strong acid and strong base proceeds almost to completion; however, the weak acid–strong base reaction is incomplete, since Ac^- reacts in part with water, that is, it hydrolyzes to regenerate the free acid.

The neutralization of 10 mL of 0.1 *N* HCl (curve I) and 10 mL of 0.1 *N* acetic acid (curve II) by 0.1 *N* NaOH is shown in Figure 8–1. The plot of pH versus milliliters of NaOH added produces the titration curve. It is computed as follows for HCl. Before the first increment of NaOH is added, the hydrogen ion concentration of the 0.1-*N* solution of HCl is 10^{-1} mole/liter and the pH = 1, disregarding activities and assuming HCl to be completely ionized. The addition of 5 mL of 0.1 *N* NaOH neutralizes 5 mL of 0.1 *N* HCl, leaving 5 mL of the original HCl in 10 + 5 = 15 mL of solution, or $[H_3O^+] = \frac{5}{15} \times 0.1 = 3.3 \times 10^{-2}$ mole per liter and pH = 1.48. When 10 mL of base has been added, all the HCl is converted to NaCl, and the pH, disregarding the difference between activity and concentration resulting from the ionic strength of the NaCl solution, is 7. This is known as the equivalence point of the titration. Curve I in Figure 8–1 results from plotting such data. It is seen that the pH does not change markedly until nearly all the HCl is neutralized. Hence, a solution of a strong acid has a high buffer capacity below a pH of 2. Likewise, a strong base has a high buffer capacity above a pH of 12.

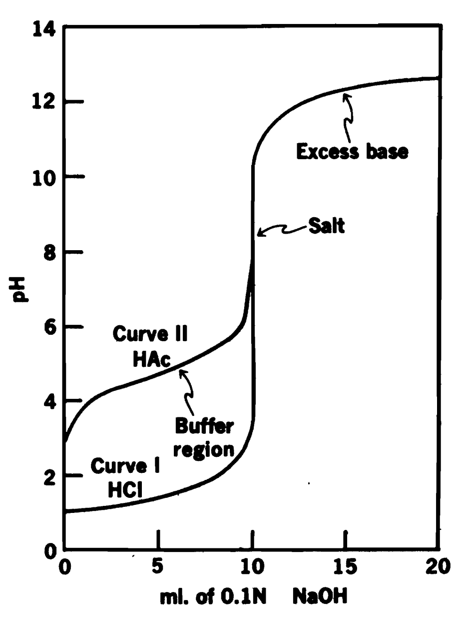


Fig. 8–1. Neutralization of a strong acid and a weak acid by a strong base.

The buffer capacity equations considered thus far have pertained exclusively to mixtures of weak electrolytes and their salts. The buffer capacity of a solution of a strong acid was shown by Van Slyke to be directly proportional to the hydrogen ion concentration, or

$$\beta = 2.303\,[H_3O^+] \qquad (8-31)$$

The buffer capacity of a solution of a strong base is similarly proportional to the hydroxyl ion concentration,

$$\beta = 2.303\,[OH^-] \qquad (8-32)$$

The total buffer capacity of a water solution of a strong acid or base at any pH is the sum of the separate capacities just given, equations (8–31) and (8–32), or

$$\beta = 2.303([H_3O^+] + [OH^-]) \qquad (8-33)$$

Example 8–9. What is the buffer capacity of a solution of hydrochloric acid having a hydrogen ion concentration of 10^{-2} mole per liter?

The hydroxyl ion concentration of such a solution is 10^{-12}, and the total buffer capacity is

$$\beta = 2.303(10^{-2} + 10^{-12})$$
$$\beta = 0.023$$

The OH^- concentration is obviously so low in this case that it may be neglected in the calculation.

Three equations are normally used to obtain the data for the titration curve of a weak acid (curve II of Figure 8–1), although a single equation that is somewhat complicated can be used. Suppose that increments of 0.1 *N* NaOH are added to 10 mL of a 0.1-*N* HAc solution.

(*a*) The pH of the solution, before any NaOH has been added, is obtained from the equation for a weak acid (p. 155, equation (7–99)).

$$pH = \tfrac{1}{2}pK_a - \tfrac{1}{2}\log c$$
$$= 2.38 - \tfrac{1}{2}\log 10^{-1} = 2.88$$

(*b*) At the equivalence point, where the acid has been converted completely into sodium ions and acetate ions, the pH is computed from the equation for a salt of a weak acid and strong base (p. 156, equation (7–103)) in log form:

$$pH = \tfrac{1}{2}\,pK_w + \tfrac{1}{2}\,pK_a + \tfrac{1}{2}\log c$$
$$= 7.00 + 2.38 + \tfrac{1}{2}\log(5 \times 10^{-2})$$
$$= 8.73$$

The concentration of the acid is given in the last term of this equation as 0.05, because the solution has been reduced to half its original value by mixing it with an equal volume of base at the equivalence point.

(*c*) Between these points on the neutralization curve, the increments of NaOH convert some of the acid to its conjugate base Ac^- to form a buffer mixture, and the pH of the system is calculated from the buffer equation. When 5 mL of base is added, the equivalent of 5 mL of 0.1 N acid remains and 5 mL of 0.1 N Ac^- is formed, and using the Henderson–Hasselbalch equation,

$$pH = pK_a + \log \frac{[\text{salt}]}{[\text{acid}]}$$

$$= 4.76 + \log \frac{5}{5} = 4.76$$

The slope of the curve is a minimum and the buffer capacity is greatest at this point, where the solution shows the smallest pH change per gram equivalent of base added. The buffer capacity of a solution is the reciprocal of the slope of the curve at a point corresponding to the composition of the buffer solution. As seen in Figure 8–1, the slope of the line is a minimum, and the buffer capacity is greatest at half-neutralization, where pH = pK_a.

The titration curve for a tribasic acid such as H_3PO_4 consists of three stages, as shown in Figure 8–2. These may be considered as being produced by three separate acids (H_3PO_4, $pK_1 = 2.21$; $H_2PO_4^-$, $pK_2 = 7.21$; and HPO_4^{2-}, $pK_3 = 12.67$) whose strengths are sufficiently different so that their curves do not overlap. The curves may be plotted by using the buffer equation and their ends joined by smooth lines to produce the continuous curve of Figure 8–2.

A mixture of weak acids, whose pK_a values are sufficiently alike (differing by no more than about 2 pH units) so that their buffer regions overlap, can be used as a *universal buffer* over a wide range of pH values. A buffer of this type was introduced by Britton and Robinson.[9] The three stages of citric acid—$pK_1 = 3.15$, $pK_2 = 4.78$, $pK_3 = 6.40$—are sufficiently close to provide overlapping of neutralization curves and efficient buffering over this range. Adding Na_2HPO_4, whose conjugate acid $H_2PO_4^-$ has a pK_2 of 7.2,

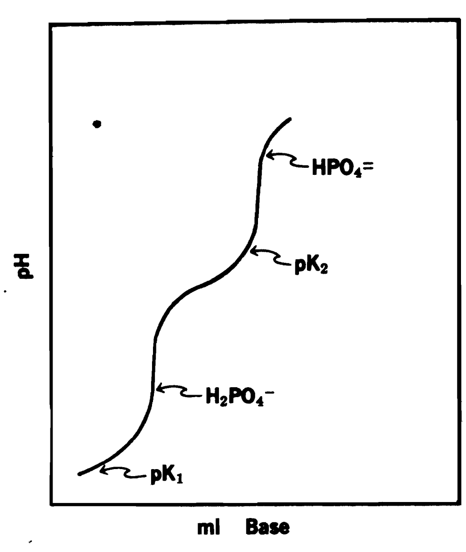


Fig. 8–2. Neutralization of a tribasic acid.

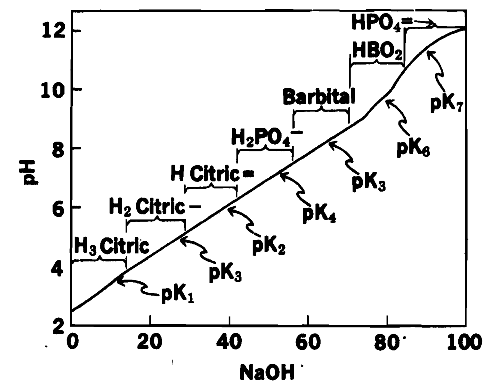


Fig. 8–3. Neutralization curve for a universal buffer. The horizontal axis is marked off in milliliters of 0.2 N NaOH. (After H. T. Britton, *Hydrogen Ions*, Vol. I, D. Van Nostrand, New York, 1956, p. 368.)

diethylbarbituric acid, $pK_1 = 7.91$, and boric acid, $pK_1 = 9.24$, provides a universal buffer that covers the pH range of about 2.4 to 12. The neutralization curve for the universal buffer mixture is linear between pH 4 and 8, as seen in Figure 8–3, because the successive dissociation constants differ by only a small value.

A titration curve depends on the ratio of the successive dissociation constants. Theoretically, when one K is equal to or less than 16 times the previous K, that is, when successive pKs do not differ by greater than 1.2 units, the second ionization begins well before the first is completed, and the titration curve is a straight line with no inflection points. Actually the inflection is not noticeable until one K is about 50 to 100 times that of the previous K value.

The buffer capacity of several acid–salt mixtures is plotted against pH in Figure 8–4. A buffer solution is useful within a range of about ±1 pH unit about the pK_a of its acid, where the buffer capacity is roughly greater than 0.01 or 0.02, as observed in Figure 8–4. Accordingly, the acetate buffer should be effective over a pH range of about 3.8 to 5.8, and the borate buffer should be effective over a range of 8.2 to 10.2. In each case, the greatest capacity occurs where [salt]/[acid] = 1 and pH = pK_a. Because of interionic effects, buffer capacities do not in general exceed a value of 0.2. The buf-

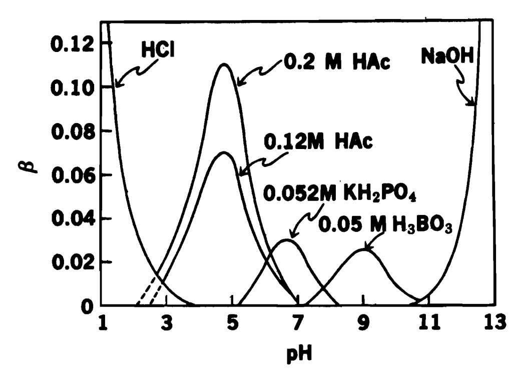


Fig. 8–4. The buffer capacity of several buffer systems as a function of pH. (Modified from R. G. Bates, *Electrometric pH Determinations*, Wiley, New York, 1954.)

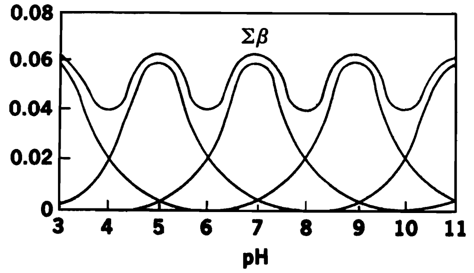


Fig. 8–5. The total buffer capacity of a universal buffer as a function of pH. From I. M. Kolthoff and C. Rosenblum, *Acid–Base Indicators*, Macmillan, New York, 1937, p. 29.)

fer capacity of a solution of the strong acid HCl becomes marked below a pH of 2, and the buffer capacity of a strong base NaOH becomes significant above a pH of 12.

The buffer capacity of a combination of buffers, the pK_a values of which overlap to produce a universal buffer, is plotted in Figure 8–5. It is seen that the total buffer capacity $\Sigma\beta$ is the sum of the β values of the individual buffers. In this figure, it is assumed that the maximum β's of all buffers in the series are identical.

BUFFERS IN PHARMACEUTICAL AND BIOLOGIC SYSTEMS

In Vivo Biologic Buffer Systems. *Blood* is maintained at a pH of about 7.4 by the so-called primary buffers in the plasma and the secondary buffers in the erythrocytes. The plasma contains carbonic acid/bicarbonate and acid/alkali sodium salts of phosphoric acid as buffers. Plasma proteins, which behave as acids in blood, can combine with bases and so act as buffers. In the erythrocytes, the two buffer systems consist of hemoglobin/oxyhemoglobin and acid/alkali potassium salts of phosphoric acid.

The dissociation exponent pK_1 for the first ionization stage of carbonic acid in the plasma at body temperature and an ionic strength of 0.16 is about 6.1. The buffer equation for the carbonic acid/bicarbonate buffer of the blood is

$$pH = 6.1 + \log \frac{[HCO_3^-]}{[H_2CO_3]} \qquad (8\text{–}34)$$

in which $[H_2CO_3]$ represents the concentration of CO_2 present as H_2CO_3 dissolved in the blood. At a pH of 7.4, the ratio of bicarbonate to carbonic acid in normal blood plasma is

$$\log \frac{[HCO_3^-]}{[H_2CO_3]} = 7.4 - 6.1 = 1.3$$

or

$$[HCO_3^-]/[H_2CO_3] = 20/1 \qquad (8\text{–}35)$$

This result checks with experimental findings, since the actual concentrations of bicarbonate and carbonic acid in the plasma are about 0.025 *M* and 0.00125 *M* respectively.

The buffer capacity of the blood in the physiologic range pH 7.0 to 7.8 is obtained as follows. According to Peters and Van Slyke,[10] the buffer capacity of the blood owing to hemoglobin and other constituents, exclusive of bicarbonate, is about 0.025 gram equivalents per liter per pH unit. The pH of the bicarbonate buffer in the blood (i.e. pH 7.4) is rather far removed from the pH (6.1) where it exhibits maximum buffer capacity; therefore, the bicarbonate's buffer action is relatively small with respect to that of the other blood constituents. According to the calculation just given, the ratio $[NaHCO_3]/[H_2CO_3]$ is 20:1 at pH 7.4. Using equation (8–27), the buffer capacity for the bicarbonate system ($K_1 = 4 \times 10^{-7}$) at a pH of 7.4 ($[H_3O^+] = 4 \times 10^{-8}$) is found to be roughly 0.003. Therefore, the total buffer capacity of the blood in the physiologic range, the sum of the capacities of the various constituents, is 0.025 + 0.003 = 0.028. Salenius[11] reported a value of 0.0318 ± 0.0035 for whole blood, whereas Ellison et al.[12] obtained a buffer capacity of about 0.039 gram equivalents per liter per pH unit for whole blood, of which 0.031 was contributed by the cells and 0.008 by the plasma.

Usually when the pH of the blood goes below 6.9 or above 7.8, life is in serious danger. The pH of the blood in diabetic coma is alleged to drop as low as about 6.8.

Lacrimal fluid, or tears, have been found to have a great degree of buffer capacity, allowing a dilution of 1:15 with neutral distilled water before an alteration of pH is noticed.[13] In the terminology of Bates,[14] this would be referred to today as *dilution value* rather than buffer capacity (p. 171). The pH of tears is about 7.4, with a range of 7 to 8 or slightly higher. Pure conjunctival fluid is probably more acidic than the tear fluid commonly used in pH measurements. This is because pH increases rapidly when the sample is removed for analysis because of the loss of CO_2 from the tear fluid.

Urine. The 24-hour urine collection of a normal adult has a pH averaging about 6.0 units; it may be as low as 4.5 or as high as 7.8. When the pH of the urine is below normal values, hydrogen ions are excreted by the kidneys. Conversely, when the urine is above pH 7.4, hydrogen ions are retained by action of the kidneys in order to return the pH to its normal range of values.

Pharmaceutical Buffers. Buffer solutions are used frequently in pharmaceutical practice, particularly in the formulation of ophthalmic solutions. They also find application in the colorimetric determination of pH and for those research studies in which pH must be held constant.

Gifford[15] suggested two stock solutions, one containing boric acid and the other monohydrated sodium carbonate, which, when mixed in various proportions, yield buffer solutions with pH values from about 5 to 9.

Sörensen[16] proposed a mixture of the salts of sodium phosphate for buffer solutions of pH 6 to 8. Sodium chloride is added to each buffer mixture to make it isotonic with body fluids.

A buffer system suggested by Palitzsch[17] and modified by Hind and Goyan[18] consists of boric acid, sodium borate, and sufficient sodium chloride to make the mixtures isotonic. It is used for ophthalmic solutions in the pH range of 7 to 9.

The buffers of Clark and Lubs,[19] based on the original pH scale of Sörensen, have been redetermined at 25° C by Bower and Bates[7] so as to conform to the present definition of pH (p. 200). Between pH 3 and 11, the older values were about 0.04 unit lower than the values now assigned, and at the ends of the scale, the differences were greater. The original values were determined at 20° C, whereas most experiments today are performed at 25° C.

The Clark–Lubs mixtures and their corresponding pH ranges are:

(*a*) HCl and KCl, pH 1.2 to 2.2

(*b*) HCl and potassium hydrogen phthalate, pH 2.2 to 4.0

(*c*) NaOH and potassium hydrogen phthalate, pH 4.2 to 5.8

(*d*) NaOH and KH_2PO_4, pH 5.8 to 8.0

(*e*) H_3BO_3, NaOH and KCl, pH 8.0 to 10.0

With regard to mixture (*a*), consisting of HCl and KCl and used for the pH range from 1.0 to 2.2, it will be recalled from the discussion of the neutralization curve (I), Figure 8–1, that HCl alone has considerable buffer efficiency below pH 2. KCl is a neutral salt and is added to adjust the ionic strength of the buffer solutions to a constant value of 0.10; the pH calculated from the equation, $-\log a_{H^+} = -\log (\gamma_{\pm} c)$, corresponds closely to the experimentally determined pH. The role of the KCl in the Clark–Lubs buffer is sometimes erroneously interpreted as that of a salt of the buffer acid, HCl, corresponding to the part played by sodium acetate as the salt of the weak buffer acid, HAc. Potassium chloride is added to (*e*), the borate buffer, to produce an ionic strength comparable to that of (*d*), the phosphate buffer, where the pH of the two buffer series overlap.

Buffer solutions are discussed in the USP XXII on pp. 1598, 1599, 1784, and 1785. A buffer commonly used in biologic research (pH 7 to 9) and reported in the *Merck Index* is TRIS, aminohydroxymethyl propanediol.

Preparation of Pharmaceutical Buffer Solutions. The pharmacist may be called upon at times to prepare buffer systems, the formulas for which do not appear in the literature. The following steps should be helpful in the development of a new buffer.

(*a*) Select a weak acid having a pK_a approximately equal to the pH at which the buffer is to be used. This will ensure maximum buffer capacity.

(*b*) From the buffer equation, calculate the ratio of salt and weak acid required to obtain the desired pH. The buffer equation is satisfactory for approximate calculations within the pH range of 4 to 10.

(*c*) Consider the individual concentrations of the buffer salt and acid needed to obtain a suitable buffer capacity. A *concentration* of 0.05 to 0.5 *M* is usually sufficient; and a *buffer capacity* of 0.01 to 0.1 is generally adequate.

(*d*) Other factors of some importance in the choice of a pharmaceutical buffer include availability of chemicals, sterility of the final solution, stability of the drug and buffer on aging, cost of materials, and freedom from toxicity. For example, a borate buffer, because of its toxic effects, certainly cannot be used to stabilize a solution to be administered orally or parenterally.

(*e*) Finally, one should determine the pH and buffer capacity of the completed buffered solution using a reliable pH meter. In some cases, sufficient accuracy is obtained by the use of pH papers. Particularly when the electrolyte concentration is high, it may be found that the pH calculated by use of the buffer equation is somewhat different from the experimental value. This is to be expected when activity coefficients are not taken into account, and it emphasizes the necessity for carrying out the actual determination.

Influence of Buffer Capacity and pH on Tissue Irritation. Solutions to be applied to tissues or administered parenterally are liable to cause irritation if their pH is greatly removed from the normal pH of the relevant body fluid. Consequently, the pharmacist must consider this point when formulating ophthalmic solutions, parenteral products, and fluids to be applied to abraded surfaces. Of possible greater significance than the actual pH of the solution is its buffer capacity and the volume to be used in relation to the volume of body fluid with which the buffered solution will come in contact. The buffer, capacity of the body fluid should also be considered. Tissue irritation, due to large pH differences between the solution being administered and the physiologic environment in which it is used, will be minimal (*a*) the lower the buffer capacity of the solution, (*b*) the smaller the volume used, for a given concentration, and (*c*) the larger the volume and buffer capacity of the physiologic fluid.

Friedenwald et al.[20] claimed that the pH of solutions for introduction into the eye may vary from 4.5 to 11.5 without marked pain or damage. This statement evidently would be true only if the buffer capacity were kept low. Martin and Mims[21] found that Sörensen's phosphate buffer produced irritation in the eyes of a number of subjects when used outside the narrow pH range of 6.5 to 8, whereas a boric acid solution of pH 5 produced no discomfort in the eyes of the same subjects. Martin and Mims concluded that a pH range of nonirritation cannot be established absolutely but rather depends upon the buffer employed. In light of the previous discussion, this apparent anomaly can be explained partly in terms of the low buffer capacity of boric acid as compared with that of the phosphate buffer (cf. *Problems 8–12* and *8–13*, p. 188) and partly to the difference of the physiologic response to various ion species.

Riegelman and Vaughn[22] assumed that the acid-neutralizing power of the tears when 0.1 mL of a 1% solution of a drug is instilled into the eye is roughly equivalent to 10 microliters of a 0.01-*N* strong base. They point out that while in a few cases irritation of the eye may result from the presence of the free base form of a drug at the physiologic pH, it is more often due to the acidity of the eye solution. For example, since only one carboxyl group of tartaric acid is neutralized by epinephrine base in epinephrine bitartrate, a 0.06-*M* solution of the drug has a pH of about 3.5. The prolonged pain resulting from instilling two drops of this solution into the eye is presumably due to the unneutralized acid of the bitartrate, which requires ten times the amount of tears to restore the normal pH of the eye as compared with the result following two drops of epinephrine hydrochloride. Solutions of pilocarpine salts also possess sufficient buffer capacity to cause pain or irritation owing to their acid reaction when instilled into the eye.

Parenteral solutions for injection into the blood are usually not buffered, or they are buffered to a low capacity so that the buffers of the blood may readily bring them within the physiologic pH range. If the drugs are to be injected only in small quantities and at a slow rate, their solutions can be buffered weakly to maintain approximate neutrality.

Following oral administration, aspirin is absorbed more rapidly in systems buffered at low buffer capacity than in systems containing no buffer or in highly buffered preparations, according to Mason.[23] Thus, the buffer capacity of the buffer should be optimized to produce rapid absorption and minimal gastric irritation of orally administered aspirin.

In addition to the adjustment of tonicity and pH for ophthalmic preparations, similar requirements are demanded for nasal delivery of drugs. This has become all the more important in recent years since the nasal passage is now used for the administration of systemic drugs (see pp. 525–527 for nasal dosage forms). Insulin, for example, is more effective by nasal administration than by other nonparenteral routes.[24]

Stability vs. Optimum Therapeutic Response. For the sake of completeness, some mention must be made at this point of the effect of buffer capacity and pH on the stability and therapeutic response of the drug being used in solution.

As will be discussed later (Chapter 10), the undissociated form of a weakly acidic or basic drug often has a higher therapeutic activity than the dissociated salt form. This is because the former is lipid soluble and can penetrate body membranes readily, whereas the ionic form, not being lipid soluble, can penetrate membranes only with greater difficulty. Thus Swan and White[25] and Cogan and Kinsey[26] observed an increase in therapeutic response of weakly basic alkaloids (used as ophthalmic drugs) as the pH of the solution, and hence concentration of the undissociated base, was increased. At a pH of about 4, these drugs are predominantly in the ionic form, and penetration is slow or insignificant. When the tears bring the pH to about 7.4, the drugs may exist to a significant degree in the form of the free base, depending on the dissociation constant of the drug.

Example 8–10. The pK_b of pilocarpine is 7.15 at 25° C. Compute the mole percent of free base present on 25° C and at a pH of 7.4.

$$\underset{\text{Pilocarpine base}}{C_{11}H_{16}N_2O_2} + H_2O \rightleftharpoons \underset{\text{Pilocarpine ion}}{C_{11}H_{16}N_2O_2H^+} + OH^-$$

$$pH = pK_w - pK_b + \log\frac{[\text{base}]}{[\text{salt}]}$$

$$7.4 = 14.00 - 7.15 + \log\frac{[\text{base}]}{[\text{salt}]}$$

$$\log\frac{[\text{base}]}{[\text{salt}]} = 7.40 - 14.00 + 7.15 = 0.55$$

$$\frac{[\text{base}]}{[\text{salt}]} = \frac{3.56}{1}$$

$$\text{mole percent of base} = \frac{[\text{base}]}{[\text{salt}] + [\text{base}]} \times 100$$

$$= [3.56/(1 + 3.56)] \times 100 = 78\%$$

Hind and Goyan[27] pointed out that the pH for maximum stability of a drug for ophthalmic use may be far below that of the optimum physiologic effect. Under such conditions, the solution of the drug can be buffered at a low buffer capacity and at a pH that is a compromise between that of optimum stability and the pH for maximum therapeutic action. The buffer is adequate to prevent changes in pH due to the alkalinity of the glass or acidity of CO_2 from dissolved air. Yet, when the solution is instilled in the eye, the tears participate in the gradual neutralization of the solution; conversion of the drug occurs from the physiologically inactive form to the undissociated base. The base can then readily penetrate the lipoidal membrane. As the base is absorbed at the pH of the eye, more of the salt is converted into base to preserve the constancy of pK_b; hence, the alkaloidal drug is gradually absorbed.

pH and Solubility. The relationship of pH and the solubility of weak electrolytes will be treated in some detail in Chapter 10. At this point it is necessary only to point out briefly the influence of buffering on the solubility of an alkaloidal base. At a low pH, a base is predominantly in the ionic form, which is usually very soluble in aqueous media. As the pH is raised, more undissociated base is formed as calculated by the method illustrated in *Example 8–10*. When the amount of base exceeds the limited water solubility of this form, free base precipitates from solution. Therefore, the solution should be buffered at a sufficiently low pH so that the concentration of alkaloidal base in equilibrium with its salt is calculated to be less than the solubility of the free base at the storage temperature. Stabilization against precipitation can thus be maintained.

BUFFERED ISOTONIC SOLUTIONS

Reference has already been made to the in vivo buffer systems, such as blood and lacrimal fluid, and the desirability for buffering pharmaceutical solutions under certain conditions. In addition to carrying out pH adjustment, pharmaceutical solutions that are meant for application to delicate membranes of the body should also be adjusted to approximately the same osmotic pressure (Chapter 5) as that of the body fluids. Isotonic solutions cause no swelling or contraction of the tissues with which they come in contact, and produce no discomfort when instilled in the eye, nasal tract, blood, or other body tissues. Isotonic sodium chloride is a familiar pharmaceutical example of such a preparation.

The need to achieve isotonic conditions with solutions to be applied to delicate membranes is dramatically illustrated by mixing a small quantity of blood with aqueous sodium chloride solutions of varying tonicity. For example, if a small quantity of blood, defibrinated to prevent clotting, is mixed with a solution containing 0.9 g NaCl per 100 mL, the cells retain their normal size. The solution has essentially the same salt concentration and hence the same osmotic pressure as the red blood cell contents, and is said to be *isotonic* with blood. If the red blood cells are suspended in a 2.0% NaCl solution, the water within the cells passes through the cell membrane in an attempt to dilute the surrounding salt solution until the salt concentrations on both sides of the erythrocyte membrane are identical. This outward passage of water causes the cells to shrink and become wrinkled or *crenated*. The salt solution in this instance is said to be *hypertonic* with respect to the blood cell contents. Finally, if the blood is mixed with 0.2% NaCl solution or with distilled water, water enters the blood cells, causing them to swell and finally burst, with the liberation of hemoglobin. This phenomenon is known as *hemolysis*, and the weak salt solution or water is said to be *hypotonic* with respect to the blood.

The student should appreciate that the red blood cell membrane is not impermeable to all drugs; that is, it is not a perfect semipermeable membrane. Thus, it will permit the passage of not only water molecules, but also solutes such as urea, ammonium chloride, alcohol, and boric acid.[28] A 2.0% solution of boric acid has the same osmotic pressure as the blood cell contents when determined by the freezing point method and is therefore said to be *isosmotic* with blood. The molecules of boric acid pass freely through the erythrocyte membrane, however, regardless of concentration. As a result, this solution acts essentially as water when in contact with blood cells. Being extremely hypotonic with respect to the blood, boric acid solution brings about rapid hemolysis. Therefore, a solution containing a quantity of drug calculated to be isosmotic with blood is isotonic *only* when the blood cells are impermeable to the solute molecules and permeable to the solvent, water. It is interesting to note that the mucous lining of the eye acts as a true semipermeable membrane to boric acid in solution. Accordingly, a 2.0% boric acid solution serves as an isotonic ophthalmic preparation.

To overcome this difficulty, Husa[29] has suggested that the term *isotonic* should be restricted to solutions having equal osmotic pressures with respect to a particular membrane. Goyan and Reck[30] felt that, rather than restricting the use of the term in this manner, a new term should be introduced that is defined on the basis of the sodium chloride concentration. These workers defined the term *isotonicity value* as the concentration of an aqueous NaCl solution having the same colligative properties as the solution in question. Although all solutions having an isotonicity value of 0.9 g NaCl per 100 mL of solution need not *necessarily* be isotonic with respect to the living membranes concerned. Nevertheless, many of them are roughly isotonic in this sense, and all may be considered isotonic across an ideal membrane. Accordingly, the term *isotonic* is used with this meaning throughout the present chapter. Only a few substances—those that penetrate animal membranes at a sufficient rate—will show exception to this classification.

The remainder of this chapter is concerned with a discussion of isotonic solutions and the means by which they may be buffered.

Measurement of Tonicity. The tonicity of solutions may be determined by one of two methods. First, in the *hemolytic* method, the effect of various solutions of the drug is observed on the appearance of red blood cells suspended in the solutions. The various effects produced have been described in the previous section. Husa and his associates[29] have used this method. In their later work, a quantitative method developed by Hunter[31] was used based on the fact that a hypotonic solution liberates oxyhemoglobin in direct proportion to the number of cells hemolyzed. By such means, the van't Hoff i factor (p. 129) can be determined and the value compared with that computed from cryoscopic data, osmotic coefficient, and activity coefficient.[32]

Husa has found that a drug having the proper i value as measured by freezing point depression or computed from theoretic equations nevertheless may hemolyze human red blood cells; it was on this basis that he suggested restriction of the term *isotonic* to solutions having equal osmotic pressures with respect to a particular membrane.

The second approach used to measure tonicity is based on any of the methods that determine colligative properties, as discussed in Chapter 5. Goyan and Reck[30] investigated various modifications of the Hill–Baldes technique[33] (p. 111) for measuring tonicity. This method is based on a measurement of the slight temperature differences arising from differences in the vapor pressure of thermally insulated samples contained in constant-humidity chambers.

One of the first references to the determination of the freezing point of blood and tears (as was necessary to make solutions isotonic with these fluids) was that of Lumiere and Chevrotier,[34] in which the values of −0.56° and −0.80° C were given respectively for the two fluids. Following work by Pedersen-Bjergaard and co-workers,[35,36] however, it is now well established that −0.52° is the freezing point of both human blood and lacrimal fluid. This temperature corresponds to the freezing point of a 0.90% NaCl solution, which is therefore considered to be isotonic with both blood and lacrimal fluid.

Calculating Tonicity Using L_{iso} Values. Since the freezing point depressions for solutions of electrolytes of both the weak and strong types are always greater than those calculated from the equation, $\Delta T_f = K_f c$, a new factor, $L = iK_f$, is introduced to overcome this difficulty.[37] The equation already discussed in Chapter 6, p. 137, is

$$\Delta T_f = Lc \tag{8-36}$$

The L value may be obtained from the freezing point lowering of solutions of representative compounds of a given ionic type at a concentration c that is isotonic with body fluids. This specific value of L is symbolized as L_{iso} (p. 137).

The L_{iso} value for a 0.90% (0.154-M) solution of sodium chloride, which has a freezing point depression of 0.52° and is thus isotonic with body fluids, is 3.4:

$$L_{iso} = \frac{\Delta T_f}{c} \tag{8-37}$$

$$L_{iso} = \frac{0.52°}{0.154} = 3.4$$

The interionic attraction in solutions that are not too concentrated is roughly the same for all uni-univalent electrolytes regardless of the chemical nature of the various compounds of this class, and all have about the same value for L_{iso}, namely 3.4. As a result of this similarity between compounds of a given ionic type, a table can be arranged listing the L value for each class of electrolytes at a concentration that is isotonic with body fluids. The L_{iso} values obtained in this way are found in Table 8−3.

It will be observed that for dilute solutions of nonelectrolytes, L_{iso} is approximately equal to K_f. Table 8−3 is used to obtain the approximate ΔT_f for a solution of a drug, if the ionic type can be correctly ascertained. A plot of iK_f against molar concentration of various types of electrolytes, from which the values of L_{iso} can be read, is shown in Figure 6−7, p. 137.

Example 8−11. What is the freezing point lowering of a 1% solution of sodium propionate (molecular weight 96)? Since sodium propionate is a uni-univalent electrolyte, its L_{iso} value is 3.4. The molar concentration of a 1% solution of this compound is 0.104.

$$\Delta T_f = 3.4 \times 0.104 = 0.35° \tag{8-38}$$

Although 1 g per 100 mL of sodium propionate is not the isotonic concentration, it is still proper to use L_{iso} as a simple average that agrees with the concentration range expected for the finished solution. The selection of L values in this concentration region is not sensitive to minor changes in concentration; no pretense to an accuracy greater than about 10% is implied or needed in these calculations.

The calculation of *Example 8−11* may be simplified by expressing molarity c as grams of drug contained in a definite volume of solution. Thus

$$\text{Molarity} = \frac{\text{moles}}{\text{liter}}$$

$$= \frac{\text{weight in grams}}{\text{molecular weight in g/mole}} \div \frac{\text{volume in mL}}{1000\text{ mL/liter}} \tag{8-39}$$

or

$$c = \frac{w}{MW} \times \frac{1000}{v} \tag{8-40}$$

in which w is the grams of solute, MW is the molecular weight of the solute, and v is the volume of solution in milliliters. Substituting in equation (8−36)

TABLE 8−3. ***Average L_{iso} Values for Various Ionic Types****

Type	L_{iso}	Examples
Nonelectrolytes	1.9	Sucrose, glycerin, urea, camphor
Weak electrolytes	2.0	Boric acid, cocaine, phenobarbital
Di-divalent electrolytes	2.0	Magnesium sulfate, zinc sulfate
Uni-univalent electrolytes	3.4	Sodium chloride, cocaine hydrochloride, sodium phenobarbital
Uni-divalent electrolytes	4.3	Sodium sulfate, atropine sulfate
Di-univalent electrolytes	4.8	Zinc chloride, calcium bromide
Uni-trivalent electrolytes	5.2	Sodium citrate, sodium phosphate
Tri-univalent electrolytes	6.0	Aluminum chloride, ferric iodide
Tetraborate electrolytes	7.6	Sodium borate, potassium borate

*From J. M. Wells, J. Am. Pharm. Assoc., Pract. Ed. **5**, 99, 1944.

$$\Delta T_f = L_{iso} \times \frac{w \times 1000}{MW \times v} \quad (8-41)$$

The problem in *Example (8–11)* can be solved in one operation by the use of equation (8–41) without the added calculation needed to obtain the molar concentration.

$$\Delta T_f = 3.4 \times \frac{1 \times 1000}{96 \times 100} = 3.4 \times 0.104$$

$$= 0.35°$$

The student is encouraged to derive expressions of this type; certainly equations (8–40) and (8–41) should not be memorized, for they are not remembered long. The L_{iso} values may also be used for calculating sodium chloride equivalents and Sprowls' V values, as discussed in subsequent sections of this chapter.

METHODS OF ADJUSTING TONICITY AND pH

One of several methods may be used to calculate the quantity of sodium chloride, dextrose, and other substances that may be added to solutions of drugs to render them isotonic.

For discussion purposes, the methods are divided into two classes. In the Class I methods, sodium chloride or some other substance is added to the solution of the drug to lower the freezing point of the solution to −0.52° and thus make it isotonic with body fluids. Under this class are included the *Cryoscopic* method and the *Sodium Chloride Equivalent* method. In the Class II methods, water is added to the drug in a sufficient amount to form an isotonic solution. The preparation is then brought to its final volume with an isotonic or a buffered isotonic dilution solution. Included in this class are the *White–Vincent* method and the *Sprowls* method.

Class I Methods

Cryoscopic Method. The freezing point depressions of a number of drug solutions, determined experimentally or theoretically, are found in Table 8–4. According to the previous section, the freezing point depressions of drug solutions that have not been determined experimentally can be estimated from theoretic considerations, knowing only the molecular weight of the drug and the L_{iso} value of the ionic class.

The calculations involved in the cryoscopic method are explained best by an example.

Example 8–12. How much sodium chloride is required to render 100 mL of a 1% solution of apomorphine hydrochloride isotonic with blood serum?

From Table 8–4 it is found that a 1% solution of the drug has a freezing point lowering of 0.08°. To make this solution isotonic with blood, sufficient sodium chloride must be added to reduce the freezing point by an additional 0.44° (0.52 − 0.08). In the freezing point table, it is also observed that a 1% solution of sodium chloride has a freezing point lowering of 0.58°. By the method of proportion,

$$\frac{1\%}{X} = \frac{0.58°}{0.44°}; \; X = 0.76\%$$

Thus, 0.76% sodium chloride will lower the freezing point the required 0.44° and will render the solution isotonic. The solution is prepared by dissolving 1.0 g of apomorphine hydrochloride and 0.76 g of sodium chloride in sufficient water to make 100 mL of solution.

Sodium Chloride Equivalent Method. A second method for adjusting the tonicity of pharmaceutical solutions was developed by Mellen and Seltzer.[38] The *sodium chloride equivalent* or, as referred to by these workers, the "tonicic equivalent" of a drug is the amount of sodium chloride that is equivalent to (i.e., has the same osmotic effect as) 1 gram, or other weight unit, of the drug. The sodium chloride equivalents E for a number of drugs are listed in Table 8–4.

When the E value for a new drug is desired for inclusion in Table 8–4, it can be calculated from the L_{iso} value or freezing point depression of the drug according to the formulas derived by Goyan et al.[39] For a solution containing 1 g of drug in 1000 mL of solution, the concentration c expressed in moles per liter may be written as

$$c = \frac{1 \text{ g}}{\text{molecular weight}} \quad (8-42)$$

and from equation (8–36)

$$\Delta T_f = L_{iso} \frac{1 \text{ g}}{MW}$$

Now E is the weight of NaCl with the same freezing point depression as 1 g of the drug, and for a NaCl solution containing E grams of drug per 1000 mL,

$$\Delta T_f = 3.4 \frac{E}{58.45} \quad (8-43)$$

in which 3.4 is the L_{iso} value for sodium chloride and 58.45 is its molecular weight. Equating these two values of ΔT_f yields

$$\frac{L_{iso}}{MW} = 3.4 \frac{E}{58.45} \quad (8-44)$$

$$E \cong 17 \frac{L_{iso}}{MW} \quad (8-45)$$

Example 8–13. Calculate the approximate E value for a new amphetamine hydrochloride derivative (molecular weight 187).

Since this drug is a uni-univalent salt, it has an L_{iso} value of 3.4. Its E value is calculated from equation (8–45):

$$E = 17 \frac{3.4}{187} = 0.31$$

Calculations for determining the amount of sodium chloride or other inert substance to render a solution isotonic (across an ideal membrane) simply involve multiplying the quantity of each drug in the prescription by its sodium chloride equivalent and subtracting

TABLE 8–4. ***Isotonic Values****

Substance	*MW*	E	V	$\Delta T_f^{1\%}$	L_{iso}
Alcohol, dehydrated	46.07	0.70	23.3	0.41	1.9
Aminophylline	456.46	0.17	5.7	0.10	4.6
Ammonium chloride	53.50	1.08	36	0.64	3.4
Amphetamine sulfate (benzedrine sulfate)	368.49	0.22	7.3	0.13	4.8
Antipyrine	188.22	0.17	5.7	0.10	1.9
Antistine hydrochloride (antazoline hydrochloride)	301.81	0.18	6.0	0.11	3.2
Apomorphine hydrochloride	312.79	0.14	4.7	0.08	2.6
Ascorbic acid	176.12	0.18	6.0	0.11	1.9
Atropine sulfate	694.82	0.13	4.3	0.07	5.3
Aureomycin hydrochloride	544	0.11	3.7	0.06	3.5
Barbital sodium	206.18	0.29	10.0	0.29	3.5
Benadryl hydrochloride (diphenhydramine hydrochloride)	291.81	0.20	6.6	0.34	3.4
Boric acid	61.84	0.50	16.7	0.29	1.8
Butacaine sulfate (butyn sulfate)	710.95	0.20	6.7	0.12	8.4
Caffeine	194.19	0.08	2.7	0.05	0.9
Caffeine and sodium benzoate	—	0.25	8.7	0.28	—
Calcium chloride · $2H_2O$	147.03	0.51	17.0	0.30	4.4
Calcium gluconate	448.39	0.16	5.3	0.09	4.2
Calcium lactate	308.30	0.23	7.7	0.14	4.2
Camphor	152.23	0.20	6.7	0.12	1.8
Chloramphenicol (chloromycetin)	323.14	0.10	3.3	0.06	1.9
Chlorobutanol (chloretone)	177.47	0.24	8.0	0.14	2.5
Cocaine hydrochloride	339.81	0.16	5.3	0.09	3.2
Cupric sulfate · $5H_2O$	249.69	0.18	6.0	0.11	2.6
Dextrose · H_2O	198.17	0.16	5.3	0.09	1.9
Dibucaine hydrochloride (nupercaine hydrochloride)	379.92	0.13	4.3	0.08	2.9
Emetine hydrochloride	553.56	0.10	3.3	0.06	3.3
Ephedrine hydrochloride	201.69	0.30	10.0	0.18	3.6
Ephedrine sulfate	428.54	0.23	7.7	0.14	5.8
Epinephrine bitartrate	333.29	0.18	6.0	0.11	3.5
Epinephrine hydrochloride	219.66	0.29	9.7	0.17	3.7
Ethylhydrocupreine hydrochloride (optochin)	376.92	0.17	5.7	0.10	3.8
Ethylmorphine hydrochloride (dionin)	385.88	0.16	5.3	0.09	3.6
Eucatropine hydrochloride (euphthalmine hydrochloride)	327.84	0.18	6.0	0.11	3.5
Fluorescein sodium	376	0.31	10.3	0.18	6.9
Glycerin	92.09	0.34	11.3	0.20	1.8
Homatropine hydrobromide	356.26	0.17	5.7	0.10	3.6
Lactose	360.31	0.07	2.3	0.04	1.7
Magnesium sulfate · $7H_2O$	246.50	0.17	5.7	0.10	2.5
Menthol	156.26	0.20	6.7	0.12	1.8
Meperidine hydrochloride (demerol hydrochloride)	283.79	0.22	7.3	0.12	3.7
Mercuric chloride (mercury bichloride)	271.52	0.13	4.3	0.08	2.1
Mercuric cyanide	252.65	0.15	5.0	0.09	2.2
Mercuric succinimide	396.77	0.14	4.8	0.08	3.3
Methacholine chloride (mecholyl chloride)	195.69	0.32	10.7	0.19	3.7
Methamphetamine hydrochloride (desoxyephedrine hydrochloride)	185.69	0.37	12.3	0.22	4.0
Metycaine hydrochloride	292.82	0.20	6.7	0.12	3.4
Mild silver protein	—	0.18	6.0	0.11	—
Morphine hydrochloride	375.84	0.15	5.0	0.09	3.3
Morphine sulfate	758.82	0.14	4.8	0.08	6.2
Naphazoline hydrochloride (privine hydrochloride)	246.73	0.27	7.7	0.16	3.3
Neomycin sulfate	—	0.11	3.7	0.06	—
Neostigmine bromide (prostigmine bromide)	303.20	0.22	6.0	0.11	3.2
Nicotinamide	122.13	0.26	8.7	0.15	1.9
Penicillin G potassium	372.47	0.18	6.0	0.11	3.9
Penicillin G Procaine	588.71	0.10	3.3	0.06	3.5
Penicillin G sodium	356.38	0.18	6.0	0.11	3.8
Phenacaine hydrochloride (holocaine hydrochloride)	352.85	0.20	5.3	0.11	3.3

TABLE 8–4. (continued)

Substance	*MW*	*E*	*V*	$\Delta T_f^{1\%}$	L_{iso}
Phenobarbital sodium	254.22	0.24	8.0	0.14	3.6
Phenol	94.11	0.35	11.7	0.20	1.9
Phenylephrine hydrochloride (neosynephrine hydrochloride)	203.67	0.32	9.7	0.18	3.5
Physostigmine salicylate	413.46	0.16	5.3	0.09	3.9
Physostigmine sulfate	648.45	0.13	4.3	0.08	5.0
Pilocarpine nitrate	271.27	0.23	7.7	0.14	3.7
Potassium acid phosphate (KH_2PO_4)	136.13	0.43	14.2	0.25	3.4
Potassium chloride	74.55	0.76	25.3	0.45	3.3
Potassium iodide	166.02	0.34	11.3	0.20	3.3
Procaine hydrochloride	272.77	0.21	7.0	0.12	3.4
Quinine hydrochloride	396.91	0.14	4.7	0.08	3.3
Quinine and urea hydrochloride	547.48	0.23	7.7	0.14	7.4
Scopolamine hydrobromide (hyoscine hydrobromide)	438.32	0.12	4.0	0.07	3.1
Silver nitrate	169.89	0.33	11.0	0.19	3.3
Sodium acid phosphate ($NaH_2PO_4 \cdot H_2O$)	138.00	0.40	13.3	0.24	3.2
Sodium benzoate	144.11	0.40	13.3	0.24	3.4
Sodium bicarbonate	84.00	0.65	21.7	0.38	3.2
Sodium bisulfite	104.07	0.61	20.3	0.36	3.7
Sodium borate·$10H_2O$	381.43	0.42	14.0	0.25	9.4
Sodium chloride	58.45	1.00	33.3	0.58	3.4
Sodium iodide	149.92	0.39	13.0	0.23	3.4
Sodium nitrate	85.01	0.68	22.7	0.39	3.4
Sodium phosphate, anhydrous	141.98	0.53	17.7	0.31	4.4
Sodium phosphate·$2H_2O$	178.05	0.42	14.0	0.25	4.4
Sodium phosphate·$7H_2O$	268.08	0.29	9.7	0.17	4.6
Sodium phosphate·$12H_2O$	358.21	0.22	7.3	0.13	4.6
Sodium propionate	96.07	0.61	20.3	0.36	3.4
Sodium sulfite, exsiccated	126.06	0.65	21.7	0.38	4.8
Streptomycin sulfate	1457.44	0.07	2.3	0.04	6.0
Strong silver protein	—	0.08	2.7	0.05	—
Sucrose	342.30	0.08	2.7	0.05	1.6
Sulfacetamide sodium	254.25	0.23	7.7	0.14	3.4
Sulfadiazine sodium	272.27	0.24	8.0	0.14	3.8
Sulfamerazine sodium	286.29	0.23	7.7	0.14	3.9
Sulfanilamide	172.21	0.22	7.3	0.13	2.2
Sulfathiazole sodium	304.33	0.22	7.3	0.13	3.9
Tannic acid	—	0.03	1.0	0.02	—
Tetracaine hydrochloride (pontocaine hydrochloride)	300.82	0.18	6.0	0.11	3.2
Tetracycline hydrochloride	480.92	0.14	4.7	0.08	4.0
Tripelennamine hydrochloride (pyribenzamine hydrochloride)	291.83	0.30	7.3	0.17	3.8
Urea	60.06	0.59	19.7	0.35	2.1
Zinc chloride	139.29	0.62	20.3	0.37	5.1
Zinc phenolsulfonate	555.84	0.18	6.0	0.11	5.9
Zinc sulfate·$7H_2O$	287.56	0.15	5.0	0.09	2.5

*The values in Table 8–4 have been obtained from the data of E. R. Hammarlund and K. Pedersen-Bjergaard, J. Am. Pharm. Assoc., Pract. Ed. **19**, 39, 1958; ibid., Sci. Ed. **47**, 107, 1958, and other sources. The values vary somewhat with concentration, and those in the table are for 1 to 3% solutions of the drugs in most instances. A complete table of *E* and ΔT_f values is found in the *Merck Index*, 11th Edition, Merck, Rahway, NJ, 1989, pp. MISC-79 to MISC-103. For the most recent results of Hammarlund, see J. Pharm. Sci. **70**, 1161, 1981; ibid. **78**, 519, 1989.

Key: MW is the molecular weight of the drug; *E* is the sodium chloride equivalent of the drug; *V* is the volume in mL of isotonic solution that can be prepared by adding water to 0.3 g of the drug (the weight of drug in 1 fluid ounce of a 1% solution); $\Delta T_f^{1\%}$ is the freezing point depression of a 1% solution of the drug; and L_{iso} is the molar freezing point depression of the drug at a concentration approximately isotonic with blood and lacrimal fluid.

this value from the concentration of sodium chloride that is isotonic with body fluids, namely, 0.9 g/100 mL.

Example 8–14. A solution contains 1.0 g ephedrine sulfate in a volume of 100 mL. What quantity of sodium chloride must be added to make the solution isotonic? How much dextrose would be required for this purpose?

The quantity of the drug is multiplied by its sodium chloride equivalent *E*, giving the weight of sodium chloride to which the quantity of drug is equivalent in osmotic pressure

$$\text{Ephedrine sulfate: } 1.0 \text{ g} \times 0.23 = 0.23 \text{ g}$$

The ephedrine sulfate has contributed a weight of material osmotically equivalent to 0.23 g of sodium chloride. Since a total of 0.9 g of sodium chloride is required for isotonicity, 0.67 g (0.90 − 0.23) of NaCl must be added.

If one desired to use dextrose instead of sodium chloride to adjust the tonicity, the quantity would be estimated by setting up the following proportion. Since the sodium chloride equivalent of dextrose is 0.16,

$$\frac{1 \text{ g dextrose}}{0.16 \text{ g NaCl}} = \frac{X}{0.67 \text{ g NaCl}}$$

$$X = 4.2 \text{ g of dextrose}$$

Other agents than dextrose may of course be used to replace NaCl. It is recognized that thimerosal becomes less stable in eye drops when a halogen salt is used as an "isotonic agent" (i.e., an agent like NaCl ordinarily used to adjust the tonicity of a drug solution). Reader[40] found that mannitol, propylene glycol, or glycerin—isotonic agents that did not have a detrimental effect on the stability of thimerosal—could serve as alternatives to sodium chloride. The concentration of these agents for isotonicity is readily calculated by use of the equation (see *Example 8–14*):

$$X = \frac{Y\text{ (additional amount of NaCl for isotonicity)}}{E\text{ (grams of NaCl equivalent to 1 g of the isotonic agent)}} \quad (8\text{–}46)$$

where X is the grams of isotonic agent required to adjust the tonicity; Y is the additional amount of NaCl for isotonicity, over and above the osmotic equivalence of NaCl provided by the drugs in the solution; and E is the sodium chloride equivalence of the isotonic agent.

Example 8–15. Let us prepare 200 mL of an isotonic aqueous solution of thimerosal, molecular weight 404.84 g/mole. The concentration of this antiinfective drug is 1:5000, or 0.2 g/1000 mL. The L_{iso} for such a compound, a salt of a weak acid and a strong base (a 1:1 electrolyte), is 3.4 and the sodium chloride equivalent E is

$$E = 17\frac{L_{iso}}{MW} = 17\frac{3.4}{404.84} = 0.143$$

The quantity of thimerosal, 0.04 gram for the 200-mL solution, multiplied by its E value, gives the weight of NaCl to which the drug is osmotically equivalent:

$$0.04\text{ g thimerosal} \times 0.143 = 0.0057\text{ g NaCl}$$

Since the total amount of NaCl needed for isotonicity is 0.9 g/100 mL, or 1.8 g for the 200-mL solution, and since an equivalent of 0.0057 g of NaCl has been provided by the thimerosal, the additional amount of NaCl needed for isotonicity, Y, is

$$Y = 1.80\text{ g NaCl needed} - 0.0057\text{ g NaCl supplied by the drug}$$
$$= 1.794\text{ g}$$

This is the additional amount of NaCl needed for isotonicity. The result, ~1.8 g NaCl, shows that the concentration of thimerosal is so small that it contributes almost nothing to the isotonicity of the solution. Thus, a concentration of 0.9% NaCl or 1.8 g/200 mL is required.

However, from the work of Reader[40] we know that sodium chloride interacts with mercury compounds such as thimerosal to reduce the stability and effectiveness of this preparation. Therefore, we have decided to replace NaCl with propylene glycol as the isotonic agent.

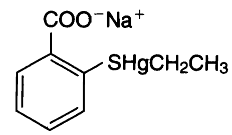
From equation (8–45) we calculate the E value of propylene glycol, a nonelectrolyte with an L_{iso} value of 1.9 and a molecular weight of 76.09 g/mole.

$$E = 17\frac{1.9}{76.09} = 0.42$$

Using equation (8–46), $X = Y/E$,

$$X = 1.794/0.42 = 4.3\text{ g}$$

in which $X = 4.3$ g is the amount of propylene glycol required to adjust the 200-mL solution of thimerosal to isotonicity.



Thimerosal (merthiolate, sodium)

Class II Methods

White–Vincent Method. The Class II methods of computing tonicity involve the addition of water to the drugs to make an isotonic solution, followed by the addition of an isotonic or isotonic-buffered diluting vehicle to bring the solution to the final volume. Stimulated by the need to adjust the pH in addition to the tonicity of ophthalmic solutions, White and Vincent[41] developed a simplified method for such calculations. The derivation of the equation is best shown as follows.

Suppose that one wishes to make 30 mL of a 1% solution of procaine hydrochloride isotonic with body fluid. First, the weight of the drug w is multiplied by the sodium chloride equivalent E.

$$0.3\text{ g} \times 0.21 = 0.063\text{ g} \quad (8\text{–}47)$$

This is the quantity of sodium chloride osmotically equivalent to 0.3 g of procaine hydrochloride.

Second, it is known that 0.9 g of sodium chloride, when dissolved in enough water to make 100 mL, yields a solution that is isotonic. The volume V of isotonic solution that can be prepared from 0.063 g of sodium chloride (equivalent to 0.3 g of procaine hydrochloride) is obtained by solving the proportion

$$\frac{0.9\text{ g}}{100\text{ mL}} = \frac{0.063\text{ g}}{V} \quad (8\text{–}48)$$

$$V = 0.063 \times \frac{100}{0.9} \quad (8\text{–}49)$$

$$V = 7.0\text{ mL} \quad (8\text{–}50)$$

In equation (8–49), the quantity 0.063 is equal to the weight of drug w multiplied by the sodium chloride equivalent E as seen in equation (8–47). The value of the ratio 100/0.9 is 111.1. Accordingly, equation (8–49) may be written

$$V = w \times E \times 111.1 \quad (8\text{–}51)$$

in which V is the volume in milliliters of isotonic solution that may be prepared by mixing the drug with water, w the weight in grams of the drug given in the problem, and E the sodium chloride equivalent obtained from Table 8–4. The constant, 111.1, represents the volume in milliliters of isotonic solution obtained by dissolving 1 g of sodium chloride in water.

The problem may be solved in one step using equation (8–51):

$$V = 0.3 \times 0.21 \times 111.1$$
$$V = 7.0\text{ mL}$$

TABLE 8–5. *Isotonic and Isotonic-Buffered Diluting Solutions**

Isotonic Diluting Solutions	
Isotonic sodium chloride solution	USP
Dextrose solution	5.6%
Sodium nitrate solution	1.3%
Ringer's solution	USP
Isotonic-Buffered Diluting Solutions	
Diluting Solution I, pH 4.7	
Used for salts such as those of epinephrine, cocaine, dionin, metycaine, nupercaine, optochin, phenacaine, pontocaine, procaine, physostigmine, syntropan, and zinc. For dispensing salts of physostigmine and epinephrine, 2g of sodium bisulfite may be added to the solution to minimize discoloration.	
Boric acid, c.p. (H_3BO_3)	20.0 g
Suitable preservative, q.s.	
Sterile distilled water, q.s. ad	1000 mL
Diluting Solution II, pH 6.8	
Primarily used for salts of pilocarpine, which are stable for about a month in this buffer.	
Sodium acid phosphate ($NaH_2PO_4 \cdot H_2O$) monohydrate	4.60 g
Disodium phosphate (Na_2HPO_4) anhydrous	4.73 g
Sodium chloride, c.p.	4.80 g
Suitable preservative, q.s.	
Sterile distilled water, q.s. ad	1000 mL
Diluting Solution III, pH 7.4	
May be used as a neutral collyrium or as a solvent for drugs that are stable in a neutral solution.	
Potassium acid phosphate (KH_2PO_4) anhydrous	1.90 g
Disodium phosphate (Na_2HPO_4) anhydrous	8.10 g
Sodium chloride, c.p.	4.11 g
Suitable preservative, q.s.	
Sterile distilled water q.s. ad	1000 mL
Diluting Solution IV, pH 9	
Used where an alkaline buffer is desired for ophthalmic drugs.	
Boric acid	0.43 g
Sodium borate	4.20 g
Suitable preservative, q.s.	
Sterile distilled water, q.s. ad	1000 mL

*From H. W. Hind and F. M. Goyan, J. Am. Pharm. Assoc., Sci. Ed. **36**, 33, 413, 1947; H. W. Hind and I. J. Szekely, J. Am. Pharm. Assoc., Pract. Ed. **14**, 644, 1953; H. B. Kostenbauder, F. B. Gable and A. Martin, J. Am. Pharm. Assoc., Sci. Ed. **42**, 210, 1953.

In order to complete the isotonic solution, enough isotonic sodium chloride solution, another isotonic solution, or an isotonic-buffered diluting solution is added to make 30 mL of the finished product. Several isotonic and isotonic-buffered diluting solutions are found in Table 8–5. These solutions all have isotonicity values of 0.9% NaCl.

When more than one ingredient is contained in an isotonic preparation, the volumes of isotonic solution, obtained by mixing each drug with water, are additive.

Example 8–16. Make the following solution isotonic with respect to an ideal membrane.

Phenacaine hydrochloride	0.06 g
Boric acid	0.30 g
Sterilized distilled water, enough to make	100.0 mL

$$V = [(0.06 \times 0.20) + (0.3 \times 0.50)] \times 111.1$$

$$V = 18 \text{ mL}$$

The drugs are mixed with water to make 18 mL of an isotonic solution, and the preparation is brought to a volume of 100 mL by adding an isotonic diluting solution.

Sprowls Method. A further simplification of the method of White and Vincent was introduced by Sprowls.[42] He recognized that equation (8–51) could be used to construct a table of values of V when the weight of the drug w was arbitrarily fixed. Sprowls chose as the weight of drug 0.3 g, the quantity for 1 fluid ounce of a 1% solution. The volume V of isotonic solution that can be prepared by mixing 0.3 g of a drug with sufficient water may be computed for drugs commonly used in ophthalmic and parenteral solutions. The method as described by Sprowls[42] is further discussed in several reports by Martin and Sprowls[43] It is now found in the U.S. Pharmacopeia, XXI, p. 1339. A modification of the original table has been made by Hammarlund and Pedersen-Bjergaard[44] and is given in column 4 of Table 8–4, where the volume in milliliters of isotonic solution for 0.3 g of the drug, the quantity for 1 fluid ounce of a 1% solution, is listed. (The volume of isotonic solution in milliliters for 1 g of the drug can also be listed in tabular form if desired by multiplying the values in column 4 by 3.3). The primary quantity of isotonic solution is finally brought to the specified volume with the desired isotonic or isotonic-buffered diluting solutions.

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Problems

8–1. One desires to adjust a solution to pH 8.8 by the use of a boric acid–sodium borate buffer. What approximate ratio of acid and salt is required?

Answer: The acid:salt ratio is 1:0.36

8–2. What is the pH of a solution containing 0.1 mole of ephedrine and 0.01 mole of ephedrine hydrochloride per liter of solution?

Answer: pH = 10.36

8–3. **(a)** What is the pH of a buffer consisting of 0.12 M NaH_2PO_4 and 0.08 M Na_2HPO_4, the former acting as the acid and the latter as the salt or conjugate base (see Cohen et al.[45])? **(b)** What is the value when the ionic strength corrections are made using the Debye–Hückel law? *Hint:* Use equation (8–15). The value for n in the terms pK_n and $(2n - 1)$ is 2 in this problem since the second stage of ionization of phosphoric acid is involved. Thus the equation becomes

$$pH = 7.21 + \log \frac{[Na_2HPO_4]}{[NaH_2PO_4]} - \frac{0.51 \times 3\sqrt{\mu}}{1 + \sqrt{\mu}}$$

Answers: **(a)** pH = 7.03; **(b)** pH = 6.46

8–4. What is the pH of an elixir containing 0.002 mole/liter of the free acid sulfisoxazole, and 0.20 mole/liter of the 1:1 salt sulfisoxazole diethanolamine? The pK_a of the acid is 5.30. The activity coefficient γ_{sulf} can be obtained from the appropriate Debye–Hückel equation for this ionic strength. The effect of any alcohol in the elixir on the value of the dissociation constant may be neglected.

Answer: pH = 7.14

8–5. Ascorbic acid (molecular weight 176.12) is too acidic to administer by the parenteral route. The acidity of ascorbic acid is partially neutralized by adding a basic compound, usually sodium carbonate or sodium bicarbonate. Thus, the injectable product contains sodium ascorbate, ascorbic acid, and the neutralizing agent. The molecular weight of ascorbic acid, together with its pK_a, is found in Table 7–2.

(a) What is the pH of an injectable solution containing only ascorbic acid in the concentration of 55 g per liter of solution? $K_1 = 5 \times 10^{-5}$ and $K_2 = 1.6 \times 10^{-12}$.

(b) What is the molar ratio of sodium ascorbate to ascorbic acid, and the percentage of each compound required to prepare an injectable solution with a pH of 5.7?

Answers: **(a)** pH = 2.40; **(b)** a 25.1:1 ratio of sodium ascorbate to ascorbic acid, or 96.2 mole percent sodium ascorbate and 3.8 percent of ascorbic acid

8–6. Physostigmine salicylate is used in ophthalmic solutions as a mydriatic and to decrease the intraocular pressure in glaucoma.

(a) What is the pH of a 0.5 percent aqueous solution of physostigmine salicylate, molecular weight 413.5? This compound is the salt of a weak acid, and the pH of the solution may be obtained using equation (7–127) as long as the concentration of the salt, C_s, is much greater than $[H_3O^+]$. The *acidity* constant for the physostigmine cation, K_1, is $10^{-14}/(7.6 \times 10^{-7})$, and the acidity constant for salicylic acid, K_2, is 1.06×10^{-3}. The calculation of the pH of a salt of a weak base and a weak acid is demonstrated in *Example 7–22*. We can disregard the second step in the ionization of physostigmine.

(b) How much is the pH increased by addition to the solution of 0.1% physostigmine base, molecular weight 275.34? See the Henderson–Hasselbalch equation (8–10) for the pH of a solution of a weak base and its corresponding salt.

Answers: **(a)** pH = 5.43; **(b)** an increase of 1.93 pH units

8–7. The thermodynamic dissociation exponent pK_1 for carbonic acid at 30° C is 6.33. According to Van Slyke et al.[46] the ionic strength of the blood is roughly 0.16. Compute the apparent dissociation exponent pK'_1 to be used for the carbonic acid of blood at 30° C. Notice that the pH or $-\log a_{H^+}$ is given by the expression

$$\text{pH} = \text{p}K_1' + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

$$= \text{p}K_1 + \log \frac{[HCO_3^-]}{[H_2CO_3]} + \log \gamma_{HCO_3^-}$$

Therefore,

$$\text{p}K_1' = \text{p}K_1 + \log \gamma_{(HCO_3^-)} \cong \text{p}K_1 - 0.5\sqrt{\gamma}$$

Answer: $\text{p}K_1' = 6.13$

8–8. Plot the buffer capacity–pH curve for a barbituric acid–sodium barbiturate buffer of total concentration 0.2 M over the range of pH 1 to 7. What is the maximum buffer capacity and at what pH does β_{max} occur?

Answer: $\beta_{max} = 0.115$ and it occurs at pH 3.98

8–9. What is the buffer capacity of a solution containing 0.20 M acetic acid and 0.10 M sodium acetate?

Answer: $\beta = 0.15$

8–10. Your product research director asks you to prepare a buffer solution of pH 6.5 having a buffer capacity of 0.10. Choose a suitable combination of buffer species and compute the concentrations needed.

One possible answer: Na_2HPO_4 (salt) = 0.052 M
NaH_2PO_4 (acid) = 0.265 M

8–11. To a buffer containing 0.1 mole/liter each of sodium formate and formic acid, 0.01 gram equivalent/liter of sodium hydroxide was added. What is the average buffer capacity of the solution over this pH range?

Answer: $\beta = 0.111$ (if pH is not rounded to 3.84 one may get $\beta =$ 0.115 instead of 0.111)

8–12. What is the buffer capacity of a solution containing 0.36 M boric acid at a pH of 7.0? What is the buffer capacity at pH 9.24, i.e., where pH = $\text{p}K_a$? At what pH is β a maximum and what is the value of β_{max}? What is the buffer capacity at pH 10.8? Using the calculated values of β, plot the buffer capacity versus pH. If the student wishes to smooth the buffer curve a little better, he or she may also calculate β at pH 8.20 and at 10.0. When these six points are plotted on the graph and a smooth line is drawn through them, a bell-shaped buffer curve is obtained. See Figure 8–4 for the shapes of several buffer curves.

Partial Answer: β at pH 7.0 = 0.0048; β at pH 8.2 = 0.064; β at pH 9.24 = 0.21; β at pH 10.8 = 0.021, β_{max} is found at pH 9.24 where pH = $\text{p}K_a$; $\beta_{max} = 0.576C = 0.21$.

8–13. What is the buffer capacity for a Sörensen phosphate buffer **(a)** at pH 5.0 and **(b)** at pH 7.2? The total buffer concentration is 0.067 M, and the dissociation constant is $K_2 = 6.2 \times 10^{-8}$

Answers: **(a)** $\beta = 0.001$; **(b)** $\beta = 0.04$

8–14. A borate buffer contains 2.5 g of sodium chloride (molecular weight 58.5 g/mole); 2.8 g of sodium borate, decahydrate (molecular weight 381.43); 10.5 g of boric acid (molecular weight 61.84); and sufficient water to make 1000 mL of solution. Compute the pH of the solution **(a)** disregarding the ionic strength, and **(b)** taking into account the ionic strength.

Answers: **(a)** pH disregarding ionic strength is 7.87; **(b)** including ionic strength, pH = 7.79

8–15. Calculate the buffer capacity of an aqueous solution of the strong base sodium hydroxide having a hydroxyl ion concentration of 3.0×10^{-3} molar.

Answer: $\beta = 0.0069$

8–16. **(a)** What is the final pH of a solution after mixing 10 mL of a 0.10-M HCl solution with 20 mL of a 0.10-M procaine solution? The $\text{p}K_b$ for procaine is found in Table 7–2. **(b)** Does the solution exhibit buffer capacity?

Answers: **(a)** pH = 8.8; **(b)** $\beta_{max} = 0.039$; it shows a weak buffer capacity.

8–17. Assuming that the total bicarbonate buffer concentration in normal blood is about 0.026 mole/liter, what would be the maximum buffer capacity of this buffer and at what pH would β_{max} occur?

Answer: $\beta_{max} = 0.015$ at pH 6.1 (see pp. 177, 178)

8–18. Describe in detail how you would formulate a buffer having approximately the same pH, ionic strength, and buffer capacity as that of blood. The ionic strength of the blood plasma is about 0.16 and the buffer capacity in the physiologic pH range is approximately 0.03 (p. 177). Use the Na_2HPO_4/NaH_2PO_4 buffer and $\text{p}K_2$ of phosphoric acid. Activity coefficients must be considered, and the thermodynamic $\text{p}K_2$ of phosphoric acid must be used to obtain the answer.

Answer: A mixture of 0.044 Na_2HPO_4 and 0.0105 NaH_2PO_4 has a buffer capacity of 0.03 and provides a pH of 7.4. The ionic strength of this mixture is 0.12. The ionic strength may be raised to 0.16 by the addition of 0.04 M NaCl or KCl.

8–19. A titration is conducted beginning with 50 mL of 0.2 N acetic acid and adding **(a)** 10 mL; **(b)** 25 mL; **(c)** 50 mL; and **(d)** 50.1 mL of 0.2 N NaOH. What is the pH after each increment of base has been added?

Answers: **(a)** 4.16; **(b)** 4.76; **(c)** 8.88; **(d)** 10.3

8–20. Plot the pH titration curve for the neutralization of 0.1 N barbituric acid by 0.1 N NaOH. What is the pH of the solution at the equivalence point?

Answer: pH = 8.34

8–21. A 1 fluid ounce (29.573 mL) solution contains 4.5 grains (291.60 mg) of silver nitrate. How much sodium nitrate must be added to this solution to make it isotonic with nasal fluid? Assume that nasal fluid has an isotonicity value of 0.9% NaCl.

Answer: 3.83 grains = 248 mg

8–22. Compute the Sprowls V value, the E value, and the freezing point depression of a 1% solution of diphenhydramine hydrochloride.

Answer: $V = 6.7$ mL, $E = 0.20$, $\Delta T_f = 0.12$

8–23. A 25% solution of phenylpropanolamine hydrochloride is prepared. The physician desires that 0.25 fluid ounce (7.393 mL) of this solution be made isotonic and adjusted to a pH of 6.8. The Sprowls V value is 12.7. Discuss the difficulties that are encountered in filling the physician's request. How might these difficulties be overcome?

8–24. **(a)** Compute the isotonic concentration (molarity) from the L_{iso} values given in Table 8–4 for the following substances: sodium borate·$10H_2O$ (sodium tetraborate), phenylephrine hydrochloride, physostigmine sulfate, and calcium gluconate.

(b) What is the volume of water that should be added to 0.3 gram of these substances to produce an isotonic solution?

Partial Answer: **(a)** 0.0553, 0.149, 0.104, 0.124 mole/liter; **(b)** check your results against Table 8–4—they may differ from the table values.

8–25. Compute the freezing point depression of 1% solutions of the following drugs: **(a)** ascorbic acid, **(b)** calcium chloride, **(c)** ephedrine sulfate, and **(d)** methacholine chloride. The percentages of sodium chloride required to make 100 mL of 1% solutions of these drugs isotonic are 0.81%, 0.48%, 0.76%, and 0.67%, respectively. *Hint:* Refer to *Example 8–11*.

Answers: Check your results against Table 8–4.

8–26. **(a)** Compute the approximate sodium chloride equivalent of MgO (molecular weight = 40.3 g/mole), $ZnCl_2$ (molecular weight = 136.3 g/mole), $Al(OH)_3$ (molecular weight = 77.98 g/mole), and isoniazid (a tuberculostatic drug, weak electrolyte, molecular weight = 137.2 g/mole), using the average L_{iso} values given in Table 8–3. **(b)** From the E value you calculated in (a), compute the freezing point depression of a 1% solution of these drugs. **(c)** Can one actually obtain a 1% aqueous solution of MgO or $Al(OH)_3$?

Answers: **(a)** $E = 0.84$, 0.60, 1.31, and 0.25; **(b)** $\Delta T_f^{1\%} = 0.49°$ C, 0.35° C, 0.76° C, and 0.15° C

8–27. Using the sodium chloride equivalent method, make the following solutions isotonic with respect to the mucous lining of the eye (ocular membrane).

(a) Tetracaine hydrochloride — 10 grams
NaCl — x grams
Sterilize distilled water, enough to make 1000 mL

(b) Tetracaine hydrochloride — 0.10 gram
Boric acid — x grams
Sterile distilled water, enough to make 10 mL

Answers: (a) add 7.2 grams of NaCl; (b) add 0.14 gram of boric acid.

8–28. Make the following solution isotonic with respect to blood:

Chlorpromazine hydrochloride	2.5 grams
Ascorbic acid	0.2 gram
Sodium bisulfite	0.1 gram
Sodium sulfate, anhydrous	0.1 gram
Sterile distilled water, enough to make	100 mL

Hint: First, compute the E values of chlorpromazine HCl and sodium sulfate, not given in Table 8–4, from the approximate L_{iso} values given in Table 8–3. The molecular weight of chlorpromazine hydrochloride is 318.9 daltons* and the molecular weight of sodium sulfate is 142.06 daltons.

Answer: Dissolve the drugs in 66.44 mL of water. This solution is isotonic. Add 0.3 gram of NaCl and bring to a volume of 100 mL.

8–29. A new drug having a molecular weight of 300 g/mole produced a freezing point depression of 0.52° C in a 0.145-M solution. What are the calculated L_{iso} value, the E value, and the V value for this drug?

Answer: $L_{iso} = 3.6$, $E = 0.20$, $V = 6.7$ mL

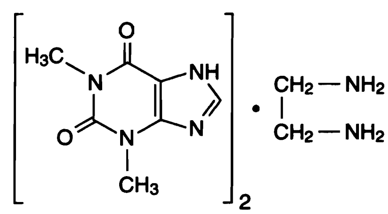
8–30. Using the sodium chloride method, calculate the grams of sodium chloride needed to make 30 mL of a 2% isotonic physostigmine salicylate solution.

Answer: 0.174 gram

8–31. Compute the percent nonionized aminophylline ($pK_b = 5.0$ and molecular weight 421.2 daltons) and its molar concentration after intravenous injection of 10 mL of an aqueous 2.5 w/v solution of aminophylline at 25° C. The normal pH of blood is about 7.4 and the total blood volume is approximately 5 liters. Use the Henderson–Hasselbalch equation in the form

$$pH = pK_w - pK_b - \log \frac{[BH^+]}{[B]}$$

where $\frac{[BH^+]}{[B]}$ is the ratio of ionized to nonionized drug.



Aminophylline

Answer: Percent of nonionized aminophylline = 2.5%, corresponding to 3.0×10^{-6} mole/liter.

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*The word *dalton* is used in connection with molecular weight: 1 dalton = 1 g/mole.