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Pharmaceutical calculation

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Isotonic and Buffer Solutions

Lec 2

When a solvent passes through a semipermeable membrane from a dilute solution into a more concentrated one, the concentrations become equalized and the phenomenon is known as ***osmosis***. The pressure responsible for this phenomenon is termed ***osmotic pressure*** and varies with the nature of the solute.

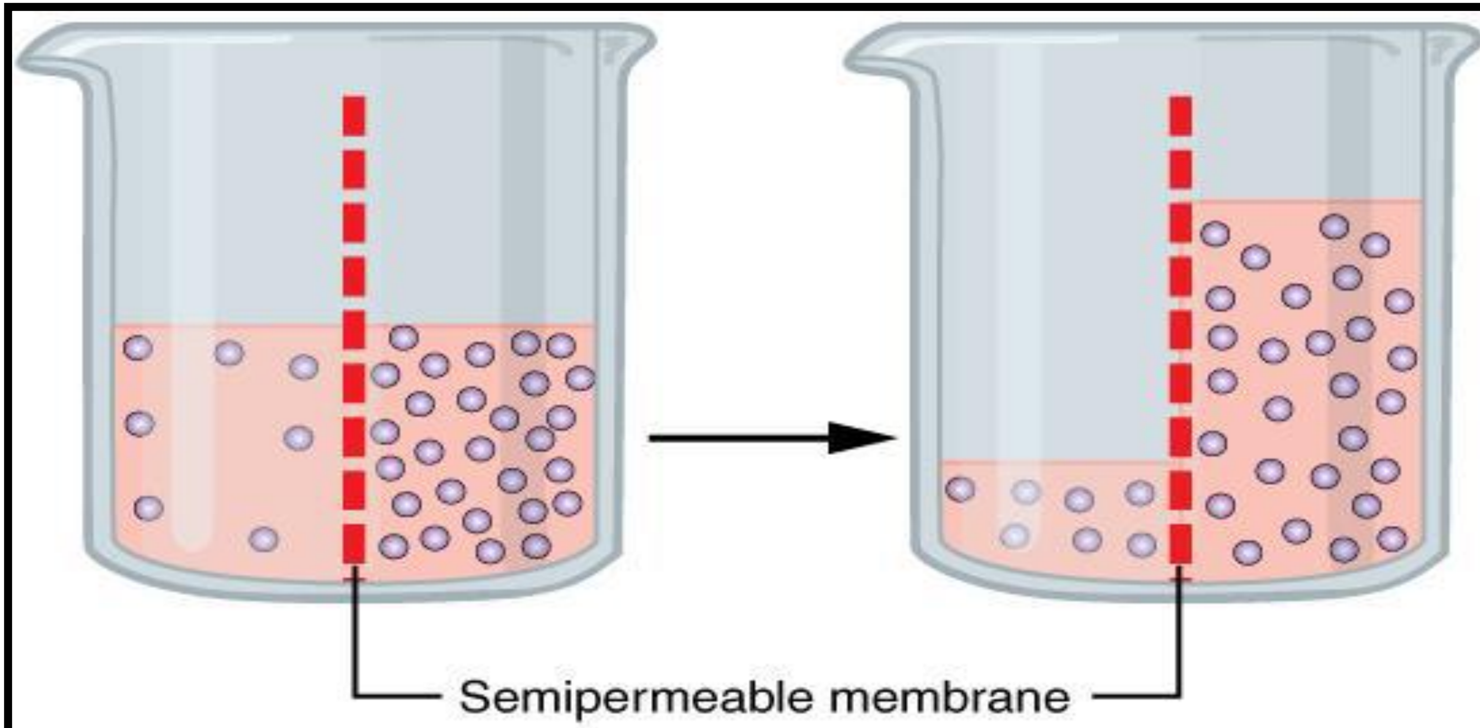
If the solute is a **nonelectrolyte**, its solution contains only molecules and the osmotic pressure varies with the concentration of the solute. If the solute is an **electrolyte**, its solution contains ions and the osmotic pressure varies with both the concentration of the solute and its degree of 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.

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

Osmosis



Osmosis:

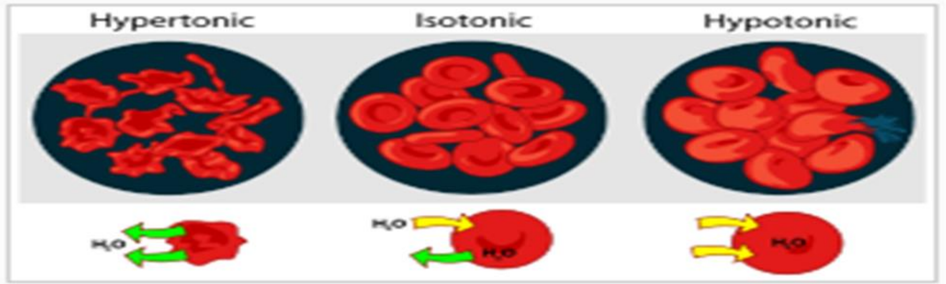
2 solutions of different concentrations are separated by a semi-permeable membrane (only permeable to the solvent) the solvent will move from the solution of lower conc. to that of higher conc

Types of Tonicity

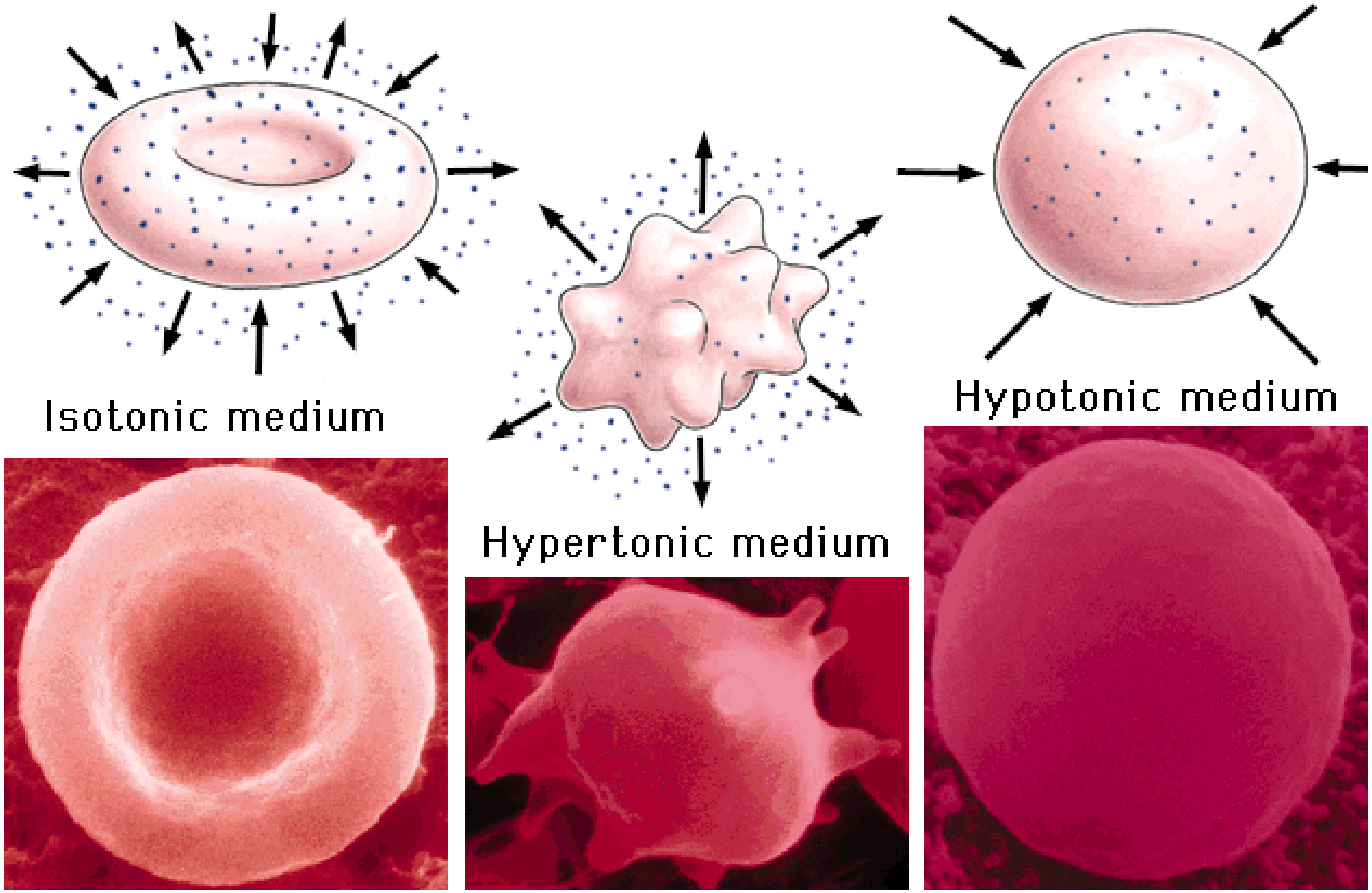
Solutions of lower osmotic pressure than that of a body fluid are termed **hypotonic**, whereas those having a higher osmotic pressure are termed **hypertonic**.

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

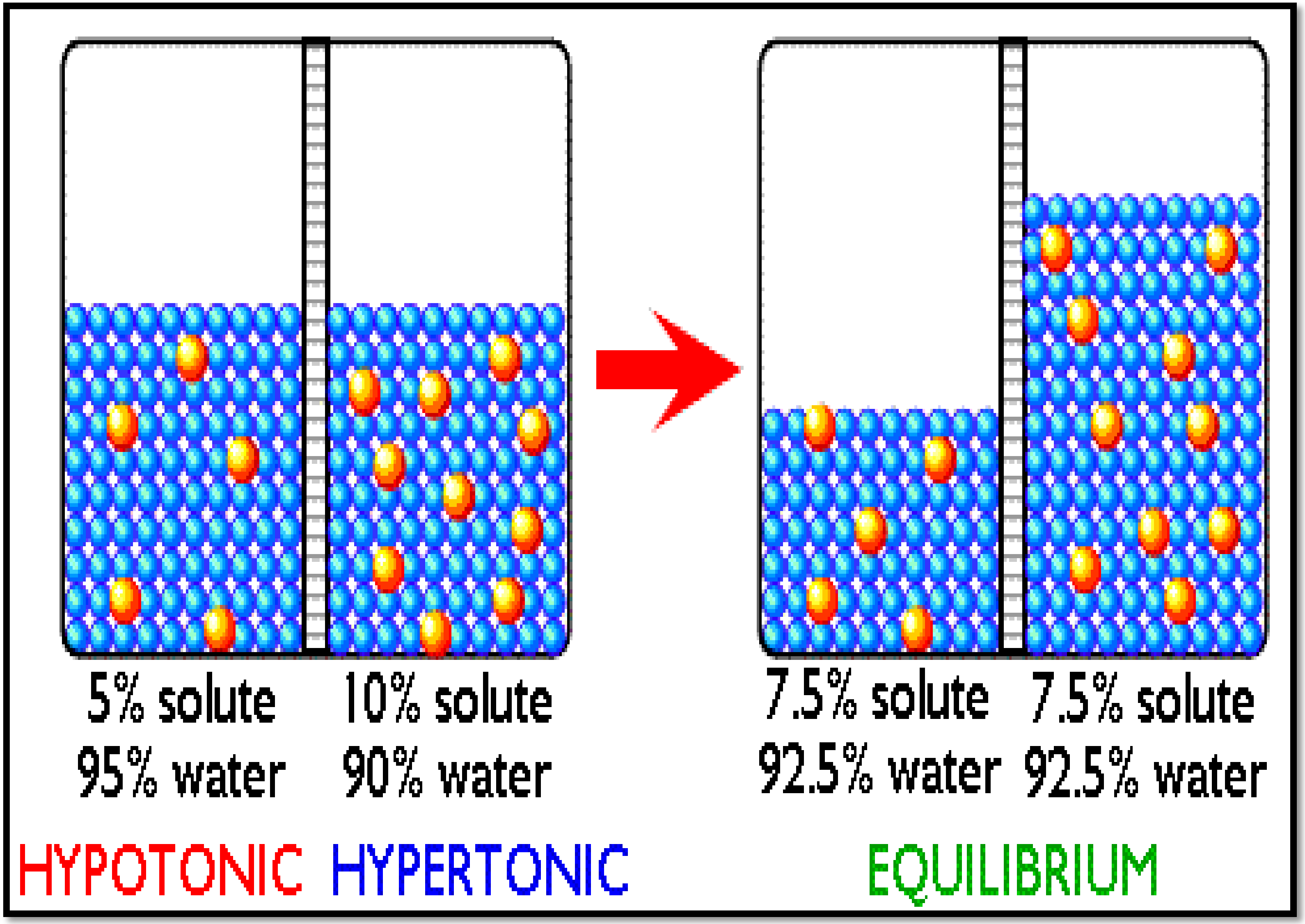
The calculations involved in preparing **isotonic solutions** may be made in terms of data relating to the colligative properties of solutions



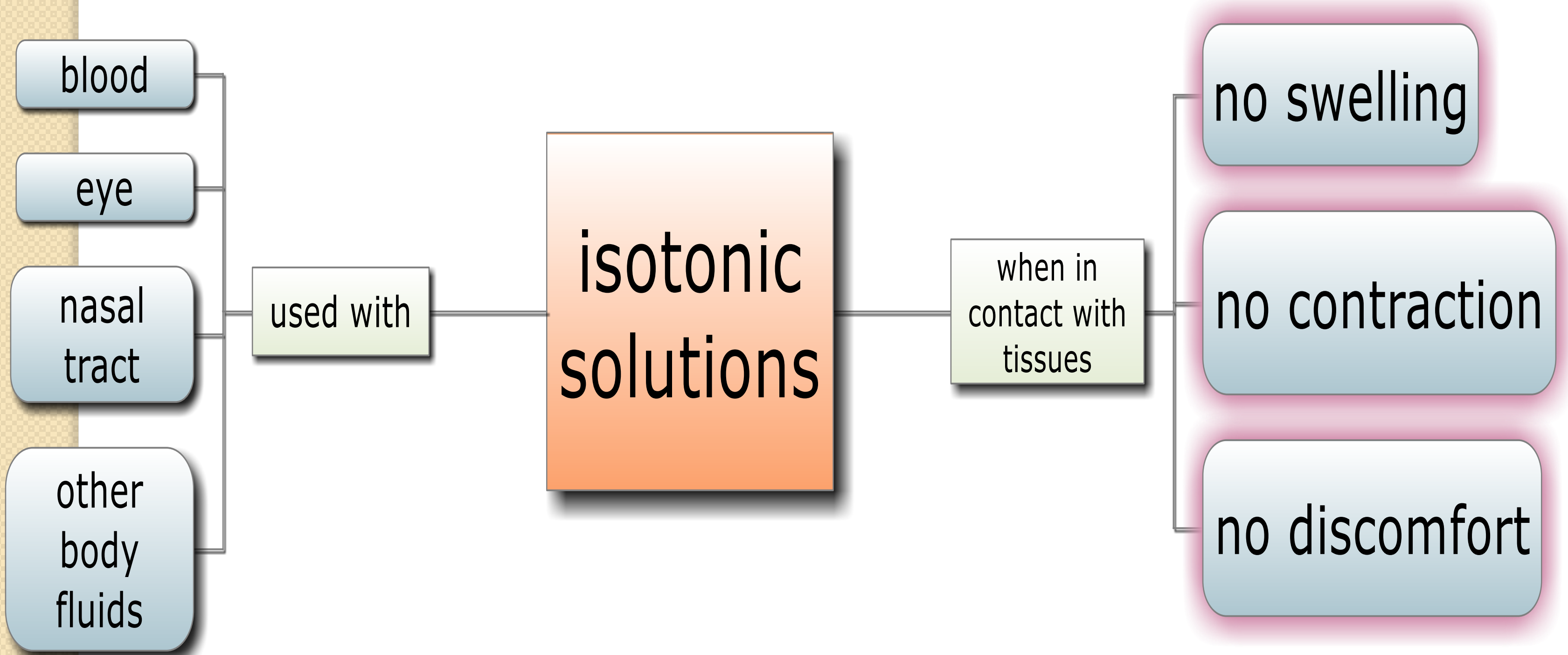
Effect of different solutions on blood cells



Isotonic medium
Hypertonic medium
Hypotonic medium


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

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

Theoretically, any one of these properties **(colligative properties)** may be used as a basis for determining tonicity. Practically and most conveniently, a comparison of **freezing points** is used for this purpose. It is generally accepted that -0.52℃ is the freezing point of both blood serum and lacrimal fluid.

When one gram molecular weight of any nonelectrolyte, that is, a substance with negligible dissociation, such as boric acid, is dissolved in 1000 g of water, the freezing point of the solution is about -1.86℃ below the freezing point of pure water. By simple proportion, therefore, we can calculate the weight of any nonelectrolyte that should be dissolved in each 1000 g of water if the solution is to be isotonic with body fluids.

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

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

$$x = 17.3\ g$$

In short, 17.3 g of boric acid in 1000 g of water, having a weight-in-volume strength of approximately 1.73%, should make a solution isotonic with lacrimal fluid.

With **electrolytes**, the problem is not so simple. Because osmotic pressure depends more on the number than on the kind of particles, substances that dissociate have a tonic effect that increases with the degree of dissociation; the **greater** the dissociation, the **smaller** the quantity required to produce any given osmotic pressure. If we assume that sodium chloride in weak solutions is about 80% dissociated, then each 100 molecules yields 180 particles, or 1.8 times as many particles as are yielded by 100 molecules of a nonelectrolyte. This dissociation factor, commonly symbolized by the letter *i,* must be included in the proportion when we seek to determine the strength of an isotonic solution of sodium chloride (m.w. 58.5):

$$\frac{1.86\ (^\circ C) \times 1.8}{0.52\ (^\circ C)} = \frac{58.5\ (g)}{x\ (g)}$$

$$x = 9.09\ g$$

Hence, 9.09 g of sodium chloride in 1000 g of water should make a solution isotonic with blood or lacrimal fluid. In practice, a 0.90% w/v sodium chloride solution is considered isotonic with body fluids. Simple isotonic solutions may then be calculated by using this formula

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

The value of *i* for many a medicinal salt has not been experimentally determined. Some salts (such as zinc sulfate, with only some 40% dissociation and an *i* value therefore of 1.4) are exceptional, but most medicinal salts approximate the dissociation of sodium chloride in weak solutions. If the number of ions is known, we may use the following values, lacking better information:

Nonelectrolytes and substances of slight dissociation1.0
Substances that dissociate into 2 ions: 1.8
Substances that dissociate into 3 ions: 2.6
Substances that dissociate into 4 ions: 3.4
Substances that dissociate into 5 ions: 4.2
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.

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

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

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.*

Example Calculations of the Sodium Chloride Equivalent

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

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

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.

$$\frac{58.5}{1.8} \times \frac{1.8}{376} = 0.156, \text{ or } 0.16, \textit{ answer.}$$

Calculate the sodium chloride equivalent for glycerin, a nonelectrolyte with a molecular weight of 92.2

Glycerin, *i* factor 1.0

$$\frac{58.5}{1.8} \times \frac{1.0}{92} = 0.35, \textit{ answer.}$$

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

TABLE 11.2 FREEZING POINT DATA FOR SELECT AGENTS

AGENT	FREEZING POINT DEPRESSION, 1% SOLUTIONS ($\Delta T_f^{1\%}$)
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 of Tonicic Agent Required

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

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

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

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

Step 3. 0.270 g (from Step 2) -0.069 g (from Step 1)
=0.201 g of sodium chloride to be used, *answer.*

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

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

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

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

Thus, to make 30 mL of solution,

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

30 mL x 0.76% = 0.228 g= 228 mg sodium chloride, *answers*


THANK YOU