

PHARMACEUTICAL AND CLINICAL CALCULATIONS



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PHARMACEUTICAL AND CLINICAL CALCULATIONS

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Calculations Involving Topical Ophthalmic, Nasal, and Otic Preparations

A variety of pharmaceutical dosage forms are applied topically to the eye, nose, and ear which include solutions, suspensions, and ointments. In general, drugs are applied to the eye for the local effects of the medication, either on the surface of the eye or its interior. Amongst the various types of dosage forms for the eye, aqueous solutions are the most frequently used. In the extemporaneous preparation of ophthalmic formulations, one should consider sterility, preservation, isotonicity, pH and buffering, and viscosity. Nasal preparations are generally used for their decongestant activity on the nasal mucosa. Important considerations in the preparation of nasal solutions include isotonicity, pH and buffering, and viscosity. Ear preparations are also referred to as *otic* or *aural* preparations. Most of the official ear preparations are aqueous solutions of medications. They are used for treating mild infections, softening wax, cleansing after infections, drying wet surfaces, and as antiseptics. The important considerations in the formulation of otic products include pH and buffering. For example, an otic product with a pH value of less than 4 may cause burning and stinging sensation in the ear canal.

The present chapter deals with calculations involving isotonicity, pH, and buffering of topical preparations. The discussion presented here is also relevant to the dosage forms for other routes of administration including parenteral routes.

ISOTONICITY

Whenever a solution is separated from a solvent by a membrane permeable only to solvent molecules but impermeable to solutes (referred to as a "semi-

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permeable membrane"), the solvent passes across the membrane into the solution. This is the phenomenon of osmosis, which may be defined as the passage of solvent molecules across a semipermeable membrane against the concentration gradient. Osmosis can also occur when a concentrated solution is separated from a less concentrated solution by a semipermeable membrane. The pressure differential that develops across the membrane is called "osmotic pressure."

Osmotic pressure is a colligative property and is dependent on the number of particles of solute(s) in a solution. The total number of particles of a solute in a solution is the sum of the undissociated molecules and the number of ions into which the molecule dissociates. The number of ions, in turn, depends on the degree of ionization. Thus, a chemical that is highly ionized contributes a greater number of particles to the solution than the same amount of a poorly ionized chemical. When a chemical is a nonelectrolyte such as sucrose or urea, the concentration of the solution depends only on the number of molecules present. The values of the osmotic pressure and other colligative properties are approximately the same for equal concentrations of different nonelectrolyte solutions.

Body fluids, including blood and tears, have the same osmotic pressure as that of a 0.9% w/v sodium chloride solution. Solutions having the same osmotic pressure as that of 0.9% w/v NaCl solution are said to be *isotonic* with blood. Solutions with a higher osmotic pressure than body fluids are called *hypertonic* and those with a lower osmotic pressure are called *hypotonic*.

Osmotic effects are very important from a physiological standpoint. This is because biological membranes including the membrane of red blood cells behave like semipermeable membranes. Consequently, when red blood cells are immersed in a hypertonic solution (e.g., D₅ ½ NS or D₅NS), they shrink as water leaves the blood cells in an attempt to dilute and establish a concentration equilibrium across the blood cell membrane. Thus, when hypertonic solutions are administered into the blood stream, the fluid moves from interstitial and cellular space into the intravascular space. Conversely, when cells are placed in hypotonic environment (e.g., ½ NS), they swell because of the entry of fluid from the intravascular compartment, and may eventually undergo lysis.

In the eye, hypertonic solutions may cause drawing of water towards the site of application; whereas hypotonic solutions may cause water to move from the topical application site through the tissues of the eye. When instilled into the eye, isotonic solutions cause no contraction or swelling of the tissues with which they come in contact, and cause no discomfort. Therefore, it is very important to adjust the isotonicity of topical ophthalmic products. Isotonic adjustments are also important for nasal and aural preparations, parenteral products, and irrigating solutions. In a given product, all the

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additives including the active and inactive ingredients, contribute to the osmotic pressure of the solution.

CALCULATION OF DISSOCIATION (i) FACTOR

Since osmotic pressure depends upon the number of particles of solute(s) in solution, the osmotic pressure of an electrolyte is directly proportional to the degree (or extent) of dissociation. The dissociation factor, symbolized by the letter i , can be calculated by dividing the total number of particles (which include undissociated molecules and ions) in a solution by the number of particles before dissociation, i.e.,

$$i = \frac{\text{Total number of particles of solute in a solution after dissociation}}{\text{Number of particles before dissociation}}$$

Example 1:

What is the dissociation factor of NaCl, having 80% dissociation in water?

Assume that we have 100 particles of NaCl prior to dissociation. Upon 80% dissociation, 100 molecules of sodium chloride yield:

80	sodium ions
80	chloride ions
20	undissociated sodium chloride particles
180	total particles in solution

$$\text{answer: } i = 180/100 = 1.8$$

Note: About 80% of NaCl is dissociated in water. Thus, the dissociation factor, i , of NaCl is assumed to be 1.8.

Example 2:

What is the dissociation factor of zinc sulfate, having 40% dissociation in water?

Assume that we have 100 particles of zinc sulfate prior to dissociation. Upon 40% dissociation, 100 molecules of zinc sulfate yield:

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40	zinc ions
40	sulfate ions
60	undissociated zinc sulfate particles
140	total particles in solution

$$\text{answer: } i = 140/100 = 1.4$$

Example 3:

What is the dissociation factor of zinc chloride, having 80% dissociation in water?

Assume that we have 100 particles of zinc chloride prior to dissociation. Upon 80% dissociation, 100 molecules of zinc chloride yield:

80	zinc ions
160	(2 × 80) chloride ions
20	undissociated zinc chloride particles
260	total particles in solution

$$\text{answer: } i = 260/100 = 2.6$$

SODIUM CHLORIDE EQUIVALENTS OF DRUG SUBSTANCES

The sodium chloride equivalent of a chemical is defined as the amount of sodium chloride (in grams or grains) that has the same osmotic pressure as that of 1 g of the chemical. The sodium chloride equivalents are symbolized by the letter *E*. The quantities of two substances that are isotonic equivalents are proportional to the molecular weight of each multiplied by the *i* value of the other. Thus, if the molecular weight and *i* value of a given chemical are known, one can calculate the sodium chloride equivalent, *E*, of that chemical as follows:

$$E = \frac{\text{MW of NaCl}}{i \text{ value of NaCl}} \times \frac{i \text{ value of the chemical}}{\text{MW of the chemical}}$$

Example 1:

Calculate the sodium chloride equivalent of a 1% solution of pilocarpine nitrate.

Pilocarpine nitrate has a molecular weight of 271 and *i* of 1.8.

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$$E = \frac{\text{MW of NaCl}}{i \text{ value of NaCl}} \times \frac{i \text{ value of pilocarpine nitrate}}{\text{MW of pilocarpine nitrate}}$$

$$E = \frac{58.5}{1.8} \times \frac{1.8}{271}$$

$$= 105.3/487.8$$

= 0.22, i.e., 1 g of pilocarpine nitrate is equivalent to 0.22 g of NaCl

answer: $E = 0.22$

Example 2:

Calculate the sodium chloride equivalent of a 1% zinc chloride.

Zinc chloride has a molecular weight of 136 and i of 2.6.

$$E = \frac{\text{MW of NaCl}}{i \text{ value of NaCl}} \times \frac{i \text{ value of zinc chloride}}{\text{MW of zinc chloride}}$$

$$E = \frac{58.5}{1.8} \times \frac{2.6}{136}$$

$$= 152.1/244.8$$

= 0.62, i.e., 1 g of zinc chloride is equivalent to 0.62 g of NaCl

answer: $E = 0.62$

Example 3:

Calculate the sodium chloride equivalent of a 1% boric acid.

Boric acid has a molecular weight of 62 and i of 1.

$$E = \frac{\text{MW of NaCl}}{i \text{ value of NaCl}} \times \frac{i \text{ value of boric acid}}{\text{MW of boric acid}}$$

$$E = \frac{58.5}{1.8} \times \frac{1}{62}$$

$$= 58.5/111.6$$

= 0.52, i.e., 1 g of boric acid is equivalent to 0.52 g of NaCl

answer: $E = 0.52$

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TABLE 8.1. Number of Ions, Dissociation Factor (*i*), and Molecular Weight (MW) of Selected Compounds.

	Ions	<i>i</i>	MW
Boric acid	1	1.0	62
Chlorobutanol	1	1.0	177
Dextrose, anhydrous	1	1.0	180
Dextrose, H ₂ O	1	1.0	198
Mannitol	1	1.0	182
Benzalkonium chloride	2	1.8	360
Cocaine HCl	2	1.8	340
Cromolyn sodium	2	1.8	512
Dipivefrin HCl	2	1.8	388
Ephedrine HCl	2	1.8	202
Epinephrine bitartrate	2	1.8	333
Eucatropine HCl	2	1.8	328
Homatropine HBr	2	1.8	356
Oxymetazoline HCl	2	1.8	297
Oxytetracycline HCl	2	1.8	497
Phenylephrine HCl	2	1.8	204
Procaine HCl	2	1.8	273
Scopolamine HBr·3H ₂ O	2	1.8	438
Silver nitrate	2	1.8	170
Sodium chloride	2	1.8	58
Sodium phosphate, monobasic, anhydrous	2	1.8	120
Sodium phosphate, monobasic·H ₂ O	2	1.8	138
Tetracaine HCl	2	1.8	301
Zinc sulfate·7H ₂ O	2	1.8	288
Atropine sulfate, H ₂ O	3	2.6	695
Ephedrine sulfate	3	2.6	429
Sodium phosphate, dibasic, anhydrous	3	2.6	142
Sodium phosphate, dibasic·7H ₂ O	3	2.6	268

Table 8.1 lists number of ions produced upon dissociation, dissociation factor (*i*), and molecular weight of selected compounds.

ISOTONICITY ADJUSTMENTS BY SODIUM CHLORIDE EQUIVALENT METHOD

The sodium chloride equivalent method is the most frequently used method in the calculation of the amount of sodium chloride needed to prepare isotonic drug solutions. The sodium chloride equivalent of any drug substance, as discussed earlier, is the amount (in grams) of sodium chloride that is osmotically equivalent to 1 g of the drug. The sodium chloride equivalents for selected compounds are listed in Table 8.2.

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Any hypotonic solution containing one or more drugs can be rendered isotonic by adding appropriate quantity of sodium chloride. Following is a sample prescription that requires isotonic adjustments:

R	
Atropine Sulfate	1%
Sodium Chloride	q.s.
Purified Water ad	100
Make isoton. sol.	
Sig. Gtt. i.o.u.	

TABLE 8.2. Sodium Chloride Equivalents (*E*) and Freezing Point Depression (ΔT_f°) Values of Selected Compounds.

Substance	<i>E</i>	ΔT_f°
Ammonium chloride	1.08	0.64
Apomorphine hydrochloride	0.14	0.08
Atropine sulfate	0.13	0.07
Boric acid	0.52	0.29
Chlorobutanol	0.18	0.14
Cocaine hydrochloride	0.16	0.09
Dextrose monohydrate	0.16	0.09
Ephedrine hydrochloride	0.30	0.18
Ephedrine sulfate	0.23	0.14
Epinephrine bitartrate	0.18	0.11
Epinephrine hydrochloride	0.29	0.17
Eucatropine hydrochloride	0.18	0.11
Fluorescein sodium	0.31	0.18
Glycerin	0.34	0.20
Naphazoline hydrochloride	0.27	0.16
Neomycin sulfate	0.11	0.06
Oxymetazoline	0.20	0.11
Phenol	0.35	0.2
Phenylephrine hydrochloride	0.32	0.18
Pilocarpine nitrate	0.22	0.14
Procaine hydrochloride	0.21	0.11
Scopolamine hydrobromide	0.12	0.07
Silver nitrate	0.33	0.19
Sodium chloride	1.00	0.58
Sulfacetamide sodium	0.23	0.14
Tetracaine hydrochloride	0.18	0.11
Zinc chloride	0.62	0.37
Zinc sulfate·7H ₂ O	0.15	0.09

E = Sodium chloride equivalent.

ΔT_f° = Freezing point depression of 1% solution.

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In the prescription above, 1% atropine sulfate is ordered. The sodium chloride equivalent of atropine sulfate is 0.13 (refer to Table 8.2). This means that 1% solution of atropine sulfate has same osmotic pressure as that of 0.13% solution of sodium chloride. This solution is hypotonic. Addition of 0.77 g (i.e., $0.9 - 0.13 = 0.77$) of sodium chloride per 100 mL of the 1% solution of atropine sulfate results in an isotonic solution. To determine the amount of sodium chloride required to render a given solution isotonic, the following steps may be used:

- Step 1: Find how much sodium chloride is needed to render the formulation isotonic with body fluids. (Remember isotonicity refers to 0.9% or 0.9 g/100 mL).
- Step 2: Find the amount of sodium chloride represented by the ingredients in the prescription by multiplying the quantity of each ingredient by its *E* value. Add up all the values obtained. This is the total amount of sodium chloride represented by all the ingredients in the prescription.
- Step 3: Subtract the total value obtained in Step 2 from the amount of sodium chloride required to render the formulation isotonic (i.e., the value obtained in Step 1). The value obtained in this step represents the amount of sodium chloride required to render the solution isotonic.

Example 1:

Find the quantity of sodium chloride required in compounding the following prescription. The sodium chloride equivalent of cocaine HCl is 0.16.

R	
Cocaine Hydrochloride	0.2
Sodium Chloride	q.s.
Purified Water ad	30.0
Make isoton. sol.	
Sig. One drop in each eye.	

Step 1: $(0.9/100) \times 30 = 0.27$ g

Step 2: $0.20 \times 0.16 = 0.032$ g

Step 3: answer: $0.27 - 0.032 = 0.238$ or 0.24 g

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Example 2:

Find the quantity of sodium chloride to be used in compounding the following prescription. The sodium chloride equivalent of ephedrine sulfate is 0.23.

R	
Ephedrine Sulfate	0.5
Sodium Chloride	q.s.
Purified Water ad	50
Make isoton. sol.	
Sig. Use as directed.	

Step 1: Sodium chloride needed to render the prescribed volume isotonic

$$(0.9/100) \times 50 = 0.45 \text{ g}$$

Step 2: $0.50 \times 0.23 = 0.115 \text{ g}$

Step 3: answer: grams of sodium chloride needed to make the solution isotonic = $0.45 - 0.115 = 0.335$ or 0.34 g

Example 3:

Find the quantity of sodium chloride to be used in compounding the following prescription. The values of sodium chloride equivalent of epinephrine HCl and scopolamine HBr are 0.29 and 0.12, respectively.

R	
Epinephrine Hydrochloride	1%
Scopolamine Hydrobromide	0.5%
Sodium Chloride	q.s.
Purified Water ad	60.0
Make isoton. sol.	
Sig. Use in the eye.	

Step 1: Sodium chloride needed to render the prescribed volume isotonic

$$(0.9/100) \times 60 = 0.54 \text{ g}$$

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Step 2: (a) Epinephrine HCl:

$$(1/100) \times 60 = 0.60$$

$$0.60 \times 0.29 = 0.174 \text{ g}$$

(b) Scopolamine HCl:

$$(0.5/100) \times 60 = 0.30$$

$$0.30 \times 0.12 = 0.036 \text{ g}$$

The total of sum of the weights (in grams) of epinephrine HCl and scopolamine HCl multiplied by their *E* values, i.e., the total of (a) + (b)

$$= 0.174 + 0.036 \text{ g} = 0.21 \text{ g}$$

Step 3: answer: sodium chloride required to make the solution isotonic

$$0.54 - 0.21 = 0.33 \text{ g}$$

TONICITY AGENTS OTHER THAN SODIUM CHLORIDE

If one desires to use a chemical other than sodium chloride, such as dextrose or boric acid, the quantity of that chemical can be calculated by dividing the value obtained in Step 3 (i.e., the amount of sodium chloride needed to render the solution isotonic with body fluids) with the *E* value of that chemical. A proportion can be set up which can be treated as Step 4 in addition to the three steps described earlier.

Example 1:

Find the quantity of boric acid (in grams) to be used in compounding the following prescription.

R	
Atropine Sulfate	1%
Boric Acid	q.s.
Purified Water ad	30.0
Make isoton. sol.	
Sig. One drop in each eye.	

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Step 1: $(0.9/100) \times 30 = 0.27 \text{ g}$

Step 2: $(1/100) \times 30 = 0.3 \text{ g}$

$$0.3 \times 0.13 = 0.039 \text{ g}$$

Step 3: $0.27 - 0.039 = 0.231 \text{ g}$

Step 4: From Step 3, 0.231 g of sodium chloride is required to make the preparation isotonic. But the prescription calls for boric acid as the tonicity agent. Boric acid has an *E* value of 0.52. This means that 1% boric acid is osmotically equivalent to 0.52% NaCl or 1 g of boric acid is equivalent to 0.52 g of NaCl.

$$\frac{1 \text{ g}}{0.52 \text{ g}} = \frac{X}{0.231 \text{ g}}$$

where *X* is grams of boric acid equivalent to 0.231 g of sodium chloride.

answer: solving for *X*, we get: $(0.231 \times 1) \div 0.52 = 0.444 \text{ grams}$

Example 2:

Find the quantity of boric acid (in grams) to be used in compounding the following prescription.

R	
Tetracaine Hydrochloride	0.1
Zinc Sulfate	0.05
Boric Acid	q.s.
Purified Water ad	30.0
Make isoton. sol.	
Sig. Drop in eye.	

Sodium chloride equivalents are as follows:

Tetracaine HCl = 0.18

Zinc sulfate = 0.15

Boric Acid = 0.52

Step 1: $(0.9/100) \times 30 = 0.27$

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Step 2: (a) Tetracaine HCl:

$$0.1 \times 0.18 = 0.018 \text{ g}$$

(b) Zinc Sulfate:

$$0.05 \times 0.15 = 0.0075 \text{ g}$$

$$(a) + (b) = 0.018 + 0.0075 \text{ g} = 0.0255 \text{ g}$$

Step 3: $0.27 - 0.0255 = 0.2445$ or 0.245 g

Step 4: From Step 3, 0.245 g of sodium chloride is required to make the preparation isotonic. But the prescription calls for boric acid as the tonicity agent. Boric acid has an *E* value of 0.52 . To find the quantity of boric acid equivalent to 0.245 grams of sodium chloride, a proportion can be set up as follows:

$$\frac{1 \text{ g}}{0.52 \text{ g}} = \frac{X}{0.245 \text{ g}}$$

answer: solving for *X*, we get: $(0.245 \times 1) \div 0.52 = 0.471 \text{ grams}$

Example 3:

How many grams of dextrose should be used in compounding the prescription?

R	
Ephedrine Hydrochloride	0.5
Chlorobutanol	0.25
Dextrose	q.s.
Rose Water ad	50.0
Make isoton. sol.	
Sig. Nose drops.	

Sodium chloride equivalents are as follows:

Ephedrine HCl = 0.30
 Chlorobutanol = 0.18
 Dextrose = 0.16

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Step 1: $(0.9/100) \times 50 = 0.45 \text{ g}$

Step 2: (a) Ephedrine HCl:

$$0.50 \times 0.30 = 0.15 \text{ g}$$

(b) Chlorobutanol:

$$0.25 \times 0.18 = 0.045 \text{ g}$$

$$(a) + (b) = 0.15 + 0.045 \text{ g} = 0.195 \text{ g}$$

Step 3: $0.45 - 0.195 = 0.255 \text{ g}$

Step 4:

$$\frac{1 \text{ g}}{0.16 \text{ g}} = \frac{X}{0.255 \text{ g}}$$

$$\text{answer: } X = 1.59 \text{ g}$$

Practice Problems

When solving these problems, refer to Tables 8.1 and 8.2 as needed.

- (1) Calculate the dissociation factor of pilocarpine hydrochloride dissociating 80% (2 ions) in a certain concentration.
- (2) Calculate the *E* values of the following aqueous solutions at 1% concentration:
 - (a) Chlorobutanol
 - (b) Tetracaine hydrochloride
 - (c) Ephedrine sulfate
- (3) How many grams of sodium chloride should be used in compounding the prescription?

R

Procaine Hydrochloride	1%
Sodium Chloride	q.s.
Sterile Water for Injection ad	100
Make isoton. sol.	
Sig. For injection.	

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- (4) How many grams of sodium chloride should be used in compounding the prescription?

R

Cocaine Hydrochloride	0.6
Eucatropine Hydrochloride	0.6
Chlorobutanol	0.1
Sodium Chloride	q.s.
Purified Water ad	30.0
Make isoton. sol.	
Sig. For the eye.	

- (5) How many grams of boric acid should be used in compounding the prescription?

R

Zinc Sulfate	0.06
Boric Acid	q.s.
Purified Water ad	30.0
Make isoton. sol.	
Sig. Drop in eyes.	

- (6) How many milliliters of a 0.9% solution of sodium chloride should be used in compounding the prescription?

R

Phenylephrine Hydrochloride	1.0
Chlorobutanol	0.5
Sodium Chloride	q.s.
Purified Water ad	100.0
Make isoton. sol.	
Sig. Use as directed.	

- (7) How many grams of sodium chloride should be used in preparing the solution?

Dextrose, Monohydrate	2.0%
Sodium Chloride	q.s.
Sterile Water for Injection ad	1000 mL
Label: Isotonic Dextrose and Saline Solution.	

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- (8) How many milliliters of a 5% solution of boric acid should be used in compounding the prescription?

R

Oxymetazoline Hydrochloride	2%
Boric Acid Solution	q.s.
Purified Water ad	15.0
Make isoton. sol.	
Sig. For the nose, as decongestant.	

- (9) How many grams of dextrose monohydrate should be used in preparing a liter of a 1/2% isotonic ephedrine sulfate nasal spray?
- (10) How many grams of boric acid should be used in compounding the prescription?

R

Tetracaine Hydrochloride	1.0
Boric Acid	q.s.
Purified Water ad	30.0
Make isoton. sol.	
Sig. Eye drops.	

ISOTONICITY ADJUSTMENTS BY CRYOSCOPIC METHOD

Since osmotic pressure of a solution is not a readily measurable quantity, other easily measurable colligative properties such as the *freezing point depression* is used in the isotonicity calculations. The normal freezing (or melting) point of a pure compound is the temperature at which the solid and the liquid phases are in equilibrium at a pressure of 1 atm. Pure water has a freezing point of 0°C. When solutes are added to water, its freezing point is lowered. The freezing point depression (or lowering) of a solvent is dependent *only* on the number of particles in the solution. Blood plasma has a freezing point of -0.52 (or freezing point depression of 0.52, i.e., $(-[-0.52])$). If freezing point depression value of a chemical in certain concentration is known, one can calculate the concentration of that chemical required for isotonicity by setting a proportion as follows:

$$\frac{\text{Known percentage conc. of a given chemical}}{\text{Freezing point depression of the chemical at that concentration}} = \frac{X}{\text{Freezing point depression of blood plasma}}$$

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where X = percentage concentration of the chemical required to be isotonic with blood plasma.

Since *freezing point depression* of a series of compounds at 1% concentration is readily available from standard references, the above expression can be represented as:

$$\frac{1\% \text{ chemical}}{\Delta T_f^\circ \text{ of the chemical}} = \frac{X}{\Delta T_f^\circ \text{ of blood plasma or tears}}$$

where X = percentage concentration of the chemical required to be isotonic with blood plasma or tears.

Example 1:

1% NaCl solution has a freezing point depression of 0.576°C. What is the percentage concentration of NaCl required to make isotonic saline solution?

One can calculate the percentage concentration of NaCl by setting up the following proportion and solving for X :

$$\frac{1\%}{0.576} = \frac{X}{0.52}$$

$$X = (0.52 \times 1)/0.576$$

$$= 0.903 \text{ or } 0.9\% \text{ w/v}$$

Thus, 0.9% sodium chloride has the same osmotic pressure and the same freezing point depression of 0.52 as that of blood plasma, red blood cells, and tears. Drug solutions which have a freezing point depression of 0.52 are, therefore, isotonic with blood. A list of freezing point depression values of selected compounds at 1% concentration is presented in Table 8.2. These ΔT_f values may be used to calculate the concentration of tonicity agents, such as sodium chloride or boric acid, needed to render a hypotonic drug solution isotonic with blood plasma. The following steps may be used to find the percentage concentration of NaCl required to render hypotonic drug solutions isotonic with blood plasma:

Step 1: Find the value of freezing point depression of the drug at 1% concentration, ΔT_f° from Table 8.2.

Step 2: Subtract ΔT_f° of the drug from the value of freezing point

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depression of 0.9% sodium chloride solution, i.e., 0.52. This difference may be symbolized as ΔT_f , which is the freezing point lowering needed for isotonicity.

Step 3: Since 0.9% sodium chloride has a freezing point depression of 0.52, one can calculate the percentage concentration of sodium chloride required to lower the difference in freezing points, i.e., the value obtained in Step 2, ΔT_f , by the method of proportion. The calculations involved in this method are explained best by following examples.

Example 2:

Compound the following prescription.

R	
Atropine Sulfate	1%
Sodium Chloride	q.s.
Purified Water ad	100
Make isoton. sol.	
Sig. One drop in each eye.	

Step 1: Freezing point depression (ΔT_f) of 1% atropine solution (from Table 8.2) is 0.07.

Step 2: Find ΔT_f by subtracting the ΔT_f value of 1% atropine sulfate from the ΔT_f of blood plasma, i.e., $0.52 - 0.07 = 0.45$. This means, sufficient sodium chloride must be added to lower the freezing point by an additional 0.45°.

Step 3: Find the percentage concentration of sodium chloride required by setting up the proportion as follows:

$$\frac{0.9\%}{0.52} = \frac{X}{0.45}$$

In Table 8.2, it is observed that 1% solution of sodium chloride has a freezing point lowering of 0.58. Therefore, one can also express the proportion as:

$$\frac{1\%}{0.58} = \frac{X}{0.45}$$

answer: solving for X, we get: $(0.45/0.58) \times 1 = 0.78\%$

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0.78% sodium chloride will render the above preparation isotonic. Thus, the isotonic solution will be prepared by dissolving 1.0 g of atropine sulfate and 0.78 g of sodium chloride in sufficient water to make 100 mL of solution.

Example 3:

Compound the following prescription.

R	
Apomorphine Hydrochloride	1%
Sodium Chloride	q.s.
Purified Water ad	100
Ft isoton. sol.	
Sig. gtts ii OD T.I.D.	

Step 1: Freezing point depression (ΔT_f) of 1% apomorphine HCl solution (from Table 8.2) is 0.08.

Step 2: Find $\Delta T_f'$ by subtracting the ΔT_f value of 1% atropine sulfate from the ΔT_f of blood plasma, i.e., $0.52 - 0.08 = 0.44$. This means, sufficient sodium chloride must be added to reduce the freezing point by an additional 0.44°.

Step 3: Find the percentage concentration of sodium chloride required by setting up the proportion as follows:

$$\frac{0.9\%}{0.52} = \frac{X}{0.44}$$

or

$$\frac{1\%}{0.58} = \frac{X}{0.44}$$

solving for X, we get: $(0.44/0.58) \times 1 = 0.76\%$

answer: $X = 0.76\%$

0.76% sodium chloride will render the above preparation isotonic. Thus, the isotonic solution will be prepared by dissolving 1.0 g of apomorphine hydrochloride and 0.76 g of sodium chloride in sufficient water to make 100 mL of solution.

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VOLUMES OF ISO-OSMOTIC SOLUTIONS

White-Vincent Method

White and Vincent² provided a method for readily finding the correct volume of water in which to dissolve a drug to produce a solution iso-osmotic with tears, followed by the addition of an isotonic vehicle to bring the solution to the final volume. The volume (V) of isotonic solution that can be prepared from any given drug is obtained by the equation:

$$V = \omega \times E \times 111.1$$

where

ω = weight of the drug in grams

E = sodium chloride equivalent

If more than one ingredient is contained in an isotonic preparation, the volumes of isotonic solution, obtained by mixing each drug with water, are additive. If that is the case, V can be calculated as follows:

$$V = [(\omega_1 \times E_1) + (\omega_2 \times E_2) + \dots + (\omega_n \times E_n)] \times 111.1$$

Example 1:

Make the following solution isotonic with tears.

Procaine Hydrochloride	1%
Sodium Chloride	q.s.
Purified Water ad	60

The weight of procaine hydrochloride = $(60/100) \times 1 = 0.6$ g.

The E value of procaine hydrochloride = 0.21.

The volume (V) of isotonic solution that can be prepared from 0.6 g of the drug:

$$\begin{aligned} V &= \omega \times E \times 111.1 \\ &= 0.6 \times 0.21 \times 111.1 \\ &= 13.99 \text{ or } 14 \text{ mL} \end{aligned}$$

²White A. I. and Vincent H. C. *J. Am. Pharm. Assoc. Pract. Ed.*, 8, 406, 1947.

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