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Gordon L. Flynn

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Buffers—pH Control within Pharmaceutical Systems

GORDON L. FLYNN

University of Michigan
Ann Arbor, Michigan

A buffer is a solution of chemicals (buffering agents) which imparts an ability to resist change in the effective acidity or alkalinity of a medium upon the addition of increments of acid or base. Thus, buffers are used to stabilize dosage forms with respect to pH. For practical purposes, quantitative treatment of buffering (the deployment of buffers) is limited to aqueous systems or, stretching a point, to solvent systems containing large proportions of water as it is only in water that the hydrogen ion activity (concentration) and its negative logarithm, pH, are sufficiently defined to construct meaningful scales of acidity and alkalinity, the latter indirectly through the well-characterized dissociation of water involved. In principle, chemical control of alkalinity or acidity extends well beyond the aqueous realm.

Acidity and pH

If one is going to deal with aqueous buffering one must fully understand the relationship between hydrogen ion activity[1] and pH; the latter is the most useful index of acidity as it is the direct output of the common laboratory pH-meter. Sorenson, in 1909, proposed that the relative acidity of a medium be expressed for convenience in terms of the logarithm of its reciprocal hydrogen ion concentration and be called pH. This had the effect of putting acidity essentially in positive terms[2] and on a manageable scale capable of displaying the full range of acidities normally encountered in aqueous systems. Thus

$$\mathrm{pH} = \frac{1}{\log_{10} a_{\mathrm{H}^+}} \simeq \frac{1}{\log_{10}(\mathrm{H}^+)} = -\log_{10}(\mathrm{H}^+) \qquad \text{(Eq. 1)}$$

where (H^+) is the molal hydrogen ion concentration (molal and molar are virtually equal in dilute aqueous solution). The molal concentration is essentially equal to the thermodynamic activity of the hydrogen ion at pH values between 3 and 11 at low ionic strength ($\mu < 0.1$).

The relationship between the concentrations of hydrogen ions and hydroxyl ions in aqueous media is fixed by the dissociation equilibrium of water and it is through this relationship that a useful scale of basicity develops. The equilibrium is expressed by:

$$H_2O \rightleftharpoons H^+ + OH^- \qquad \text{(Eq. 2)}$$

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[1] In some references, (H^+) is used to represent the hydrogen ion in discussions of acid-base equilibria; other authors prefer (H_3O^+), the hydronium ion, as the acidic species. Both are oversimplifications of the existing state of a proton in aqueous medium and either is adequate symbolically. In this article (H^+) will be used as the concentration of the hydrated proton.

[2] For extremely acidic aqueous solutions with hydrogen ion activity in excess of 1.0 the pH is negative or less than zero.

and it has an ion product equilibrium constant rigorously defined in terms of species activities by:

$$K_W = (a_H)(a_{OH^-}) \qquad \text{(Eq. 3}a\text{)}$$

but which approximates at low ionic strength and intermediate pH to:

$$K_W = (H^+)(OH^-) \qquad \text{(Eq. 3}b\text{)}$$

The latter is couched in terms of species concentrations. The constant, K_W, for pure water at 25 °C is 1.008×10^{-14} but is highly temperature sensitive; the temperature dependency is shown in Table I which gives K_W and pKw values for pure water as a function of temperature. It follows from Eqs. 1-3 that the hydroxyl ion concentration of a solution can be formulated in terms of a pOH ($-\log (OH^-)$) and that the pKw or the negative logarithm of the ion product is:

$$\text{pKw} = \text{pH} + \text{pOH} \qquad \text{(Eq. 4)}$$

Since acidity [(H^+) or pH] and not basicity [(OH^-) or pOH] is directly measured experimentally, equilibria involving organic bases are often written in terms of the hydrogen ion concentration by substituting for (OH^-) its equivalent, $K_W/(H^+)$. This will be illustrated momentarily.

Pharmaceutical Uses of Buffers

A discussion of buffering applications might profitably precede the treatment of specific buffer equilibria and the theories of buffering, to demonstrate the relevancy and broad applicability of pH control and buffering in pharmacy. Buffering techniques find utility in research, in the formulation of dosage forms, as adjunctive treatment in therapy, and in direct topical and systemic therapy.

In research, buffers are employed to provide controlled acidity [or basicity (pOH)] in investigations of rates of physical and chemical processes and of equilibria. This is so because pH is a critical variable in most studies involving aqueous systems as both chemical reaction rates and the positions of diverse equilibria such as acid/base equilibria, partitioning equilibria, and solubility equilibria are *directly* affected by the acidity of the media. Further, acidity or alkalinity affect the viability and function of cells and tissues and research on such preparations must be performed at carefully controlled pH.

TABLE I. Ionization Constant for Water As A Function of Temperature

Temperature, °C	**$K_W \times 10^{14}$**	**pKw**
0	0.1139	14.9435
5	0.1846	14.7338
10	0.2920	14.5346
15	0.4505	14.3463
20	0.6809	14.1669
25	1.008	13.9965
30	1.469	13.8330
35	2.089	13.6801
40	2.919	13.5348
45	4.018	13.3960
50	5.474	13.2617
55	7.296	13.1369
60	9.614	13.0171

Such sensitivities of chemical and biological systems to pH are readily illustrated. In Fig. 1 the classic log ($k_{observed}$) vs. pH-profile for aspirin (acetylsalicylic acid) at 17 °C is displayed. The chemical species undergoes both acid and base catalysis of its solvolysis and, in addition, the chemical forms in which it exists as a function of pH, free acid, and acid anion, exhibit markedly different solvolytic sensitivities. To study such reactions at a given hydrogen ion or hydroxyl ion concentration, buffers must be used. In Fig. 2 the buccal absorption of a series of simple alkanoic acids (R-COOH) is shown as a function of pH. In this case the process is pH dependent because the partitioning equilibrium between the buccal mucosal tissue and the applied solutions is pH dependent. Changes in the chemical structure—in this case, changes in the alkyl chain length—alter this equilibrium at a given pH and thereby cause a shift in the pH profile for each chemical species on the pH axis. Importantly, the systems must be buffered to obtain the absorption rate for a particular acid at a predetermined pH to offset the natural

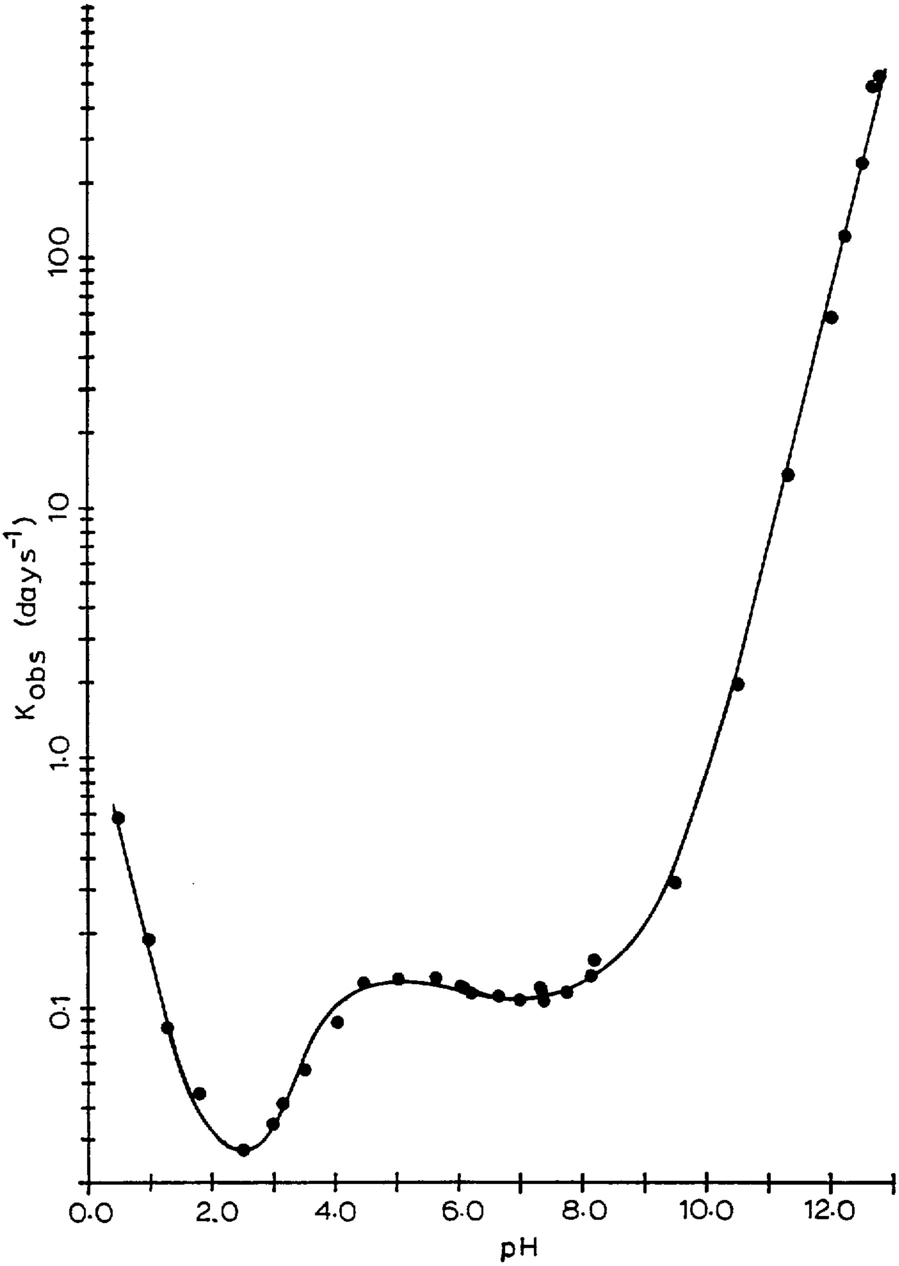

Figure 1—The observed rate constant for the hydrolysis of aspirin at 17 °C as a function of pH. Various buffers were used to keep the pH constant at specific points on the pH profile. Data of L. J. Edwards [Trans. Faraday. Soc., **46**, 723 (1950)] replotted.

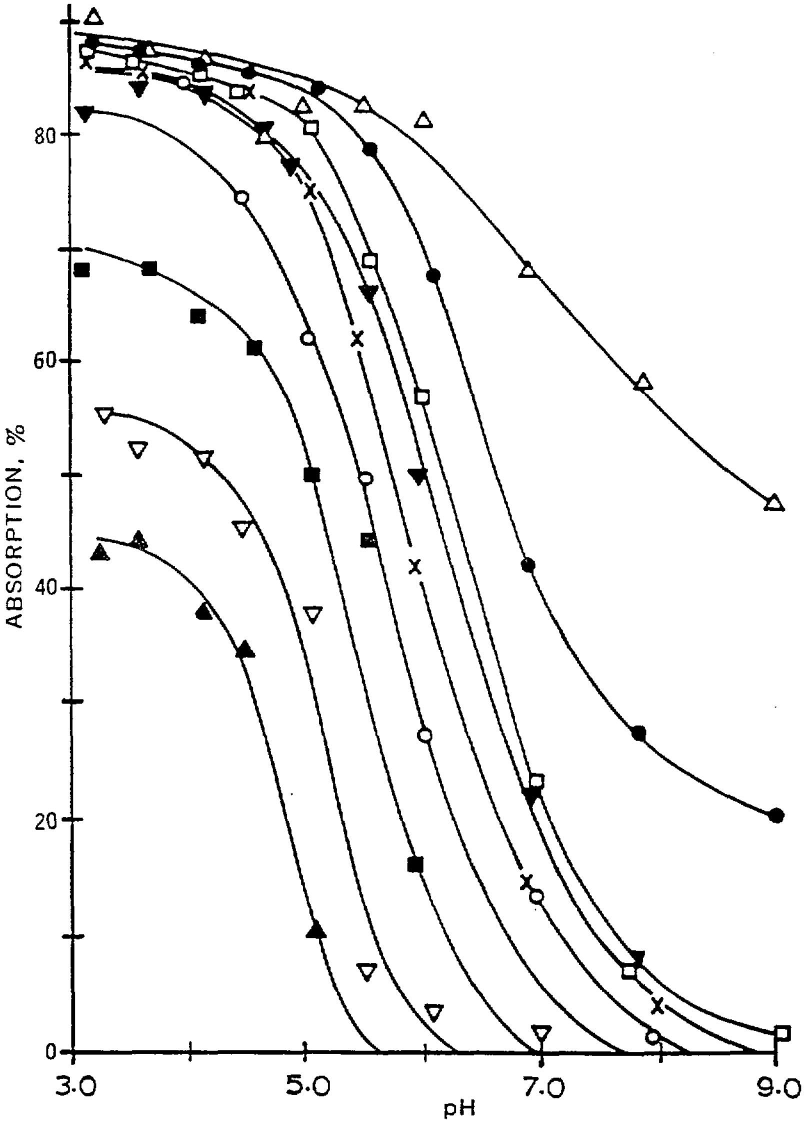

Figure 2—Percent of alkanoic acid absorbed after 5-min duration in the buccal cavity as a function of pH and as a function of alkyl chain length. Data are from Beckett and Moffat [*J. Pharm. Pharmacol.*, **20**, 239S (1968)] *as treated by Ho and Higuchi* [*J. Pharm. Sci.*, **60**, *537* (*1971*)]. *The compounds represented are butanoic acid,* ▲; *pentanoic acid,* ▽; *hexanoic acid,* ■; *heptanoic acid,* O; *octanoic acid, x; nonanoic acid,* ▼; *decanoic acid,* □; *undecanoic acid,* ●; *and dodecanoic acid,* △.

buffering capacity of saliva. A variety of buffering systems has been developed and characterized for such research purposes. Standard buffer solutions used to calibrate pH measuring instruments are representative examples of these (Table II).

Buffering may also play a role indirectly or directly in therapy. For instance, certain drugs

TABLE II The Seven Standard Buffer Solutions

1. Preparation:
   - A. *Tetroxalate* (0.05 molal) – 12.61 g of $KH_3(C_2O_4)_2 \cdot 2H_2O$ and qs to 1 liter with distilled water.
   - B. *Tartrate* (about 0.034 molal)– shake an excess of reagent grade potassium hydrogen tartrate with water at 25 ± 5 °C for about 3 min.
   - C. *Phthalate* (0.05 molal)—10.12 g of reagent grade potassium hydrogen phthalate and qs to 1 liter with distilled water that has been boiled and then cooled. (As a preservative 0.06 g of thymol may be added per liter without adverse effect.)
   - D. *Phosphate* (0.025 molal KH_2PO_4; 0.025 molal Na_2HPO_4)-3.39 g of reagent grade potassium dihydrogen phosphate and 3.53 g of reagent grade anhydrous disodium hydrogen phosphate in sufficient boiled and cooled distilled water to make 1 liter of solution.
   - E. *Phosphate* (for physiological pH region—0.008695 molal KH_2PO_4 and 0.03043 molal Na_2HPO_4) 1.179 g of reagent grade potassium dihydrogen phosphate and 4.30 g of reagent grade anhydrous disodium hydrogen phosphate in sufficient boiled and cooled distilled water to make 1 liter of solution.
   - F. *Borax* (0.01 molal)-3.80 g of $Na_2B_3O_7 \cdot 10\ H_2O$ and qs to 1 liter with boiled and cooled distilled water. Protect from air to prevent CO_2 absorption.
   - G. *Calcium hydroxide* (0.0203 molal)-shake an excess of reagent grade calcium hydroxide with water for about 3 min at 25 °C.
2. Standard Values of pH at 0°-95-°C

Temperature	Tetroxalate, 0.05 molal	Tartrate, 0.0341 molal (sat'd at 25 °C)	Phthalate, 0.05 molal	Phosphate (D)	Phosphate (E)	Borax, 0.01 molal	Calcium hydroxide (sat'd at 25 °C)
0	1.666	—	4.003	6.984	7.534	9.464	13.423
5	1.668	—	3.999	6.951	7.500	9.395	13.207
10	1.670	—	3.998	6.923	7.472	9.332	13.003
15	1.672	—	3.999	6.900	7.448	9.276	12.810
20	1.675	—	4.002	6.881	7.429	9.225	12.627
25	1.679	3.557	4.008	6.865	7.413	9.180	12.454
30	1.683	3.552	4.015	6.853	7.400	9.139	12.289
35	1.688	3.549	4.024	6.844	7.389	9.102	12.133
38	1.691	3.548	4.030	6.840	7.384	9.081	12.043
40	1.694	3.547	4.035	6.838	7.380	9.068	11.984
45	1.700	3.547	4.047	6.834	7.373	9.038	11.841
50	1.707	3.549	4.060	6.833	7.367	9.011	11.705
55	1.715	3.554	4.075	6.834	—	8.985	11.574
60	1.723	3.560	4.091	6.836	—	8.962	11.449
70	1.743	3.580	4.126	6.845	—	8.921	—
80	1.766	3.609	4.164	6.859	—	8.885	—
90	1.792	3.650	4.205	6.877	—	8.850	—
95	1.806	3.674	4.227	6.886	—	8.833	—

such as the sulfa drugs, are concentrated in post-administration urine. Therapeutic effectiveness within the bladder and a urine solubility sufficient to prevent crystallization of the sulfa drugs (crystaluria) depend on the pH of the urine. Therefore, urine acidifying or alkalizing agents are coadministered with urinary tract drugs to promote their medicinal activity and to ward off untoward effects. Buffering may be therapy itself. All antacids are buffers and the control of excessive stomach acidity or "heart burn" is a direct buffering process. Certain pathophysiological states, such as the respiratory acidosis of asthma (status asthmaticus) and metabolic acidosis of diabetic coma, require direct and prompt intervention with physiologic buffers, such as tromethamine, to reestablish a normal body acidity (pH).

But of greatest importance to pharmaceutical formulators are adjunctive uses of buffers in dosage forms. For such applications buffers must be physiologic, that is, compatible with the body by the selected route of administration. The first and most general purpose of buffering agents in pharmaceutical systems is to establish and sustain a precise chemical environment consistent with maintaining the highest possible degree of physical and chemical integrity of the dosage form, that is, a chemical environment consistent with "good stability." In a limited number of preparations, such as ophthalmic preparations which are directly applied to the ultrasensitive conjunctival membranes of the eye, buffers also function to minimize direct contact irritation and pain due to otherwise nonphysiological pH of formulated drugs. A nonophthalmic example of the latter purpose is the use of sodium bicarbonate to buffer sodium hypochlorite irrigation solution (modified Dakin's solution). When this solution is adjusted to pH 9–10 it is least irritating and it exerts a debriding action on pus and dead tissue but does not dissolve blood clots, which could induce bleeding. Buffers may also function to promote or control the absorption of drugs. For example, the rates of absorption of pilocarpine into the eye and of oral tetracyclines and aspirin have been increased or modified using buffers. Even palatability of preparations may be influenced by buffering. The addition of citric acid to magnesia magma prevents the formation of a bitter taste associated with spontaneously increasing alkalinity, possibly as a result of a magma reaction with glass surfaces.

Buffering—Theoretical Aspects

Ordinary, potable water (tap water, deionized water or distilled water) may be slightly acidic (pH < 7) or slightly alkaline (pH > 7) due to trace contaminants such as dissolved carbon dioxide (acidic) and alkali metals (alkaline) picked up in its purification or storage, but it is, nevertheless, essentially devoid of buffering ability. For instance, the addition of 1/1000 gram equivalent of a strong acid like hydrochloric acid[3] to 1 liter of essentially neutral water decreases the pH from about 7 to 3, which corresponds to a 1000-fold increase (100,000% increase) in hydrogen ion concentration. The same addition to a liter of 0.05 molal phosphate solution at pH = pKa = 6.685 produces a pH drop of 0.035 units to pH 6.65, only an approximately 8% increase in hydrogen ion concentration. The difference in pH sensitivities of these two media, water and phosphate solution, is due to the buffering ability of the latter attributable to the phosphate species equilibrium.

The pH of a buffer solution and the change in pH upon the addition of an acid or base may be estimated from the acid/base equilibrium of the buffering agent or from the so-called "buffer equation." For example, when acetic acid and/or sodium acetate are added to water, in any relative proportion, they interact according to the following reaction scheme:

$$\mathrm{HAc} + \mathrm{H_2O} \overset{K_a}{\rightleftharpoons} \mathrm{H_3O^+} + \mathrm{Ac^-} \qquad \text{(Eq. 5}a\text{)}$$

or, written in a simpler form with the involvement of water implicit:

$$\mathrm{HAc} \overset{K_a}{\rightleftharpoons} \mathrm{H^+} + \mathrm{Ac^-} \qquad \text{(Eq. 5}b\text{)}$$

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[3] One millimole of HCl.

and the dissociation constant, K_a, governing the equilibrium is defined by:

$$K_a = \frac{[H^+][Ac^-]}{[HAc]} = K'_a\,[H_2O] \qquad \text{(Eq. 6}a\text{)}$$

K_a as defined incorporates the concentration of water, about 55.5 molar at 25 °C. For this particular weak acid, $K_a = 1.75 \times 10^{-5}$. Once the equilibrium has been established, and it is established virtually instantaneously, for a given ratio of acid and salt (conjugate base), the pH of the system is fixed by the requirements of the equilibrium and may be calculated from the fact that the molar hydrogen ion concentration is:

$$[H^+] = K_a \frac{[HAc]}{[Ac^-]} \qquad \text{(Eq. 6}b\text{)}$$

or, in a general form for any weak acid,

$$[H^+] = K_a \frac{[\text{undissociated acid}]}{[\text{acid anion}]} = K_a \frac{[\text{“acid”}]}{[\text{“salt”}]} \qquad \text{(Eq. 6}c\text{)}$$

This equation may be expressed in logarithmic form as:

$$\log [H^+] = \log K_a + \log [\text{“Acid”}] - \log [\text{“salt”}] \qquad \text{(Eq. 7}a\text{)}$$

from which is obtained the general buffer equation, often referred to as the Henderson-Hasselbalch equation, for a weak acid and its anionic species:

$$\text{pH} = \text{pKa} + \log \frac{[\text{“salt”}]}{[\text{“acid”}]} \qquad \text{(Eq. 7}b\text{)}$$

The development of the buffer equation here is not rigorous. However, it is very satisfactory for pH and buffer capacity calculations when moderate buffer concentrations are involved at a fixed ionic strength in the pH range 3 to 11. For accurate calculations the influence of ionic strength on the equilibrium must be accounted for. For example, the dissociation constant of acetic acid is rigorously defined by:

$$K_a = \frac{a_{H^+} \cdot a_{Ac^-}}{a_{HAc}} \qquad \text{(Eq. 8)}$$

in which thermodynamic activities have replaced the concentrations in Eq. 6*a*. The relationship between thermodynamic activity of a species and its molal concentration is:

$$a_x = \gamma_x [X] \qquad \text{(Eq. 9)}$$

where γ_x is a normalizing multiplier called the activity coefficient. Substituting this form for each species in Eq. 8 yields:

$$K_a = \frac{\gamma_{H^+}[H^+]\gamma_{Ac^-}[Ac^-]}{\gamma_{HAc}[HAc]} \qquad \text{(Eq. 10}a\text{)}$$

Since it is the thermodynamic activity of the hydrogen ion which is obtained in pH meter measurement, rearrangement of Eq. 10*a* yields:

$$a_{H^+} = \gamma_{H^+}[H^+] = K_a \left(\frac{\gamma_{HAc}}{\gamma_{Ac^-}}\right)\left(\frac{[HAc]}{[Ac^-]}\right) \qquad \text{(Eq. 10}b\text{)}$$

which can be put in terms of the experimental dissociation constant, $(K_a)_{\text{exp}}$, for a given solution as:

$$a_{H^+} = (K_a)_{\text{exp}} \frac{[HAc]}{[Ac^-]} \qquad \text{(Eq. 10}c\text{)}$$

and

$$\text{pH} = (\text{pKa})_{\text{exp}} + \log \frac{[Ac^-]}{[HAc]} \qquad \text{(Eq. 11)}$$

The activity coefficient of the undissociated acid is approximately unity and, for an aqueous solution of a univalent ion, such as the acetate anion, the ion activity coefficient at 25 °C is given by the Debye-Hückel expression:

$$\log \gamma_{Ac^-} = \frac{-0.5\sqrt{\mu}}{1 + \sqrt{\mu}} \qquad \text{(Eq. 12)}$$

where μ is the ionic strength, as long as the ionic strength does not exceed about 0.1. Based on these relationships and approximations, the apparent dissociation constant is related to the thermodynamic dissociation constant in a monobasic acid dissociation approximately by:

$$\text{pKa} = (\text{pKa})_{\text{exp}} + \frac{0.5\sqrt{\mu}}{1 + \sqrt{\mu}} \qquad \text{(Eq. 13)}$$

Analogous buffer equations can be derived for polybasic acids. Of utmost importance is the fact that an operational dissociation constant may not be equal to the thermodynamic one and, since it is pragmatic to work in concentrations, it is necessary to correct tabulated thermodynamic dissociation constants by calculation or to use experimentally determined dissociation constants in actual practice.

A buffer equation may also be defined for weakly basic substances. A weak base may be regarded as a substance with an unshared pair of electrons which reacts with water according to the following generalized, primary equilibrium:

$$B{:} + H_2O \overset{K_b}{\rightleftharpoons} HB^+ + OH^- \qquad \text{(Eq. 14)}$$

The equilibrium constant for the primary equilibrium is defined by:

$$K_b = \frac{[BH^+][OH^-]}{[B{:}]} \qquad \text{(Eq. 15}a\text{]}$$

where again the aqueous molarity is taken up in the dissociation constant. Accordingly,

$$[OH^-] = K_b \frac{[B{:}]}{[BH^+]} \qquad \text{(Eq. 15}b\text{)}$$

which yields

$$\text{pOH} = \text{pKb} + \log \frac{[BH^+]}{[B]} \qquad \text{(Eq. 16)}$$

Substituting the relationship pOH = pKw − pH, one obtains upon rearrangement of terms:

$$\text{pH} = \text{pKw} - \text{pKb} - \log \frac{[BH^+]}{[B{:}]} \qquad \text{(Eq. 17)}$$

and, more generally

$$\text{pH} = \text{pKa} - \log \frac{[\text{conjugate acid}]}{[\text{free base}]}$$

$$= \text{pKa} - \log \frac{[\text{“salt”}]}{[\text{“base”}]} \qquad \text{(Eq. 18)}$$

where pKa is now equal to pKw − pKb and is in fact the dissociation constant for the equilibrium defined in terms of the dissociation of the conjugate acid species, BH^+, according to:

$$BH^+ \overset{K_a}{\rightleftharpoons} H^+ + B{:} \qquad \text{(Eq. 19)}$$

It is implicit in the above that: (*a*), both weak acid and weak base equilibria may be treated in terms of the reaction of either of the pair of involved species with water; (*b*), that it is easier to deal with $[H^+]$ and pH than $[OH^-]$ and pOH in that the former are readily measured; (*c*), that for the pair of possible equilibria reactions associated with a given dissociation the product of K_a and K_b is equal to $K_W (K_aK_b = K_W)$, the previously defined ion product equilibrium constant in water; and (*d*), that the concentration of water is invariant in such equilibria and can therefore be "taken up" in the equilibrium constant.

The use of the buffer equations can now be illustrated. The following examples involving inorganic phosphate equilibria quantitatively define how the buffering effect of weak acids and bases originates. One thousandth gram equivalent of HCl amounts to only 0.086 ml of concentrated HCl (36% w/w) or 1.0 ml of a 1.0 normal solution. As previously mentioned, a milliequivalent of concentrated HCl added to a liter of unbuffered water produces a hydrogen ion concentration of 10^{-3} molar or a pH of 3. In the presence of the phosphate buffer, 0.025 molar in concentration in each of the mono and dianion species, the same addition was seen to have a far different effect. The involved equilibria is defined by:

$$H_2PO_4^- \overset{K_{a2}}{\rightleftharpoons} H^+ + HPO_4^{2-} \qquad \text{(Eq. 20)}$$

where K_{a2} is the second dissociation constant for this polybasic acid. The HCl increment shifts the equilibrium in favor of the $H_2PO_4^-$ form *via* a mass law effect. The concentrations of the phosphate species become:

$$[H_2PO_4^-] = 0.025 + 0.001 = 0.026$$

$$[HPO_4^{2-}] = 0.025 - 0.001 = 0.024$$

and the pH becomes:

TABLE III. Influence of Concentration on Buffering at a Fixed pH

C_T, total buffer conc., M/liter	Assumed pKa	Initial ratio of species	Initial pH	Final ratio of species	Final pH	ΔpH
0.005	6.685	1.0	6.685	0.428	6.317	0.368
0.050[a]	6.685	1.0	6.685	0.923	6.650	0.035
0.500	6.685	1.0	6.685	0.992	6.682	0.003

[a] Detailed example in text.

$$\begin{aligned} pH &= pKa + \log \frac{0.024}{0.026} \\ &= 6.685 - 0.035 \\ &= 6.65 \end{aligned}$$

where 6.685 is the experimentally determined pKa at this total phosphate concentration. If we allow the pKa to be independent of concentration for illustrative purposes and repeat the calculation for buffer solutions respectively 10 times as concentrated and one-tenth as concentrated the results in Table III are obtained. It can be seen from Table III that the capacity to buffer, as measured by ΔpH, the change in pH upon addition of the milliequivalent of strong acid, appears essentially directly dependent on buffer concentration.

The capacity of the phosphate system to resist change in pH by mass law effects at different initial pH values or corresponding species ratios at a constant total phosphate concentration, say 0.05 *M*, is similarly revealing. In Table IV results of calculations on the sensitivities of 0.05M systems prepared to contain 1/10, 1/5, 1/1, 5/1, and 10/1 ratios of $[HPO_4^{2-}]$ to $[H_2PO_4^-]$ are given. It can be seen that the pH alteration produced by a fixed increment of strong acid differs depending on how close the pH is to the pKa. These calculations indicate the capacity to buffer is greatest at the pKa.

The ability of a buffer to resist pH change is, indeed, referred to as the *buffer capacity.* It can be seen that this is, roughly speaking, inversely related to the change in pH induced by a small increment of acid (or base). It is precisely defined as the number of equivalent weights of a strong acid or strong base required to effect a unit change in pH according to:

$$\beta = \left(\frac{dW}{d\,\text{pH}}\right) \qquad \text{(Eq. 22)}$$

where β is the buffer capacity, dW is an infinitesimal increment of acid or base in terms of equivalents and d pH is the infinitesimal alteration in pH produced by dW. Van Slyke

TABLE IV. Influence of pH on Buffering at a Fixed Concentration

C_T, total buffer conc., M/liter	pKa	Initial[a] ratio of species	Initial pH	Final ratio of species	Final pH	ΔpH
0.05	6.685	0.1	5.685	0.0763	5.568	0.117
0.05	6.685	0.2	5.986	0.172	5.921	0.065
0.05[b]	6.685	1.0	6.685	0.923	6.650	0.035
0.05	6.685	5	7.384	4.36	7.323	0.060
0.05	6 685	10	7.685	8.02	7.589	0.096

[a] As defined in text, $[HPO_4^{2-}]/[H_2PO_4^{-}]$.
[b] Detailed example in text.

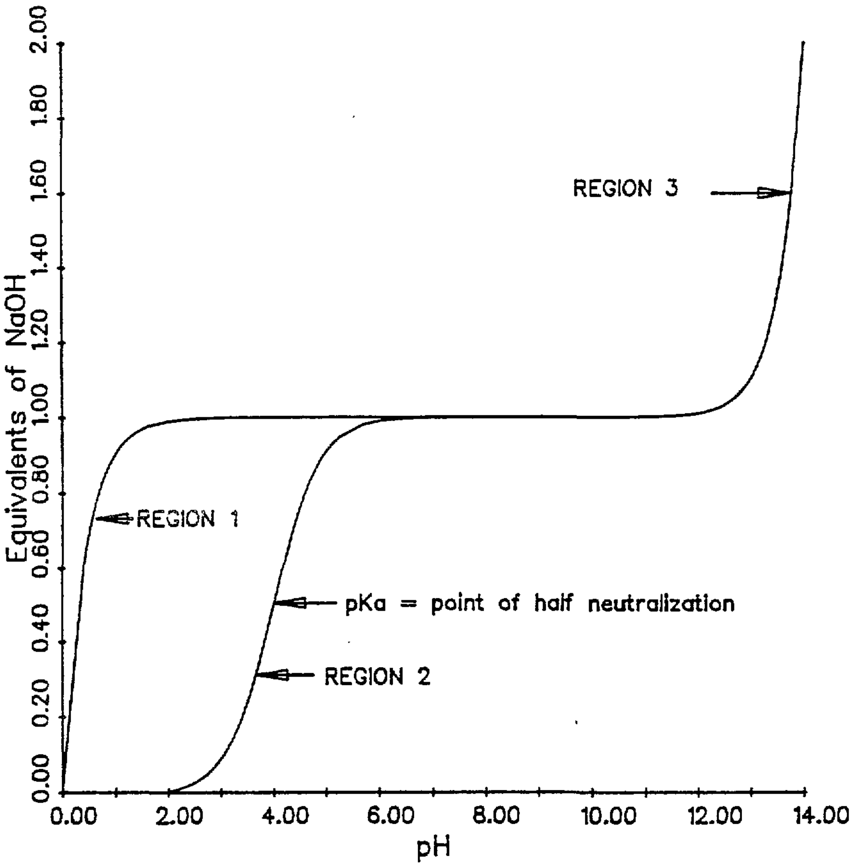


Figure 3—"Reverse" neutralization curves for the neutralization of a strong acid (regions 1 and 3) and a weak acid (regions 2 and 3). The buffer capacity is the tangent to the curve at a given pH. Region 2, which corresponds to the neutralization of a weak acid of pKa = 4 at 1.0 m/liter, has its maximum slope at the midpoint of neutralization, the pKa. Regions 1 and 3 are at pH's where the concentrations of hydrogen ions and hydroxyl ions respectively are sufficiently concentrated to exert a significant buffer effect by themselves (Eqs. 26 and 27).

has shown that this equation may be expressed in the following useful form at intermediate pH values (roughly the pH range 3 to 11):

$$\beta = 2.303\ C_T \frac{K_a[\mathrm{H}^+]}{(K_a + [\mathrm{H}^+])^2} \quad \text{(Eq. 23)}$$

where C_T is the total buffer concentration (sum of the concentrations of the species participating in the equilibrium defined by K_a). Either form of the buffer capacity equation, Eqs. 22 or 23, is the slope (tangent to the curve) of a plot of the equivalent weights of acid (or base) added to a system against pH. Examination of Eq. 23 leads to the conclusion that buffer capacity is directly proportional to total buffer concentration at a given pH, as previously surmised. Furthermore, it was implied that the maximum buffer capacity or point of least sensitivity to added acid occurred at pH = pKa or $[\mathrm{H}^+] = K_a$ (Table IV). This is evident from the mathematical form of Eq. 23 as the quotient $k_a[\mathrm{H}^+]/(K_a + [\mathrm{H}^+])^2$ is maximal at $K_a = [\mathrm{H}^+]$. At this point one obtains:

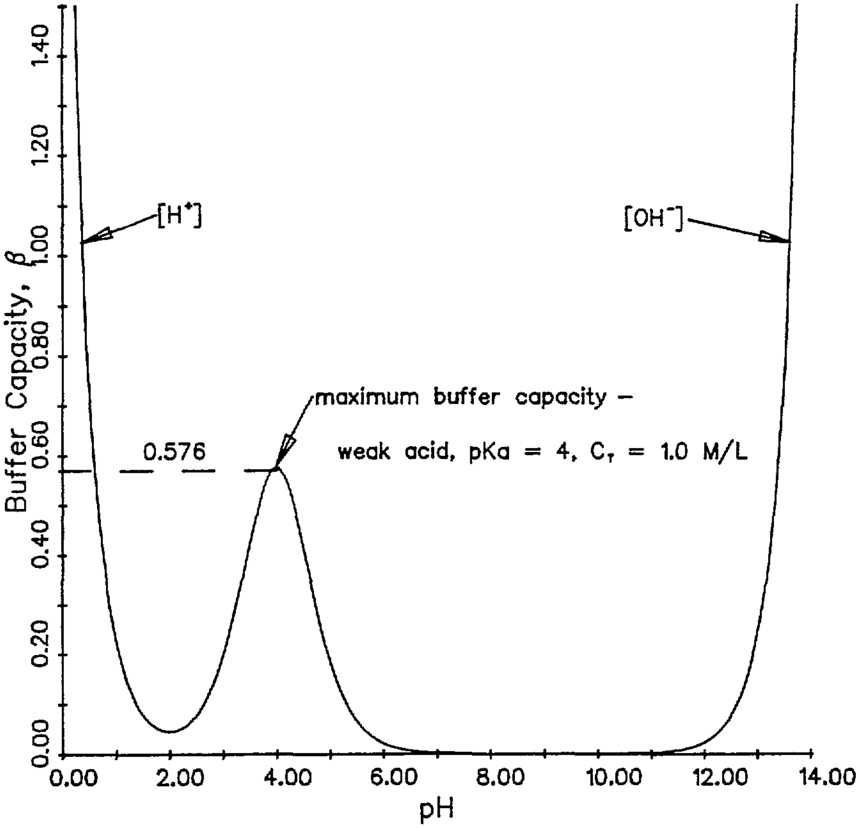


Figure 4—Buffer capacity of a solution containing 1.0 M/liter of a weak acid of pKa = 4 over widely ranging pH. The weak acid only exerts a buffering effect between pH 2 and pH 6. The buffer capacity induced by extremes in pH are also evident. It is notable that there is essentially zero buffer capacity between pH 6 and pH 12.

$$\beta_{\text{maximum}} = 2.303\ C_T \frac{[H^+]^2}{(2[H^+])^2} \quad \text{(Eq. 24)}$$

$$= 0.576\ C_T \quad \text{(Eq. 25)}$$

showing that the maximum obtainable buffer capacity for a given buffer system is simply a fraction of the total buffer concentration. Thus, in the phosphate buffer example at the 0.05 molar strength, the maximum buffer capacity would be 0.029.

The buffer capacity of a system can be best understood in terms of neutralization curves, normally plotted as pH versus equivalents of acid or base added. However to directly evaluate buffer capacity, a reversal of the axes is appropriate as the buffer capacity then becomes the tangent to the curve at any specified value of pH. In Fig. 3 neutralization curves for both a strong acid solution and weak acid solution, each 1.0 normal and of 1 liter volume, neutralized with sodium hydroxide are given. The weak acid is assumed to have a dissociation constant of 1×10^{-4}, typical of a carboxylic acid.

The first thing qualitatively notable is that the curves have the property that the tangent (slope at a fixed point) is always positive. The steeper the curve the greater the buffer capacity. Three regions of high buffer capacity are apparent and designated as regions 1, 2, and 3.

The strong acid initially has a high buffer

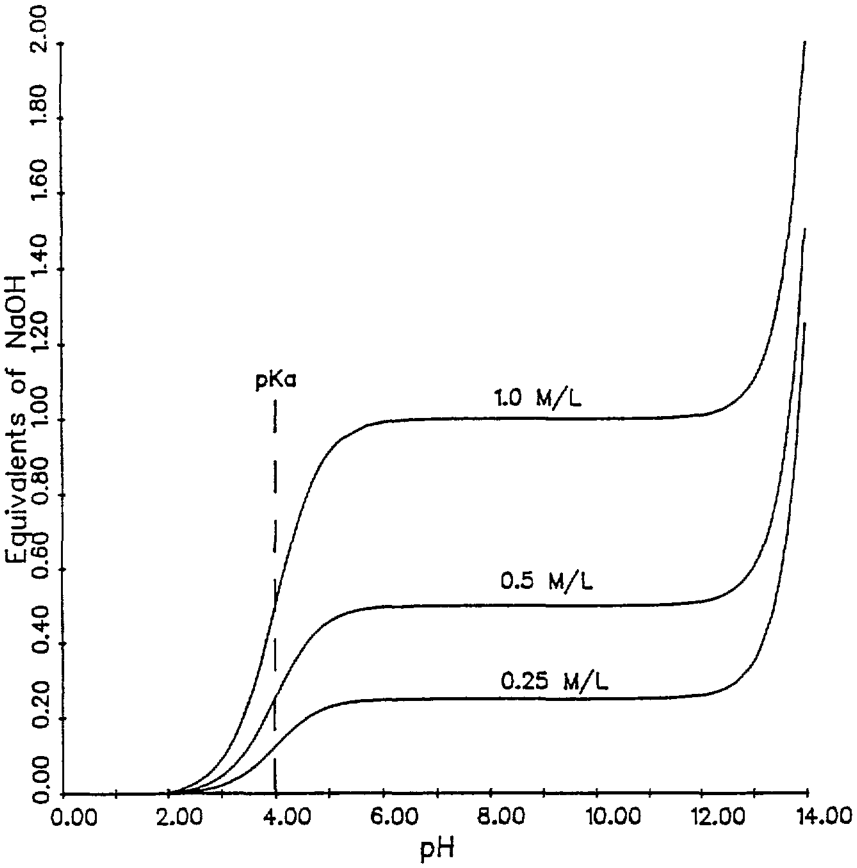


Figure 5—"Reverse" neutralization curves for the neutralization of weak acid solutions respectively 1.0, 0.5, and 0.25 M/liter in concentration. The concentration dependency of buffering is evident in the lessening of the slopes about the pKa as the concentration is reduced.

capacity, region 1, and Van Slyke has shown that this is equal to:

$$\beta = 2.303\ (H^+) \qquad \text{(Eq. 26)}$$

Similarly, the buffer capacity in strong base, region 3, is proportional to the hydroxyl ion concentration according to:

$$\beta = 2.303\ [OH^-] \qquad \text{(Eq. 27)}$$

Region 2 indicates the buffer capacity of the weak acid electrolyte. The tangent to the curve is steepest at the pKa ($\simeq 4$) as predicted by Eq. 23. The intervening regions where the curves are flat represent pH values where there is very little capacity to buffer.

The tangent to the curve, β, around the pK of a weak acid or base forms a symmetrical, bell shaped curve, as depicted in the center of Fig. 4. The buffer capacities in the highly acid and basic regions due to $[H^+]$ and $[OH^-]$ concentrations are also depicted. In Figures 5 and 6 the influence of weak electrolyte concentration on buffering is illustrated. Figure 5 is the "reversed" neutralization curve at several concentrations. The tangents to the curves dW/dpH, in the weak acid buffering region can be seen to be greater at higher total buffer concentration as required. This con-

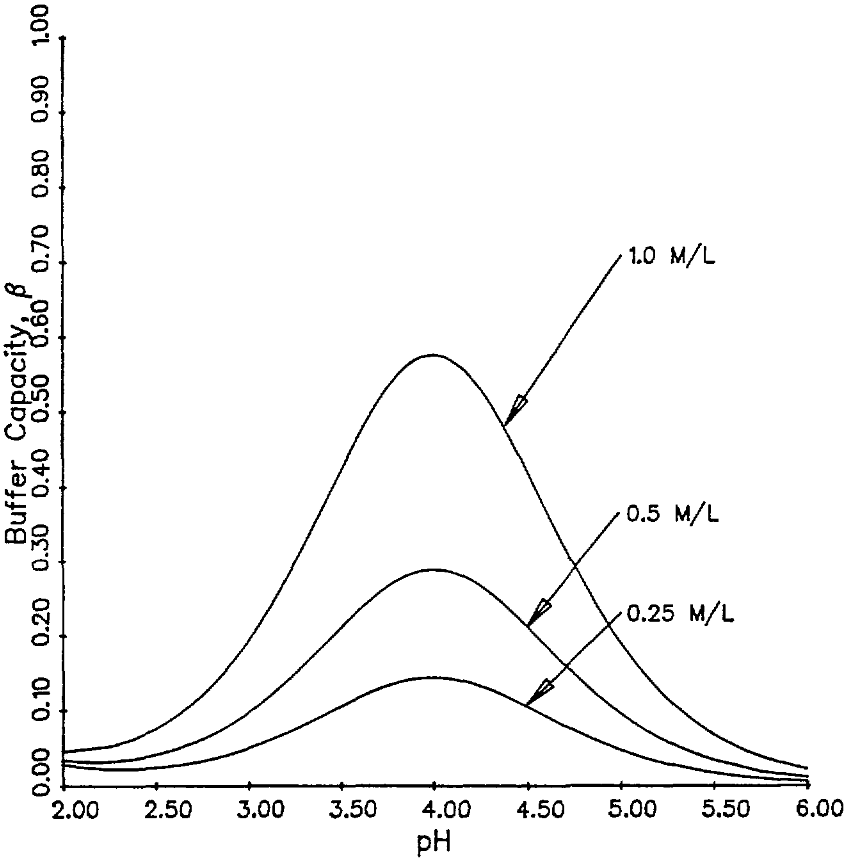


Figure 6—Buffer capacity of a weak acid as a function of pH and a function of concentration. The curves are drawn for an acid with a pKa = 4. This is actually a plot of the tangents to the curves in Figure 5 over the pH range 2 to 6.

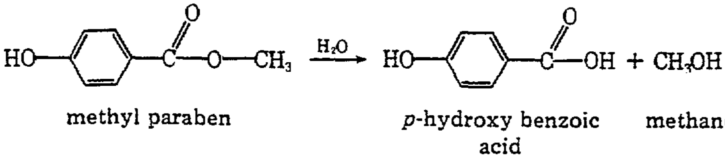
centration effect on buffering is even better illustrated when the tangents (buffer capacities) are plotted as a function of pH (Fig. 6).

The final important point to be made about buffer capacity is that the total buffer capacity of a system containing multiple buffering chemicals and/or a buffering species with multiple equilibria, such as succinic acid ($HOOC\text{-}CH_2\text{-}CH_2\text{-}COOH$), is simply the sum of the buffer capacities of the operating equilibria considered separately. This is illustrated in Figure 7 as the individual and summed (upper curve) buffer capacities of the triacid, citric acid, which has relatively close pK values. Thus, mole for mole, one gets more buffering action with poly-acids and poly-bases over a broader pH range than with mono-acidic and mono-basic species.

Buffering of Dosage Forms

How buffers function has been carefully dealt with and it is easy to see from the provided examples why buffers are an integral part of research and therapy. Just why buffering is necessary in aqueous pharmaceutical systems which can be readily titrated to any desired initial pH may not be clear, however, because the acidic and basic challenges suffered by packaged pharmaceuticals have not been discussed. There are three main causes of pH alteration: (*a*) production of acid or base in the formulation medium itself as it spontaneously undergoes chemical change as byproducts of the chemical reactions; (*b*) introduction of acid or base by the container and closures in contact with the formulation, either by leaching or by surface chemical reaction; and (*c*) acidification *via* absorption of CO_2 from air.

If there are hydrolytic and oxidative reactions involving the drug and/or adjuvants, the net effect can be the production of acid or base, depending on the chemical bonds broken and the products formed. For instance, the hydrolysis of an ester such as the preservative, methyl paraben, produces a more acidic species, *p*-hydroxy benzoic acid, than the parent phenol:



(Eq. 28)

Such chemical breakdown can be a source of pH drift. The possible magnitude of such chemically induced pH change can be roughly estimated as follows. Many parenteral and ophthalmic drugs are formulated in the 0.1 to 5% range. Taking a convenient mid-range value, 1%, and assuming a molecular weight of about 200 to be representative, the typical pharmaceutical solution would be on the order of 0.05 molar or would lie in the range 0.005 to 0.25 molar. Considering that a pharmaceutical is not considered subpotent legally until it has dropped below 90% of labeled potency, 0.005 moles per liter of acid or base could be formed in the typical dosage form from reactions involving the therapeutic agent during the useful life of a product. In addition, chemical deterioration of adjuvants as in Eq. 28 may be contributive. Taken together these can amount to several times the pH challenge dealt with in the phosphate buffer example.

Glass is the preferred container for parenteral products and a commonly used container for ophthalmic and other solutions as well. It is composed principally of silicon dioxide polymer which has had its properties modified by the addition of alkaline oxides of sodium, potassium, calcium, magnesium, aluminum, iron, and boron. The two principal types of glass used for pharmaceutical containers are soda-lime and borosilicate glass. The former has a high degree of leachable constituents (K_2O, Na_2O, MgO, CaO) and is not considered suitable for parenteral solutions in particular and buffered solutions in general. The latter is the preferred glass for most solution use because it is much more chemically resistant; but still alkaline oxides are extracted with time. Therefore, unbuffered systems which are formulated on the acid side of neutral pH may exhibit slow but relentless pH shifts to higher pH in the course of their storage in glass containers and buffers are required to maintain pH within specifications. Other packaging materials such as plastic bottles, stoppers, and closures may react acidicly or basicly with solutions. Rarely are they inert. The particulate fillers in rubbery materials used for parenteral multi-dose closures, for instance, tend to be alkaline carbonates, silicates, and oxides.

Air contains a small percentage carbon dioxide and, when it is equilibrated with pure water, the water gradually assumes a pH of about 5 as carbonic acid is formed through reaction of the dissolved gas with water. Since gases diffuse readily through rubber and plastic parts, many pharmaceuticals are in effect exposed to atmospheric CO_2 even if tightly sealed. The same is true for oxygen

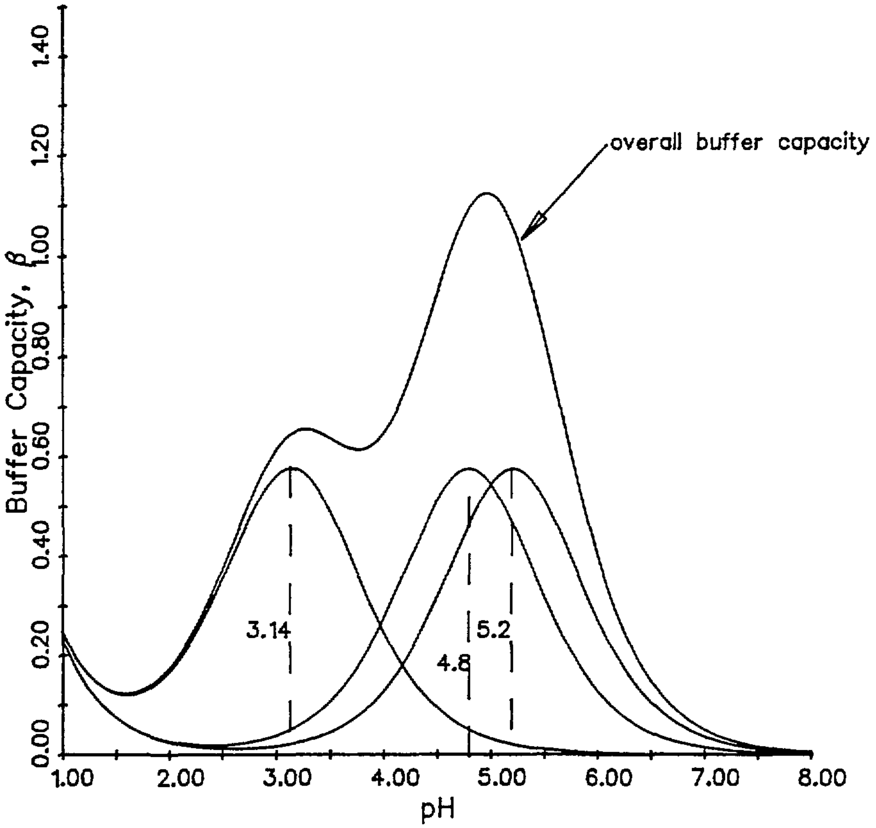


Figure 7—Buffer capacity of a 1.0 M/liter citric acid solution as a function of pH. The three small curves are the contributions of the respective ionizations of this tri-basic acid, pKa's at 3.14, 4.8, and 5.2. The greater curve is simply a summation of the individual contributions. This treatment was originally presented by Windheuser [Bull. Parenteral Drug Assoc., **17** *1 (1963)].*

(O_2) which may participate directly in redox reactions. Only sealed glass ampuls are fully protected. The use of plastic bottles in lieu of glass increases the exposure many-fold and gaseous exchange with the atmosphere is rapid.

For one or another of the above reasons, virtually all pharmaceutical systems tend to drift in pH if unbuffered. Thus, having established the need for buffers, it only remains to consider the practical aspects of choice of buffer and amount of buffer for a particular system. Some of the important considerations affecting the choice of buffer for a pharmaceutical are: (*a*) the buffer must be physiologically compatible by the route of administration considered; it must neither be irritating nor toxic; (*b*) the buffer must be chemically compatible with both the drug and other adjuvants (preservatives, flavors, aromatics, colorants, antioxidants, etc.), comprising the finished pharmaceutical; and (*c*) the buffer must have adequate buffer capacity at the chosen pH of the system.

The restriction of biological safety, the first consideration above, severely limits the choice of buffering agents for parenteral, oral and other routes of administration which allow systemic access of the buffering chemicals. There is a little more latitude with ophthalmics

TABLE V. Systemically Compatible Buffers

Buffering agent	K_a values (pKa)[a]	Approximate buffering range
	Monobasic Acids	
Acetic	1.8×10^{-5} (4.8)	3.8–5.8
Benzoic	6.5×10^{-5} (4.2)	3.2–5.2
Gluconic	2.5×10^{-4} (3.6)	2.6–4.6
Glyceric	2.8×10^{-4} (3.55)	2.6–4.6
Lactic	8.4×10^{-4} (3.1)	2.1–4.1
	Dibasic Acids	
Aconitic	(1) 1.58×10^{-3} (2.8)	2–5.5
	(2) 3.5×10^{-5} (4.46)	
Adipic	(1) 3.9×10^{-5} (4.41)	3.4–6.3
	(2) 5.29×1^{-6} (5.28)	
Ascorbic	(1) 6.76×10^{-5} (4.17)	3.2–5.2
	(2) 2.51×10^{-12} (11.6)	
Carbonic	(1) 4.3×10^{-7} (6.4)	5.4–7.4
	(2) 5.6×10^{-11} (10.3)	
Gluratic	(1) 4.6×10^{-5} (4.34)	3.3–6.4
	(2) 3.9×10^{-6} (5.4)	
Glutamic	(1) 7.4×10^{-3} (2.1)	2–5.3
	(2) 4.9×10^{-5} (4.3)	
Malic	(1) 3.9×10^{-4} (3.4)	2.4–6.1
	(2) 7.8×10^{-6} (5.1)	
Succinic	(1) 6.9×10^{-5} (4.2)	3.2–6.6
	(2) 2.5×10^{-6} (5.6)	
Tartaric	(1) 1×10^{-3} (3.0)	2.0–5.3
	(2) 4.55×10^{-5} (4.3)	
	Polybasic Acids	
	(1) 8.4×10^{-4} (3.14)	
Citric	(2) 1.7×10^{-5} (4.8)	2.1–6.2
	(3) 6.4×10^{-6} (5.2)	
Ethylene diamine tetraacetic (EDTA)		~3.5–7[b]
Phosphoric	(1) 7.5×10^{-3} (2.1)	2–3.1 and
	(2) 6.3×10^{-8} (7.2)	
	(3) 2.2×10^{-13} (12.7)	6.2–8.2
	Bases[c]	
Ammonia (ammonium chloride)	5.6×10^{-10} (9.25)	8.25–10.25
Diethanolamine	1.0×10^{-9} (9.0)	8.0–10.0
Glycine	1.7×10^{-10} (9.8)	8.8–10.8
Triethanolamine	1×10^{-8} (8.0)	7–9
Tromethamine (TRIS, THAM)	8.3×10^{-9} (8.1)	7.1–9.1

Continued

[a] K_a or pKa taken from *Merck Index* or *Handbook of Chemistry and Physics*. Experimental values may differ due to non-ideality of solutions.

[b] pKa values not available in cited references; buffering range based on general carboxylic acid dissociation and the fact that the pH of an aqueous solution of the disodium salt is about 5.3 (*Merck Index*).

[c] Values given are the dissociation equilibrium constant of the conjugate acid, K_a, nominally at 25 °C.

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and preparations applied to intact skin. However, as there is always some systemic absorption by the latter routes, especially when topical application is to damaged tissues; buffering agents for topicals should be selected to be systemically acceptable when possible.

Table V presents a list of buffers which have been used or considered for use as systemically compatible materials. Many of these, such as tartaric acid, and succinic acid, are physiologic or part of the normal biochemical pathways of the body. Carbonic acid and phosphoric acid are the buffers of blood, lymph, and intracellular fluid. A phosphate buffer system (Sorensen's) has been used in pharmacy for extemporaneous compounding (Table VI). In addition to these buffers, a buffer frequently deployed in ophthalmic systems is boric acid (H_3BO_3). This is often used as a 1.9% solution, which is isotonic against the membranes of the eye and which has a pH of 4.7, for extemporaneous compounding of ophthalmics. It is also used in conjunction with sodium carbonate (Na_2CO_3) (Gifford's Buffer System) and with sodium acetate to make ophthalmic buffers ranging in pH from about 5 to about 8.6 (as shown in Tables VII and VIII). A related material, sodium borate or borax, $Na_2B_4O_7$, has utility as a topical buffer in the alkaline pH range 9–11. Since boric acid and borax can be lethal if they are swallowed or are otherwise systemically absorbed, they should be used with extreme care and only when there are no suitable alternatives.

TABLE VI. Sorensen Phosphate Buffer System

1. Stock solutions

Monobasic sodium phosphate solution:

Monobasic sodium phosphate, anhydrous (NaH_2PO_4)	8.00 g
Sterile preserved water, *qs*	1000 ml

Dibasic sodium phosphate solution:

Dibasic sodium phosphate, anhydrous, (Na_2HPO_4)	9.47 g
Sterile preserved water, *qs*	1000 ml

2. Buffer mixtures

Monobasic sodium phosphate solution, ml	**Dibasic sodium phosphate solution, ml**	**Resulting buffer solution, pH**	**NaCl to render isotonic, g**
90	10	5.91	0.52
80	20	6.24	0.51
70	30	6.47	0.50
60	40	6.64	0.49
50	50	6.81	0.48
40	60	6.98	0.46
30	70	7.17	0.45
20	80	7.38	0.44
10	90	7.73	0.43
5	95	8.04	0.42

The selection of a buffer from the "safe group" depends on the desired pH of the system to be buffered and the compatibility of the buffer with all other formulation ingredients. A factor to be kept in mind is that both ionic strength and inorganic solvents affect pKa values as illustrated in Figures 8 and 9. Therefore thermodynamic pKa values as found in Table V have to be adjusted or reworked depending on the composition of a system. Also, all buffers are ionic and therefore buffer species can potentially react to

TABLE VII. Giffords Buffer System

1. Stock solutions

Stock acid solution:

Boric acid	12.4 g
Potassium chloride	7.4 g
Sterile preserved water	1000 ml

Stock alkaline solution:

Sodium carbonate, anhydrous	21.2 g
Sterile preserved water	1000 ml

2. Buffer mixtures

Stock acid solution, ml	**Alkaline solution, ml**	**pH of resulting buffer solution**
30	0.00	5.0
30	0.05	6.0
30	0.10	6.2
30	0.15	6.4
30	0.20	6.6
30	0.30	6.8
30	0.60	7.0
30	1.00	7.2
30	1.50	7.4
30	2.00	7.6
30	3.00	7.8
30	4.00	8.0
30	8.00	8.6

TABLE VIII. Sodium Acetate—Boric Acid Buffer System

1. Stock solutions

Sodium acetate stock solution:

Sodium acetate $3H_2O$	20 g
Sterile preserved water *qs* to	1000 ml

Boric acid stock solution:

Boric acid	19 g
Sterile preserved water *qs* to	1000 ml

2. Buffer mixtures

Sodium acetate solution, ml	**Boric acid solution ml**	**pH of resulting solution**
—	100	5
10	90	6.05
20	80	6.3
30	70	6.5
40	60	6.65
50	50	6.75
60	40	6.85
70	30	6.95
80	20	7.1
90	10	7.25
100	5	7.4
100	—	7.6

form insoluble salts with ions from other sources (drug, other adjuvants) of opposite charge. Acid buffering chemicals are anionic (dissociate into an anion or negatively charged ion and protons) and may form insoluble salts with heavy metal cations or large organic cations. Therefore, anionic buffers should be used where the drug, preservative, or other ionic adjuvants are either non-ionic or anionic. For similar reasons, cationic buffers (amine buffers) are preferred for cationic drugs, all of this providing the pH of interest is compatible with obtaining adequate buffer capacity.

Another chemical compatibility problem involves the direct catalytic attack of certain buffer species on the drug or an adjuvant. The dianions of many of the di and poly carboxylic acids and the dianion of phosphoric acid are powerful nucleophiles and are known to directly facilitate many hydrolytic processes. They may also serve as proton acceptors in the general base catalysis mechanism, a less dramatic effect. Moreover, in some rare instances, buffer species and related species like bisulfite anion have been shown to actually combine with organic structures, forming stable adducts.

To illustrate catalytic effects, the influence of succinate buffer on the hydrolysis of phthalic anhydride as a function of pH (each curve is for a unique pH) is shown in Figure 10. The common intercept of the plot on the *y*-axis proves that the reaction rate is independent of pH in the region displayed. The positive slope, which dramatically steepens as the pH is raised, indicates that the succinate dianion is a catalytic species for this reaction.

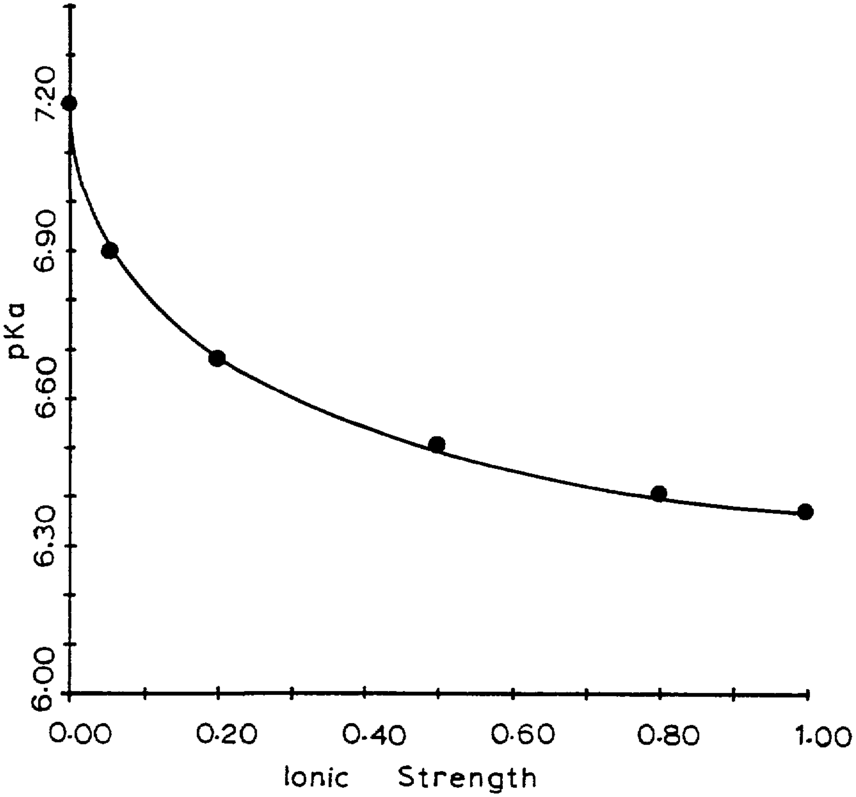

Figure 8—Influence of ionic strength on the observed pKa_2 of phosphoric acid. Data taken from Windheuser [Bull. Parenteral Drug Assoc., **17** *1 (1963)].*

For such reasons the chemical interactivity of buffers with the drug should be investigated before the final choice of a buffer is made.

The last concern influencing the choice of a buffer is adequate buffer capacity. It has been shown that the maximum buffer capacity is at the pKa of a compound, unless it is a di-acid in which case it may lie between the two pKa values, depending on how close they are to one another. At ±1 unit of pH away from the pKa the buffer capacity is about one-third of its maximum and this is generally taken as the useful limit of application. The pH ranges of practical use given in Table V have been established on this basis.

How much buffer capacity is needed is the next question of the formulator. The answer to this question depends on the system at hand, but a rough rule of thumb can be formulated. In previous discussion it was shown that a reasonable estimate of the amount of acid or base produced via a hydrolytic decomposition might be on the order of about 0.005 moles/liter over the shelf-life of a product. Effective buffering would be obtained, providing one was near the pKa, with ten times as much buffer or about 0.05 molar buffer. In fact, if one examines marketed pharmaceutical systems, one finds buffer concentrations typically to lie between 0.01 and 0.1 molar. Thus buffer capacities of many pharmaceuticals (Eq. 23) approach or exceed 0.01 and a buffer capacity between 0.01 and 0.1 appears generally adequate. Interestingly, the natural buffer ca-

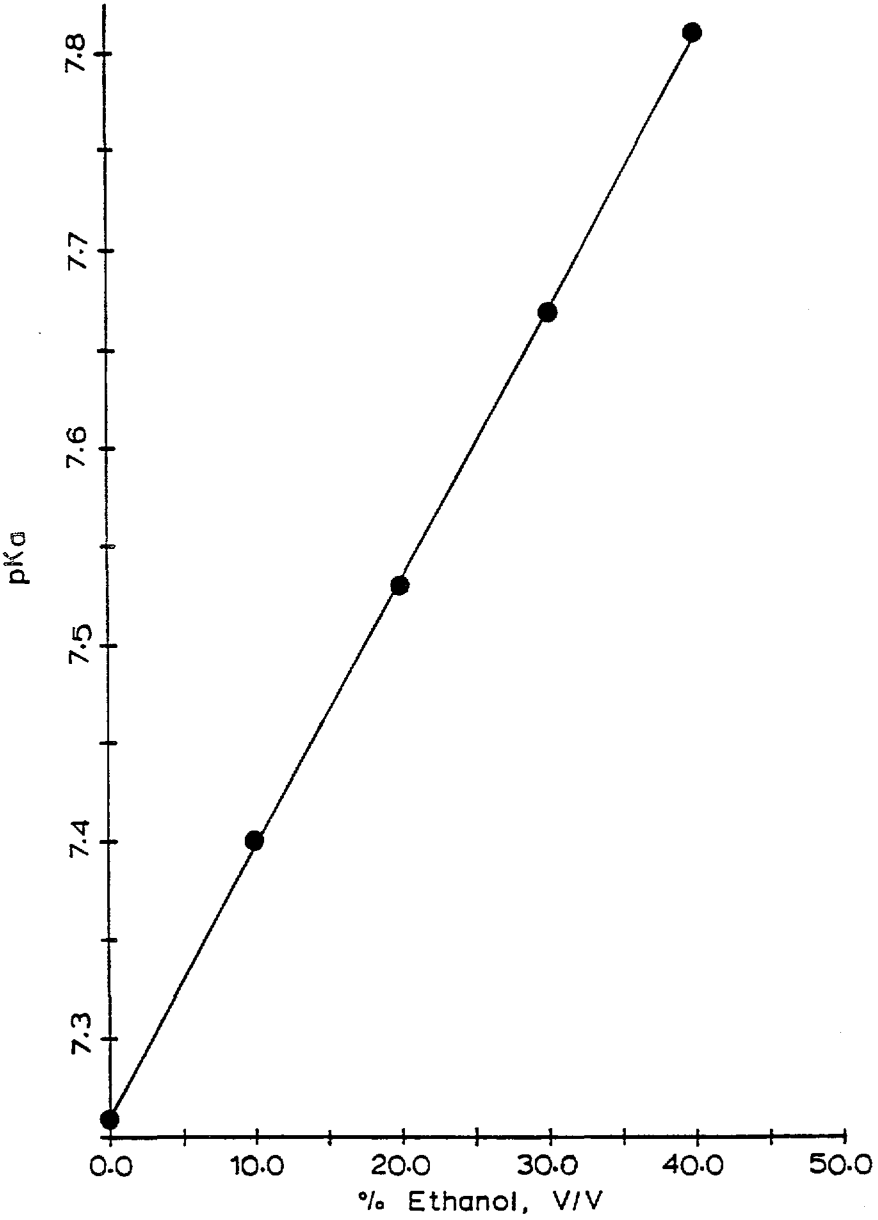

Figure 9—Influence of ethanol on the dissociation constant of sulfathiazole. Redrawn from Higuchi et al [*J. Am. Pharm. Assoc., Sci. Ed.*, **42**, *157* (*1953*)].

pacity of blood at physiological pH (pH 7.4) is estimated to lie within this range at 0.03 ± 0.004. Note that the upper limit of recommended buffer capacity, 0.1, at a unit of pH away from the buffer's pKa corresponds to a total buffer concentration of about 0.5 molar

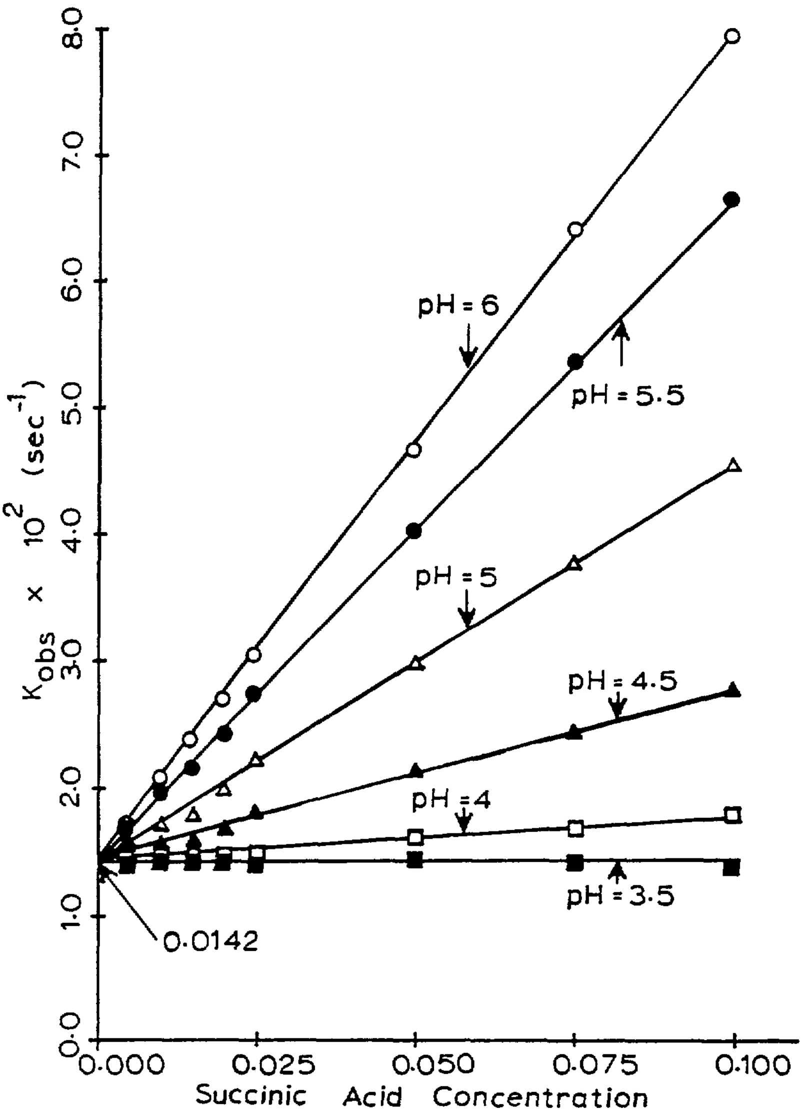

Figure 10—Hydrolysis of phthalic anhydride as a function of concentration of a succinic acid buffer at 30 °C. Each curve is for a different pH. As the pH is raised, the rate increases at all buffer concentrations but the extrapolated rate at zero buffer concentration is invarient (0.0142 sec^{-1}). The behavior is due to succinate dianion catalysis of the solvolysis, presumably via the formation of a very unstable mixed anhydride which itself rapidly hydrolyses. Because of such effects, one should be careful to use buffers which are chemically compatible with formulated drugs or other adjuvants. Data are from the PhD thesis of Flynn ("Some Chemistry Of Phthalic Anhydride And Phthaloyl Monophosphate," Thesis, University of Wisconsin, Madison, 1965).

for a monoacidic acid. An upper limit on amount of buffer is of course set by the principle that buffers, like all other adjuvants, are exogenous chemicals and the safest, practical amount to use is the minimum amount which gets the buffering job done.

A last point to be made concerning buffering is that one should not overlook the buffering capacity of weak electrolyte drugs and/or other weak electrolytes used primarily for nonbuffering purposes (preservation for instance) in estimating the buffer requirements for a particular system. One may find that the choice of sorbic acid as a preservative or EDTA as a heavy metal complexing agent, etc., provides for significant buffering and that a system requires little additional buffering agent. The innate capacity of a system to buffer prior to the addition of a specific buffering agent can either be calculated using the pK's of drug and non-buffer adjuvants or can be roughly experimentally determined by preparing the system at the desired pH and then adding a known increment of acid and/or base as a buffering challenge.

In summary, a discussion of theory concerning weak electrolyte equilibria in aqueous media has been presented as the premise for a discussion of buffering, especially the buffering of pharmaceutical systems. Selection and use of buffers was next discussed in an attempt to put the choice of buffering agent(s) for a particular situation in a general and practical framework. Data on buffering materials have been collected and organized which should be of benefit to both researcher and formulator. In this regard, some additional tables are appended which provide essential information on the strengths of acids and bases as commonly commercially obtained (Appendix I) and on the pH of common laboratory reagents (Appendix II). Included in the latter are approximate pH values for some common foods and beverages and of body fluids, which give a physiologic perspective.

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2. J. Windheuser, "The Effect of Buffers on Parenteral Solutions," *Bull. Parenteral Drug Assoc.*, 17, 1 (1963).
3. R. G. Bates, "Revised Standard Values for pH Measurements from 0° to 95°," *J. Res. Natl. Bureau Stand.*, 66A, 179.
4. *Scientific Tables*, 7th ed., K. Diem and C. Lentner, Ciba-Geigy, Ardsley, NY, 1971.

APPENDIX I. Concentration of Acids and Bases in Common Commercial Strengths[a]

	Molecular weight	Moles per liter	Grams per liter	Percent by weight	Specific gravity
		Acids			
Acetic acid	60.05	17.4[b]	1045	99.5	1.05
		6.27	376	36	1.045
Hydroiodic acid	127.9	7.57	969	57	1.70
		5.51	705	47	1.50
Hydrobromic acid	80.92	8.89	720	48	1.50
		6.82	552	40	1.38
Hydrochloric acid	36.5	11.6	424	36	1.18
		2.9	105	10	1.05
Hydrofluoric acid	20.01	32.1	642	55	1.167
		28.8	578	50	1.155
Hypophosphorous acid	66.0	9.47	625	50	1.25

Continued

APPENDIX I. *Continued*

	Molecular Weight	Moles per liter	Grams per liter	Percent by weight	Specific gravity
Lactic acid	90.1	11.3	1020	85	1.2
Nitric acid	63.02	15.99	1008	71	1.42
		14.9	938	67	1.40
		13.3	837	61	1.37
Perchloric acid	100.5	11.65	1172	70	1.67
		9.2	923	60	1.54
Phosphoric acid	98	14.7	1445	85	1.70
Sulfuric acid	98.1	18.0	1766	96	1.84
Sulfurous acid	82.1	0.74	61.2	6	1.02
		Bases			
Ammonia water	17.0	14.8	252	28	0.898
Potassium hydroxide	56.1	13.5	757	50	1.52
Sodium carbonate	106.0	1.04	110	10	1.10
Sodium hydroxide	40.0	19.1	763	50	1.53

[a] Data excerpted from *Merck Index*.

[b] Glacial acetic acid.

APPENDIX II. Approximate pH Values of Common Laboratory Solutions at 25 °C and of Select Foods and Physiologic Fluids

Laboratory Solutions			Laboratory Solutions		
Reagent	**Molarity**	**pH**	**Reagent**	**Molarity**	**pH**
Acetic acid	0.001	3.9	Borax (sodium tetraborate)	0.1	9.4
	0.01	3.4			
	0.1	2.9	Boric acid	0.1	5.3
	1.0	2.4	Calcium carbonate	saturated	9.4
Ammonia water	0.001	10.3	Calcium hydroxide	saturated	12.4
	0.01	10.8	Carbonic acid	saturated	3.8
	0.1	11.3	Citric acid	0.1	2.1
	1.0	11.8	Diammonium hydrogen phosphate	0.1	7.9
Ammonium chloride	0.1	4.6			
Ammonium dihydrogen phosphate	0.1	4.0	Disodium hydrogen phosphate	0.1	9.2
Ammonium oxylate	0.1	6.4	Ferrous hydroxide	saturated	9.5
Ammonium sulfate	0.1	5.5	Formic acid	0.1	2.3
Arsenious acid	saturated	5.0	Hydrochloric acid	0.001	3.01
Benzoic acid	0.01	3.1		0.01	2.02
	saturated	2.8		0.1	1.07
				1.0	0.1

Continued

APPENDIX II. *Continued*

Laboratory Solutions		
Reagent	**Molarity**	**pH**
Hydrogen sulfide	0.1	4.1
Lactic acid	0.1	2.4
Magnesium hydroxide	saturated	10.5
Malic acid	0.1	2.2
Orthophosphoric acid	0.1	1.5
Oxalic acid	0.1	1.3
Potassium acetate	0.1	9.7
Potassium aluminum sulfate	0.1	4.2
Potassium bicarbonate	0.1	8.2
Potassium carbonate	0.1	11.5
Potassium dihydrogen phosphate	0.1	4.5
Potassium hydroxide	0.01	12.0
	0.1	13.0
	1.0	14.0
Salicylic acid	saturated	2.4
Sodium acetate	0.1	8.9
Sodium benzoate	0.1	8.0
Sodium bicarbonate	0.1	8.3
Sodium bisulfate	0.1	1.4
Sodium carbonate	0.1	11.5
Sodium dihydrogen phosphate	0.1	4.5
Sodium hydroxide	0.001	11.1
	0.01	12.1
	0.1	13.1
	1.0	14.1
Sodium sesquicarbonate	0.1	10.1
Succinic acid	0.1	2.7

Laboratory Solutions		
Reagent	**Molarity**	**pH**
Sulfuric acid	0.01	2.1
	0.1	1.2
	1.0	0.3
Sulfurous acid	0.1	1.5
Tartaric acid	0.1	2.0
Trichloroacetic acid	0.1	1.2
Trisodium phosphate	0.1	12.0

Foods and Beverages

	pH
Apples	~3.1
Beer	4–5
Cider	~3
Grapefruit	~3
Lemons	~2.3
Limes	~1.9
Oranges	~3.5
Water, potable	6–8
Wines	2.8–3.8

Human Physiological Fluids

Blood (plasma)	7.32–7.45
Gastrointestinal	
Gastric	1–4
Duodenal	5–8
Saliva	5.8–7.1
Spinal fluid	7.33–7.37
Tears	7.2–7.4
Urine	4.8–7.5

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