Unit- V

pH, Buffers and Isotonic solutions

Buffered isotonic solution:

Isotonic buffered solution is defined as a solution which maintains the iso-tonicity and the pHas that of the body fluids.

Isotonic buffer solution should be compatible with the body fluids for the following reasons.

- ✓ Blood and lacrimal fluids are in vivo buffer systems. Any solution that comes in contact with these fluids should be buffered to a desired pH, so that these are compatible with the body fluids.
- ✓ Some solutions are meant for the application on delicate membranes of the body. Such solutions may cause haemolysis, tissue irritation, necrosis and tissue toxicity. In such cases, solutions must be just to the same osmotic pressure and tonicity as that of the body fluids.

Applications:

Isotonicity should be adjusted for several dosage forms.

1. Parenteral preparations should be isotonic with blood plasma. There can be some flexibility depending on the route of administration and Quantity of solution to be injected.
    - ✓ Intravenous infusions, irrigating solutions, lotions for open wound
    - ✓ Subcutaneous injection.
    - ✓ Parenteral preparations meant for diagnostic purposes, in order to

avoid false reaction

- ✓ Solutions meant for intrathecal injection, because the volume of CSF (Cerebro Spinal Fluid) is only 60 to 80 mL. Hence, hence or hypotonic solutions though in small volumes, will disturb the osmotic pressure and may cause vomiting and other effects.

2. Aqueous solutions used as nasal drops.
3. Ophthalmic drops

Preparation of Isotonic Buffer Solution:

1. The drug and other ingredients are dissolved in water.
2. The pH of the solution is determined and adjusted to the desired value.
3. The tonicity value of the solution is calculated procedures using standard procedures.
4. The amount of sodium chloride required to adjust the tonicity is calculated.
5. The required amount of sodium chloride is added to the solution, so that the final solutionbecomes isotonic.
6. Isotonic diluting solution is added for maintaining the drug concentration to the desired level(dose).
7. If the pH is also needs to be maintained, then buffered isotonic diluting solution is added tomake up the desired volume (dose).

Since the drug solution is already isotonic, any isotonic diluting solution (electrolytes) can beused to dilute the solution.

Some of the isotonic diluting solutions are: Isotonic sodium chloride solution, Dextrose solution, Ringer solution etc.

The isotonic buffered diluting solutions are available in acidic, neutral and alkaline range.

Isotonic buffered diluting solutions are:

- ✓ Isotonic sodium chloride solution USP
- ✓ Dextrose solution 5.0 %
- ✓ Ringer solution USP

Osmosis - Osmotic Pressure:

Osmosis is defined as a process in which the solvent molecules pass through a semipermeable membrane from a pure solvent to a solution or from a dilute solution to a concentrated solution.

Experiment:

Consider a case in which a solution is confined in a membrane that is permeable to solvent. When it is placed in a solvent, diffusion of solvent molecule is observed. This phenomenon istermed as osmosis.

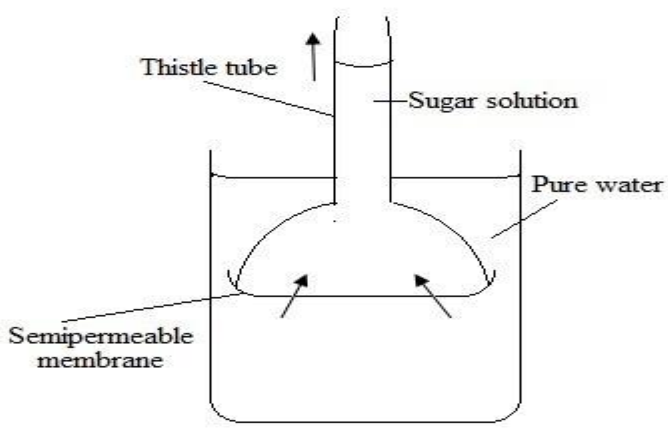


Figure 1: Demonstration of osmotic experiment

The semipermeable membranes (animal and vegetable) regulate the passage of solvent molecules by electrostatic and chemical interactions. The process of osmosis proceeds to equalize the concentration in contact with each other. Thus equilibrium state is achieved. A semipermeable membrane is a barrier which selectively permits the passage of solvent molecules, but not the solute molecules.

The experimental setup for demonstrating the osmosis experiment is shown in Fig-1. Thistle tube has a wide opening at one end. A piece of untreated cellophane is stretched and tied. The tube is partly filled with a concentrated solution of sucrose (a non-volatile substance). The thistle tube is immersed in a beaker of water (Fig-1).

The diffusion of solvent molecules takes place in both directions. But more number of water molecules passes from the beaker (escaping tendencies) through the semipermeable membrane into the tube. This is an attempt to dilute the solute and rise the vapour pressure to its original value. This process creates enough pressure to drive the sugar solution rise up in the tube. At one point, the rise of solution in the tube stops, i.e. equilibrium is achieved.

At equilibrium: Hydrostatic pressure of the column of liquid is equal to flow of water (osmotic pressure) causing the water to pass through the membrane and enters the tube.

Since vapour pressure of the solvent is higher than that of the solute, water molecules diffuse.

Osmotic pressure:

Osmotic pressure may be defined as the hydrostatic pressure build up on the solution, which just stops the osmosis of pure water into the solution through a semipermeable membrane.

The external pressure may be adjusted so as to prevent the osmosis of pure water into solution this provides another definition of osmotic pressure. Osmotic pressure may be defined as the external pressure applied to the solution in order to stop the osmosis of solvent into solution separated by a semipermeable membrane.

Applications:

- ✓ Osmotic pressure principles are used in the preparation of isotonic intravenous and isotonic lacrimal fluids. Such solutions are compatible to body fluids and prevent the damage of delicate biological membranes.
- ✓ In experimental physiology, the tissue is immersed in salt solutions, which are isotonic. Otherwise, tissue gets damaged due to osmosis.
- ✓ A similar behaviour is observed with red blood cells (RBS).
- ✓ When the solutions are in contact with the cells or membranes, tonicity of the cells may be altered, i.e. functions are altered. Based on this behaviour, solutions are designated in different ways.

Iso-osmotic Solutions:

- ✓ Iso-osmotic solutions are those osmotic pressure as that of the cell contents in question, but the solute is solutions which produce the same permeable through the cell membrane thereby altering the tone of the cell.
- ✓ Example of iso-osmotic solution is 1.8 % solution of urea. Iso- osmocity does not necessarily mean isotonic.
- ✓ For example, 1.8 % solution of urea has the same osmotic pressure as that of 0.9% solution of sodium chloride, but former solution produces haemolysis due to permeability of water.
- ✓ Therefore, 1.8% solution of urea is not isotonic, though iso-osmotic.

Isotonic Solutions:

- Isotonic solutions are those solutions which produce the same osmotic pressure as that of the cell contents in question, without net gain or loss of both solutions, provided the cell membrane is impermeable to the solutes.
- Isotonic solutions are iso-osmotic as well as isotonic with the cells and membranes. 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 same- level 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:

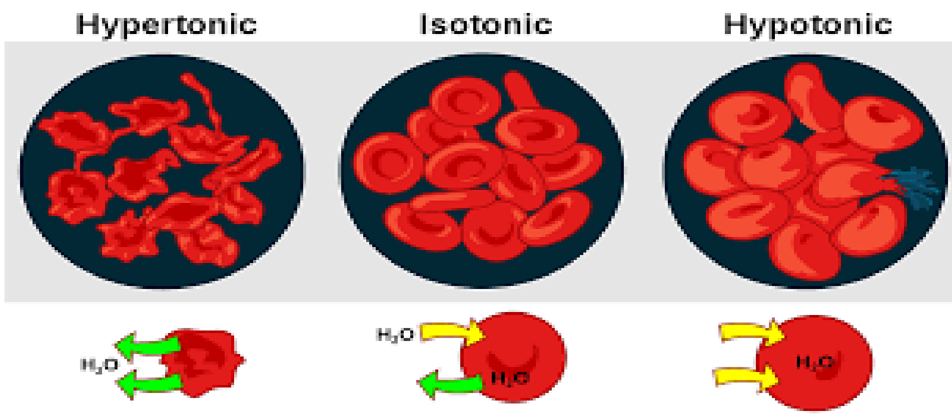
- Hypertonic solutions are defined as those solutions containing the solute in higher concentration than that is required for isotonic solutions.
- Some hypertonic solutions are:
  - 2.0% w/v Normal saline (sodium chloride) solution (concentration > 0.9 % w/v).
  - 10.0 % w/v Dextrose solution (concentration > 5.0% w/v).

- ❖ 3.0 % w/v Boric acid solution (concentration > 2.0% w/v).

- ✓ When red blood cells are suspended in a 2.0 % w/v solution of sodium chloride, the water within the cells passes out through the cell membranes in an attempt to dilute the surrounding salt solution.
- ✓ This process continues until the salt concentrations on both sides of the erythrocyte membrane are equal.
- ✓ Thus outward passage of water causes the cells to shrink and becomes wrinkled or crenated. Such a salt solution is said to be hypertonic with respect to blood.

Hypotonic Solution:

- ✓ Hypotonic solutions are defined as those solutions containing the Solute in lower concentration than that is required for isotonic solutions
- ✓ Some hypotonic solutions are:
  - ❖ 0.2% w/v Normal saline (sodium chloride) solution (concentration <0.9 % w/v).
  - ❖ 3.0% w/v Dextrose solution (concentration <5.0% w/v).
  - ❖ 1.0% w/v Boric acid solution (concentration < 2.0 % w/v).
- ✓ When blood cells are suspended in a 0.2 % w/v solution of sodium chloride (or in distilled water), water enters the blood cells causing them to swell and finally burst with the liberation of haemoglobin.
- ✓ This process is known as haemolysis. Such a weak salt solution is said to be hypotonic with respect to blood.



Measurement of Tonicity

Isotonicity value is defined as the concentration of an aqueous sodium chloride solution having same colligative properties as the solution in question.

Apart from sodium chloride, a number of chemicals and drugs are also included in the formulations. These ingredients also contribute to the tonicity of the solution. Therefore, methods are needed for verifying the tonicity and adjusting the tonicity.

Two methods are mentioned below.

***Hemolytic method*:**

Red blood cells (RBCs) are suspended in various drug solutions and the swelling of RBCs is observed bursting, shrinking and wrinkling of the blood cells.

In hypotonic solutions, oxyhemoglobin is released, which is in direct proportion to the number of cells hemolyzed.

- ❖ In hypertonic solutions, the cells shrink and become wrinkled or crenated
- ❖ In isotonic solutions, the cells do not change their morphology.

This method is used for the determination of isotonicity value.

***Cryoscopic method or depression of freezing point*:**

Colligative properties of solutions are helpful in determining the isotonicity values. Among them, freezing point depression is extensively applied.

Water has the freezing point of 0 °C.

When substances such as sodium chloride are added to water, the freezing point of water decreases.

The depression of the freezing point (ΔT_f) of blood and tears is 0.52 °C. Therefore, the value of 0.9 % w/w NaCl solution should also be -0.52 °C.

Such a solution shows same osmotic pressure as that of the blood. Hence, the functions of RBC and tissues do not alter.

Methods of adjusting the tonicity:

Normally, solution dosage forms contain drugs of desired dose and several excipients needed for formulation. In order to render such solutions isotonic, sodium chloride, dextrose, etc. are added. Several methods are available for adjusting the tonicity.

Osmotic pressure is not a readily measurable quantity, but freezing point depression (another colligative property) is more easily measured.

Class I methods:

In this type, sodium chloride or other substances are added to the solution in sufficient quantity to make it isotonic. Then the preparation is brought to its final volume withan isotonic or a buffered isotonic diluting solution.

These methods are of two types:

- Cryoscopic method
- Sodium chloride equivalent method.

Class II methods:

In this type, water is added in sufficient quantity make the preparation isotonic. Then the preparation is brought to its volume with an isotonic or a buffered isotonic diluting solution.

These methods are of two types:

- White-Vincent method
- Sprowls method.

Cryoscopic Method of Adjusting the Tonicity:

Principle:

Water has the freezing point of 0 °C. Blood contains a number of substances such as carbonic acid, carbonates, salts of phosphoric acid and hemoglobin. As a result, the depression in the freezing point of the blood is -0.52 °C.

When substances such as sodium chloride are added to water, the freezing point of water decreases. The extent of depression in the freezing point depends on the concentration of the added substance.

For example, sodium chloride at 1 % w v solution decreases the freezing point of water to - 0.58°. In order to make the drug solution isotonic, the freezing point depression of the solution must be maintained at-0.52°.

Initially the drug solution is prepared whose depression in the freezing point (ΔTf) is known. The remaining (ΔTf) value is adjusted by adding additional substances such as sodium chloride.

For the purpose of calculate, the freezing point depression of a number of drugs are determined experimentally or theoretically a concentration of 10 % w/v (or sometimes 0.5 % w/v). Similarly the freezing point depression values of 1 w/v solution of sodium chloride and other general ingredients are also determined.

Derivation:

Freezing point depression (ΔTf) of blood is 0.52°C. Since the drug solution must be isotonic, it must have ΔTf, same as that of the blood, i.e. $\Delta Tf = 0.52°C$.

Total drug solution ΔTf = ΔTf of drug + ΔTf adjusting substance ---------- (1)

Freezing point depression (ΔTf) of the total drug solution = 0.52°C

ΔTf value of the drug = x X ΔTf of 1 % drug solution = d

Where,

x = drug concentration in the preparation, g/100 mL

ΔTf for adjusting solution = w X a

Where,

W = weight of the adjusting substance, g/100 mL

a = ΔTf of the adjusting substance (sodium chloride), 1% (=0.58)

For an isotonic solution, equation (1) is substituted by the terms mentioned above.

$$0.52° = d + wa$$

The % w/v of adjusting substance needed is:

$$W = (0.52-d)/a = (0.52-d)/0.58 \text{ --------- } (2)$$

Equation (2) is valid, if 1 % drug solution is specified. For any given percentage strength of medicament (PSM), equation (2) may be modified as:

$$W = [0.52- (PSM \times d)]/ 0.58 \text{ ----------- } (3)$$

Thus, the desired concentration of adjusting substance is calculated and added in order to make the drug preparation isotonic with blood. Each solute exerts its effect on the freezing point, although others are present.

Hence, if two or more substances are present, a sum of their freezing point depression should be considered.

Advantage:

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

Sodium Chloride Equivalent Method:

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

Sodium chloride equivalent (D) of a drug is the amount of sodium chloride that is equivalent to 1 g of the drug. In this definition, equivalent refers to sodium chloride concentration having the same osmotic effect as that of the drug. In the absence of available data, the E value of a new drug can be calculated from equation (4).

$$E = [17 \times L_{iso}]/M \text{ -------------- } (4)$$

Where,

M = molecular mass, AMU

Liso = freezing point depression of the drug solution for showing isotonicity

Method:

The percent of sodium chloride required for adjusting isotonicity can be calculated using equation (5).

$$PSA = 0.9 - (PSM\ E \text{ of medicament}) \text{ ----------- } (5)$$

Where,

PSM= Percent strength of medicament

PSA = Percent of sodium chloride for adjustment of isotonicity.

Equation (5) is used to calculate the amount of adjusting substance (sodium chloride) required for making the solution isotonic. It is valid for 100 mL solution.