International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
DOI: 10.22192/ijarbs Coden: IJARQG(USA) Volume 3, Issue 10 - 2016

Review Article

DOI: http://dx.doi.org/10.22192/ijarbs.2016.03.10.028

Methods of adjusting tonicity and pH values of some drugs and substances.

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Abstract

Lachrymal fluid is isotonic with blood having an isotonicity valve corresponding to that of a 0.9% Nacl solution. Ideally, an ophthalmic solution should have this isotonicity valve, but the eye can tolerate isotonicity valves as low as that of a 0.6% Nacl solution and as high as that of a 2% Nacl solution without marked discomfort. Some ophthalmic solutions are necessarily hypertonic in order to enhance absorption and to provide a concentration of the active ingradient(s) strong enough to exert a prompt and effective action. The amount of such solution used is small because, on administration, the dilution with lachrymal fluid takes place rapidly with minimal discomfort from the hypertonicity which is only temporary. However, any adjustment toward isotonicity by dilution with tears is negligible where large volumes of solutions are used as collyria to wash the eyes. It is, therefore, important that solutions used for this purpose be approximately isotonic.

Keywords: Lachrymal fluid, ophthalmic solution, Isotonicity, Hypertonic, Collyria, Nacl solution.

Introduction

Tonicity is a measure of effective osmolarity in cell biology. Osmolarity and osmolarity are properties of a particular solution, independent of any membrane. Osmolarity is a concentration scale to express the total concentration of solute particles and is directly related to any of the four colligative properties. It is derived from molality by factoring in the dissociation of electrolytic solutes. Tonicity is a property of a solution in reference to a particular membrane, and is equal to the sum of the concentrations of the solutes which have the capacity to exert an osmotic force across the membrane. Tonicity depends on solute permeability. The permeable solutes do not affect tonicity. If a semi-permeable membrane is used to separate solutions of different solute concentrations, a phenomenon known as osmosis occurs to establish concentration equilibrium. The pressure driving this movement is called osmotic pressure and governed by the number of particles of solute in a solution. If solute is a non-electrolyte, then number of particles is determined solely by the solute concentration. If the solute is an electrolyte, the number of particles is governed by the concentration and degree of dissociation of the substance.

The distinction between the isosmotic and isotonic terms comes with the realization that red blood cell membrane are not perfect semi-permeable membranes but allow passage of some solutes, such as alcohol, ammonium chloride, glycerin, ascorbic acid, lactic acid etc. As mentioned earlier a 2% solution of boric acid, when physically measured, is found to be isosmotic (containing the same number of particles) with blood and not isotonic (exerting equal pressure or tone) with blood but is isotonic with tears. This difference does not have any great significance and,

therefore, isotonicity values are calculated on the basis of the number of particles in solution. The clinical significance of all this is to insure that isotonic or isosmotic solutions do not damage tissue or produce pain when administered.

Tonicity is generally classified in three types:

1. Hypertonicity
2. Hypo tonicity
3. Isotonicity

Hypertonic, isotonic and hypotonic solutions are defined in reference to a cell membrane by comparing the tonicity of the solution with the tonicity within the cell.

Hypertonicity

A solution having higher osmotic pressure than the body fluids (0.9% Nacl) is known as hypertonic solution. These solutions draw water from the body tissues to dilute and establish equilibrium. An animal cell in a hypertonic environment is surrounded by a higher concentration of impermeable solute than exists in the inside of the cell.

For example, if 2% Nacl solution is added to blood (defibrinated),osmotic pressure directs a net movement of water out of the cell, causing it to shrink (the shape of the cell becomes distorted) and wrinkled (crenated),as water leaves the cell. This movement is continued until the concentrations of salt on both sides of the membrane are identical. Hence, 2% Nacl solution is hypertonic with the blood.

Isotonicity

Solutions that have the same osmotic pressure as that of body fluids are said to be isotonic with the body fluid. Body fluids such as blood and tears have osmotic pressure corresponding to that of 0.9% Nacl or dextrose aqueous solution; thus, a 0.9% Nacl or 5 %**,** dextrose solution is called as isosmotic or isotonic. The term isotonic means equal tone, and is used interchangeably with isosmotic with reference to specific body fluids.

For example, a 0.9% w/v solution of Nacl in water is considered to be isotonic in relation to RBC's and their semi-permeable membranes.

Requirements of isotonic solutions are that they must not cause any contraction or swelling of the tissues. The product must not produce discomfort when installed in the eye, nasal tract, blood, or other body tissue. On addition of 0.9gm Nacl/100ml (0.9%) in to blood (defibrinated), the cells retain their normal size. Isotonic solution should be restricted to solutions having equal osmotic pressure with respect to a particular membrane.

The addition of any compound to a solution affects its isotonicity, causing changes in osmotic pressure of a solution. It should not be affected only by drugs but also by any buffer components added in the formulation. Therefore, it is necessary to add additional Nacl to bring the solution to isotonicity. Adjustment of isotonicity is required for several dosage forms such as parenteral solutions, e.g., IV infusions, irritating solutions, lotions for open wounds, subcutaneous injections, preparations meant for diagnostic applications, solutions meant for intrathecal injections, nasal drops and ophthalmic drops.

Hypo tonicity

A solution with low osmotic pressure than body fluids is known as hypotonic solution. The effects of administering a hypotonic solution are generally more severe than with hypertonic solutions, since ruptured cells can never be repaired. Hypertonic solutions show the opposite effect when compared to hypertonic solutions where the net movement of water into the cell causes them to swell. If the cell contains more impermeable solute than its surroundings, water enters it. In case of animal cells, they swell until they burst; but this doesn't happen to plant cells, i.e., they do not burst due to the reinforcement their cell wall provides. If 0.2% Nacl solution is added to blood (defibrinated) , the cells swell and burst. Therefore, 0.2% Nacl solution is hypotonic with respect to the blood.

Methods used to determine tonicity value

Many chemicals and drugs are used in pharmaceutical formulations. These substances contribute to the tonicity of the solution. Hence, methods are needed to verify the tonicity and adjust isotonicity. Two methods used to determine tonicity valve are described below

Hemolytic method

Isotonicity valve is calculated by using the hemolytic method in which the effect of various solutions of drug is observed on the appearance of red blood cells suspended in solution. In this method, RBC's are suspended in various solutions and the appearance of RBC's is observed for swelling, bursting, shrinking

and wrinkling of the blood cells. In hypertonic solutions, the oxyhaemoglobin released is proportional to the number of cells haemolysed; in case of hypertonic solutions, the cells shrink and become wrinkled or crenated whereas in case of isotonic solutions the cells do not change their morphology.

Cryoscopic method

Isotonicity values can be determined from the colligative properties of the solutions. For this purpose, freezing point depression property is most extensively used. The freezing point of water is 0°C, and when any substance such as Nacl is added to it, the freezing point of water decreases. The freezing point of depression (ΔTf) of blood is -0.52°C. Hence, the $\Delta Tf\ value\ of\ the$ drug solution must be -0.52°C. This solution shows an osmotic pressure equal to the blood.

Methods of adjusting Tonicity and pH

Several methods are used to adjust the isotonicity of pharmaceutical solutions. Isotonicity can be calculated from the colligative properties of drug solutions. If solutions are injected or introduced in to eyes and nose, these are to be made isotonic in order to avoid haemolysis of RBC's and to avoid pain and discomfort. This is possible for either manufactured or extemporaneous prepared solutions. By using the appropriate calculations based on colligative properties of solutions, it is easy to determine the amount of adjusting agents to be added. It helps to overcome the side effects caused from administering solutions which contain adjusting agents less or more than isotonic solutions. The three frequently used methods to calculate isotonicity of the solutions are described below.

Class-1 Methods: Nacl or some other substances is added to the solution of the drug to lower the freezing point of the solution to -0.52°C and thus make the solution isotonic.

Examples of this class-

1) Cryoscopic method
2) Sodium chloride equivalent method.

Class-2 Methods: Water is added to the drug in a sufficient amount to make it isotonic. Then the preparation is brought to its final volume with an isotonic or buffered isotonic solution.

Examples of this class- White Vincent method

Class-3 Methods: Freezing point depression and L iso values for number of drugs are estimated theoretically from the molecular weight of the drug and can be used to calculate the amount of adjusting substance to be added in order to make the solution isotonic.

Cryoscopic method

In this method, the quantity of each substance required for an isotonic solution can be calculated from the freezing point depression values. A solution which is isotonic with blood has a ΔTf of 0.52°C. Therefore, the freezing point of drug solution must be adjusted to this valve. Many pharmaceutical text books usually list the freezing point of depression x needed to achieve isotonicity from these values In case of drug solutions, if it is not possible to adjust tonicity by altering the drug concentration, then an adjusting substance is added to achieve desired tonicity.

The weight (in grams) of adjusting substance can be calculated in manner described below. For example, the drug concentration in 100ml solution is a grams, then

ΔTf (For drug solution) = $a \times \Delta Tf\ of\ 1\%\ drug\ solution$

$= x$

If w be in grams of the adjusting substance to be added to 100 Ml of drug solution to make it isotonic then:

ΔTf(For adjusting solution) = w $\times\ \Delta Tf$ of 1% adjusting substance

$= w \times b$

For making a solution isotonic:

$$x + wb = 0.52$$

$$\text{Or,} \quad w = 0.52 - x/b$$

If sodium chloride is used as adjusting substance whose ΔTf of solution is 0.58°C (0.576°C) then

$$w = 0.52 - x/0.58$$

Example- If 1% w/v solution of Nacl has freezing point depression of 0.576 °C; calculate the concentration of Nacl required in making this solution isotonic.

Solution: Since the freezing point of depression of blood is 0.52°C, the concentration of Nacl required to make this solution isotonic is calculated as:

Concentration of Nacl = 0.52/0.576 × 1
= 0.9% w/v

The concentration of Nacl required to this make isotonic is 0.9%w/v.

Sodium chloride equivalent method

Tonicity equivalent or sodium chloride equivalent method is used to adjust the tonicity of pharmaceutical solutions.

Sodium chloride equivalent (E) of a drug is the amount of sodium chloride that is equivalent to 1 gm of the drug.

The percent of sodium chloride required for adjusting the isotonicity can be calculated using the following equation.

PSA = 0.9 – (PSM × E of medicament)

Where,

PSM = Percent strength of medicament
PSA = Percent of sodium chloride for adjustment of isotonicity

Above equation is used to calculate the amount of adjusting substance (sodium chloride) required for making the solution isotonic. It is valid for 100 ml solution.

Example - Calculate the gram of sodium chloride needed to make 30 ml of a 2% isotonic physostigmine salicilate solution using sodium chloride method.

Solution:

E value of physostigmine salicilate = 0.16
PSM =2.0 %
Volume of preparation required = 30 ml

For equation

PSM = 0.9 – (PSM × E of medicament)
= 0.9 – (2.0 × 0.16)
= 0.9 - 0.32 = 0.58 %

The above strength is valid for 100 ml since is expressed in percent. It should be prepared from 30 ml of solution

For 100 ml of solution, sodium chloride required = 0.58
For 30 ml of solution, sodium chloride required =?

30 × 0.58/100 = 17.4/100 =0.174 g of sodium chloride

Freezing point depression (ΔTf) and E values of some drugs added substances:

Solution, 1% w/v drug	ΔTf, °C	E
Apomorphine hydrochloride	0.08	0.14
Boric acid	0.29	0.50
Calcium gluconate	0.09	0.16
Pilocarpine nitrate	0.14	0.23
Potassium chloride	0.45	0.76
Sodium chloride	0.58	1.00
Sodium sulphacetamide	0.14	0.23

The L ISO – Method

The E Nacl value of tonicity adjusting substances can also be calculated from the substances. The L iso values of the tonicity adjusting substances are given in table and are mentioned as constants in many references.

In this method, the freezing point depression equation is used to calculate the amount of the isotonicity adjusting substance that must be added to hypotonic solution of drug to bring to tonicity. As the freezing point depression for solutions of electrolytes are than those calculated by the equation, $\Delta Tf = Kfm$, a new constant L iso is introduced to account for this deviation. The equation then becomes

ΔTf = L iso C

Where ΔTf = L iso is the molal freezing point depression of water considering the ionization of electrolyte. i.e., iKf and C is the concentration of the solution in molarity. In dilute solutions, the molal concentrations are not much different from the molal concentration and can be used interchangeably.

The following equation helps to calculate the E Nacl value from L iso value of the substances. The ΔTf of 1 g of drug per 100ml of solution is equal to L iso C. Therefore,

$$\Delta Tf = \text{L iso 1 g /M}$$
$$= \text{L iso /M}$$

Where M is molecular weight of solute Since, the L iso value of Nacl is 3.4,

$$\Delta Tf = 3.4 \times E\,Nacl\,/58.45$$

Where E Nacl is the weight of Nacl with the same freezing point as 1 g of drug. Thus

$$\text{L iso} = 3.4 \times E\frac{Nacl}{58.45}$$
$$\text{E Nacl} = 17 \times L\,iso/\text{M}$$

In some cases instead of Nacl, another isotonic agent such as mannitol, propylene glycol, or glycerin is used. Using E Nacl values, isotonic solutions are prepared by just multiplying quantity of each drug in the formulation by its E Nacl values and subtracting them from the 0.9g/100ml. Thus, for x grams of drug, the amount of Nacl required to obtain 100 ml solution isotonic is obtained as

$$\text{Amount of Nacl (Y)} = 0.9 - [(x) \times (E\,Nacl)]$$

For using another isotonic agent, its amount (X) required to make solution isotonic is obtained by

$$X = Y/E\ Nacl$$

L ISO Values of the Tonicity adjusting substances

Type of substance	Examples	L iso values
Non-electrolytes	Sucrose, Urea, Propylene glycol	1.9
Weak- electrolytes	Boric acid, Phenobarbital	2.0
Di-divalent electrolytes	Zinc sulphate, Magnesium sulphate	2.0
Uni-univalent electrolytes	Sodiumchloride,Amphetaminehydrochloride	3.4
Uni- divalent electrolytes	Sodium sulphate, Atropine sulphate	4.3
Di- univalent electrolytes	Zinc chloride, Calcium bromide	4.8
Uni- trivalent electrolytes	Sodium phosphate, Sodium citrate	5.2
Tri- univalentelectrolytes	Aluminum chloride, ferric iodide	6.0
Tetra borate- electrolytes	Sodium borate, potassium borate	7.6

White-Vincent method: This method involves use of addition of water to the solution to make isotonic followed by final volume adjustment with addition of isotonic or isotonic buffered solution. White Vincent, from their study of need of Ph adjustment in addition to tonicity of ophthalmic solution, developed an equation

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DOI:10.22192/ijarbs.2016.03.10.028	

How to cite this article:
M. Hareesh Reddy, K. Sambasivarao, Chandrasekhara Rao Baru (2016). Methods of adjusting tonicity and pH values of some drugs and substances. Int. J. Adv. Res. Biol. Sci. 3(10): 207-212.
DOI: http://dx.doi.org/10.22192/ijarbs.2016.03.10.028