Pharmaceutical calculation
Lecture-4
Isotonic solution
Part 2

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Example Calculations of Tonicic Agent Required

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

Rx Pilocarpine Nitrate 0.3 g

Sodium Chloride q.s.

Purified Water ad 30 mL

Make isoton. sol.

Sig. For the eye.

- Step 1. 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.

  0.23 x 0.3 g = 0.069 g of sodium chloride represented by the pilocarpine nitrate

- 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).

  30 x 0.009 = 0.270 g of sodium chloride in 30 mL of an isotonic sodium chloride solution

- 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 3.

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

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

Rx Phenacaine Hydrochloride 1% (E value = 0.2)

Chlorobutanol ½ % (E value = 0.24)

Boric Acid q.s. (E value = 0.52)

Purified Water ad 60

Make isoton. sol.

Sig. One drop in each eye.

- (1/100) X 60 = 0.6 g phenacaine hydrochloride
- (0.5/ 100) X 60 = 0.3 g chlorobutanol

The prescription calls for 0.6 g of phenacaine hydrochloride and 0.3 g of chlorobutanol.

Step 1.

0.20 x 0.6 g = 0.120 g of sodium chloride represented by phenacaine hydrochloride

0.24 x 0.3 g = 0.072 g of sodium chloride represented by chlorobutanol

Total: 0.192 g of sodium chloride represented by both ingredients

Step 2.

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

Step 3.

0.540 g (from Step 2) - 0.192 g (from Step 1) = 0.348 g of sodium chloride required to make the solution isotonic

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.

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 (E value 0.58) could be used to make the following prescription isotonic?

Rx Sol. Silver Nitrate 60

1: 500 w/v

Make isoton. sol.

Sig. For eye use.

- The prescription contains (1/ 500) x 60 = 0.12 g of silver nitrate.
- Knowing that E value of silver nitrate = 0.33

Step 1.

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

- Step 2.

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

- Step 3.

  0.54 g (from step 2) - 0.04 g (from step 1) 0.50 g of sodium chloride required to make solution isotonic

- Because, in this solution, sodium chloride is incompatible with silver nitrate, the tonic agent of choice is potassium nitrate. Therefore,

- Step 4.

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

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

Rx Ingredient X 0.5

Sodium Chloride q.s.

Purified Water ad 50 Make isoton. sol.

Sig. Eye drops.

- Let us assume that ingredient X is a new substance for which no sodium chloride equivalent is to be found in Table 11.1, and that its molecular weight is 295 and its i factor is 2.4. The sodium chloride equivalent of ingredient X may be calculated as follows:

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

- Then, Step 1.

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

- Step 2.

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

- Step 3.

0.45 g (from Step 2) - 0.13 g (from Step 1) = 0.32 g of sodium chloride to be used, answer.

Using an Isotonic Sodium Chloride Solution to Prepare Other Isotonic Solutions

- A 0.9% w/v sodium chloride solution may be used to compound isotonic solutions of other drug substances as follows:

Step 1. Calculate the quantity of the drug substance needed to fill the prescription or medication order.

Step 2. Use the following equation to calculate the volume of water needed to render a solution of the drug substance isotonic:

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

Step 3.

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

- Using this method, determine the volume of purified water and 0.9% w/v sodium chloride solution needed to prepare 20 mL of a 1% w/v solution of hydromorphone hydrochloride (E = 0.22).
- Step 1.

  20 mL x 1% w/v = 0.2 g hydromorphone needed

Step 2.

$$\frac{0.2 \times 0.22}{0.009} = 4.89 \, mL \; of \; purified \, water$$

4.89 mL of purified water required to make an isotonic solution of hydromorphone hydrochloride, answer.

- Step 3.

20 mL- 4.89 mL =15.11 mL 0.9% w/v sodium chloride solution required, answer.

- Proof: 20 mL x 0.9% = 0.18 g sodium chloride or equivalent required 0.2 x 0.22 = 0.044g (sodium chloride represented by 0.2g hydromorphonehydrochloride)

15.11 mL x 0.9 % = 0.136 g sodium chloride present

0.044 g + 0.136 g = 0.18 g sodium chloride required for isotonicity

Use of Freezing Point Data in Isotonicity Calculations

- Freezing point data (ΔT_f) can be used in isotonicity calculations when the agent has a tonicic effect and does not penetrate the biologic membranes in question (e.g., red blood cells). As stated previously, the freezing point of both blood and lacrimal fluid is - 0.52°C.
- Thus, a pharmaceutical solution that has a freezing point of -0.52°C is considered isotonic. Representative data on freezing point depression by medicinal and pharmaceutical substances are presented in Table 11.2.

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

- 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.

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:

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

- x = 0.76% (the concentration of sodium chloride needed to lower the freezing point by 0.44°, required to make the solution isotonic). Thus, to make 30 mL of solution, 30 mL X 1% = 0.3 g = 300 mg dibucaine hydrochloride, and

  30 mL X 0.76% = 0.228 g = 228 mg sodium chloride, answers.

CASE IN POINT 11.1[3]**:** A local ophthalmologist is treating one of his patients for a post-LASIK eye infection that is not responding to topical ciprofloxacin. These infections, although rare, can occur after laser in situ keratomileusis (LASIK) surgery for vision correction.

Topical amikacin sulfate has been shown to be effective for the treatment of eye infections due to ciprofloxacin-resistant *Pseudomonas*,[4–5] *Burkholderia ambifaria*,[6] Mycobacterium chelonae, and *Mycobacterium* fortuitum.[7–9]

The ophthalmologist prescribes 60 mL of a 2.5% amikacin sulfate isotonic solution, 2 drops in the affected eye every 2 hours.
Amikacin sulfate USP ($C_{22}H_{43}N_5O_{13}\cdot 2H_2SO_2$), m.w., 781.76, is an aminoglycoside-type antibiotic containing 3 ions.

(a) Determine the weight in grams of amikacin sulfate needed to prepare the solution.
(b) Calculate the sodium chloride equivalent (*E* value) for amikacin sulfate.
(c) Calculate the amount of sodium chloride needed to make the prepared solution isotonic.
(d) How many milliliters of 23.5 % sodium chloride injection should be used to obtain the needed sodium chloride?

a- 60 ml x 2.5% w/v = 1.5 g amikacin sulfate

b- sodium chloride m.w = 58.5

amikacin m.w = 781.76

amikacin give 3 ions, i = 2.6

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

- E value

$$\frac{58.5}{1.8} \times \frac{2.6}{781.7} = 0.108$$

c- 60 ml x 0.9 % w/v = 0.54 g or

60 ml x 0.009 = 0.54 g

1.5 g (amikacin sulfate) x 0.108 (Na Cl equivalent) = 0.162 g

0.54 g – 0.162 g = 0.378 g sodium chloride required

d- 23.5 g / 100 = 0.378 / (x) ml

x = 1.61 ml sodium chloride injection should be used