BUFFERED ISOTONIC SOLUTIONS

The pH of pharmaceutical solutions that are meant to be applied on the delicate membranes of the body must be adjusted nearly to the same osmotic pressure as that of the body fluids. After coming in contact with the body tissue, the isotonic solutions do not cause swelling or tissue contraction. These buffered isotonic solutions should not produce any discomfort when instilled in nasal passage, eye, blood or other body tissues.

Isotonic Solutions:

Isotonic solutions are those solutions having the same osmotic pressure as a specific body fluid. In an isotonic solution, the concentration of solutes is the same on both sides of the cell membrane.

For example, If blood cells retain their normal size on mixing with 0.9% NaCl solution. Therefore, they have same osmotic pressue as the RBCs and are recognised to be isotonic with the blood.

Some of the standard isotonic solutions are:

0.9% w/v Normal saline (sodium chloride) solution
5.0% w/v Dextrose solution
2.0% w/v Boric acid solution

These solutions do not cause swelling or shrinking of tissues when applied. Therefore, discomfort would not be caused when instilled into the eyes, nasal tract and when injected into blood or other body fluids.

In the human body, different types of cell membranes are available. All are not having samelevel of permeability to a single substance. For example, red blood cell membrane and mucous lining of the eye are not the same. Therefore, isotonic solutions of 0.9% w/v sodium chloride also need not necessarily be isotonic with respect to all the living membranes, but many of them are roughly isotonic.

Hypertonic Solutions:

Hypertonic solutions are those solutions having the higher osmotic pressure as a specific body fluid. In an hypertonic solution, the concentration of solutes is higher compared to the cell.

For example, If the RBCs are mixed in a solution of 2% NaCl the water contents of cells passes through the cell membrane in order to dilute the surrounding salt solution until the salt concentratioons on both sides of the cell membrane becomes equal.

Thus outward movement of water causes shrinking of cells and make them wrinkled or crescent shaped. Such solutions are recognised as hypertonic solutions with respect to the blood cell contents.

Some hypertonic solutions are:

2.0% w/v Normal saline (sodium chloride) solution
10.0 % w/v Dextrose solution
3.0 % w/v Boric acid solution

Hypotonic Solutions:

Hypotonic solutions are those solutions having the lower osmotic pressure as a specific body fluid. Hypotonic solutions have a lower concentration of solutes compared to the cell.

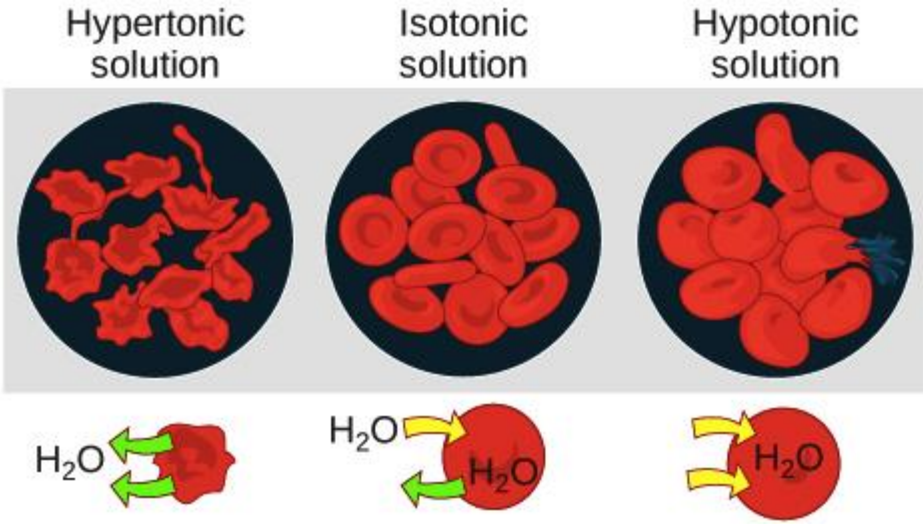
For example, If RBCs are suspended in 0.2% NaCl solution the water enters into the blood cell and makes them swell or burst to liberate hemoglobin. This phenomenon is termed as haemolysis.Such solutions are recognised as hypotonic solutions with respect to the blood cell contents.

Some hypotonic solutions are:

0.2% w/v Normal saline (sodium chloride) solution

3.0% w/v Dextrose solution

1.0% w/v Boric acid solution



MEASUREMENT OF TONICITY

Tonicity is defined as the concentration of only solutes that are unable to cross the membrane because an osmotic pressure is exerted by the solutes on that membrane.The tonicity of a solution has significant implications for cell function, and maintaining the appropriate tonicity is essential for the normal physiological functioning of cells and organisms.

There are broadly two methods to measure tonicity:

1. Haemolytic Method

This method is based on effects of various solutions of drug on the appearance of RBCs suspended in the solutions. It was developed by Hunter.

This method can be made more accurate by using a hematocrit, which is a centrifuge head in which a graduated capillary tube is held in each of the two arms.

One capillary tube(tube A) is filled with blood diluted with 5ml of 0.9% w/v NaCl solution.The other capillary tube (tube B) is filled with blood diluted with 5ml of test solution.

Both tubes are centrifuged. After centrifuge, the blood cells are concentrated at one end of the capillary tubes and the volume occupied by the cells (PCV-Packed cell volume) is measured.

Finally, the PCV of test solution (tube B) is compared with PCV of isotonic solution(tube A) and the following inferences are made.

- If PCV of test solution (tube B) = tube A, then test solution is regarded as isotonic.
- If PCV of tube B is more than that of tube A, then test solution is regarded as hypotonic solution.
- If PCV of tube B is less than that of tube A, then test solution is regarded as hypertonic solution.

2. 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 of blood is -0.52°C. Hence, the drug solution must be -0.52°C. This solution shows an osmotic pressure equal to the blood.

The freezing point of the solution is compared to the freezing point of a reference solution.This method involves measuring the change in the freezing point of a solution as a result of the solutes present. The degree of depression is proportional to the concentration of solutes in the solution and can be used to calculate the tonicity.

Measuring tonicity is an important step in the development and formulation of pharmaceuticals, as it can help to ensure the safety and efficacy of drugs and other therapeutics.

CALCULATIONS AND METHODS OF ADJUSTING TONICITY

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.

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 methods to calculate isotonicity of the solutions are described below.

Class-I Method:

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.

These methods are of two types:

1) Cryoscopic method

2) Sodium chloride equivalent method

1) 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 Δ Tf of 0.52°C. Therefore, the freezing point of drug solution must be adjusted to this value. 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.

$$W = \frac{0.52 - a}{b}$$

Where, W = weight of substance that need to be adjusted to make it isotonic substance in gm.

a = the depression of the freezing point of water produced by the medicament already in the solution.

b = the depression of freezing of water produced by 1 % w/v of the added substance.

Advantage: Determination of depression in the freezing point is much simpler and more convenient.

NUMERICAL:

Find concentration of NaCl required to make 1% solution of boric acid isotonic with blood plasma. Freezing point depression of 1%w/v of boric acid= -0.288^{0}C and freezing point depression of 1%w/v of NaCl is -0.576^{0}C

Solution

$$W = \frac{0.52 - a}{b}$$

$$= \frac{0.52 - 0.288}{0.576}$$

= 0.402 gm/100 ml

2) Sodium chloride equivalent method

Sodium chloride equivalent of a drug is defined as the gms of NaCl that will produce the same osmotic effect as 1gm of that drug.

It is used to convert a specified concentration of medicament to the concentration of sodium chloride which will produce the same osmotic effect.

Amount of NaCl required for isotonicity adjustment = 0.9 - (% of medicament solution × E)

NUMERICAL:

Find out the amount of sodium chloride needed to make a solution of 0.5% KCl isotonic with blood plasma. NaCl equivalent value of KCl is 0.76

Solution

Amount of NaCl required for isotonicity adjustment = 0.9 - (% of medicament solution × E)

= 0.9 - (0.5 × 0.76)
= 0.9 - 0.38
= 0.52 gm

Therefore 0.52 gm of NaCl must be added in 0.5% KCl solution to make it isotonic.

Class-II Method:

This method invloves addition of water to the given amount of drug to make isotonic solution followed by the addition of some other isotonic solution (ex. 0.9 % NaCl) to make the final volume.

These methods are of two types:

1) White-Vincent method
2) Sprowls method.

1) White-Vincent method

The White–Vincent method uses the NaCl equivalent value of the material to obtain isotonic volume by multiplying the mass of the material and its NaCl equivalent value by 111.1 as a constant. White –Vincent developed a simplified equation for calculating the volume V (ml) of osmotic solution prepared by mixing drug with water.

$$\boxed{V = w \times E \times 111.1}$$

Where, V = volume of isotonic solution (in ml) that is prepared by mixing the drug with water.

w = Weight of the drug (in gm)

E = Sodium chloride equivalent of the drug

<u>NUMERICAL:</u>

Make 50ml isotonic solution from 0.5 gm of boric acid. E value of boric acid is 0.50

Solution

Weight of boric acid = 0.5 gm

Required volume = 50 ml

E value of boric acid = 0.50

$\boxed{V = w \times E \times 111.1}$

$V = 0.5 \times 0.5 \times 111.1$

$= 27.8$ ml

So 0.5 gm of boric acid is dissolved in 27.8 ml of water to make isotonic solution. But final volume requied is 50 ml. Hence remaining 22.2 ml of some other isotonic solution is added to makeup the final 50ml volume.

2) Sprowls method

Sprowls developed a simplified version of the White-Vincent method. For this experiment, 0.3 g of a 1% solution was chosen for use because it is the amount for one fluid ounce. The volume of an isotonic solution that can be prepared by the addition of enough water to 0.3 gm drug. This solution can be used in the formulation of ophthalmic and parentral solutions.

$$\boxed{V = 33.33 \times E}$$

Where, E = Sodium chloride equivalent of the drug

<u>NUMERICAL:</u>

Calculate the volume of an isotonic solution containing 0.3 g phenobarbitone sodium. E value of phenobarbitone sodium = 0.23.

Solution

$\boxed{V = 33.33 \times E}$

$V = 33.33 \times 0.23$

$= 7.67$ ml

So 7.67 ml of water is needed to produce an isotonic solution containing 0.3 g phenobarbitone sodium.

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