ISOTONIC AND BUFFER SOLUTIONS

LECTURE :1

DR. SHAIMAA MUNTHER

No	Lecture title	hours
1	**Dilution and concentration of pharmaceutical preparations.**	10
2	**Isotonic and buffer solutions.**	6
3	**Electrolyte solutions (milliequivalents, millimoles and milliosmoles).**	6
4	**Constituted solutions, I.V admixtures and flow rate calculations.**	8

Colligative Properties

- Colligative properties**,** From Greek word" collected together", depend mainly on the number of particles in solution.

- Thus 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.

- The solute particles displace some solvent molecules in the liquid phase and therefore reduce the concentration of solvent, so that the colligative properties are independent of the nature of the solute.

- The word colligative is derived from the Latin *colligatus* meaning *bound together*

Colligative Properties

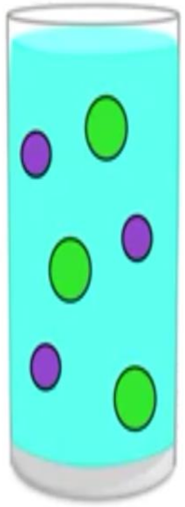
Colligative properties include·

– Vapor pressure lowering

– Freezing point depression

– Boiling point elevation

– Osmotic pressure



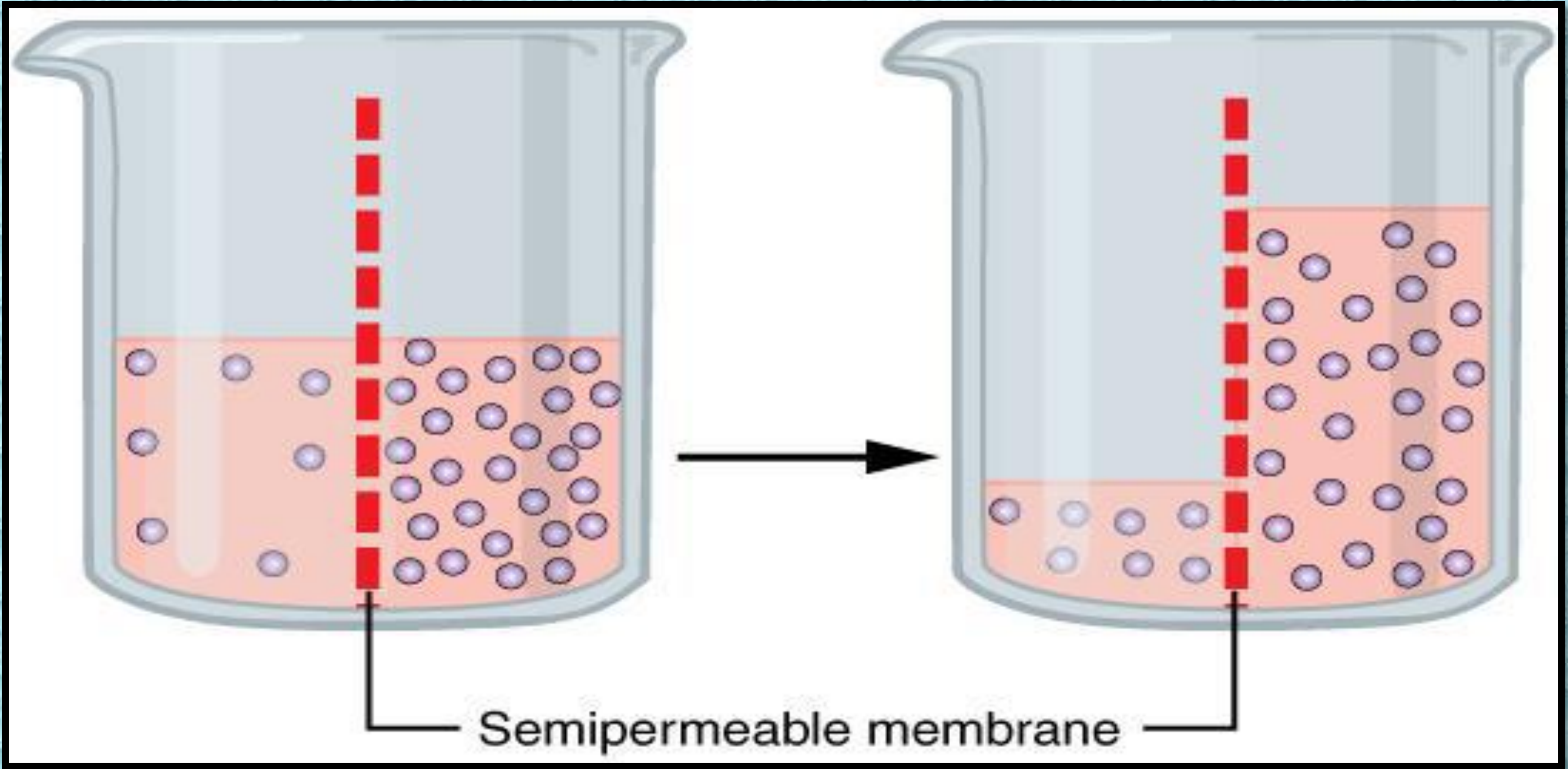
Osmosis and Osmotic pressure

- **Osmosis**
- Is the diffusion of solvent through a semi-permeable membrane.
- Water always flows from lower solute concentration [dilute solution] to higher solute concentration until a balance is produced.

- **Osmotic pressure**
- Is the pressure that must be applied to the solution to prevent the passage of the solvent through a perfect semipermeable membrane.

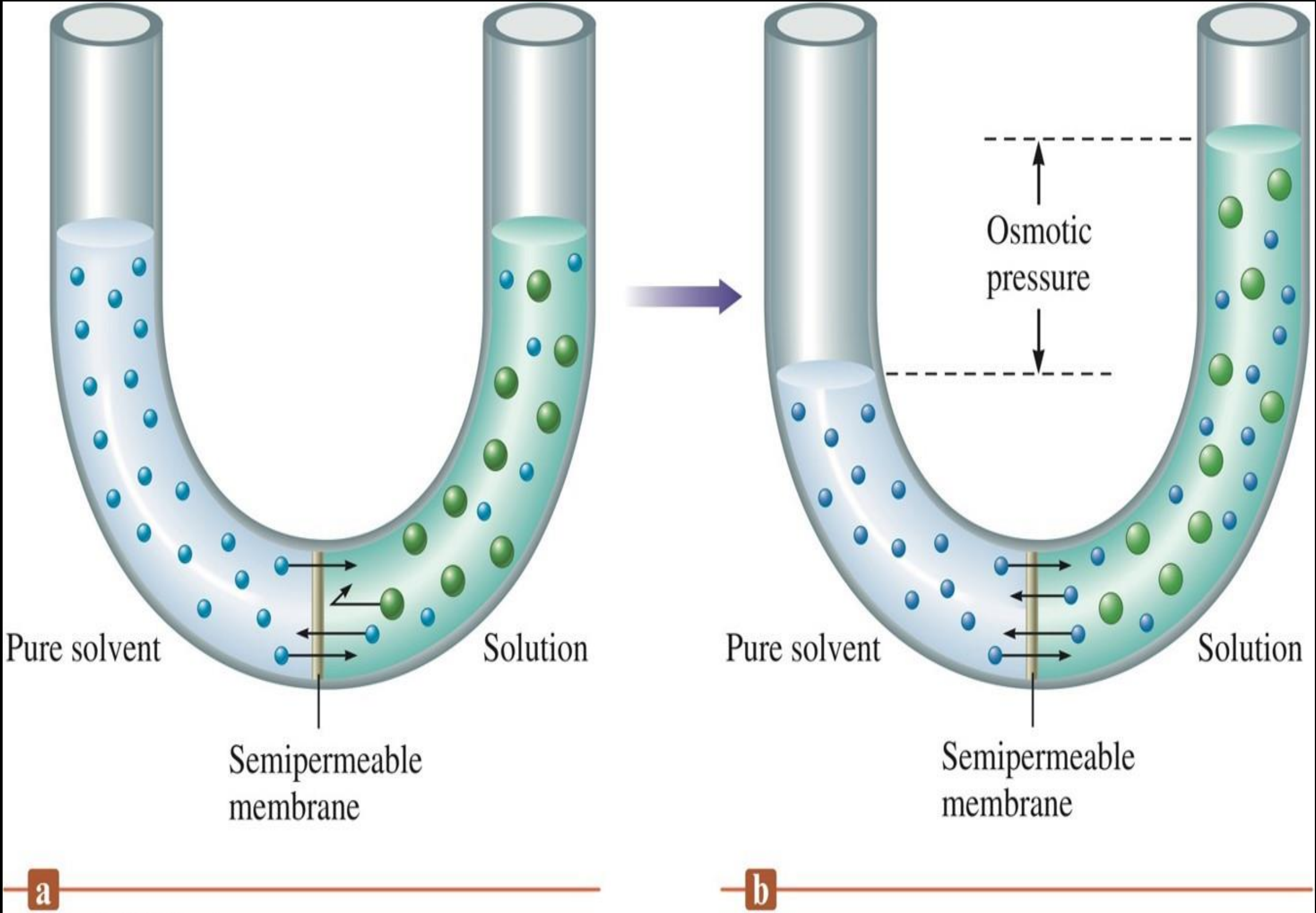
- **Tonicity**
- Is a measure of the osmotic pressure of two solutions separated by a semi-permeable membrane.

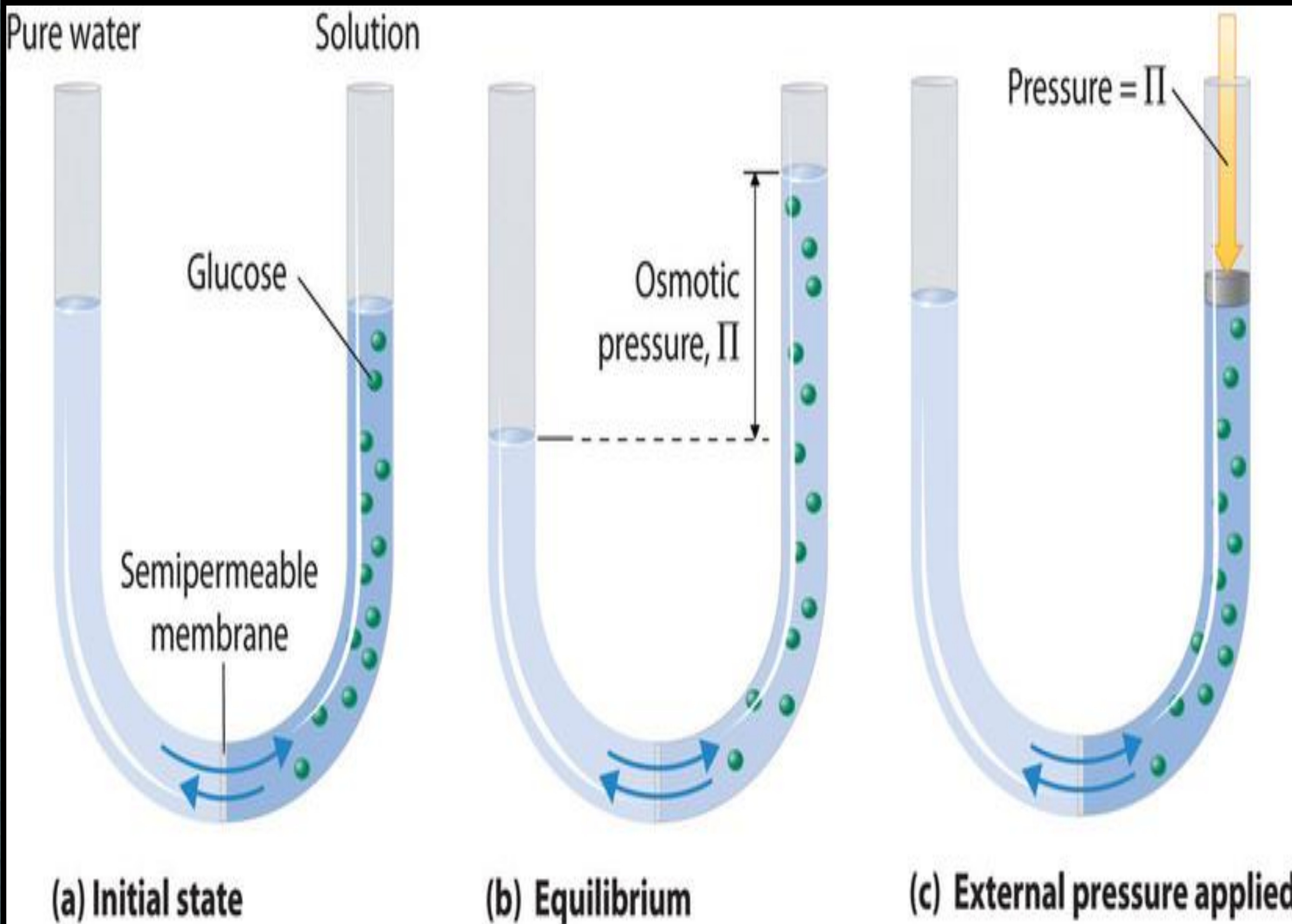
Osmosis

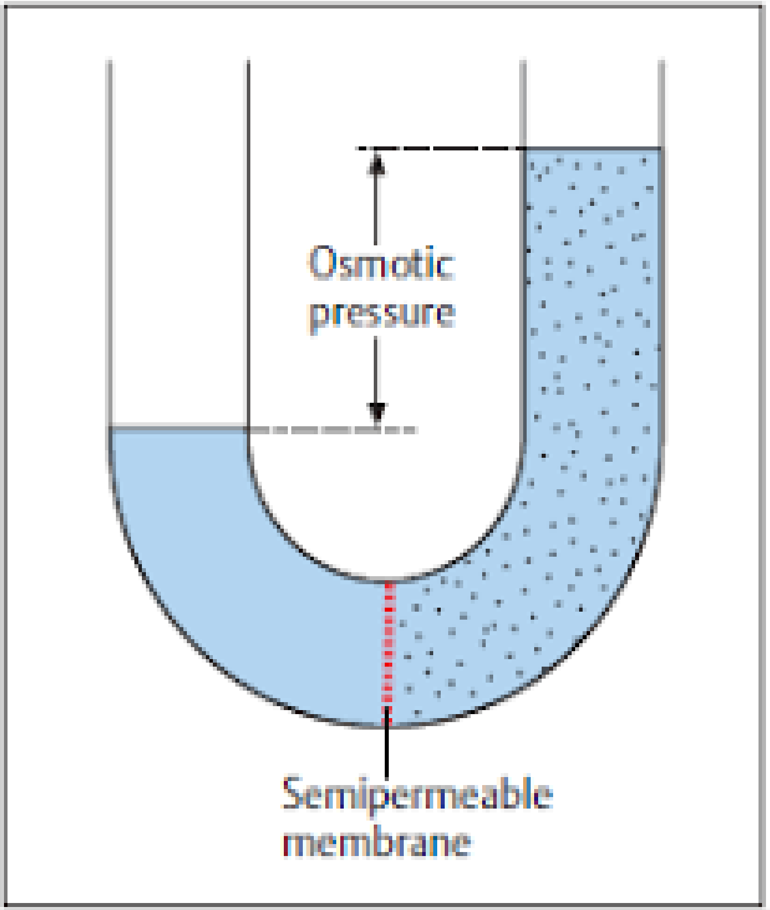


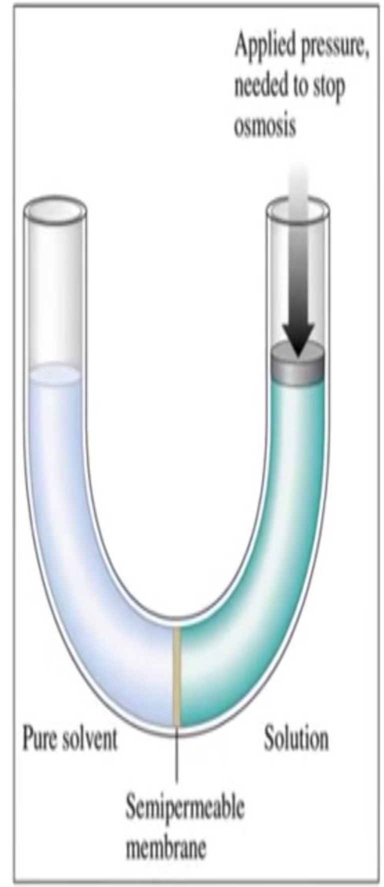
Osmosis:

2 solutions of different concentrations are separated by a semi-permeable membrane (only permeable to the solvent) the solvent will move from the solution of lower conc. to that of higher conc.


Pure solvent
Solution
Semipermeable membrane
a
Osmotic pressure
Pure solvent
Solution
Semipermeable membrane
b


Pure water
Solution
Glucose
Semipermeable
membrane
Osmotic
pressure, Π
Pressure = Π
(a) Initial state
(b) Equilibrium
(c) External pressure applied





- The pressure needed to stop the flow of the solvent is the osmotic pressure, Π.
- $\Pi = MRT$

Osmosis

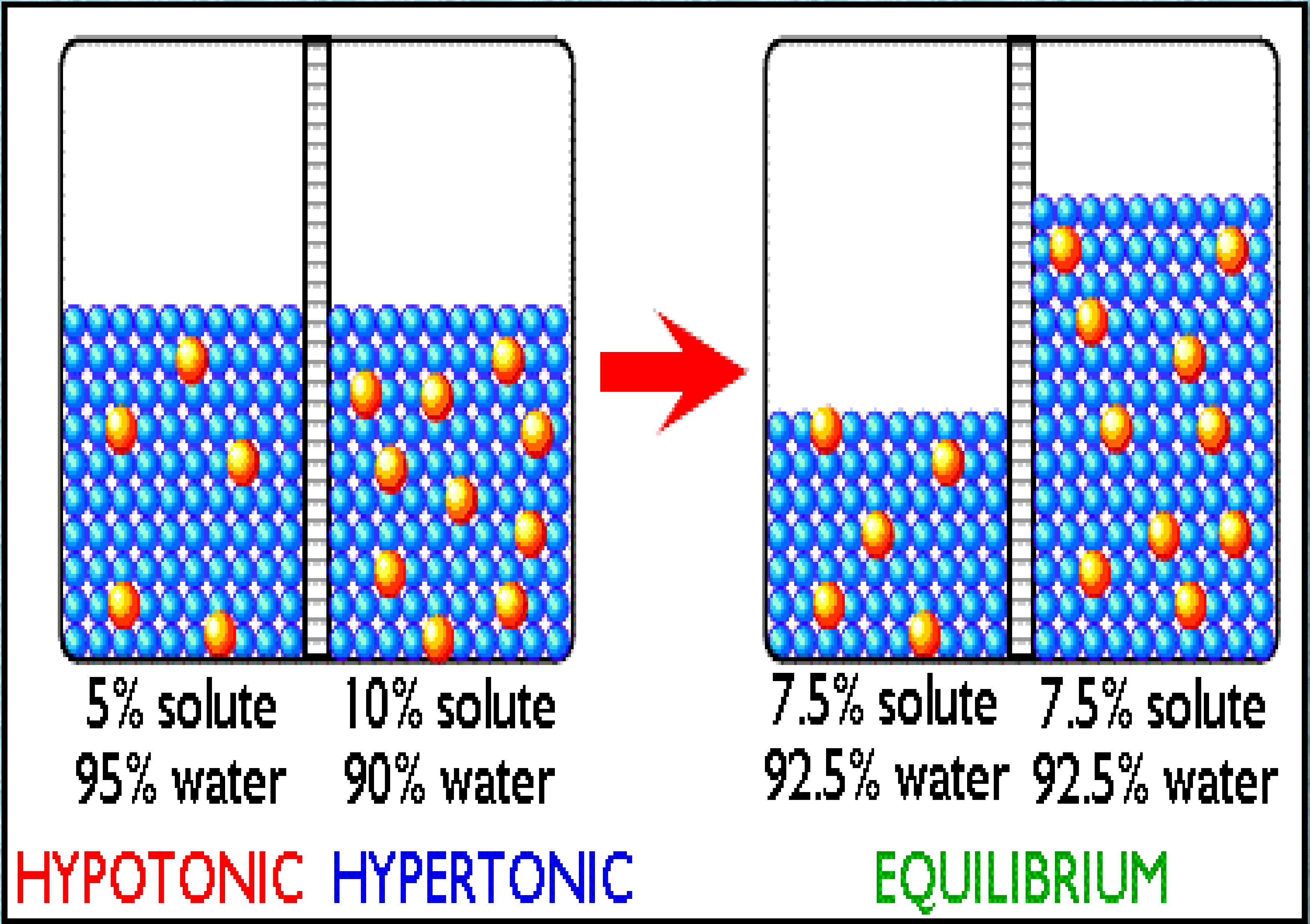
- If the solute is a non electrolyte, its solution contains only this type of molecules and the osmotic pressure varies with the concentration of the solute.

- If the solute is an electrolyte, its solution contains ions and the osmotic pressure varies with both the concentration of the solute and its degree of dissociation. Thus, solutes that dissociate present a greater number of particles in solution and exert a greater osmotic pressure than undissociated molecules.

- Like osmotic pressure, the other colligative properties of solutions, vapor pressure, boiling point, and freezing point, depend on the number of particles in solution. Therefore, these properties are interrelated and a change in any one of them will result in a corresponding change in the others.

Isosmotic vs Isotonic Solutions

- Two solutions that have the same osmotic pressure are termed **isosmotic.**
- Many solutions intended to be mixed with body fluids are designed to have the same osmotic pressure for greater patient comfort, efficacy, and safety.
- A solution having the same osmotic pressure as a specific body fluid is termed **isotonic** (meaning of equal tone) with that specific body fluid.
- Solutions of lower osmotic pressure than that of a body fluid are termed **hypotonic**, whereas those having a higher osmotic pressure are termed **hypertonic.**
- Pharmaceutical dosage forms intended to be added directly to the blood or mixed with biological fluids of the eye, nose, and bowel are of principal concern to the pharmacist in their preparation and clinical application.



5% solute
95% water
10% solute
90% water
7.5% solute
92.5% water
7.5% solute
92.5% water
HYPOTONIC
HYPERTONIC
EQUILIBRIUM

Important Definitions

- **Nonelectrolytes solutions:**

  Solution will contain only molecules, and the osmotic pressure will vary only with concentration of the solute.

- **Electrolytes solutions :**

  Solution will contain ions, and the osmotic pressure of the solution will vary not only with the concentration but also with the degree of dissociation of the solute.

- **Isosmotic solutions:**

  Solutions that have the same osmotic pressure

- **Isotonic solution:**

  A solution having the same osmotic pressure as a specific body fluid

- **Hypotonic solution**:

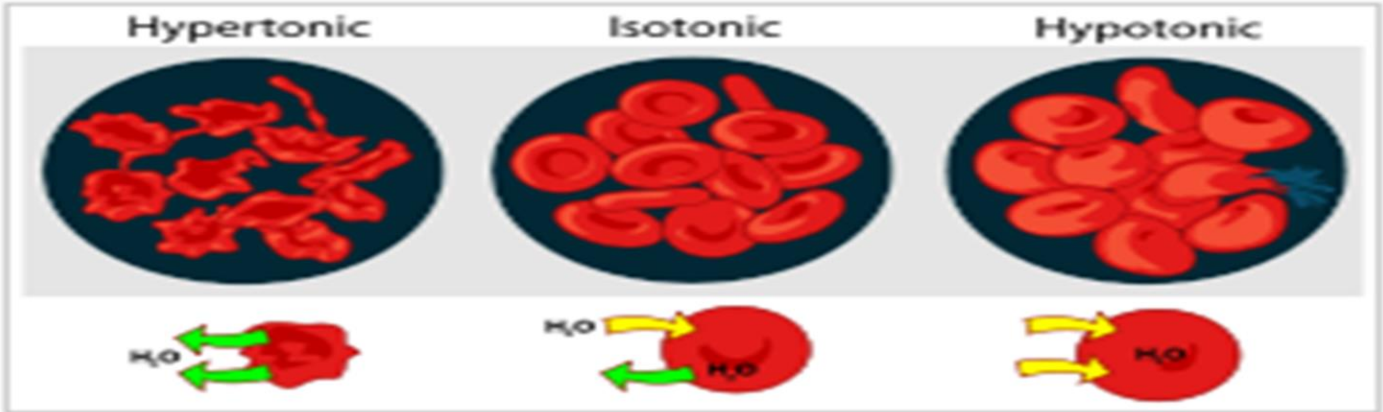
  A solution of lower osmotic pressure than that of body fluids.

- **Hypertonic solution:**

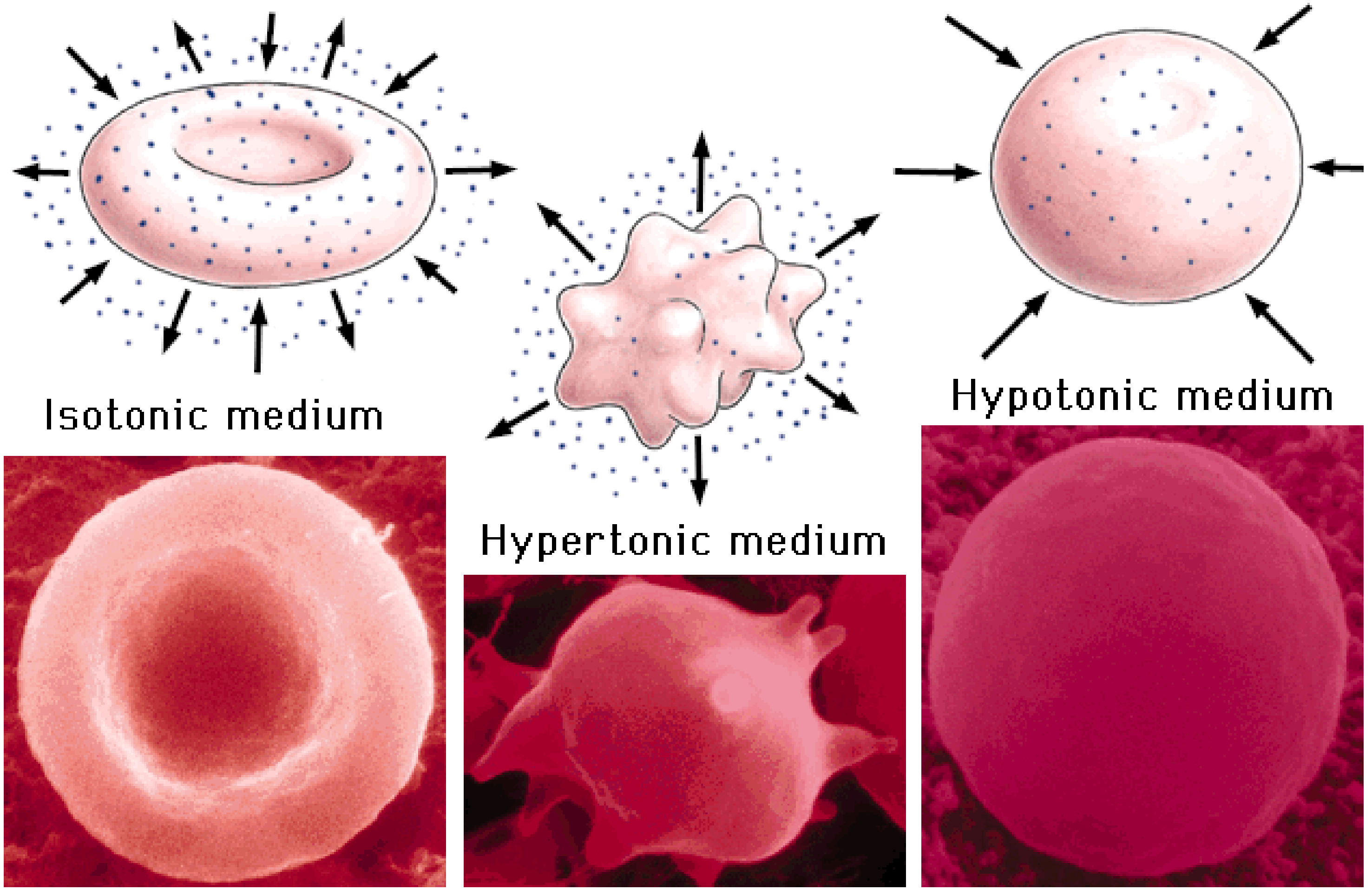
  A solution of higher osmotic pressure than that of body fluids.

Types of Tonicity

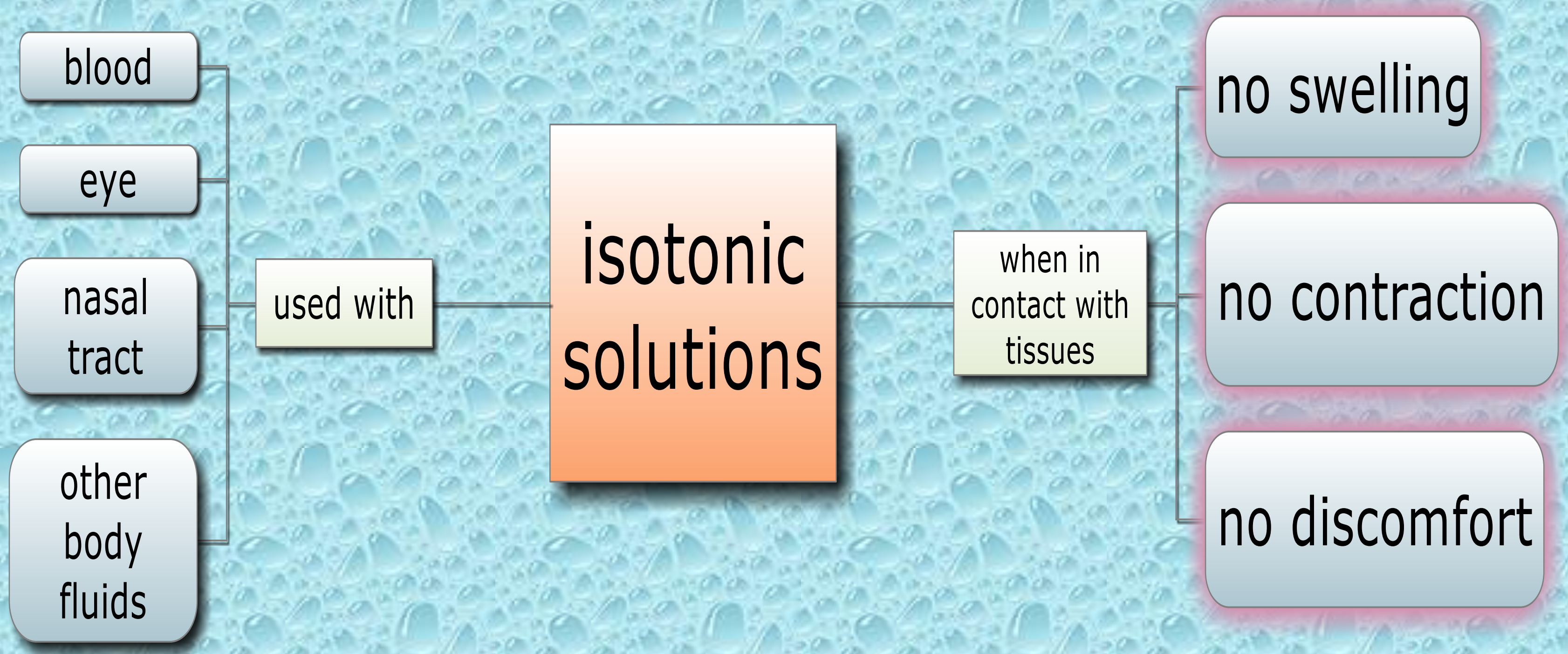
Hypertonic	isotonic	Hypotonic
NaCl 2%	NaCl 0.9%	NaCl 0.2%
solute Inside < solute outside	solute Inside = solute outside	solute Inside > solute outside
shrinkage	equilibrium	swelling



Effect of different solutions on blood cells


Isotonic medium
Hypertonic medium
Hypotonic medium

Why using isotonic solutions?



Isotonicity & Route of Administration

- Subcutaneous injection:
  - not necessarily “small dose” but isotonicity reduce pain.
- Hypodermoclysis
  - should be isotonic “Large volume”
- Intramuscular injection
  - should be isotonic or slightly hypertonic to increase penetration
- Intravenous injection
  - should be isotonic “Large volume ”
  - Hypotonic cause haemolysis
  - Hypertonic solution may be administered slowly into a vein
  - Hypertonic large volume administered through a cannula into large vessels.

Isotonicity & Route of Administration

- Intrathecal injestion
  - Should be isotonic
- Eye drops
  - Rapid diluted by tear, but most of it is isotonic to decrease irritation
- Eye lotions
  - Preferably isotonic
- Nasal drops
  - Isotonic, but not essentially

BODY FLUID COMPARTMENTS

- In lean adults, body fluids constitute 55% of female and 60% of male total body mass these divided into:

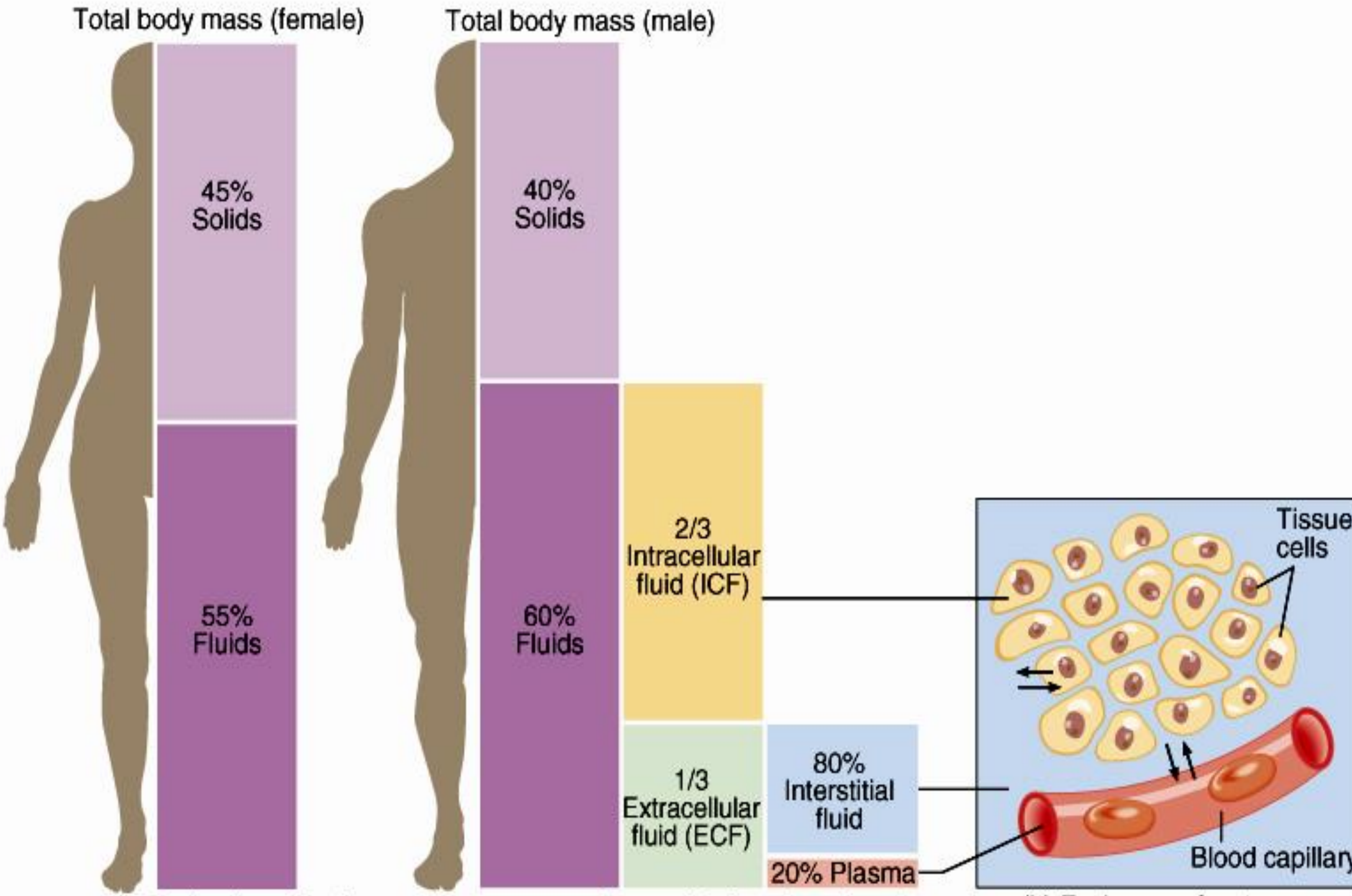
  - **<u>Intracellular fluid (ICF)</u> inside cells**

    About 2/3 of body fluid

  - **<u>Extracellular fluid (ECF)</u> outside cells divided into :**

    1. **Interstitial fluid** (fluid between cell) is 80% of ECF
    2. **Intravascular fluid** (Plasma in blood)is 20% of ECF

BODY FLUID COMPARTMENTS



(a) Distribution of body water in an average lean, adult female and male

(b) Exchange of water among body fluid compartments

COMPOSITION OF BODY FLUIDS

- **In addition to water, the body contains solutes; substances that separate in solution**
- **Solution = Solute + Solvent**
  - **Solution = the fluid compartment (ICF or ECF)**
  - **Solvent = water**
  - **Solutes:**
    - **Electrolytes**
      - **Charged inorganic ions**
        - » **They dissolve in water**
        - » **They can conduct an electric current**
      - **Major cations:**
        - » **ECF = sodium** **ICF = potassium**
      - **Major anions:**
        - » **ECF = chloride, bicarbonate** **ICF = proteins neg charge**
    - **Non-electrolytes**
      - **Polar = those that are water soluble (sugars, proteins)**
      - **Non-polar = those that are water insoluble (lipids)**

BASIC CONCEPTS RELATING TO REGULATION OF FLUID & ELECTROLYTES

Maintenance of normal protein and electrolyte concentrations controls water distribution in the body compartments

1. Water passes freely across cell membranes
2. Ions and proteins cannot freely diffuse across most cell membranes
3. Water moves passively in response to changes in solute concentration
4. All monitors to homeostatic balance occur in ECF and not ICF
   - Fluid shifts occur between ICF & ECF in response to changes only in ECF
   - Key to equilibrium is maintaining solute concentration (osmolality)

Note: water follows salt ,thus, regulation of fluid balance & electrolyte balance are intertwined


THANK YOU

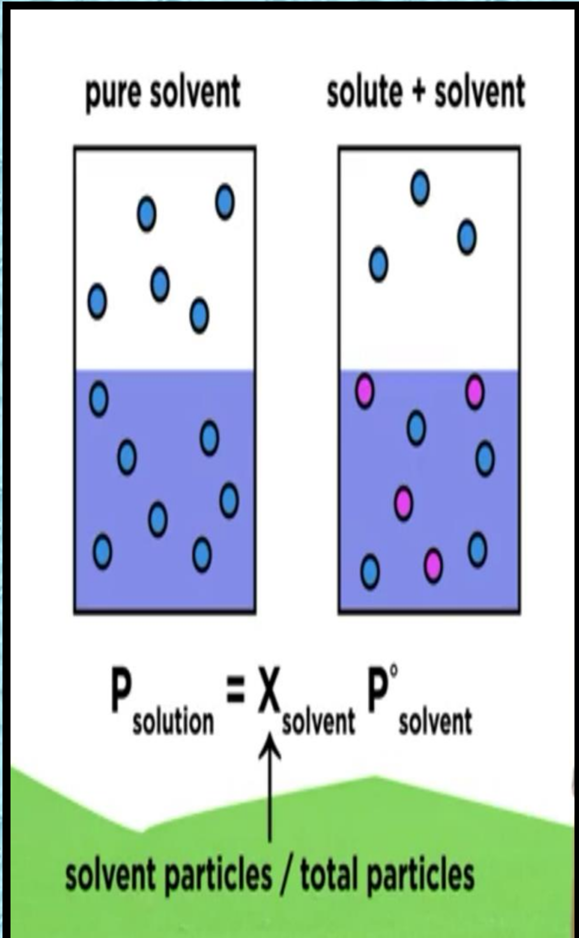
ISOTONIC AND BUFFER SOLUTIONS

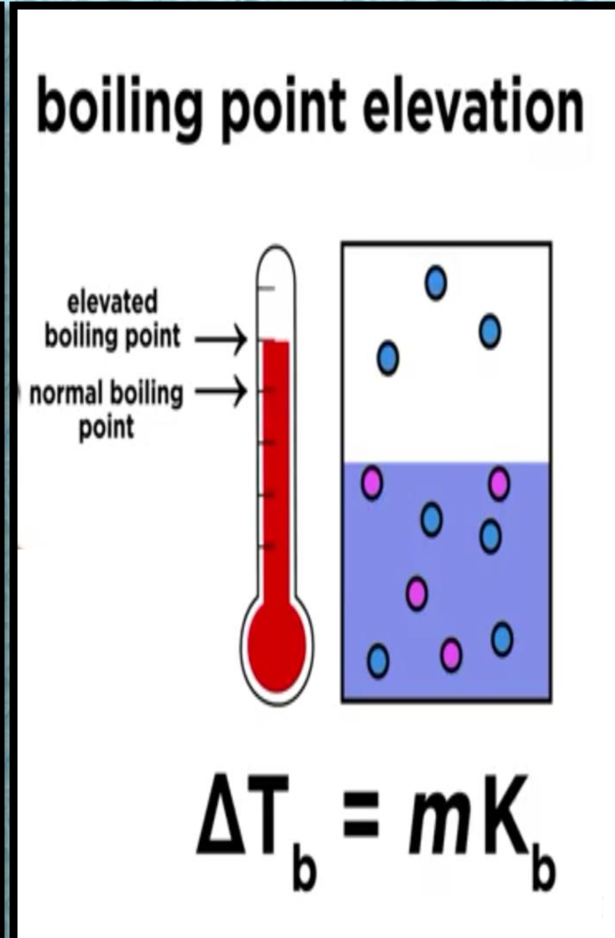
LECTURE : 2 & 3

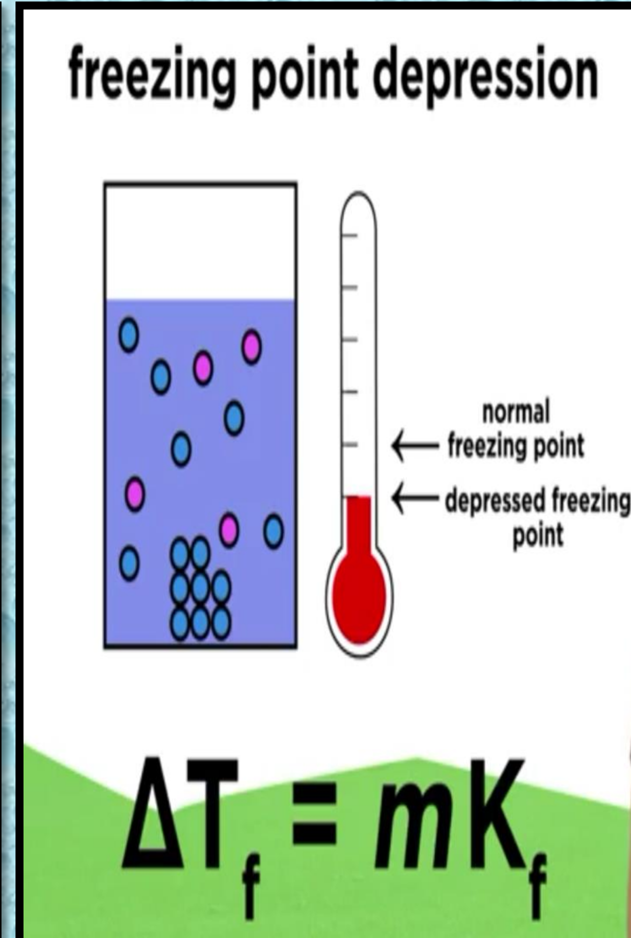
DR. SHAIMAA MUNTHER

Colligative properties

- A solution will behave differently from a pure solvent because there are a particles of solutes that interfere with the physical processes like phases changes .
- A solution will displays certain colligative properties which depends only on the concentration of the solute and not on the identity of the solute particles.
- Adding a solute to a solvent will change the colligative properties in different ways:
  - Vapor pressure lowering
  - Freezing point depression
  - Boiling point elevation







normal boiling point + ΔT_b = new boiling point

normal freezing point - ΔT_f = new freezing point

$$\Delta T_b = mK_b$$

$$\Delta T_f = mK_f$$

Classes of adjustment of isotonicity

1. Freezing point depression (FPD) "cryoscopic method".
   - Adding substance to lower FP of solution to -0.52º

2. NaCL Equivalent Method.

Freezing point depression method

- **Calculations for preparation of isotonic solution:**
- **Freezing point depression** (colligative properties)
- - 0.52 is the freezing point of both blood serum and lacrimal fluids
- **For nonelectrolytes :** (negligible dissociation) as boric acid
- Boric acid: MWt 61.8 thus if 61.8 g in 1000 g of water should produce a freezing point of -1.86 ^{o}C
- $$\frac{1.86\,(^\circ C)}{0.52\,(^\circ C)} = \frac{61.8\,(g)}{X\,(g)}$$ 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.

Freezing point depression method

- **Calculations for preparation of isotonic solution:**
- **Freezing point depression** (colligative properties)
- - 0.52 is the freezing point of both blood serum and lacrimal fluids
- **<u>For electrolytes:</u>** 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* .
- $$\frac{1.86\left(°C\right)\times 1.8}{0.52\left(°C\right)}=\frac{58.5\left(g\right)}{X\left(g\right)}$$ $X = 9.09\ g$
- 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.

Freezing point depression method

- **Calculations for preparation of isotonic solution:**
- **Isotonic solutions are calculated by the following formula**

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

- 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

Freezing point depression method
Examples for dissociation factor calculations

- **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.

Freezing point depression method
Examples for dissociation factor calculations

- **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

  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.

The Sodium Chloride Equivalent Method

- A special problem arises when a prescription directs us to make a solution isotonic by adding the proper amount of some substance other than the active ingredient or ingredients.

- Given a 0.5% w/v solution of sodium chloride, we may easily calculate that 0.9 g - 0.5 g = 0.4 g of additional sodium chloride that should be contained in each 100 mL if the solution is to be made isotonic with a body fluid.

- But how much sodium chloride should be used in preparing 100 mL of a 1% w/v solution of **atropine sulfate**, which is to be made isotonic with lacrimal fluid?

- **The answer depends on how much sodium chloride is in effect represented by the atropine sulfate.**

The Sodium Chloride Equivalent Method

- ***The Sodium Chloride Equivalent (E value)*** **of a drug:** is the amount of sodium chloride which has the same **osmotic** effect as 1 gram of the drug.

$$\frac{Mwt\ of\ NaCl}{i\ factor\ of\ NaCl} \times \frac{i\ factor\ of\ substance}{Mwt\ of\ substance} = Sodium\ Chloride\ equivalent$$

- How much NaCl should be used in preparing 100 ml of 1% w/v solution of atropine sulfate, which is to be made isotonic with lacrimal fluids?
- M.Wt of NaCl = 58.5, i = 1.8
- M.Wt of atropine sulfate = 695, i = 2.6

58.5/1.8 x 2.6/695 = 0.12 g

- X = 0.12 g of sodium chloride represented by 1 g of atropine sulfate
- Sodium chloride equivalent of atropine sulfate (E value) is = 0.12
- 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.

Example Calculations of the Sodium Chloride Equivalent

Example1:

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

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

58.5/1.8 x 1.8/376 = 0.156, or 0.16, answer.

Example 2:

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

58.5/1.8 x 1/92 = 0.35 , answer.

Example 3:

Calculate the sodium chloride equivalent for timolol maleate, which dissociates into two ions and has a molecular weight of 432 Timolol maleate, i factor =1.8

58.5/1.8 x 1.8/432 = 0.14 , answer.

TABLE 11.1 SODIUM CHLORIDE EQUIVALENTS (*E* VALUES)

SUBSTANCE	MOLECULAR WEIGHT	IONS	*i*	SODIUM CHLORIDE EQUIVALENT (E VALUE)
Antazoline phosphate	363	2	1.8	0.16
Antipyrine	188	1	1.0	0.17
Atropine sulfate·H_2O	695	3	2.6	0.12
Benoxinate hydrochloride	345	2	1.8	0.17
Benzalkonium chloride	360	2	1.8	0.16
Benzyl alcohol	108	1	1.0	0.30
Boric acid	61.8	1	1.0	0.52
Chloramphenicol	323	1	1.0	0.10
Chlorobutanol	177	1	1.0	0.24
Chlortetracycline hydrochloride	515	2	1.8	0.11
Cocaine hydrochloride	340	2	1.8	0.16
Cromolyn sodium	512	2	1.8	0.11
Cyclopentolate hydrochloride	328	2	1.8	0.18
Demecarium bromide	717	3	2.6	0.12
Dextrose (anhydrous)	180	1	1.0	0.18
Dextrose·H_2O	198	1	1.0	0.16
Dipivefrin hydrochloride	388	2	1.8	0.15
Ephedrine hydrochloride	202	2	1.8	0.29
Ephedrine sulfate	429	3	2.6	0.23
Epinephrine bitartrate	333	2	1.8	0.18
Epinephryl borate	209	1	1.0	0.16
Eucatropine hydrochloride	328	2	1.8	0.18
Fluorescein sodium	376	3	2.6	0.31
Glycerin	92	1	1.0	0.34
Homatropine hydrobromide	356	2	1.8	0.17
Hydroxyamphetamine hydrobromide	232	2	1.8	0.25
Idoxuridine	354	1	1.0	0.09
Lidocaine hydrochloride	289	2	1.8	0.22
Mannitol	182	1	1.0	0.18
Morphine sulfate·$5H_2O$	759	3	2.6	0.11
Naphazoline hydrochloride	247	2	1.8	0.27
Oxymetazoline hydrochloride	297	2	1.8	0.20
Oxytetracycline hydrochloride	497	2	1.8	0.12
Phenacaine hydrochloride	353	2	1.8	0.20
Phenobarbital sodium	254	2	1.8	0.24
Phenylephrine hydrochloride	204	2	1.8	0.32
Physostigmine salicylate	413	2	1.8	0.16
Physostigmine sulfate	649	3	2.6	0.13
Pilocarpine hydrochloride	245	2	1.8	0.24
Pilocarpine nitrate	271	2	1.8	0.23
Potassium biphosphate	136	2	1.8	0.43
Potassium chloride	74.5	2	1.8	0.76
Potassium iodide	166	2	1.8	0.34
Potassium nitrate	101	2	1.8	0.58
Potassium penicillin G	372	2	1.8	0.18
Procaine hydrochloride	273	2	1.8	0.21
Proparacaine hydrochloride	331	2	1.8	0.18
Scopolamine hydrobromide·$3H_2O$	438	2	1.8	0.12
Silver nitrate	170	2	1.8	0.33
Sodium bicarbonate	84	2	1.8	0.65
Sodium borate·$10H_2O$	381	5	4.2	0.42

(continued)

TABLE 11.1 *continued*

SUBSTANCE	MOLECULAR WEIGHT	IONS	*i*	SODIUM CHLORIDE EQUIVALENT (E VALUE)
Sodium carbonate	106	3	2.6	0.80
Sodium carbonate·H_2O	124	3	2.6	0.68
Sodium chloride	58	2	1.8	1.00
Sodium citrate·$2H_2O$	294	4	3.4	0.38
Sodium iodide	150	2	1.8	0.39
Sodium lactate	112	2	1.8	0.52
Sodium phosphate, dibasic, anhydrous	142	3	2.6	0.53
Sodium phosphate, dibasic·$7H_2O$	268	3	2.6	0.29
Sodium phosphate, monobasic, anhydrous	120	2	1.8	0.49
Sodium phosphate, monobasic·H_2O	138	2	1.8	0.42
Tetracaine hydrochloride	301	2	1.8	0.18
Tetracycline hydrochloride	481	2	1.8	0.12
Tetrahydrozoline hydrochloride	237	2	1.8	0.25
Timolol maleate	432	2	1.8	0.14
Tobramycin	468	1	1.0	0.07
Tropicamide	284	1	1.0	0.11
Urea	60	1	1.0	0.59
Zinc chloride	136	3	2.6	0.62
Zinc sulfate·$7H_2O$	288	2	1.4	0.15

The Sodium Chloride Equivalent Method

- The procedure for the calculation of isotonic solutions with sodium chloride equivalents may be outlined as follows:
- Step 1. Calculate the amount (in grams) of sodium chloride represented by the ingredients in the prescription. **Multiply the amount (in grams) of each substance by its sodium chloride equivalent.**
- **Step 2.** Calculate the amount (in grams) of sodium chloride, alone, **that would be contained in an isotonic solution of the volume specified in the prescription**, namely, the amount of sodium chloride in a 0.9% solution of the specified volume. (Such a solution would contain 0.009 g/mL.)
- **Step 3. Subtract the amount of sodium chloride represented by the ingredients in the prescription (Step 1) from the amount of sodium chloride, alone, that would be represented in the specific volume of an isotonic solution (Step 2).** The answer represents the amount (in grams) of sodium chloride to be added to make the solution isotonic.
- **Step 4. If an agent other than sodium chloride**, such as boric acid, dextrose, or potassium nitrate, is to be used to make a solution isotonic, **divide the amount of sodium chloride (Step 3) by the sodium chloride equivalent of the other substance**.

The Sodium Chloride Equivalent Method

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

R/ Pilocarpine nitrate 0.3 g

Sodium chloride q.s.

Purified water 30 ml

Make isoton. Sol.

Sig. for the eye

- Sod. Chloride equivalent for Pilocarpine nitrate = 0.23 (from table or calculated)

1- 0.23 X 0.3 = 0.069 g of NaCl represented by the pilocarpine nitrate

2- 0.9 g NaCl 100 ml water to be isotonic

X g 30 ml

X = 0.9 X 30 / 100 = 0.27 g

3- 0.27 - 0.069 = 0.201 g of sodium chloride to be used

The Sodium Chloride Equivalent Method

- **Example: How many grams of boric acid should be used in compounding the following prescription?**

Phenacaine Hydrochloride	1%
Chlorobutanol	1⁄2%
Boric Acid	q.s.
Purified Water ad	60

Make isoton. sol.

Sig. One drop in each eye.

- The prescription calls for **0.6 g** of phenacaine hydrochloride and **0.3 g** of chlorobutanol.

1- 0.20 x 0.6 g = 0.120 g of sodium chloride represented by phenacaine hydrochloride
0.24 x 0.3 g = 0.072 g of sodium chloride represented by chlorobutanol

Total: 0.192 g of sodium chloride represented by both ingredients

2- 60 x 0.009 = 0.540 g of sodium chloride in 60 mL of an isotonic sodium chloride solution

3- 0.540 g (from Step 2)
- 0.192 g (from Step 1)

0.348 g of sodium chloride required to make the solution isotonic

But because the prescription calls for boric acid:

4- 0.348 g ÷ 0.52 (sodium chloride equivalent of boric acid) = **0.669 g of boric acid to be used, answer**.

The Sodium Chloride Equivalent Method

- **Example: How many grams of potassium nitrate could be used to make the following prescription isotonic?**

  Sol. Silver Nitrate 60 ml

  1500 w/v

  Make isoton. sol.

  Sig. For eye use.

  The prescription contains **0.12 g** of silver nitrate.

1- 0.33 x 0.12 g = 0.04 g of sodium chloride represented by silver nitrate

2- 60 x 0.009 = 0.54 g of sodium chloride in 60 mL of an isotonic sodium chloride solution

3- 0.54 g (from step 2)

- 0.04 g (from step 1)

———————

0.50 g of sodium chloride required to make solution isotonic

- Because, in this solution, sodium chloride is incompatible with silver nitrate, the tonic agent of choice is potassium nitrate. Therefore we use potassium nitrate

4- 0.50 g ÷ 0.58 (sodium chloride equivalent of potassium nitrate) = **0.86 g of potassium nitrate to be used, answer**.

The Sodium Chloride Equivalent Method

- **Example: How many grams of sodium chloride should be used in compounding the following prescription?**

  Ingredient X 0.5

  Sodium Chloride q.s.

  Purified Water ad 50

  Make isoton. sol.

  Sig. Eye drops.

- Let us assume that ingredient X is a new substance for which no sodium chloride equivalent is to be found in Table 11.1, and that its molecular weight is 295 and its i factor is 2.4.
- The sodium chloride equivalent of ingredient X may be calculated as follows:

  58.5/1.8 x 2.4/295 = 0.26 g the sodium chloride equivalent for ingredient X

- Then,

1- 1. 0.26 x 0.5 g = 0.13 g of sodium chloride represented by ingredient X

2- 50 x 0.009 = 0.45 g of sodium chloride in 50 mL of an isotonic sodium chloride solution

3- 0.45 g (from Step 2)

- 0.13 g (from Step 1)

0.32 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:

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

(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 1:
- **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.

  0.2 g x 0.22 / 0.009 = 4.89 mL purified water required to make an isotonic solution of hydromorphone hydrochloride, answer.
- Step 3.
- 20 mL- 4.89 mL =15.11 mL 0.9% w/v sodium chloride solution required, answer.

- **Proof:**

  20 mL x 0.9% = 0.18 g sodium chloride

  Equivalent required 0.2 x 0.22 = 0.044g (sodium chloride represented by 0.2g hydromorphonehydrochloride)

  15.11 mL x 0.9 % = 0.136 g sodium chloride present

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

- **Example 1:**
- **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.

  0.2 g x 0.22 / 0.009 = 4.89 mL

g NaCl (or equivalent)	ml of water	
0.009 g	1 ml	
0.2 x0.22 g	x ml	x= 0.2 g x 0.22 / 0.009

x= 4.9 ml purified water required to make an isotonic solution of hydromorphone hydrochloride, answer.

- Step 3.
- 20 ml is to be prepeared isotonic so
- 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** (Tf) 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. Thus, a pharmaceutical solution that has a freezing point of -0.52C is considered isotonic.

- Representative data on freezing point depression by medicinal and pharmaceutical substances are presented in Table 11.2.

- Although these data are for solution strengths of 1% (Tf 1%), data for other solution strengths and for many additional agents may be found in physical pharmacy textbooks and in the literature.

TABLE 11.2 FREEZING POINT DATA FOR SELECT AGENTS

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

Example Calculations Using Freezing Point Data

- **How many milligrams each of sodium chloride and dibucaine hydrochloride are required to prepare 30 mL of a 1% solution of dibucaine hydrochloride isotonic with tears?**
- To make this solution isotonic, the freezing point must be lowered to - 0.52. From Table 11.2, it is determined that a 1% solution of dibucaine hydrochloride has a freezing point lowering of 0.08°. Thus, sufficient sodium chloride must be added to lower the freezing point an additional 0.44° (0.52° - 0.08°).
- Also from Table 11.2, it is determined that a 1% solution of sodium chloride lowers the freezing point by 0.58°.
- By proportion:

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

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

- Thus, to make 30 mL of solution,

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

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

Note:

- Should a prescription call for more than one medicinal and/or pharmaceutic ingredient,the sum of the freezing points is subtracted from the required value in determining the additional lowering required by the agent used to provide isotonicity.

CALCULATIONS CAPSULE

Isotonicity

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

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

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

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

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

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

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

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

CASE IN POINT 11.1[3]: 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,*[6] Mycobacterium chelonae, and *Mycobacterium* fortuitum.[7–9]

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 ($C_{22}H_{43}N_5O_{13}{\bullet}2H_2SO_2$), 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?

Case in Point 11.1

(a) 60 mL × 2.5% w/v = 1.5 g amikacin sulfate, *answer.*

(b) sodium chloride m.w. = 58.5

amikacin m.w. = 781.76

$i = 2.6$

$$\frac{58.5}{1.8} \times \frac{2.6}{781.76} = E$$

$E = 0.108$, *answer.*

(c) 60 mL × 0.9% w/v = 0.54 g sodium chloride, *answer.*

(d) 1.5 g (amikacin sulfate) × 0.108 (NaCl equivalent) = 0.162 g

0.54 g – 0.162g = 0.378 g sodium chloride required for isotonicity

$$\frac{23.5\ g}{100\ mL} = \frac{0.378\ g}{x\ mL},$$

x = 1.61 mL sodium chloride injection, *answer.*


T H A N K Y O U