



Buffered and Isotonic Solutions

Lecture by:

Assist. Prof. Anas Tarik Nafei

PHYSICAL PHARMACY

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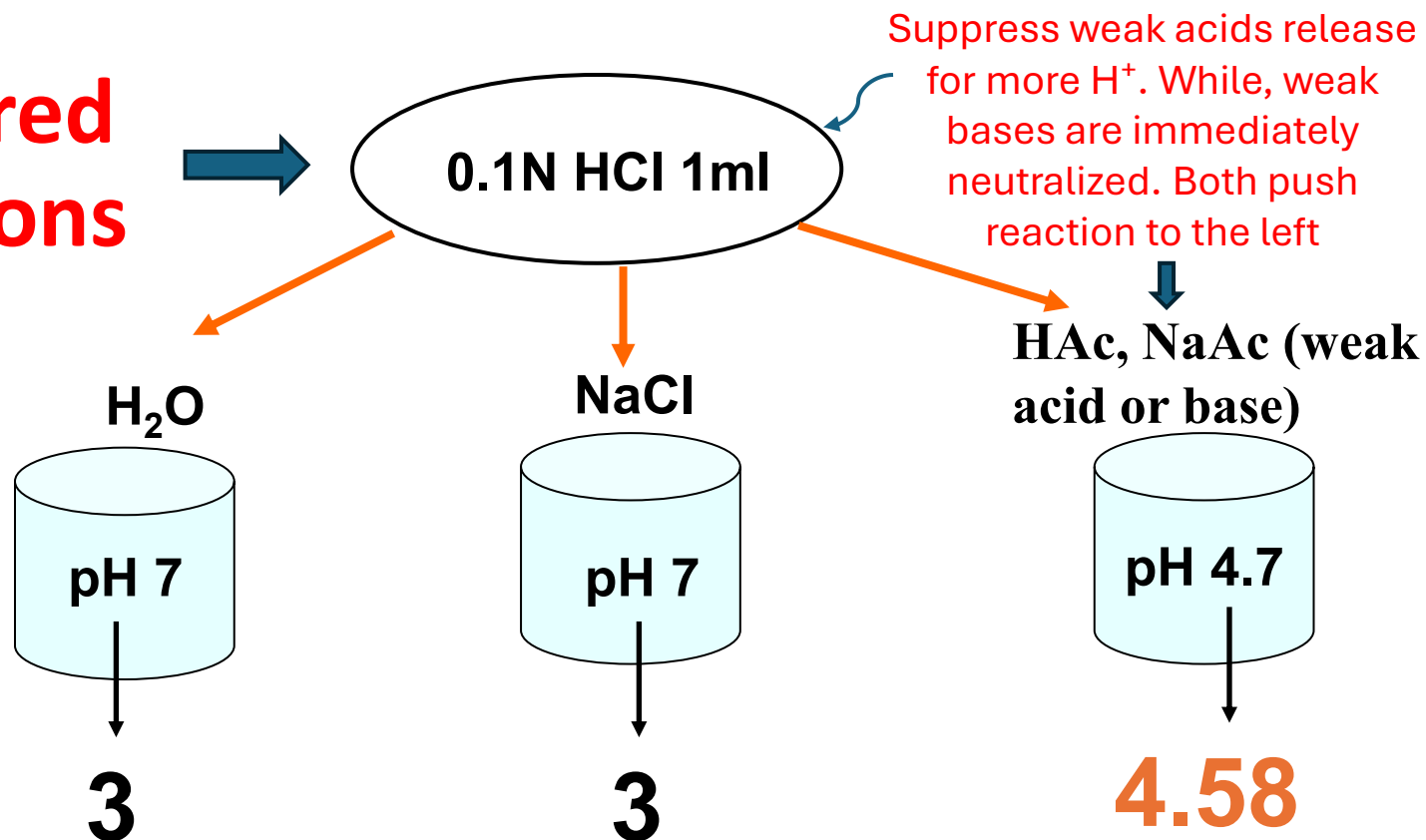


Buffers are compounds or mixtures of compounds that, by their presence in solution, resist changes in pH upon the addition of small quantities of acid or alkali.

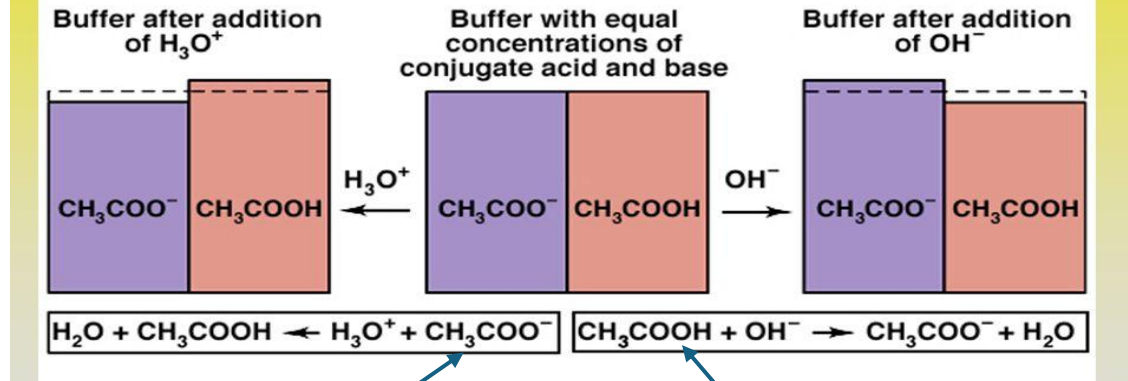


The resistance to a change in pH is known as **buffer action**.

Buffered Solutions



How a Buffer Works



Conjugate base accepts proton so neutralize added acid (remove added H^+)

Weak acid donates proton so neutralize added base (remove added OH^-)

Buffered Solutions

- **Combination of a weak acid and its conjugate base**

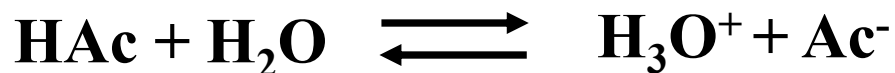


- **Combination of a weak base and its conjugate acid**



The Buffer Equation

- **A Weak Acid and Its Salt**
- 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



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

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{Ac}^-] \xrightarrow{\text{salt}}}{[\text{HAc}] \xrightarrow{\text{acid}}}$$

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

A Weak Acid and Its Salt

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

**Dissociation
exponent**

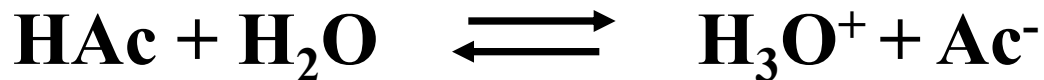
Buffer equation or
Henderson-Hasselbalch
equation

Common ion effect

* When Sod. acetate is added to acetic acid...



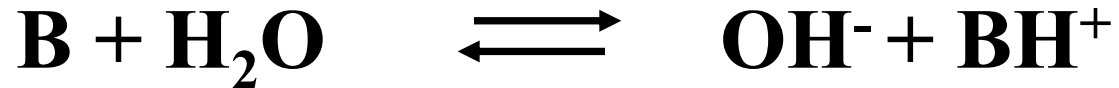
is momentarily disturbed since the acetate ion supplied by the salt increases the $[Ac^-]$



The ionization of HAc is repressed upon the addition of the common ion $[Ac^-]$

The Buffer Equation

- A Weak Base and Its Salt



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

salt
base

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

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

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

- **A Weak Acid and Its Salt**

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

* **Note:**

Buffers are not ordinarily prepared from weak bases because of:

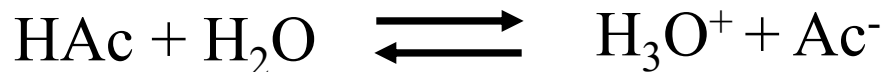
1. **Volatility & instability of the bases.**
2. **Dependence of their pH on $\text{p}K_w$, which is often affected by temp. changes.**

Example

- For example, when sodium acetate is added to acetic acid, the dissociation constant for the weak acid, is

$$K_a = \frac{[H_3O^+][Ac^-]}{[HAc]} = 1.75 \times 10^{-5}$$

- Is momentarily disturbed because the acetate ion supplied by the salt increases the $[Ac^-]$ term in the numerator.
- To reestablish the constant K_a at 1.75×10^{-5} , the hydrogen ion term in the numerator $[H_3O^+]$ is instantaneously decreased, with a corresponding increase in $[HAc]$. Therefore, the constant K_a remains unaltered, and the equilibrium is shifted in the direction of the reactants.
- Consequently, the ionization of acetic acid is repressed upon the addition of the common ion, Ac^- . This is an example of the common ion effect.



Example 8.2:

What is the molar ratio, $[\text{Salt}]/[\text{Acid}]$, required to prepare an acetate buffer of pH 5.0? If you know that pK_a is 4.76. Also express the result in mole percent.

$$\text{pH} = \text{pK}_a + \log \frac{[\text{Salt}]}{[\text{Acid}]}$$

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

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

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

- 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%.

Factors influencing the PH of buffer solutions

1. Altering the ionic strength

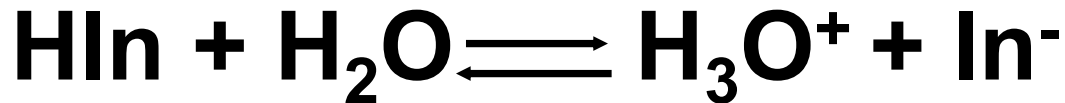
- ① Addition of neutral salts
- ② Dilution (alter activity coefficients) small pH change

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 .

pH indicator

- Acid indicator



Acid color (at low
pH- high H^+)

Alkaline color (at high pH- low H^+)

$$K_{In} = \frac{[\text{H}_3\text{O}^+][\text{In}^-]}{[\text{HIn}]}$$

← base
← acid

$$\text{pH} = \text{p}K_{In} + \log \frac{[\text{base}]}{[\text{acid}]} \longrightarrow 1/10 \sim 10/1$$

- * From experience, one cannot discern a change from the acid color to the salt color or conjugate base until the ratio of [base] to [acid] is about 1 to 10 (-1 acid) and from [acid] to [base] 10 to 1 (+1 base)
- * The effective range of the indicator is...

$$\text{pH} = \text{p}K_{In} \pm 1$$



Characteristics of colorimetric method

- ① Less accurate
- ② Less convenient but less expensive than electrometric method
- ③ Difficult to apply for the unbuffered pharmaceutical preparation (change the pH - indicator itself is acids or base)
- ④ Error may be introduced by the presence of salts & proteins

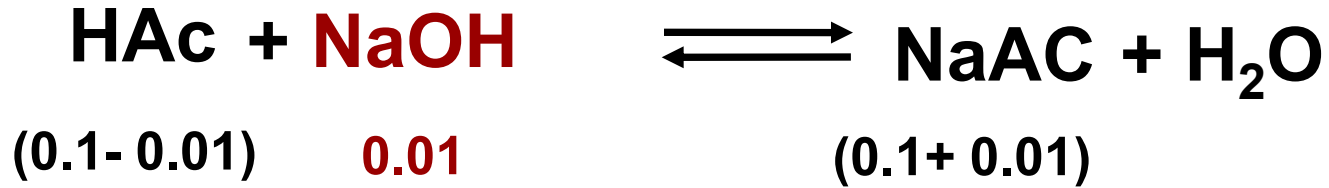
Buffer capacity

- 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 : small increment in gram equivalents/Liter of strong base (or acid) added to the buffer soln. to produce a pH change of ΔpH



- Before the addition of NaOH

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

- After the addition of NaOH

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

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

TABLE 8-2. 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

- In Table 8-2, 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, **pH = pKa**.

- The buffer capacity is also influenced by **C** (total buffer concentration), that is, the **sum of the molar concentrations of the acid and the salt**. The buffer capacity can be computed at any hydrogen ion concentration, at the point **where no acid or base has been added to the buffer**.

- A more exact equation for buffer capacity (1914, 1922)

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

c : total buffer conc. (sum of the molar conc. of the acid & the salt)

• β ---- at any $[\text{H}_3\text{O}^+]$

Example 8-6:

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 per liter, and the dissociation constant is 1.75×10^{-5} .

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

Maximum Buffer capacity

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

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

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

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

Example 8.8: What is the maximum buffer capacity of an acetate buffer with a total concentration of 0.02 mole per liter?

$$\beta_{\max} = 0.576 \times 0.020 = 0.01152 \text{ or } 0.012$$

Characteristics of Buffer Capacity

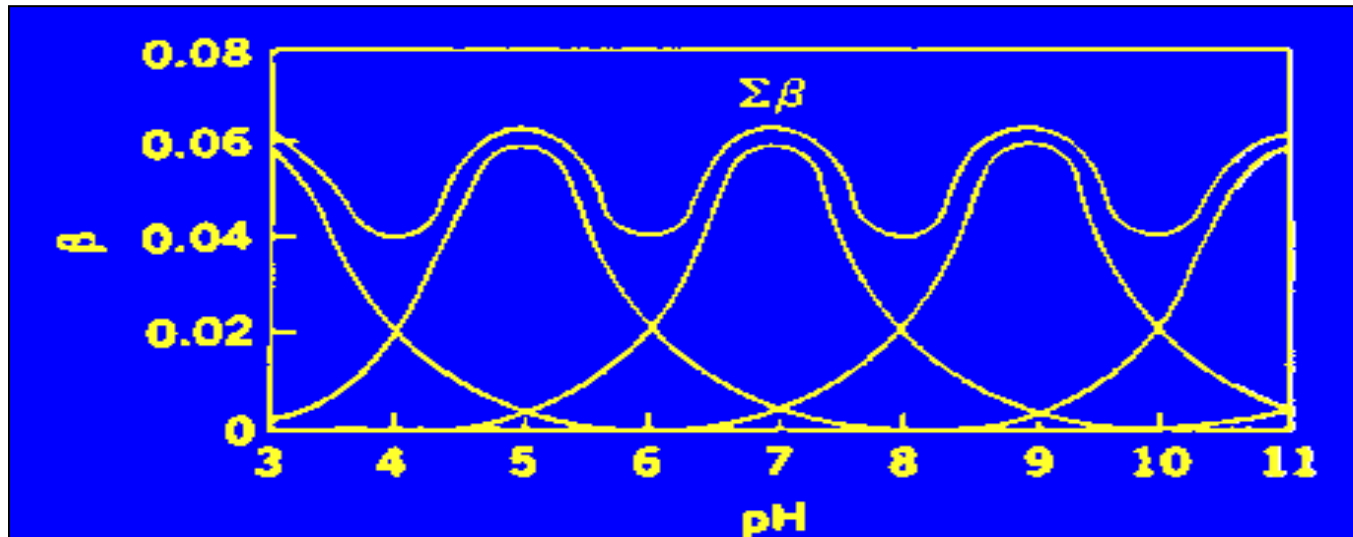
- ...is not a fixed value, but rather depend on the amount of base added
- ...depends on the value of the ratio [salt]/[acid] and magnitude of the individual concentrations of the buffer components
- The greatest capacity (β_{\max}) occurs where [salt]/[acid] = 1 and pH = pKa
- Because of interionic effects, buffer capacities do not in general exceed a value of 0.2

Universal Buffer

The buffer capacity of a combination of buffers, the **pKa values of which overlap to produce a universal buffer.**

Total buffer capacity ($\Sigma\beta$): is the sum of the β values of the individual buffers.

In this figure, it is assumed that the **maximum β 's of all buffers in the series are identical.**



Buffers in Pharmaceutical and Biologic Systems

In Vivo Biologic Buffer Systems

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 parenterally 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**:
 1. its **buffer capacity** and
 2. the **volume** to be used in relation to the volume of body fluid with which the buffered solution will come in contact.
 3. 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 :**

- A. the lower **is the buffer capacity of the solution,**

- B. the **smaller is the volume** used for a given concentration.

- 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.

Preparation of pharmaceutical buffer solutions

- **Steps for development of a new buffer**

- ① Select a **weak acid having a pK_a approximately equal to the pH** at which the buffer is to be used.
- ② Calculate the **ratio of salt & weak acid required to obtain the desired pH.**
- ③ Consider the **individual conc. of the buffer salt & acid needed** to obtain a **suitable buffer capacity**
 - * Individual conc. : 0.05 ~ 0.5M
 - * buffer capacity : 0.01 ~ 0.1
- ④ **Availability of chemicals, sterility of the final sol., stability of the drug & buffer, cost of materials, freedom from toxicity**
 - ex) borate buffer – toxic effect – not be used for oral or parenteral products.
- ⑤ Determine the **pH and buffer capacity using a reliable pH meter.**

- **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**.

- If a solution is instilled in the eye



- Tears participate in the gradual **neutralization of the solution**



- **Conversion of the drug from inactive form to the undissociated base.**



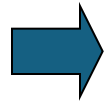
- **Base penetrate readily the lipoidal membrane.**

Note: 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.

THANK

YOU

+

Buffered Isotonic Solutions

Pharmaceutical solutions (applied to delicate membranes of the body) should be adjusted to:

1. pH
2. **osmotic pressure** as that of the body fluids.

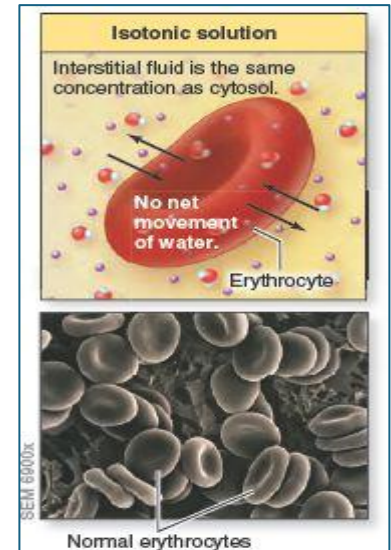
Isotonic solutions



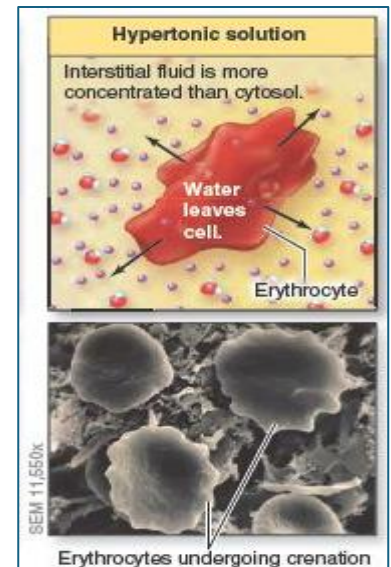
Cause **no swelling** or **contraction of the tissues** with which they come in contact and produce no discomfort **when instilled in the eye, nasal tract, blood, or other body tissues.**

Tonicity classifications:

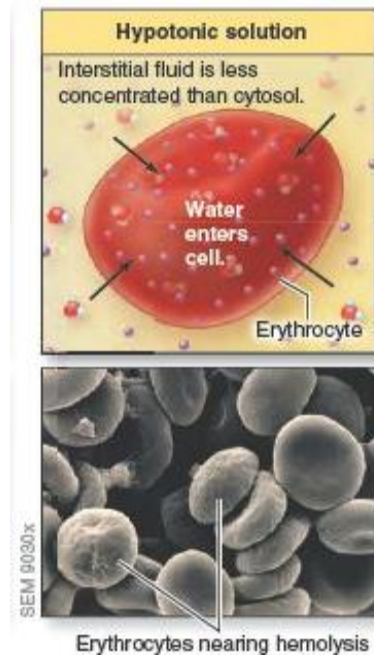
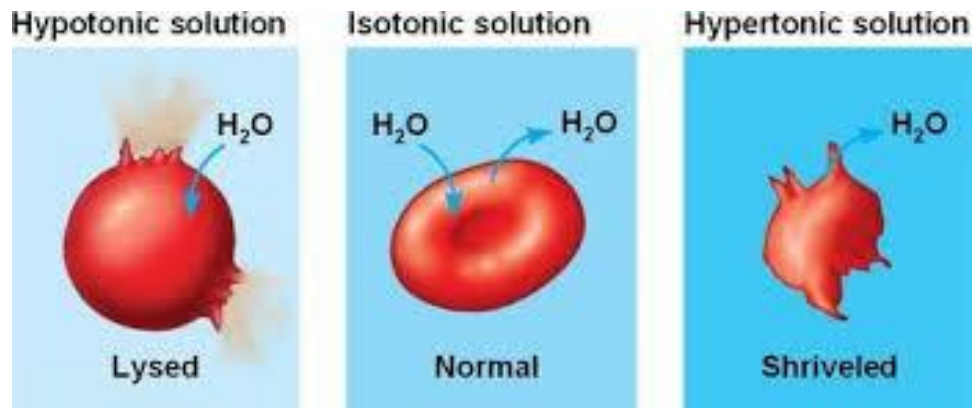
1. **Isotonic:** If a small quantity of blood, is mixed with a solution containing **0.9 g of NaCl per 100 mL (0.9%)**, the **cells retain their normal size**. The solution has the same salt concentration and the same osmotic pressure as RBC contents and is said to be **isotonic** with blood.



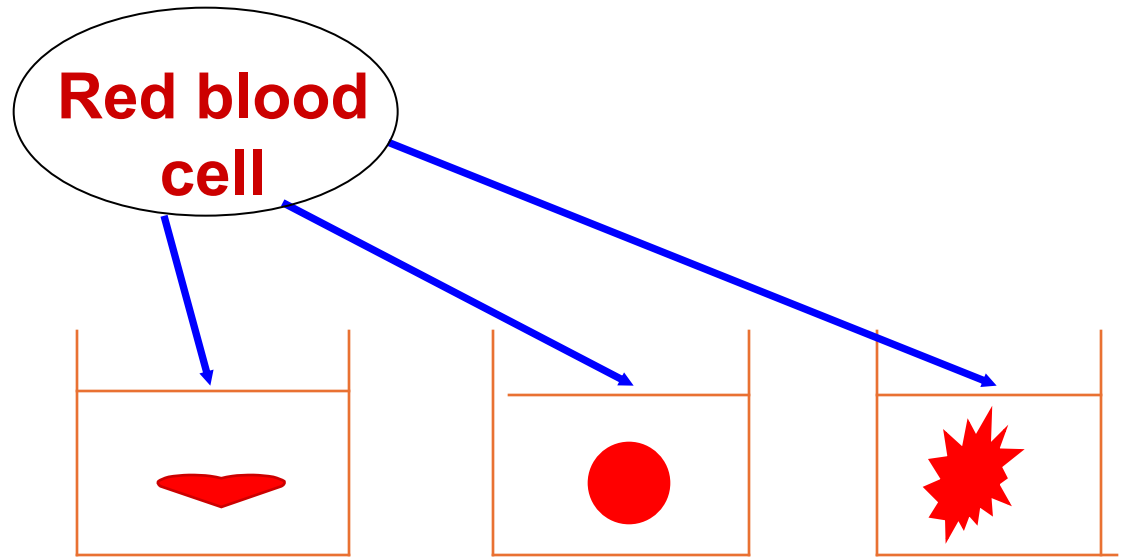
2. **Hypertonic:** If RBC are suspended in a **2.0% NaCl** solution, the water within the cells passes through the cell membrane to dilute the surrounding salt solution until the salt concentrations on both sides of the erythrocyte membrane are identical. This outward passage of water causes the **cells to shrink and become wrinkled**. The salt solution is said to be **hypertonic** with respect to the blood cell contents.



3. Hypotonic: If the blood is mixed with **0.2% NaCl** solution or with distilled water (0% NaCl), water enters the blood cells, causing **cells to swell and finally burst, with the liberation of hemoglobin.** This phenomenon is known as hemolysis, and the weak salt solution or water is said to be **hypotonic** with respect to the blood.



Buffered isotonic solution



NaCl solution

**2.0 %
Hypertonic,
Shrink**

**0.9 %
Isotonic**

**0.2 %
Hypotonic,
Hemolysis**

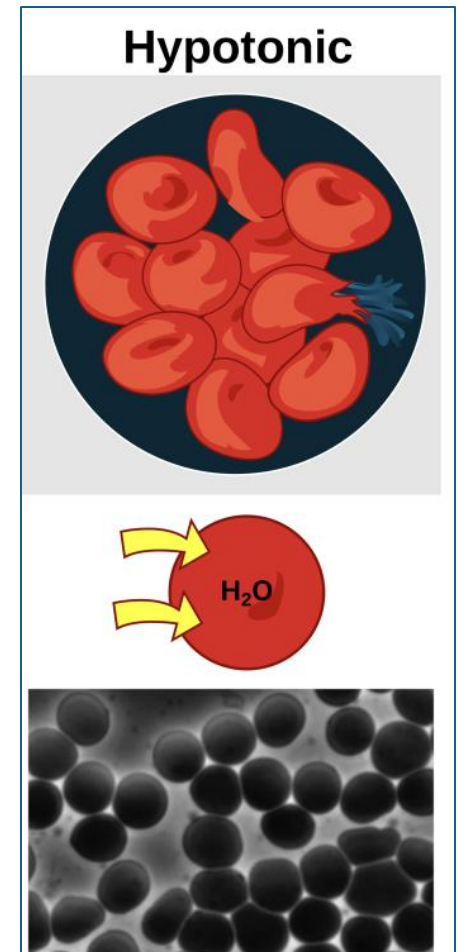
Measurement of Tonicity

The tonicity of solutions can be determined by one of two methods:

1st - quantitative (hemolytic) method:

Based on the fact that a hypotonic solution liberates oxyhemoglobin in direct proportion to the number of cells hemolyzed.

By such means, the **van't Hoff i factor** can be determined.



2nd - approach (measure tonicity)

Based on any of the methods that determine **colligative properties** [osmotic pressure, freezing point depression, boiling point elevation, lowering of vapor pressure] (depend **only on the number of dissolved particles** (solute particles) in the solution).

Example: It is well established that **both human blood and lacrimal fluid has the freezing point of -0.52°C .**



This temp. corresponds to the freezing point of a 0.90% NaCl solution



Considered to be isotonic with both blood and lacrimal fluid.

Calculating Tonicity Using L_{iso} values

- The Van't Hoff expression

Freezing point lowering (weak and strong electrolyte)

$$\Delta T_f = L \cdot C$$

Molal freezing point depression of water

$$L_{iso} = \frac{\Delta T_f}{C}$$

Represents Freezing point lowering of solutions of representative compounds of a given ionic type at a conc.

0.52°

Conc. that is isotonic with body fluids

Calculating Tonicity Using Liso Values

$$\Delta T_f = LC$$

This specific value of L is written as L_{iso} .

It has a value equal to :

- L_{iso} for non-electrolyte = 1.9 (Sucrose)
- L_{iso} for weak electrolyte = 2 (Phenobarbital)
- L_{iso} for uni-univalent electrolyte = 3.4 (NaCl)
- L_{iso} for uni-divalent electrolyte = 4.3 (Na_2SO_4)
- L_{iso} for di-univalent electrolyte = 4.8 (ZnCl_2)

Example 8-11:

Freezing point lowering

What is the freezing point lowering of a 1% solution of sodium propionate (molecular weight 96)? Because sodium propionate is a uni-univalent electrolyte its L_{iso} value is 3.4. The molar concentration of a 1% solution of this compound is 0.104.

$$\Delta T_f = 3.4 \times 0.104 = 0.35 \text{ }^\circ\text{C}$$

(means hypotonic < 0.52 °C)

Method of adjusting tonicity and pH

Class I ...add Sod. Chloride to lower the freezing point of soln. to -0.52°

- ① **Cryoscopic method**
- ② **Sodium chloride equivalent method**

Class II ...add Water to form an isotonic soln.

- ① **White-Vincent method**
- ② **Sprows method**

Class I methods

- **Cryoscopic method** (amount NaCl added to make isotonic)

Example 8-12:

How much NaCl is required to render 100mL of a 1% soln. of apomorphine HCl isotonic with blood serum?

➡ $\Delta T_f^{0.9\%}$ of NaCl soln : 0.52° (Isotonic with blood)

$\Delta T_f^{1\%}$ of apomorphine HCl soln : 0.08° (from table)

To make this solution isotonic with blood, sufficient NaCl must be added to reduce the freezing point by an additional 0.44° ($0.52 - 0.08$)

In the freezing point table: $\Delta T_f^{1\%}$ of NaCl soln : 0.58°

$\frac{1(\%)}{X} = \frac{0.58}{0.44}$: $X = 0.76$ (%) sodium chloride will lower the freezing point the required 0.44 and will render the solution isotonic.

➡ Dissolve 1 g apomorphine HCl + 0.76g NaCl make 100mL soln. with water

Sodium Chloride Equivalent Method

Sodium chloride equivalent of a drug [the amount of NaCl that is equivalent to (i.e., has the same osmotic effect as) 1 g, or other weight unit, of the drug].

- The sodium chloride equivalents E for a number of drugs are listed in Table 8-4.
- E value for new drug can be calculated using the following equation:

$$E \cong 17 \frac{L_{iso}}{MW}$$

Class I methods

- Sodium chloride equivalent(**E**) method by Mellen & Seltzer

$$1\text{g drug tonicity} = \text{Eg NaCl tonicity}$$

E : weight of NaCl with the same freezing point depression as 1g of the drug.

$$\Delta T_f = L_{iso} \cdot c$$

$c = 1 \text{ g} / \text{molecular weight}$

$$\Delta T_f = \underbrace{L_{iso}}_{3.4} \cdot \underbrace{1\text{g}/\text{MW}}_E$$
$$E \cong 17 \cdot L_{iso} / \text{MW}$$

Example 8-13:
Sodium chloride equivalents

Calculate the approximate E value for a new amphetamine hydrochloride derivative (MW =187). Because this drug is a uni-univalent salt, it has an L_{iso} of 3.4.

$$E = \frac{3.4}{187} = 0.31$$

Calculations for determining the amount of NaCl or other insert substance to render a solution isotonic (across an ideal membrane):
Multiplying the quantity of each drug in the prescription by its NaCl equivalent and subtracting this value from the concentration of NaCl this is isotonic with body fluids, namely, 0.9g/100 ml

Example 8-14:

Tonicity Adjustment

A solution Contains 1 g of ephedrine sulfate in a volume of 100 ml. What quantity of NaCl must be added to make the solution isotonic? How much dextrose would be required for this purpose?

The quantity of the drug is multiplied by its NaCl equivalent, E, giving the weight of NaCl to which the quantity of drug is equivalent in osmotic pressure:

$$\text{Ephedrine sulfate: } 1 \times 0.23 = 0.23 \text{ g}$$

The ephedrine sulfate has contributed a weight of material osmotically equivalent to 0.23 g of NaCl. Because a total of 0.9 gram of NaCl is required for isotonicity, **0.67g (0.9 g - 0.23g) of NaCl must be added.**

- If one desired to use dextrose instead of NaCl to adjust the tonicity, the quantity would be estimated by setting up the following proportion. Because the NaCl equivalent of dextrose is 0.16:

$$\bullet \frac{1 \text{ g dextrose}}{0.16 \text{ g NaCl}} = \frac{x}{0.67 \text{ g NaCl}} : \mathbf{x = 4.2 \text{ g of dextrose.}}$$

Class II Methods

White–Vincent Method

The class II methods of computing tonicity involve:

1. **Addition of water to the drugs** to make an isotonic solution.
2. Followed by the **addition of an isotonic or isotonic-buffered diluting vehicle** to bring the solution to the final volume.

For example: Suppose that one wishes to make 30 ml of a 1% solution of procaine HCl isotonic with body fluid.

1. The weight of the drug, w , is multiplied by NaCl equivalent, E :

$$0.3 \times 0.21 = 0.063 \text{ g}$$

This is the quantity of NaCl osmotically equivalent to 0.3 g of procaine HCl.

2. It is known that 0.9 g of NaCl, when dissolved in enough water to make 100 ml, yields a solution that is isotonic.
3. The volume V of isotonic solution that can be prepared from 0.063 g of NaCl (equivalent to 0.3 g of procaine hydrochloride) is obtained by solving the proportion:

$$\frac{0.9 \text{ g}}{100 \text{ ml}} = \frac{0.063 \text{ g}}{v}$$
$$V = 0.063 \times \frac{100}{0.9} = 7 \text{ ml}$$

The quantity 0.063 is equal to the weight of drug, w , multiplied by the NaCl equivalent E . The value of the ratio $100/0.9$ is 111.1. Accordingly, equation may be written as:

$$V = w \times E \times 111.1$$

Where V is the volume in milliliters of isotonic solution that may be prepared by mixing the drug with water.

w is the weight in grams of the drug given in the problem

E the NaCl equivalent.

The **constant, 111.1**, represents the volume in milliliters of isotonic solution obtained by dissolving 1 g of NaCl in water.

The problem may be solved in one step using equation (8-51):

$$V = 0.3 \times 0.21 \times 111.1 = 7.0 \text{ ml}$$

In order to complete the isotonic solution (**enough isotonic NaCl solution, another isotonic solution, or an isotonic-buffered diluting solution is added to make 30 ml of the finished product**).

Several isotonic and isotonic-buffered diluting solutions are found in Table 8-5. These solutions all have isotonicity values of 0.9% NaCl.

Note: When more than one ingredient is contained in an isotonic preparation, the volumes of isotonic solution, obtained by mixing each drug with water, are additive.

Example 8-16:

Make the following solution isotonic with respect to an ideal membrane.

Phenacaine hydrochloride0.06 g
Boric acid. 0.3 g
Sterilized distilled water, enough to make100.0 ml

$$V = [(0.06 \times 0.20) + (0.3 \times 0.50)] \times 111.1$$
$$V = 18\text{ml}$$

The drugs are mixed with water to make 18 ml of an isotonic solution, and the preparation is brought to a volume of 100 mL by adding an isotonic diluting solution.

THANK YOU

