Pharmaceutical calculation
Chapter 11
Isotonic solutions

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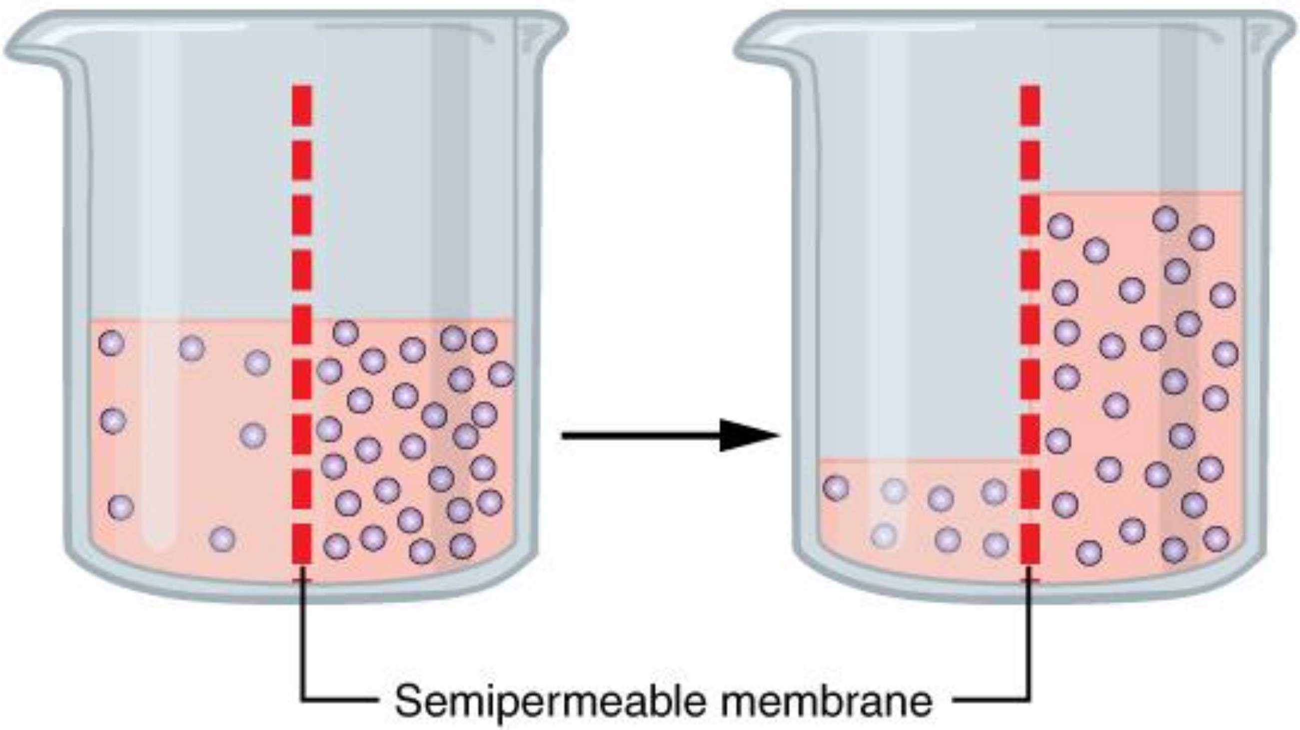
Introduction

- When a solvent passes through a semi-permeable 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.

Osmosis



- 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.

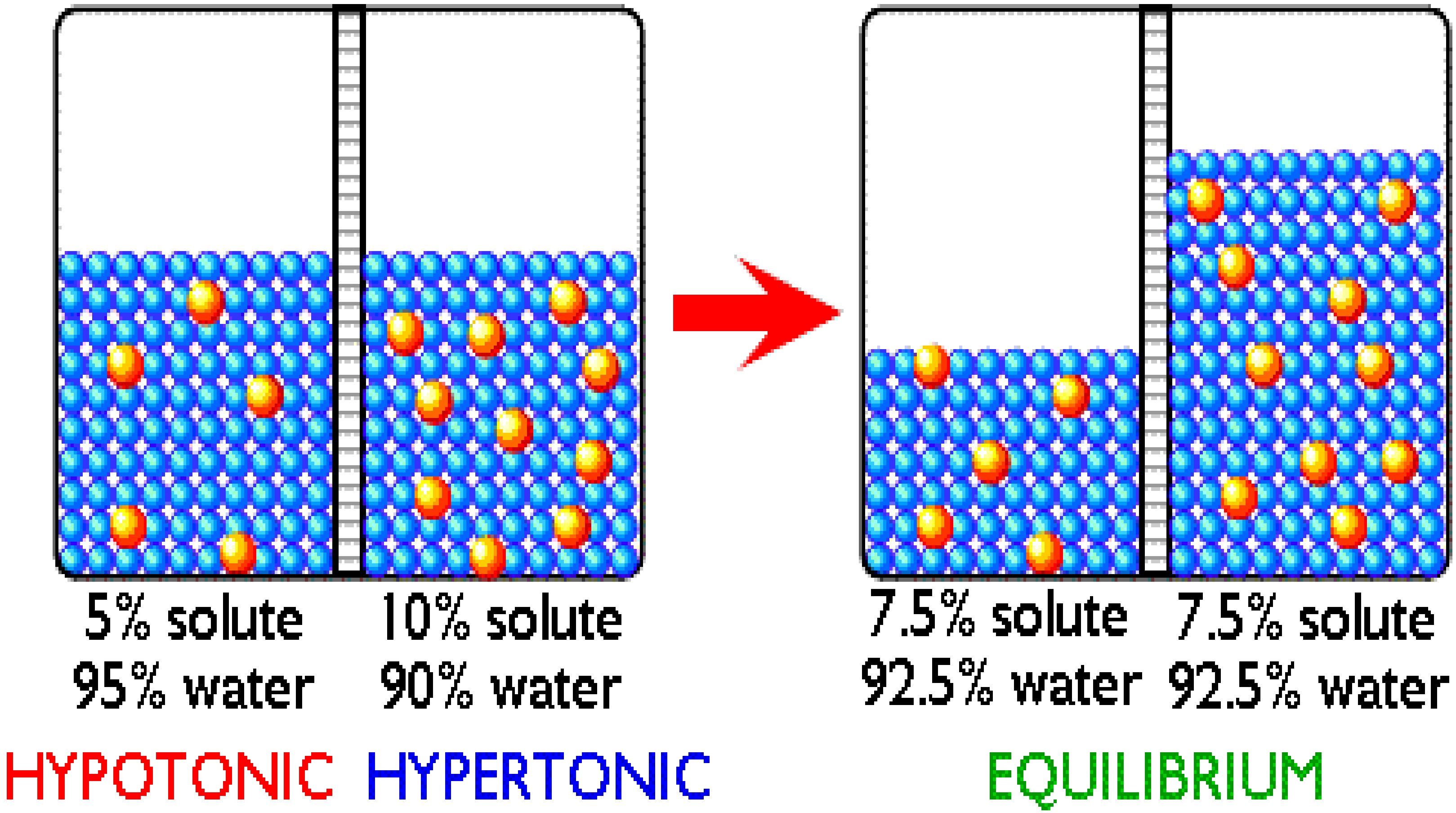
- Two solutions that have the same osmotic pressure are termed isosmotic.
- Many solutions intended to be mixed with body fluids are designed to have the same osmotic pressure for greater patient comfort, efficacy, and safety.
- A solution having the same osmotic pressure as a specific body fluid is termed isotonic (meaning of equal tone) with that specific body fluid.
- 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.

Definitions

- *Isotonic Solution*: is a solution having the same osmotic pressure as a body fluid. Ophthalmic (eye), nasal(nose), and parenteral (injection) solutions should be isotonic.

- *Hypotonic solution*: is a solution of lower osmotic pressure than that of a body fluid.

- *Hypertonic solution*: is a solution having a higher osmotic pressure than that of a body fluid.

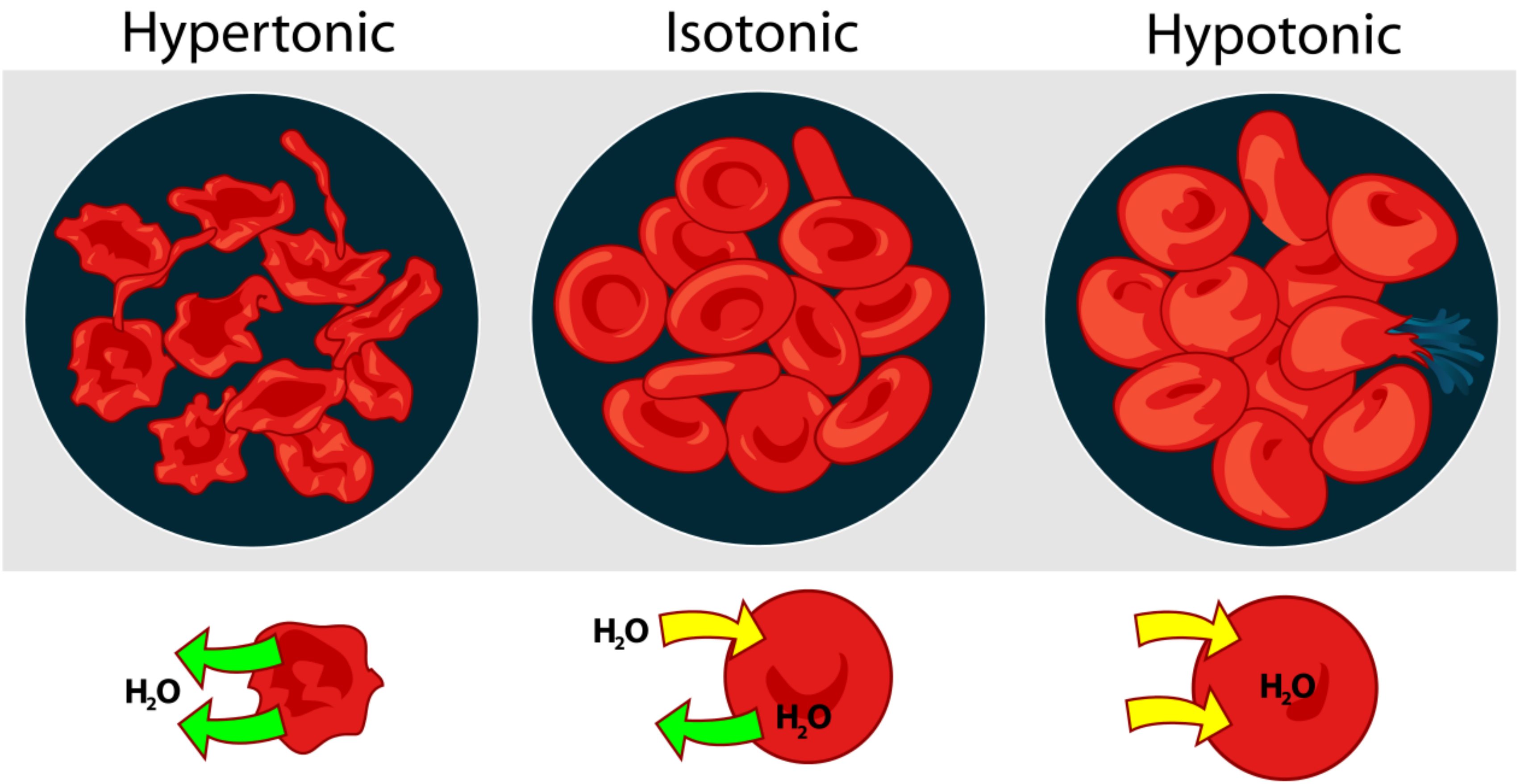

5% solute
95% water
10% solute
90% water
7.5% solute
92.5% water
7.5% solute
92.5% water
HYPOTONIC
HYPERTONIC
EQUILIBRIUM

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.
- With the administration of an isotonic solution, there is a homeostasis with the body's intracellular fluids. Thus, in most instances, preparations that are isotonic, or nearly so, are preferred.
- 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 duplicate ophthalmic tears for the comfort of the patient.
- These solutions are also prepared and buffered at an appropriate pH, both to reduce the likelihood of irritation to the eye’s tissues and to maintain the stability of the preparations.
- Injections that are not isotonic should be administered slowly and in small quantities to minimize tissue irritation, pain, and cell fluid imbalance. The tonicity of small-volume injections is generally inconsequential when added to large-volume parenteral infusions because of the presence of tonic substances, such as sodium chloride or dextrose in the large-volume infusion, which serve to adjust the tonicity of the smaller added volume.

- Intravenous infusions, which are hypotonic or hypertonic, can have profound adverse effects because they generally are administered in large volumes.
- Large volumes of hypertonic infusions containing dextrose, for example, can result in hyperglycemia, osmotic diuresis, and excessive loss of electrolytes.
- Excess infusions of hypotonic fluids can result in the osmotic hemolysis of red blood cells and surpass the upper limits of the body's capacity to safely absorb excessive fluids. Even isotonic fluids, when infused intravenously in excessive volumes or at excessive rates, can be deleterious due to an overload of fluids placed into the body's circulatory system.


Hypertonic
Isotonic
Hypotonic
H_2O
H_2O
H_2O
H_2O

Physical/chemical considerations in the preparation of isotonic solutions

- The calculations involved in preparing isotonic solutions may be made in terms of data relating to the colligative properties of solutions.
- Theoretically, any one of these 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°C 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 °C 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°C. Therefore:

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

$$x = 17.3 \text{ g}$$

- 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):

$$\frac{1.86(°C) \text{ X } 1.8}{0.52(°C)} = \frac{58.5(g)}{x(g)}$$

$$x = 9.09 \text{ g}$$

- 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 dissociation: 1.0
- 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

- 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 relative tonic effect of two substances—that is, the quantity of one that is the equivalent in tonic effects to a given quantity of the other—may be calculated if the quantity of one having a certain effect in a specified quantity of solvent is divided by the quantity of the other having the same effect in the same quantity of solvent.
- For example, we calculated that 17.3 g of boric acid per 1000 g of water and 9.09 g of sodium chloride per 1000 g of water are both instrumental in making an aqueous solution isotonic with lacrimal fluid.
- If, however, 17.3 g of boric acid are equivalent in tonicity to 9.09 g of sodium chloride, then 1 g of boric acid must be the equivalent of 9.09 g ÷ 17.3 g or 0.52 g of sodium chloride. Similarly, 1 g of sodium chloride must be the ‘‘tonicic equivalent’’ of 17.3 g ÷ 9.09 g or 1.90 g of boric acid.

- We have seen that one quantity of any substance should in theory have a constant tonic effect if dissolved in1000 g of water:1 g molecular weight of the substance divided by its i or dissociation value. Hence, the relative quantity of sodium chloride that is the tonicic equivalent of a quantity of boric acid may be calculated by these ratios:

$$\frac{58.5 \div 1.8}{61.8 \div 1.0} \; or \; \frac{58.5 \times 1.0}{61.8 \times 1.8}$$

and we can formulate a convenient rule: quantities of two substances that are tonicic equivalents are proportional to the molecular weights of each multiplied by the i value of the other.

- To return to the problem involving 1 g of atropine sulfate in 100 mL of solution:
- Molecular weight of sodium chloride = 58.5; i = 1.8
- Molecular weight of atropine sulfate = 695; i = 2.6

$$\frac{695 \times 1.8}{58.5 \times 2.6} = \frac{1(g)}{x(g)}$$

x = 0.12 g of sodium chloride represented by 1 g of atropine sulfate

- 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.

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

- Table 11.1 gives the sodium chloride equivalents (E values) of each of the substances listed. These values were calculated according to the rule stated previously. **If the number of grams of a substance included in a prescription is multiplied by its sodium chloride equivalent, the amount of sodium chloride represented by that substance is determined.**
- 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.)
- Step3.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
- Because140 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-ionelectrolyte,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:

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

- 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.

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

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

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

- Calculate the sodium chloride equivalent for timolol maleate, which dissociates into two ions and has a molecular weight of 432.2
- Timolol maleate, *i* factor = 1.8

$$\frac{58.5}{1.8} \times \frac{1.8}{432} = 0.14, \mathit{answer}$$

- Calculate the sodium chloride equivalent for fluorescein sodium, which dissociates into three ions and has a molecular weight of 376.2

Fluorescein sodium, *i* factor = 2.6

$$\frac{58.5}{1.8} \times \frac{2.6}{376} = 0.23, \textit{answer}$$

Example Calculations of Tonicic Agent Required

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

Rx 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.

How many grams of boric acid should be used in compounding the following prescription?

Rx Phenacaine Hydrochloride 1%

Chlorobutanol ½ %

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.

Step 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

Step 2.

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

Step 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:

Step 4.

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

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

Rx Sol. Silver Nitrate 60

1: 500 w/v

Make isoton. sol.

Sig. For eye use.

The prescription contains 0.12 g of silver nitrate.

Step 1.

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

Step 2.

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

Step 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,

Step 4.

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

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

Rx 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:

$$\frac{58.5}{1.8} \times \frac{2.4}{295} = 0.26\text{, the sodium chloride equivalent for ingredient X}$$

Then, Step 1.

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

Step 2.

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

Step 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:

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

Step 3.

Add 0.9% w/v sodium chloride solution to complete the required volume of the prescription or medication order. Using this method, 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 or 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

Use of Freezing Point Data in Isotonicity Calculations

- Freezing point data (ΔT_f) 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 - 0.52°C. Thus, a pharmaceutical solution that has a freezing point of -0.52°C 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% ($\Delta T_f^{1\%}$), data for other solution strengths and for many additional agents may be found in physical pharmacy textbooks and in the literature. Freezing point depression data may be used in isotonicity calculations as shown by the following.

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 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:

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

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.

Note: Should a prescription call for more than one medicinal and/or pharmaceutic ingredient, thesumofthefreezingpointsissubtractedfromtherequiredvalueindeterminingtheadditional 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 ($C_{22}H_{43}N_5O_{13} \cdot 2H_2SO_2$), 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

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

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