Isotonic and Buffer Solutions

11

PHARMACEUTICAL CALCULATIONS
LECTURE 2
LEVEL1 (2022/2023)

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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.

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:

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.

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

$$x = 17.3\ g$$

If we assume that sodium chloride in weak solutions is about 80% dissociated, then each 100 molecules yields 180 particles, or 1.8 times as many particles as are yielded by 100 molecules of a nonelectrolyte. This dissociation factor, commonly symbolized by the letter *i*, must be included in the proportion when we seek to determine the strength of an isotonic solution of sodium chloride (m.w. 58.5):

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

$$x = 9.09\ g$$

Hence, 9.09 g of sodium chloride in 1000 g of water should make a solution isotonic with blood or lacrimal fluid. In practice, a 0.90% w/v sodium chloride solution is considered isotonic with body fluids.

Simple isotonic solutions may then be calculated by using this formula:

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

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*.

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.

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

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

Glycerin, i factor = 1.0

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

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

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

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

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 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. $30 \times 0.009 = 0.270$ 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.*

1. Multiply the amount (in grams) of each substance by its sodium chloride equivalent
2. The amount of sodium
chloride in a 0.9% solution of the specified volume. (Such a solution would contain 0.009 g/mL.)
3. Subtract the amount of sodium chloride Step 1- Step 2 = amount (in grams) of sodium chloride to be added to make the solution isotonic.
4. If an agent other than sodium chloride; divide the amount of sodium chloride (Step 3) by the sodium chloride equivalent of the other substance.

Note:
1gm 100ml
X 60ml = 0.6gm

0.5gm 100ml
X 60ml=0.3gm

℞	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. $0.20 \times 0.6\ g = 0.120$ g of sodium chloride represented by phenacaine hydrochloride
$0.24 \times 0.3\ g = \underline{0.072}$ g of sodium chloride represented by chlorobutanol
Total: 0.192 g of sodium chloride represented by both ingredients

Step 2. $60 \times 0.009 = 0.540$ g of sodium chloride in 60 mL of an isotonic sodium chloride solution

Step 3. 0.540 g (from Step 2)
− $\underline{0.192}$ 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 mL
1 : 500 w/v
Make isoton. sol.
Sig. For eye use.

Note:
1:500 = 0.2%

0.2 100 ml
X 60 ml = 0.12 gm

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 gm
	Sodium Chloride	q.s.
	Purified Water ad	50 mL
	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. $50 \times 0.009 = 0.45$ 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.*

CALCULATIONS CAPSULE

Isotonicity

To calculate the ''equivalent tonic effect'' to sodium chloride represented by an ingredient in a preparation, multiply its weight by its *E* value:

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

To make a solution isotonic, calculate and ensure the quantity of sodium chloride and/or the equivalent tonic effect of all other ingredients to total 0.9% w/v in the preparation:

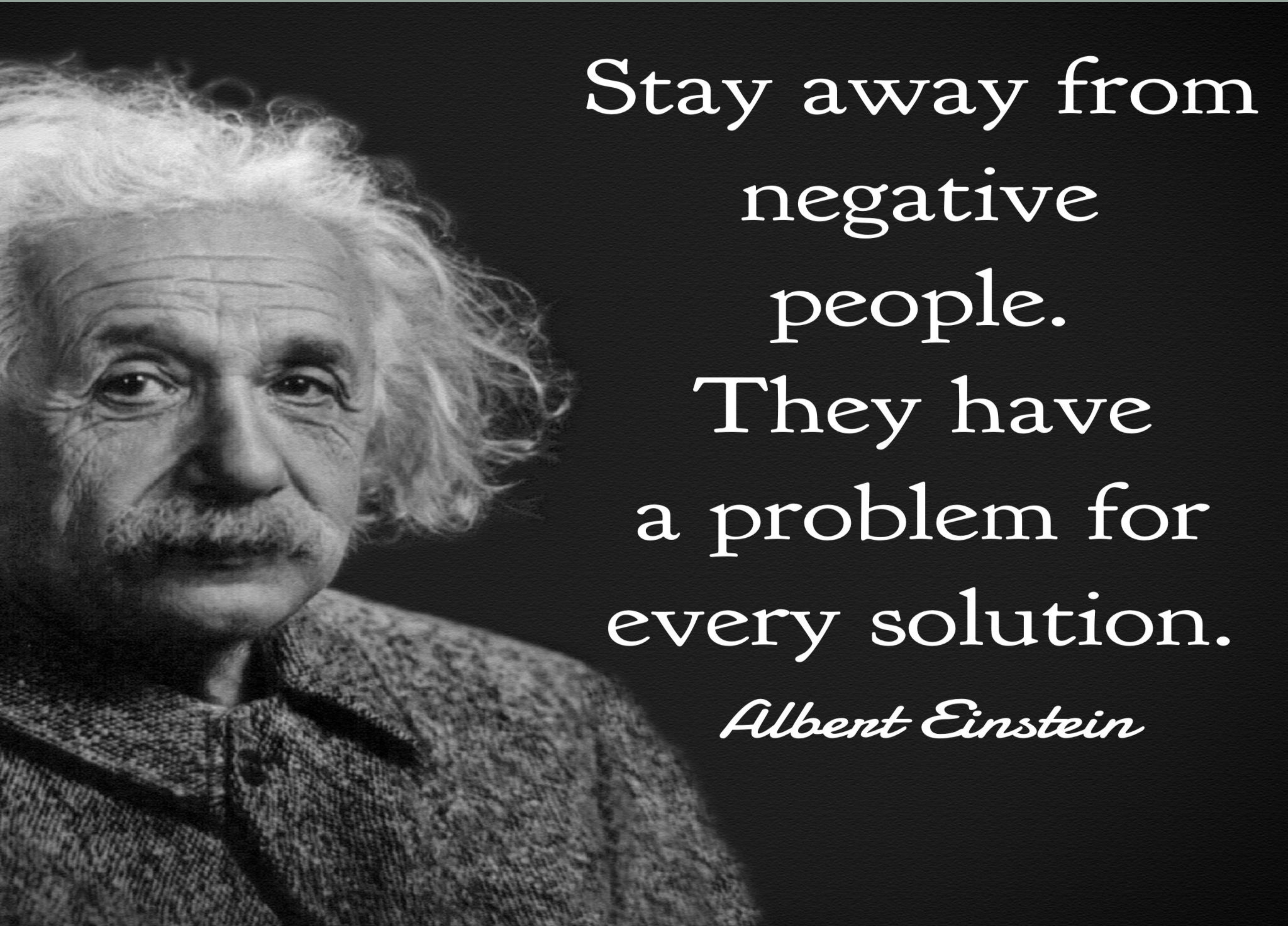
$$\frac{g\ (NaCl) + g\ (NaCl\ tonic\ equivalents)}{mL\ (preparation)} \times 100 = 0.9\%\ \text{w/v}$$

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

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

This solution may then be made to any volume with isotonic sodium chloride solution to maintain its isotonicity.

The *E* value can be derived from the same equation, given the grams of drug substance and the milliliters of water required to make an isotonic solution.


Stay away from
negative
people.
They have
a problem for
every solution.
Albert Einstein