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Physical pharmacy I

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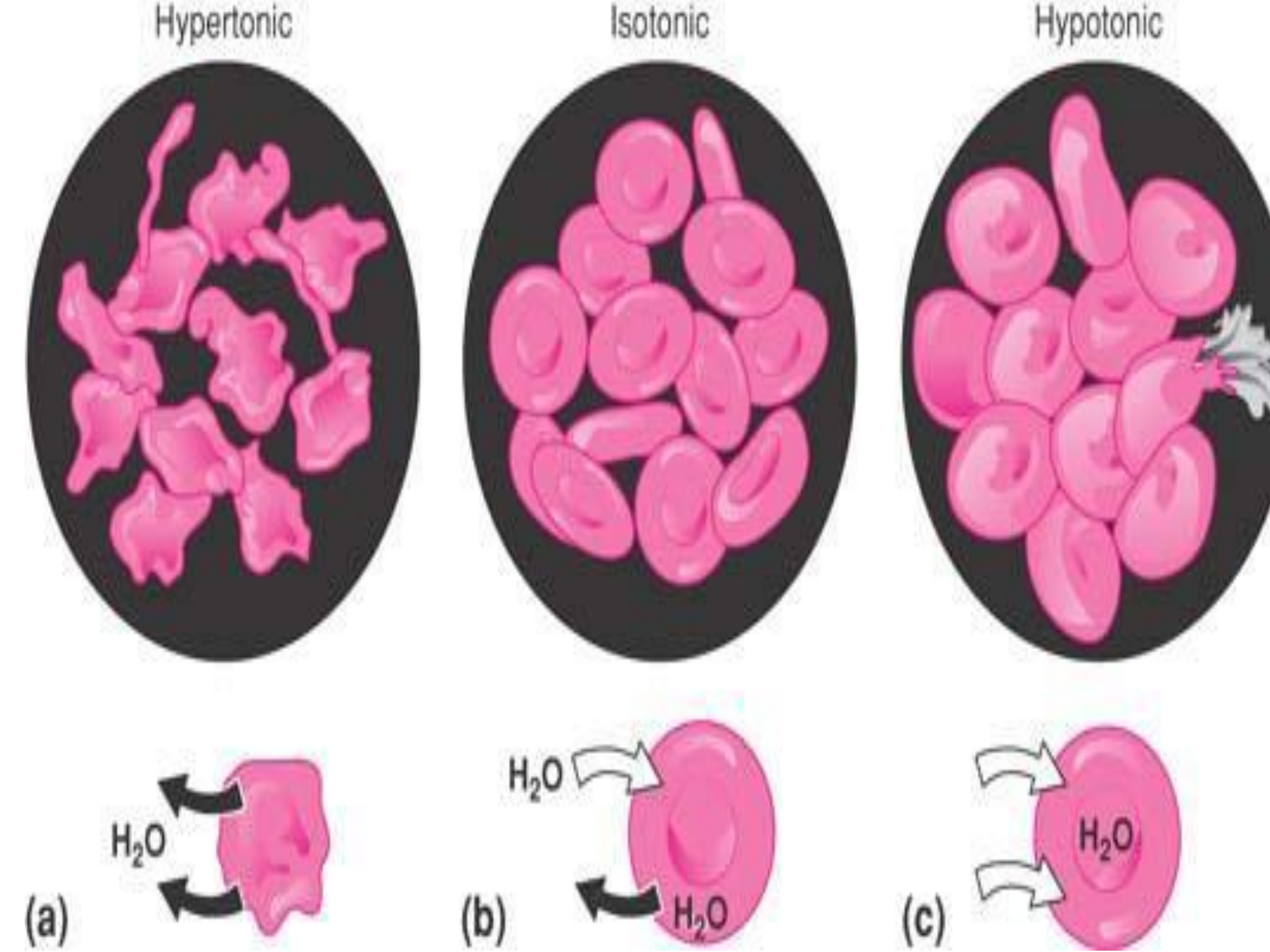
Buffered isotonic solutions

- In addition to carrying out pH adjustment, pharmaceutical solutions that are meant for application to delicate membranes of the body should also be adjusted to approximately the same osmotic pressure as that of the body fluids.
- Isotonic solutions cause no swelling or contraction of the tissues with which they come in contact and produce no discomfort when instilled in the eye, nasal tract, blood, or other body tissues
- if a small quantity of blood, is mixed with a solution containing 0.9 g of NaCl per 100 mL, the cells retain their normal size. The solution has essentially the same salt concentration and hence the same osmotic pressure as the red blood cell contents and is said to be **isotonic** with blood

- If the red blood cells are suspended in a 2.0% NaCl solution, the water within the cells passes through the cell membrane in an attempt to dilute the surrounding salt solution until the salt concentrations on both sides of the erythrocyte membrane are identical. This outward passage of water causes the cells to shrink and become wrinkled . The salt solution in this instance is said to be **hypertonic** with respect to the blood cell contents
- Finally, if the blood is mixed with 0.2% NaCl solution or with distilled water, water enters the blood cells, causing them to swell and finally burst, with the liberation of hemoglobin. This phenomenon is known as **hemolysis,** and the weak salt solution or water is said to be **hypotonic** with respect to the blood.


Hypertonic
Isotonic
Hypotonic
H_2O
H_2O
H_2O
H_2O
(a)
(b)
(c)

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 insignificant 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

Intravenous infusions, which are **hypotonic** or **hypertonic**, can have profound adverse effects because they generally are administered in large volumes. Large volumes of ***hypertonic*** **infusions** containing dextrose, for example, can result in hyperglycemia, osmotic diuresis, and excessive loss of electrolytes. Excess infusions of ***hypotonic*** **fluids** can result in the osmotic hemolysis of red blood cells and exceed 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.

Measurement of tonicity

The tonicity of solutions can be determined by one of two methods:

- **First, Hemolytic method**: a quantitative method based on the fact that a hypotonic solution liberates oxyhemoglobin in direct proportion to the number of cells hemolyzed . By such means, the van't Hoff i factor can be determined.
- The **second, from measured colligative properties of the solution:** approach used to measure tonicity is based on any of the methods that determine colligative properties.

- it is now well established that -0.52°C is the freezing point of both human blood and lacrimal fluid.
- This temperature corresponds to the freezing point of a 0.9% NaCl solution, which is therefore considered to be isotonic with both blood and lacrimal fluid.

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 11.86°C. Therefore:

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

$$x = 17.3\ g$$

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):

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

$$x = 9.09\ g$$

Calculating tonicity using L_{iso} values

$$\Delta T_f = Lc$$

- This specific value of L is written as L_{iso}.
- It has a value equal to :

AVERAGE L_{iso} VALUES FOR VARIOUS IONIC TYPES*

Type	L_{iso}	Examples
Nonelectrolytes	1.9	Sucrose, glycerin, urea, camphor
Weak electrolytes	2.0	Boric acid, cocaine, phenobarbital
Di-divalent electrolytes	2.0	Magnesium sulfate, zinc sulfate
Uni-univalent electrolytes	3.4	Sodium chloride, cocaine hydrochloride, sodium phenobarbital
Uni-divalent electrolytes	4.3	Sodium sulfate, atropine sulfate
Di-univalent electrolytes	4.8	Zinc chloride, calcium bromide
Uni-trivalent electrolytes	5.2	Sodium citrate, sodium phosphate
Tri-univalent electrolytes	6.0	Aluminum chloride, ferric iodide
Tetraborate electrolytes	7.6	Sodium borate, potassium borate

Example

Freezing Point Lowering

What is the freezing point lowering of a 1% solution of sodium propionate (molecular weight 96)?

Because sodium propionate is a uni-univalent electrolyte, its L_{iso} value is 3.4 . The molar concentration of a 1% solution of this compound is 0.104.We have

$$\text{Molarity} = \frac{\text{Moles}}{\text{Liter}}$$

$$= \frac{\text{Weight in grams}}{\begin{array}{c}\text{Molecular weight}\\ \text{in g/mole}\end{array}} \div \frac{\text{Volume in mL}}{1000\ \text{mL/liter}}$$

or

$$c = \frac{w}{MW} \times \frac{1000}{v}$$

$$\Delta T_f = 3.4 \times 0.104 = 0.35°\text{C}$$

Methods of adjusting tonicity and PH

The methods are divided into two classes.

- In the **class I** methods, sodium chloride or some other substance is added to the solution of the drug to lower the freezing point of the solution to -0.52°C and thus make it isotonic with body fluids. Under this class are included:
  - cryoscopic method .
  - sodium chloride equivalent method
- In the **class II** methods, water is added to the drug in a sufficient amount to form an isotonic solution.
  - Included in this class are the White–Vincent method
  - and the Sprowls method

Class I Methods

Cryoscopic Method

the freezing point depressions of drug solutions that have not been determined experimentally can be estimated from theoretical considerations, knowing only the molecular weight of the drug and the L_{iso} value of the ionic class

The calculations involved in the cryoscopic method are explained best by an example.

ISOTONIC VALUES*,†

Substance	MW	*E*	*V*	$\Delta T_f^{1\%}$	L_{iso}
Alcohol, dehydrated	46.07	0.70	23.3	0.41	1.9
Aminophylline	456.46	0.17	5.7	0.10	4.6
Amphetamine sulfate	368.49	0.22	7.3	0.13	4.8
Antipyrine	188.22	0.17	5.7	0.10	1.9
Apomorphine hydrochloride	312.79	0.14	4.7	0.08	2.6
Ascorbic acid	176.12	0.18	6.0	0.11	1.9
Atropine sulfate	694.82	0.13	4.3	0.07	5.3
Diphenhydramine hydrochloride	291.81	0.20	6.6	0.34	3.4
Boric acid	61.84	0.50	16.7	0.29	1.8
Caffeine	194.19	0.08	2.7	0.05	0.9
Dextrose · H_2O	198.17	0.16	5.3	0.09	1.9
Ephedrine hydrochloride	201.69	0.30	10.0	0.18	3.6
Ephedrine sulfate	428.54	0.23	7.7	0.14	5.8
Epinephrine hydrochloride	219.66	0.29	9.7	0.17	3.7
Glycerin	92.09	0.34	11.3	0.20	1.8
Lactose	360.31	0.07	2.3	0.04	1.7
Morphine hydrochloride	375.84	0.15	5.0	0.09	3.3
Morphine sulfate	758.82	0.14	4.8	0.08	6.2
Neomycin sulfate	–	0.11	3.7	0.06	–
Penicillin G potassium	372.47	0.18	6.0	0.11	3.9
Penicillin G Procaine	588.71	0.10	3.3	0.06	3.5
Phenobarbital sodium	254.22	0.24	8.0	0.14	3.6
Phenol	94.11	0.35	11.7	0.20	1.9
Potassium chloride	74.55	0.76	25.3	0.45	3.3
Procaine hydrochloride	272.77	0.21	7.0	0.12	3.4
Quinine hydrochloride	396.91	0.14	4.7	0.08	3.3
Sodium chloride	58.45	1.00	33.3	0.58	3.4
Streptomycin sulfate	1457.44	0.07	2.3	0.04	6.0
Sucrose	342.30	0.08	2.7	0.05	1.6
Tetracycline hydrochloride	480.92	0.14	4.7	0.08	4.0
Urea	60.06	0.59	19.7	0.35	2.1
Zinc chloride	139.29	0.62	20.3	0.37	5.1

Example

Isotonicity

How much sodium chloride is required to render 100 mL of a 1% solution of apomorphine hydrochloride isotonic with blood serum?

From table it is found that a 1% solution of the drug has a freezing point lowering of 0.08 °C. To make this solution isotonic with blood, sufficient sodium chloride must be added to reduce the freezing point by an additional 0.44 °C (0.52 °C − 0.08 °C). In the freezing point table, it is also observed that a 1% solution of sodium chloride has a freezing point lowering of 0.58 °C. By the method of proportion,

$$\frac{1\%}{X} = \frac{0.58^{\circ}}{0.44^{\circ}};\ X = 0.76\%$$

Thus, 0.76% sodium chloride will lower the freezing point the required 0.44 °C and will render the solution isotonic. The solution is 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.

sodium chloride equivalent method

- The sodium chloride equivalent of a drug is the amount of sodium chloride that is equivalent to (i.e., has the same osmotic effect as) 1 g, or other weight unit, of the drug.
- The sodium chloride equivalents *E* for a number of drugs are listed in table(**Isotonic value).**
- *E* value for new drug can be calculated using the following equation

$$E \cong 17 \frac{L_{iso}}{MW}$$

Example

Sodium Chloride Equivalents

Calculate the approximate *E* value for a new amphetamine hydrochloride derivative (molecular weight 187).

Because this drug is a uni-univalent salt, it has an *L*iso value of 3.4. Its *E* value is calculated from equation :

$$E \cong 17 \frac{L_{iso}}{MW}$$

$$E = 17 \frac{3.4}{187} = 0.31$$

Calculations for determining the amount of sodium chloride or other inert substance to render a solution isotonic (across an ideal membrane) simply involve multiplying the quantity of each drug in the prescription by its sodium chloride equivalent and subtracting this value from the concentration of sodium chloride that is isotonic with body fluids, namely, 0.9 g/100 mL

Example

Tonicity Adjustment

A solution contains 1.0 g of ephedrine sulfate in a volume of 100 ml. What quantity of sodium chloride must be added to make the solution isotonic? How much dextrose would be required for this purpose? The quantity of the drug is multiplied by its sodium chloride equivalent, *E*, giving the weight of sodium chloride to which the quantity of drug is equivalent in osmotic pressure

$$\text{Ephedrine sulfate: } 1.0\text{ g} \times 0.23 = 0.23\text{ g}$$

The ephedrine sulfate has contributed a weight of material osmotically equivalent to 0.23 g of sodium chloride. Because a total of 0.9 g of sodium chloride is required for isotonicity, 0.67 g (0.90 − 0.23 g) of NaCl must be added

If one desired to use dextrose instead of sodium chloride to adjust the tonicity, the quantity would be estimated by setting up the following proportion. Because the sodium chloride equivalent of dextrose is 0.16,

$$\frac{1\text{ g dextrose}}{0.16\text{g NaCl}} = \frac{X}{0.67\text{ g NaCl}}$$

$$X = 4.2\text{ g of dextrose}$$

class II methods

White–Vincent method

- The class II methods of computing tonicity involve the addition of water to the drugs to make an isotonic solution, followed by the addition of an isotonic or isotonic-buffered diluting vehicle to bring the solution to the final volume
- Suppose that one wishes to make 30 mL of a 1% solution of procaine hydrochloride isotonic with body fluid.
- First, the weight of the drug, w, is multiplied by the sodium chloride equivalent, E:

$$0.3\,g \times 0.21 = 0.063\,g$$

This is the quantity of sodium chloride osmotically equivalent to 0.3 g of procaine hydrochloride. Second, it is known that 0.9 g of sodium chloride, when dissolved in enough water to make 100 mL, yields a solution that is isotonic. The volume, *V*, of isotonic solution that can be prepared from 0.063 g of sodium chloride (equivalent to 0.3 g of procaine hydrochloride) is obtained by solving the proportion

$$\frac{0.9\ \text{g}}{100\ \text{mL}} = \frac{0.063\ \text{g}}{V}$$

$$V = 0.063 \times \frac{100}{0.9}$$

$$V = 7.0\ \text{mL}$$

the quantity 0.063 is equal to the weight of drug, *w*, multiplied by the sodium chloride equivalent, *E*, The value of the ratio 100/0.9 is 111.1. Accordingly, equation can be written as

$$V = w \times E \times 111.1$$

where V is the volume in milliliters of isotonic solution that may be prepared by mixing the drug with water, w is the weight in grams of the drug given in the problem, and E is the sodium chloride equivalent obtained from table(**Isotonic value)**

The constant, 111.1, represents the volume in milliliters of isotonic solution obtained by dissolving 1 g of sodium chloride in water.

The problem can be solved in one step using equation

$$V = w \times E \times 111.1$$

$$V = 0.3 \times 0.21 \times 111.1$$

$$V = 7.0\,\mathrm{mL}$$

To complete the isotonic solution, enough isotonic sodium chloride solution, another isotonic solution, or an isotonic buffered diluting solution is added to make 30 mL of the finished product. When more than one ingredient is contained in an isotonic preparation, the volumes of isotonic solution, obtained by mixing each drug with water, are additive

Example

Isotonic Solutions

Make the following solution isotonic with respect to an ideal membrane

Phenacaine hydrochloride	0.06 g
Boric acid	0.30 g
Sterilized distilled water, enough to make	100.0 mL

$$V = [(0.06 \times 0.20) + (0.3 \times 0.50)] \times 111.1$$

$$V = 18 \text{ mL}$$

The drugs are mixed with water to make 18 mL of an isotonic solution, and the preparation is brought to a volume of 100mLby adding an isotonic diluting solution


THANK YOU