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Chapter 11

Isotonic and Buffer Solutions

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USING AN ISOTONIC SODIUM CHLORIDE SOLUTION TO PREPARE OTHER ISOTONIC SOLUTIONS

- A 0.9% w/v sodium chloride solution may be used to compound isotonic solutions of other drug substances as follows:

1. **Step 1.** Calculate the quantity of the drug substance needed to fill the prescription or medication order.
2. **Step 2.** Use the following equation to calculate the volume of water needed to render a solution of the drug substance isotonic:

$$\frac{\text{g of drug} \times \text{drug's } E \text{ value}}{0.009} = \begin{array}{l}\text{mL of water needed to make an isotonic solution of the drug} \\ \text{(the volume of the drug substance is considered negligible)}\end{array}$$

3. **Step 3.** Add 0.9% w/v sodium chloride solution to complete the required volume of the prescription or medication order.

Using this method, determine the volume of purified water and 0.9% w/v sodium chloride solution needed to prepare 20 mL of a 1% w/v solution of hydromorphone hydrochloride (E = *0.22*).

Step 1. 20 mL × 1% w/v = 0.2 g hydromorphone needed

Step 2. $\frac{0.2 \text{ g} \times 0.22}{0.009}$ = 4.89 mL purified water required to make an isotonic solution of hydromorphone hydrochloride, *answer.*

Step 3. 20 mL − 4.89 mL = 15.11 mL 0.9% w/v sodium chloride solution required, *answer.*

Proof: 20 mL × 0.9% = 0.18 g sodium chloride or equivalent required

0.2 × 0.22 = 0.044 g (sodium chloride represented by 0.2 g hydromorphone hydrochloride)

15.11 mL × 0.9 % = 0.136 g sodium chloride present

0.044 g + 0.136 g = 0.18 g sodium chloride required for isotonicity

USE OF FREEZING POINT DATA IN ISOTONICITY CALCULATIONS

- Freezing point data (ΔTf) can be used in isotonicity calculations when the agent has a tonicic effect and does not penetrate the biologic membranes in question (e.g., red blood cells). As stated previously, the freezing point of both blood and lacrimal fluid is -0.52°C

TABLE 11.2 FREEZING POINT DATA FOR SELECT AGENTS

AGENT	FREEZING POINT DEPRESSION, 1% SOLUTIONS ($\Delta T_f^{1\%}$)
Atropine sulfate	0.07
Boric acid	0.29
Butacaine sulfate	0.12
Chloramphenicol	0.06
Chlorobutanol	0.14
Dextrose	0.09
Dibucaine hydrochloride	0.08
Ephedrine sulfate	0.13
Epinephrine bitartrate	0.10
Ethylmorphine hydrochloride	0.09
Glycerin	0.20
Homatropine hydrobromide	0.11
Lidocaine hydrochloride	0.063
Lincomycin	0.09
Morphine sulfate	0.08
Naphazoline hydrochloride	0.16
Physostigmine salicylate	0.09
Pilocarpine nitrate	0.14
Sodium bisulfite	0.36
Sodium chloride	0.58
Sulfacetamide sodium	0.14
Zinc sulfate	0.09

How many milligrams each of sodium chloride and dibucaine hydrochloride are required to prepare 30 mL of a 1% solution of dibucaine hydrochloride isotonic with tears?

To make this solution isotonic, the freezing point must be lowered to −0.52. From Table 11.2, it is determined that a 1% solution of dibucaine hydrochloride has a freezing point lowering of 0.08°. Thus, sufficient sodium chloride must be added to lower the freezing point an additional 0.44° (0.52° − 0.08°).

Also from Table 11.2, it is determined that a 1% solution of sodium chloride lowers the freezing point by 0.58°. By proportion:

Also from Table 11.2, it is determined that a 1% solution of sodium chloride lowers the freezing point by 0.58°. By proportion:

$$\frac{1\%\ (\text{NaCl})}{x\%\ (\text{NaCl})} = \frac{0.58°}{0.44°}$$

$x = 0.76\%$ (the concentration of sodium chloride needed to lower the freezing point by 0.44°, required to make the solution isotonic)

Thus, to make 30 mL of solution,

30 mL × 1% = 0.3 g = 300 mg dibucaine hydrochloride, and

30 mL × 0.76% = 0.228 g = 228 mg sodium chloride, *answers.*

Isotonicity

To calculate the ''equivalent tonic effect'' to sodium chloride represented by an ingredient in a preparation, multiply its weight by its *E* value:

$$g \times \mathrm{E}\ value = g,\ equivalent\ tonic\ effect\ to\ sodium\ chloride$$

To make a solution isotonic, calculate and ensure the quantity of sodium chloride and/or the equivalent tonic effect of all other ingredients to total 0.9% w/v in the preparation:

$$\frac{g\ (NaCl) + g\ (NaCl\ tonic\ equivalents)}{mL\ (preparation)} \times 100 = 0.9\%\ \mathrm{w/v}$$

To make an isotonic solution from a drug substance, add sufficient water by the equation:

$$\frac{g\ (drug\ substance) \times \mathrm{E}\ value\ (drug\ substance)}{0.009} = mL\ water$$

This solution may then be made to any volume with isotonic sodium chloride solution to maintain its isotonicity.

The *E* value can be derived from the same equation, given the grams of drug substance and the milliliters of water required to make an isotonic solution.

BUFFER AND BUFFER SOLUTIONS

- water alone cannot neutralize even traces of acid or base, that is, it has no ability to resist changes in hydrogen-ion concentration or pH.
- A solution of a neutral salt, such as sodium chloride, also lacks this ability. Therefore, it is said to be unbuffered.
- The presence of certain substances or combinations of substances in an aqueous solution imparts to the system the ability to maintain a desired pH at a relatively constant level, even with the addition of materials that may be expected to change the hydrogen–ion concentration.
- These substances or combinations of substances are called buffers; their ability to resist changes in pH is referred to as buffer action; their efficiency is measured by the function known as buffer capacity; and solutions of them are called buffer solutions.

- By definition, then, a **buffer solution** is a system, usually, an aqueous solution, that possesses the property of resisting changes in pH with the addition of small amounts of a strong acid or base.
- Buffers are used to establish and maintain an ion activity within rather narrow limits.
- In pharmacy, the most common buffer systems are used in:

1. The preparation of such dosage forms as injections and ophthalmic solutions, which are placed directly into pH-sensitive body fluids.
2. The manufacture of formulations in which the pH must be maintained at a relatively constant level to ensure maximum product stability.
3. pharmaceutical tests and assays requiring adjustment to or maintenance of a specific pH for analytic purposes.

- A buffer solution is usually composed of a weak acid and a salt of the acid, such as acetic acid and sodium acetate, or a weak base and a salt of the base, such as ammonium hydroxide and ammonium chloride.
- Typical buffer systems that may be used in pharmaceutical formulations include the following pairs: acetic acid and sodium acetate, boric acid and sodium borate, and disodium phosphate and sodium acid phosphate.
- In the selection of a buffer system, due consideration must be given to the **dissociation constant** of the weak acid or base to ensure maximum buffer capacity.
- This dissociation constant, in the case of an acid, is a measure of the strength of the acid; the more readily the acid dissociates, the higher its dissociation constant and the stronger the acid.
- The dissociation constant, or Ka value, of a weak acid, is given by the equation:

$$K_a = \frac{(H^+)(A^-)}{(HA)} \qquad \text{where } A^- = \text{salt}, \quad HA = \text{acid}$$

- The buffer equation for weak acids :

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

- The buffer equation for weak bases :

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

- The buffer equation is useful for calculating:

1. the pH of a buffer system if its composition is known.
2. the molar ratio of the components of a buffer system required to give a solution of a desired pH.

- The equation can also be used to calculate the change in pH of a buffered solution with the addition of a given amount of acid or base.

pKa Value Of A Weak Acid With Known Dissociation Constant

The dissociation constant of acetic acid is 1.75×10^{-5} *at* $25°C$*. Calculate its* pK_a *value.*

$$K_a = 1.75 \times 10^{-5}$$

and

$$\log K_a = \log 1.75 + \log 10^{-5}$$
$$= 0.2430 - 5 = -4.757 \text{ or } -4.76$$

Because

$$pK_a = -\log K_a$$
$$pK_a = -(-4.76) = 4.76, \textit{ answer.}$$

pH Value Of A Salt/Acid Buffer System

What is the pH of a buffer solution prepared with 0.05 M sodium borate and 0.005 M boric acid? The pK_a value of boric acid is 9.24 at 25°C.

Note that the ratio of the components of the buffer solution is given in molar concentrations. Using the buffer equation for weak acids:

$$\begin{aligned} pH &= pK_a + \log \frac{\text{salt}}{\text{acid}} \\ &= 9.24 + \log \frac{0.05}{0.005} \\ &= 9.24 + \log 10 \\ &= 9.24 + 1 \\ &= 10.24, \textit{ answer.} \end{aligned}$$

pH Value Of A Base/Salt Buffer System

What is the pH of a buffer solution prepared with 0.05 M ammonia and 0.05 M ammonium chloride? The K_b value of ammonia is 1.80×10^{-5} at 25°C.

Using the buffer equation for weak bases:

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

Because the K_w value for water is 10^{-14} at 25°C, $pK_w = 14$.

$$\begin{aligned} K_b &= 1.80 \times 10^{-5} \\ \text{and} \qquad \log K_b &= \log 1.8 + \log 10^{-5} \\ &= 0.2553 - 5 = -4.7447 \text{ or } -4.74 \\ pK_b &= -\log K_b \\ &= -(-4.74) = 4.74 \end{aligned}$$

$$\begin{aligned} \text{and} \qquad pH &= 14 - 4.74 + \log \frac{0.05}{0.05} \\ &= 9.26 + \log 1 \\ &= 9.26, \textit{ answer.} \end{aligned}$$

MOLAR RATIO OF SALT/ACID FOR A BUFFER SYSTEM OF DESIRED PH

What molar ratio of salt/acid is required to prepare a sodium acetate-acetic acid buffer solution with a pH of 5.76? The pK_a value of acetic acid is 4.76 at 25°C.

Using the buffer equation:

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

$$\log \frac{\text{salt}}{\text{acid}} = pH - pK_a$$

$$= 5.76 - 4.76 = 1$$

$$\text{antilog of } 1 = 10$$

$$\text{ratio} = 10/1 \text{ or } 10:1, \textit{ answer.}$$

CHANGE IN pH WITH ADDITION OF AN ACID OR BASE

Calculate the change in pH after adding 0.04 mol of sodium hydroxide to a liter of a buffer solution containing 0.2 M concentrations of sodium acetate and acetic acid. The pK_a value of acetic acid is 4.76 at 25°C.

The pH of the buffer solution is calculated by using the buffer equation as follows:

$$\begin{aligned} pH &= pK_a + \log \frac{\text{salt}}{\text{acid}} \\ &= 4.76 + \log \frac{0.2}{0.2} \\ &= 4.76 + \log 1 \\ &= 4.76 \end{aligned}$$

The addition of 0.04 mol of sodium hydroxide converts 0.04 mol of acetic acid to 0.04 mol of sodium acetate. Consequently, the concentration of acetic acid is *decreased* and the concentration of sodium acetate is *increased* by equal amounts, according to the following equation:

$$pH = pK_a + \log \frac{\text{salt} + \text{base}}{\text{acid} - \text{base}}$$

and

$$\begin{aligned} pH &= pK_a + \log \frac{0.2 + 0.04}{0.2 - 0.04} \\ &= pK_a + \log \frac{0.24}{0.16} \\ &= 4.76 + 0.1761 = 4.9361 \text{ or } 4.94 \end{aligned}$$

Because the pH before the addition of the sodium hydroxide was 4.76, the change in pH = 4.94 − 4.76 = 0.18 unit, *answer*.

Isotonic and Buffer Solutions