8 Buffered and Isotonic Solutions

Chapter Objectives

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

1. Understand the common ion effect.
2. Understand the relationship between pH, pK_a, and ionization for weak acids and weak bases.
3. Apply the buffer equation, also known as the Henderson–Hasselbalch equation, for a weak acid or base and its salt.
4. Understand the relationship between activity coefficients and the buffer equation.
5. Discuss the factors influencing the pH of buffer solutions.
6. Understand the concept and be able to calculate buffer capacity.
7. Describe the influence of concentration on buffer capacity.
8. Discuss the relationship between buffer capacity and pH on tissue irritation.
9. Describe the relationship between pH and solubility.
10. Describe the concept of tonicity and its importance in pharmaceutical systems.
11. Calculate solution tonicity and tonicity adjustments.

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

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 can 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.

Key Concept

What is a Buffer?

A combination of a weak acid and its conjugate base (i.e., its salt) or a weak base and its conjugate acid acts as a buffer. 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

$$Ac^- + H_3O^+ \rightleftharpoons HAc + H_2O \qquad (8\text{–}1)$$

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

$$HAc + OH^- \rightleftharpoons H_2O + Ac^- \qquad (8\text{–}2)$$

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

$$K_a = \frac{[H_3O^+][Ac^-]}{[HAc]} = 1.75 \times 10^{-5} \qquad (8\text{–}3)$$

is momentarily disturbed because 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,

$$HAc + H_2O \rightleftharpoons H_3O^+ + Ac^- \qquad (8\text{–}4)$$

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:

$$[H_3O^+] = K_a \frac{[HAc]}{[Ac^-]} \qquad (8\text{–}5)$$

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 $[Ac^-]$ can be considered as having come entirely from the salt, sodium acetate. Because 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 as

$$[H_3O^+] = K_a \frac{[Acid]}{[Salt]} \qquad (8\text{–}6)$$

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

$$-\log [H_3O^+] = -\log K_a - \log [Acid] + \log [Salt] \qquad (8\text{–}7)$$

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

$$pH = pK_a + \log \frac{[Salt]}{[Acid]} \qquad (8\text{–}8)$$

The ratio [Acid]/[Salt] in equation (8-6) has been inverted by undertaking the logarithmic operations in equation (8-7), and it appears in equation (8-8) as [Salt]/[Acid]. The term pK_a, the negative logarithm of K_a, is called the *dissociation exponent*.

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
pH Calculation

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 (7-102):

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

$$pH = 2.38 + 0.50 = 2.88$$

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 1/100 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. The following example demonstrates the calculation involved in such a problem.

Example 8-2
pH and [Salt]/[Acid] Ratio

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 can be derived in a manner analogous to that for the weak acid buffers. Accordingly,

$$[\text{OH}^-] = K_b \frac{[\text{Base}]}{[\text{Salt}]} \qquad (8\text{–}9)$$

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

$$\text{pH} = \text{p}K_w - \text{p}K_b + \log \frac{[\text{Base}]}{[\text{Salt}]} \qquad (8\text{–}10)$$

Example 8-3

Using the Buffer Equation

What is the pH of a solution containing 0.10 mole of ephedrine and 0.01 mole of ephedrine hydrochloride per liter of solution? Since the pK_b of ephedrine is 4.64,

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

$$\text{pH} = 9.36 + \log 10 = 10.36$$

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:

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

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_{H3O}^+, yields the equations

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

$$\text{pH} = \text{p}K_a + \log \frac{[\text{Salt}]}{[\text{Acid}]} + \log \gamma_{Ac^-} \qquad (8\text{–}13)$$

From the Debye–Hückel expression 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

$$\text{pH} = \text{p}K_a + \log \frac{[\text{Salt}]}{[\text{Acid}]} - \frac{0.5\sqrt{\mu}}{1 + \sqrt{\mu}} \qquad (8\text{–}14)$$

The general equation for buffers of polybasic acids is

$$\mathrm{pH} = \mathrm{p}K_n + \log \frac{[\mathrm{Salt}]}{[\mathrm{Acid}]} - \frac{\mathrm{A}(2n-1)\sqrt{\mu}}{1+\sqrt{\mu}} \qquad (8\text{–}15)$$

where *n* is the stage of the ionization.

Example 8-4

Activity Coefficients and Buffers

A buffer contains 0.05 mole/liter of formic acid and 0.10 mole/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*)

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

$$= 3.93$$

(*b*)

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

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 can also be brought about by dilution. The addition of water in moderate amounts, although 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. Bates3 expressed this quantitatively in terms of a *dilution value*, which is the change in pH on diluting the buffer solution to one half of its original strength. Some dilution values for National Bureau of Standards buffers are given in Table 8-1. 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.

Table 8-1 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

Temperature also influences buffers. Kolthoff and Tekelenburg4 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 changes significantly with temperature. Bates3 referred 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 the study by Bates.

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 of 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.

The dissociation of an acid indicator is given in simplified form as

$$\underset{\substack{\text{Acid}_1\\(\text{Acid color})}}{\text{HIn}} + \underset{\text{Base}_2}{\text{H}_2\text{O}} \rightleftharpoons \underset{\text{Acid}_2}{\text{H}_3\text{O}^+} + \underset{\substack{\text{Base}_1\\(\text{Alkaline color})}}{\text{In}^-} \qquad (8\text{–}16)$$

The equilibrium expression is

$$\frac{[\text{H}_3\text{O}^+][\text{In}^-]}{[\text{HIn}]} = K_{\text{In}} \qquad (8\text{–}17)$$

Table 8-2 Color, pH, and Indicator Constant, pK_{In}, of Some Common Indicators

Indicator	Color		pH Range	pK_{In}
	Acid	Base		
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	–

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 8-2.

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

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

and because [HIn] represents the acid color of the indicator and the conjugate base [In^-] represents the basic color, these terms can be replaced by the concentration expressions [Acid] and [Base]. The formula for pH as derived from equation (8-18) becomes

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

Example 8-5
Calculate pH

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 8-2 a pK_{In} of 5.1 is observed for methyl red. What is the pH of this solution? We have

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

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 can 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 can thus be expressed as

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

Chemical indicators are typically compounds with chromophores that can be detected in the visible range and change color in response to a solution's pH. Most chemicals used as indicators respond only to a narrow pH range. Several indicators can be combined to yield so-called *universal indicators* just as buffers can be mixed to cover a wide pH range. A universal indicator is a pH indicator that displays different colors as the pH transitions from pH 1 to 12. A typical universal indicator will display a color range from red to purple8

For example, a strong acid (pH 0–3) may display as red in color, an acid (pH 3–6) as orange–yellow, neutral pH (pH 7) as green, alkaline pH (pH 8–11) as blue, and purple for strong alkaline pH (pH 11–14). The colorimetric method for the determination of pH is probably less accurate and less convenient but is also less expensive than electrometric methods and it can be used in the determination of the pH of aqueous solutions that are not colored or turbid. This is particularly useful for the study of acid–base reactions in nonaqueous solutions. A note of caution should be added regarding the colorimetric method. Because 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 and can withstand the addition of an indicator without a significant change in pH. Errors in the result can also be introduced by the presence of salts and proteins, and these errors must be determined for each indicator over the range involved.

Recently, Kong et al.5 reported on a rapid method for determining pK_a based on spectrophotometric titration using a universal pH indicator. Historically, potentiometric titration, which typically uses pH electrodes, has been the most commonly used method for determining pK_a values. This method takes time and requires the daily calibration of the pH electrode. Spectrophotometric titration has the advantage that less sample is required, it is not affected by CO_2 interference, and it can provide multiwavelength absorbance information. The method can be applied only to compounds with chromophores placed close to the titratable groups. The indicator spectra can then be used to calculate the pH value of a solution from the pK_a values, concentration, and molar extinction coefficients of the indicator species. In contrast to pH electrodes, chemical indicators respond rapidly and do not require frequent calibration.

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 combinations of weak acids and weak bases together with their salts manifest this buffer action. 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 Spiro1 and Van Slyke2 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

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

can be used, in which delta, Δ, has its usual meaning, a *finite change*, and Δ*B* is the small increment in gram equivalents (g Eq)/liter of strong base added to the buffer solution to produce a pH change of Δ pH. According to equation **(**8-23**)**, the buffer capacity of a solution has a value of 1 when the addition of 1 g 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

$$\underset{(0.1-0.01)}{\text{HAc}} + \underset{(0.01)}{\text{NaOH}} \rightleftharpoons \underset{(0.1+0.01)}{\text{NaAc}} + \text{H}_2\text{O} \qquad \textbf{(8–24)}$$

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

$$\text{pH} = \text{p}K_a + \log\frac{[\text{Salt}] + [\text{Base}]}{[\text{Acid}] - [\text{Base}]} \qquad \textbf{(8–25)}$$

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

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

The results of the continual addition of sodium hydroxide are shown in Table 8-1. The student should verify the pH values and buffer capacities by the use of equations **(**8-25**)** and **(**8-23**)**, respectively.

As can be seen from Table 8-1, the buffer capacity is not a fixed value for a given buffer system but instead 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, 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 because, 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 Spiro1 and Van Slyke2 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
Calculating Buffer Capacity

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/liter, and the dissociation constant is 1.75×10^{-5}. We have

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

Example 8-7
Buffer Capacity and pH

Prepare a buffer solution of pH 5.00 having a capacity of 0.02. The steps in the solution of the problem are as follows:

a. Choose 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. Use the buffer capacity equation (8-27) 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 8-1, when 0.01 mole of base is added to a 0.1 molar acetate buffer, the pH increases from 4.76 to 4.85, for a ΔpH of 0.09.

If the concentration of acetic acid and sodium acetate is raised to 1 M, 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, for a ΔpH of only 0.01. The calculation, disregarding activity coefficients, is

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

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.

Maximum Buffer Capacity

An equation expressing the maximum buffer capacity can be derived from the buffer capacity formula of Koppel and Spiro1 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 the denominator of equation (8-27) gives

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

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

where C is the total buffer concentration.

Example 8-8

Maximum Buffer Capacity

What is the maximum buffer capacity of an acetate buffer with a total concentration of 0.020 mole/liter? We have

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

Key Concept

Buffer Capacity

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.

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 can be expressed according to the method of Brönsted and Lowry. The neutralization of a strong acid by a strong base and a weak acid by a strong base is written in the form

$$\begin{array}{cccccc} \text{Acid}_1 & \text{Base}_2 & \text{Acid}_2 & \text{Base}_1 \\ H_3O^+(Cl^-) + (Na^+)OH^- = & H_2O & + H_2O + Na^+ + Cl^- \\ HAc \quad + (Na^+)OH^- = & H_2O & + (Na^+)Ac^- \end{array}$$

where $(H_3O^+)(Cl^-)$ 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 as

$$H_3O^+ + OH^- = 2H_2O \qquad (8\text{–}30)$$

Because (Cl^-) and (Na^+) appear on both sides of the reaction equation just given, they may be disregarded without influencing the result. The reaction between the strong acid and the strong base proceeds almost to completion; however, the weak acid–strong base reaction is incomplete because 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 is 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 $[H_3O^+] = 5/15 \times 0.1 = 3.3 \times 10^{-2}$ mole/liter, and the pH is 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.

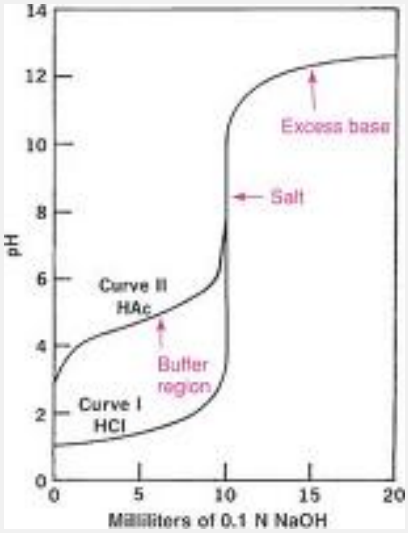

Fig. 8-1. Neutralization of a strong acid and a weak acid by a strong base.

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

$$\beta = 2.303[H_3O^+] \qquad (8\text{–}31)$$

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

$$\beta = 2.303[OH^-] \qquad (8\text{–}32)$$

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

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

Example 8-9
Calculate Buffer Capacity

What is the buffer capacity of a solution of hydrochloric acid having a hydrogen ion concentration of 10^{-2} mole/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 Fig. 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,

$$\begin{aligned} \text{pH} &= \frac{1}{2}\text{p}K_\text{a} - \frac{1}{2}\log c \\ &= 2.38 - \frac{1}{2}\log 10^{-1} = 2.88 \end{aligned}$$

b. At the equivalence point, where the acid has been converted completely into sodium ions and acetate ions, the

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pH is computed from the equation for a salt of a weak acid and strong base in log form:

$$\begin{aligned} \text{pH} &= \frac{1}{2}\text{p}K_\text{w} + \frac{1}{2}\text{p}K_\text{a} + \frac{1}{2}\log c \\ &= 7.00 + 2.38 + \frac{1}{2}\log (5 \times 10^{-2}) \\ &= 8.73 \end{aligned}$$

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, we obtain

$$\begin{aligned} \text{pH} &= \text{p}K_\text{a} + \log \frac{[\text{Salt}]}{[\text{Acid}]} \\ &= 4.76 + \log \frac{5}{5} = 4.76 \end{aligned}$$

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 g Eq 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 inFigure 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 can 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 can be plotted by using the buffer equation and their ends joined by smooth lines to produce the continuous curve of Figure 8-2.

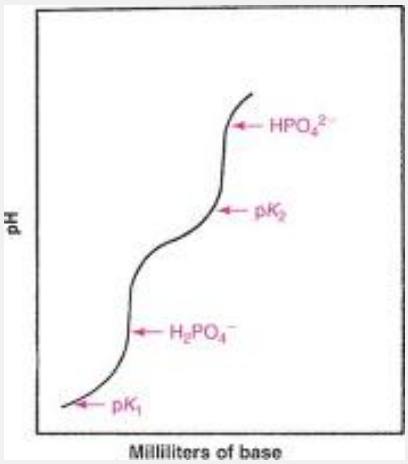

Fig. 8-2. Neutralization of a tribasic acid.

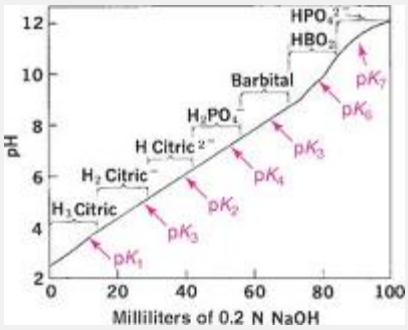

Fig. 8-3. Neutralization curve for a universal buffer. (From H. T. Britton, *Hydrogen Ions*, Vol. I, Van Nostrand, New York, 1956, p. 368.)

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.6 The three stages of citric acid, pK_1 = 3.15, pK_2 = 4.78, and 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, 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 pK_s 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 buffer 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.

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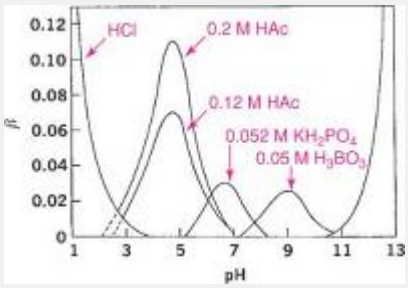


Fig. 8-4. The buffer capacity of several buffer systems as a function of pH. (Modified from R. G. Bates, *Electrometric pH Determinations*, Wiley, New York, 1954.)

The buffer capacity of a combination of buffers whose pK_a values 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 βs 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

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

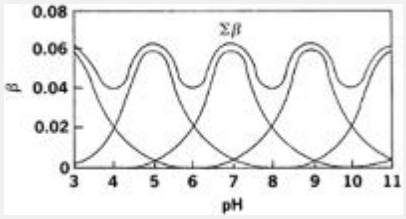


Fig. 8-5. The total buffer capacity of a universal buffer as a function of a pH. (From I. M. Kolthoff and C. Rosenblum, *Acid–Base Indicators*, Macmillan, New York, 1937, p. 29.)

where $[H_2CO_3]$ 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

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

This result checks with experimental findings because 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,7 the buffer capacity of the blood owing to hemoglobin and other constituents, exclusive of bicarbonate, is about 0.025 g 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**)**, we find the buffer capacity for the bicarbonate system ($K_1 = 4 \times 10^{-7}$) at a pH of 7.4 ($[H_3O^+] = 4 \times 10^{-8}$) 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. Salenius8 reported a value of 0.0318 ± 0.0035 for whole blood, whereas Ellison et al.9 obtained a buffer capacity of about 0.039 g equivalents per liter per pH unit for whole blood, of which 0.031 was contributed by the cells and 0.008 by the plasma.

It is usually life-threatening for the pH of the blood to go below 6.9 or above 7.8. The pH of the blood in diabetic coma is 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.10 In the terminology of Bates,11 this would be referred to today as *dilution value* rather than buffer capacity. The pH of tears is about 7.4, with a range of 7 to 8 or slightly higher. It is generally thought that eye drops within a pH range of 4 to 10 will not harm the cornea.12 However, discomfort and a flow of tears will occur below pH 6.6 and above pH 9.0.12 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-hr 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 research studies in which pH must be held constant.

Gifford13 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.

Sörensen14 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 Palitzsch15 and modified by Hind and Goyan16 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,17 based on the original pH scale of Sörensen, have been redetermined at 25°C by Bower and Bates18 so as to conform to the present definition of pH. 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 as follows:

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 inFigure 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 $-\log a_{H^+} = -\log (y \pm c)$ 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 overlaps.

Key Concept

Phosphate Buffered Saline

There are several variations in the formula for preparing PBS. Two common examples follow:

Formula One: Take 8 g NaCl, 0.2 g KCl, 1.44 g Na_2HPO_4, and 0.24 g KH_2PO_4 in 800 mL distilled water. Adjust pH to 7.4 using HCl. Add sufficient (*qs ad*) distilled water to achieve 1 liter.

Formula Two: Another variant of PBS. This one is designated as “10X PBS (0.1 M PBS, pH 7.2)” since it is much more concentrated than PBS and the pH is not yet adjusted to pH 7.4. Take 90 g NaCl, 10.9 g Na_2HPO_4, and 3.2 g NaH_2PO_4 in 1000 mL distilled water. Dilute 1:10 using distilled water and adjust pH as necessary.

Many buffers are available today. One of the most common biological buffers is phosphate buffered saline (PBS). Phosphate buffered saline contains sodium chloride (NaCl) and dibasic sodium phosphate

(Na_2PO_4). It may also contain potassium chloride (KCl), monobasic potassium phosphate (KH_2PO_4), calcium chloride ($CaCl_2$), and magnesium sulfate ($MgSO_4$).

General Procedures for Preparing Pharmaceutical Buffer Solutions

The pharmacist may be called upon at times to prepare buffer systems for which the formulas 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, 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.

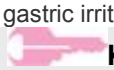
Influence of Buffer Capacity and pH on Tissue Irritation

Friedenwald et al.18 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 Mims19 found that Sörensen's phosphate buffer produced irritation in the eyes of a number of individuals 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 individuals. Martin and Mims concluded that a pH range of nonirritation cannot be established absolutely but instead 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 and partly to the difference of the physiologic response to various ion species.

Riegelman and Vaughn20 assumed that the acid-neutralizing power of tears when 0.1 mL of a 1% solution of a drug is instilled into the eye is roughly equivalent to 10 μL of a 0.01 N strong base. They pointed out that although 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, because 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 10 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.

According to Mason,21 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. Thus, the buffer capacity of the buffer should be optimized to produce rapid absorption and minimal gastric irritation of orally administered aspirin.



Key Concept

Parenteral Solutions

Solutions to be applied to tissues or administered parenterally are liable to cause irritation if their pH is greatly different 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 is the buffer capacity of the solution, (*b*) the smaller is the volume used for a given concentration, and (*c*) the larger are the volume and buffer capacity of the physiologic fluid.

In addition to the adjustment of tonicity and pH for ophthalmic preparations, similar requirements are demanded for nasal delivery of drugs. Conventionally, the nasal route has been used for delivery of drugs for treatment of local diseases such as nasal allergy, nasal congestion, and nasal infections.22 The nasal route can be exploited for the systemic delivery of drugs such as small molecular weight polar drugs, peptides and proteins that are not easily administered via other routes than by injection, or where a rapid onset of action is required. Examples include buserelin, desmopressin, and nafarelin.

Stability versus 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, the undissociated form of a weakly acidic or basic drug often has a higher therapeutic activity than that of 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 White23 and Cogan and Kinsey24 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

Mole Percent of Free Base

The pK_b of pilocarpine is 7.15 at 25°C. Compute the mole percent of free base present at 25°C and at a pH of 7.4. We have

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

$$pH = pK_w - pK_b + \log \frac{[\text{Base}]}{[\text{Salt}]}$$

$$7.4 = 14.00 - 7.15 + \log \frac{[\text{Base}]}{[\text{Salt}]}$$

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

$$\frac{[\text{Base}]}{[\text{Salt}]} = \frac{3.56}{1}$$

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

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

Hind and Goyan25 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

Since the relationship between pH and the solubility of weak electrolytes is treated elsewhere in the book, it is only necessary 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 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 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.

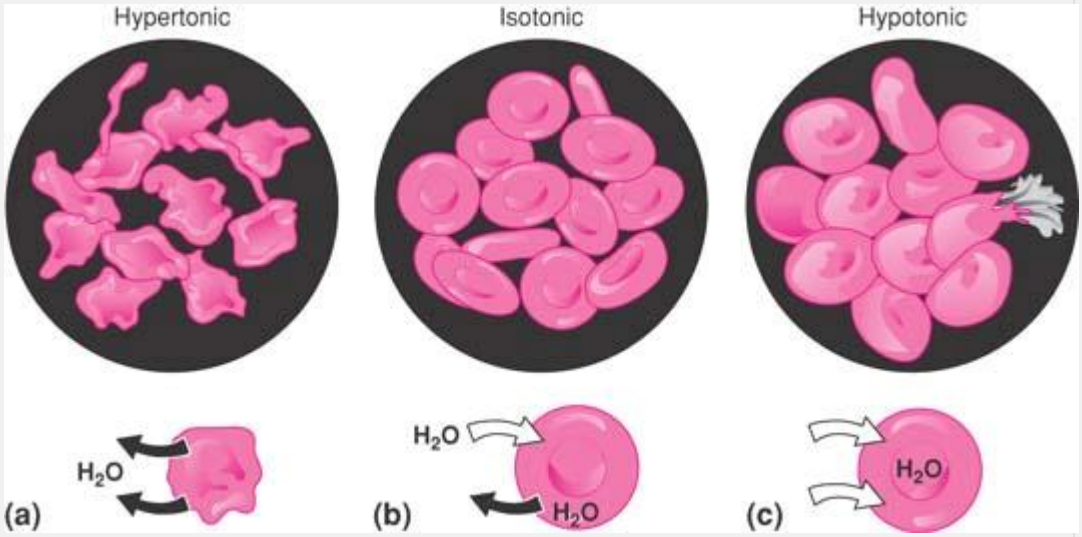
The need to achieve isotonic conditions with solutions to be applied to delicate membranes is dramatically illustrated by mixing a small quantity of blood with aqueous sodium chloride solutions of varying tonicity. For example, if a small quantity of blood, defibrinated to prevent clotting, is mixed with a solution containing 0.9 g of 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.26 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. Because it is 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.

Key Concept

Tonicity



Osmolality and osmolarity are colligative properties that measure the concentration of the solutes independently of their ability to cross a cell membrane. Tonicity is the concentration of only the solutes that cannot cross the membrane since these solutes exert an osmotic pressure on that membrane. Tonicity is *not* the difference between the two osmolarities on opposing sides of the membrane. A solution might be hypertonic, isotonic, or hypotonic relative to another solution. For example, the relative tonicity of blood is defined in reference to that of the red blood cell (RBC) cytosol tonicity. As such, a hypertonic solution contains a higher concentration of impermeable solutes than the cytosol of the RBC; there is a net flow of fluid out of the RBC and it shrinks (Panel A). The concentration of impermeable solutes in the solution and cytosol are equal and the RBCs remain unchanged, so there is no net fluid flow (Panel B). A hypotonic solution contains a lesser concentration of such solutes than the

RBC cytosol and fluid flows into the cells where they swell and potentially burst (Panel C). In short, 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 (drug) molecules and permeable to the solvent, water.

To overcome this difficulty, Husa27 suggested that the term *isotonic* should be restricted to solutions having equal osmotic pressures with respect to a particular membrane. Goyan and Reck28 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 of NaCl per 100 mL of solution need not *necessarily* be isotonic with respect to the living membranes concerned, 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 can be buffered.

Measurement of Tonicity

The tonicity of solutions can 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 associates27used this method. In their later work, a quantitative method developed by Hunter29 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 can be determined and the value compared with that computed from cryoscopic data, osmotic coefficient, and activity coefficient.30 Husa found that a drug having the proper *i* value as measured by freezing point depression or computed from theoretical 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.

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.

The second approach used to measure tonicity is based on any of the methods that determine colligative properties earlier in the book. Goyan and Reck28investigated various modifications of the Hill–Baldes technique31 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) is that of Lumiere and Chevrotier,32 in which the values of -0.56°C and -0.80°C were given, respectively, for the two fluids. Following work by Pedersen-Bjergaard and coworkers,33,34 however, it is now well established that -0.52°C 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

Because 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, $L = i K_f$, is introduced to overcome this difficulty.35 The equation, already discussed is

$$\Delta T_f = Lc \qquad \textbf{(8–36)}$$

The L value can 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 written as L_{iso}.

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

$$L_{iso} = \frac{\Delta T_f}{c} \qquad \textbf{(8–37)}$$

we have

$$L_{iso} = \frac{0.52^\circ\text{C}}{0.154} = 3.4$$

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 given 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 $i K_f$ against molar concentration of various types of electrolytes, from which the values of L_{iso} can be read, is shown in Figure 6-7 (in Chapter 6, "Electrolytes and Ionic Equilibria").

Example 8-11

Freezing Point Lowering

What is the freezing point lowering of a 1% solution of sodium propionate (molecular weight 96)? Because 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. We have

$$\Delta T_f = 3.4 \times 0.104 = 0.35^\circ\text{C} \qquad \textbf{(8–38)}$$

Although 1 g/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 accuracy greater than about 10% is implied or needed in these calculations.

The calculation of Example 8-11 can be simplified by expressing molarity c as grams of drug contained in a definite volume of solution. Thus,

$$\text{Molarity} = \frac{\text{Moles}}{\text{Liter}} = \frac{\text{Weight in grams}}{\text{Molecular weight in g/mole}} \div \frac{\text{Volume in mL}}{1000\ \text{mL/liter}} \qquad \textbf{(8–39)}$$

or

$$c = \frac{w}{\text{MW}} \times \frac{1000}{v} \qquad \textbf{(8–40)}$$

where 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) gives

$$\Delta T_f = L_{iso} \times \frac{w \times 1000}{\text{MW} \times v} \qquad \textbf{(8–41)}$$

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:

$$\Delta T_f = 3.4 \times \frac{1 \times 1000}{96 \times 100} = 3.4 \times 0.104 = 0.35^\circ\text{C}$$

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 for long. The L_{iso} values can 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 can 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°C 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 given 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 theoretical 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

Isotonicity

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

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

Thus, 0.76% sodium chloride will lower the freezing point the required 0.44°C 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.36 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 g, 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 formulas derived by Goyan et al.37 For a solution containing 1 g of drug in 1000 mL of solution, the concentration *c* expressed in moles/liter can be written as

$$c = \frac{1\text{ g}}{\text{Molecular weight}} \qquad (8\text{–}42)$$

and from equation (8-36)

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

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,

$$\Delta T_f = 3.4\frac{E}{58.45} \qquad (8\text{–}43)$$

where 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

$$\frac{L_{iso}}{\text{MW}} = 3.4\frac{E}{58.45} \qquad (8\text{–}44)$$

$$E \cong 17\frac{L_{iso}}{\text{MW}} \qquad (8\text{–}45)$$

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
Amphetamine sulfate	368.49	0.22	7.3	0.13	4.8
Antipyrine	188.22	0.17	5.7	0.10	1.9
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
Diphenhydramine hydrochloride	291.81	0.20	6.6	0.34	3.4
Boric acid	61.84	0.50	16.7	0.29	1.8
Caffeine	194.19	0.08	2.7	0.05	0.9
Dextrose·H_2O	198.17	0.16	5.3	0.09	1.9
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 hydrochloride	219.66	0.29	9.7	0.17	3.7

Glycerin	92.09	0.34	11.3	0.20	1.8
Lactose	360.31	0.07	2.3	0.04	1.7
Morphine hydrochloride	375.84	0.15	5.0	0.09	3.3
Morphine sulfate	758.82	0.14	4.8	0.08	6.2
Neomycin sulfate	–	0.11	3.7	0.06	–
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
Phenobarbital sodium	254.22	0.24	8.0	0.14	3.6
Phenol	94.11	0.35	11.7	0.20	1.9
Potassium chloride	74.55	0.76	25.3	0.45	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
Sodium chloride	58.45	1.00	33.3	0.58	3.4
Streptomycin sulfate	1457.44	0.07	2.3	0.04	6.0
Sucrose	342.30	0.08	2.7	0.05	1.6
Tetracycline hydrochloride	480.92	0.14	4.7	0.08	4.0

Urea	60.06	0.59	19.7	0.35	2.1
Zinc chloride	139.29	0.62	20.3	0.37	5.1

*The values were obtained from the data of E. R. Hammarlund and K. Pedersen-Bjergaard, J. Am. Pharm. Assoc. Pract. Ed. **19,** 39, 1958; J. Am. Pharm. Assoc. 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 Ed., Merck, Rahway, N. J., 1989, pp. MISC-79 to MISC-103. For the most recent results of Hammarlund, see J. Pharm. Sci. **70,** 1161, 1981; **78,** 519, 1989.
Key: MW = molecular weight of the drug; *E* = sodium chloride equivalent of the drug; *V* = 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); $\Delta T_f^1\%$ = freezing point depression of a 1% solution of the drug; L_{iso} = the molar freezing point depression of the drug at a concentration approximately isotonic with blood and lacrimal fluid.

†The full table is available at the book's companion website at thepoint.lww.com/Sinko6e.

Example 8-13
Sodium Chloride Equivalents
Calculate the approximate *E* value for a new amphetamine hydrochloride derivative (molecular weight 187).
Because 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 this value from the concentration of sodium chloride that is isotonic with body fluids, namely, 0.9 g/100 mL.

Example 8-14
Tonicity Adjustment
A solution contains 1.0 g of 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. Because a total of 0.9 g of sodium chloride is required for isotonicity, 0.67 g (0.90 - 0.23 g) 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. Because 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 can 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). Reader38 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)

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

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
Isotonic Solutions

Let us prepare 200 mL of an isotonic aqueous solution of thimerosal, molecular weight 404.84 g/mole. The concentration of this anti-infective 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 g for the 200-mL solution, multiplied by its E value gives the weight of NaCl to which the drug is osmotically equivalent:

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

Because the total amount of NaCl needed for isotonicity is 0.9 g/100 mL, or 1.8 g for the 200-mL solution, and because 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 of 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 Reader38 we know that sodium chloride interacts with mercury compounds such as thimerosal to reduce the stability and effectiveness of this preparation. Therefore, we 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), $X = Y/E$, we obtain

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

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

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 Vincent39 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*:

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

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

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

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

$$V = 7.0\,\text{mL} \qquad \textbf{(8–50)}$$

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**)** can be written as

$$V = w \times E \times 111.1 \qquad \textbf{(8–51)}$$

where *V* is the volume in milliliters of isotonic solution that may be prepared by mixing the drug with water, *w* is the weight in grams of the drug given in the problem, and *E* is 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.

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The problem can be solved in one step using equation **(**8-51**)**:

$$V = 0.3 \times 0.21 \times 111.1$$

$$V = 7.0\,\text{mL}$$

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.

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

Isotonic Solutions

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.

The Sprowls Method

A further simplification of the method of White and Vincent was introduced by Sprowls.40 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 can be computed for drugs commonly used in ophthalmic and parenteral solutions. The method as described by Sprowls40 is further discussed in several reports by Martin and Sprowls.41 The table can be found in the *United States Pharmacopeia.* A modification of the original table was made by Hammarlund and Pedersen-Bjergaard42 and the values of *V* are 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.

Chapter Summary

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*. If a small amount of a strong acid or base is added to water or a solution of sodium chloride, the pH is altered considerably; such systems have no buffer action. In this chapter, the theory of buffers was introduced as were several formulas for making commonly used buffers. Finally, the important concept of tonicity was introduced. Pharmaceutical buffers must usually be made isotonic so that they cause no swelling or contraction of biological tissues, which would lead to discomfort in the patient being treated. Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

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Recommended Readings

R. J. Benyon, *Buffer Solutions (The Basics)*, BIOS Scientific Publishers, Oxford, UK, 1996.

Chapter Legacy

Fifth Edition: published as Chapter 9 (Buffered and Isotonic Solutions). Updated by Patrick Sinko.
Sixth Edition: published as Chapter 8 (Buffered and Isotonic Solutions). Updated by Patrick Sinko.