11

Isotonic and Buffer Solutions

Objectives

Upon successful completion of this chapter, the student will be able to:

- Differentiate between the terms *isosmotic*, *isotonic*, *hypertonic*, and *hypotonic*.
- Apply physical chemical principles in the calculation of isotonic solutions.
- Perform the calculations required to prepare isotonic compounded prescriptions.
- State the buffer equation and apply it in calculations.

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 *un*dissociated 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.

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.[1]

Intravenous infusions, which are hypotonic or hypertonic, can have profound adverse effects because they generally are administered in large volumes.[1] 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.

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:

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

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

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):

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

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

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 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 tonicic equivalent of a quantity of boric acid may be calculated by these ratios:

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

and we can formulate a convenient rule: *quantities of two substances that are 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

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

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 g − 0.12 g = 0.78 g of sodium chloride.

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 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.*

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

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.

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

Calculate the sodium chloride equivalent for glycerin, a nonelectrolyte with a molecular weight of 92.[2]

Glycerin, *i* factor = 1.0

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

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

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

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

$$\frac{58.5}{1.8} \times \frac{2.6}{367} = 0.23, \textit{ answer.}$$

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 × 0.3 g = 0.069 g of sodium chloride represented by the pilocarpine nitrate
Step 2. 30 × 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?

℞	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 × 0.6 g = 0.120 g of sodium chloride represented by phenacaine hydrochloride
0.24 × 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 × 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?

℞	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 × 0.12 g = 0.04 g of sodium chloride represented by silver nitrate
Step 2. 60 × 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?

℞	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 × 0.5 g = 0.13 g of sodium chloride represented by ingredient X
Step 2. 50 × 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:

$$\frac{\text{g of drug} \times \text{drug's } E \text{ value}}{0.009} = \begin{array}{l}\text{mL of water needed to make an isotonic solution of the drug} \\ \text{(the volume of the drug substance is considered negligible)}\end{array}$$

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 × 1% w/v = 0.2 g hydromorphone needed*

Step 2. $\frac{0.2 \text{ g} \times 0.22}{0.009}$ = 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 × 0.9% = 0.18 g sodium chloride or equivalent required
0.2 × 0.22 = 0.044 g (sodium chloride represented by 0.2 g hydromorphone hydrochloride)
15.11 mL × 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:

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

$x = 0.76\%$ (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 × 1% = 0.3 g = 300 mg dibucaine hydrochloride, and

30 mL × 0.76% = 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:

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

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:

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

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

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

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

Buffers and Buffer Solutions

When a minute trace of hydrochloric acid is added to pure water, a significant increase in *hydrogen-ion* concentration occurs immediately. In a similar manner, when a minute trace of sodium hydroxide is added to pure water, it causes a correspondingly large increase in the *hydroxyl-ion* concentration. These changes take place because water alone cannot neutralize even traces of acid or base, that is, it has no ability to resist changes in hydrogen-ion concentration or pH. A solution of a neutral salt, such as sodium chloride, also lacks this ability. Therefore, it is said to be *unbuffered.*

The presence of certain substances or combinations of substances in aqueous solution imparts to the system the ability to maintain a desired pH at a relatively constant level, even with the addition of materials that may be expected to change the hydrogen–ion concentration. These substances or combinations of substances are called ***buffers***; their ability to resist changes in pH is referred to as ***buffer action***; their efficiency is measured by the function known as ***buffer capacity***; and solutions of them are called ***buffer solutions***. By definition, then, a ***buffer solution*** is a system, usually an aqueous solution, that possesses the property of resisting changes in pH with the addition of small amounts of a strong acid or base.

Buffers are used to establish and maintain an ion activity within rather narrow limits. In pharmacy, the most common buffer systems are used in (i) the preparation of such dosage forms as injections and ophthalmic solutions, which are placed directly into pH-sensitive body fluids; (ii) the manufacture of formulations in which the pH must be maintained at a relatively constant level to ensure maximum product stability; and (iii) pharmaceutical tests and assays requiring adjustment to or maintenance of a specific pH for analytic purposes.

A buffer solution is usually composed of a weak acid and a salt of the acid, such as acetic acid and sodium acetate, or a weak base and a salt of the base, such as ammonium hydroxide and ammonium chloride. Typical buffer systems that may be used in pharmaceutical formulations include the following pairs: acetic acid and sodium acetate, boric acid and sodium borate, and disodium phosphate and sodium acid phosphate. Formulas for standard buffer solutions for pharmaceutical analysis are given in the *United States Pharmacopeia.*[10]

TABLE 11.3 DISSOCIATION CONSTANTS OF SOME WEAK ACIDS AT 25°C

ACID	K_a
Acetic	1.75×10^{-5}
Barbituric	1.05×10^{-4}
Benzoic	6.30×10^{-5}
Boric	6.4×10^{-10}
Formic	1.76×10^{-4}
Lactic	1.38×10^{-4}
Mandelic	4.29×10^{-4}
Salicylic	1.06×10^{-3}

In the selection of a buffer system, due consideration must be given to the dissociation constant of the weak acid or base to ensure maximum buffer capacity. This dissociation constant, in the case of an acid, is a measure of the strength of the acid; the more readily the acid dissociates, the higher its dissociation constant and the stronger the acid. Selected dissociation constants, or K_a values, are given in Table 11.3.

The dissociation constant, or K_a value, of a weak acid is given by the equation:

$$K_a = \frac{(H^+)\,(A^-)}{(HA)} \qquad \text{where } A^- = \text{salt}, \quad HA = \text{acid}$$

Because the numeric values of most dissociation constants are small numbers and may vary over many powers of 10, it is more convenient to express them as negative logarithms:

$$pK_a = -\log K_a$$

When equation $K_a = \frac{(H^+)\,(A^-)}{(HA)}$ is expressed in logarithmic form, it is written:

$$pK_a = -\log\,(H^+) - \log \frac{\text{salt}}{\text{acid}}$$

and because $pH = -\log\,(H^+)$:

then $$pK_a = pH - \log \frac{\text{salt}}{\text{acid}}$$

and $$pH = pK_a + \log \frac{\text{salt}}{\text{acid}}$$

Buffer Equation

The equation just derived is the Henderson-Hasselbalch equation for weak acids, commonly known as the ***buffer equation***.

Similarly, the dissociation constant, or K_b value, of a weak base is given by the equation:

$$K_b = \frac{(B^+)\,(OH^-)}{(BOH)} \qquad \text{in which } B^+ = \text{salt} \quad \text{and } BOH = \text{base}$$

and the buffer equation for weak bases, which is derived from this relationship, may be expressed as:

$$pH = pK_w - pK_b + \log \frac{\text{base}}{\text{salt}}$$

The buffer equation is useful for calculating (1) the pH of a buffer system if its composition is known and (2) the molar ratio of the components of a buffer system required to give a solution of a desired pH. The equation can also be used to calculate the change in pH of a buffered solution with the addition of a given amount of acid or base.

pK_a Value of a Weak Acid with Known Dissociation Constant

Calculating the pK_a value of a weak acid, given its dissociation constant, K_a:

The dissociation constant of acetic acid is 1.75×10^{-5} at 25°C. *Calculate its* pK_a *value.*

$$K_a = 1.75 \times 10^{-5}$$

and

$$\log K_a = \log 1.75 + \log 10^{-5}$$
$$= 0.2430 - 5 = -4.757 \text{ or } -4.76$$

Because

$$pK_a = -\log K_a$$
$$pK_a = -(-4.76) = 4.76, \textit{ answer.}$$

pH Value of a Salt/Acid Buffer System

Calculating the pH value:

What is the pH of a buffer solution prepared with 0.05 M sodium borate and 0.005 M boric acid? The pK_a *value of boric acid is 9.24 at 25°C.*

Note that the ratio of the components of the buffer solution is given in molar concentrations. Using the buffer equation for weak acids:

$$\text{pH} = pK_a + \log \frac{\text{salt}}{\text{acid}}$$
$$= 9.24 + \log \frac{0.05}{0.005}$$
$$= 9.24 + \log 10$$
$$= 9.24 + 1$$
$$= 10.24, \textit{ answer.}$$

pH Value of a Base/Salt Buffer System

Calculating the pH value:

What is the pH of a buffer solution prepared with 0.05 M ammonia and 0.05 M ammonium chloride? The K_b *value of ammonia is* 1.80×10^{-5} at 25°C.

Using the buffer equation for weak bases:

$$\text{pH} = pK_w - pK_b + \log \frac{\text{base}}{\text{salt}}$$

Because the K_w value for water is 10^{-14} at 25°C, $pK_w = 14$.

$$K_b = 1.80 \times 10^{-5}$$

and

$$\log K_b = \log 1.8 + \log 10^{-5}$$
$$= 0.2553 - 5 = -4.7447 \text{ or } -4.74$$
$$pK_b = -\log K_b$$
$$= -(-4.74) = 4.74$$

and $$\text{pH} = 14 - 4.74 + \log \frac{0.05}{0.05}$$
$$= 9.26 + \log 1$$
$$= 9.26,\ \textit{answer}.$$

Molar Ratio of Salt/Acid for a Buffer System of Desired pH

Calculating the molar ratio of salt/acid required to prepare a buffer system with a desired pH value:

What molar ratio of salt/acid is required to prepare a sodium acetate-acetic acid buffer solution with a pH of 5.76? The pK_a value of acetic acid is 4.76 at 25°C.

Using the buffer equation:

$$\text{pH} = \text{pK}_a + \log \frac{\text{salt}}{\text{acid}}$$
$$\log \frac{\text{salt}}{\text{acid}} = \text{pH} - \text{pK}_a$$
$$= 5.76 - 4.76 = 1$$
$$\text{antilog of } 1 = 10$$
$$\text{ratio} = 10/1 \text{ or } 10{:}1,\ \textit{answer}.$$

Quantity of Components in a Buffer Solution to Yield a Specific Volume

Calculating the amounts of the components of a buffer solution required to prepare a desired volume, given the molar ratio of the components and the total buffer concentration:

The molar ratio of sodium acetate to acetic acid in a buffer solution with a pH of 5.76 is 10:1. Assuming the total buffer concentration is 2.2×10^{-2} mol/L, how many grams of sodium acetate (m.w. 82) and how many grams of acetic acid (m.w. 60) should be used in preparing a liter of the solution?

Because the molar ratio of sodium acetate to acetic acid is 10:1,

$$\text{the mole fraction of sodium acetate} = \frac{10}{1 + 10} \text{ or } \frac{10}{11}$$
$$\text{and the mole fraction of acetic acid} = \frac{1}{1 + 10} \text{ or } \frac{1}{11}$$

If the total buffer concentration $= 2.2 \times 10^{-2}$ mol/L,

$$\text{the concentration of sodium acetate} = \frac{10}{11} \times (2.2 \times 10^{-2})$$
$$= 2.0 \times 10^{-2} \text{ mol/L}$$
$$\text{and the concentration of acetic acid} = \frac{1}{11} \times (2.2 \times 10^{-2})$$
$$= 0.2 \times 10^{-2} \text{ mol/L}$$

then 2.0×10^{-2} or $0.02 \times 82 = 1.64$ g of sodium acetate per liter of solution, *and*
0.2×10^{-2} or $0.002 \times 60 = 0.120$ g of acetic acid per liter of solution, *answers.*

The efficiency of buffer solutions—that is, their specific ability to resist changes in pH—is measured in terms of *buffer capacity*; the *smaller* the pH change with the addition of a given amount of acid or base, the *greater* the buffer capacity of the system. Among other factors, the buffer capacity of a system depends on (1) the relative concentration of the buffer components and (2) the ratio of the components. For example, a 0.5 M-acetate buffer at a pH of 4.76 would have a higher buffer capacity than a 0.05 M-buffer.

If a strong base such as sodium hydroxide is added to a buffer system consisting of equimolar concentrations of sodium acetate and acetic acid, the base is neutralized by the acetic acid forming more sodium acetate, and the resulting *increase* in pH is slight. Actually, the addition of the base increases the concentration of sodium acetate and decreases *by an equal amount* the concentration of acetic acid. In a similar manner, the addition of a strong acid to a buffer system consisting of a weak base and its salt would produce only a small *decrease* in pH.

Change in pH with Addition of an Acid or Base

Calculating the change in pH of a buffer solution with the addition of a given amount of acid or base:

Calculate the change in pH after adding 0.04 mol of sodium hydroxide to a liter of a buffer solution containing 0.2 M concentrations of sodium acetate and acetic acid. The pK_a *value of acetic acid is 4.76 at 25°C.*

The pH of the buffer solution is calculated by using the buffer equation as follows:

$$\begin{aligned} pH &= pK_a + \log \frac{\text{salt}}{\text{acid}} \\ &= 4.76 + \log \frac{0.2}{0.2} \\ &= 4.76 + \log 1 \\ &= 4.76 \end{aligned}$$

The addition of 0.04 mol of sodium hydroxide converts 0.04 mol of acetic acid to 0.04 mol of sodium acetate. Consequently, the concentration of acetic acid is *decreased* and the concentration of sodium acetate is *increased* by equal amounts, according to the following equation:

$$pH = pK_a + \log \frac{\text{salt} + \text{base}}{\text{acid} - \text{base}}$$

and

$$\begin{aligned} pH &= pK_a + \log \frac{0.2 + 0.04}{0.2 - 0.04} \\ &= pK_a + \log \frac{0.24}{0.16} \\ &= 4.76 + 0.1761 = 4.9361 \text{ or } 4.94 \end{aligned}$$

Because the pH before the addition of the sodium hydroxide was 4.76, the change in pH = 4.94 − 4.76 = 0.18 unit, *answer*.

PRACTICE PROBLEMS

Calculations of Tonicity

1. Isotonic sodium chloride solution contains 0.9% w/v sodium chloride. If the *E* value of boric acid is 0.52, calculate the percentage strength (w/v) of an isotonic solution of boric acid.

2. Sodium chloride is a 2-ion electrolyte, dissociating 90% in a certain concentration. Calculate (a) its dissociation factor, and (b) the freezing point of a molal solution.

3. A solution of anhydrous dextrose (m.w. 180) contains 25 g in 500 mL of water. Calculate the freezing point of the solution.

4. Procaine hydrochloride (m.w. 273) is a 2-ion electrolyte, dissociating 80% in a certain concentration.
   (a) Calculate its dissociation factor.
   (b) Calculate its sodium chloride equivalent.
   (c) Calculate the freezing point of a molal solution of procaine hydrochloride.

5. The freezing point of a molal solution of a nonelectrolyte is −1.86°C. What is the freezing point of a 0.1% solution of zinc chloride (m.w. 136), dissociating 80%? (For lack of more definite information, assume that the volume of the molal solution is approximately 1 liter.)

6. The freezing point of a 5% solution of boric acid is −1.55°C. How many grams of boric acid should be used in preparing 1000 mL of an isotonic solution?

7. ℞ Ephedrine Sulfate 0.3 g
   Sodium Chloride q.s.
   Purified Water ad 30 mL
   Make isoton. sol.
   Sig. Use as directed.

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

8. ℞ Dipivefrin Hydrochloride ½%
   Scopolamine Hydrobromide ⅓%
   Sodium Chloride q.s.
   Purified Water ad 30
   Make isoton. sol.
   Sig. Use in the eye.

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

9. ℞ Zinc Sulfate 0.06
   Boric Acid q.s.
   Purified Water ad 30
   Make isoton. sol.
   Sig. Drop in eyes.

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

10. ℞ Cromolyn Sodium 4% (w/v)
    Benzalkonium Chloride 1:10,000 (w/v)
    Buffer Solution (pH 5.6) q.s.
    Water for Injection ad 10 mL
    Sig. One (1) drop in each eye b.i.d.

    How many milliliters of the buffer solution (E = 0.30) should be used to render the solution isotonic?

11. Dextrose, anhydrous 2.5%
    Sodium Chloride q.s.
    Sterile Water for Injection ad 1000 mL
    Label: Isotonic Dextrose and Saline Solution.

    How many grams of sodium chloride should be used in preparing the solution?

12. ℞ Sol. Silver Nitrate 0.5% 15
    Make isoton. sol.
    Sig. For the eyes.

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

13. ℞ Cocaine Hydrochloride 0.15
    Sodium Chloride q.s.
    Purified Water ad 15
    Make isoton. sol.
    Sig. One drop in left eye.

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

14. ℞ Cocaine Hydrochloride 0.6
Eucatropine Hydrochloride 0.6
Chlorobutanol 0.1
Sodium Chloride q.s.
Purified Water ad 30
Make isoton. sol.
Sig. For the eye.

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

15. ℞ Tetracaine Hydrochloride 0.1
Zinc Sulfate 0.05
Boric Acid q.s.
Purified Water ad 30
Make isoton. sol.
Sig. Drop in eye.

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

16. ℞ Sol. Homatropine Hydrobromide 1% 15
Make isoton. sol. with boric acid.
Sig. For the eye.

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

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

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

18. ℞ Phenylephrine Hydrochloride 1%
Chlorobutanol 0.5%
Sodium Chloride q.s.
Purified Water ad 15
Make isoton. sol.
Sig. Use as directed.

How many milliliters of an 0.9% solution of sodium chloride should be used in compounding the prescription?

19. ℞ Oxymetazoline Hydrochloride ½%
Boric Acid Solution q.s.
Purified Water ad 15
Make isoton. sol.
Sig. For the nose, as decongestant.

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

20. ℞ Ephedrine Hydrochloride 0.5
Chlorobutanol 0.25
Dextrose, monohydrate q.s.
Rose Water ad 50
Make isoton. sol.
Sig. Nose drops.

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

21. ℞ Naphazoline Hydrochloride 1%
Sodium Chloride q.s.
Purified Water ad 30 mL
Make isoton. sol.
Sig. Use as directed in the eye.

How many grams of sodium chloride should be used in compounding the prescription? Use the freezing point depression method.

22. ℞ Oxytetracycline Hydrochloride 0.05
Chlorobutanol 0.1
Sodium Chloride q.s.
Purified Water ad 30
Make isoton. sol.
Sig. Eye drops.

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

23. ℞ Tetracaine Hydrochloride 0.5%
Sol. Epinephrine Bitartrate 1:1000 10
Boric Acid q.s.
Purified Water ad 30
Make isoton. sol.
Sig. Eye drops.

The solution of epinephrine bitartrate (1:1000) is already isotonic. How many grams of boric acid should be used in compounding the prescription?

24. Monobasic Sodium Phosphate, anhydrous 5.6 g
Dibasic Sodium Phosphate, anhydrous 2.84 g
Sodium Chloride q.s.
Purified Water ad 1000 mL
Label: Isotonic Buffer Solution, pH 6.5.

How many grams of sodium chloride should be used in preparing the solution?

25. How many grams of anhydrous dextrose should be used in preparing 1 liter of a ½% isotonic ephedrine sulfate nasal spray?

26. ℞ Ephedrine Sulfate 1%
Chlorobutanol ½%
Purified Water ad 100
Make isoton. sol. and buffer to pH 6.5
Sig. Nose drops.

You have on hand an isotonic buffered solution, pH 6.5. How many milliliters of purified water and how many milliliters of the buffered solution should be used in compounding the prescription?

27. ℞ Oxytetracycline Hydrochloride 0.5%
Tetracaine Hydrochloride Sol. 2% 15 mL
Sodium Chloride q.s.
Purified Water ad 30 mL
Make isoton. sol.
Sig. For the eye.

The 2% solution of tetracaine hydrochloride is already isotonic. How many milliliters of an 0.9% solution of sodium chloride should be used in compounding the prescription?

28. Determine if the following commercial products are hypotonic, isotonic, or hypertonic:
(a) An ophthalmic solution containing 40 mg/mL of cromolyn sodium and 0.01% of benzalkonium chloride in purified water.
(b) A parenteral infusion containing 20% (w/v) of mannitol.
(c) A 500-mL large volume parenteral containing D5W (5% w/v of anhydrous dextrose in sterile water for injection).
(d) A FLEET saline enema containing 19 g of monobasic sodium phosphate (monohydrate) and 7 g of dibasic sodium phosphate (heptahydrate) in 118 mL of aqueous solution.

29. For agents having the following sodium chloride equivalents, calculate the percentage concentration of an isotonic solution:
(a) 0.20
(b) 0.32
(c) 0.61

30. How many milliliters each of purified water and an isotonic sodium chloride solution should be used to prepare 30 mL of a 1% w/v isotonic solution of fentanyl citrate ($E = 0.11$)?

31. Using the *E* values in Table 11.1, calculate the number of milliliters of water required to make an isotonic solution from 0.3 g of each of the following:
    (a) antipyrine
    (b) chlorobutanol
    (c) ephedrine sulfate
    (d) silver nitrate
    (e) zinc sulfate

32. Calculate the *E* values for each of the following, given that the number of milliliters of water shown will produce an isotonic solution from 0.3 g of drug substance.
    (a) apomorphine hydrochloride, 4.7 mL water
    (b) ethylmorphine hydrochloride, 5.3 mL water
    (c) holocaine hydrochloride, 6.7 mL water
    (d) procainamide hydrochloride, 7.3 mL water
    (e) viomycin sulfate, 2.7 mL water

Calculations of Buffer Solutions

33. The dissociation constant of ethanolamine is 2.77×10^{-5} at 25°C. Calculate its pK_b value.

34. What is the pH of a buffer solution prepared with 0.055 M sodium acetate and 0.01 M acetic acid? The pK_a value of acetic acid is 4.76 at 25°C.

35. What is the pH of a buffer solution prepared with 0.5 M disodium phosphate and 1 M sodium acid phosphate? The pK_a value of sodium acid phosphate is 7.21 at 25°C.

36. What molar ratio of salt to acid would be required to prepare a buffer solution with a pH of 4.5? The pK_a value of the acid is 4.05 at 25°C.

37. What is the change in pH on adding 0.02 mol of sodium hydroxide to a liter of a buffer solution containing 0.5 M of sodium acetate and 0.5 M acetic acid? The pK_a value of acetic acid is 4.76 at 25°C.

38. The molar ratio of salt to acid needed to prepare a sodium acetate-acetic acid buffer solution is 1:1. Assuming that the total buffer concentration is 0.1 mol/L, how many grams of sodium acetate (m.w. 60) should be used in preparing 2 liters of the solution?

39. What is the change in pH with the addition of 0.01 moL hydrochloric acid to a liter of a buffer solution containing 0.05 M of ammonia and 0.05 M of ammonium chloride? The K_b value of ammonia is 1.80×10^{-5} at 25°C.

ANSWERS TO "CASE IN POINT" AND PRACTICE PROBLEMS

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*.

Practice Problems

1. 1.73% w/v
2. (a) 1.9
   (b) −3.53°C
3. −0.52°C
4. (a) 1.8
   (b) 0.21
   (c) −3.35°C
5. −0.036°C
6. 16.8 g
7. 201 mg sodium chloride
8. 0.236 g sodium chloride
9. 0.502 g boric acid
10. 0.153 mL buffer solution
11. 4.5 g sodium chloride
12. 0.19 g potassium nitrate
13. 0.111 g sodium chloride
14. 0.042 g sodium chloride
15. 0.47 g boric acid
16. 0.211 g boric acid
17. 0.69 g sodium chloride
18. 7.667 mL sodium chloride solution
19. 4.62 mL boric acid solution
20. 1.531 g dextrose monohydrate
21. 0.189 g sodium chloride
22. 240 mg sodium chloride
23. 0.294 g boric acid
24. 4.751 g sodium chloride
25. 43.61 g anhydrous dextrose
26. 38.89 mL purified water
    61.11 mL buffered solution
27. 13 mL sodium chloride solution
28. (a) hypotonic
    (b) hypertonic
    (c) isotonic
    (d) hypertonic
29. (a) 4.5%
    (b) 2.81%
    (c) 1.48%
30. 3.67 mL purified water
    26.33 mL sodium chloride solution
31. (a) 5.7 mL water
    (b) 8.0 mL water
    (c) 7.7 mL water
    (d) 11.0 mL water
    (e) 5.0 mL water
32. (a) 0.14
    (b) 0.16
    (c) 0.20
    (d) 0.22
    (e) 0.08
33. 4.56
34. 5.5
35. 6.91
36. 2.82:1
37. 0.03 unit
38. 8.2 g
    6.0 g
39. 0.18 unit

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