LECTURE 1:
Isotonic solutions.

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Objectives

Upon successful completion of this chapter, the student will be able to:

- Differentiate between the terms isosmotic, isotonic, hypertonic, and hypotonic.
- Apply physical chemical principles in the calculation of isotonic solutions.
- Perform the calculations required to prepare isotonic compounded prescriptions.
- State the buffer equation and apply it in calculations.

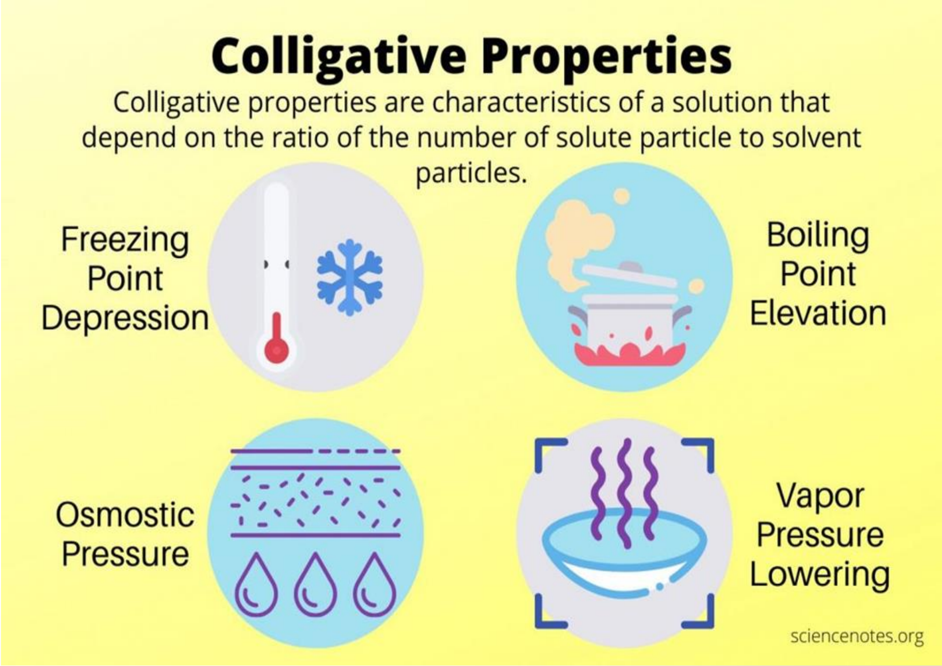
Isotonic and Buffer solutions

- **Colligative properties,** From Greek word" collected together",
- Properties that depend mainly on the number of solute molecules or ions, but not upon the identity of the solute

→ Therefore, these properties are interrelated and a change in any one of them will result in a corresponding change in the others.

They are:

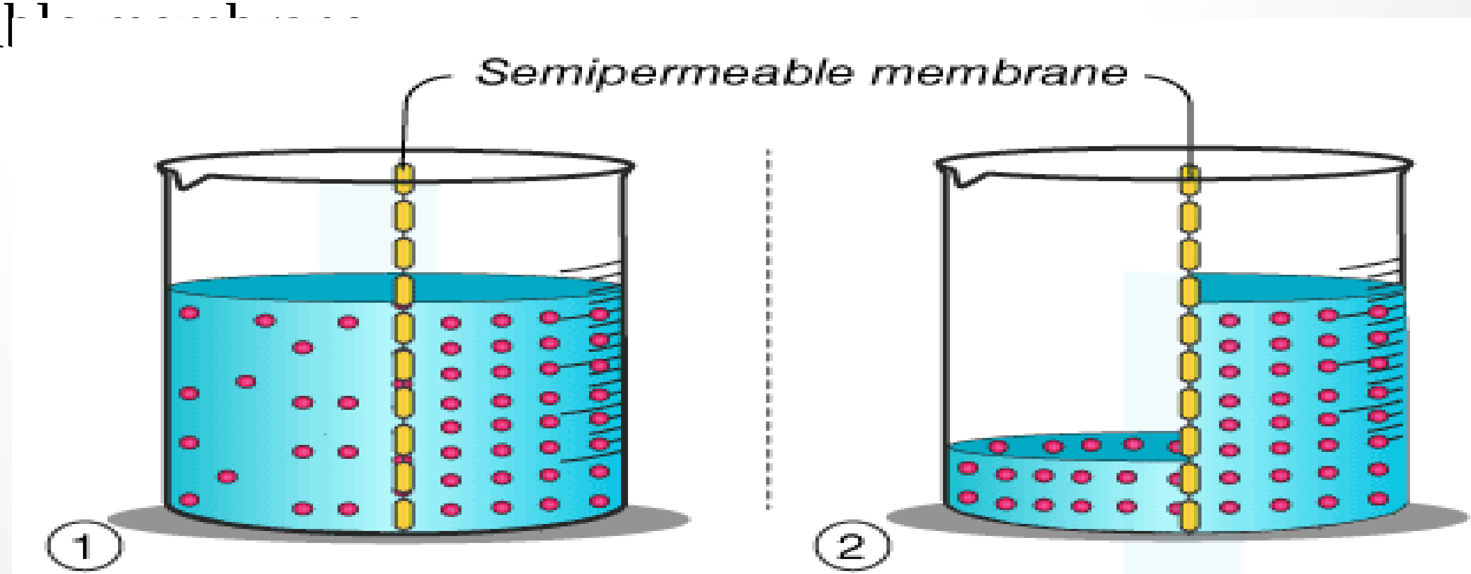
- vapor pressure lowering
- freezing point depression
- boiling point elevation
- osmotic pressure



Introduction

- ***Osmosis is a process*** **of movement of solvents** through a semipermeable membrane (only permeable to the solvent) from a region of low solute concentration **(**dilute solution**)** to an area of high solute concentration → so the differences in concentration disappear

- The pressure responsible for this phenomenon is termed osmotic pressure and varies with the nature of the solute.
- Osmotic pressure (OP): is a minimum P that must be applied to a solution to stop the flow of solvent molecules through a a perfect semipermeable membrane.



Osmotic pressure (OP):

- OP is determined by the concentration of the solute and varies with the nature of the solute.

OP of Non-electrolytes (not ionized)

- If the solute is a nonelectrolyte, its solution contains only molecules.
- OP α concentration
- twice conc. → twice OP
- OP α No. of molecules
- OP of two solutions having the same molal concentration are identical

OP of electrolytes (ionized)

- They dissociate into ions
- OP varies with both the conc. of the solute and its degree of dissociation.
- ↑ No. of ions formed → so ↑ OP.
- NaCl ionized into 2 ions each has the same effect on OP as molecules

→ So will be exert a greater OP twice than of non-ionized (undissociated) substance.

Definition

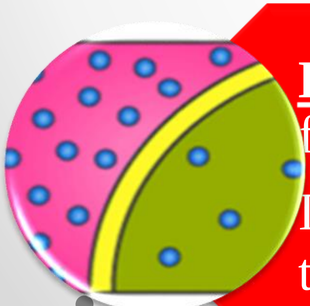
- Isosmotic solutions: Two solutions that have the same OP.

Isotonic solution: is a solutions having the same OP as a body fluid at a given temperature.

When such solutions are separated by a semi-permeable membrane than there is no osmosis.

Hypotonic solution: is a solution has a lower OP than that of a body fluid i.e., the conc. of solute particles is < that of the surrounding.

If the hypotonic solution is separated by semipermeable membrane, then water moves out of the hypotonic soln.



Hypertonic solution: is a solution has a higher OP than that of a body fluid i.e., the conc. of solute particles is > that of the surrounding.

If the hypertonic solution is separated by semipermeable membrane, then water moves inside the hypertonic solution.

- all Iso-osmotic solutions are not necessarily isotonic.

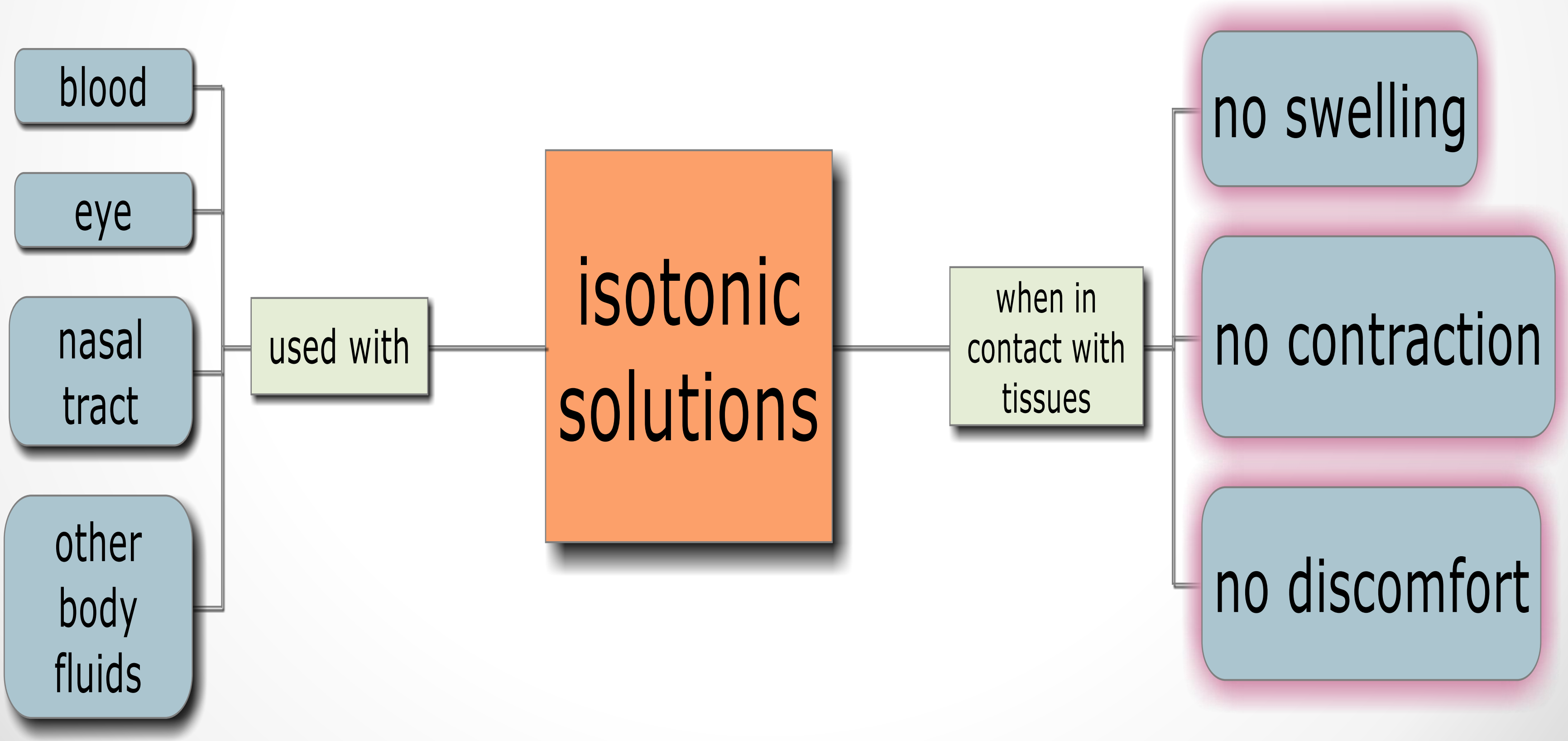
isosmotic ≠ isotonic

- The term isotonic should be restricted to solutions having equal OP with respect to a true semipermeable membrane (solute doesn't pass)
- it is important to notice that the
- The red blood cell membrane is not a perfect semipermeable barrier; therefore, drugs can pass through it. Consequently, water molecules and solutes like urea, ammonium chloride, alcohol, and boric acid can pass across.
- Example:

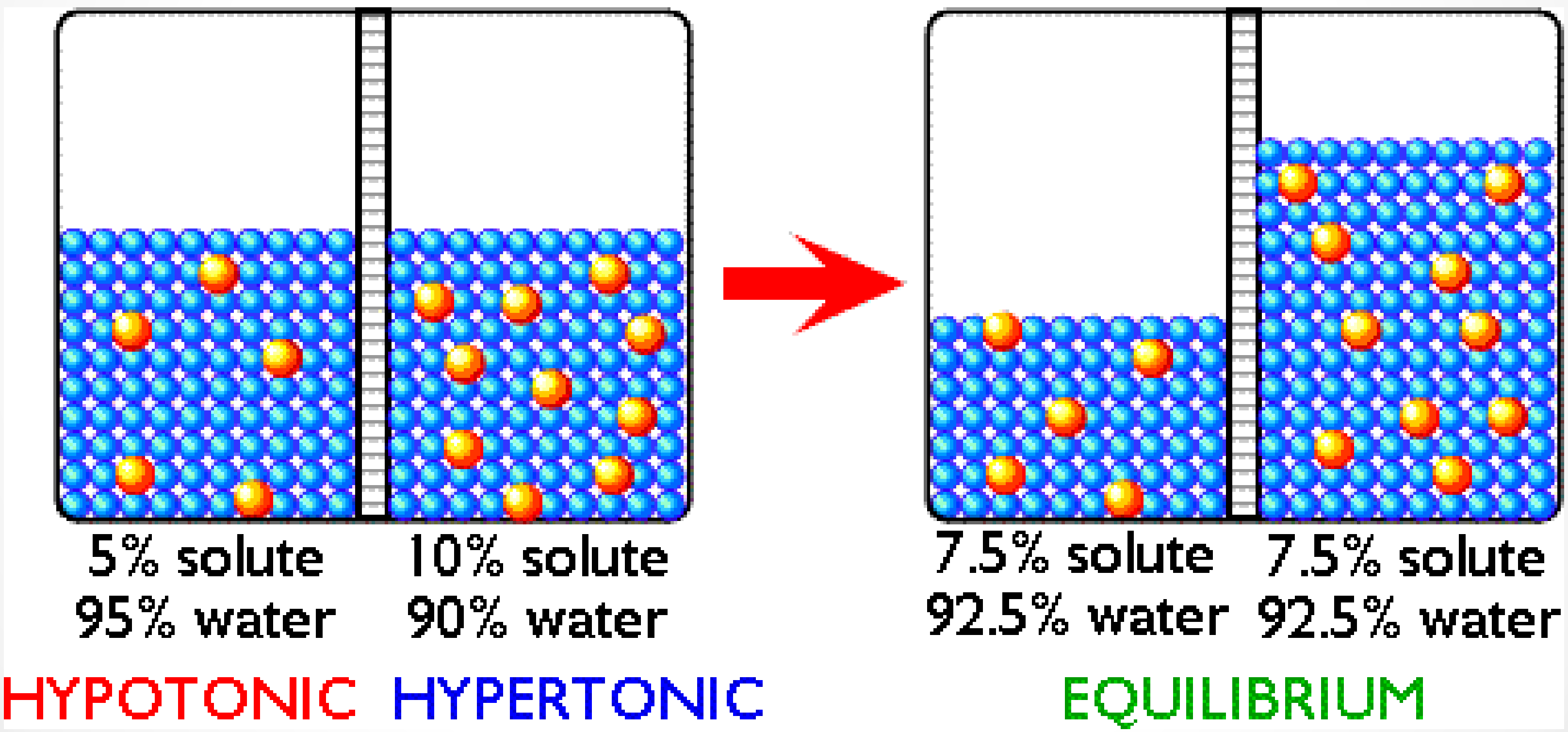
2% boric acid soln. iso osmotic but hypotonic for blood cells unlike in the eye

Why using isotonic solutions?

- Many solutions intended to be mixed with body fluids are designed to have the same osmotic pressure for greater patient comfort, efficacy, and safety,



Why using isotonic solutions?



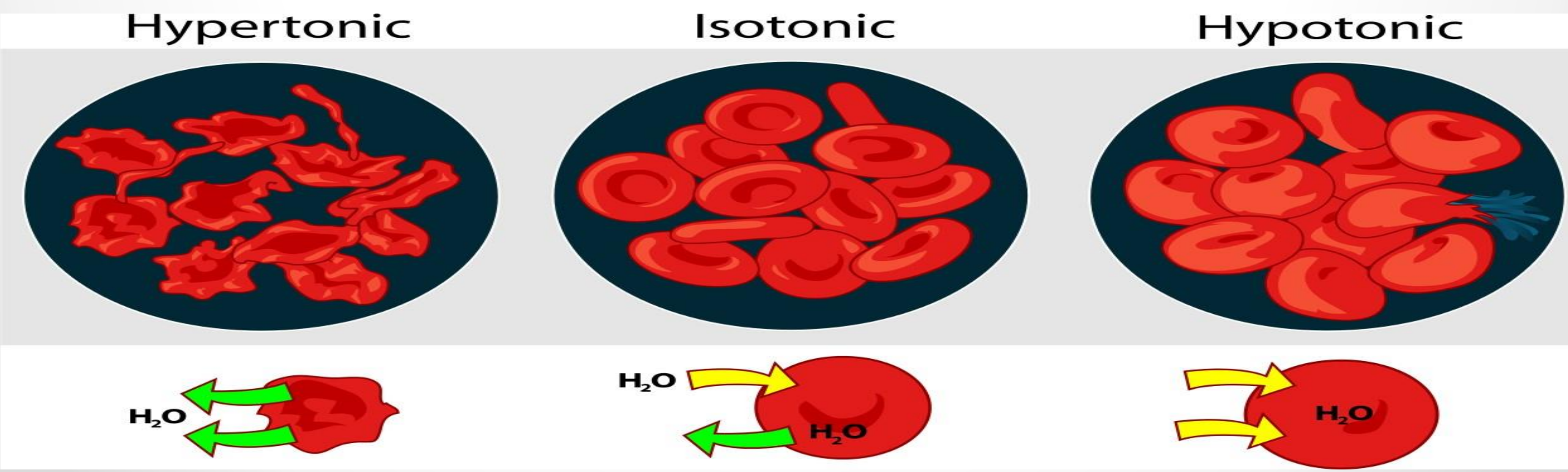
Special Clinical Considerations of Tonicity

- It is generally accepted that for ophthalmic and parenteral administration, isotonic solutions are better tolerated by the patient than those at the extremes of hypo- and hypertonicity.
- However, there are exceptions, as in instances in which hypertonic solutions are used to "draw" fluids out of edematous tissues and into the administered solution.

- Most ophthalmic preparations are formulated to be isotonic, or approximately isotonic, to mimic ophthalmic tears in order to
  - be comfort to the patient .
  - To prevent eye tissue irritation and maintain stability
- Injections that are not isotonic should be administered slowly and in small quantities to minimize tissue irritation, pain, and cell fluid imbalance.
- **Intravenous** infusions which are hypotonic or hypertonic can have adverse effects because they generally are administered in large volumes

Osmosis and Blood Cells

Hypertonic	isotonic	Hypotonic
NaCl 2%	NaCl 0.9%	NaCl 0.2%
solute ‹ solute Inside outside	solute = solute Inside outside	solute › solute Inside outside
a net flow of water out of the cell,	The net movement of water in and out of the cell is zero	a net flow of water into the
Shrinkage	equilibrium	swelling



Classes of adjustment of isotonicity

Class I

- We can calculate the isotonicity depending on colligative properties especially freezing point.
- **Adding substance to lower f.p of solution to -0.52 ºC**

1. Freezing point depression (FPD) "cryoscopic method".
2. NaCl equivalent method.

Class II

- **Adding H2O**
    - White –Vincent method

Freezing point depression

Freezing point depression (f.p.d)

- Freezing point of water = 0 ^{o}C
- It is generally accepted that FP of blood serum and lacrimal fluid = - 0.52 ^{o}C
- It is Colligative property depend on concertation
- Same freezing point depression $\rightarrow$ same osmotic pressure
- same f.p.d $\rightarrow$ same conc. $\rightarrow$ same tonicity
- Any solution have F.P. › - 0.52 ^{o}C (e.g., -0.4 ^{o}C) is hypotonic
- To calculate the % of subs. that render the soln. isotonic we use the following equation

$$\%\ w/v \text{ of adjusting subs (required)} = \frac{0.52 - a}{b}$$

a = FP of unadjusted soln.

b = FP of 1% w/v of adjusting subs. (required)

Example I

- How much NaCl is required to render 100 ml of a 1% soln. of apomorphine HCL isotonic?
- F.p.d of 1%NaCl=0.58º, F.p.d of 1%drug=0.08º

$$w\% = \frac{0.52^{o} - a}{b}$$

$$w\% = \frac{0.52^{o} - 0.08^{o}}{0.58^{o}}$$

$$w\% = 0.76\%$$

- 1% drug → 0.08º (0.52º- 0.08º=0.44º)
- 1% NaCl → 0.58º
- w% NaCl ← 0.44º

$$w\% = 0.76\%$$

isotonic solution

Freezing point depression (f.p.d)

- **For nonelectrolytes** (negligible dissociation) as boric acid
- Boric acid: M.wt 61.8 thus if 61.8 g in 1000 g of water should produce a freezing point of -1.86 ^{o}C

$$61.8 \rightarrow 1.86\ ^{o}C$$
$$X\ (g) \rightarrow 0.52\ ^{o}C \qquad \text{so} \rightarrow \quad X = 17.3\ g$$

- So, 17.3 g of boric acid in 1000 g of water (1.73 %) should make a solution isotonic with lacrimal fluid.

- **For electrolytes,** it depends on the degree of dissociation
- NaCl (M.wt. 58.5) in weak solutions is 80 % dissociated, then each 100 molecules yields 180 particles, 1.8 times nonelectrolyte. This dissociation factor is symbolized by the letter *i* .

$$58.5\ g \times 1.8 \rightarrow 1.86\ ^{o}C$$
$$X\ (g) \rightarrow 0.52\ ^{o}C \qquad \text{so} \rightarrow \quad X = \mathit{9.09\ g}$$

- So, 9.09 g of NaCl in 1000 g of water (0.9 % w/v) should make a solution isotonic with blood or lacrimal fluid.

- **Isotonic solutions are calculated by the following formula**

$$\textbf{g of solute per 1000 g of water} = \frac{0.52\times M.wt}{1.86\times dissociation\ (i)}$$

- The value *i* for many medicinal salts has not been experimentally determined
- Some salts as zinc sulfate with 40% dissociation and *i* value = 1.4 are exceptional.
- Most medicinal salts approximate the dissociation of NaCl.

If the number of ions is known so:

- ***Nonelectrolytes*** *and substances of slight dissociation* *i = 1*
- *Substances that dissociate into* ***2*** *ions* *i = 1.8*
- *Substances that dissociate into* ***3*** *ions* *i = 2.6*
- *Substances that dissociate into* ***4*** *ions* *i = 3.4*
- *Substances that dissociate into* ***5*** *ions* *i = 4.2*

Example Calculations of the *i* Factor

- 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.
- Because140 particles represent 1.4 times as many particles as were present before dissociation, the dissociation (i) factor is 1.4, answer.

Problems

1. What proportion of procaine HCl will yield a solution isotonic with blood plasma . $\Delta T_f^{1\%}$ or FPD of 1% w/v soln. of procaine HCl is -0.122.

Answer

$$\% \text{ of procaine HCl (req.)} = \frac{0.52-a}{b} = \frac{0.52-0}{0.122} = 4.26\ \%\ \text{w/v}$$

2. find the proportion of sodium chloride required to render a 1% weight per volume solution of cocaine hydrochloride isotonic with blood plasma

FPD of 1% w/v soln. of cocaine HCl is -0.09

FPD of 1% w/v soln. of NaCl is -0.576

Answer

$$\% \text{ of NaCl (req.)} = \frac{0.52-a}{b} = \frac{0.52-0.09}{0.576} = 0.746\ \%\ \text{w/v}$$

3. Find the proportion of sodium chloride required to render a 1.5% w/v solution of procaine hydrochloride isotonic with blood plasma

$\Delta T_f^{1\%}$ or FPD of 1% w/v soln. of procaine HCl is -0.122

Answer

FPD of 1% procaine = 0.122

FPD of 1.5 % procaine = X so, X = 0.122 × 1.5 = 0.183

% of NaCl (req.) = $\frac{0.52-a}{b} = \frac{0.52-0.183}{0.576}$ = 0.585 % w/v

5. How many grams each of morphine sulfate and sodium chloride are required to prepare 50 mL of a 1% w/v morphine sulfate solution isotonic with blood plasma?

- FPD of a 1% w/v solution of morphine sulfate is 0.08°C
- FPD 1% w/v sodium chloride solution is 0.576

Answer

% of NaCl (req.) = $\frac{0.52-a}{b} = \frac{0.52-0.08}{0.576}$ = 0.763 % w/v

In 100 ml , 0.763 g NaCl + 1 g morphine = isotonic , in 50 ml divide by 2

5. Find the amount of sodium chloride necessary to be included in 100 ml of a 0.3% w/v solution of zinc sulfate so that on dilution with equal quantity of water it will be isotonic with lacrimal secretion

- Δ Tf 1% or FPD of 1% w/v soln. of zinc sulphate is -0.086

Answer

before dilution : (100 ml soln.)

% of NaCl (req.) = = $\frac{0.52-a}{b}$

$= \frac{0.52-(0.08\times 0.086)}{0.576}$ = 0.858 % w/v → for 100 ml water

% of NaCl (req.) = $\frac{0.52-a}{b} = \frac{0.52-0}{0.576}$ = 0.902 % w/v

So, 1 + 2 = 0.858 + 0.902 = 1.76 gm

5. Find the amount of sodium chloride necessary to be included in 100 ml of a 0.3% w/v solution of zinc sulfate so that on dilution with equal quantity of water it will be isotonic with lacrimal secretion

- Δ Tf 1% or FPD of 1% w/v soln. of zinc sulphate is -0.086

Another answer

FPD of 1% ZnSO4 = 0.086

FPD of 0.3 % ZnSO4 = X so, X = 0.086 × 0.3 = 0.0258

% of NaCl (req.) = = $\frac{0.52-a}{b}$

$= \frac{0.52-0.258}{0.576}$ = 0.858 % w/v → for 100 ml water

0.858 % w/v → for 100 ml water

X % w/v → for 200 ml water

X = 1.716 g

NaCl equivalent method

NaCl equivalent "E"

- NaCl equivalent "E"
  - Amount of NaCl which has the same osmotic effect (same f.p.d) as 1 gram of the drug.
  - 0.9 g NaCl in 100m water is isotonic .
- 1st calculate E_{NaCl}

$$E_{NaCl} = \frac{17\, L_{iso\,(Drug)}}{M.wt_{\,Drug}}$$

- 2nd add NaCl to reach 0.9%

$$W\,\% = 0.9 - (\text{drug}\,\% \times E_{NaCl})$$

Where:

- W % = weight of NaCl in gm /100 ml (to make soln isotonic)
- Drug % = weight of drug in gm /100 ml
- E_{NaCl} = NaCl equivalent weight to 1 gm of drug
- 0.9 = isotonic soln of NaCl

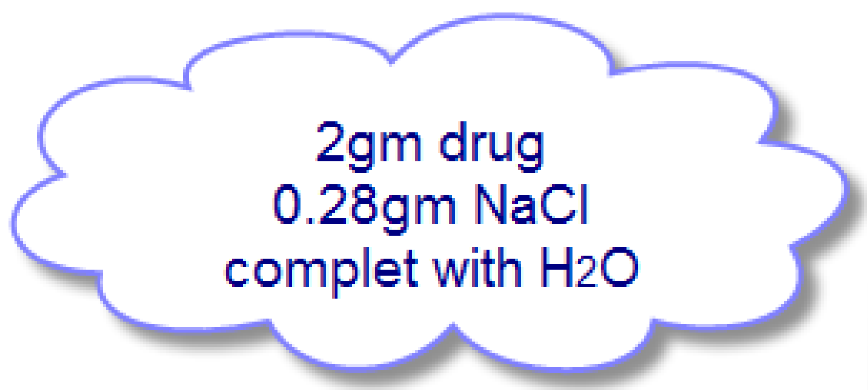
- Calculate E_{NaCl} of drug (M.wt=187, L_{iso}=3.4)? How much NaCl needed to make 2% of this drug isotonic?

Answer

$$E_{NaCl} = \frac{17\, L_{iso\,(Drug)}}{M.wt_{\,Drug}} = \frac{3.4}{187} = 0.31 \text{ gm}$$

0.31 gm NaCl = 1gm drug   so, 0.62 gm NaCl = 2 gm drug

W % = 0.9 – (drug % × E_{NaCl}) = 0.9 – 0.62 = 0.28 gm NaCl



NaCl equivalent "E"

Another method for calculation of sodium chloride equivalent

sodium chloride equivalent $= \dfrac{M.wt\ of\ NaCl}{i\ factor\ of\ NaCl} \times \dfrac{i\ factor\ of\ substance}{M.wt\ of\ substance}$

1. Papaverine hydrochloride (m.w. 376) is a 2-ion electrolyte, dissociating 80% in a given concentration. Calculate its sodium chloride equivalent.

.**Answer**

Because papaverine hydrochloride is a 2-ion electrolyte, dissociating 80%, its i factor is 1.8

NaCl equivalent $= \dfrac{\mathbf{58.5}}{\mathbf{1.8}} \times \dfrac{1.8}{376} = 0.16$

2. Calculate the sodium chloride equivalent for glycerin, a nonelectrolyte with a molecular weight of 92.2, Glycerin, i factor =1.0

.**Answer**

NaCl equivalent $= \dfrac{\mathbf{58.5}}{\mathbf{1.8}} \times \dfrac{1}{92.2} = 0.352$

Problems

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

R/ Phenacaine Hydrochloride 1%

Chlorobutanol 0.5 %

Boric Acid q.s.

Purified water ad 60 ml

Make isoton. Sol.

Sig. One drop in each eye.

E of Phenacaine HCl is 0.2, E of Chlorobutanol is 0.24, E for boric acid = 0.52

Answer

Step 1. 0.20×0.6 g =0.120 g of NaCl represented by phenacetine HCl

0.24× 0.3 g = 0.072 g of NaCl represented by chlorobutanol

0.9 g NaCl $\rightarrow$ 100 ml water to be isotonic

X g NaCl $\rightarrow$ 60 ml

X = 0.9 X 30 / 100 = 0.54 g

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

R/ Phenacaine Hydrochloride 1%

Chlorobutanol 0.5 %

Boric Acid q.s.

Purified water ad 60 ml

Make isoton. Sol.

Sig. One drop in each eye.

E of Phenacaine HCl is 0.2, E of Chlorobutanol is 0.24, E for boric acid = 0.52

Answer

W % = 0.9 – (drug % × E NaCl)

0.54 - (0.12 + 0.072)= 0.348 g of sodium chloride to be used

But because the prescription calls for boric acid:

Step 4. 0.348 g ÷ 0.52 = 0.669 g of boric acid to be used.

2. A solution contains 1 gram of ephedrine sulfate in a volume of 100 ml what quantity of sodium chloride must be added to make the solution isotonic? How much dextrose would be required for this purpose?

- E value of ephedrine sulfate is 0.23
- E value of dextrose is 0.16

Answer

1 g ephedrine ≡ 0.23 g NaCl

So , NaCl req. = 0.9 – 0.23 = 0.67 g

For dextrose , 1 g dextrose ≡ 0.16 NaCl

X g dextrose ≡ 0.67 NaCl   so, X = 4.187 g

3. How many grams of anhydrous dextrose should be used in preparing 1 liter of a 0.5% isotonic ephedrine sulphate nasal spray?

(E of ephedrine sulphate = 0.23, and E of dextrose = 0.16)

Solution

0.5% ephedrine sulphate means 0.5 x 0.23 = 0.115 % NaCl

Then we need to add 0.9 % - 0.115 % = 0.785 % NaCl

$$0.785\ \%\ \text{NaCl} = \frac{0.785}{0.16} = 0.1256\ \%\ \text{dextrose}$$

then add 1.256 g dextrose to 1 L

4. How many grams of potassium nitrate could be used to make the following prescription isotonic?

Sol. Silver Nitrate 60 1: 500 w/v

Make isoton. sol.

Sig. For eye use.

E of potassium nitrate = 0.58 E of Silver Nitrate = 0.33

Answer

1 g Silver Nitrate → 500 ml water to be isotonic

X g → 60 ml x = 0.12

$0.12 \times 0.33 = 0.0396$

1 g NaCl→ 100 ml water to be isotonic

X g → 60 ml x = 0.54

W % = 0.9 – (drug % × E NaCl)

= 0.54 – 0.0396 = 0.5004 of NaCl required to make solution isotonic

→ 0.5004 g ÷ 0.58 = 0.862 g of potassium nitrate to be used.

5. ℞

Tetracaine Hydrochloride		0.5%	(E Value = 0.18)
Sol. Epinephrine Bitartrate		1:1000	
Boric Acid		q.s.	(E Value = 0.5)
Purified Water	ad	30.0 ml	

Make isoton. sol.

Sig. Eye drops.

- The solution epinephrine bitartrate (1:1000) is already isotonic. How many grams of boric acid should be used in compounding the prescription?

Answer

0.5 % w/v tetracaine HCl in 30 ml = 0.15 g

0.9 % w/v NaCl in 30 ml = 0.27 g

1 g tetracaine HCl ≡ 0.18 g NaCl

0.15 g Tetracaine HCl ≡ X g NaCl so, X = 0.027 g NaCl

6. The solution epinephrine bitartrate (1:1000) is already isotonic. How many grams of boric acid should be used in compounding the prescription?

Answer

So, the amount of NaCl req. = 0.27 – 0.027 = 0.243 g

1 g boric acid ≡ 0.5 g NaCl

X g boric acid ≡ 0.243 g NaCl so X = 0.486 g boric acid

Another method

We need to add 0.9 % - (0.5 % x 0.18) = 0.81% NaCl

$$\frac{0.81\%\ \text{NaCl}}{0.5} = 1.62\ \%\ \text{boric acid}$$

1.62 g boric acid → 100 ml

X g boric acid → 30 ml so X = 0.486 g Boric acid

CASE: A local ophthalmologist is treating one of his patients for a post-LASIK eye infection that is not responding to topical ciprofloxacin. These infections, although rare, can occur after laser in situ keratomileusis (LASIK) surgery for vision correction.

Topical amikacin sulfate has been shown to be effective for the treatment of eye infections due to ciprofloxacin-resistant *Pseudomonas,4–5 Burkholderia ambifaria,* Mycobacterium chelonae, and *Mycobacterium* fortuitum. The ophthalmologist prescribes 60 mL of a 2.5% amikacin sulfate isotonic solution, 2 drops in the affected eye every 2 hours. Amikacin sulfate USP (C22H43N5O13•2H2SO2), m.w., 781.76, is an aminoglycoside-type antibiotic containing 3 ions.

a. Determine the weight in grams of amikacin sulfate needed to prepare the solution.
b. Calculate the sodium chloride equivalent (*E* value) for amikacin sulfate.
c. Calculate the amount of sodium chloride needed to make the prepared solution isotonic.
d. How many milliliters of 23.5%sodium chloride injection should be used to obtain the needed sodium chloride?

White-Vincent method

3-White – Vincent method

- Principle:

White-Vincent method involves

- 1st Addition of H_2O to the given amount of drug to make it isotonic
- 2nd addition of some other isotonic vehicle (e.g., 0.9% NaCl) to bring solution to final volume

General equations

- For one drug $V = w \times E \times 111.1$
- For multiple drugs $V = [(w_1 \times E_1) + (w_2 \times E_2) ....] \times 111.1$

Where:

- V = The volume in ml of isotonic solution that may be prepared by mixing the drug with water.
- w = the weight of the drug in grams.
- E = NaCl equivalent
- $111.1 = \frac{100\ ml}{0.9\ g}$ NaCl (representing isotonicity)

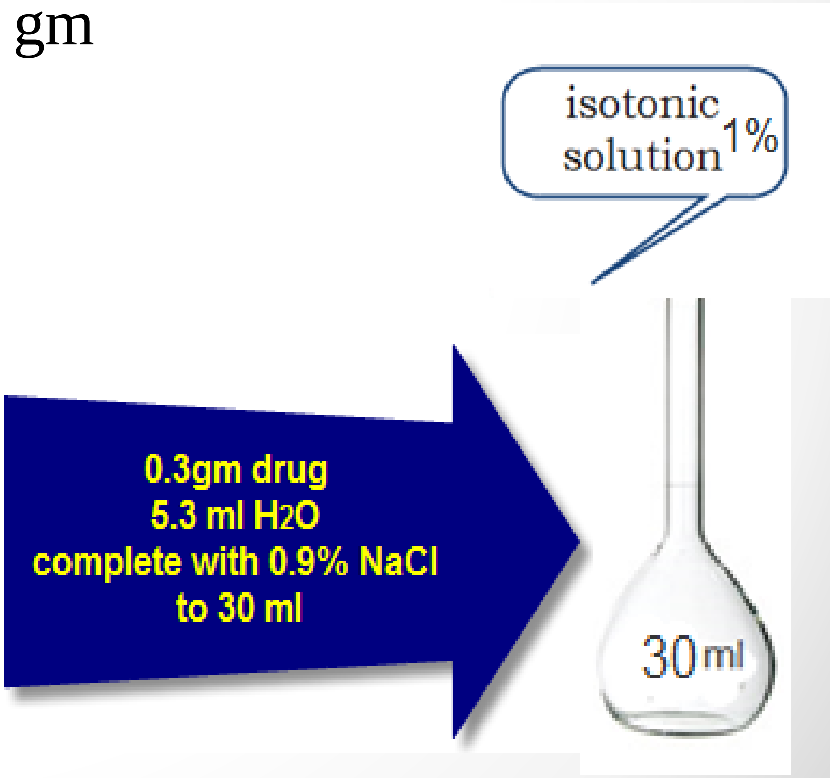
How to calculate amount of H_2O ?

- Suppose preparing 30ml of 1% drug isotonic with body fluid (E_{NaCl} = 0.16 gm)
- 1gm → 100ml

  ? ← 30ml = 0.3 gm
- Amount of NaCl eq. to 0.3 drug

  = 0.3 x 0.16 =0.048 gm
- 0.9 gm → 100 ml
- 0.048 gm → ? ml

  =5.3 ml



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

$$V = 0.3 \times 0.16 \times 111.1 = 5.3 \text{ ml}$$

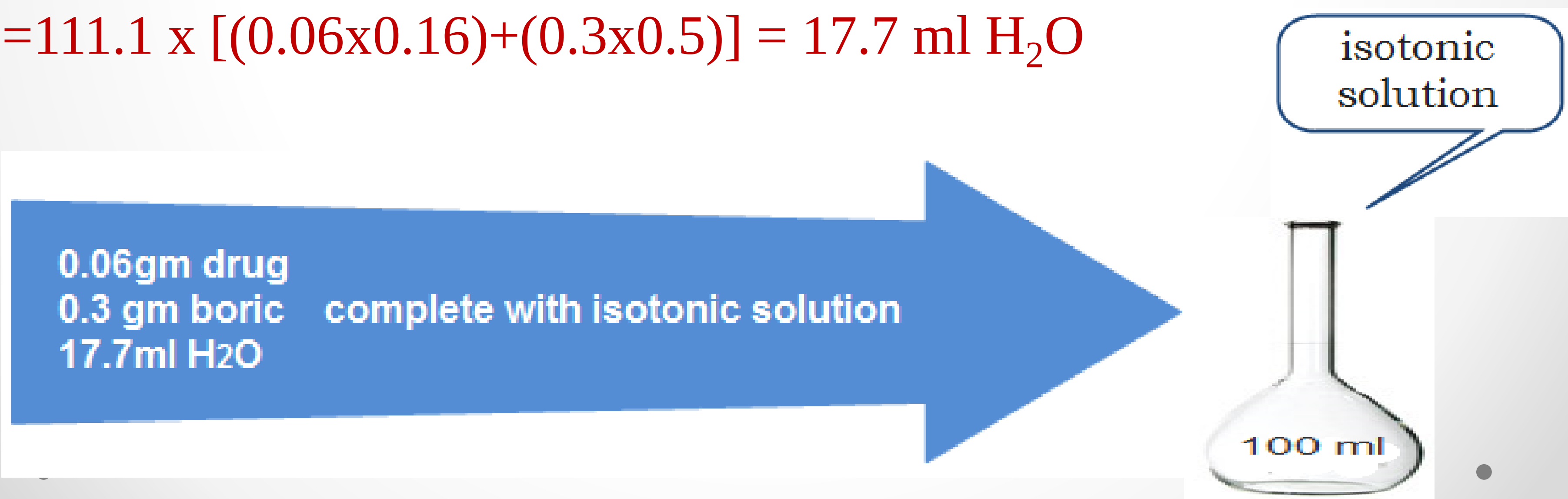
Example II

Add volume of H_2O and then complete with isotonic solution

Phenacaine HCl	0.06 gm	$(E_{NaCl}=0.16)$
Boric acid	0.3 gm	$(E_{NaCl}=0.5)$
sterile distilled H_2O up to	100 ml	

$V = 111.1 \text{ x } (\text{weight x } E_{NaCl})$

$V = 111.1 \text{ x } [(0.06\text{x}0.16)+(0.3\text{x}0.5)] = 17.7 \text{ ml } H_2O$



Problems

℞

Phenacaine Hydrochloride		0.06 g	(E Value = 0.16)
Boric Acid		0.3 g	(E Value = 0.5)
Purified Water	ad	100 ml	

Make isoton. sol.

Answer

$V = [(w_1 \times E_1) + (w_2 \times E_2)] \times 111.1$

$V = [(0.06 \times 0.16) + (0.3 \times 0.5)] \times 111.1$

$V = 17.7$ ml

- The drugs are mixed with water to make 17.7 ml of an isotonic solution and the preparation is brought to a volume of 100 ml by adding an isotonic diluting solution

℞

Epinephrine Hydrochloride 0.5% (E Value = 0.29)

Sterile preserved Water q.s to make 15 ml

Make isoton. sol.

Answer

- weight of drug = 0.5% × 15 = 0.075 g

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

$$V = 0.075 \times 0.29 \times 111.1 = 2.4 \text{ ml}$$

℞

Ephedrine Hydrochloride		1 g	(E Value = 0.3)
chlorobutol		0.5 g	(E Value = 0.24)
NaCl		q.s.	
Distilled Water	ad	200 ml	

- $V = [(w_1 \times E_1) + (w_2 \times E_2)] \times 111.1$

$V = [(1 \times 0.3) + (0.5 \times 0.24)] \times 111.1 = 46.66$ ml

so, 200 – 46.66 = 153.34 ml

0.9 g NaCl → 100 ml soln.

X g NaCl → 153.34 ml soln. X= 1.38 g NaCl

1. A solution contains 1 gram of ephedrine sulfate in a volume of 100 ml what quantity of sodium chloride must be added to make the solution isotonic? How much dextrose would be required for this purpose?

E value of ephedrine sulfate is 0.23

E value of dextrose is 0.16

Answer by NaCl Equivalent method

1 g ephedrine ≡ 0.23 g NaCl

So , NaCl req. = 0.9 – 0.23 = 0.67 g

For dextrose , 1 g dextrose ≡ 0.16 NaCl

X g dextrose ≡ 0.67 NaCl   so, X = 4.187 g

Answer by white-Vincent method

V of Ephedrine sulfate = w × E × 111.1 → = 1 × 0.23 × 111.1 = 25.53

V_{iso} = 100 – 25.53 = 74.44

0.9 g NaCl → 100 ml soln.

X g NaCl → 74.44 ml soln.   X= 0.67 g NaCl

For Dextrose , V = w × E × 111.1

74.44 = w × 0.16 × 111.1   w = 4.18 g