UNIT - V

PH, BUFFER AND ISOTONIC SOLUTION

Sorensen's Scale (pH Scale)

pH is a unit that measures a degree of acidity or basicity of a solution.

It was given by Sorensen in 1909 (Soren peter Lauritz Sorensen) and it was defined as "negative logarithm of the Hydrogen Ion $[H^+]$ Concentration"

$$pH = -\log [H^+]$$

$$pH = \log \frac{1}{[H^+]}$$

$$H^+ = 10^{-pH}$$

So, the pH value ranges from 0 to 14

The scale on which pH value are computed or mentioned is known as pH scale.

Water dissociates to H^+ and OH^- Ions

$$H_2O \rightleftharpoons H^+ + OH^- \quad ---- (1)$$

From law of mass action

$$K = \frac{[H^+][OH^-]}{[H_2O]} \quad ---- (2)$$

$$[H^+][OH^-] = K[H_2O] = K_w = \text{Constant} \quad \ldots$$

K_w = Water dissociation constant
$K_w = 1.0 \times 10^{-14}$

From eq (1) - one molecule of water dissociate to give one H^+ ion and one OH^- ion.

∴ Concentration of OH^- and H^+ is same

$$[H^+] = [OH^-] = \sqrt{K_w} = \sqrt{1.0 \times 10^{-14}}$$

$$[H^+] = [OH^-] = 10^{-7} \text{ mol/L}$$

So, H^+ and OH^- ion is 10^{-7} mol/L at 25°C it is said neutral

Neutral Solution	$[H^+] = [OH^-]$
Acidic Solution	$[H^+] > [OH^-]$
Basic Solution	$[H^+] < [OH^-]$

pH Scale -

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

0 ↓ Acidic highly acidic

7 ↓ Neutral

14 ↓ Basic alkali

0-7 → Acidic
7 → Neutral
7-14 → Basic

Measurement of pH (Important for Semester)

- pH papter
- Electrometric Method
- Colorimetric Method

- pH paper :-

→ In this method pH is measured by using pH paper.

→ A piece of pH paper is diped into the sample and colour of pH paper is compared with the standard pH measure chart.

→ Basicity and acidity of the sample is determined according to pH value.

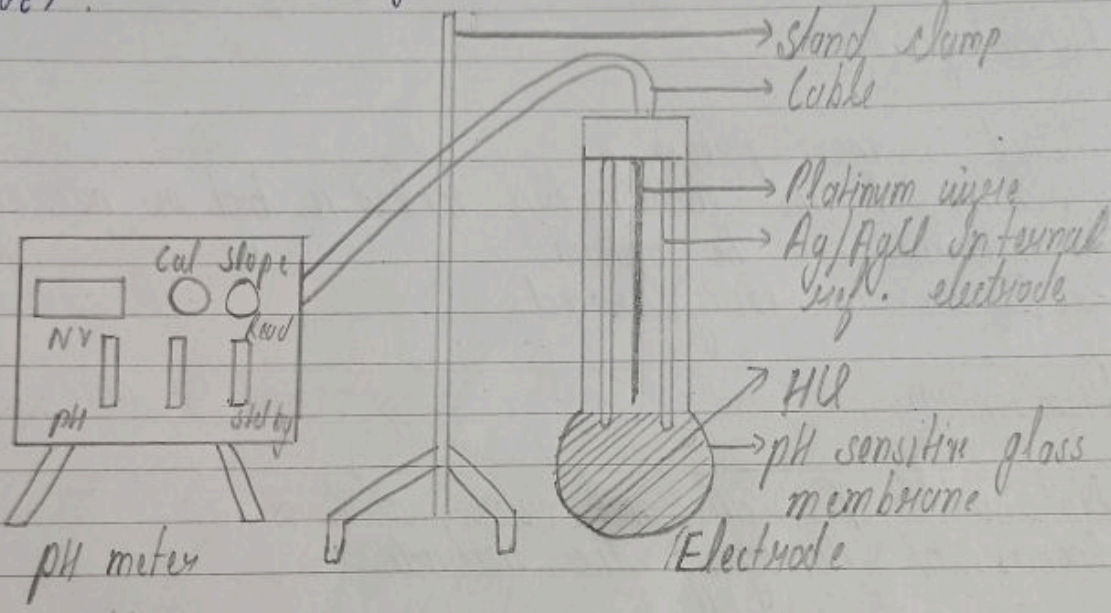
- Electrometric Method : It is the most accurate method for determination of pH (from 0-

In this method pH of a solution can be determined by means of an electrode, whose potential depends upon the hydrogen activity.

pH meter consist of 2 electrode -

1. potential electrode or standard electrode
2. Special electrode or pro electrode (voltameter enclosed in a glass membrane that allows migration of hydrogen ion)

Principle Of Electrometric Method :- Basic principle of this method is determination of the activity of the H^+ ion by potentiometric measurement using a standard (hydrogen electrode and reference electrode).



pH METER WITH GLASS MEMBRANE ELECTRODE.

procedure :-

Initially the temperature is set to the solution temperature

↓

The electrode are emersed in a standard buffer solution pH 7.0 and buffer solution pH 4

↓

The instrument is calibrated using acidic buffer and basic buffer

↓

The electrode is rinsed with distilled water

↓

The bulb of the glass membrane electrode is emersed in

the test solution

↓

The pH value of the test solution is directly read from pH meter.

Advantages

→ Method is more precise
→ Sensitivity of the electrometric method is high as accurate measurement can be obtained
→ Results can be easily read

Disadvantages

→ Not suitable for gels and viscous solutions
→ Chances of damaging the electrode

• Colourimetric Method:

principle behind this method lies in the developing colours in the sample with an indicator dye and comparing the colour of the solution of unknown concentration or pH with intensity of solution of known concentration or pH.

In this method chemicals are added to the sample solutions and those chemicals produce a colour change which indicates the pH of the sample.

BUFFERS

- Buffers are the solution that are able to resist change in pH value.
- It is an aqueous solution consist of mixture of weak acid and its conjugate base

Types Of Buffer

(i) Acidic Buffer
(ii) Basic Buffer

Acidic Buffer :- These type of buffer are used in acidic solutions and it is the mixture of weak acid and salts. Eg: Weak Acid + Salt

$$CH_3COOH + NaOH \rightarrow CH_3COONa + H_2O$$

Basic Buffer :- It is used in basic solutions and it is the mixture of weak acid base and salt

Eg: Weak Base +

$$NH_4OH + HCl \rightarrow NH_4Cl + H_2O$$

Application Of Buffer

- Buffer solutions are used in fermentation processes
- Buffers can also be used to maintain the drug in its ionised as well as unionised form. The ionised form

of drug are more water soluble than unionised form of drug
- Buffers maintain a drug in its salt form (ionised) for aqueous solution.
- Buffers are used in chemical analysis.
- Buffers are used for calibration of pH measurment systems (an electrode and the meter)
- Buffers resistant to change in pH makes these solutions very useful for biochemical processes and chemical manufacturing
- Buffer solution are necessary to kept the correct pH in many organism to live. Many enzyme work only under very ~~pH~~ precise condition i.e if pH is too for the enzymes stop working and denatured.

Eg :- A buffer of carbonic acid and bicarbonate present in blood plasma help to maintain a buffer of pH 7.35 to 7.45.

The pH can effect the stability of a drug in aqueous solution.
for eg :- Ester drugs are very prone to hydrolytic reactions.

- Buffer solution of low pH reduces the rate of hydrolysis
for eg :- buffer improve stability of aspartent
- Buffer helps to maintain texture in gelled product by controlled gelling.
- Buffers are also used to prevent colour and flavour in food changes in the beverages system.
for eg : Red colour of cherry, rosberries syrup has

been maintained at acidic pH which become pale yellow to colourless at alkaline pH.

- Buffers are also used for maintaing the tissues because high or low pH can cause tissue irritation. The pH of formulation must match the body fluid otherwise it may cause body irritation or discomfort.
- Solubility of compounds can be controlled by providing a medium of suitable pH. If the pH of the solution is not properly maintained then the drug dissolution can precipitate.

BUFFER EQUATION

The pH of a buffer solution and the change in pH with the addition of acid and base is calculated by use of buffer equation

The buffer equation is also known as Henderson Hasselbach Equation

Two separate equation are obtained for each types of buffer i.e acidic & basic

Buffer equation for weak acid and its salt

The pH of the acidic buffer can be calculated from dissociation constant (K_a) of the weak acid and the concentration of acid and salt used.

The dissociation expression of weak acid can be represented by -

$$HA \rightleftharpoons H^+ + A^-$$

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

$$[H^+] = \frac{k_a [HA]}{[A^-]}$$

$$\text{or } [H^+] = \frac{K_a [Acid]}{[salt]}$$

Taking -log on both side

$$-\log [H^+] = -\log k_a - \log \frac{[acid]}{[salt]}$$

$$-\log [H^+] = pH$$

$$-\log k_a = pk_a$$

This equation known as HHE $\quad pH = pk_a - \log \frac{[acid]}{[salt]}$

Buffer equation for weak base and its salt

It consist of a weak base and its salt with strong acid

Ionisation of the weak base / BOH →

$$BOH \rightleftharpoons B^+ + OH^-$$

$$[OH^-] = K_b \frac{[BOH]}{[B^+]}$$

$$OH^- = \frac{Kb\ [base]}{[salt]}$$

Taking log on both side

$$\log [OH^-] = \log Kb + \log \frac{[base]}{[salt]}$$

On multiplying both sides by -ve

$$-\log [OH^-] = -\log Kb - \log \frac{[base]}{[salt]}$$

$$-\log [OH^-] = pOH$$
$$-\log Kb = pKb$$

$$pOH = pKb - \log \frac{[Base]}{[salt]}$$

BUFFER CAPACITY

The amount of an acid that can be added to a 1 litre of a buffer solution before its pH change

It is also known as buffer index, buffer value, buffer efficiency and buffer co-efficient.

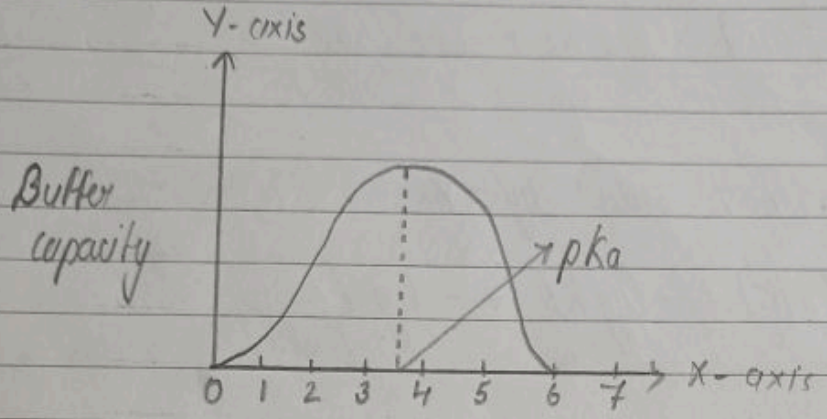
It is defined as "a measure of its magnitude of its resistance to change in pH by the addition of an acid or a base."

Buffer capacity ← $\beta = \frac{\Delta B}{\Delta pH}$ → ΔB → Amount of acid/base added to change the pH by one unit

ΔpH → Change in pH

Buffer capacity is not a fixed value.

Buffer capacity is defined on the acid / base added.



plot showing maximum buffer capacity

Colourimetric Method

The principle behind this method lies in developing colour in the sample with an indicator dye and comparing the colour of solution of unknown concentration or pH with intensity of solution of known concentration or pH.

Therefore, the concentration of unknown solution or sample can be determined.

Colourimetric means two major colour.
In the colourimetric method chemicals are added to the sample and those produces a colour change.
The colour change indicate pH of the sample.
The colour can be measured visually or electronically

Visual method of estimation - differents kits are available to determine pH. After adding reagent the colour of unknown solution in testtube is compared with standard to determine pH value.

Electronic method of estimation - An electronic colourimeter is used to determine pH.

Take the sample in two square tubes upto same level

↓

Put 2-3 drops of indicator in one tube and put it in right compartment

↓

Place the blank (tube without indicator) in left hand compartment

↓

Rotate the disc till the colour developed in the right hand side sample coinsides with the disc colour

↓

Note the corresponding pH and record it

BUFFERS IN PHARMACEUTICAL AND BIOLOGICAL SYSTEM

Buffers are added in pharmaceutical product to maintain the required stability and pharmacological effect.

Buffers also controls the pH of the formulated product.

Buffering agents are added to ensure that the drug will be stable throughout the shelf live of the product and also during their administration.

Buffer stabilize various formulation such as: parentral

parenteral :- pH of the parenteral preparation should be 7.4 (same as systemic circulation). As pH deviates serious consciousness occurs.
Most commonly used buffer parenteral products are Acetate buffer, phosphate buffer, citrate buffer, glutamate buffer, phtalate buffer

The pH optimization is generally carried out to have better solubility, stability and reducing irritancy of the product.

Solid dosage form :- Buffers have been used widely in solid doses form such as tablet capsule and powder for controling the pH of the environment around the solid particles

One of the important application of buffers is to reduce the gastric irritation caused by acidic drug! Eg: Buffer aspirin has a buffering agent (Magnesium Oxide) that maintain the pH of the aspirin as it passes through the stomach of the patient.

Buffering agent are used to lower or reduce the acidity in stomach.

Buffering agent used in solid dosage forms are sodium bicarbonate
magnesium carbonate
sodium citrate

Opthalmic :- Many drugs such as alkolidal salt are most effective at pH levels that favours the undissocided free bases. However at such pH levels

drug ~~ma~~ must be obtained by use of buffers.

Opthalmic preparation includes eyedrops, eyelotion, eyesolution.

pH of lacrimal fluid is 7-8 therefore opthalmic preparation should have pH between 7-8

Opthalmic preparation are buffered for
greater comfort to the eye
to stablize the formulation
to inhance or improve drug bioavalibility

Buffers used in opthalmic preparations are
Carbonate Buffer
Borate Buffer
Phosphate Buffer

An opthalmic preparation with a buffer system aproching the physiological pH can be obtained by mixing a sterile solution of the drug with a sterile buffer solution using aseptic technique.
Aseptic
Many drugs when buffered to a therapeutic exceptable pH would be stable in a solution for longer period of time.

Therefore, these products are liophilized.
Eg:- Acetyl coline chloride opthalmic solution

Semi-Solid Dosage form - Semi-solid dosage form such as cream, lotion, ointments undergo

pH changes upon storage for longtime resulting in its reduced stability.

For semi-solid dosage form pH should be between 5.5 - 6.8 which compiles with the same as pH of skin

Ointments and creams are fairly acidic in nature help to avoid the effect of harmful bacteria and fungi

Buffers used in semi-solid dosage form are
Citric Acid Buffer
Sodium Citrate
Sodium phosphate

Parenteral	Semi solid dosage form	opthalmic	Solid - dosage form
Acetate Buffer	Citric Acid Buffer	Carbonate Buffer	Sodium Bicarbonate
Phosphate Buffer	Sodium Citrate	Borate Buffer	Magnesium Carbonate
Citrate Buffer	Sodium phosphate	Phosphate Buffer	Sodium Citrate
Glutamate Buffer			
Phthalate Buffer			

BUFFER IN BIOLOGICAL SYSTEM

Body Fluid	PH Value	Buffer system
Extracellular Fluid	7.3 - 7.4	Bicarbonate buffer system Phosphate buffer system Intracellular protein

Blood	7.4 - 7.5	Bicarbonate buffer system Phosphate buffer system Hemoglobin Plasma protein
Intracellular fluid	7.0 - 7.4	Protein Phosphate
Urine	4.5 - 80	Ammonia Buffer Phosphate Buffer

Body fluids have balanced pH

Small changes in pH can alter the biochemical reaction that takes place therefore the maintainence of normal range of pH is essential for body functioning

Biological Buffer System -

Blood - The physiological pH range of blood is 7 - 7.8

When pH of blood decreases or increases beyond its range serious consciousness may occur.

The blood is maintained by a pH 7.4 by using two buffer :-

Primary buffer :- These are present in plasma Plasma contain carbonic acid - carbonate and acid alkali sodium salt of phosphoric acid.

Secondary Buffer: These are present in RBCs
It consist of acid alkali potassium salts of phosphoric acid and Oxyhaemoglobin.

Lacrimal Fluid :- The pH of lacrimal fluid or tears is about 7.4 with a range of 7 - 8

Eye preparations should have acceptable pH range of lacrimal fluid. Below or above this range of pH eye preparation can cause discomfort.

Tears have been found to have a rate degree of buffer capacity and dilution of tears upto 1:5 with distilled water is possible before an appreciable change in pH is noticed.

Urine :- The average pH of urine is 6 with a range of 4.5 - 7.8.

Hydrogen ion The pH of urine is maintained by the process of excretion and reabsorption of hydrogen ion through kidney.

BUFFERED ISOTONIC SOLUTIONS

It is defined as the solution which maintain the isotonicity and the pH as that of the body fluid

Pharmaceutical solutions that are used for application to delicate membrane should be adjusted to same osmotic

pressure as that of body fluid.

The isotonic solution do not cause swelling or contraction of the tissues and do not produce any discomfort when injected into eye nasal mucosa, blood or other body tissue.

Tonicity is a measure of effective osmolarity in cell biology.

Osmolarity is a concentration scale to express the total concentration of solute particles and is directly ~~related~~ related to any of the four colligative properties.

Tonicity is generally classified in three types :-

1. Hypertonicity
2. Hypotonicity
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 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.

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.

HYPOTONICITY

The 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.

METHODS USED TO DETERMINE TONICITY VALUE

Hemolytic method :- Isonotivity value 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 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 ΔTf 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 tonicity of pharmaceutical solutions. Isotonicity can be calculated from the colligative properties of drug solutions.

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.

Example 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.

Example of this class - White Vincent method

Class-3 Methods: Freezing point depression and L iso values for a 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 ΔT_f of 0.52°C.

Therefore, the freezing point of drug solution must be adjusted to this value.

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.

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

where,

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

The LISO - 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.

$$\Delta T_f = L_{iso} C$$

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 opthalmic solution, developed an equation

$$V = W . E \times 111.1$$

where,

V = Volume of isotonic solution prepared by mixing drug with water
W = Weight of drug in gram
E = Sodium chloride equivalent