Buffered Isotonic Solutions

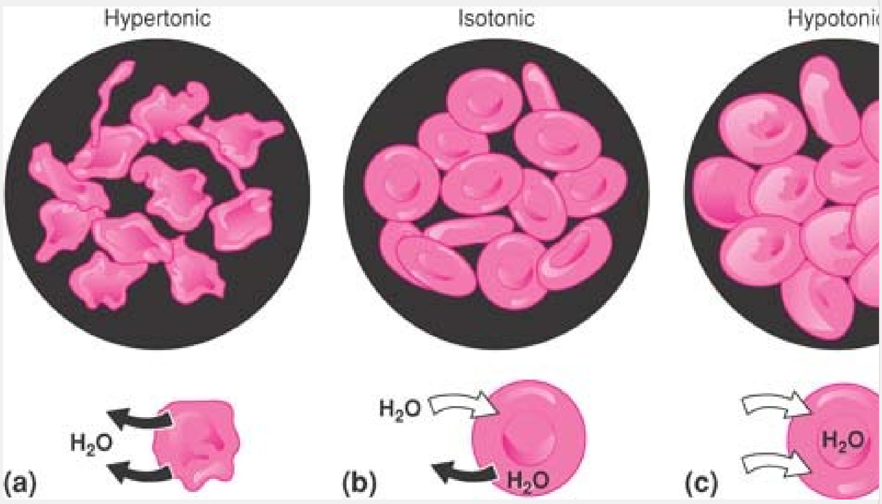
Pharmaceutical solutions that are meant for application to delicate membranes of the body should also be adjusted to approximately the same osmotic pressure as that of the body fluids. Isotonic solutions cause no swelling or contraction of the tissues with which they come in contact and produce no discomfort when instilled in the eye, nasal tract, blood, or other body tissues. Isotonic sodium chloride is a familiar pharmaceutical example of such a preparation

The need to achieve isotonic conditions with solutions to be applied to delicate membranes is dramatically illustrated by mixing a small quantity of blood with aqueous sodium chloride solutions of varying tonicity.

a) ***isotonic***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
b) ***hypertonic***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. This outward passage of water causes the cells to shrink and become wrinkled or***crenated***.
c) ***hypotonic*** 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.The salt solution in this instance is said to be with respect to the blood cell contents. Finally, This phenomenon is known as***hemolysis*** .

Isosmotic solutions

The red blood cell membrane is not impermeable to all drugs; that is, it is not a perfect semipermeable membrane. Thus, it will permit the passage of not only water molecules but also solutes such as urea, ammonium chloride, alcohol, and boric acid.These solutes are regarded as solvent and they do not exert an osmotic pressure on the membrane (the solutions are ***isosmotic*** but not isotonic) A 2.0% solution of boric acid has the same osmotic pressure as the blood cell contents when determined by the freezing point method and is therefore said to be ***isosmotic with blood***. The molecules of boric acid pass freely through the erythrocyte membrane, however, regardless of concentration. As a result, this solution acts essentially as water when in contact with blood cells. Because it is extremely hypotonic with respect to the blood, boric acid solution brings about rapid hemolysis. Therefore, a solution containing a quantity of drug calculated to be isosmotic with blood is isotonic .Accordingly, a 2.0% boric acid solution serves as an isotonic ophthalmic preparation.



Tonicity

Osmolality and osmolarity:- are colligative properties that measure the concentration of the solutes independently of their ability to cross a cell membrane.

Tonicity:- is the concentration of only the solutes that cannot cross the membrane since these solutes exert an osmotic pressure on that membrane.

Tonicity is *not* the difference between the two osmolarities on opposing sides of the membrane. A solution might be hypertonic, isotonic, or hypotonic relative to another solution.

A solution containing a quantity of drug calculated to be isosmotic with blood is isotonic *only* when the blood cells are impermeable to the solute (drug) molecules and permeable to the solvent, water.

Measurement of Tonicity

1)hemolytic method:- the effect of various solutions of the drug is observed on the appearance of red blood cells suspended in the solutions.

a quantitative method developed by Hunter was used based on the fact that a hypotonic solution liberates oxyhemoglobin in direct proportion to the number of cells hemolyzed. The van't Hoff *i* factor can be determined and the value compared with that computed from cryoscopic data, osmotic coefficient, and activity coefficient.

2)***measurement of the slight temperature differences***:-The second method is based on a arisingmeasurement of the slight temperature differences from differencesin the vapor pressure of thermally insulated samples contained in constant-humidity chambers.

One of the first references to the determination of the freezing point of blood and tears (as was necessary to make solutions isotonic with these fluids) is that -0.52°C is the freezing point of both human blood and lacrimal fluid. This temperature corresponds to the freezing point of a 0.90% NaCl solution, which is therefore considered to be isotonic with both blood and lacrimal fluid.

3)Calculating Tonicity Using $_{Liso}$ Values

Because the freezing point depressions for solutions of electrolytes of both the weak and strong types are always greater than those calculated from the equation $\Delta T_f = K_f c$, a new factor, $L = iK_f$, is introduced to overcome this difficulty. The equation, already discussed is

$$\Delta T_f = Lc \qquad (8\text{–}36)$$

The *L* value can be obtained from the freezing point lowering of solutions of representative compounds of a given ionic type at a concentration *c* that is isotonic with body fluids. This specific value of *L* is written as L_{iso}.

The L_{iso} value for a 0.90% (0.154 M) solution of sodium chloride, which has a freezing point depression of 0.52°C and is thus isotonic with body fluids, is 3.4: From

$$L_{iso} = \frac{\Delta T_f}{c} \qquad (8\text{–}37)$$

we have

$$L_{iso} = \frac{0.52°C}{0.154} = 3.4$$

The interionic attraction in solutions that are not too concentrated is roughly the same for all uni-univalent electrolytes regardless of the chemical nature of the various compounds of this class, and all have about the same value for L_{iso}, namely 3.4. As a result of this similarity between compounds of a given ionic type,

It will be observed that for dilute solutions of nonelectrolytes, L_{iso} is approximately equal to K_f. . A plot of iK_f against molar concentration of various types of .electrolytes, from which the values of L_{iso} can be read

Methods of Adjusting Tonicity and pH

One of several methods can be used to calculate the quantity of sodium chloride, dextrose, and other substances that may be added to solutions of drugs to render them isotonic.

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 the ***cryoscopic method*** and the ***sodium chloride equivalent method.*** In the class II methods, water is added to the drug in a sufficient amount to form an isotonic solution. The preparation is then brought to its final volume with an isotonic or a buffered isotonic dilution solution. Included in this class are the ***White–Vincent method*** and the ***Sprowls method.***

Class I Methods

a)*Cryoscopic Method*

The freezing point depressions of a number of drug solutions, determined experimentally or theoreticallyfrom the equation:-

$\Delta T_f = iK_f c$

For solution of electrolytesanew factor($L = iK_f$) is used :

$\Delta T_f = Lc$

TheL value for solution that is isotonic with the body fluid is written as L_{iso}

$\Delta T_f = L_{iso} c$

If the concentration of drug is chosen to be 1% then ΔT_fcan be calculated by the equation :

$$\Delta T_f = L_{iso} \frac{10}{M.Wt}$$

b)Sodium Chloride Equivalent (E) Method

Sodium Chloride Equivalent (E)of a drug ug is the amount of sodium chloride that has the same osmotic effect of 1 g, or other weight unit, of the drug.

The *E* value can be calculated from the L_{iso} value or freezing point depression. For a solution containing 1 g of drug in 1000 mL of solution

$$\Delta T_f = L_{iso} \frac{1\text{ g}}{\text{MW}}$$

Now, *E* is the weight of NaCl with the same freezing point depression as 1 g of the drug, and for a NaCl solution containing *E* grams of drug per 1000 mL,

$$\Delta T_f = 3.4 \frac{E}{58.45} \qquad (8\text{–}43)$$

where 3.4 is the L_{iso} value for sodium chloride and 58.45 is its molecular weight. Equating these two values of ΔT_f yields

$$\frac{L_{iso}}{\text{MW}} = 3.4 \frac{E}{58.45} \qquad (8\text{–}44)$$

$$E \cong 17 \frac{L_{iso}}{\text{MW}} \qquad (8\text{–}45)$$

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.

Other agents than dextrose can of course be used to replace NaCl.

$$X = \frac{Y\text{(Additional amount of NaCl for isotonicity)}}{E\text{(Grams of NaCl equivalent to 1 g of the isotonic agent)}} \quad (8\text{–}46)$$

where *X* is the grams of isotonic agent required to adjust the tonicity, *Y* is the additional amount of NaCl for isotonicity over and above the osmotic equivalence of NaCl provided by the drugs in the solution, and *E* is the sodium chloride equivalence of the isotonic agent.

Class II Methods

a) 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. Stimulated by the need to adjust the pH in addition to the tonicity of ophthalmic solutions.

White –Vincent developed a simplified equation for calculating the volume V (mls) of osmotic solution prepared by mixing drug with water.

$$V = w \times E \times 111.1 \quad (8\text{–}51)$$

w is the weight in grams of the drug and E NaCl equivalent

b) The Sprowls Method

A further simplification of the method of White and Vincent method in which V value for drugs of fixed weight 0.3 g in 1% solusion are computed and constructed as a table.