Buffers

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.

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**.

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:**

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

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.**

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

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

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.**

The Buffer Equation for a Weak Base and Its Salt

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,

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

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

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

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

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

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

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

The general equation for buffers of polybasic acids is

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

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**. Bates 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. **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 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. Bates 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.

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

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

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

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 Spiro and Van Slyke 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

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

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.

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

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

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

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

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

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

The results of the continual addition of sodium hydroxide are shown in Table below. 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 below, 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.

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

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 and Van Slyke 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.

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 above, 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

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

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*.

Maximum Buffer Capacity

An equation expressing the maximum buffer capacity can be derived from the buffer capacity formula of Koppel and Spiro and Van Slyke, 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

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

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

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

where *C* is the total buffer concentration.

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

$$\underset{\text{Acid}_1}{H_3O^+(Cl^-)} + \underset{\text{Base}_2}{(Na^+)OH^-} = \underset{\text{Acid}_2}{H_2O} + \underset{\text{Base}_1}{H_2O + Na^+ + Cl^-}$$

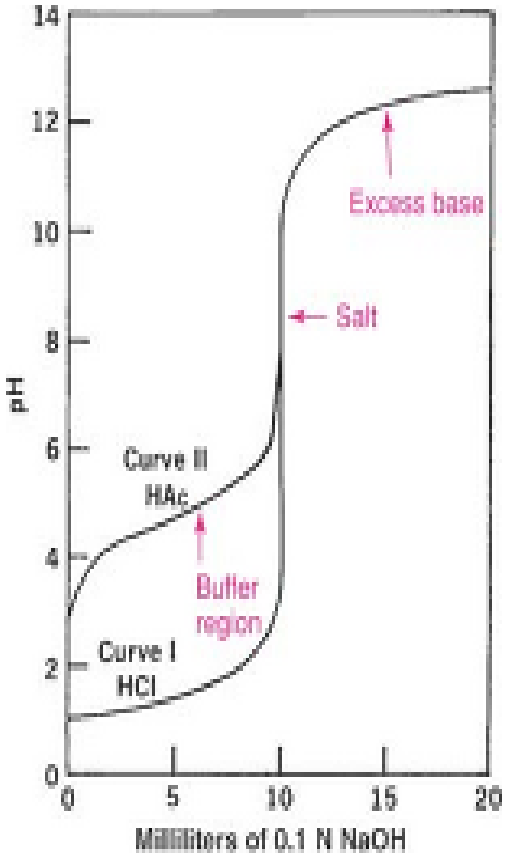
$$HAc + (Na^+)OH^- = H_2O + (Na^+)Ac^-$$

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 . 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 beside 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.

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 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

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

Three equations are normally used to obtain the data for the titration curve of a weak acid (curve II of Fig. above), 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.

1-The pH of the solution before any NaOH has been added is obtained from the equation for a weak acid,

$$\begin{aligned} \mathrm{pH} &= \tfrac{1}{2}\mathrm{p}K_a - \tfrac{1}{2}\log c \\ &= 2.38 - \tfrac{1}{2}\log 10^{-1} = 2.88 \end{aligned}$$

2-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 in log form:

$$\begin{aligned} \mathrm{pH} &= \tfrac{1}{2}\mathrm{p}K_w + \tfrac{1}{2}\mathrm{p}K_a + \tfrac{1}{2}\log c \\ &= 7.00 + 2.38 + \tfrac{1}{2}\log (5 \times 10^{-2}) \\ &= 8.73 \end{aligned}$$

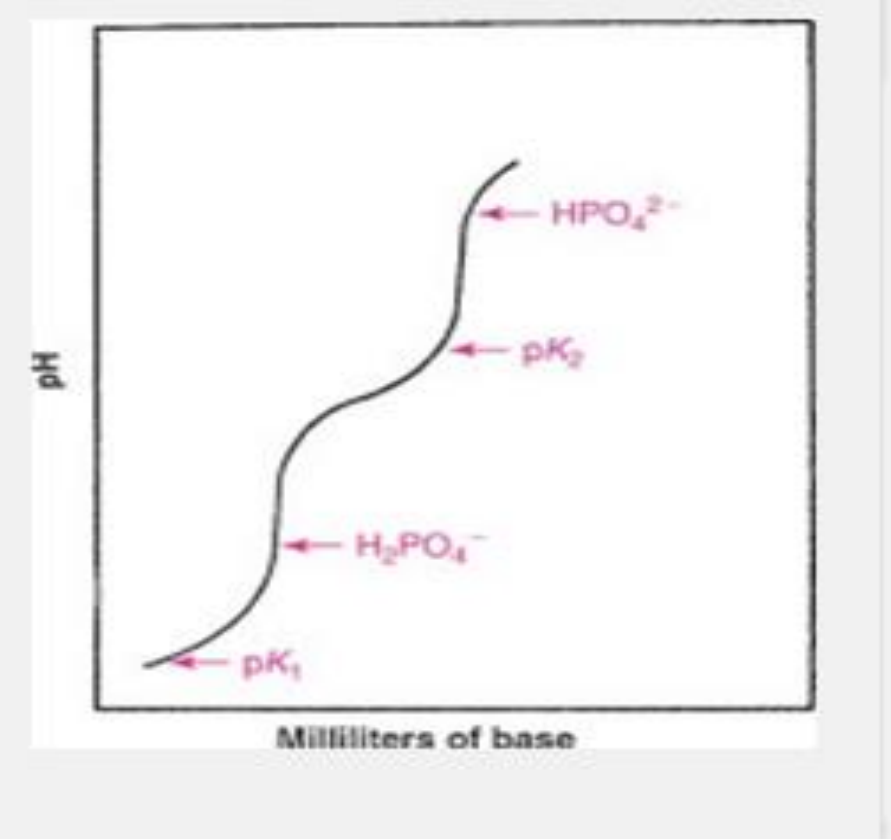
The concentration of the acid is given in the last term of this equation as 0.05 because the solution has been reduced to half its original value by mixing it with an equal volume of base at the equivalence point.

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

$$\mathrm{pH} = \mathrm{p}K_a + \log \frac{[\mathrm{Salt}]}{[\mathrm{Acid}]}$$
$$= 4.76 + \log \frac{5}{5} = 4.76$$

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 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 in Figure above, 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 below. 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.



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

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

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

$$\log \frac{[\mathrm{HCO_3^-}]}{[\mathrm{H_2CO_3}]} = 7.4 - 6.1 = 1.3 \qquad \text{or} \qquad [\mathrm{HCO_3^-}]/[\mathrm{H_2CO_3}] = 20/1 \qquad \textbf{(8–35)}$$

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. In the terminology of Bates, 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. However, discomfort and a flow of tears will occur below pH 6.6 and above pH 9.0.

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.

General Procedures for Preparing Pharmaceutical Buffer Solutions

The following steps should be helpful in the development of a new buffer.

1-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.

2- 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.

3-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.

4-Other factors of some importance in the choice of a pharmaceutical buffer include availability of chemicals, sterility of 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.

5-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

Martin and Mims 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 non irritation 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.

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, 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.

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. 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.

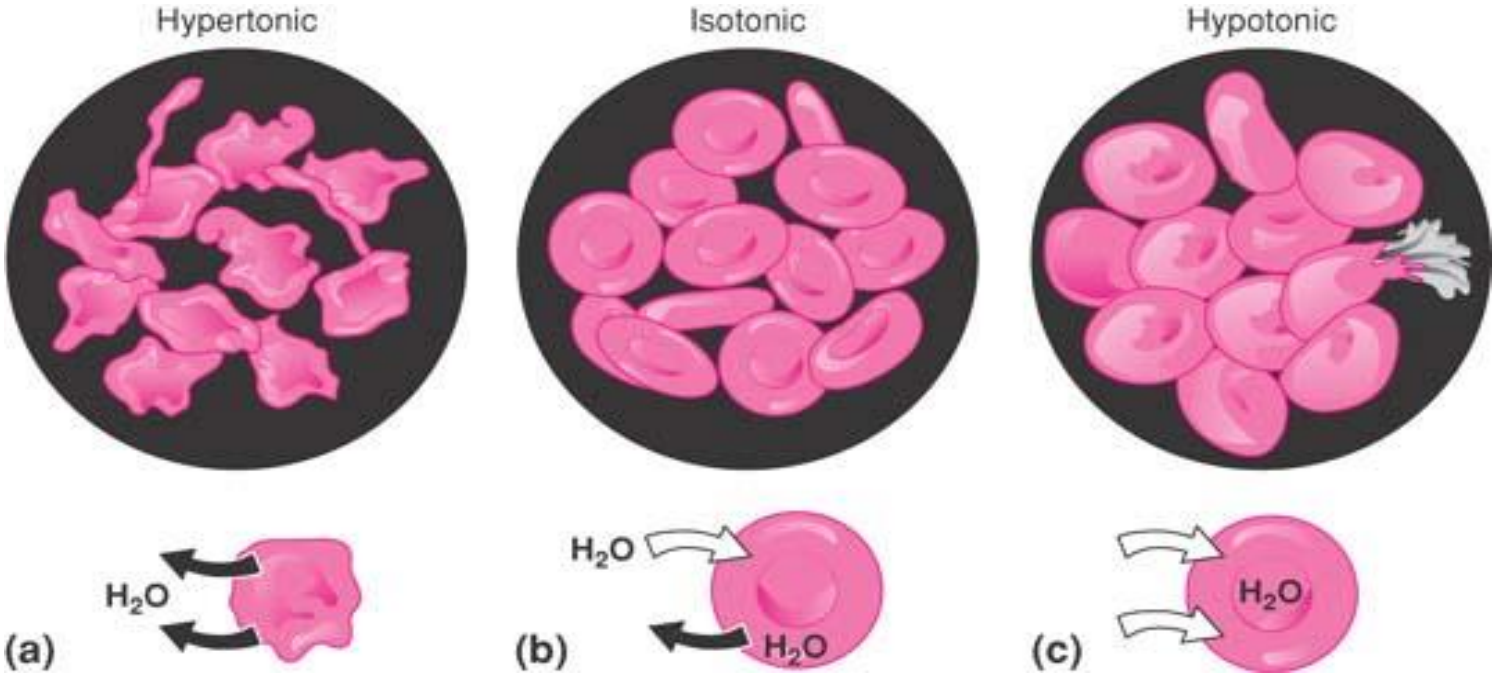
- Stability versus Optimum Therapeutic Response

- pH and Solubility

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.


Hypertonic
Isotonic
Hypotonic
H_2O
H_2O
H_2O
H_2O
(a)
(b)
(c)

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. **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.

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.

To overcome this difficulty, Husa suggested that the **term isotonic should be restricted to solutions having equal osmotic pressures with respect to a particular membrane**. Goyan and Reck 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.

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. The equation, already discussed is

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

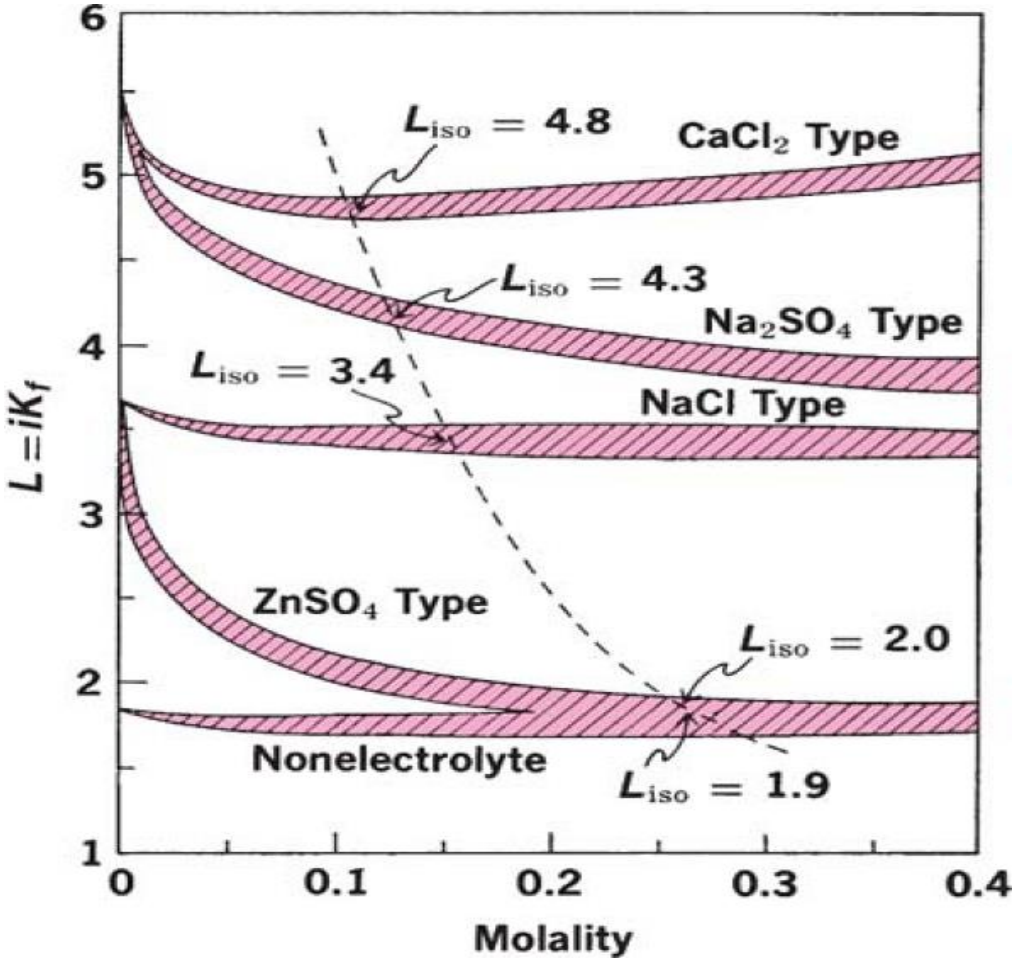
The *L* value can be obtained from *the freezing point lowering* of solutions of representative compounds of a given ionic type at a concentration *c* that is isotonic with body fluids. This specific value of *L* is written as L_{iso}.

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

$$L_{iso} = \frac{\Delta T_f}{c} \qquad (8\text{–}37) \qquad L_{iso} = \frac{0.52^\circ\text{C}}{0.154} = 3.4$$

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.

It will be observed that for dilute solutions of **nonelectrolytes**, L_{iso} is approximately equal to K_f. 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 in Chapter of "Electrolytes and Ionic Equilibria").


6
5
4
3
2
1
$L = iK_f$
$L_{iso} = 4.8$
$CaCl_2$ Type
$L_{iso} = 4.3$
Na_2SO_4 Type
$L_{iso} = 3.4$
NaCl Type
$ZnSO_4$ Type
$L_{iso} = 2.0$
Nonelectrolyte
$L_{iso} = 1.9$
0
0.1
0.2
0.3
0.4
Molality

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.**

The freezing point depressions of a number of drug solutions, determined experimentally or theoretically. 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.

Sodium Chloride Equivalent Method

A second method for adjusting the tonicity of pharmaceutical solutions was developed by Mellen and Seltzer. 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 in the book), it can be calculated from the L_{iso} value or freezing point depression of the drug according to formulas derived by Goyan et al. For a solution containing 1 g of drug in 1000 mL of solution, the concentration *c* expressed in moles/liter can be written as

$$c = \frac{1\text{ g}}{\text{Molecular weight}} \qquad (8\text{–}42) \qquad \Delta T_f = L_{iso}\frac{1\text{ g}}{MW}$$

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,

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

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

$$\frac{L_{iso}}{MW} = 3.4\frac{E}{58.45} \qquad (8\text{–}44) \qquad E \cong 17\frac{L_{iso}}{MW} \qquad (8\text{–}45)$$

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.

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). Reader 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.

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

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.

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 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*:

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

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

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

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

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