Chapter 11
Isotonic and Buffer Solutions

Reference text: 1-Pharmaceutical Calculation by Stoklosa; Latest edition.
2- Principles of Pharmaceutical Calculations by Howard C. Ansel

Physical/Chemical Considerations in the Preparation of Isotonic Solutions

Colligative properties are properties of solutions that depend on the ratio of the number of solute particles to the number of solvent molecules in a solution, and not on the nature of the chemical species present.[

Colligative properties include:

1. Relative lowering of vapor pressure
2. Elevation boiling point
3. Depression of freezing point
4. Osmotic pressure

Theoretically, any one of these properties may be used as a basis for determining tonicity.

Practically, a comparison of freezing points is used for this purpose. It is generally accepted that - 0.52 ^{o}C is the freezing point of both blood serum and lacrimal fluid.

When one gram molecular weight of any nonelectrolyte, that is, a substance with negligible dissociation, such as boric acid, is dissolved in 1000 g of water, the freezing point of the solution is about 1.86 ^{o}C below the freezing point of pure water.

By simple proportion, therefore, we can calculate the weight of any nonelectrolyte that should be dissolved in each 1000 g of water if the solution is to be isotonic with body fluids.

For example: Boric acid has a molecular weight of 61.8; thus (in theory), 61.8 g in 1000 g of water should produce a freezing point of -1.86 °C.

Therefore:

$$\frac{1.86\ ^{o}C}{0.52\ ^{o}C} = \frac{61.8\ (g)}{x\ (g)}$$

$$x = 17.3\ g$$

- 9.09 g of sodium chloride in 1000 g of water should make a solution isotonic with blood or lacrimal fluid. Means that, In practice, a 0.90% w/v sodium chloride solution is considered isotonic with body fluids.

- Simple isotonic solutions may then be calculated by using this formula:

$$\frac{0.52 \times \text{molecular weight}}{1.86 \times \text{dissociation (i)}} = \text{g of solute per 1000 g of water}$$

The dissociation factor (i), must be included in the proportion when we seek to determine the strength of an isotonic solution of sodium chloride

- If the number of ions is known, we may use the following values (i):

a) Nonelectrolytes and substances of slight dissociation1.0

b) Substances that dissociate into 2 ions: 1.8

c) Substances that dissociate into 3 ions: 2.6

d) Substances that dissociate into 4 ions: 3.4

e) Substances that dissociate into 5 ions: 4.2

- 17.3 g of boric acid are equivalent in tonicity to 9.09 g of sodium chloride,
- Then 1 g of boric acid must be the equivalent of 9.09 g /17.3 g or 0.52 g of sodium chloride.
- Similarly, 1 g of sodium chloride must be the ‘‘tonicic equivalent’’ of 17.3 g / 9.09 g or 1.90 g of boric acid.

- We can formulate a convenient rule: quantities of two substances that are tonicic equivalents are proportional to the molecular weights of each multiplied by the i value of the other.
- To return to the problem involving 1 g of atropine sulfate in 100 mL of solution:
- Molecular weight of sodium chloride = 58.5; i =1.8
- Molecular weight of atropine sulfate = 695; i = 2.6

$$\frac{695 \times 1.8}{58.5 \times 2.6} = \frac{1\ (g)}{x\ (g)}$$

$$x = 0.12 \text{ g of sodium chloride represented by 1 g of atropine sulfate}$$

Because a solution isotonic with lacrimal fluid should contain the equivalent of 0.90 g of sodium chloride in each 100 mL of solution, the difference to be added must be 0.90 g - 0.12 g = 0.78 g of sodium chloride.

Calculations of the (i) Factor

Examples 1:

Zinc sulfate is a 2-ion electrolyte, dissociating 40% in a certain concentration. Calculate its dissociation (i) factor.

On the basis of 40% dissociation, 100 particles of zinc sulfate will yield:

40 zinc ions
40 sulfate ions
60 undissociated particles
----
or 140 particles

Because 140 particles represent 1.4 times as many particles as were present before dissociation, the dissociation (i) factor is 1.4, answer.

Examples 2:

Zinc chloride is a 3-ion electrolyte, dissociating 80% in a certain concentration. Calculate its dissociation (i) factor.

On the basis of 80% dissociation, 100 particles of zinc chloride will yield:

80 zinc ions
80 chloride ions
80 chloride ions
20 undissociated particles
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or 260 particles

Because 260 particles represents 2.6 times as many particles as were present before dissociation, the dissociation (i) factor is 2.6, answer.

Calculations of the Sodium Chloride Equivalent

The sodium chloride equivalent of a substance may be calculated as follows:

$$\frac{\text{Molecular weight of sodium chloride}}{\text{i factor of sodium chloride}} \times \frac{\text{i factor of the substance}}{\text{Molecular weight of the substance}} = \text{Sodium chloride equivalent}$$

Example: Calculate the sodium chloride equivalent for timolol maleate, which dissociates into two ions and has a molecular weight of 432.2

Timolol maleate, i factor = 1.8

$$\frac{58.5}{1.8} \times \frac{1.8}{432} = 0.14, \textit{ answer.}$$

Calculations of Tonicic Agent Required

How many grams of sodium chloride should be used in compounding the following prescription?

℞

Pilocarpine Nitrate	0.3 g
Sodium Chloride	q.s.
Purified Water ad	30 mL
Make isoton. sol.	
Sig. For the eye.	

Pilocarpine nitrate	271	2	1.8	0.23

Step 1. 0.23 x 0.3 g = 0.069 g of sodium chloride represented by the pilocarpine nitrate

Step 2. 30 x 0.009 = 0.270 g of sodium chloride in 30 mL of an isotonic sodium chloride solution

Step 3. 0.270 g (from Step 2)

- 0.069 g (from Step 1)

0.201 g of sodium chloride to be used, *answer.*

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:

Step 1. Calculate the quantity of the drug substance needed to fill the prescription or medication order.

Step 2. Use the following equation to calculate the volume of water needed to render a solution of the drug substance isotonic:

$$\frac{\text{g of drug x drug's E value}}{0.009} = \text{mL of water needed to make an isotonic solution of the drug}$$

(the volume of the drug substance is considered negligible)

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

Example: 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 x 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.

Use of Freezing Point Data in Isotonicity Calculations

- Freezing point data (ΔT_f) 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 - 0.52C.

Example: 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).

it is determined that a 1% solution of sodium chloride lowers the freezing point by 0.58. By proportion:

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

$x = 0.76\%$ (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,

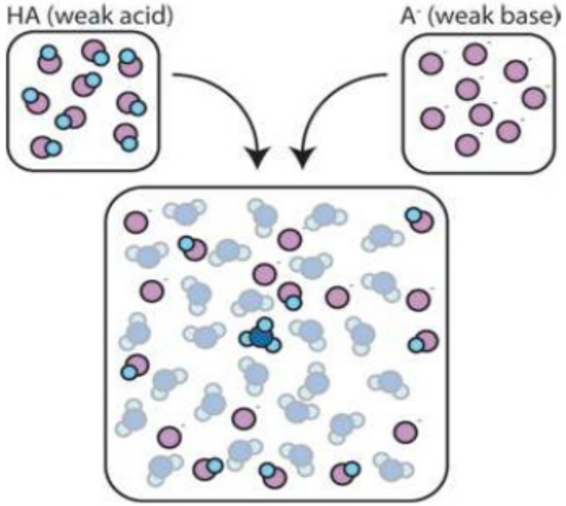
$30\ \text{mL} \times 1\% = 0.3\ \text{g} = 300\ \text{mg}$ dibucaine hydrochloride, and

$30\ \text{mL} \times 0.76\% = 0.228\ \text{g} = 228\ \text{mg}$ sodium chloride, *answers.*

Buffers and Buffer Solutions

Buffer Solutions

- DEFINITION: A buffer solution contains a weak acid mixed with its conjugate base (or weak base and conjugate acid)
- Buffers resist changes in pH when a **small** amount of a strong acid or base is added to it.



$$HA \prod H^{+} + A^{-}$$

Water alone cannot neutralize traces of acid or base when added to it and 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.

In pharmacy, the most common buffer systems are used in

(i) the preparation of such dosage forms as injections and ophthalmic solutions, which are placed directly into pH-sensitive body fluids;

(ii) the manufacture of formulations in which the pH must be maintained at a relatively constant level to ensure maximum product stability; and

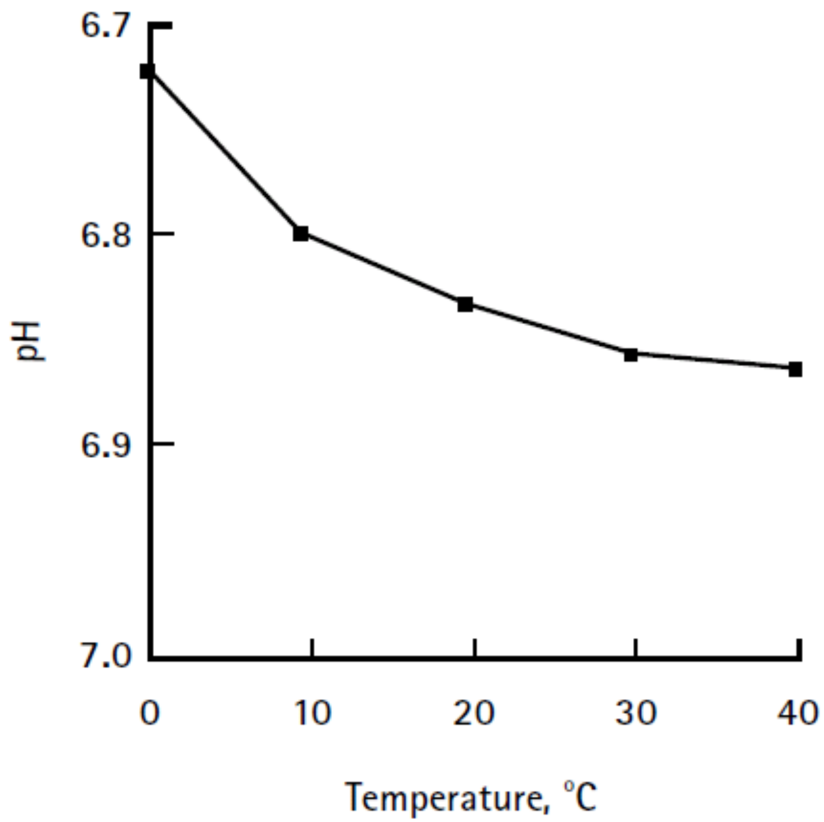
(iii) pharmaceutical tests and assays requiring adjustment to or maintenance of a specific pH for analytic purposes.

Typical buffer systems that may be used in pharmaceutical formulations include the following pairs:

- **Citrate-Phosphate Buffer** (dibasic sodium phosphate and citric acid; **pH range 2.6 to 7.0)**
- **Acetate Buffer** (acetic acid and sodium acetate; **pH range 3.6 to 5.6)**
- **Phosphate buffer** (dibasic sodium phosphate and sodium acid phosphate; **pH range 5.8 to 8.0)**
- **Borate buffer** (boric acid and sodium borate; **pH range 6.8-9**)

Effect of Temperature on pH

Figure presents the effect of temperature on the pH of phosphate buffer



HENDERSON-HASSELBALCH EQUATION

For acids:

$$pH = pK_a + \log\left(\frac{[A^-]}{[HA]}\right)$$

When $[A^-] = [HA]$, $pH = pK_a$

For bases:

$$pH = pK_a + \log\frac{[B]}{[BH^+]}$$

pK_a applies to this acid

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

$$\underset{\text{base}}{B} + \underset{\text{acid}}{H_2O} \underset{K_a}{\overset{K_b}{\rightleftarrows}} \underset{\text{acid}}{BH^+} + \underset{\text{base}}{OH^-}$$

Derivation:

$$\boxed{HA \rightarrow H^+ + A^-}$$

$$K_a = \frac{[H^+][A^-]}{[HA]} \qquad -\log K_a = -\log\left(\frac{[H^+][A^-]}{[HA]}\right) = -\log[H^+] - \log\left(\frac{[A^-]}{[HA]}\right) \qquad pK_a = pH - \log\left(\frac{[A^-]}{[HA]}\right)$$

$$pH = pK_a + \log\left(\frac{[A^-]}{[HA]}\right)$$

Example for acidic buffer:

What is the pH of a buffer solution prepared with 0.05 M sodium borate and 0.005 M boric acid? The pKa value of boric acid is 9.24 at 25 ^{o}C.

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

Example for Basic buffer:

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 x10^{-5} at 25 ^{o}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, $pK_w = 14$.

and

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

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

Quantity of Components in a Buffer Solution to Yield a Specific Volume

Calculating the amounts of the components of a buffer solution required to prepare a desired volume, given the molar ratio of the components and the total buffer concentration:

The molar ratio of sodium acetate to acetic acid in a buffer solution with a pH of 5.76 is **10:1**. Assuming the total buffer concentration is 2.2×10^{-2} mol/L, how many grams of sodium acetate (m.w. 82) and how many grams of acetic acid (m.w. 60) should be used in preparing a liter of the solution?

Because the molar ratio of sodium acetate to acetic acid is 10:1,

$$\text{the mole fraction of sodium acetate} = \frac{10}{1 + 10} \text{ or } \frac{10}{11}$$
$$\text{and the mole fraction of acetic acid} = \frac{1}{1 + 10} \text{ or } \frac{1}{11}$$

If the total buffer concentration $= 2.2 \times 10^{-2}$ mol/L,

$$\begin{aligned}\text{the concentration of sodium acetate} &= \frac{10}{11} \times (2.2 \times 10^{-2}) \\ &= 2.0 \times 10^{-2} \text{ mol/L} \\ \text{and the concentration of acetic acid} &= \frac{1}{11} \times (2.2 \times 10^{-2}) \\ &= 0.2 \times 10^{-2} \text{ mol/L}\end{aligned}$$

then 2.0×10^{-2} or $0.02 \times 82 = 1.64$ g of sodium acetate per liter of solution, *and* 0.2×10^{-2} or $0.002 \times 60 = 0.120$ g of acetic acid per liter of solution, *answers.*