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BUFFERED AND ISOTONIC SOLUTIONS

Overview

Buffered Solutions

Definition

Buffer Equation

Buffer Capacity

Buffer in Biological Systems

Pharmaceutical Buffers

Objectives

- Understand the common ion effect.
- Understand the relationship between pH, pK_a , and ionization for weak acids and weak bases.
- Apply the buffer equation, also known as the Henderson–Hasselbalch equation, for a weak acid or base and its salt.
- Understand the relationship between activity coefficients and the buffer equation.
- Discuss the factors influencing the pH of buffer solutions
- Understand the concept and be able to calculate buffer capacity.
- Describe the influence of concentration on buffer capacity.
- Discuss the relationship between buffer capacity and pH on tissue irritation.
- Describe the relationship between pH and solubility

❖ **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**.

❖ **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

- ❖ 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



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



Common ion effect and the buffer equation for a weak acid 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..
- ❖ For example, when sodium acetate is added to acetic acid, the dissociation constant for the weak acid, is

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{Ac}^-]}{[\text{HAc}]} = 1.75 \times 10^{-5}$$

Is momentarily disturbed because the acetate ion supplied by the salt increases the $[\text{Ac}^-]$ 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 is inhibited upon the addition of the common ion, Ac^- . This is an example of the common ion effect.



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

$$[H_3O^+] = K_a \frac{[Acid]}{[Salt]}$$

This Equation can be expressed in logarithmic form, with the signs reversed, as

$$-\log [\text{H}_3\text{O}^+] = -\log K_a - \log [\text{Acid}] + \log [\text{Salt}]$$

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

$$\text{pH} = \text{p}K_a + \log \frac{[\text{Salt}]}{[\text{Acid}]}$$

The Buffer Equation

- **A Weak Acid and Its Salt**

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

**Dissociation
exponent**

Buffer equation or
Henderson-Hasselbalch
equation

Example

What is the molar ratio, [Salt]/[Acid], required to prepare an acetate buffer of pH 5.0? Also express the result in mole percent

$$5.0 = 4.76 + \log \frac{[\text{Salt}]}{[\text{Acid}]}$$

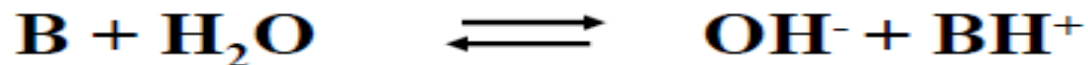
$$\log \frac{[\text{Salt}]}{[\text{Acid}]} = 5.0 - 4.76 = 0.24$$

$$\frac{[\text{Salt}]}{[\text{Acid}]} = \text{antilog } 0.24 = 1.74$$

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

The Buffer Equation

- **A Weak Base and Its Salt**



$$K_b = \frac{[\text{OH}^-][\text{BH}^+]}{[\text{B}]}$$

→ salt
→ base

The Buffer Equation

- A weak base and its salt

$$[\text{OH}^-] = K_b \frac{[\text{base}]}{[\text{salt}]}$$

$$\downarrow [\text{H}_3\text{O}^+] \cdot [\text{OH}^-] = K_w$$

$$-\log[\text{H}_3\text{O}^+] = -\log K_w - \log 1/K_b - \log[\text{salt}]/[\text{base}]$$

$$\text{pH} = \text{p}K_w - \text{p}K_b + \log \frac{[\text{base}]}{[\text{salt}]}$$

- * Buffers are not ordinarily prepared from weak bases because of the volatility & instability of the bases and because of the dependence of their pH on $\text{p}K_w$, which is often affected by temp. changes.

Factors influencing the PH of buffer solutions

1. Altering the ionic strength

- ① Addition of neutral salts
- ② Dilution (alter activity coefficients)

2. Temperature

The pH of the most basic buffer was found to change more markedly with temp. than that of acid buffers, owing to K_w .

Buffer capacity

- ...the magnitude of the resistance of a buffer to pH changes

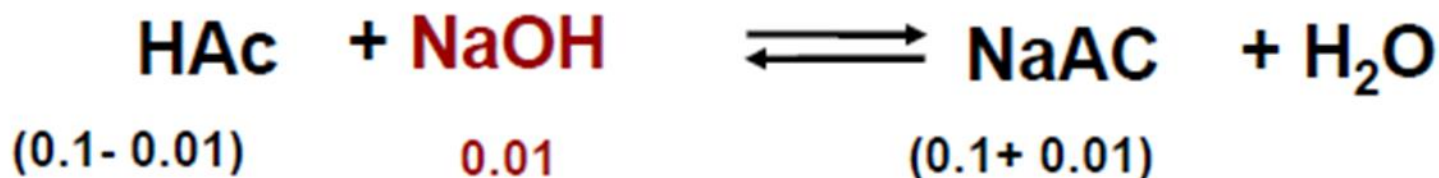
$$\beta = \frac{\Delta B}{\Delta \text{pH}}$$

buffer capacity
= buffer efficiency
= buffer index
= buffer value

ΔB : is the small increment in gram equivalents(g Eq)/liter of strong base added to the buffer solution to produce a pH change of ΔpH .

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



- Before the addition of NaOH

$$\text{pH} = \text{pK}_a + \log \frac{[\text{salt}]}{[\text{acid}]} = 4.76$$

- After the addition of NaOH

$$\text{pH} = \text{pK}_a + \log \frac{[\text{salt}] + [\text{base}]}{[\text{acid}] - [\text{base}]} = 4.85$$

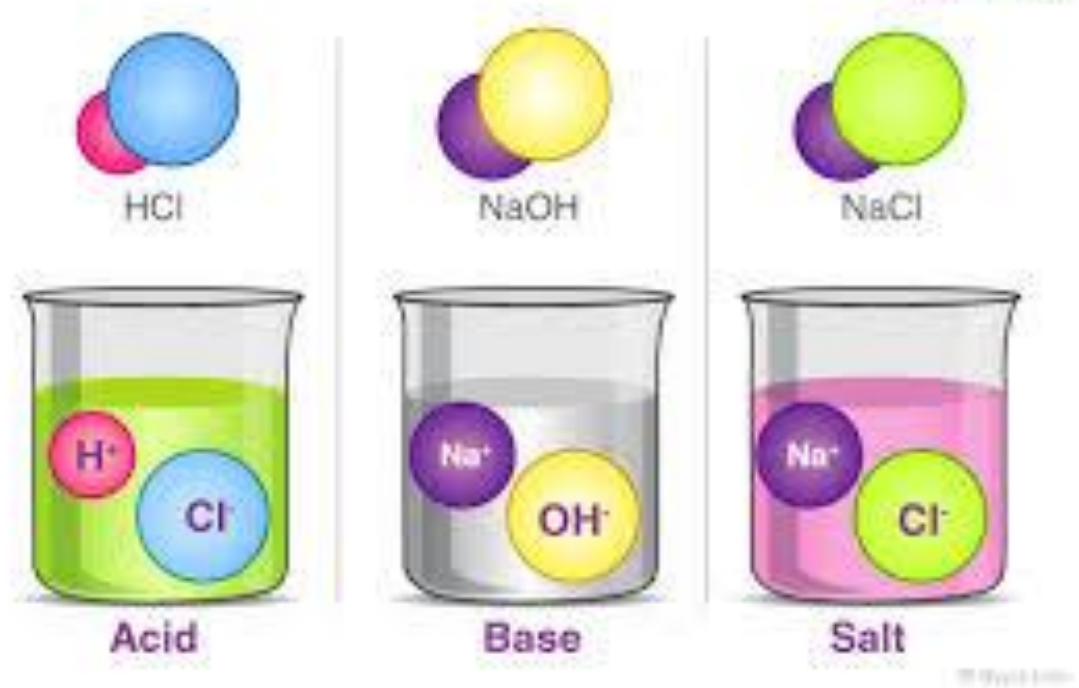
$$\longrightarrow \beta = \frac{\Delta B}{\Delta \text{pH}} = \frac{0.01}{0.09} = 0.11$$

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

- ❖ As can be seen from Table , 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 $\log([\text{Salt}]/[\text{Acid}])$ 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 $[\text{Salt}]/[\text{Acid}] = 1$, and, therefore, $\text{pH} = \text{pK}_a$.
- ❖ 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.



A more exact equation for buffer capacity

$$\beta = 2.3 C \frac{K_a [\text{H}_3\text{O}^+]}{(K_a + [\text{H}_3\text{O}^+])^2}$$

- ❖ where C is the total buffer concentration, that is, the sum of the molar concentrations of the acid and the salt.
- ❖ Equation above 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.

Calculating Buffer Capacity

At a hydrogen ion concentration of 1.75×10^{-5} (pH = 4.76), what is the capacity of a buffer containing 0.10 mole each of acetic acid and sodium acetate per liter of solution? The total concentration, $C = [\text{Acid}] + [\text{Salt}]$, is 0.20 mole/liter, and the dissociation constant is 1.75×10^{-5} . We have

$$\beta = 2.3C \frac{K_a [\text{H}_3\text{O}^+]}{(K_a + [\text{H}_3\text{O}^+])^2}$$

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



Maximum Buffer capacity

- β_{\max} occurs where $\text{pH} = \text{p}K_a$ ($[\text{H}_3\text{O}^+] = K_a$)

$$\beta_{\max} = 2.303 \cdot C \cdot \frac{[\text{H}_3\text{O}^+]^2}{(2 [\text{H}_3\text{O}^+])^2} = \frac{2.303}{4} \cdot C$$

$$\beta_{\max} = 0.576 \cdot C$$

($\text{pH} = \text{p}K_a$)

Maximum Buffer Capacity

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

$$\begin{aligned}\beta_{\max} &= 0.576 \times 0.020 \\ &= 0.01152 \text{ or } 0.012\end{aligned}$$

Buffers in pharmaceutical and biologic systems in vivo biologic buffer system

Blood is maintained at a pH of about 7.4 by :

- ❖ primary buffers in the **plasma** : The plasma contains carbonic acid/bicarbonate and acid/alkali sodium salts of phosphoric acid as buffers
- ❖ secondary buffers in the **erythrocytes**: hemoglobin/oxyhemoglobin and acid/alkali potassium salts of phosphoric acid.
- ❖ Plasma proteins, which behave as acids in blood, can combine with bases and so act as buffers.
- ❖ 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.

❖ The pH of tears is about 7.4, with a range of 7 to 8 or slightly higher.

Urine

❖ pH: 6.0 (range 4.5 –7.8)

❖ below normal...hydrogen ions are excreted by the kidney.

❖ above pH 7.4...hydrogen ions are retained by action of the kidney.

Influence of Buffer Capacity and pH on Tissue Irritation

- ❖ Solutions to be applied to tissues or administered parentally are liable to cause irritation if their pH is greatly different from the normal pH of the relevant body fluid.
- ❖ Consequently, the pharmacist must consider when formulating ophthalmic solutions, parenteral products:
 - ❖ its buffer capacity and
 - ❖ the volume to be used in relation to the volume of body fluid with which the buffered solution will come in contact.
 - ❖ The buffer capacity of the body fluid should also be considered.

- ❖ Tissue irritation, due to large pH differences between the solution being administered and the physiologic environment in which it is used, will be minimal :
- ❖ the lower is the buffer capacity of the solution,
- ❖ the smaller is the volume used for a given concentration, and
- ❖ the larger are the volume and buffer capacity of the physiologic fluid.

- ❖ Martin and Mims found that Sørensen'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.
- ❖ It 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

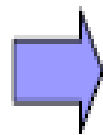
- **Stability vs. optimum therapeutic response**
 - * **Undissociated form** of a weakly acidic or basic drug has a higher therapeutic activity than the **dissociated salt form**.
 - * **Molecular form** is lipid soluble & can penetrate body membranes readily, where the **ionic form**, not being lipid soluble, can penetrate membranes only with greater difficulty.

- ❖ the solution of the drug can be buffered at a low buffer capacity and at a pH that is a compromise between that of optimum stability and the pH for maximum therapeutic action.
- ❖ The buffer is adequate to prevent changes in pH due to the alkalinity of the glass or acidity of CO₂ from dissolved air.
- ❖ Yet, when the solution is instilled in the eye, the tears participate in the gradual neutralization of the solution;
- ❖ conversion of the drug occurs from the physiologically inactive form to the undissociated base. The base can then readily penetrate the lipoidal membrane. As the base is absorbed at the pH of the eye, more of the salt is converted into base to preserve the constancy of pK_b; hence, the alkaloidal drug is gradually absorbed

- **pH and solubility**

- * Influence of buffering on the solubility of base

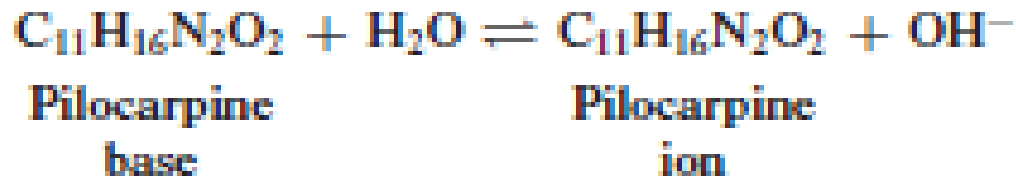
- At a low pH : base is in the ionic form & usually very soluble in aqueous media
 - As the pH is raised : more undissociated base is formed when the amount of base exceeds the limited water solubility of this form, free base precipitates from soln.



Base soln. should be buffered at a sufficiently low pH for stabilization against precipitation.

Mole Percent of Free Base

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



$$\text{pH} = \text{p}K_w - \text{p}K_b + \log \frac{[\text{Base}]}{[\text{Salt}]}$$

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

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

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

$$\begin{aligned} \text{mole percent of base} &= \frac{[\text{Base}]}{[\text{Salt}] + [\text{Base}]} \times 100 \\ &= [3.56 / (1 + 3.56)] \times 100 = 78\% \end{aligned}$$

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Thank you