

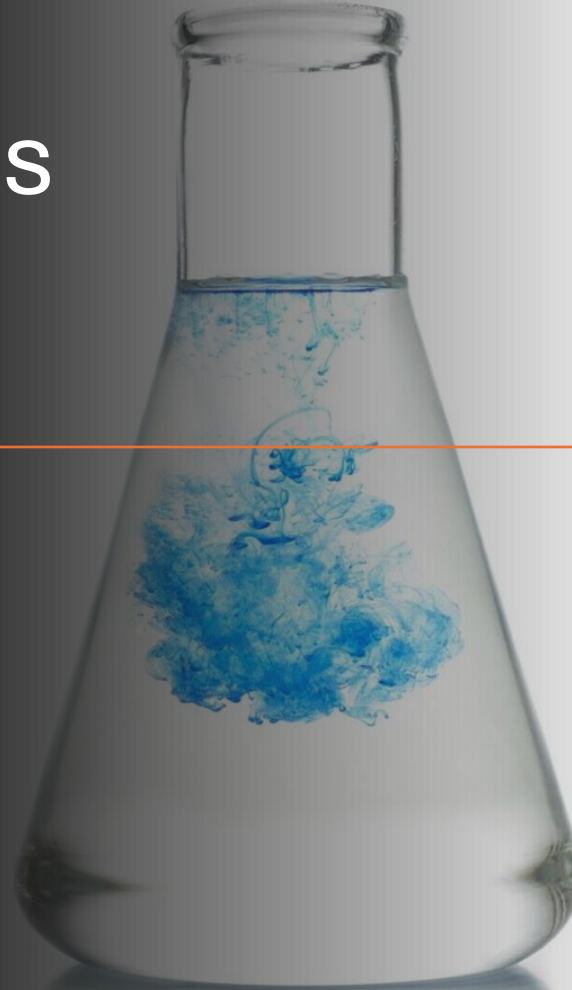


Buffered and Isotonic Solutions (Part 2)



Lecture by:
Assist. Prof. Anas Tarik Nafei

PHYSICAL PHARMACY
1ST SEMESTER / 2026-2027



Preparation of pharmaceutical buffer solutions

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

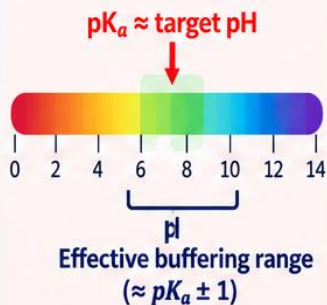
- ① Select a **weak acid having a pK_a approximately equal to the pH** at which the buffer is to be used.
- ② Calculate the **ratio of salt & weak acid required to obtain the desired pH.**
- ③ Consider the **individual conc. of the buffer salt & acid needed** to obtain a **suitable buffer capacity**
 - * 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.**

Clarification

Preparation of Pharmaceutical Buffer Solutions

1 Choose a weak acid

Select a weak acid having a pK_a approximately equal to the pH at which the buffer is to be used.

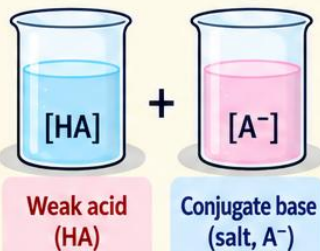


Best buffering occurs when $\text{pH} \approx pK_a$ (about ± 1 pH unit)

2 Calculate the acid-salt ratio

Use the Henderson-Hasselbalch equation to determine the required ratio of the salt (conjugate base) and weak acid to obtain the desired pH.

$$\text{pH} = pK_a + \log \frac{[A^-]}{[HA]}$$



3 Set concentrations and buffer capacity

Consider the individual concentrations of the buffer salt and acid needed to obtain a suitable buffer capacity.

Typical individual concentrations (not a universal rule)

0.05 – 0.5 M

Typical buffer capacity (not a universal rule)

0.01 – 0.1 (mol/L per pH unit)

4 Check pharmaceutical suitability

Consider the following factors:



Availability of chemicals



Sterility of the final solution



Stability of the drug & buffer



Cost of materials



Freedom from toxicity



Example:

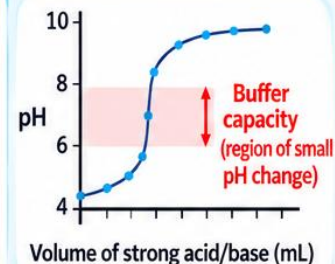
Borate buffer – toxic effect – not to be used for oral or parenteral products.

5 Measure and verify

Determine the pH and buffer capacity using a reliable, calibrated pH meter.



Calibrated 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.

Clarification

Stability vs. Optimum Therapeutic Response

1 Drug ionization in solution

A weak acid or weak base exists in equilibrium between a **unionized (molecular)** form and an **ionized form**, depending on the drug pKa and the local pH.

Weak acid (HA)



HA
Unionized
(molecular)
form
(lipid soluble)

A⁻
Ionized
form
(water soluble)

Weak base (B)

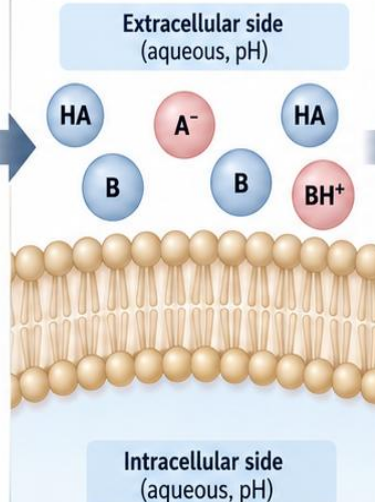


B
Unionized
(molecular)
form
(lipid soluble)

BH⁺
Ionized
form
(water soluble)

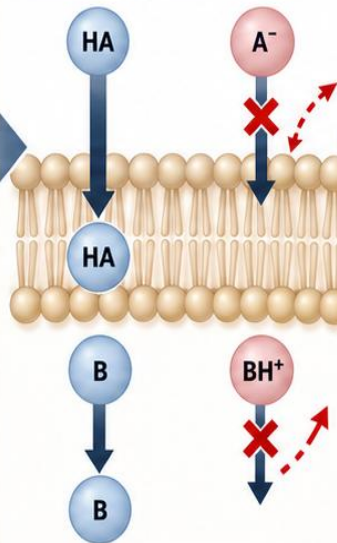
2 Approach to the membrane

Both unionized and ionized forms are present in the aqueous environment (extracellular fluid).



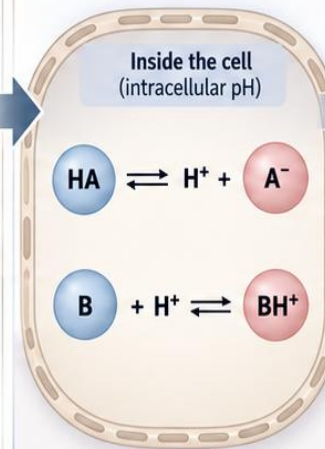
3 Membrane penetration

Only the **unionized** (lipid soluble) form can easily diffuse through the lipid bilayer. The ionized form crosses with great difficulty.



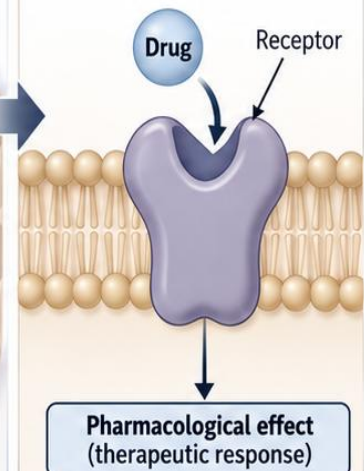
4 Inside the body

After entering the cell, the drug may ionize again depending on the intracellular pH, so an equilibrium exists on both sides of the membrane.



5 Therapeutic response

The drug must reach its site of action (receptor) in the required form and concentration to produce a therapeutic effect.



Key takeaways

- The **unionized (molecular)** form is more lipid soluble and crosses biological membranes more readily.
- The **ionized form** is hydrophilic and penetrates membranes with difficulty.
- The ratio of unionized to ionized form depends on the drug pKa and the **local pH** (Henderson-Hasselbalch equation).
- Higher membrane permeability does not always mean higher therapeutic activity.



Factors affecting therapeutic response

- Membrane permeability (unionized form)
- Receptor affinity
- Drug distribution
- Metabolism and elimination
- Drug dose and concentration at the site of action
- Drug stability and formulation factors (e.g., salt form improves aqueous solubility and dissolution)



Summary

Unionized form
(lipid soluble)
Easier membrane
penetration

Ionized form
(water soluble)
Difficult membrane
penetration

Optimum therapeutic response
requires the right balance of multiple factors,
not only membrane permeability.

- 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.**

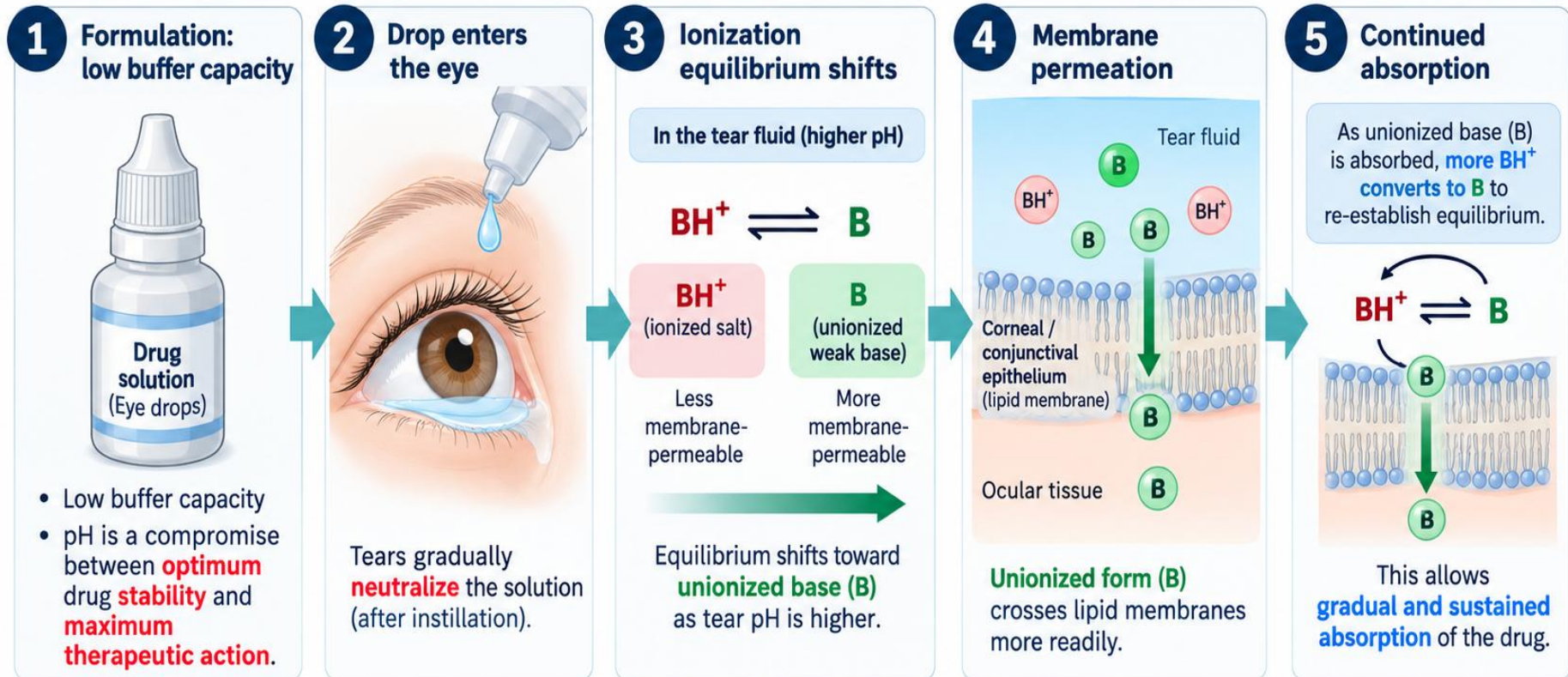


- Base penetrate readily the lipoidal membrane.

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.

Clarification

How a Weakly Basic Drug Is Absorbed from Eye Drops



Note:

The buffer must be strong enough to limit pH shifts caused by the **alkalinity of the glass** or the **acidity of CO₂** from dissolved air, but low enough to **allow tears to adjust the ocular pH**.

- **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.



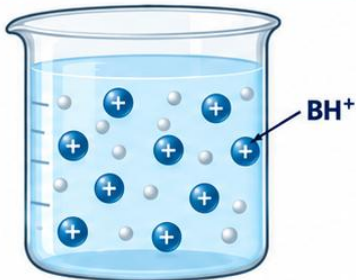
Base soln. should be buffered at a sufficiently low pH for stabilization against precipitation.

Clarification

How a Buffer Balances Solubility and Stability of a Weak Base

Low pH (acidic)

High solubility – Good stability



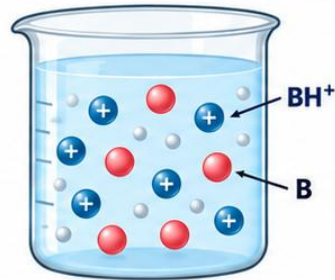
Base mainly in ionized form (BH^+)
→ high aqueous solubility

Buffer controls pH

Prevents pH from rising too high (avoids precipitation)

Buffered pH (optimal range)

Balance between solubility and stability



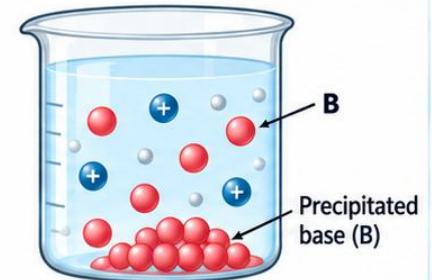
Both ionized (BH^+) and neutral (B) forms coexist
→ sufficient solubility while minimizing degradation

Buffer controls pH

Prevents pH from dropping too low (maintains stability)

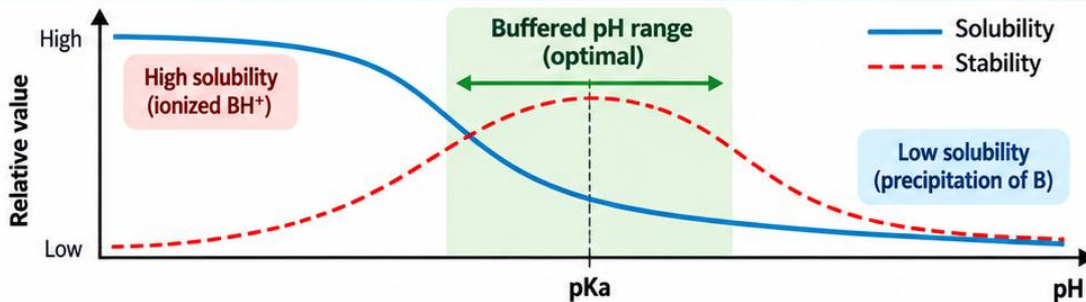
High pH (neutral/basic)

Low solubility – Risk of precipitation



More neutral base (B) is formed.
When its amount exceeds the limited water solubility, precipitation occurs.

Effect of pH on Solubility and Stability of a Weak Base



Role of the Buffer

- 1 Maintains pH in the optimal range**
Keeps pH sufficiently low to retain the base in the more soluble ionized form (BH^+).
 - 2 Prevents precipitation**
Resists increases in pH, limiting formation of excess neutral base (B).
 - 3 Improves stability**
Avoids very low pH that may cause acid-catalyzed degradation of the drug.
- ✓ **A properly selected buffer pH provides a balance: adequate solubility + good chemical stability.**

Mole Percent of Free Base

$$\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2 + \text{H}_2\text{O} \rightleftharpoons \text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2\text{H}^+ + \text{OH}^-$$

(Pilocarpine base) (Pilocarpine ion)

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

$$7.4 = 14 - 7.15 + \log \frac{[\text{base}]}{[\text{salt}]}$$

$$\frac{[\text{base}]}{[\text{salt}]} = 3.56 / 1$$

At pH 4.0

$$4.0 = 14 - 7.15 + \log \frac{[\text{base}]}{[\text{salt}]}$$

$$\frac{[\text{base}]}{[\text{salt}]} = 0.0014 / 1$$

10

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.

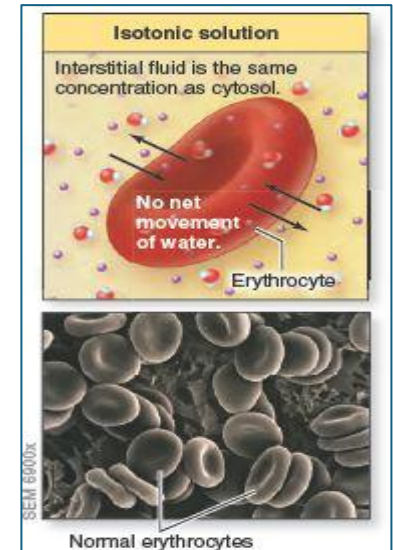
Isotonic solutions



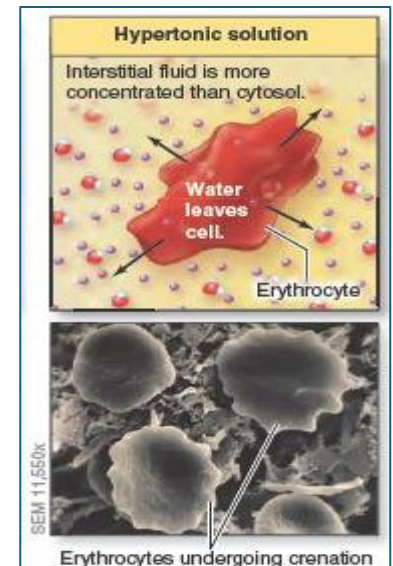
Cause no swelling or contraction of the tissues with which they come in contact and produce no discomfort when instilled in the eye, nasal tract, blood, or other body tissues.

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.



Clarification

Tonicity and Red Blood Cells (RBCs): Step-by-Step Illustration

Isotonic solution

0.9% NaCl
(0.9 g/100 mL)

Same effective
solute concentration
as RBC contents

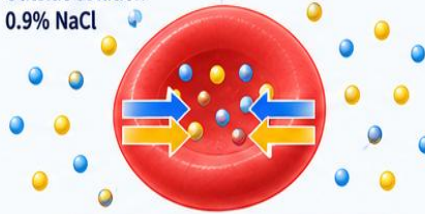
1 Before mixing
RBC interior
(~ 0.9% NaCl equivalent)



Water and solutes are
in dynamic equilibrium
across the membrane.

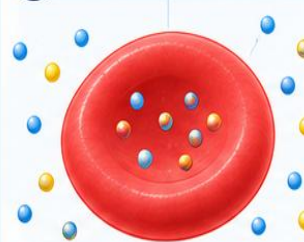
2 After adding 0.9% NaCl

Outside solution
0.9% NaCl



Water moves in and out
at equal rates
(no net movement).

3 Final state



**RBC retains its
normal size and shape.**

Key points (Isotonic)

- 0.9% NaCl has the same effective salt concentration and osmotic pressure as RBC contents.
- Water moves in both directions at equal rates.
- RBC maintains normal size and shape.

Hypertonic solution

2.0% NaCl
(2.0 g/100 mL)

Higher effective
solute concentration
than RBC contents

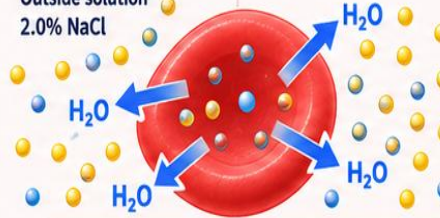
1 Before mixing
RBC interior
(~ 0.9% NaCl equivalent)



Water and solutes are
in dynamic equilibrium.

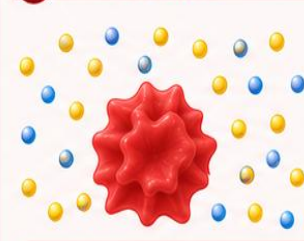
2 After adding 2.0% NaCl

Outside solution
2.0% NaCl



Water moves out of the cell
toward the higher solute concentration
until concentrations become equal.

3 Final state

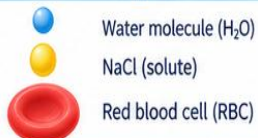


**RBC shrinks and
becomes wrinkled
(crenation).**

Key points (Hypertonic)

- 2.0% NaCl has a higher effective solute concentration than RBC contents.
- Water moves out of the cell (osmosis) to dilute the surrounding solution.
- RBC loses water, shrinks and becomes wrinkled (crenated).

Legend



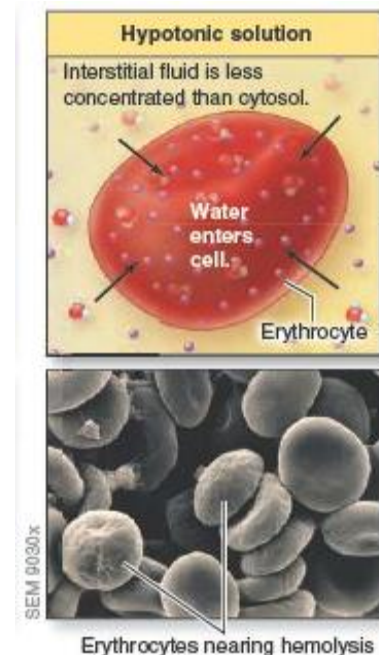
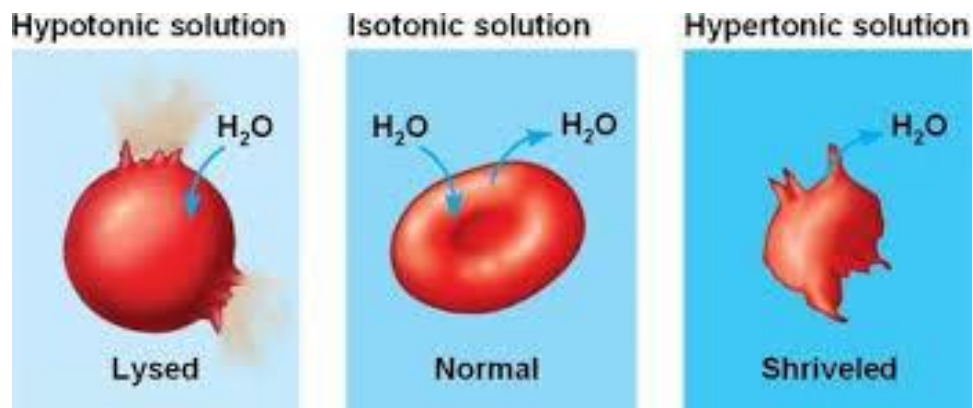
Direction of water movement



Summary table

Solution	NaCl concentration	Water movement	RBC appearance
Isotonic	0.9% (0.9 g/100 mL)	No net movement (equal in and out)	 Normal size
Hypertonic	2.0% (2.0 g/100 mL)	Out of the cell	 Shrunk / wrinkled

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.



Clarification

HYPOTONIC SOLUTION (0.2% NaCl or Distilled Water)

0.2% NaCl
(0.2 g/100 mL)

Lower effective solute
concentration than blood.

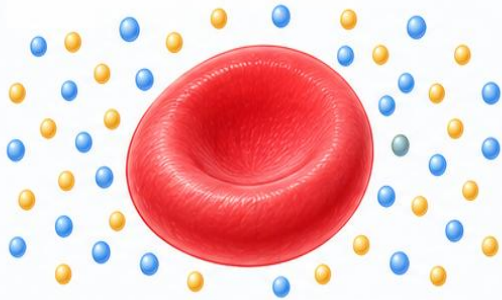
Distilled water
(0% NaCl)

No effective solute
(very low osmolarity).

1

BEFORE EXPOSURE

Normal RBC in isotonic environment
(blood plasma, ~0.9% NaCl)

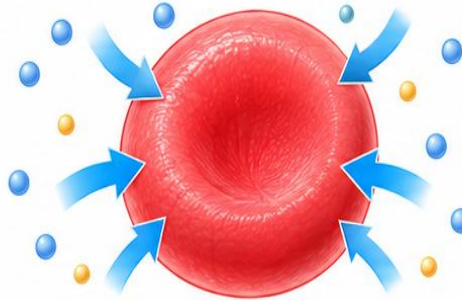


RBC with normal size and shape
(normal intracellular solute concentration).

2

WATER MOVES IN

RBC in a **hypotonic solution**
(0.2% NaCl or distilled water)

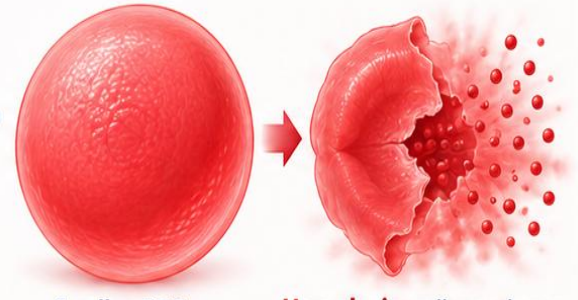


Net water movement into the cell
(osmosis)

3

FINAL STATE

RBC swells and may rupture
(**hemolysis**) if swelling is sufficient.



Swollen RBC
(increased volume)

Hemolysis: cell membrane
ruptures and hemoglobin
is released.

PROCESS SUMMARY

Lower effective
solute concentration
outside the cell
(0.2% NaCl or 0% NaCl)

Water enters
the cell
(osmosis)

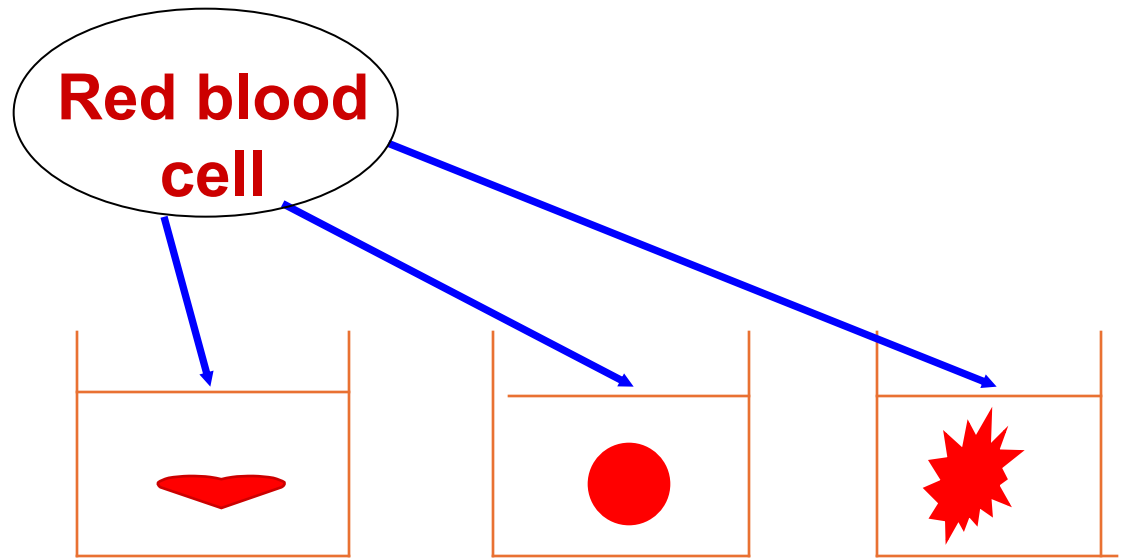
Cell swells
(increased volume)

Possible rupture
(hemolysis) with
release of hemoglobin

KEY POINTS

- 1** Hypotonic = lower effective solute concentration outside the cell.
- 2** RBC swells as water enters the cell.
- 3** Severe swelling may cause hemolysis with release of hemoglobin.

Buffered isotonic solution



NaCl solution

**2.0 %
Hypertonic,
Shrink**

**0.9 %
Isotonic**

**0.2 %
Hypotonic,
Hemolysis**

Clarification

Movement of Solute and Solvent Across RBC Membrane in Different Tonicity Conditions



Water molecule (H_2O)
(moves toward higher solute concentration)



Na^+ / Cl^- (solute)
(moves from higher to lower concentration)



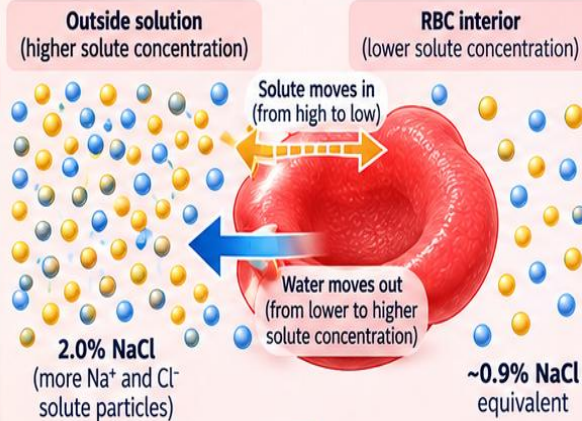
Direction of water movement
(osmosis)



Direction of solute movement (diffusion)

HYPERTONIC SOLUTION

(2.0% NaCl)

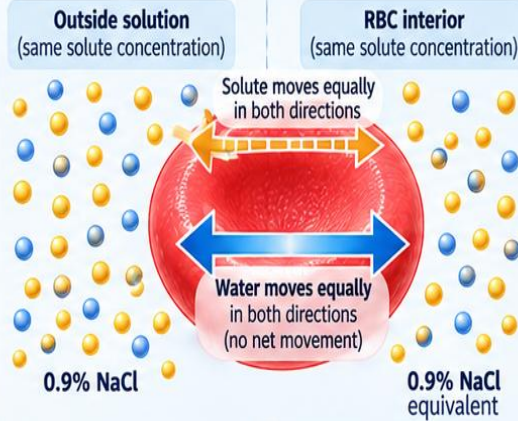


Final result:

- Loss of water
- Cell shrinks and becomes wrinkled (crenation)

ISOTONIC SOLUTION

(0.9% NaCl)

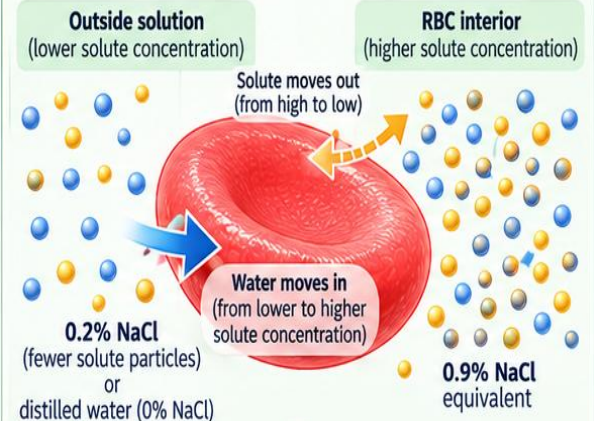


Final result:

- No net water flow
- No net solute flow
- Cell maintains its normal size and shape

HYPOTONIC SOLUTION

(0.2% NaCl or Distilled Water)



Final result:

- Gain of water
- Cell swells and may burst (hemolysis)
- Hemoglobin is released

Key concept: Water (solvent) moves toward the **higher solute concentration**, while solute moves from **higher to lower concentration** until equilibrium is reached.

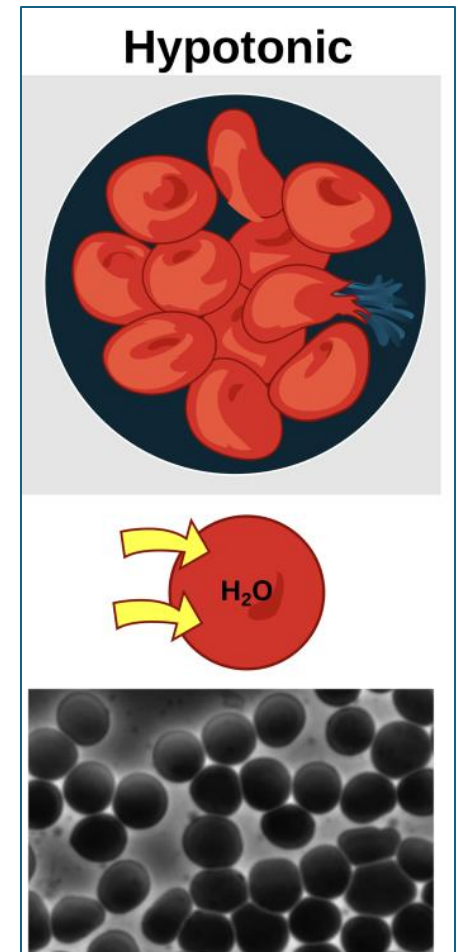
Measurement of Tonicity

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 .**

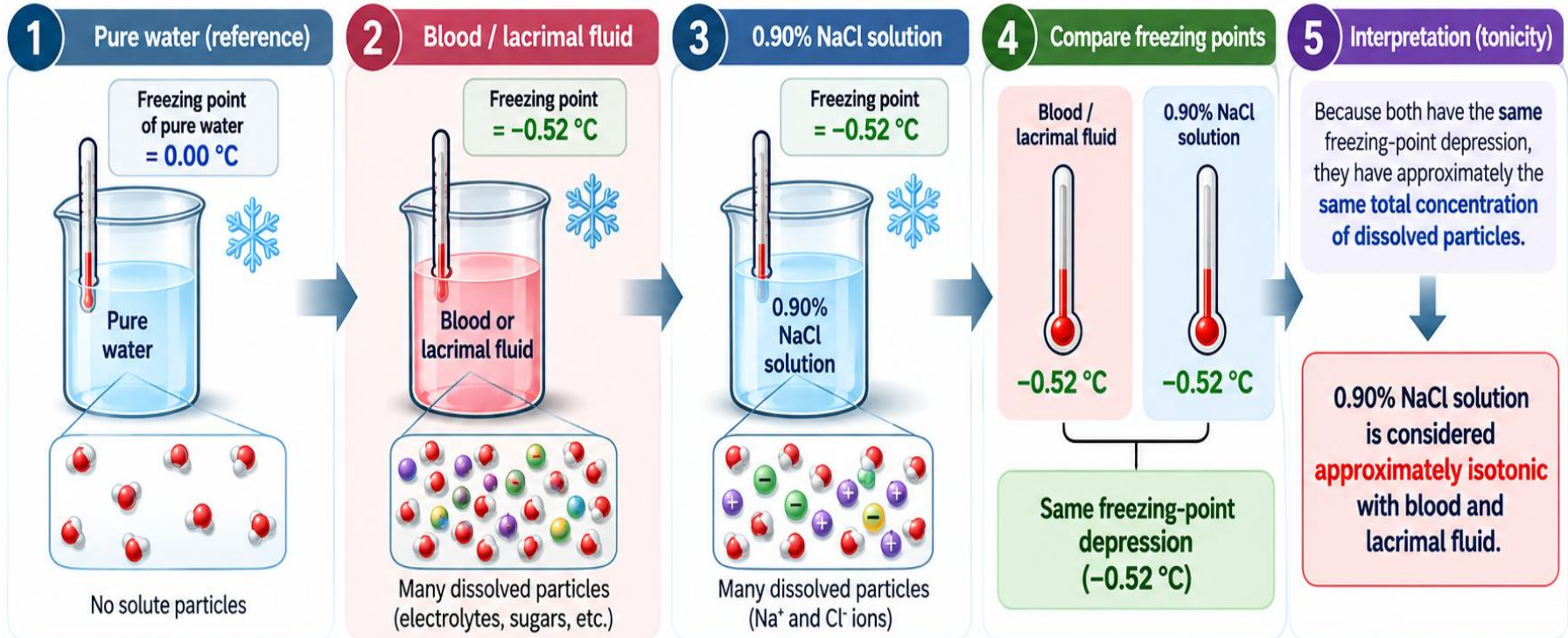


This temp. corresponds to the freezing point of a 0.90% NaCl solution

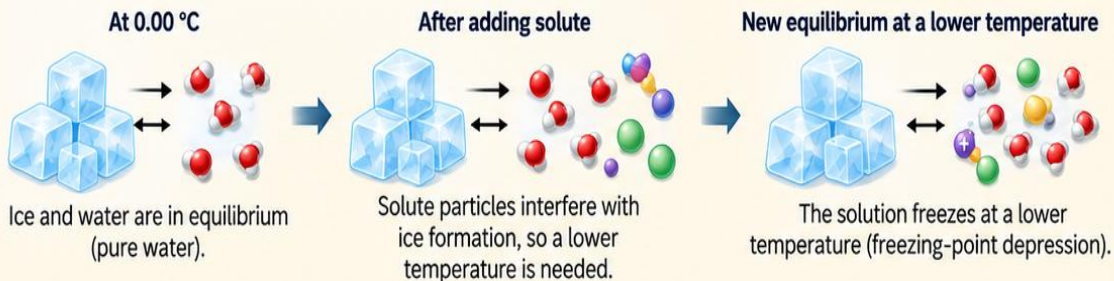


Considered to be isotonic with both blood and lacrimal fluid.

Clarification



Why does adding solute lower the freezing point?



✓ Key points for students

- 1 Colligative properties (freezing-point depression, osmotic pressure, boiling-point elevation, lowering of vapor pressure) depend only on the number of dissolved particles, not their identity.
- 2 Blood and lacrimal fluid have a freezing point of -0.52°C .
- 3 A 0.90% NaCl solution also has a freezing point of -0.52°C .
- 4 Therefore, 0.90% NaCl is approximately isotonic with 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

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

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

Clarification

Calculating Tonicity Using **Liso** Values

The Van't Hoff expression

1

Adding solute particles lowers the freezing point

The diagram illustrates the process of adding solute particles to pure water. On the left, a beaker of pure water at 0 °C contains several large ice crystals. A red arrow labeled 'Add solute particles' points to a second beaker on the right. This beaker contains a solution at a temperature below 0 °C, with fewer and smaller ice crystals. Below the first beaker is the label 'Pure water' with the text 'Higher freezing point (more ice crystals)'. Below the second beaker is the label 'Solution' with the text 'Lower freezing point (fewer ice crystals)'.

2

Van't Hoff expression

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

L

Molal freezing-point depression constant for water ($1.86\text{ }^{\circ}\text{C}\cdot\text{kg}\cdot\text{mol}^{-1}$)

C

Concentration of the solution isotonic with body fluids

3

Calculate **Liso**

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

For a solution isotonic with body fluids (water):

$$\Delta T_f = 0.52\text{ }^{\circ}\text{C}$$



L_{iso} is characteristic of the solute and reflects its electrolyte behavior (dissociation).

$$L_{\text{iso}} = \frac{0.52\text{ }^{\circ}\text{C}}{C}$$

L_{iso} represents the freezing point lowering of solutions of representative compounds of a given ionic type at a fixed concentration.

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.

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

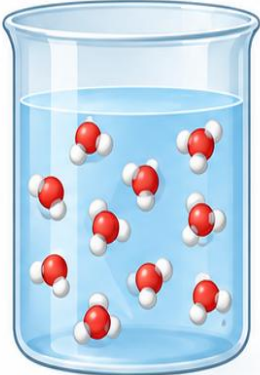
(means hypotonic < 0.52 °C)

Clarification

Example 8-11: Freezing Point Lowering

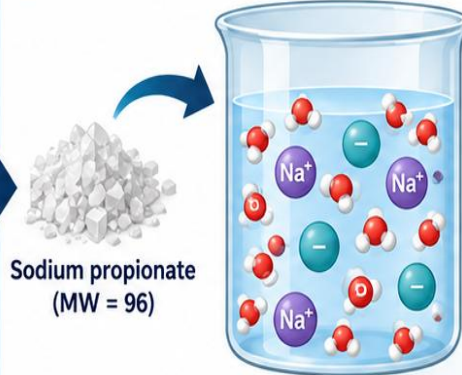
What is the freezing point lowering of a 1% solution of sodium propionate (MW = 96)?

1 Pure water



Pure water:
freezes at 0 °C

2 Sodium propionate dissolves in water



Sodium propionate
(MW = 96)

Dissolves into ions
 $\text{Na}^+ + \text{Propionate}^-$

Propionate⁻

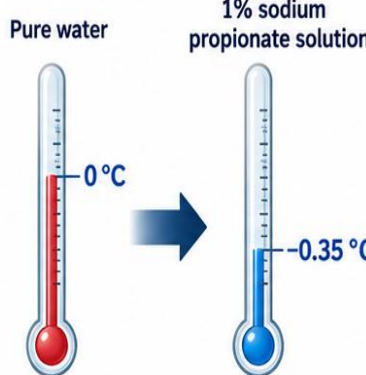
CC(=O)[O-]

$\text{H}_3\text{C}-\text{CH}_2-\text{C}(=\text{O})\text{O}^-$

Na^+ Sodium ion

$\text{CH}_3\text{CH}_2\text{COO}^-$ Propionate ion

3 Freezing point decreases



Pure water 0 °C

1% sodium propionate solution -0.35 °C

4 Calculation

Molar concentration of 1% solution

1% = 1 g per 100 mL = 10 g per 1 L

Molecular weight = 96

$$C = \frac{10}{96} = 0.104 \text{ M}$$

Freezing point depression (ΔT_f)

$$\Delta T_f = L_{iso} \times C$$
$$= 3.4 \times 0.104$$
$$= 0.35 \text{ °C}$$

Result

Freezing-point depression = 0.35 °C

Thus, the freezing point of the 1% sodium propionate solution is approximately **-0.35 °C**.

Tonicity note

Below **0.52 °C** → **hypotonic**
relative to isotonic reference.

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 **Sprol's method**

Clarification

METHODS OF ADJUSTING TONICITY AND pH

CLASS I

ADD SODIUM CHLORIDE

Lower the freezing point to -0.52°C

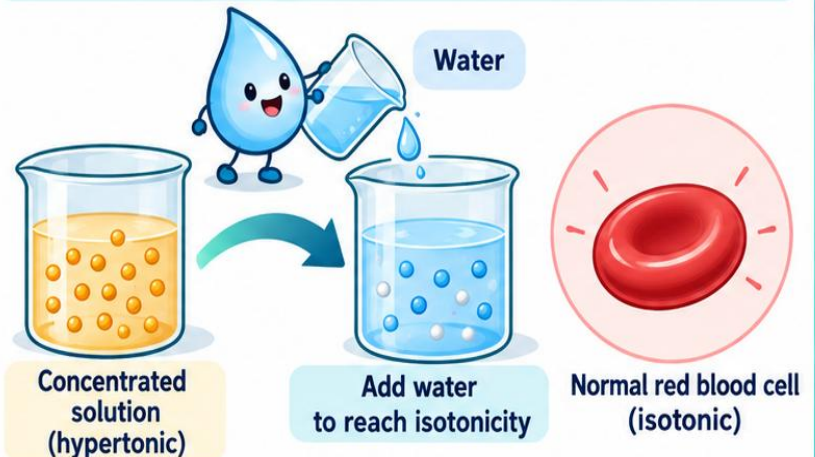


- 1 Cryoscopic method
- 2 Sodium chloride equivalent method

CLASS II

ADD WATER

Bring the preparation to isotonicity



- 1 White-Vincent method
- 2 Sprowls method

1 **Class I:** add tonicity-adjusting solute (e.g., NaCl).

2 **Class II:** calculate the water needed for isotonicity.

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

Clarification

Cryoscopic Method: Making a Solution Isotonic

Example 8-12: How much NaCl is required to render 100 mL of a 1% solution of apomorphine HCl isotonic with blood serum?

1 Start with 100 mL of 1% apomorphine HCl

1% w/v apomorphine HCl (1 g in 100 mL)



1.00 g apomorphine HCl

100 mL

Dissolve 1.00 g apomorphine HCl and make up to 100 mL with purified water.

2 Compare freezing-point depression (ΔT_f)

0.9% NaCl solution (isotonic with blood)

$\Delta T_f = 0.52^\circ\text{C}$



0°C

-0.52°C

Blood serum (0.9% NaCl)

1% apomorphine HCl solution

$\Delta T_f = 0.08^\circ\text{C}$



0°C

-0.08°C

Apomorphine HCl (1% w/v)

3 Calculate the remaining depression

Additional freezing-point depression required from NaCl:

$0.52 - 0.08 = 0.44^\circ\text{C}$

From the freezing-point table: 1% NaCl solution lowers the freezing point by 0.58°C

Required concentration of NaCl:

$$\frac{1\%}{X} = \frac{0.58}{0.44}$$

$X = \frac{0.44}{0.58} = 0.76\% \text{ NaCl}$

4 Prepare the isotonic solution

1.00 g apomorphine HCl (1% w/v)

0.76 g NaCl (to make isotonic)



100 mL

Add purified water to a final volume of 100 mL.

Isotonic with blood



Equal water movement in and out (no net flow)



Key takeaway: The drug contributes 0.08°C ; NaCl supplies the remaining 0.44°C .

Sodium Chloride Equivalent (E) 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].

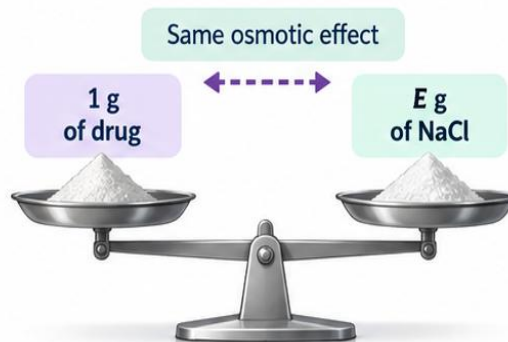
- The sodium chloride equivalents E for a number of drugs are listed in Table 8-4.
- E value for new drug can be calculated using the following equation:

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

Clarification

Sodium Chloride Equivalent (E) Method

Sodium chloride equivalent of a drug (**E**) is 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.

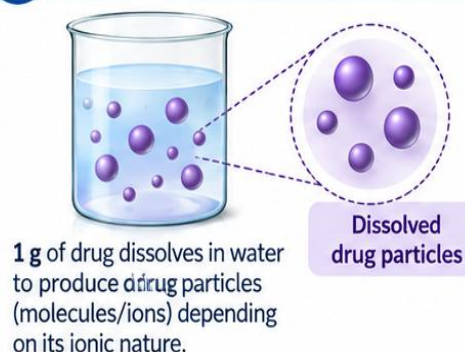


Calculation of E value

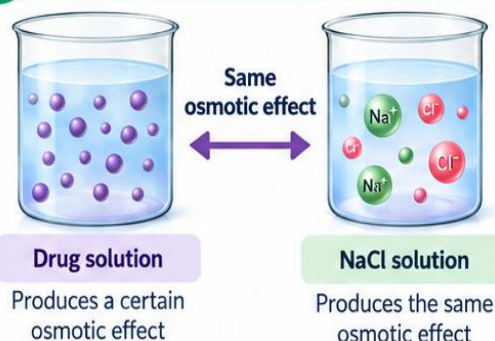
$$E \cong 17 \frac{L_{iso}}{MW}$$

E = sodium chloride equivalent
L_{iso} = specific value related to the drug's ionic nature
MW = molecular weight

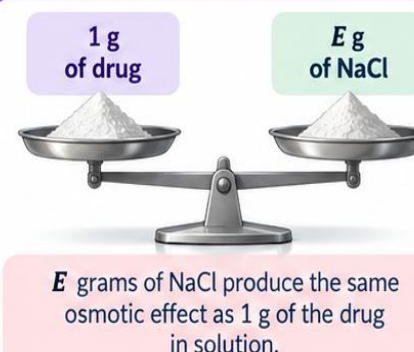
1 Dissolve the drug in water



2 Compare osmotic effect



3 Express as an equivalent NaCl mass



- The sodium chloride equivalents (E) for a number of drugs are listed in standard tables.
- For a new drug, the E value can be calculated using: $E \cong 17 \frac{L_{iso}}{MW}$ (where L_{iso} is a specific value related to the drug's ionic nature, and **MW** is the molecular weight).

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.

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

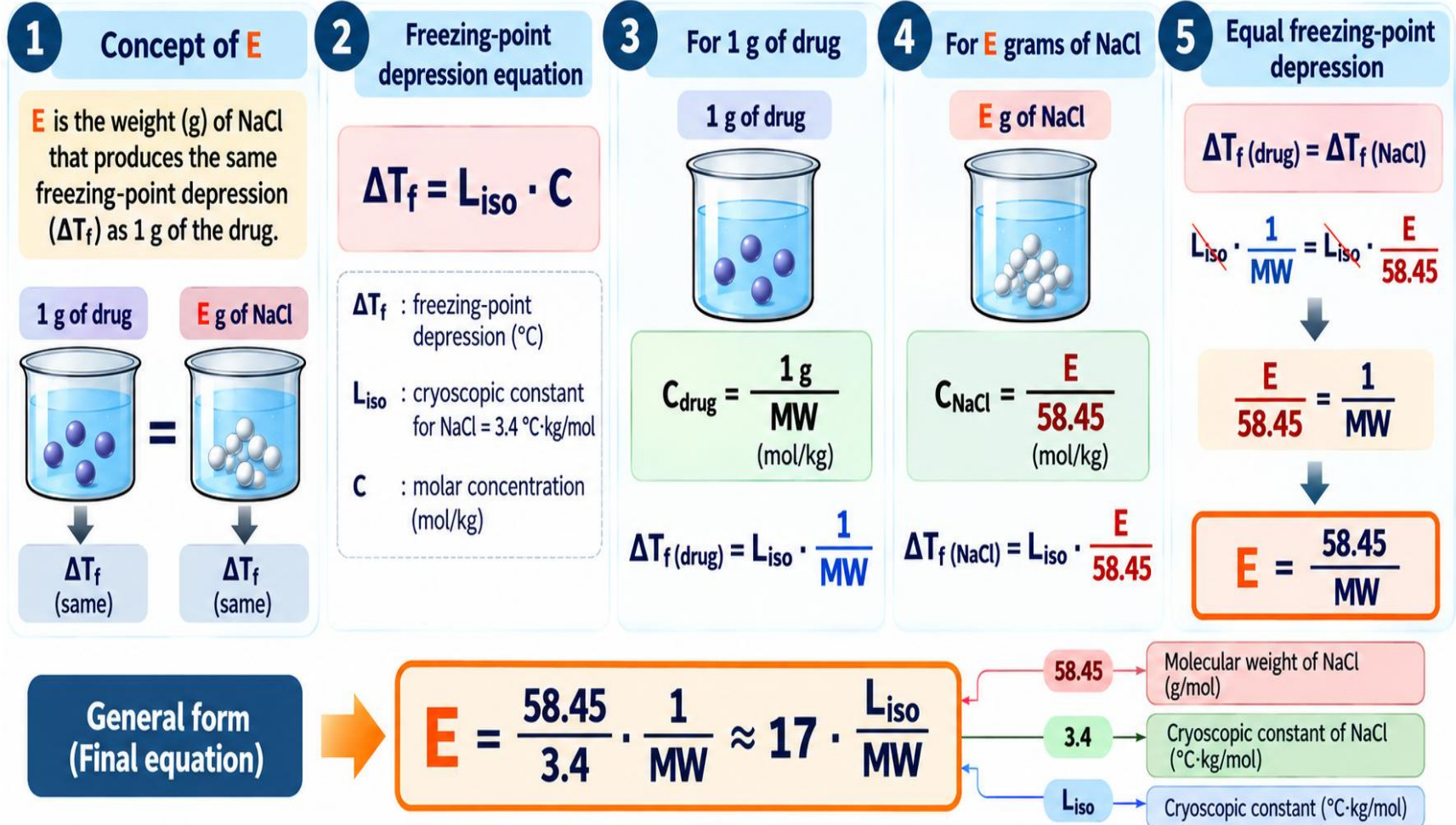
$c = 1 \text{ g} / \text{molecular weight}$

$$\Delta T_f = \underbrace{L_{iso}}_{3.4} \cdot \underbrace{1\text{g}/\text{MW}}_{\text{E} \quad 58.45}$$

$$E \cong 17 \cdot L_{iso} / \text{MW}$$

Clarification

Sodium chloride equivalent (E) method by Mellen & Seltzer



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.

$$E = \frac{17 * 3.4}{187} = 0.31$$

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:

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

Clarification

TONICITY ADJUSTMENT: NaCl EQUIVALENT METHOD

Multiply the quantity of each drug by its NaCl equivalent (E-value) and subtract from the isotonic amount of NaCl (**0.9 g/100 mL**). Alternatively, dextrose can be used instead of NaCl using its NaCl equivalent (**0.16**).

1 Find the NaCl equivalent contributed by the drug



NaCl equivalent (E-value) of ephedrine sulfate
= 0.23

NaCl equivalent contributed by the drug = Drug amount × E-value

$$1 \text{ g} \times 0.23 = 0.23 \text{ g NaCl equivalent}$$

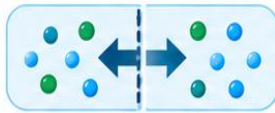


The drug contributes to osmotic pressure (equivalent to 0.23 g NaCl).

2 Determine the isotonic target for 100 mL

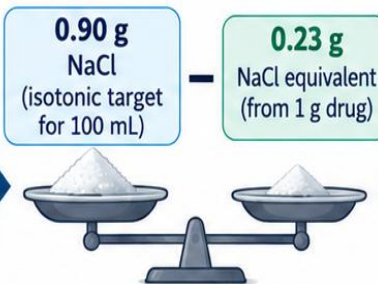


0.9 g NaCl per 100 mL
(isotonic target)
(≈ 300 mOsm/L)



Isotonic: equal osmotic pressure across the membrane (no net water movement).

3 Calculate the amount of NaCl to add



$$\text{NaCl to add} = 0.90 \text{ g} - 0.23 \text{ g} = \mathbf{0.67 \text{ g}}$$



ADD 0.67 g NaCl
to the 100 mL solution

(Make final volume up to 100 mL)

4 Using dextrose instead of NaCl (alternative)



NaCl equivalent of dextrose
= 0.16

Set up the following proportion:

$$\frac{1 \text{ g dextrose}}{0.16 \text{ g NaCl}} = \frac{x \text{ g dextrose}}{0.67 \text{ g NaCl}}$$

Solve for x:

$$x = \frac{0.67 \times 1}{0.16} = 4.19 \text{ g} \approx \mathbf{4.2 \text{ g}}$$



Use 4.2 g dextrose
instead of 0.67 g NaCl
for the 100 mL solution

(Make final volume up to 100 mL)

General formula:

$$\text{Amount of NaCl to add} = 0.9 \text{ g} - (\text{Drug amount} \times \text{E-value})$$

(for 100 mL final volume)



- Use **one** tonicity-adjusting agent at a time (either NaCl or dextrose).
- Make the final volume up to 100 mL.
- Do not add both NaCl and dextrose together for tonicity adjustment.

Class II Methods

White–Vincent Method

The class II methods of computing tonicity involve:

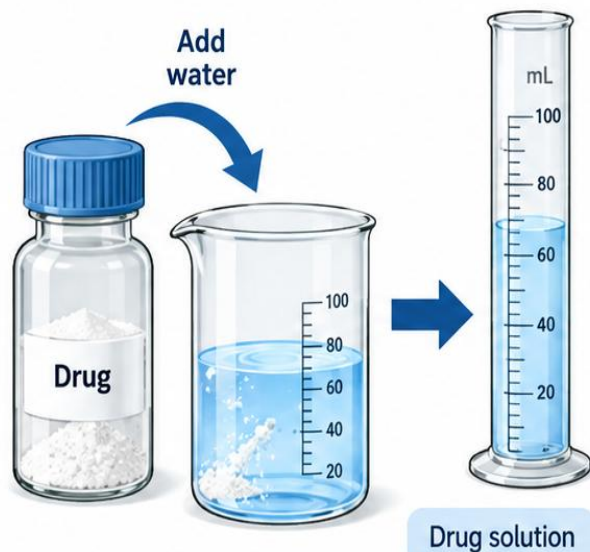
1. Addition of water to the drugs to make an isotonic solution.
2. Followed by the addition of an isotonic or isotonic-buffered diluting vehicle to bring the solution to the final volume.

Clarification

Class II Methods

White-Vincent Method

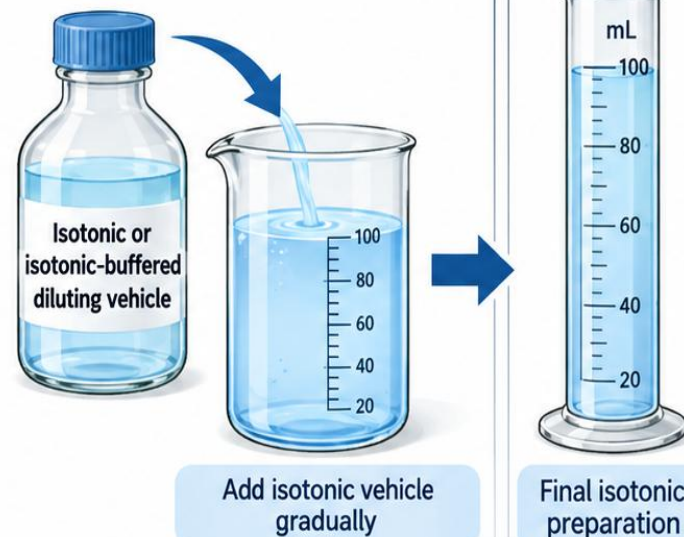
1 Step 1: Add water to the drug



2 Make the drug solution isotonic first

Calculate the amount of water needed so that the drug solution becomes isotonic.

3 Step 2: Add isotonic vehicle to the final volume



White-Vincent Method:

Calculate the volume of **water** needed to **make the drug solution isotonic**; then **complete the final volume** with an isotonic or isotonic-buffered diluting vehicle.

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.

Clarification

Isotonicity Adjustment: NaCl Equivalent Method

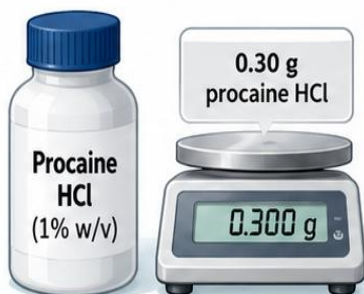
Example: Prepare 30 mL of 1% procaine HCl solution isotonic with body fluids.

1 Calculate the weight of drug (w)

1% w/v means 1 g of drug in 100 mL of solution.

Drug amount for 30 mL:

$$w = 1 \text{ g}/100 \text{ mL} \times 30 \text{ mL} = \mathbf{0.30 \text{ g}}$$

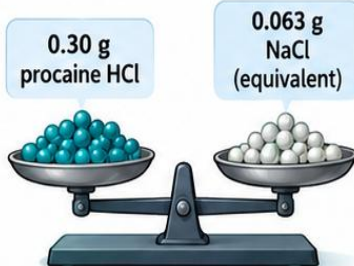


2 Convert to NaCl equivalent

NaCl equivalent (E) of procaine HCl = **0.21** (from reference tables).

NaCl equivalent weight:

$$0.30 \text{ g} \times 0.21 = \mathbf{0.063 \text{ g}}$$



0.30 g of procaine HCl has the same osmotic effect as **0.063 g** of NaCl.

3 Calculate the isotonic volume represented by 0.063 g NaCl

0.9 g of NaCl in 100 mL of water (0.9% w/v NaCl) is isotonic with body fluids.

$$V = \frac{0.063 \text{ g} \times 100 \text{ mL}}{0.9 \text{ g}} = \mathbf{7.0 \text{ mL}}$$

Therefore, 0.063 g of NaCl produces **7.0 mL** of isotonic solution.

Shortcut equation:

$$V (\text{mL}) = w (\text{g}) \times E \times 111.1$$

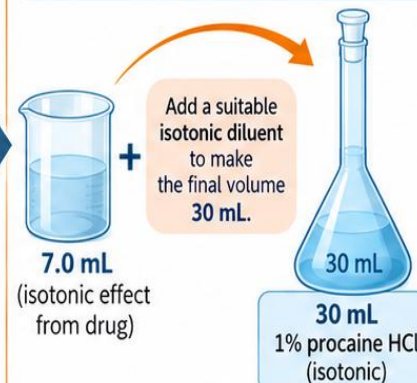
w = weight of drug in grams

E = NaCl equivalent

111.1 = 100/0.9 (mL per 1 g NaCl) for 0.9% NaCl

4 Prepare the final 30 mL isotonic solution

The drug contributes isotonicity equivalent to 7.0 mL.



Do not simply add 23 mL of water.

Use an appropriate isotonic diluent (e.g., isotonic NaCl solution, another isotonic solution, or an isotonic-buffered diluting solution) according to the formulation.



Final result:

7.0 mL is the isotonic-equivalent volume contributed by the drug—**not the final preparation volume.**

Key points:

- Use NaCl equivalent (E) from reference tables.
- $V = w \times E \times 111.1$ (for 0.9% NaCl, 0.9 g/100 mL).
- The drug provides isotonicity equivalent to 7.0 mL.
- Add a suitable isotonic diluent to bring the final volume to 30 mL.

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 hydrochloride	0.06 g
Boric acid.	0.3 g
Sterilized distilled water, enough to make	100.0 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

