UNIT II   **10 Hours**

- **Acids, Bases and Buffers:** Buffer equations and buffer capacity in general, buffers in pharmaceutical systems, preparation, stability, buffered isotonic solutions, measurements of tonicity, calculations and methods of adjusting isotonicity.

- **Major extra and intracellular electrolytes:** Functions of major physiological ions, Electrolytes used in the replacement therapy: Sodium chloride*, Potassium chloride, Calcium gluconate* and Oral Rehydration Salt (ORS), Physiological acid base balance.

- **Dental products:** Dentifrices, role of fluoride in the treatment of dental caries, Desensitizing agents, Calcium carbonate, Sodium fluoride, and Zinc eugenol cement.

ACID, BASES AND BUFFERS

CONTENTS

- **Acid and bases concept**
- **Buffer equations**
- **Buffer capacity**
- **Buffer in pharmaceutical systems**
- **Measurement of tonicity**
- **Methods of adjusting tonicity**

ACIDS, BASES AND BUFFERS

ACIDS

- Turns blue litmus red.
- Tastes sour
- pH<7
- Ex:- HCl , H_2SO_4, CH_3COOH

BASES

. Turns red litmus blue
. Tastes bitter
. pH>7
. Ex :- NaOH, KOH

ACID AND BASES CONCEPT

The theory of acids and bases, like many other chemical theories, has undergone numerous changes in recent times. Always the changes have been such as to make the theory more general. The three main theories in use today are:
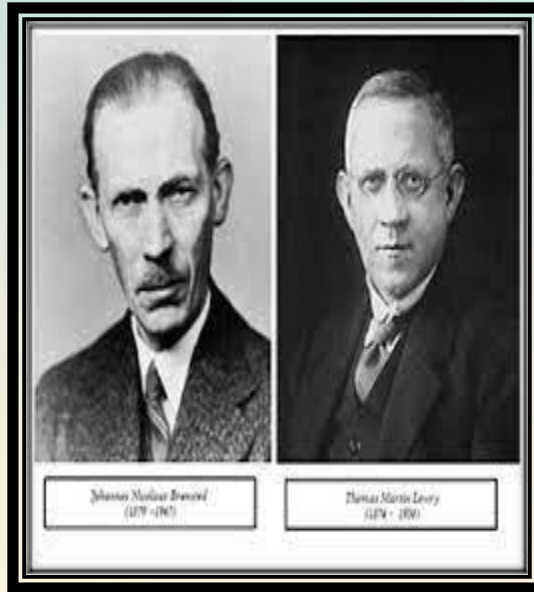
(I) Arrhenius Theory;

(2) Bronsted- Lowry Theory;

(3) Lewis Theory

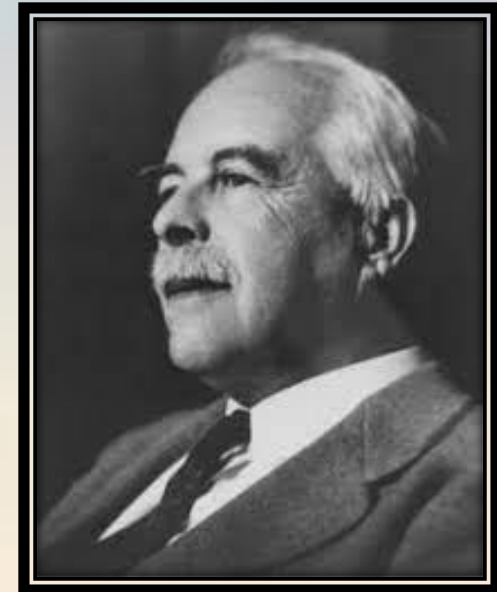# Arrhenius Theory of electrolyte dissociation

➢ Swedish scientist Svante Arrhenius,1887.

➢ Electrolyte

➢ Positive and negative charges.

➢ Ionization

➢ Carry electric current.

Arrhenius Theory of acids and bases
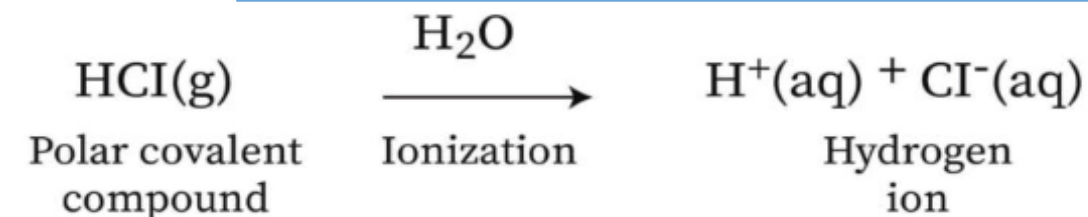
ACIDS

Acids are substances that produce H^+ in solutions:

HCl undergoes dissociation reaction to produce H^+ ion and Cl^- ion,
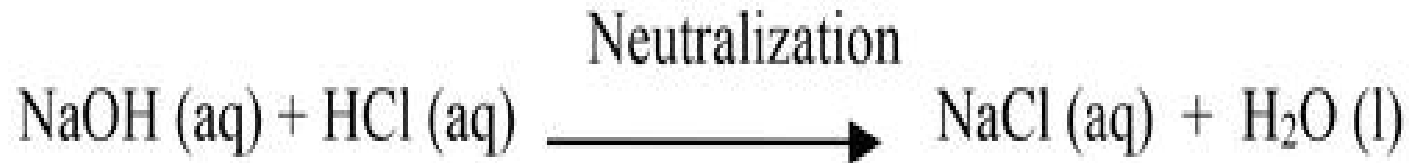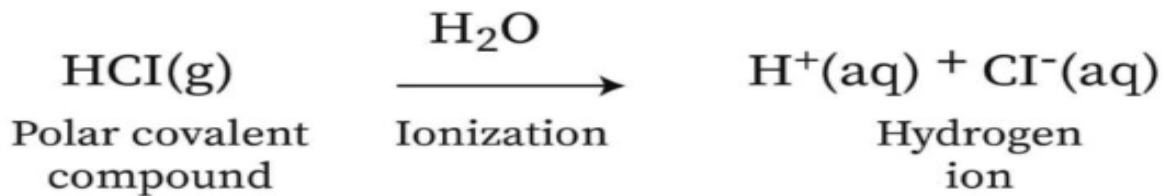
BASES

Bases are substances that dissociate giving off OH^-

NaOH completely dissolves to give hydroxide ion and sodium ion, to increase the concentration of hydroxide ions.

$$HCl(g) \xrightarrow[\text{Ionization}]{H_2O} H^+(aq) + Cl^-(aq)$$

Polar covalent compound ... Hydrogen ion

$$NaOH(aq) \xrightarrow{\text{Water}} Na^+(aq) + OH^-(aq)$$

ACIDS,BASES AND BUFFERS

Acids and Bases react with each other to yield water and Salt.

$$HCl(g) \xrightarrow[\text{Ionization}]{H_2O} H^+(aq) + Cl^-(aq)$$

Polar covalent compound   Hydrogen ion

$$NaOH(aq) \xrightarrow{\text{Water}} Na^+(aq) + OH^-(aq)$$

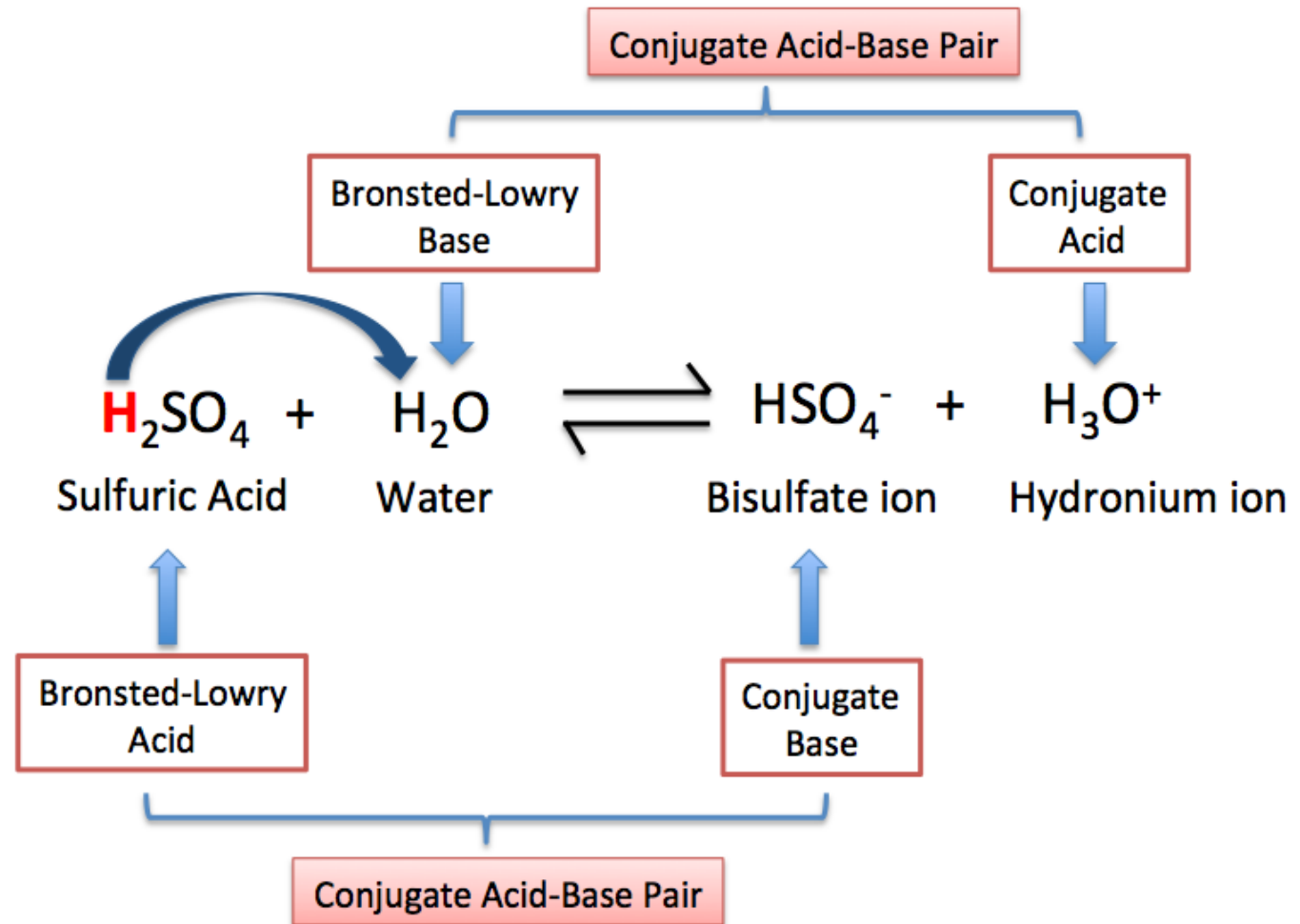$$NaOH(aq) + HCl(aq) \xrightarrow{\text{Neutralization}} NaCl(aq) + H_2O(l)$$

Neutralization takes place in presence of solvent.

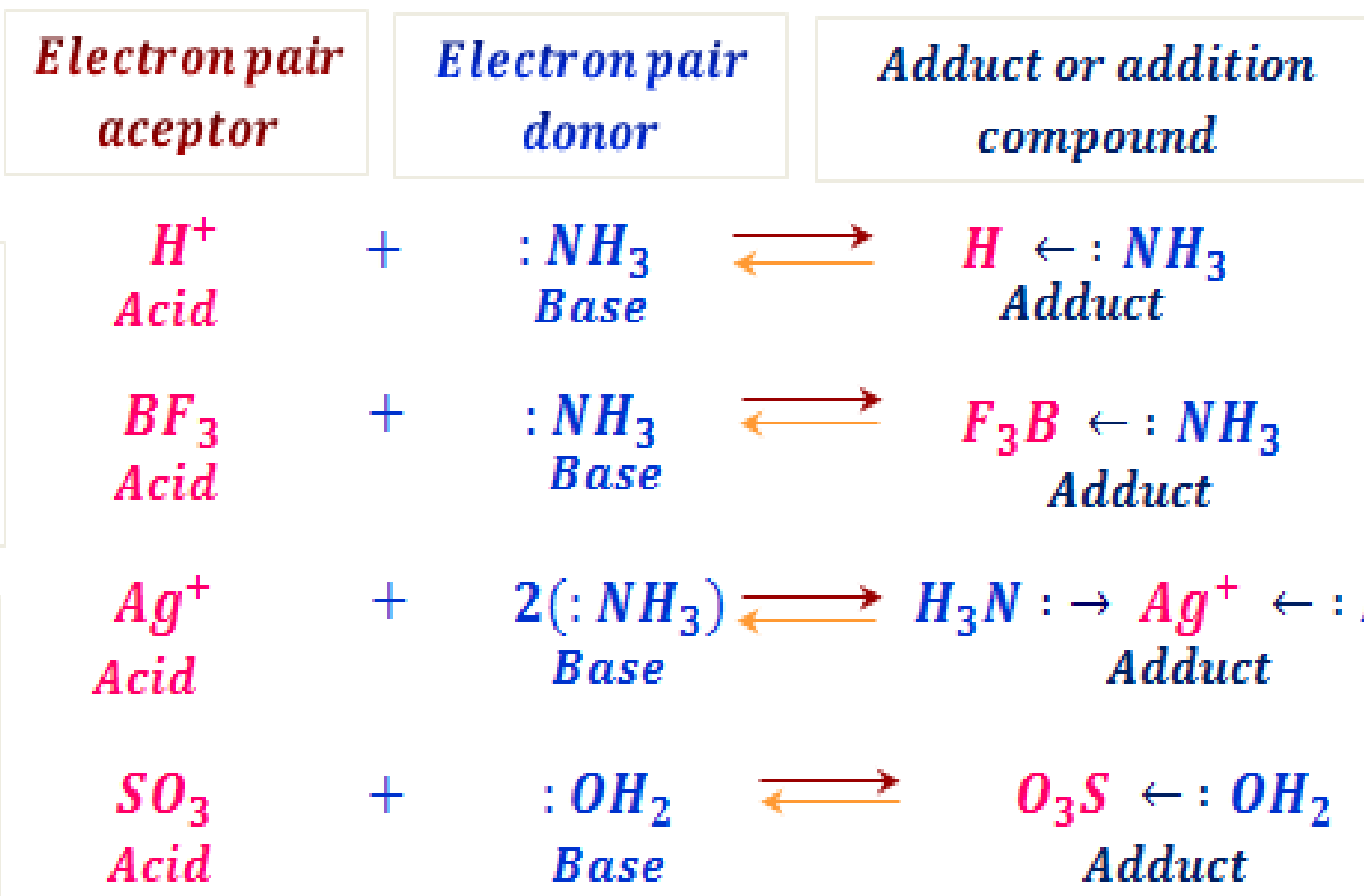# BRONSTED-LOWRY CONCEPT

➢ Acid is a substance that can donate a proton.

➢ Base is a substance that can accept a proton.

Conjugate Acid-Base Pair

Bronsted-Lowry Base

Conjugate Acid

$$H_2SO_4 \ + \ H_2O \ \rightleftharpoons \ HSO_4^- \ + \ H_3O^+$$

Sulfuric Acid   Water   Bisulfate ion   Hydronium ion

Bronsted-Lowry Acid

Conjugate Base

Conjugate Acid-Base Pair

LEWIS CONCEPT OF ACIDS AND BASES

	Electron pair aceptor	Electron pair donor	Adduct or addition compound
An acid is an electron pair aceptor	H^+ Acid	$+$	$: NH_3$ Base	$H \leftarrow : NH_3$ Adduct
	BF_3 Acid	$+$	$: NH_3$ Base	$F_3B \leftarrow : NH_3$ Adduct
A base is an electron pair donner	Ag^+ Acid	$+$	$2(: NH_3)$ Base	$H_3N : \rightarrow Ag^+ \leftarrow : NH_3$ Adduct
	SO_3 Acid	$+$	$: OH_2$ Base	$O_3S \leftarrow : OH_2$ Adduct

BUFFERS

- Buffers are compounds or mixtures of compounds that, by their presence in solution, resist changes in pH upon the addition of small quantities of acid or alkali.

- The resistance to a change in pH is known as Buffer Action. It is a combination of a weak acid and its conjugate base (i.e., its salt) or a weak base and its conjugate acid acts as a buffer

BUFFERS

Types of buffers: 2 types

Acidic buffers: is a combination of weak acid and its salt (conjugate base) with a strong base. E.g.

CH_3COOH / CH_3COONa H_2CO_3 / $NaHCO_3$

H_3PO4 / NaH_2PO_4 $HCOOH$ / $HCOONa$

Basic buffers: A basic buffer is a combination of weak base and its salt with a strong acid (Conjugate Acids). E.g.

NH_4OH / NH_4Cl NH_3 /NH_4Cl NH_3 /$(NH_4)_2CO_3$

BUFFERS

Phosphate Buffers (Double salt buffers):

Besides the two general types of buffers (i.e. acidic & basic), a third appears to exist.

This is buffer system composed of two salts:

❑ Monobasic potassium phosphate (KH_2PO_4)
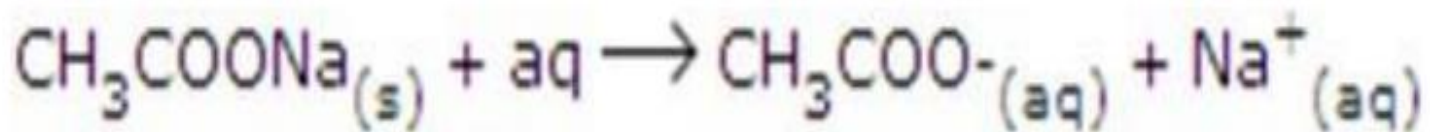
❑ Dibasic potassium phosphate (K_2HPO_4)

BUFFER SOLUTION OR BUFFER SYSTEMS

- Solutions composed of a weak acid and one of its salts (e.g. $CH_3COOH + CH_3COONa$ or CH_3COONH_4)

- Weak base and one of its salts (e.g. $NH_4OH + NH_4Cl$).

- Purpose: to resist to a greater/lesser extent the changes in pH when some acid or base is added to them

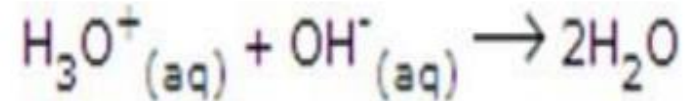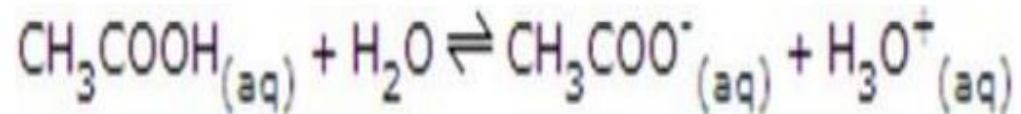• Strong acid buffers: concentration of oxonium ions ($H3O^+$) is high. Eg:- Nitric acid

• Strong base buffers: checked using the equation:

$$pH + pOH = 14$$

• Weak acid buffers: Buffer solutions with constant pH values of between 4 and 7 can be prepared from a weak acid and one of its salts.
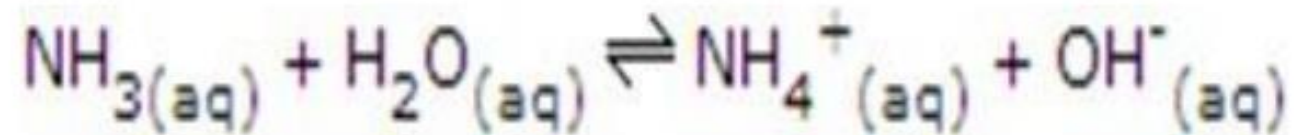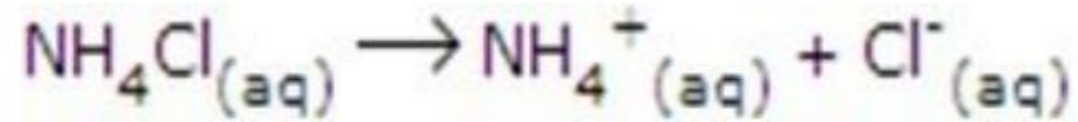
$$CH_3COONa_{(s)} + aq \rightarrow CH_3COO-_{(aq)} + Na^+_{(aq)}$$

- ethanoic acid is only partially ionised:

$$CH_3COOH_{(aq)} + H_2O \rightleftharpoons CH_3COO^-_{(aq)} + H_3O^+_{(aq)}$$

$$H_3O^+_{(aq)} + OH^-_{(aq)} \longrightarrow 2H_2O$$

- Weak base buffers: Buffer solutions with constant pH values between 7 and 10 can be prepared from a weak base and one of its salts.
- E.g.. A solution of ammonium hydroxide and ammonium chloride is typically used.

$$NH_4Cl_{(aq)} \rightarrow NH_4^+{}_{(aq)} + Cl^-{}_{(aq)}$$

$$NH_{3(aq)} + H_2O_{(aq)} \rightleftharpoons NH_4^+{}_{(aq)} + OH^-{}_{(aq)}$$

- Uses of Buffers:

In standardizing pH meter Buffering biological systems (e.g. blood) Maintaining the pH of eye drops and shampoos etc

BUFFER EQUATION

- Consider a buffer solution obtained by mixing a weak acid HA and its salt MA.

- The dissociation of HA is given as:

  HA $\rightleftharpoons$ H$^+$ + A$^-$ & MA $\rightleftharpoons$ M$^+$ + A$^-$

- Degree of dissociation will depend on the value of the dissociation constant Ka.

- Greater the magnitude of Ka, greater is the dissociation of HA into H$^+$ & A$^-$

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

Note: Making the approximation that in dilute solution, activity is equal to concentration. This relationship exists in the mixture of HA and MA
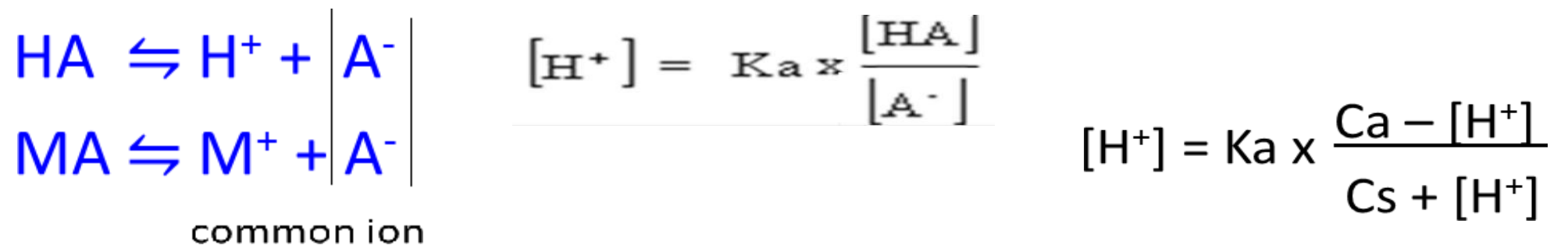
- Therefore,

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

- Suppose the concentration of the acid is Ca and that of the salt is Cs. The concentration of the undissociated acid will be:

Ca − [H⁺], i.e., [HA] = Ca − [H⁺]

- In this buffer solution, A^- ions will be produced from the dissociation of MA and also from that of HA.

- The concentration of MA [salt] is Cs, the conc. of A- ions will also be Cs.

- A molecule of HA on dissociation gives a H^+ ion and a A^- ion, Hence $[A^-] = [H^+]$. Thus

- The total conc. of A- ion in the solution will be Cs + $[H^+]$.

$$HA \rightleftharpoons H^+ + \boxed{A^-}$$
$$MA \rightleftharpoons M^+ + \boxed{A^-}$$

common ion

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

$$[H^+] = Ka \times \frac{Ca - [H^+]}{Cs + [H^+]}$$

- Due to common ion effect, the dissociation of weak acid HA will be further decreased.
- [H+] will be small and can be neglected in comparison to Cs and Ca.

$$[H^+] = Ka \times \frac{[Acid]}{[Salt]}$$

$$\log [H^+] = \log \left[Ka \times \frac{[Acid]}{[Salt]} \right]$$

$$-\log [H^+] = -\log Ka - \log \frac{[Acid]}{[Salt]}$$

$$\log [H^+] = \log Ka + \log \frac{[Acid]}{[Salt]}$$

Remember:

- - log is and /or can written as *p.*
- *Log a/b = -log b/a*

$$-\log[H^+] = -\log Ka - \log \frac{[Acid]}{[Salt]}$$

- *pH = pKa + log*

$$\frac{[Salt]}{[Acid]}$$

- *Similarly for a buffer solution containing a weak base and its salt, it can be shown that:*

- *pOH = pKb + log [Salt] / [Base]*

BUFFER ACTION OR BUFFER CAPACITY

Buffer action

- The reactions responsible for maintaining constant pH on the addition of acid or base in buffer solution are called buffer action. The buffer action of acetic acid and sodium acetate mixture can be explained as follows.

Acetic acid is a weak acid and is partially ionised in solution.

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+$$

Sodium acetate is a strong electrolyte and is completely ionised.

$$CH_3COONa \rightarrow CH_3COO^- + Na^+$$
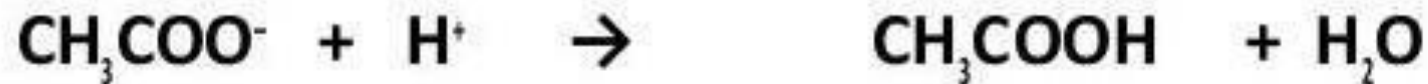
BUFFER CAPACITY

The buffer capacity of a buffer solution is "a measure of its magnitude of its resistance to change in the pH on an addition of an acid or a base."

Buffer capacity is also referred as buffer index, buffer value, buffer efficiency or buffer coefficient.

Buffer action

- When a small amount of acid is added to this mixture, H^+ ions of the acid combines with equal number of acetate ions to form acetic acid molecule. Therefore, the net pH remains constant.

$$CH_3COO^- + H^+ \rightarrow CH_3COOH + H_2O$$

When a small amount of base is added, the OH^- ions of the base neutralise acid molecules to form sodium acetate. Therefore, the net pH remains constant.

$$CH_3COOH + OH^- \rightarrow CH_3COO^- + H_2O$$
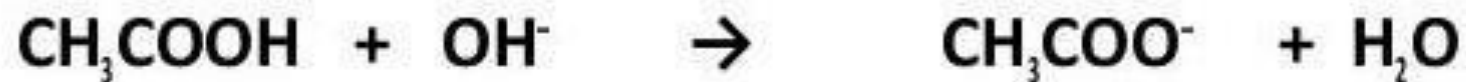
Buffer Capacity

- The resistance to changes of pH now remains to be discussed in a more quantitative way.

- The magnitude of the resistance of a buffer to pH changes is referred to as the buffer capacity.

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

- Koppel, Spiro and Van Slyke introduced the concept of buffer capacity and defined it as:

- the ratio of the increment of strong base (or acid) to the small change in pH brought about by this addition.

- For the present discussion, the approximate formula.

$$\beta = \frac{\Delta B}{\Delta pH}$$

✓ delta, Δ: a finite/limited change

✓ ΔB is the small increment in gram equivalents (g Eq)/liter of strong base added to the buffer solution.

✓ ΔpH: change in a pH

- According to this equation, the buffer capacity of a solution has a value of 1 when the addition of 1 g Eq of strong base (or acid) to 1 liter of the buffer solution results in a change of 1 pH unit.

- The changes in concentration of the salt and the acid by the addition of a base are represented using the modified form of buffer equation

$$pH = pK_a + \log\frac{[Salt] + [Base]}{[Acid] - [Base]}$$

- the buffer capacity is not a fixed value for a given buffer system but instead depends on the amount of base added.

- The buffer has its greatest capacity before any base is added, where [Salt]/[Acid] = 1, and, therefore, pH = pKa.

- The buffer capacity is also influenced by an increase in the total concentration of the buffer constituents - a great concentration of salt and acid provides a greater alkaline and acid reserve.

- The buffer capacity calculated is only approximate.

- It gives the average buffer capacity over the increment of base added.

- Koppel and Spiro and Van Slyke developed a more exact equation:

$$\beta = 2.3C \frac{K_a[H_3O^+]}{(K_a + [H_3O^+])^2}$$

- C is the total buffer concentration, that is, the sum of the molar concentrations of the acid and the salt.

DEPTH OF BIOLOGY

Buffer Capacity of Solutions Containing Equimolar Amounts (0.1 M) of Acetic Acid And Sodium Acetate

Moles of NaOH Added	pH of Solution	Buffer Capacity, β
0	4.76	
0.01	4.85	0.11
0.02	4.94	0.11
0.03	5.03	0.11
0.04	5.13	0.10
0.05	5.24	0.09
0.06	5.36	0.08

BUFFER SYSTEM

- Blood is maintained at a pH of about .

- The plasma contains carbonic acid/bicarbonate and acid/alkali sodium salts of phosphoric acid as buffers.

- Plasma proteins, which behave as acids in blood, can combine with bases and so act as buffers.

- In the erythrocytes (RBC), the two buffer systems consist of hemoglobin/oxyhemoglobin and acid/alkali potassium salts of phosphoric acid.

Pharmaceutical Buffer Systems

- Buffer solutions are used frequently in pharmaceutical practice, particularly in the formulation of ophthalmic solutions.

- One of the most common biological buffers is phosphate buffered saline (PBS).

- Contains: sodium chloride (NaCl) and dibasic sodium phosphate (Na2PO4). It may also contain potassium chloride (KCl), monobasic potassium phosphate (KH2PO4), calcium chloride (CaCl2), and magnesium sulfate (MgSO4).

BUFFERS in Pharmaceutical Systems

Urine

The 24-hr urine collection of a normal adult has a pH averaging about 6.0 units; it may be as low as 4.5 or as high as 7.8.

When the pH of the urine is below normal values, hydrogen ions are excreted by the kidneys.

Conversely, when the urine is above pH 7.4, hydrogen ions are retained by action of the kidneys in order to return the pH to its normal range of values.

General Procedures for Preparing Pharmaceutical Buffer Solutions

1.Select a weak acid having a pKa approximately equal to the pH at which the buffer is to be used.

2.From the buffer equation, calculate the ratio of salt and weak acid required to obtain the desired pH. The buffer equation is satisfactory for approximate calculations within the pH range of 4 to 10.

3.Consider the individual concentrations of the buffer salt and acid needed to obtain a suitable buffer capacity.

A concentration of 0.05 to 0.5 M is usually sufficient, and a buffer capacity of 0.01 to 0.1 is generally adequate.

4. Other factors of some importance in the choice of a pharmaceutical buffer include:

- availability of chemicals
- sterility of the final solution
- stability of the drug and buffer on aging
- cost of materials and freedom from toxicity

For example: a borate buffer, because of its toxic effects, certainly cannot be used to stabilize a solution to be administered orally or parenterally.

5. Finally, determine the pH and buffer capacity of the completed buffered solution using a reliable pH meter.
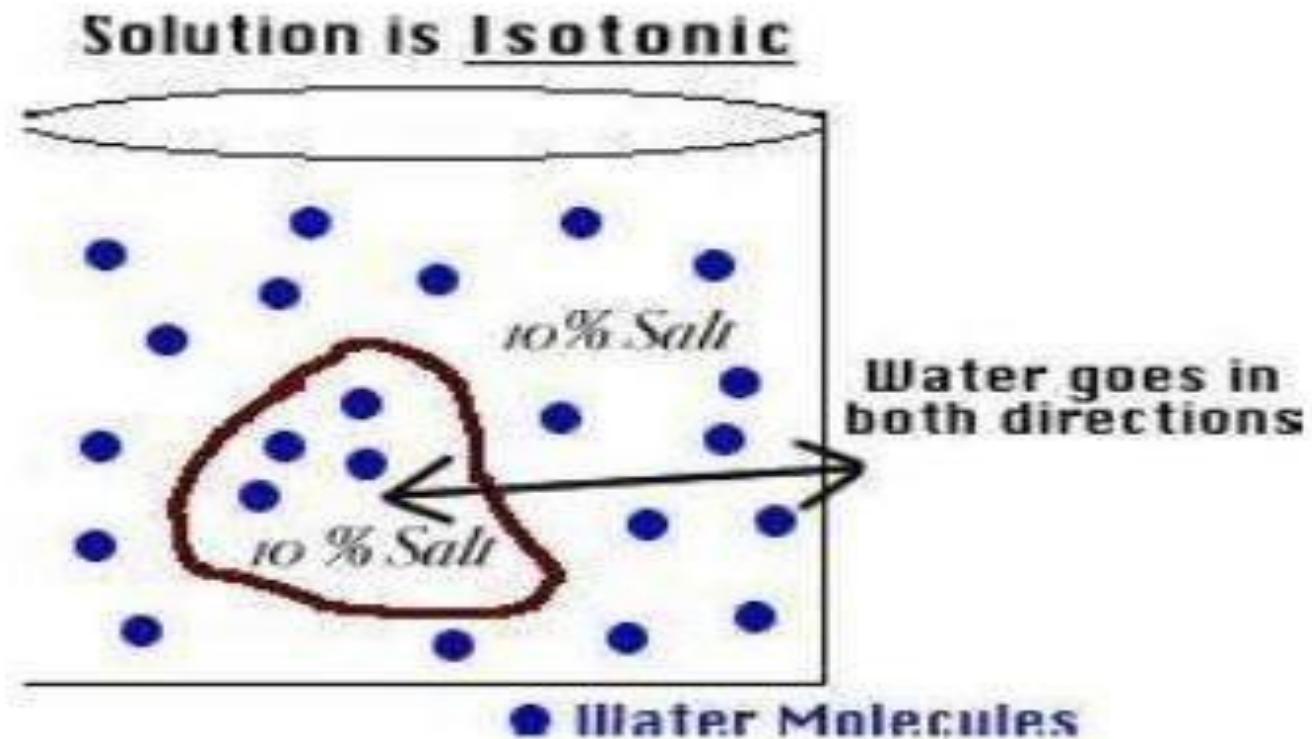
- In some cases, sufficient accuracy is obtained by the use of pH papers. Particularly when the electrolyte concentration is high,

Note: it may be found that the pH calculated by use of the buffer equation is somewhat different from the experimental value. This is to be expected when activity coefficients are not taken into account

ISOTONIC SOLUTION

ISOTONIC SOLUTION

❑ When two solutions have same osmotic pressure and salt concentration are said to be isotonic solutions. Iso (same) and tonic (concentration).

❑ Physiologically, isotonic solutions are solutions having the same osmotic pressure as that of the body fluids when separated by a biological membrane. Biological fluids including blood and lachrymal fluid normally have an osmotic pressure corresponding to that of 0.9% w/v solution of sodium chloride.

❑ 0.9% w/v solution of NaCl has essentially the same concentration and osmotic pressure as the RBCs contents. Thus it is said to be isotonic with blood, and is also known as "Physiological Saline solution", or "Normal saline solution"

❑ If RBCs are suspended in 0.9% solution of NaCl, they undergo no change in their size and shape due to isotonicity.

HYPERTONIC SOLUTION

➢ " A hyper-tonic solution is one that has greater concentration than reference solution.

➢ A hyper-tonic solution has greater osmotic pressure than that of reference solution.

➢ If RBCs are suspended in 2% w/v solution of NaCl then water present within the RBCs will come out (i.e. due to osmosis, from dilute RBCs fluid to concentrated hypertonic solution) into the surroundings to dilute the NaCl solution (hypertonic solution). This exit of water from RBCs causes their shrinkage and RBCs become wrinkled in shape. This shrinkage of RBCs is known as " Plasmolysis".

HYPOTONIC SOLUTION

" A hypo tonic solution is one that has lower concentration than reference solution"

A hypo-tonic solution has lower osmotic pressure than that of reference solution

If RBCs are suspended ;in 0.1% w/v solution of NaCl , then water from this solution will enter the

RBCs (i.e. due to osmosis, from dilute hypotonic solution of RBCs fluid) to dilute the fluid within the RBCs causing their swelling, which may later result in rupturing of RBCs and release of haemoglobin. This rupturing of RBCs is known as "Haemolysis"

ISOTONIC SOLUTIONS

Tonicity

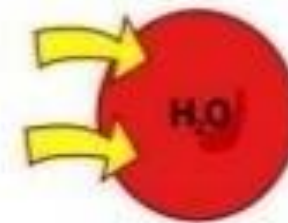Relative concentration of solute, which is dissolve in a solution, which determine the direction and extent of diffusion.

Hypertonic

A solution having higher osmotic pressure than the body fluids. The net movement of water into the cell causes them to swell up.

Isotonic

Both internal and external environment have same solute concentration (0.9% solution)

Measurement of Tonicity

The tonicity of solutions may be determined by one of the following two methods:

a) Haemolytic Method

b) Colligative Method

Haemolytic Method

In this method, RBC's are suspended in various solution and the appearance of RBCs is observed for swelling, bursting, shrinking and wrinkling of the blood cell.

Cryoscopic Method

Freezing point depression property is most widely used.

Freezing point is 0 degree Celsius and when any substance such as NaCl is added, the freezing point decreases.

Freezing point depression, ▲Tf of blood is -0.52 degree C. Hence, ▲Tf value of the drug solution must be -0.52 degree C

Methods of Adjusting Tonicity

A. Class- 1 Method :- NaCl or some other substances is added to the solution of the drug to lower the freezing point of solution to -0.52 degree C and thus make the solution isotonic.

Eg:- cryoscopic & NaCl equivalent

NaCl equivalent method :- NaCl equivalent (E) of a drug is the amount of NaCl i.e equivalent to 1g of the drug.

PSA= 0.9- (PSM * E of medicament)

PSA = Percentage strength of medicament

PSM = Percentage of NaCl for adjust tonicity

B. Class- 2 Method

H2O is added to the drug in sufficient amount to make it isotonic.

Then the preparation is brought to its final volume with an isotonic or buffer isotonic solution. (0.9% NaCl)

White Vincent method

This method involve addition of H2O to a given amount of drug. The volume of H2O that should be added in given amount of the drug to make it isotonic solution. It is calculated by using this formula,

$$V = W*E * 111.1$$

Where,

V= Volume of H2O needed to make the solution isotonic

W= Given weight

E= NaCl equivalent of the drug

OFFICIAL BUFFERS

Official Buffers :- It is essential to control pH of some solutions which are used in pharmaceutical chemistry and practice. This is brought about by using buffer solution.

These buffer solution can be categorized into two types-

a) Standard buffer system

b) Actual pharmaceutical buffers

A) Standard buffer system

These are designed to provide a solution having a pH for analytical purposes towards quality assurance.

B) Actual pharmaceutical buffers

- These are designed to maintain pH limits in pharmaceutical preparations.

- It should not take part in redox reactions

- It should not alter the solubility of other ingredients

- It should not reacts with active ingredients to form complexes

- It should not undergo any acid-base reaction other than that needed as a part of the buffer functions

- ❖ Volatile substance such as NH_3 or CO_2 should be avoided because if they escape from pharmaceutical preparation they will alter pH and the buffer capacity of the system.

Example of official buffers

a) Standard Buffer solution

1. **Boric acid and potassium chloride, 0.2 M:-** Dissolve 12.366 g of boric acid and 14.911 g of potassium chloride in water, and dilute with water to 1000 ml.

2. **Disodium Hydrogen Phosphate 0.2 M:-** Dissolve 71.630 g of disodium hydrogen phosphate in water and dilute with water to 1000 ml

3. **Hydrochloric Acid , 0.2 M :-** Hydrochloric acid diluted with freshly boiled and cooled water to contain in 1000 ml 7.292 g of HCl Standardise as directed under Volumetric Reagents and Solutions.

b) Actual Pharmaceutical Buffers

1. **Acetate buffer pH 3.9 :-** Dissolve 15.0 g of sodium acetate in 100 ml of 6 N acetic acid

2. **Ammonium buffer pH 10.0 :-** Ammonium buffer solution. Dissolve 5.4 g of ammonium chloride in 70 ml of 5 N ammonium and dilute with water to 100 ml

3. **Copper Sulphate solution pH 4.0, buffered :-** Dissolve 0.25 g of copper sulphate and 4.5 g of ammonium acetate in sufficient 2 N Acitic acid to produce 100 ml.