

Pharmaceutical calculation
Second semester-1st year students
Lecture-3

Isotonic solutions

Chapter 11

Text Book

Howard C. Ansel, Pharmaceutical calculation 13th
edition 2010, Wolters Kluwer Lippincott Williams
&Wilkins

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2019-2020

Objective

- Upon successful completion of this chapter, the student will be able to:
- Calculate the dissociation factor (i) of a chemical agent.
- Calculate the sodium chloride equivalent (E-value) of a chemical agent.
- Demonstrate by calculation whether a solution is hypotonic, isotonic, or hypertonic.
- Perform calculations required in the preparation of isotonic solutions.

Isotonic solutions

- **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.

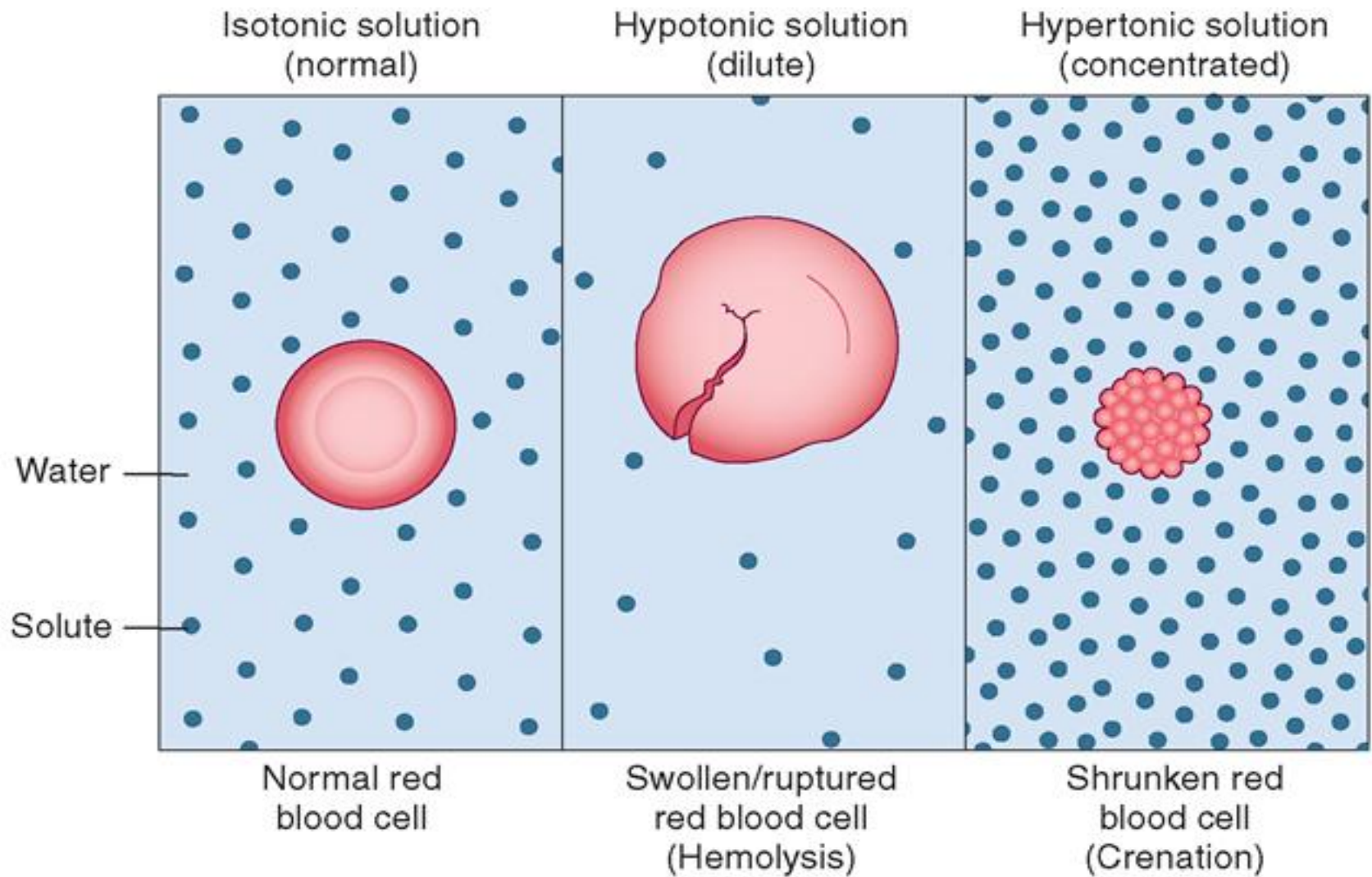
- If the solute is a nonelectrolyte, its solution contains only molecules and the osmotic pressure varies with the concentration of the solute.
- If the solute is an electrolyte, its solution contains ions and the osmotic pressure varies with both
 1. the concentration of the solute and
 2. its degree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

- 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.

- 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.



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:

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

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

- 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.
- Since NaCl give two ions on dissociation
- $80 + 80 + 20 = 180$
- 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):

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

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

- 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 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

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.

- 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
- $0.9 \text{ g} - 0.5 \text{ g} = 0.4 \text{ g}$ 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 $9.09 \text{ g} \div 17.3 \text{ g}$ or 0.52 g of sodium chloride.
- Similarly, 1 g of sodium chloride must be the “tonicic equivalent” of $17.3 \text{ g} \div 9.09 \text{ g}$ 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 in 1000 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 tonic equivalent of a quantity of boric acid may be calculated by these ratios:

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

and we can formulate a convenient rule: quantities of two substances that are tonic 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; $i = 2.6$

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

- $x = 0.12$ 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 $0.90 \text{ g} - 0.12 \text{ g} = 0.78 \text{ g}$ of sodium chloride.

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.

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

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

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

- 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

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

- 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

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

TABLE 11.1 SODIUM CHLORIDE EQUIVALENTS (E VALUES)

SUBSTANCE	MOLECULAR WEIGHT	IONS	<i>f</i>	SODIUM CHLORIDE EQUIVALENT (E VALUE)
Antazoline phosphate	363	2	1.8	0.16
Antipyrine	188	1	1.0	0.17
Atropine sulfate-H ₂ O	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
Demecartum bromide	717	3	2.6	0.12
Dextrose (anhydrous)	180	1	1.0	0.18
Dextrose-H ₂ O	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 ₂ O	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 ₂ O	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 ₂ O	381	5	4.2	0.42

(continued)

TABLE 11.1 continued

SUBSTANCE	MOLECULAR WEIGHT	IONS	<i>f</i>	SODIUM CHLORIDE EQUIVALENT (E VALUE)
Sodium carbonate	106	3	2.6	0.80
Sodium carbonate-H ₂ O	124	3	2.6	0.68
Sodium chloride	58	2	1.8	1.00
Sodium citrate-2H ₂ O	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 ₂ O	268	3	2.6	0.29
Sodium phosphate, monobasic, anhydrous	120	2	1.8	0.49
Sodium phosphate, monobasic-H ₂ O	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 ₂ O	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.)
- 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 Tonic 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.

1. Step 1.

$0.23 \times 0.3 \text{ g} = 0.069 \text{ g}$ of sodium chloride represented by the pilocarpine nitrate

2. Step 2.

$30 \times 0.009 = 0.270 \text{ g}$ of sodium chloride in 30 mL of an isotonic sodium chloride solution

3. Step 3.

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