Electrolytes used in acid base balance

Sodium bicarbonate

Molecular formula: $NaHCO_3$ •

Sodium bicarbonate contains not less than 99.0 % and not more than 101 % of sodium bicarbonate. •

Sodium bicarbonate occurs as a white odourless crystalline powder or granules.

It is soluble in water (1 in 12); partially soluble in alcohol.

Alkalinity increases on standing, agitation or heating.

Storage:It is stored in well closed containers. • Sodium bicarbonate when mixed with calcium or magnesium salts, cisplatin, dobutamine hydrochloride or oxytetracyclin forms insoluble precipitates. • The following drugs are

susceptible to inactivation on mixing with sodium bicarbonate; adrenaline hydrochloride, isoprenaline hydrochloride and succimethonium chloride.

Solutions of sodium bicarbonate are used as eye lotions, to aid the removal of crusts in blepharitis, as eardrops to soften and remove ear wax, and as lubricating fluid for contact lenses.¬an antacid to relieve dyspepsia. ¬acute poisoning from acidic drugs (phenobarbitone and salicylates) ¬diarrohoea ¬used in the treatment of metabolic acidosis

Sodium acetate

Molecular formula: CH_3COONa

Molecular weight: 84 •

Sodium acetate contains not less than 99.0 %

Colour: colourless or white Form: Transparent crystals, granular powder

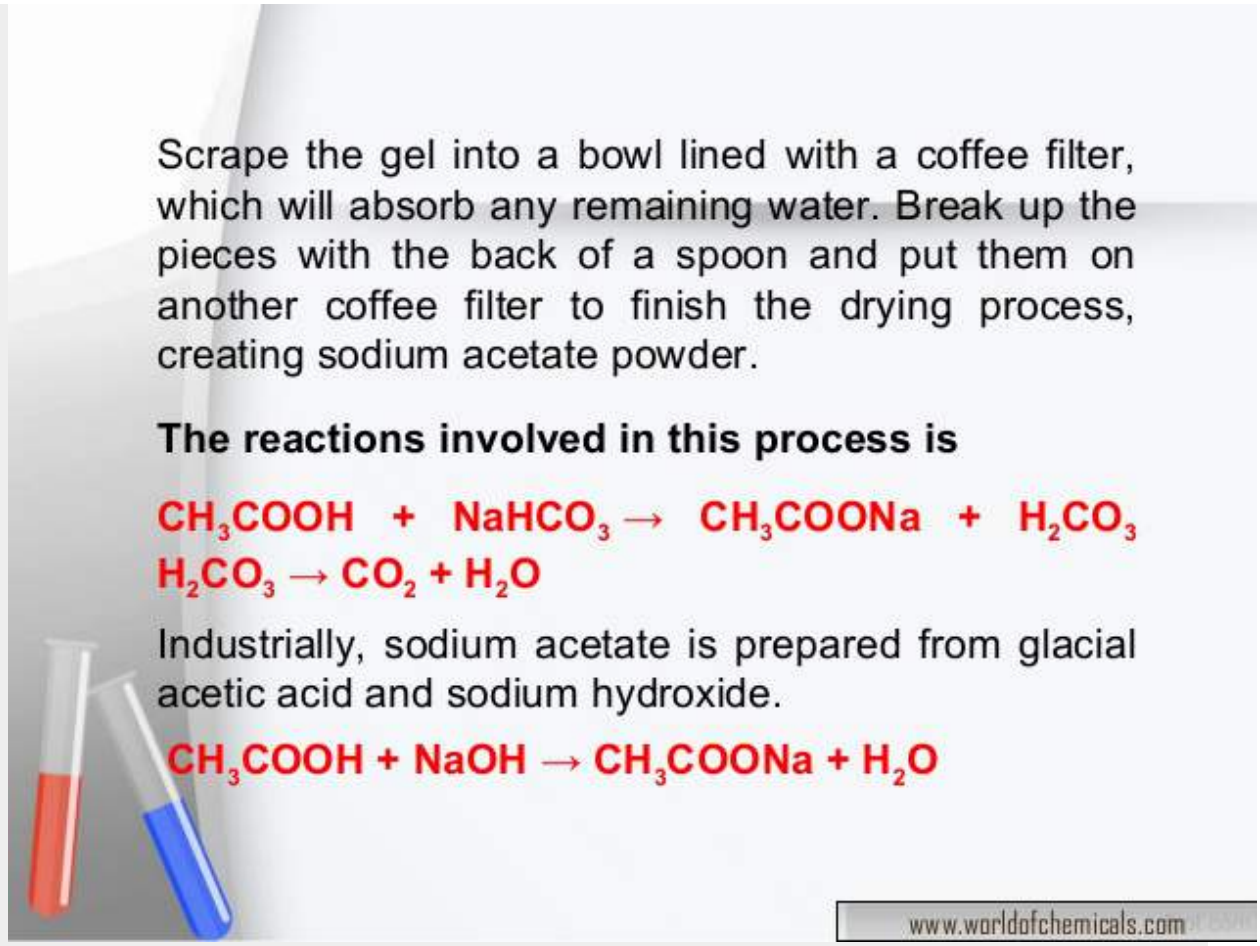
Odour: Acetic acid odour

Taste: Strong Solubility: Soluble in water & alcohol

Storage: store in air tight containers

Uses: An effective buffer in metabolic acidosis. It is used as pharmaceutical aid (for peritoneal dialysis fluid)

PREPARATION:



ASSAY:

Weigh accurately about 200 mg of the sample obtained in the test for "Loss on drying". Dissolve in

40 ml of glacial acetic acid, add 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction.

Each ml of 0.1 N perchloric acid is equivalent to 8.203 mg of C2H3NaO2.

Potassium acetate

Molecular formula: CH_3COOK

Molecular weight: 98

Potassium acetate contains from 99 to 101.0% of CH3COOK.

Colour:colourless Form: Crystalline powder

Odour: Faint acetic acid odour

Solubility: soluble in water & alcohol

pH: 7.5 to 9.5

Storage: Store in a well closed container

Uses: To Acid –base balance To make Water – electrolyte balance

METHOD OF ASSAY

Dissolve about 200 mg of the dried sample, accurately weighed, in 25 ml of glacial acetic acid. Add 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction.

Each ml of 0.1 N perchloric acid is equivalent to 9.814 mg of C2H3KO2

PREPARATION:

It can be prepared by treating a potassium-containing base such as potassium hydroxide or potassium carbonate with acetic acid:

$$CH_3COOH + KOH \rightarrow CH_3COOK + H_2O$$

Sodium citrate

Molecular formula: $C_6H_5Na_3O_7$

Molecular weight: 258

Sodium citrate contains about 99% of $C_6H_5Na_3O_7$.

Colour: white Form: Granular crystals

Deliquescent in moist air

Solubility: Freely soluble in water, Insoluble in alcohol

Storage: Store in a tightly closed container

uses It is used as 1.systemic alkalizer 2. It has anticlotting properties. 3. It is also used for dentifrices as desensitizing agent. 4. It also has a diuretic effect due to increased body salt concentration.

Assay. Dissolve about 0.15 g, accurately weighed, in 20 mL of glacial acetic acid R1, heat to about 50°C, allow to cool to room temperature, add 0.25 mL of 1-naphtholbenzein/acetic acid TS, and titrate with perchloric acid (0.1 mol/l) VS until a green colour is obtained

Each mL of perchloric acid (0.1 mol/l) VS is equivalent to 8.603 mg of C6 H5 Na3 O7 .

Preparation

Sodium citrate is not sold in supermarkets, but it is easy to prepare from the commonly available products:

- citric acid, usually available as monohydrate $C_3H_5O(COOH)_3 \cdot H_2O$, and
- baking soda: $NaHCO_3$

by reaction:

$3NaHCO_3 + C_3H_5O(COOH)_3 \rightarrow C_3H_5O(COONa)_3 + 3CO_2(g) + 3H_2O$

To prepare sodium citrate, dissolve some citric acid in water and gradually add small portions of soda. Every time you put new portion of soda, intensive reaction will start, producing lots of CO_2 gas.

Continue adding soda until the reaction stops (you'll need quite a lot of it). The process looks simple, but it took several hours, because adding large portions soda makes reaction too intense, producing lots of foam. To grow the crystals on the top photo I used only 50g of citric acid, so you don't need really much of it.

Ammonium Chloride

Molecular formula : NH_4Cl

Molecular weight:53.4

It is a sterile solution of ammonium chloride in water for injection. It contains not less than 99.5 % and not more than 105 % with reference to dried substance.

It is a product of the Solvay process used to produce sodium carbonate:[3]

$$CO_2 + 2\ NH_3 + 2\ NaCl + H_2O \rightarrow 2\ NH_4Cl + Na_2CO_3$$

In addition to being the principal method for the manufacture of ammonium chloride, that method is used to minimize ammonia release in some industrial operations.

Ammonium chloride is prepared commercially by combining ammonia (NH_3) with either hydrogen

chloride (gas) or hydrochloric acid (water solution):[3]

$$NH_3 + HCl \rightarrow NH_4Cl$$

Ammonium chloride when dissolve in water form acidic solution. Reaction between ammonium chloride and
sodium hydroxide produces some new compounds like ammonia, water and sodium chloride. Ammonia gas
liberated may combine with hydrochloric acid to form ammonium chloride and hence direct titration of
ammonium chloride with sodium hydroxide produce erroneous results.

So for the titration of ammonia chloride with base, the addition of formaldehyde would improve the titration.

The ammonium chloride reacts with formaldehyde to form hexamethylene tetramine. Because the weak acid

ammonium (pKa 9.3) is converted to the stronger hexamethylene tetramine ion (pKa 4.9). This improves the

end point.

Potassium bicarbonate

Molecular formula: $KHCO_3$

Molecular weight: 100.115

Colour: colourless

Odour: odourless

Taste: Basic and salty taste

Solubility: soluble in water Uses: To treat Hypokalemia To make normal functioning of heart Used as a mineral supplement

Assay:

Dissolve the Sample in 100 mL of water, add methyl red TS, and titrate with 1 N hydrochloric acid VS Add the acid slowly, with constant stirring, until the solution 1.0% of potassium acetate. becomes faintly pink. Heat the solution to boiling, cool, and continue the titration until the pink color no longer fades after boiling. Each mL of 1 N hydrochloric acid is equivalent to 100.1 mg of $KHCO_3$.

Sodium lactate

Molecular formula: $C_3H_5NaO_3$

Molecular weight: 112

Colour: white Form: Powder , Hygroscopic in nature

Taste: Saline taste Solubility: Soluble in water

Uses: Systemic and urinary alkalizer Electrolyte Replenisher

6. What are anticaries agents? Give examples.
7. What is dental caries? Name two anticaries agents.
8. What is desensitizing agents. Give examples.
9. What is dentifricing agents. Give examples.
10. What are dental products? Classify them with examples.
11. Write the composition and application of zinc eugenol cement.

□□□

UNIT III

Chapter...7

GASTROINTESTINAL AGENTS

♦ OVERVIEW ♦

- **Introduction**
- **Acidifying Agents**
- **Antacids**
- **Protectives and Adsorbents**
- **Cathartics or Laxatives**

6.1 INTRODUCTION

Gastrointestinal tract extends from mouth to anus. It involves movement of muscles and release of hormones and enzymes which allow the digestion and absorption of the food. It is also called as **Digestive tract** or **Alimentary tract**.

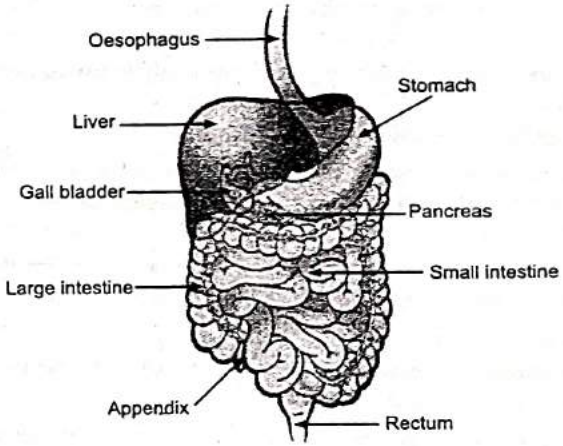


Fig. 7.1 : Gastrointestinal tract

7.1.1 Important Parts of Gastrointestinal Tract and Their Functions

(i) Oesophagus : It carries swallowed food down to stomach.

(ii) Stomach : It receives food from oesophagus. It contains hydrochloric acid and digestive enzymes (pepsin) that helps in digestion of food.

(iii) Small intestine : Absorption of digested food, vitamins and minerals occurs in the small intestine.

(iv) Large intestine : In large intestine, absorption of water and breaking down of waste to extract small amount of nutrients takes place in presence of symbiotic bacteria.

(v) Anus and rectum : It involves explusion of waste as faeces.

This group of organs together forms the digestive system. Any disturbances in the functioning of any organ of digestive system can lead to undesirable conditions.

Some of these are as follows :

1. Whenever inadequate secretion of acid takes place in stomach (i.e. secretion of acid less than the normal), this causes *achlorhydria.*
2. Whenever excess secreation of acid takes place in stomach (i.e. secretion of acid more than the normal), this leads to *hyperacidity* and *ulcer.*
3. In intestine the movement of food takes place by peristaltic movement, if there is insufficient peristaltic movement it leads to *constipation* and if the peristaltic movement is more than the normal it leads to *diarrhoea.*

Some of the gastrointestinal disorders : achlorhydria, indigestion, peptic ulcer, flatulence, diarrhoea constipation etc. The above condition can be treated by administration of gastrointestinal agents.

The Agents which are used to treat gastrointestinal disturbances are known as ***Gastrointestinal agents.***

7.1.2 Classification of Gastrointestinal Agents

Gastrointestinal agents can be broadly classified into the following categories :

I. Acidifying agents : Used to treat achlorhydria (absence of HCl in the gastric secretion) e.g. Dilute HCl.

II. Antacids : Used to treat hyperchlorhydria and peptic ulcer.
e.g. Aluminium hydroxide gel, Calcium carbonate.

III. Protectives and Adsorbents :
(i) Protectives for intestinal inflammation.
(ii) Adsorbents for intestinal toxins.
e.g. Heavy kaolin, Light kaolin, Bentonite.

IV. Cathartics or Laxatives : Cathartics and laxatives are used for constipation.
e.g. Magnesium sulphate.

7.2 ACIDIFIERS

Acidifiers are inorganic chemicals or drugs that are used to increase the gastrointestinal acidity. These agents are used in order to counteract the effect of achlorhydria (Inadequate secretion of gastric acid in stomach). In case of chronic gastritis, gastrectomy, carcinoma of stomach etc., there is total achlorhydria. Achlorhydria can be treated by various acidifying agents like ammonium chloride, dilute HCl etc.

Functions of Hydrochloric Acid in Stomach :

1. Pepsinogens are activated to pepsin in presence of hydrochloric acid.
2. It provides acidic medium which is required for effective digestion of food by pepsin.
3. It acidifies the food and stops the action of salivary amylase.
4. It kills many microbes which may be harmful to the body.

HYDROCHLORIC ACID (B.P., U.S.P.)

Chemical formula : HCl

Molecular weight : 36.46 g/mole

Category : Gastric acidifier, pharmaceutical aid.

Preparation :

1. Leblanc soda process : Hydrochloric acid can be prepared by the action of concentrated sulphuric acid on sodium chloride. This step is the first stage of the old leblanc soda process. The acid is run on to about an equal weight of salt in the cast iron pan of salt cake furnace. The hydrochloric gas is evolved and the reaction is completed by gentle heating.

$$NaCl + H_2SO_4 \longrightarrow NaHSO_4 + HCl$$

The pasty mass of $NaHSO_4$ formed in the above reaction, is collected and mixed with some more quantity of sodium chloride and heated strongly to get more hydrochloric acid.

$$NaCl + NaHSO_4 \longrightarrow Na_2SO_4 + HCl$$

The hydrogen chloride produced in these operation is passed through towers containing lumps of coke, down which there small flow of water. In this way crude hydrochloric acid is obtained.

2. Caustic soda is manufactured by electrolysis of sodium chloride, during that process large quantity of hydrogen and chlorine is obtained as byproducts.

Note : Ammonium chloride : Refer page 9.2 under expectorant topic)

These biproducts are combined to yield hydrogen chloride.

$$H_2 + Cl_2 \longrightarrow 2HCl$$

operties :

1. It is colourless liquid.
2. It is strongly acidic and has specific gravity about 1.04-1.05.

Test for Purity : It has to be tested for sulphate, free chlorine, Arsenic, heavy metals, bromide iodide.

Assay :

Assay of hydrochloric acid is based upon acid base titration method.

An accurate amount, about 2 g of hydrochloric acid is transferred to a stoppered flask which is having 30 ml of water. Now the solution is titrated with 1 M sodium hydroxide using methyl red as an indicator.

$$NaOH + HCl \longrightarrow NaCl + H_2O$$

Each ml of 1 M NaOH is equivalent to 0.03646 g of HCl.

Uses :

1. Dilute hydrochloric acid is mainly used as gastric acidifiers.
2. It can also be used as solvent and catalyst in pharmaceuticals.

DILUTE HYDROCHLORIC ACID

It contains 10 per cent w/w of HCl (limits 9.5 to 10.5 per cent).

Ingredients :

Hydrochloric acid – 274.0 g

Purified water – 726.0 g

Preparation : Hydrochloric acid (274.0 g) is added gradually to water (726.0 g) and mixed.

Properties : It is colourless liquid. It is strongly acidic and has about 1.04-1.05 specific gravity.

Test for purity : It has to be tested for As, heavy metal, bromide, iodide, sulphate, and free chlorine.

Use : It is used as an acidifiers.

Storage : It is stored in well closed containers

Dose : 0.6 ml to 8 ml.

(**Note : Ammonium chloride :** Refer page 9.2 under expectorant topic.)

7.3 ANTACIDS

Antacids are the drugs which are alkaline substance used for neutralizing excess gastric acid associated with ulceration, gastritis and peptic ulcer etc. These drugs give relief from pain caused due to hyperchlohydria or hyperacidity.

The hyperacidity can cause the following GIT disorders :

1. **Gastritis :** A general inflammation of gastric mucosa.

2. **Peptic ulcer :** It is a non-cancerous sore in the wall of stomach or intestine. It occurs only in those region that are bathed by digestive juices secreted by stomach. Digestive juices contains hydrochloric acid and pepsin. Hence, the name is peptic ulcer.

3. **Gastric and duodenal ulcer :** Sore on inside lining of stomach is called as gastric ulcer. And the sore on upper part of small intestine is called as duodenal ulcer.

Antacids are usually weak alkaline. It act by raising the pH of the stomach and duodenum. It tend to raises the pH above 4 and inactivate the proteolytic enzyme pepsin. It is not possible to use strong alkaline bases as antacid because it will exert damaging effect on mucosal layer.

7.3.1 Criteria for Ideal Antacids

1. It should not be absorbable or cause systemic alkalosis.
2. It should not liberate carbon dioxide and cause rebound hyperacidity.
3. It should not interfere with absorption of food.
4. It should not be a laxative or cause constipation.
5. It should be quick acting and exert its effect over long period of time.
6. It should buffer in the pH range 4-6.
7. It should probably inhibit pepsin.
8. It should be palatable and inexpensive.

7.3.2 Classification of Antacids

Antacids are classified as :

I. Systemyic antacids :

Systemic antacids are water soluble. It acts instantaneously, but the duration of action is short. It is a potent neutralizer, it may rise the pH above 7.

This class of antacids easily absorbed in to systemic circulation and are capable of changing blood pH. It may cause systemic alkalosis. Antacid belonging to this category is **Sodium bicarbonate.**

In general, the bicarbonate antacids preferably used when short term antacid treatment is required.

II. Non-systemic antacids :

This class of antacids are insoluble in water. They have poor absorption capacity. It has no direct effect on acid base equilibrium. They do not produce systemic alkalosis.

Non-systemic acid can be further classified as :

1. **Aluminium compound as antacids :**
   (a) Aluminium hydroxide gel (I.P.).
   (b) Dried Aluminium hydroxide gel (I.P., B.P.).
   (c) Dried Aluminium hydroxide tablets (I.P., B.P.).

Besides the above, other aluminium compound used as antacids are aluminium glycinate, aluminium carbonate, dried aluminium phosphate.

2. **Calcium compound as antacids :**
   (a) Calcium carbonate.
   (b) Tribasic calcium phosphate.
3. **Magnesium compound as antacids :**
   (a) Magnesium carbonate heavy and light.
   (b) Magnesium hydroxide mixture.

SODIUM BICARBONATE (B.P.)

Chemical formula : $NaHCO_3$

Molecular weight : 84.007 g/mol

Category : Systemic antacids, Electrolyte replenisher

Synonyms : Baking soda, Sodium hydrogen carbonate.

It possesses not less than 99 per cent and not more than 100.5 per cent of sodium bicarbonate with reference to dried substance.

Preparation :

I. Industrial method : Solvay process/ammonia soda process :

In this method of preparation, sodium chloride (Brine solution) is saturated with ammonia to render it free from traces of impurities such as Mg and Fe. The solution is then filtered and the temperature of the solution is increased by heating to 30°C. The hot solution is allowed to interact with a current of CO_2 present in carbonating tower. The carbonating tower is cooled immediately for the precipitation of sodium bicarbonate.

The precipitation of sodium bicarbonate occurs at a temperature below 15°C. The precepitate is filtered and dried.

$$H_2O + CO_2 \longrightarrow H_2CO_3$$

$$NH_3 + H_2CO_3 \longrightarrow NH_4HCO_3$$

$$NaCl + NH_4HCO_3 \longrightarrow NaHCO_3 + NH_4Cl$$

Sodium bicarbonate obtained from this method does not meet the requirment of I.P. Sodium bicarbonate can be prepared from sodium carbonate solution as described in laboratory method.

II. Laboratory method : Small scale method :

Sodium bicarbonate is prepared by passing CO_2 gas through solution of sodium hydroxide. The solution is then concentrated to get sodium bicarbonate.

$$NaOH + CO_2 \longrightarrow Na_2CO_3 + H_2O$$

$$Na_2CO_3 + H_2O + CO_2 \longrightarrow NaHCO_3$$

Properties :

1. It occurs as white crystalline or amorphous powder having a saline taste.
2. It is freely soluble in water but practically insoluble in alcohol.
3. It gives effervescence with acids.
4. When it is heated to 100°C, it converted in to sesquicarbonate (Na_2CO_3, $NaHCO_3 2H_2O$).
5. Its solution is alkaline in nature.

Identification Test :

It gives the reaction of sodium and bicarbonate.

Test for Purity :

It has to be tested for alkalinity, aluminium, calcium, arsenic, heavy metal, Fe, sulphate, ammonium compound and insoluble matter.

Assay :

The assay of sodium bicarbonate is based upon acidimetric titration.

Accurately weighed 1 g of sodium bicarbonate is transfered in conical flask and dissolved in 20 ml of carbon dioxide free water. It is then titrated with 0.5N sulphuric acid using methyl orange as an indicator.

$$NaHCO_3 + H_2SO_4 \longrightarrow Na_2SO_4 + H_2O + CO_2$$

Factor : Each ml of 0.5 N H2SO4 is equivalent to 0.042 g of $NaHCO_3$.

Storage : It is stored in tightly closed containers.

Uses :

1. It acts as an antacid because of its acid nuetralizing properties.
2. It is used to treat dyspepsia and metabolic acidosis.
3. It is widely used as an electrolyte replenisher.

Dose : 300 mg to 2 g.

Other official preparations : Sodium bicarbonate injection, Sodium bicarbonate tablets, Sodium bicarbonate oral powder.

ALUMINIUM HYDROXIDE GEL (I.P., B.P., U.S.P.)

Chemical formula : $Al(OH)_3$

Molecular weight : 78 g/mole

Category : Antacid

Synonyms : Aluminium hydroxide suspension, Aluminium hydroxide mixture

Aluminium hydroxide is an aqueous white viscous suspension of hydrated aluminium oxide having varying amount of basic aluminium carbonate. The preparation contain not less than 3.5% and not more than 4.4% of aluminium oxide.

Preparation :

Preparation of aluminium hydroxide from potash alum :

It is prepared by the adding hot solution of potash alum slowly with constant stirring to a hot solution of sodium carbonate and not vice versa. After complete removal of carbon dioxide the precipitated aluminium hydroxide is filtered. It is washed thoroughly with hot water till it is free from sulphate. The gel is then adjusted to the required volume with distilled water.

$$3NaCO_3 + 2KAl(SO_4)_2 + 3H_2O = 3Na_2SO_4 + K_2SO_4 + 2Al(OH)_3 + 3CO_2$$

Potash alum

If sodium carbonate solution is added to potash alum solution, it may yield precipitate of alkali sulphate which would be difficult to wash.

II. Preparation of aluminium hydroxide from aluminium carbonate :

When sodium carbonate is added to aluminium sulphate, aluminium carbonate and sodium sulphate are formed. Aluminium carbonate is highly unstable in nature, hence it undergoes hydrolysis to yield aluminium hydroxide and carbon dioxide as a byproduct.

$$3Na_2CO_3 + Al_2(SO_4)_3 \longrightarrow 3Na_2SO_4 + Al_2(CO_3)_3$$

$$2Al_2(CO_3)_3 + 6H_2O \longrightarrow 4Al(OH)_3 + 6CO_2$$

Properties :

1. It is white viscous suspension. A clear liquid separated when it is kept standing for sometime.
2. Aluminium hydroxide gives astringent aluminium chloride when it react with gastric acid (HCl). This results in to vomiting, nausea and constipation.

$$Al(OH)_3 + 3HCl \longrightarrow AlCl_3 + 3H_2O$$

Identification test :

A solution in hydrochloric acid gives the reaction of aluminium. When an equal volume of gel is diluted with distilled water , the pH of the solution should not be more than 7.5

Test for Purity :

It has to be tested for alkalinity, arsenic, sulphate, chloride, ammonium salt and acid consuming capacity.

Assay :

The assay of aluminium hydroxide is performed by complexometric titration. In this titration disodium edetate is allowed to complex aluminium under conditions in which metals such as calcium and magnesium do not interfere. The excess of sodium edetate is added left after complexation with aluminium is over, is back titrated with 0.05M lead nitrate solution. Hexamine is added to raise the pH to the alkaline side to facilitate the complexometric titration of the excess of EDTA with 0.05M lead nitrate.

Procedure : 5 gm of substance accurately weighed and taken in a flask. To this 3 ml hydrochloric acid is added. The solution is warmed on a water bath. After cooling, this is transferred to a 100 ml volumetric flask and the volume is made up to 100 ml. 20 ml of solution is taken from volumetric flask in to a conical flask and 40 ml of 0.05M disodium edetate added to it followed by 80 ml of water and a few drops of methyl red solution. To this 1N sodium hydroxide is added to neutralise this solution.

This can be indicated by change of colour from red to yellow. Now the flask is warmed on a water bath for 30 minutes. To this 3 g hexamine is added and 0.5 ml of xylenol orange solution is added to it as an indicator. This mixture is titrated with 0.05M lead nitrate until a violet colour appears at the end point due to the formation of lead xylenol orange complex.

Factor : Each ml of 0.5M disodium edetate is equivalent to 0.002549 g of Al_2O_3.

Storage : Store in tightly closed containers and should not be allowed to freeze.

Uses :

1. It is a very effective slow acting antacid.
2. It is able to neutralise gastric hydrochloric acid and causes absorption of toxins, and gases.

Dose : 7.5 ml to 15 ml. It causes constipation, therefore it is administered along with magnesium salt which is a mild laxative.

DRIED ALUMINIUM HYDROXIDE GEL, $Al(OH)_3$

Synonym : Aluminium hydroxide powder.

It is having not less than 47 per cent of Al_2O_3 when ignited to constant weight.

Test for Purity, Storage and Uses : Same as aluminium hydroxide gel.

MAGNESIUM HYDROXIDE MIXTURE (B.P.)

Chemical formula : $Mg(OH)_2$

Molecular weight : 58.32 g/mole

Category : Antacid, laxative

Synonyms : Milk of magnesia, Magnesium hydroxide oral suspension.

It is having not less than 95% and not more than 100.5% of magnesium hydroxide.

Preparation :

It can be prepared from sodium hydroxide and magnesium sulphate. In this method, sodium hydroxide is mixed with light magnesium oxide (MgO) and the suspension so obtained is diluted with water. It is then slowly added to magnesium sulphate with constant stirring.

The resulting solution is left undisturbed so that the precipitate settles at the bottom.

The upper clear liquid is separated and residue is collected on a calico filter which is then washed with water until it is free from sulphates. The precipitate is the finally mixed with suffficient quantity of distill water.

$$2NaOH + MgSO_4 \longrightarrow Mg(OH)_2 + Na_2SO_4$$

White and creamy magnesium hydroxide is obtained due to the addition of light magnesium oxide otherwise it would have been gelatinous translucent aqueous suspension.

Properties :

1. It is white fine amorphous powder.
2. It is almost insoluble in water and it yields a solution which is slightly alkaline.
3. It dissolves in dilute mineral acids.

Identification :

A solution of 1 ml in 2 ml dilute hydrochloric acid gives the reaction of magnesium.

Test for purity :

It has to be tested for soluble alkalies, soluble salts, carbonates, and acid insoluble matter. Besides Ca, As and heavy metals.

Assay : It is carried out by acid base back titration method using methyl red as an indicator. Initially, magnesium hydroxide mixture is made to react with sulphurc acid. The excess of sulphuric acid is back titrated with 1N sodium hydroxide.

Procedure : An accurately weighed amount of sample is taken in a flask (5 ml). To it 25 ml of 1N sulphuric acid is added. The excess of sulphuric acid is back titrated with 1N sodium hydroxide using methyl red as an indicator.

$$Mg(OH)_2 + H_2SO_4 \longrightarrow MgSO_4 + 2H_2O$$

$$H_2SO_4 + 2NaOH \longrightarrow Na_2SO_4 + 2H_2O$$

Factor : Each ml of 1N sulphuric acid is equivalent to 0.02917 g of $Mg(OH)_2$.

Storage : Store in tightly closed containers and in a cool place.

Uses :

1. It is used as an antacid and osmotic laxative.
2. It is used as an alkaline mouth wash.

Dose :

5 to 10 ml as an antacid.

15 to 30 ml as an laxative.

Labelling : The label on the container states that "shake well before use."

MAGNESIUM CARBONATE

Magnesium carbonate occurs in two forms, that is, heavy magnesium carbonate and light magnesium carbonate. They are both hydrated basic magnesium carbonate and differ only in the content of water of hydration (the heavy variety having $5H_2O$ and the light one with $3H_2O$) and in the bulk density.

HEAVY MAGNESIUM CARBONATE (B.P.)

This is a basic carbonate having an approximate chemical composition $3MgCO_3 . Mg(OH)_2 . 4H_2O$. It contains not less than 40.0% and not more than 45.0% of MgO.

Heavy magnesium carbonate is different from light magnesium carbonate in density. 15 g of heavy magnesium carbonate occupies a volume of 30 ml while light magnesium carbonate occupies a volume of 125 ml (as per IP).

Category : Antacid, Osmotic laxative.

Preparation :

Magnesium carbonate is prepared by double decomposition from magnesium sulphate and sodium carbonate. Magnesium sulphate (125 parts) and sodium carbonate (150 parts) are dissolved separately in water and the solutions are mixed (1 : 1 ratio) and concentrated. The residue is digested with boiling water for 30 minutes. The insoluble magnesium carbonate is filtered on calico cloth and washed until it becomes free from sulphate ions and dried in an oven.

$$MgSO_4 + Na_2CO_3 \longrightarrow MgCO_3 \downarrow + Na_2CO_3$$

Properties :

1. It is a white granular powder.
2. It is odourless and tasteless.
3. It is insoluble in water and alcohol.

When it is heated to redness, it gets converted to MgO, losing carbon dioxide and water.

$$3MgCO_3 \cdot Mg(OH)_2 \cdot 5H_2O \longrightarrow 4MgO + 3CO_2 + 6H_2O$$

ntification :

Its solution in acetic acid gives the reaction of magnesium and carbonate.

ests for purity :

It has to be tested for As, Ca, Fe, Cu, Pb, chloride, sulphate, residue on ignition and oluble matter.

Assay :

The assay of magnesium carbonate is based upon complexometric titration.

Accurately weighed (1.0 g) sample is dissolved in dilute hydrochloric acid and the volume is made up to 250 ml with water. To 50 ml of this solution, add 100 ml of water and 15 ml of NaOH solution. After addition of 40 mg murexide indicator and 3.0 ml of naphthol green, titrate with 0.05M disodium EDTA until deep blue colour appears.

Factor : Each ml 0.05M disodium EDTA is equivalent to 0.002015 g of MgO.

Storage : It is stored in tightly closed container.

Uses :

(i) It is used as an antacid and laxative, it comparatively weak antacid.

(ii) It can also be used as a cathartic.

LIGHT MAGNESIUM CARBONATE (B.P.)

It is a basic hydrated carbonate which differ from heavy magnesium carbonate in bulk density. Its approximate chemical composition $3MgCO_3 \cdot Mg(OH)_2 \cdot 3H_2O$.

Category : Antacid, Osmotic laxative.

Properties :

1. It is available as very light white powder.
2. It is odourless and tasteless.
3. It is insoluble in water and alcohol.

Preparation, Identification, Tests for purity, Assay and uses are same as Heavy Magnesium Carbonate.

Storage : It is stored in tightly closed container.

CALCIUM CARBONATE (B.P., U.S.P.)

Chemical formula : $CaCO_3$

Molecular weight : 100.1 gm/mole

Category : Antacid

Synonym : Precipitated chalk

It is having not less than 98.0% and not more than 100.5% of $CaCO_3$ which is calculated with reference to the sample dried at 105°C.

Occurence : It is available in different forms in nature such as limestone, calcite, dolomite, and in shell of sea animals.

Preparation :

I. It can be prepared by reacting a solution of sodium carbonate and calcium chloride in presence of high temperature i.e double decomposition reaction. The precipitate of calcium carbonate is obtained. The precipitate is filtered and dried.

$$Na_2CO_3 + CaCl_2 \longrightarrow CaCO_3 \downarrow + NaCl$$

II. When carbon dioxide is passed through lime water (aqueous calcium hydroxide), milky white precipitate of calcium carbonate is obtained.

$$CO_2 + Ca(OH)_2 \longrightarrow CaCO_3 \downarrow + 2H_2O$$

III. It can also be prepared by mixing solution of sodium carbonate and calcium nitrate.

$$Ca(NO_3)_2 + Na_2CO_3 \longrightarrow CaCO_3 + 2NaNO_3$$

Properties :

1. It occurs as fine, white microcrystalline powder.
2. It is odourless and tasteless.
3. It is soluble almost insoluble in water and alcohol. The water solubility can be increased in the presence of carbon dioxide and ammonium salts.

Identification :

It gives the reaction of calcium and carbonate.

Tests for purity :

It has to be tested for Al, Fe, phosphate, heavy metal chloride, sulphate, barium, soluble alkali, and loss on drying and insoluble matter in HCl.

Assay :

It can be assayed by the complexometric titration method.

Accurately weighed (1.0 g) sample is moisten with sufficient quantity of water and sufficient HCl is added to get a clear solution. The volume is made up to 250 ml with water. To 50 ml of this solution, add 100 ml of water and 15 ml of 1N NaOH solution. After addition of 40 mg murexide indicator and 3.0 ml of naphthol green, titrate with 0.05M disodium EDTA until deep blue colour appears.

Factor : Each ml 0.05M disodium EDTA is equivalent to 0.005005 g of $CaCO_3$.

Storage : It is stored in tightly closed container.

Ises :

1. It is internally used as an antacid and it finds use externally as a dentifrice because it is having mild abrasive quality.

It is usually administered along with magnesium salt because it has a tendency to cause onstipation.

.4 COMBINATIONS OF ANTACIDS

Several basic compounds are employed as antacids, notably aluminium salts and nagnesium salts, calcium carbonate and sodium bicarbonate. There are three complications isually seen when these antacids are used.

1. Many antacids exert an action on the bowel. For example : some have a mild laxative effect (e.g. Magnesium hydroxide) and some are constipating (e.g. Aluminium hydroxide).
2. If the cation (the metallic ion) is absorbed, systemic alkalosis may be produced (e.g. sodium bicarbonate), Calcium ions may produce hypercalcaemia (abnormally high concentration of calcium in the blood) and Phosphate bound by calcium in the gut or bone may deplete the serum phosphorus in some kidney failure patients.
3. Antacids may affect the absorption of other drugs which may be administered along with antacids such as antichlolinergics and antibiotics. These drugs may be adsorbed by the antacids.

Table 7.2 : Antacids with their unwanted effects

Antacid	Formula	Neutralizing Power	Unwanted Effects
Sodium Bicarbonate	$NaHCO_3$	Low	Fluid retention, Alkalosis
Magnesium Hydroxide	$Mg(OH)_2$	High	Diarrhoea, Magnesium toxicity
Aluminium Hydroxide	$Al(OH)_3$	Modest	Constipation, Drug or phosphate binding (inhibits absorption)
Calcium Carbonate	$CaCO_3$	Very high	Acid rebound

The defects associated with the antacids can be minimized by the use of combination of antacids. For example, magnesium hydroxide and aluminium hydroxide may be combined to balance the constipating effect of the aluminium hydroxide with the laxative effect of Magnesium hydroxide. The following combinations are in regular clinical use.

1. Magnesium and aluminium hydroxides.
2. Magensium and aluminium hydroxides, dimethicone. (If dyspepsia leading to gas formation in the gut is present, use of a drug like methylpolysiloxane/dimethicone /simethicone is necessary.)
3. Magnesium and aluminium hydroxides, methylpolysiloxane.
4. Aluminium hydroxide gel and magnesium trisilicate.

7.5 CATHARTICS

Cathartics are the agents that promotes the evacuation from the bowel. It facilitates the passage and elimination of the feaces from the intestinal tract through the colon and rectum.

Cathartics are used :

1. To relieve constipation and for expulsion of intestinal parasites.
2. It is used for cleaning the colon before colonscopy, abdominal surgery or X-ray.
3. It is used to ease defecation in patient with painful hemorrhoid or other rectal disorders. (*Hemorrhoid are clumps of blood vessels (veins) in the rectum, the hemorrhoidal veins are located in the lowest area of the recturn just above the anus. Sometimes the hemorrhoidal veins enlarge and their walls become stretched, thin and irritated by passing stool.*)

The basic difference between cathartic, purgative and laxative are the dose, nature and mechanism of action. Purgatives are also cathartics which behave similarly but have considerably milder action than cathartic. Laxatives when used at high doses are known as purgatives or laxatives are mild type of purgative. These purgatives are stronger then laxative but has milder action then cathartics.

However cathartics, purgative and laxative are administered either by oral route in the form of suspension, powder or via rectal route as enema or suppositories.

In normal habits, peristaltic movement cause defecation. Peristalsis is a radial, symmetrical contraction and relaxation of muscles which propel the content through the digestive tract. Peristaltic motion normally take place 3 to 4 times a day, by ignoring the urge to defecate or by psychological can lead to constipation. The condition in which there is difficulty in emptying bowel usually associated with hardened faeces. In such condition, the bowel movement become tough or happen less often than the normal. Constipation can be caused due to diet, use of certain drug, intestinal spasm etc. Constipation can be treated by the use laxatives and purgatives.

Purgatives or cathartics act by four different mechanisms :

1. Lubricant :

In case of constipation, the content of intestine becomes hard due to absorption of water by body this results in difficulties in emptying the bowel. In such condition, lubricants are used that causes smooth clearance of the fecal material

Examples : Mineral oil, liquid paraffin glycerin etc.

2. Bulk Purgatives :

These agents are made from cellulose or non-digestible type of material, which swells when wet. It act by increasing the bulk of intestinal contents. Due to increase in bulk of intestinal content, peristaltic movement increases which result in defecation.

Examples : Methyl cellulose, sodium carboxyl methyl cellulose.

...imulant :

These are the agents which act directly on intestinal tract and stimulate peristalsis. It act by local irritation on intestine tract which increases the peristaltic movement.

Examples : Castor oil, senna, podophyllum.

4. Saline cathartics/osmotic laxatives :

These are salt of poorly soluble anion and sometimes cations. It mainly act by increasing the osmotic load of intestine. This can be done by increasing the fluidity of intestinal content by absorbing large quantity of water and indirectly increasing the peristalsis. Saline cathartics are water soluble inorganic chemical and they are taken with plenty of water this helps in restricting excessive loss of body fluid and reduces vomiting and nausea.

Examples : Magnesium sulphate, Sodium sulphate, Sodium orthophosphate.

MAGNESIUM SULPHATE (B.P., U.S.P.)

Chemical formula : $MgSO_4 \cdot 7H_2O$

Molecular weight : 246.7 gm/mole

Category : Osmotic laxative

Synonym : Epsom salt

It is having not less than 99% and not more than 100% of $MgSO_4$, calculated reference to ignited substance.

Preparation :

1. Magnesium sulphate is prepared by the action of dilute sulphuric acid on magnesium carbonate or magnesium oxide. The solution is filtered and the filtrate is evaporated to crystallisation.

$$MgCO_3 + H_2SO_4 \longrightarrow MgSO_4 + H_2O + CO_2$$

2. It is prepared by the action of sulphuric acid on the native carbonate (magnesite) or previously calcined dolomite. Dolomite is a mixture of magnesium and calcium carbonate. In both cases magnesium sulphate being water soluble remain in the solution while the impurities such as $CaCO_3$ (in case of dolomite) undergo precipitation. Thus to remove impurities solution is filtered.

The filterate is subjected to evaporation and the product is purified by crystallisation.

$$MgCO_3 \cdot CaCO_3 + 2H_2SO_4 \longrightarrow MgSO_4 + CaSO_4 + 2H_2O + 2CO_2$$

3. It can be prepared in large quantities from magnesium salt occuring in brine solution which is used for the exactraction of bromine. The liquor after complete removal of bromine vapours is allowed to react with milk of lime, thus precipitating out magnesium hydroxide. Sulphur dioxide and air are passed through the suspension of magnesium hydroxide.

$$2Mg(OH)_2 + 2SO_2 + O_2 \longrightarrow 2MgSO_4 + 2H_2O$$

On crystallisation, crystals of $MgSO_4 \cdot 7H_2O$ are obtained.

Properties :

1. It occur as colourless crystal having a cool, saline bitter taste.
2. It is soluble in water and sparingly soluble in alcohol.

Identification :

It gives the reaction of magnesium and sulphate.

Tests for purity :

It has to be tested for As, Fe, heavy metal and loss on drying.

Assay :

The assay of magnesium sulphate is based upon complexometric titration.

Magnesium sulphate is dissolved in water and titrated with 0.05M disodium EDTA solution. During this titration EDTA-magnesium complex is formed. Strong ammonia-ammonium chloride solution is used as the buffer so that the pH may be raised to more than 10 and maintained at that level. This is because complexation of magnesium by EDTA takes place only at this pH. Mordant black II is used as an indicator. At the end point deep blue colour appears.

Factor : Each ml 0.05M disodium EDTA is equivalent to 0.00602 g of $MgSO_4$.

Storage :

It is stored in tightly closed container.

Uses :

1. It is used as a saline purgative.
2. It is used in the form of enema.
3. It is helpful to promote evacuation of gall bladder content in the treatment of cholecytitis.

SODIUM ORTHOPHOSPHATE

Chemical formulae : Na_3PO_4 (Anhydrous)

$Na_3PO_4 \cdot XH_2O$ (Hydrated)

Molecular weight : 163.94 gm/mole (Anhydrous)

Category : Osmotic laxative

Synonyms : Trisodium orthophosphate, Trisodium phosphate, Trisodium monophosphate.

Tribasic sodium phosphate is anhydrous or contain one or twelve molecules of water of hydration Na_3PO_4 (Anhydrous) and $Na_3PO_4 \cdot XH_2O$ (Hydrated) contain not less than 97.0 per cent of calculated on the ignited basis.

Preparation :

Sodium orthophosphate is prepared by treating sodium carbonate with phosphoric acid, disodium phosphate is obtained. Disodium phosphate is further neutralised with sodium hydroxide to form sodium orthophosphate.

$$Na_2CO_3 + H_3PO_4 \longrightarrow Na_2HPO_4 + CO_2 + H_2O$$

$$Na_2HPO_4 + NaOH \longrightarrow Na_3PO_4 + H_2O$$

Properties :

1. It is white odourless crystalline granules or powder.
2. It is freely soluble in water and insoluble in ethanol.

Identification :

It gives the reactions of sodium, phosphate and orthophosphate.

Tests for purity :

It has to be tested for As, lead water insoluble substance and loss on ignition.

Storage : It is stored in tightly closed container.

Uses : It is used as a laxative to cleanse the bowel.

7.6 PROTECTIVE AND ADSORBENTS

Gastrointestinal adsorbents are the chemically inert substance which are taken to adsorb gases, toxins and bacteria in the stomach and intestine. These agents are used in the treatment of mild diarrhoea or dysentery or other disturbances of gastrointestinal tract.

In diarrhoea, frequent discharge of intestinal content occur from anus in the form of watery fluid. The ion of fluid is accompanied by the loss of electrolyte frequently which in turn leads to dehydration this result in electrolyte imbalance. Diarrhoea are mainly caused due to improper digestion or bacterial infection sometimes chemical and poisonous drug also causes diarrhoea.

Dysentery is an intestinal inflammation especially in the colon that can lead to severe diarrhoea with mucous or blood in faeces.

There are two main types of dysentery :

(1) Bacillary dysentery : This caused by a *shigella* a bacterium.

(2) Amoebic dysentery : (Amoebiasis) this is caused by *Entamoeba histolytica* a type of Amoeba.

These adsorbents also acts as protective adsorbent antidiarrhoeal with little or no antibacterial action. Protectives are used to form a protective layer on painful ulcers in the GIT. It also help in reducing ulcers.

HEAVY KAOLIN (B.P.)

Synonym : Kaolin or china clay.

It is derived from the decomposition of feldspar of granite rocks and occurs in various parts of the world. Heavy kaolin consist cheifly of an hydrated aluminium silicate. It is basically a purified form of natural kaolin. Natural kaolin consists of variable amount of calcium, magnesium, and ferric oxide as impurities which can be removed to obtain heavy kaolin. Heavy kaolin meant for human being and it should be thoroughly sterlised to make it free from spore bearing bacilli and bacteria.

Chemical formula : $Al_2O_3 \cdot 2SiO_2 \cdot 2H_2O$

Category : Pharmaceutical aid

Preparation :

It is prepared by treating natural clay with hydrochloric acid, to remove impurities such as Ca, Mg, carbonates and ferric oxide present in it. It is then filtered, washed, and dried to obtain purified hydrated aluminium silicate (heavy kaolin).

Properties :

1. It is white fine and soft powder.
2. It is odourless and tasteless.
3. It is insoluble in water, mineral acid, organic solvent and alkali hydroxide solution.

LIGHT KAOLIN (B.P.)

Light kaolin is finely divided form of kaolin containing hydrated aluminium silicate, purified by elutriation. Elutriation is a process in which finely divided particles are suspended in an upward flowing stream of air or water to wash and isolate them in to size fraction. It especially meant for internal use.

Chemical formula : $Al_2O_3 \cdot 2SiO_2 \cdot 2H_2O$

Category : Antidiarrhoeal

Preparation :

It can be prepared from natural clay. Its preparation involves the following steps :

Step 1 : Powdering.

Step 2 : Particle separation by means of electrical sedimentation.

Step 3 : Purification from gritty particles and impurities elutriation.

Step 4 : Drying.

Properties :

1. It is white fine powder.
2. It is odourless and tasteless.

   It is insoluble in water and mineral acid.

...for purity :

It has to be tested for heavy metals, chlorides, sulphate etc.

Use : It is used as adsorbent to adsorb toxins in food and alkaloidal poisoning.

Storage : Stored in well closed container.

BENTONITE (B.P., U.S.P.)

Chemical formula : $Al_2O_3 \cdot 4SiO_2 \cdot XH_2O$

It is a native colloidal hydrated aluminium silicate, freed from gritty particles. It occurs naturally.

Bentonite is an aluminium silicate having SiO_2, Al_2O_3, Fe_2O_3, CaO, MgO and some sodium and potassium.

Properties :

1. It occur as a very fine, pale buff or cream coloured powder.
2. It is free from grit.
3. It is odourless and has slightly earthy taste.
4. It is insoluble in water but it swell to about twelve times its volume when added to water. It neither dissolves nor swells in organic solvents.

Idetification :

Sample of bentonite is fused with anhydrous sodium carbonate and extracted with water followed by repeated extraction with dilute HCl. It yields the residue of silica and the acid solution after neutralisation which gives the reaction characteristic of aluminium.

Test for purity :

pH : The pH of a 2.0 per cent suspension in water is 9 to 10.5.

Gel formation : 6 g of bentonite sample is mixed thoroughly with 0.3 g of MgO. This is added in several portion to 200 ml water in a 500 ml stoppered flask. It is agitated for 1 hour. Then 100 ml mixture is transferred to a 100 ml cylinder and is allowed to remain undisturbed for 24 hour. The volume of supernatant liquid appearing on the surface in the cylinder is noted. The clear supernatant is not more than 2 ml.

Swelling factor : It is measured by dropping from top 2 g of bentonite sample in divided portions upon the surface of 100 ml water contained in 100 ml capacity measuring cylinder. Each portion is allowed to get settle before the next is added. Bentonite swells at the bottom and it should occupy an apparent volume not less than 24 ml.

Fineness of powder : 2 g of sample is sprinkled on 20 ml water contained in motar. It is allowed to swell, the swollen mass is dispersed evenly with pestle and diluted with water to 100 ml. The suspension obtained is poured through sieve number 200 and sieve is washed

thoroughly with water. The test passes if no grit is felt when fingers are rubbed over the wire mesh of the sieve.

Loss on drying : Bentonite is dried to constant weight at 105°C, it should not loss less than 5 per cent and not more than 12 per cent of its weight.

Uses :

1. It is used as adsorbent and protectives.
2. It is a good pharmaceutical aid, it is used as a emulsifier for oil in water emulsions.
3. It is base for many pharmaceutical preparation including plasters and bases.

Storage : Stored in well closed container.

QUESTIONS

1. What are Antacids? Classify them with examples. Give the ideal properties of antacids.
2. Write the preparation, assay and uses of Sodium bicarbonate.
3. Write the preparation and uses of Aluminium hydroxide.
4. Write the preparation and uses of Magnesium hydroxide.
5. What are GIT agents? Write the principle and reaction for assay of sodium bicarbonate.
6. What are saline Cathartic? Expain its mechanism of action. Write the preparation and uses of magnesium sulphate.
7. Add a note on combinations of antacid therapy.
8. Define cathartics. Give the preparation, assay and uses of Magnesium sulphate.
9. Write a note on acidifiers.
10. Discuss the preparation, assay principle and medicinal uses of Baking soda.
11. What are saline cathartics? What is their mechanism of action?
12. Enlist different antacids.
13. Write the preparation of magnesium hydroxide mixture.
14. Write the method for preparation and uses of Milk of Magnesia.
15. What are antacids? Give examples.
16. Give examples of gastrointestinal agent and protective agents.
17. What is achlorhydria. Give its treatment.
18. Define saline Cathartic and give examples.
19. Write the molecular formula and uses of Milk of Magnesia.
20. Write the uses of aluminium hydroxide and magnesium hydroxide.
21. What are gastrointestingal protectives and adsorbents? Give example.

Chapter...8

TOPICAL AGENTS (PROTECTIVES, ASTRINGENTS AND ANTI-MICROBIALS)

♦ OVERVIEW ♦

- **Introduction : Protectives and adsorbents, Antimicrobial agents/Anti-infectives, Astringents, Miscellaneous compound.**
- **Astringents : Potash alum, Zinc sulphate.**
- **Antimicrobial agents : Ideal characteristics of antimicrobial agents, Classification, Mechanism, Potassium permanganate, Boric acid, Hydrogen perioxide, Chlorinated lime, Iodine and its preparations.**

8.1 INTRODUCTION

The topical means pertaining to a particular locality or place or spot. These chemical agents are applied to the skin and mucous membrane for localized effect within the skin or membrane. Locally acting topical agents have limited pharmacological activity. It generally have a physical basis of action.

Topical medication includes lotion creams, ointments. They are applied to the skin on various part of the body depending on reason for the medication. Lotion, creams and ointments usually produce a local effect.

Topical application of these drug may extend to such body cavities that are open to outside.

Sites of application for topical agents :

1. Skin
2. Ear
3. Eye
4. Nose
5. Vagina
6. Urethra
7. Rectum

Types of Formulation :

Powder, ointments, creams, lotion, spray, paste, transdermal patches etc.

Topical agents are classified based on their actions or uses :

1. Protectives and adsorbents.
2. Antimicrobial agents/Anti-infectives.
3. Astringents.
4. Miscellaneous compound.

Protectives and Adsorbents :

These are the substance which tend to form coating or a film on the site of application (like wound or burned skin) and protect the skin from harmful stimuli (like bacteria, moisture, dust)

Protectives exert its action by physically blocking the pores and firming a protective layers on the surface of skin or mucous membranes and prevent inflammation at site of application.

Adsorbents are similar to protectives. They exert their action due to their chemical properties. it acts by adsorbing moisture from the skin surface which decreases the mechanical friction and irritation.

The protective and adsorbent activities increases as the particle size decreases, small particles offer a large surface area and adhere better to surface of the skin.

Ideal properties of protectives :

1. It should be chemically and biologically inert.
2. It should be inert and insoluble in water.
3. It should appeared as fine particle forms.

   Examples : Talc, TiO_2, Zinc oxide, Calamine, Silicon polymer simethicone.

Astringent :

These are the agents which are applied locally and give protein precipitant action. Astringent exert their action by :

1. Contraction and wrinkling of the tissues.
2. Reduces the cell permeability.
3. Constrict the local blood vessels.
4. Inhibit the transcapillary movement of plasma protein.

Uses of Astringent :

1. It reduces pain (Anti-inflammatory agents).
2. It arrests hemorrhages.
3. Promotes healing of wound.
4. Reduces sweating (Anti-percipirants).

   Examples : Zno, Zinc sulphate, calamine, zinc chloride, potassium, aluminium sulphate, aluminium chloride, Aluminum.

Antimicrobial Agents :

These are the agents which inhibit or destroy the growth of micro-organism especially pathogenic micro-organism. These chemical and their preparation helps in reducing or preventing infection caused due to microbes.

Specific terminology describe exact mode or mechanism of action :

1. **Antiseptic :** These are substances that are able to kill or prevent the growth of micro-organism. This term is specific for preparation which are to be applied to living tissues. An ideal antiseptic should destroy bacteria, spores, fungi, viruses or any other infective agent without causing any harm to the tissues of the host.
2. **Disinfectants :** These are the substances that prevent infections by the destructions of pathogenic micro-organism. These are generally used with reference to the substances applied to inanimate objects. Disinfectants are widely used for home and hospitals sanitation.
3. **Germicides :** These are substances which kills micro-organism. More specific terminology like "bactericide" (against bacteria), "fungicide" (against fungi), "virucide" (against virus) etc. denotes exact actions.
4. **Bacteriostatic :** These are substances which primarily function by inhibiting the growth of bacteria. Thus, bacteriostatic drugs or agents do not kill but arrest the growth of bacteria.
5. **Sanitizers :** Disinfectants that are used to maintain general public health standards, are termed as sanitizers. Sanitation is mainly concerned with cleaning or washing away the organic matter (e.g. saliva, mucous etc.).

Ideal chracteristics of antimicrobial agents :

(i) It should possess antiseptic or germicide activity and not bacteriostatic activity. If the microrganisms do not get killed, they may resume growth and bring about infections.

(ii) It should have good therapeutic index indicating usefulness in the concentration employed.

(iii) It should have rapid onset and sustained activity. This can reduce the incedence of resistance.

(iv) It should not cause local cellular damage.

(v) It should not show systemic toxicity from topical application.

(vi) It should have broad spectrum of activity against bacteria, fungi, protozoa virus etc.

(vii) The topical antimicrobial agents should have favourable lipid-water distribution coefficient.

Mechanism of Action :

Inorganic compounds generally exhibit antimicrobial action by involving either of the following three mechanisms :

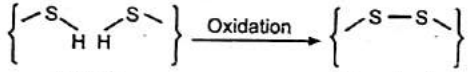
(i) Oxidation.

(ii) Halogenation.

(iii) Protein binding or precipitation.

(a) Oxidation mechanism : Anti-microbial agents acting by this mechanism belongs to class of peroxide peroxy acids, oxygen liberating like permanganate and certain oxo-halogen anions. These agents bring about oxidation of active functional group present in proteins or enzyme vital to the growth or survival of micro-organism. It causes a change in the conformation of the protein and thereby alter its function. For example, a free sulfhydryl group has been essential for functioning of a variety of proteins and enzymes. This free nature of sulfhydryl group gets destroyed by oxidation resulting into a formation of a disulfide bond.

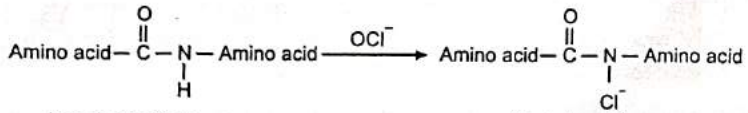
Antimicrobial agents acting by oxidation mechanism are; Hydrogen peroxide, Potassium permanganate.



Protein Altered protein

(b) Halogenation mechanism : Compounds which are able to liberate chlorine or hypochlorite or iodine act by this mechanism. These agents act on peptide linkage and alter its potential and property. The destruction of specific function of protein causes death of micro-organism.

Antimicrobial agents acting by halogenation mechanism are Chlorinated lime, sodium hypochlorite.



Protein structure Altered protein

(c) Protein Precipitation : Many metal ions exhibit protein binding or protein precipitation. The nature of interaction with protein takes place through polar group of protein which acts as ligand and metal ions as Lewis acid. The complex formed may be strong chelate giving rise to inactivation of protein. This action in general is non-specific. Protein precipitants are not able to distinguish the protein of microbe and that of host.

Antimicrobial agents acting by Protein Precipitation mechanism are Potash alum and Zinc sulphate.

Miscellaneous Agents :

Emollients : These are fatty substances which are topically applied to the skin, mucous membrane or abraded tissue. E.g. : waxes, vegetable oil.

Caustics : These are substances which are able to induce the destruction of tissue at the site of application. It is used to destroy warts, moles and hyper plastic tissue. E.g. : Potasium hydroxide, silver nitrate.

8.2 ASTRINGENT

POTASH ALUM (B.P.)

Chemical formula : $KAl(SO_4)_2 \cdot 12H_2O$.

Molecular weight : 474.4 g/mole

Category : Astringent

Synonyms : Alum, Aluminium potassium sulphate.

Alum is Aluminium potassium sulphate. It is double salt having an aluminium equivalent to not less than 99.5 per cent of $KAl(SO_4)_2 \cdot 12H_2O$.

Preparation :

It is prepared by adding a concentrated solution of potassium sulphate to a hot solution of an equvimolar proportion of aluminium sulphate. When the solution is concentrated and cooled, characteristic octahedral crystals of potash alum separates out.

$$K_2SO_4 + Al_2(SO_4)_3 + 24H_2O \longrightarrow KAl(SO_4)_2 \cdot 12H_2O$$

Properties :

1. It is colourless, transparent, or granular crystals having sweet astringent taste.
2. It is soluble in water and insoluble in alcohol.
3. When it is heated slowly on water bath temperature, it melts in its water of crystallisation.

   If it is heated at 200°C it looses its water of crystallisation and becomes anhydrous.

Identification test : It gives the reactions which are characteristics of aluminium, potassium and sulphate.

Test for purity : It is tested for As, Fe, heavy metal, zinc and ammonium salt.

Storage : Alum should be stored in well-closed container.

Uses :

1. It is used as an antiseptic and astringent.
2. It has protein precipitation property and hence it finds use in the preparation of toxoids.

ZINC SULPHATE (B.P., U.S.P.)

Chemical formula : $ZnSO_4 \cdot 7H_2O$

Molecular weight : 287.6 g/mole

Category : Astringent

Synonyms : White vitriol, zinc vitriol

It is having not less than 99.5 per cent and not more than 102.0 per cent of the hydrated Zinc sulphate, $ZnSO_4 \cdot 7H_2O$.

Preparation :

1. It is prepared by heating zinc sulphide in the presence of air under specified conditions. The heated mass is dissolved in hot water, filtered and the resulting solution is concentrated to get the crystals of zinc sulphate.

$$ZnS + 2O_2 \longrightarrow ZnSO_4$$

2. For pharmacopoeial requirement, zinc sulphate is prepared by digesting metallic zinc granules in dilute sulphuric acid. The solution is filtered to separate the undissolved metallic zinc and filtrate is treated with chlorine to oxidise any ferrous impurity in to ferric sulphate which is then precipitated by hydroxide and removed by filtration. The filterate is concentrated for crystallisation.

$$Zn + H_2SO_4 \longrightarrow ZnSO_4 + H_2 \uparrow$$

Properties :

1. It is colourless, transparent crystal, prism or needles, or as granular, crystalline powder.
2. It is odourless with an metallic and astringent taste.
3. It is soluble in water (0.6 parts) and glycerine (2.5 parts) but insoluble in alcohol.
4. An aqueous solution of zinc sulphate has been acidic to litmus, due to hydrolysis of the salt. The solution is acidic to a solution of phenol red and not acidic to a solution of methyl orange.

Identification test : Aqueous solution of zinc sulphate gives reactions of zinc and sulphate.

Test for purity : It is tested for acidity, aluminium, copper, magnesium, manganese, nickle, arsenic, iron, chloride, alkalis and alkaline earth.

Storage : It should be stored in well-closed container in a cool place.

Uses :

1. Externally, it is used in solution and powder as astringent.
2. When zinc sulphate is used internally it act as an emetic acting upon vomiting reflex.

8.3 ANTIMICROBIAL AGENTS

HYDROGEN PEROXIDE (B.P., U.S.P.)

Chemical formula : H_2O_2

Molecular weight : 34.016 g/mole

Category : Antimicrobial agent

Preparation :

Laboratory method :

1. Hydrogen peroxide is prepared by Merck's process. It is prepared by adding calculated amounts of sodium peroxide to ice cold dilute (20%) solution of H_2SO_4.

$$Na_2O_2 + H_2SO_4 \longrightarrow Na_2SO_4 + H_2O_2$$

2. By the action of sulphuric acid or phosphoric acid on hydrated barium peroxide $BaO_2 \cdot 8H_2O$.

$$3BaO_2 + 2H_3PO_4 \longrightarrow Ba_3(PO_4)_2 + 3H_2O_2$$

$$BaO_2 \cdot 8H_2O + H_2SO_4 \longrightarrow BaSO_4 \downarrow + H_2O_2 + 8H_2O$$

It must be noted that anhydrous barium peroxide does not react readily with sulphuric acid because a coating of insoluble barium sulphate is formed on its surface which stops further action of the acid. Therefore, hydrated barium peroxide, $BaO_2 \cdot 8H_2O$ must be used.

Industrial method :

H_2O_2 can be prepared by the electrolysis of 50% H_2SO_4 solution. In a cell, peroxy disulphuric acid is formed at the anode.

$$2H_2SO_4 \longrightarrow \underset{\text{Peroxy disulphuric acid}}{H_2S_2O_{8\,(aq.)}} + H_2$$

$$H_2S_2O_8 + 2H_2O \longrightarrow 2H_2SO_4 + H_2O_2$$

Peroxy disulphuric acid is formed, which on distillation under reduced pressure yields hydrogen peroxide.

Properties :

1. It is a odourless and colourless liquid having a slightly acidic taste.
2. The solution of hydrogen peroxide decomposes when it comes in contact of oxidisable matter or made alkaline.

$$H_2O_2 \longrightarrow 2H_2O + O_2$$

3. It is a strong oxidising agents and is miscible with water from which it can be extracted with solvent ether.

Identification tests :

(i) Hydrogen peroxide is made alkaline and heated, it is decomposed with effervescence, evolving oxygen.

(ii) To 1 drop of hydrogen peroxide, 20 ml of water, 1 drop of potassium chromate, 2 ml of solvent ether are added and shaken. The ether layer becomes blue.

Test for purity : It is tested for acidity, preservatives, loss on evaporation, barium and stability.

Assay :

The assay of hydrogen peroxide is based on redox titration (permanganometry method). Hydrogen peroxide is acidified with dilute sulphuric acid and titrated against 0.1N potassium permanganate. Both hydrogen peroxide and potassium permanganate are oxidising agents. These two oxidising agents reduces one another with evolution of gaseous oxygen. Hydrogen peroxide reduces potassium permanganate and causes its decolouration. At the end point addition of excess drops of $KMnO_4$ gives pink colour. $KMnO_4$ itself act as an indicator.

$$2KMnO_4 + 3H_2SO_4 + 5H_2O_2 \longrightarrow K_2SO_4 + 2MnSO_4 + 8H_2O + 5O_2$$

Permanganate in low pH is strong enough to quantitatively oxidize hydrogen peroxide to oxygen. This reaction is used for the determination of hydrogen peroxide concentration.

Factor : Each ml of 0.1N $KMnO_4$ is equivalent to 0.001701 of H_2O_2.

Storage : It is preserved in light resistant container with stopper made of glass or plastic resistant to hydrogen peroxide. It is kept in cool and dark place.

Uses :

1. It is used for cleaning cuts and wound because it acts as an antiseptic and germicide.
2. It is a strong oxidizing agent and yield nascent hydrogen, hence it can be used for bleaching.

CHLORINATED LIME (B.P.)

Chemical formula : $Ca(OCl)_2$

Molecular weight : 142.98 g/mol

Category : Disinfectant

Synonyms : Calcium hypochlorite, Calcium oxychloride, Bleaching powder

It is having not less than 30.0 per cent w/w of chlorine.

Preparation :

Chlorinated lime is prepared by the action of chlorine on calcium hydroxide. Slaked lime is spread on shelves in a suitable container. Then the chlorine gas is introduced at the top of the chamber and allowed to pass through the contents of the shelves. This process is carried out at 25°C, thereby minimising the formation of calcium chloride. After the absorbtion of chlorine, powdered lime is blown in to chamber to absorb the excess chlorine.

$$Ca(OH)_2 + Cl_2 \longrightarrow Ca(OCl)_2 + H_2O$$

This process is somewhat more complex, first basic chloride, $CaCl_2 \cdot Ca(OH)_2 \cdot H_2O$ and basic hypochlorite, $Ca(OCl)Cl$, $Ca(OH)_2$ are formed, then latter it gets changed by the further action of chlorine in to a substance which is having calcium hypochlorite.

Properties :

1. It is dull white powder having characteristic odour.
2. It is partially soluble in water and alcohol.
3. When bleaching powder is put in water, hypochlorite goes in to the solution and it shows bleaching and oxidising properties. Hypochlorites are able to oxidise many salt such as manganous to permanganate, chromous to chromates and lead to lead oxide in an alkaline medium.

Identification test : When sample is treated with HCl, chlorine gas is evolved. The resulting reactions of calcium and chloride.

Test for purity : It is tested for its stabilty by heating it at 100°C for 2 hours. It should not lose more than 3 per cent w/w of available chlorine.

Assay :

It can be assayed by redox titration (iodometry titration method).

An aqueous suspension of the substance is first treated with excess of potassium iodide and acetic acid. In presence of Acetic acid, chlorine is liberated from chlorinated lime. The free chlorine reacts with potassium iodide to liberate iodine quantitatively and the quantity of iodine is determined by titration with 0.1N sodium thiosulphate. Starch mucilage is used as an indicator.

$$Ca(OCl)_2 + 2CH_3COOH \longrightarrow (CH_3COO)_2Ca + Cl_2 + H_2O$$

$$2KI + Cl_2 \longrightarrow 2KCl + I_2$$

Potanium iodide Iodine

$$I_2 + 2Na_2S_2O_3 \longrightarrow Na_2S_4O_6 + 2NaI$$

Storage : It should be stored in well-closed container and kept in a cool place.

Uses :

1. Calcium hypochlorite used as disinfectant.
2. Calcium hypochlorite is also an ingredient in bleaching powder, used for bleaching cotton and linen. It is also used in bathroom cleaners, household disinfectaant sprays, moss and algae removers, and weed killers.

POTASSIUM PERMANGANATE (B.P., U.S.P.)

Chemical formula : $KMnO_4$

Molecular weight : 158 g/mol

Category : Antimicrobial Agents

It is having not less than 99 per cent of $KMnO_4$.

Preparation :

On large scale, it is prepared by mixing solution of KOH with powdered manganese oxide and potassium chlorate. The resulting mixture is boiled, evaporated to yield the residue which is heated in iron pan it acquires paste consistency.

$$KOH + 3MnO_2 + KClO_3 \longrightarrow \underset{\text{Potassium manganate}}{K_2MnO_4} + KCl + 3H_2O$$

Potassium manganate is so formed is extracted with boiling water and a current of chlorine, carbon dioxide, or ozonised air is passed in to liquid until it gets converted in to permanganate.

$$6K_2MnO_4 + 3Cl_2 \longrightarrow 6KMnO_4 + 6KCl$$

When carbon dioxide is pass through the solution in place of chlorine, only two-third of manganate gets converted in to potassium permanganate. One-third is converted in to MnO_2.

The MnO_2 formed is removed continously so as to prevent its breaking down to permanganate.

$$3K_2MnO_4 + 2CO_2 \longrightarrow 2KMnO_4 + MnO_2 + 2K_2CO_3$$

The solution of $KMnO_4$ is drawn off from any precipitate of MnO_2 which is then concentrated and crystallised. The crystals are centrifuged and dried.

Properties :

1. It occurs in the form of dark purple coloured monoclinic prism.
2. It is odourless and sweet and astringent in taste.
3. It is soluble in 15 parts of water and 3.5 parts of boiling water.
4. It decomposes at high temperature.

Identification test :

1. When $KMnO_4$ is heated to redness it decrepitates evolving oxygen and a black residue remains. The residue gives KOH when dissolved in water. The resulting solution gives reactions which are characteristics of potassium.
2. $KMnO_4$ solution is acidified with sulphuric acid and heated to 70°C, it gets decolourised by a solution of hydrogen peroxide.

Test for purity : It has to be tested for chloride and sulphate.

Storage : Solid $KMnO_4$ is a strong oxidizer and thus should be kept separated from oxidizable substances. Store in well-closed containers.

Uses :

1. It is used as an oxidant.
2. Potassium permanganate can act as an antiseptic.

BORIC ACID (I.P., B.P., U.S.P.)

Chemical formula : H_3BO_3

Molecular weight : 61.83 g/mol

Category : Antimicrobial Agents

Synonym : Boracic acid

It contains not less than 99.5% and not more than 100.5% of H_3BO_3, calculated with reference to the dried substances.

Preparation :

Boric acid can be prepared by decomposing boiling solution of native borates e.g. borax, colemanite, resonite etc.

1. From Borax : A hot concentrated solution of borax is treated with sulphuric acid or HCl. After decomposition the hot liquid is filtered and is kept aside so as to crystallize the boric acid.

Crystals of boric acid are collected by filtration and are washed so as to make it free from sulphate, then it is allowed to dry at ordinary temperature.

$$Na_2B_4O_7 + H_2SO_4 + 5H_2O \longrightarrow Na_2SO_4 + 4H_3BO_3$$

2. From Colemanite : Colemanite (calcium borate, $Ca_2B_6O_{11} \cdot 5H_2O$) is powdered and suspended in boiling water. SO_2 gas is then passed through the suspension, boric acid is formed. On cooling boric acid crystallizes out.

$$Ca_2B_6O_{11} \cdot 5H_2O + 2SO_2 + 4H_2O \longrightarrow 2CaSO_3 + 6H_3BO_3$$

Properties : It occurs in the form of pearly, lamellar, triclinic crystals, which are soluble in 25 parts of cold water and in 4 parts of glycerol.

Identification Tests :

1. On igniting, solution of boric acids in methanol containing few drops of sulphuric acid, a flame having a green border is produced. This is due to the formation of volatile methylortho-borate.
2. The dilute solution of boric acid in boiling distilled water (30 g in 90 ml) is when cooled a faintly acidic solution is produced. This solution is found to have pH between 3.8 and 4.8. Further free boric acid changes the colour of litmus to red but it does not produce any effect on methyl orange.

Test for purity :

It should be tested for clarity and colour of 3.5% w/v solution of boric acid in water, arsenic, heavy metals, sulphate, loss on drying and for solubility in ethanol. As per IP (1996), the 1 g of boric acid should dissolve almost completely in 10 ml of boiling ethanol (95%). This test is done to check the absence of metallic borates and insoluble impurities.

Uses :

1. It is a weak bacteriostatic agent, mainly used as local anti-infective.
2. It is used as an eyewash in the form of solutions in concentrations from 2.5 to 4.5% as it is non-irritating when applied to the intact skin and mucous antiseptic ointment for treating diaper rash.
3. It is also added to various dusting powders for its local anti-infective properties.
4. It is used to provide acidic media and buffered media for other drugs.
5. It is used in different topical medications to maintain an acidic pH in the medium.
6. It is used to prepare Boroglycerin Glycerite, which is used as a suppository base.

Warning : Boric acid can be dangerous if ingested, therefore its container must bear the warning

"NOT FOR INTERNAL USE"

Boric acid is not used internally nor applied on ruptured skin.

Storage : It should be stored in well-closed container.

IODINE (I.P., B.P., U.S.P.)

Symbol : I

Formula : I_2

Atomic mass : 126.9 g/mol

It is having not less than 99.5 per cent of I_2.

Occurence : Iodine is widely distributed in Nature, occurring as iodides or iodates but never as a free element. It is usual to find iodine in rocks, soils and underground brines. Sea water also contains traces of combined iodine, which gets absorbed by some specific plants and sea weeds like *Laminaria digitata, Fucus vesiculosus.* Iodide also occurs in the form of sodium iodate in crude Chile saltpetre.

Preparation of Iodine :

Iodine is mostly obtained from seaweeds, chile saltpetre, mother liquor and various brines. Iodine is prepared by extracting kelp (seaweed's ash) with water. The solution is concentrated, the sulphate and chloride of sodium and potassium get crystallized out leaving freely soluble sodium and potassium iodides in mother liquor. Then sulphuric acid is added to the mother liquor. After addition of sulphuric acid, small quantities of this sulphates and sulphides present are decomposed with precipitation of sulphur. The precipitate is allowed to settle down. The mother liquor is decanted and to this MnO_2 is added and iodine distils over.

Alternatively, the solution having freely soluble iodides as above is treated with required proportion of chlorine and the precipitated iodine is collected and purified by sublimation.

$$NaI + H_2SO_4 + MnO_2 \longrightarrow MnSO_4 + 2NaHSO_4 + I_2 + 2H_2O$$

Properties :

1. Iodine is a non-metallic, dark-grey/purple-black, lustrous, solid element.
2. It sublime easily on heating to give a purple vapour.
3. It dissolves in some solvents, such as carbon tetrachloride and it is slightly soluble in water.

Identification Tests :

When a clear solution of iodine in KI is treated with starch, produces blue colour in the cold conditions. On heating blue colour disappears and reappears on cooling.

Test for purity :

It is tested for chloride, bromide, cyanogen, and non-volatile matter.

Uses :

1. It is used as a counter irritant and disinfectant.
2. It is also used as local germicide.
3. For thyroid functioning iodine is supplied to the body in the form of sodium and potassium iodide

Storage : It should be stored in glass stoppered, amber coloured bottles and kept in cool place.

AQUEOUS IODINE SOLUTION (B.P.)

Synonym : Lugal's solution

It is having 5.0 per cent w/v of iodine and 10 per cent w/v of KI in purified water. It is the only official solution of iodine that contains no alcohol.

Composition :

Iodine	..... 50 g
KI	..... 100 g
Purified water sufficient to produce	..... 1000 ml

Preparation :

KI and iodine are dissolved in 100 ml of water with trituration or shaking. Than the volume is made up to 1000 ml with purified water.

Properties :

It is transparent, brown liquid having the smell of iodine.

Identification :

1. Aqueous iodine solution when treated with starch solution it gives blue colour.
2. The residue left after evaporation of the solution, on ignition gives the reaction of potassium and iodide.

Uses :

1. It is used as germicide and fungicide, it does not bring about irritation on cuts or wounds.
2. It acts as good source of iodine and it is taken internally.

Storage :

It is stored in well closed container of glass or plastic which are resistant to iodine. It cannot be stored in metal container because iodine attack metal.

WEAK IODINE SOLUTION (B.P.)

Synonym : Iodine tincture or tincture of iodine.

Composition :

It is having 2.0 per cent w/v of iodine and 2.5 per cent w/v of KI .

Iodine	..... 20 g
KI	..... 25 g
Alcohol (50%) sufficient to produce	..... 1000 ml

Preparation :

KI and iodine are dissolved in Alcohol (50%). Than the volume is made up to 1000 ml with Alcohol (50%).

Properties and Identification : Same as Aqueous iodine solution.

Alcohol content : The preparation is having 45 to 48% v/v of ethyl alcohol.

Uses : It is used as antiseptic and can be applied on cuts and wounds.

STRONG IODINE SOLUTION (U.S.P.)

It is having 10.0 per cent w/v of iodine and 6,0 percent w/v of KI.

Composition :

Iodine	..... 100 g
KI	..... 60 g
Purified water	..... 100 ml
Alcohol, 90.0% sufficient to produce	..... 1000 ml

Preparation :

KI and iodine are dissolved in water. Than the volume is made up to 1000 ml with Alcohol (90%).

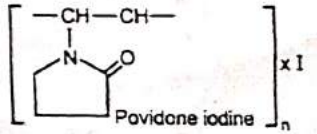
Properties and Identification : Same as Aqueous iodine solution.

Alcohol content : The preparation is having 74 to 79% v/v of ethyl alcohol.

Use : It is used as an antiseptic.

POVIDONE IODINE SOLUTION

Synonym : Iodopovidone



Molecular structure of povidone iodine

Description : Povidone iodine is a loose complex formed through the association of elemental iodine with polymer carrier povidone playing a role of carrier and facilitating solubilization. At room temperature, it is yellow-brown to red-brown amorphous powder. It is soluble in water and alcohol, its aqueous solution is acidic. The solution of povidone iodine is transparent and have reddish brown colour. It is also insoluble in ether, chloroform, acetone, ethane and carbon tetrachloride.

Uses : Povidone-iodine is a broad spectrum antiseptic for topical application in the treatment and prevention of wound infection. It may be used in first aid for minor cuts, grazes, burns, abrasions and blisters.

Storage : It should be stored in well-closed container.

Acid	Base
Sour taste	Bitter.
Blue to Red litmus	Red to colourless (Red to blue).

Theories:-

(1) Arrhenius:-

Acid

→ An acid is a subs
↓ dissolved in H_2O.
Increases the conc. of Hydrogen ion H^+ or an acid is a Compound that releases hydrogen ions (H^+) in water.

Base

Base → dissolved in water
↓
Increases conc of (OH^-) ions or Base is a Compound that releases OH^- in water.

→ A strong acid is a subs that Completely ionizes in aq. sol^n to give $H_3O^+_{(aq)}$ and an anion.

Ex:- $HClO_{4(aq)} + H_2O_{(l)} \longrightarrow H_3O^+_{(aq)} + ClO_4^-{}_{(aq)}$.

H_2SO_4, HI, HBr, HCl, HNO_3.

→ Strong base → Completely ionizes in aq. sol^n to give OH^- & an cation.

$$NaOH \xrightarrow{H_2O} Na^+_{(aq)} + OH^-_{(aq)}.$$

Weak acids & bases → doesn't ionized in solution.

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

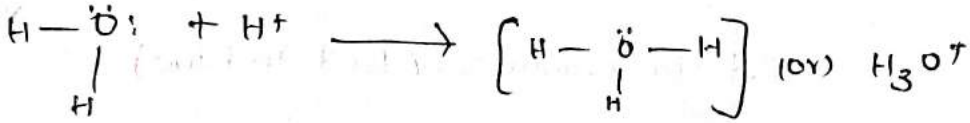
Limitations:-

(1) Free H^+ & OH^- ions do not exist in water.

→ H^+ & OH^- ions produced by acids & bases respectively do not exist in water in the free state.

→ They are associated with water molecules to form complex ions through hydrogen bonding.

H^+ ion forms a hydronium ion.



Hydronium ion.

(2) Limited to water only :- other solvents?

(3) Some bases do not contain OH^-

NH_3 & CaO

Acidic soln. – $AlCl_3$ in aq. soln.

(B) Bronsted - lowry Concept

Acid :- Any molecule or ion that can donate a proton (H^+). which has a tendency to lose a proton

Base :- Accept a proton (H^+) or a proton acceptor. tendency to gain a proton.

Ex:- $HCl \rightleftharpoons H^+ + Cl^-$

$CH_3COOH \rightleftharpoons H^+ + CH_3COO^-$

$HSO_4^- \rightleftharpoons H^+ + SO^{2-}$

$H_3O^+ \rightleftharpoons H^+ + H_2O$.

$NH_4^+ \rightleftharpoons H^+ + NH_3$

$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

ex:- bases

$OH^- + H^+ \rightleftharpoons H_2O$

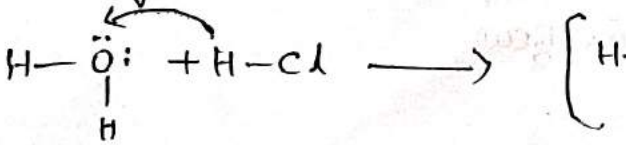
$H_2O + H^+ \rightleftharpoons H_3O$

$SO_4^{2-} + H^+ \rightleftharpoons HSO_4^-$

$NH_3 + H^+ \rightleftharpoons NH_4^+$

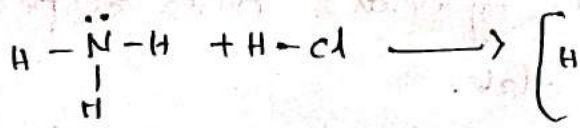
$HCO_3^- + H^+ \rightleftharpoons H_2CO_3$.

(1) HCl gas & H_2O



Hydronium ion

(2) HCl and Ammonia NH_3



Ammonium ion

Bronsted – Lowry Concept is Superior to Arrhenius Concept.

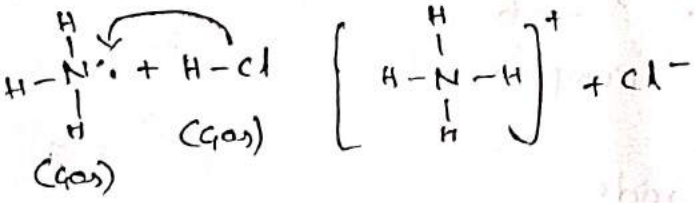
(1) **Much wider scope:-**

not restricted to release H^+ or OH^- ion in water.

(2) **Not limited to Aqueous solution:-**

Gaseous state.

Gaseous Ammonia (Bronsted base) + Hydrogen chloride gas. (bronsted acid)



↓

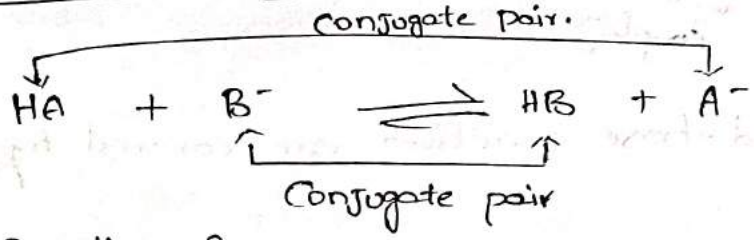
Ammonium chloride.

(3) Release of OH^- not neccesary to qualify as a base.

$$NH_3 + H^+ \rightleftharpoons NH_4^+$$

(Base). (Acid

Conjugate Acid Base pairs.

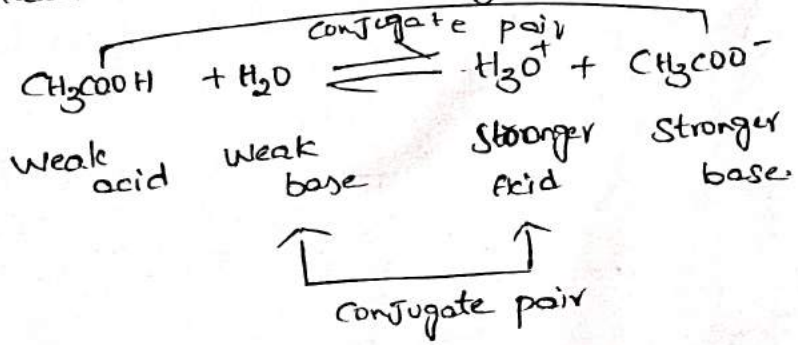


→ Reaction of NH_3 with H_2O.

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$$

Base Acid Acid Base

→ Reaction between CH_3COOH & H_2O



(c) Lewis Concept

Acid - Species that can form a covalent bond by accepting an electron pair from another species.

↓ electron pair acceptor.

Base - Species that can form a covalent bond by donating an electron pair to another species.

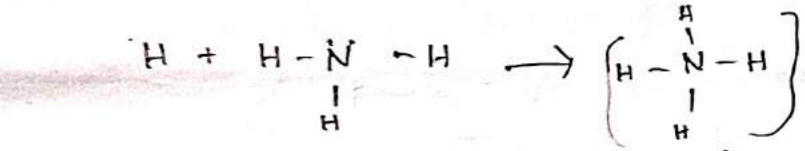
$$A + B \longrightarrow A-B$$

Lewis Acid — Lewis base — Complex.

All Cations → Lewis acids

All anions → Lewis bases.

Ex:- H^+ & NH_3.



complex

Adv:

All bronsted-lowry acid-base reactions are covered by the lewis model.

→ Many reactions which do not involved transfer of a proton.

$$BF_3 + NH_3 \longrightarrow BF_3 - NH_3.$$

→ Buffer equation
Buffer capacity in general
Buffers in pharmaceutical systems.
Preparations
Stability
Buffered isotonic solutions
Measurements of tonicity.
Calculations
Methods of adjusting isotonicity.

Functions of major physiological ions
Electrolytes used in replacement therapy.
physiological acid base balance.

Relative strengths of acids & bases.

$HCl + H_2O \longrightarrow Cl^- + H_3O^+$

$HA + H_2O \rightleftharpoons H_3O^+ + A^-$

$H_3O^+ = H^+$

$HA + H_2O \rightarrow H^+ + A^-$

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

Dissociation constant

In diluted soln HA is assumed as conc of liquid water remains essentially constant.

Strength of an acid → Conc of H^+ ions in its aq soln at a given temp.
↓
depends on value of K_a.

→ The value of K_a for particular acid → measure of its acid strength or acidity.

Relative Strength of Base:-

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

Apply law of mass action.

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

↓

measure of base strength.

Relationship b/w dissociation Constants and pH.

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

$$-\log K_a = -\log [H_3O^+] - \log \frac{[A^-]}{[HA]}.$$

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

$$-\log K_a = pK_a.$$

$$pK_a = pH - \log \frac{[A^-]}{[HA]}$$

$$pK_a = pH + \log \frac{[HA]}{[A^-]}.$$

Buffers Are the 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.

If a small amount of a strong acid or base is added to water or solution of sodium chloride.

↓

pH is altered Considerably.

Such systems have no buffer action.

Ex:- A Combination of Weak acid & its Conjugate base (its salt).

(or)

Weak base & its Conjugate acid

↓

acts as buffes.

Ex:- 1 mL of 0.1N HCl Soln + 100 mL of pure water.

↓

pH reduced to 7 to 3.

Ex:- Strong acid + 0.01M Solution Containing equal quantities of acetic acid & Sodium Acetate.

↓

pH changed only 0.09 pH units.

because base Ac^- ties up the hydrogen ions According to the reaction.

$$Ac^- + H_3O^+ \rightleftharpoons HAc + H_2O.$$

Ex:- Strong base Sodium hydroxide, is added to buffer mixture, Acetic acid neutralises the hydroxyl ions as follows:-

$$HAc + OH^- \rightleftharpoons H_2O + Ac^-$$

The Buffer equation:-

Common ion effect & the buffer equation for a weak acid and its salt.

→ pH of buffer solution and the change in pH upon the addition of an acid or base can be calculated by using the buffer equation.

This expression is developed by considering the effect of a salt on the ionization of weak acid when the salt and the acid have an ion in common.

Ex:- Sodium Acetate is added to acetic acid,

The dissociation constant for weak acid,

$$K_a = \frac{[H_3O^+]\,[Ac^-]}{[HAc]} = 1.75 \times 10^{-5}.$$

Acetate ion supplied by the salt increases the Acetate in numerator.

To reestablish the constant k_a at 1.75×10^{-5}, the hydrogen ion term in the numerator $[H_3O^+]$ is decreased with corresponding increase in [HAC].

Since k_a is Constant.

So equilibrium is shifted in the direction of the reactants Consequently, the ionization of acetic acid is repressed upon the addition of common ion Ac^-

$$HAc + H_2O \rightleftharpoons H_3O^+ + Ac^-$$

The pH of the final solution is obtained by rearranging the equilibrium expressions for acetic acid.

$$[H_3O^+] = k_a \frac{[HAc]}{[Ac^-]}.$$

If the Acid is Weak and ionizes only slightly the expression [HAC] may Considered to represent to total conc of acid [Acid].

Acetate concentration $[Ac^-]$ · (Salt]

$$[H_3O^+] = k_a \frac{[Acid]}{[salt]}.$$

$$-\log [H_3O^+] = -\log k_a - \log [Acid] + \log [salt].$$

Buffer equation / Henderson - Hasselbalch equation → Weak acid & its salt

$$p^H = pk_a + \log \frac{[salt]}{[Acid]}$$

The pka → The negative logarithm of ka → dissociation Constant

Cals within p^H 4-10.

Base ephedrine base ephedrine Hcl. Because of volatility & instability of bases.

By using.

$$[OH^-] = k_b \frac{[Base]}{[Salt]} \qquad [OH^-] = K_w / [H_3O^+]$$

$$p^H = p^{K_w} - p^{K_b} + \log \frac{[Base]}{(salt)}$$

Activity Coefficients

Treatment of buffers begins with replacement of conc. by activities in equilibrium of a weak acid.

Activity Coefficient is Multiplied by molar Concentration for the activity of each species.

$$K_a = \frac{\gamma_{H_2O} - C_{H_2O} \times \gamma_{AC^-} C_{AC^-}}{\gamma_{HAc} C_{HAc}}$$

γ = Activity Coeff

c = Molar Concentration.

$$p^H = pk_a + \log \frac{[salt]}{[Acid]} + \log \gamma_{AC^-}$$

factors influencing the pH of buffer solutions.

→ pH changes → Altering ionic strength
upon addition of water - alters activity coeff
↓ terms of
acts WA/WB in dilution value.

→ Temp → changes pH

→ pH of Acetate buffers → ↑T

" Boric a⁻ & Sodium borate ↓T

Natural buffers in Drugs

① Salicylic acid solution in soft glass bottle → ↑alkalinity of glass
↓
forms Sodium Salicylate
& salicylic a⁻
↓
So buffer is formed resist pH

② Ephedrine base & ephedrine react with HCl
↓
natural. buffer protection

pH Indicators WA/WB

Exhibit colour change → degree of dissociation varies with pH

$$HIn + H_2O \rightleftharpoons H_3O^+ + In^-$$

Acid base Acid Base

$$K_{In} = \frac{[H_3O^+]\,[In^-]}{[HIn]}$$

Indicator Constant

HIn → unionized → Acid colour

In^- → Ionized → base colour.

If Acid added → H^+ ↑ HIn acid colour forms.

If Base is added H_3O^+ reduced by reaction of acid with base → In^- ↑ base colour predominate

$$[H_3O^+] = K_{In}\frac{[HIn]}{[In^-]}$$

$$pH = pK_{In} + \log\frac{[Base]}{[Acid]}.$$

Buffers in pharmaceutical and Biological Systems.

Invivo Biological buffer Systems:-

(1) Blood :- maintained at pH 7.4.

↳ 1° buffers → in plasma → carbonic acid / bicarbonate, phosphoric acid/alkali sodium salts of HPO_4^{3-}, $H_2PO_4^-$
↳ plasma proteins → behave as acids in blood → combine with base → acts buffers

2° " → Erythrocytes.
↓
2 buffer Systems
Consist of Hemoglobin / Oxyhemoglobin and Acid/alkali potassium salts of phosphoric acid.

→ Buffer equation for Carbonic a- in plasma - Ionic strength of 0.16 is 0.1

$$pH = 6.1 + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

At pH 7.4 = Ratio of HCO_3^- to H_2CO_3 in Normal blood plasma

$$\log \frac{[HCO_3^-]}{[H_2CO_3]} = 7.4 - 6.1 = 1.3. \quad = 20/1$$

Buffer Capacity = 7.0 to 7.8.

Exp results = 0.025 M
0.00125 M.

Life threatening for pH of blood is to go below 6.9 or above 7.8

pH of diabetic coma blood → low as 6.8.

(2) Lacrimal fluid :- Tears :- greater degree of buffer capacity.
↳ It is explained in terms of dilution values rather than buffer capacity.

pH = 7.4 - range 7 to 8
discomfort → below 6.6 or above 9.0.

→ 4-10 → No harm to cornea.

(3) Urine :- 6.0 units.
varies from 4.5 - 7.8.

when pH of urine is below normal values → H^+ are excreted by kidneys.
above pH 7.4 → H^+ are retained by action of kidneys. In order to retain to pH Normal

Buffer Capacity:- (β) Buffer efficiency, B. Index, B. value.

The magnitude of the resistance of a buffer to p^H change

$$\beta = \frac{\Delta B}{\Delta p^H}$$

Δ = Finite change

Small increment in gram equivalent (geq)/L of strong base added to buffer solution to produce a p^H change of Δp^H.

→ Addition of 1 geq of strong B/A to 1 litre of buffer solution results ~~to~~ in change of 1 p^H unit.

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

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

$$\beta_{max} = 2.303c \frac{[H_3O^+]^2}{2[H_3O^+]^2} = \frac{2.303}{4} c$$

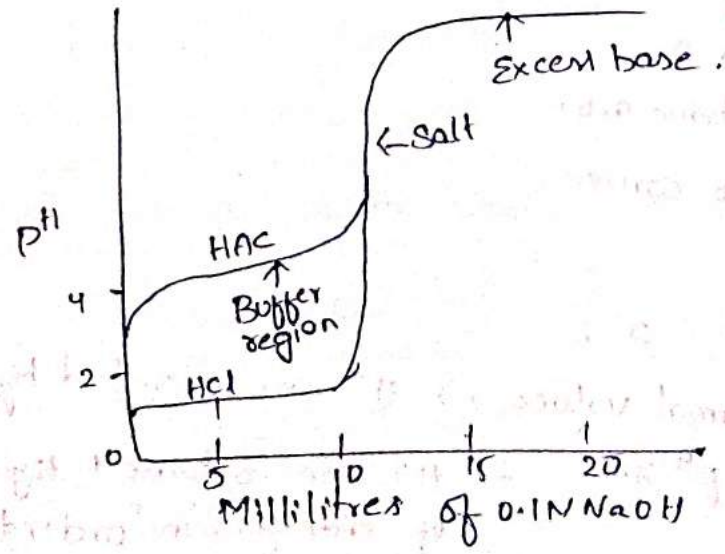
$$\beta_{max} = 0.576\, c.$$

c = Total buffer Concentration.

Neutralization curves and Buffer Capacity.

$$H_3O^+(Cl^-) + (Na^+)OH^- \Longrightarrow H_2O + H_2O + Na^+ + Cl^-$$

$$HAC + (Na^+)OH^- \Rightarrow H_2O + Na^+(AC^-)$$



Pharmaceutical Buffers

→ Buffer sol^n are used in pharmaceutical prep^n particularly in ophthalmic sol^n.

→ also find application in colorimetric determinat^n of p^H. & in research

→ phosphate buffered saline (PBS) 7.2.

↳ NaCl
Na_2PO_4 (Dibasic sodium phosphate)
may also
KCl
Monobasic potassium phosphate (KH_2PO_4)
Calcium chloride ($CaCl_2$)
Magnesium sulfate ($MgSO_4$)

→ boric acid & monohydrate sodium carbonate → various proportions - 5-9

→ salts of sodium phosphate → 6-8.

NaCl is added → Isotonic to blood fluids.

→ General procedures for preparing pharmaceutical Buffer solutions:-

(a) Select a weak acid having pK_a approx equal to p^H → buffer used ensure maxi buffer capacity

(b) from buffer equation, calculate ratio of salt & WA. ↓ desired p^H.

(c) Buffer capacity → Individual Conc of buffer salt & acid. within p^H 4-10.

conc of 0.05 - 0.5 M → } Sufficient.
B.C of 0.01 - 0.1 → }

(d) other factors → Availability of chemicals,
sterility of final sol^n
stability of drug
buffer on aging
cost of materials
freedom from toxicity.

(e) determine p^H & Buf. capacity of completed buffered sol^n using p^H meter

Influence of B.C & pH on Tissue Irritation.

So buffer capacity is optimum → to minimise

Eye / parental / oral → Aspirin absorb more rapid in system buffer at low capacity than in no buffer containing

6.5-8 ↓ not buffered / buffer at low capacity ↓

Boric - a⁻ - 5 pH - Irritation

so that readily blood bring them within the physiological pH range.

Small quantities & at slow rate.

Stability Vs Optimum Therapeutic Response

penetration

→ former is lipid soluble - body memb

undissociated form of WA / WB → high therapeutic activity than dissociated salt form. (Ions) → not lipid soluble membrane penetration → greater difficulty

→ ↑ Therapeutic → undissociated basic opthalamics Alkaloids ↑

pH above 4 → Ionic forms → penetration slow.

→ So drug are buffered at low buffer capacity → pH Compromise b/w stability & pH Max. therapeutic action

→ buffer → prevent Changes in pH due to alkalinity of glass or acidity of CO_2.

→ when soln is instilled in eye → tears participitate in neutralizatn of soln.

Conversion of drug occurs from physiological inactive form ↓ to undissociated base

base absorb at pH

more salt is Converted into base → preserve pK_b. ← Penetrate lipid membrane ← undissociated base

pH & Solubility

low pH = Base in form of Ionic form. → Soluble in aqueous media.

pH ↑ = more undissociated base is form.

↑ Base exceeds the limited water solubility → free base ppt. from soln

Stabilizatn against ppt is maintained

So soln is buffered at sufficiently ↓ pH

Base equilibrium with its salt

Buffered Isotonic Solutions

Made Invivo buffer systems, such as blood & (acrimal) fluid.

In addition to carrying out pH adjustment, pharmaceutical solutions that are meant for application to delicate membranes of the body should also be adjusted to approximately the same osmotic pressure as that of the body fluids.

Isotonic solutions cause no swelling / contraction of tissues with which they come in contact and produce no discomfort when instilled in the eye, nasal tract, blood or other body tissues

Ex:- Isotonic Sodium Chloride

Illustrated

Mixing a small quantity of blood with aqueous sodium chloride solutions of varying tonicity.

→ If a small quantity of blood, defibrinated to prevent clotting. is mixed with a solution containing 0.9g of NaCl / 100mL.

↓

The cells retain their normal size.

⇒ The solution has essentially the same salt conc & hence the same osmatic pressure as RBC contents ⇒ Isotonic with blood.

⇒ If RBCs are suspended in a 2.0% NaCl solution, the water within the cells passes through the cell membrane in an attempt to dilute the surrounding salt ~~salt~~ solution until the salt conc on both sides of the erythrocyte membrane are identical.

↓

The outward passage of water causes the cells to shrink and become wrinkled or crenated.

↓

The salt solution is said to be hypertonic with respect to blood cell contents.

=) If blood is mixed with 0.2% NaCl solution or with distilled water, water enters the blood cells

↓

Cause swell & finally burst.
with liberation of hemoglobin. → hemolysis.

The weak salt solution or water → hypotonic with respect to blood.

RBC → Membranes → not impermeable to all drugs

↓

It is not a perfect semipermeable membrane.

As it will permit the passage not only water molecules but also solutes such as urea, Ammonium chloride, alcohol & boric acid.

→ 2.0% solution of boric acid has same osmotic pressure as blood cell contents.

→ Molecules of boric acid pass freely through the erythrocyte membrane → regardless of conc.

→ Hypotonic with respect to blood → boric a⁻ soln brings rapid hemolysis.

So solution containing drug Calculation to be isosmatic with blood is isotonic only.

→ Mucous lining of eye acts as true semipermeable membrane to boric acid in solution.

2.0% boric acid solution → Isotonic ophthalmic prepn.

Measurement of Tonicity :-

(1) Van't Hoff i factor → determined

Compared from Cryoscopic data
Osmatic coefficient
Activity coefficient.

i value → measured by freezing point depression / theretical equation

Restrict drugs soln to Isotonic → may hemolyse human RBC.

(2) Measure tonicity is based that determine colligative properities

→ Slight temp diff arising from diff in vapor pressure of thermally insulated samples contained in constant humidity chambers.

freezing point of blood & tears determiniation → −0.56°c & −0.80°c

−0.52°c for both blood & lacrimal fluid

equal to 0.90 %. Nacl solution → Isotonic.

Calculating Tonicity using LIso values:-

$$\text{Liso value} = \frac{\Delta T_f}{c}$$

0.90% (0.154M) of Nacl soln.

F.P = 0.52°c

$$\text{Liso} = \frac{0.52^\circ C}{0.154} = 3.4.$$

$$\text{Molarity} = \frac{\text{moles}}{\text{Liter}} = \frac{\text{wt in g}}{\text{m.gwt in g/mole}} \div \frac{\text{vol. in mL}}{1000\ mL/L}$$

$$= c = \frac{w}{MW} \times \frac{1000}{v}$$

$$\Delta T_f = \text{Liso} \times \frac{w \times 1000}{MW \times V}$$

$$\Delta T_f = 3.4 \times \frac{1 \times 1000}{96 \times 100} = 3.4 \times 0.104$$

$$= 3.5^\circ C.$$

Type	Liso	Ex.
Non electrolytes	1.9	Sucrose, glycerin, urea, camphor.
weak electrolytes	2.0	Boric acid, cocaine, phenobarbital
Divalent electrolytes	2.0	Magnesium sulfate, zinc sulfate.
univalent electrolytes	3.4	Nacl, cocaine HCl, Sodium phenobarbital
unidivalent "	4.3	Sodium sulfate, atropine sulfate.
divalent "	4.8	zinc chloride, Calcium bromide
unitrivalent "	5.2	Sodium citrate, sodium phosphate.
Trivalent "	6.0	Aluminium Chloride, ferric iodide.
Tetraborate	7.6	sodium borate, potassium borate.

Methods of Adjusting Tonicity & pH.

Used to Calculate quantity of NaCl, dextrose & other subs that may be added to Soln of drugs to retain isotonic.

→ Class I methods

Cryoscopic method

freezing point depression of drug soln → estimated theoretical consideration.

mol. wt & Liso value of ionic class.

$$\frac{1\%}{x} = 0$$

Sodium Chloride Equivalent method

Drug is amt of NaCl that is equivalent to 1 gm

1g of drug in 1000 ml of soln.

$$c = \frac{1g}{m.w}$$

$$\Delta T_f = Liso \frac{1g}{MW}$$

$$\Delta T_f = 3.4 \frac{\epsilon}{58.45}$$

$$\frac{Liso}{MW} = 3.4 \frac{\epsilon}{58.45}$$

$$\epsilon \cong 17 \frac{Liso}{MW}$$

Multiplying Quantity of each drug by its NaCl equivalent & subtracting this value from the conc of NaCl that is isotonic with body fluids 0.9 g/100 ml.

Class II methods:-

White-Vincent methods → Addition of water to drugs to make isotonic followed by addition of an Isotonic / Isotonic-buffered diluting vehicle

$$V = w \times \epsilon \times 111.1$$

V: vol. in ml of Isotonic soln; w: wt in gm of drug; ε: Sodium chloride equivalent

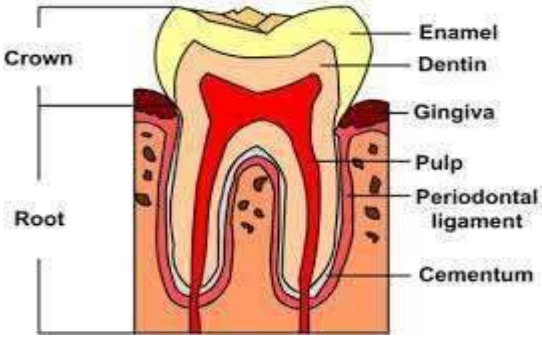
Sprowl's Methods:- → weight of drug 0.3 g & quantity of fluid ounce Sp. wt to Sprowl - Isotonic, of 1% solution.

Dental Products

Introduction

- Dental hygiene is very important.
- A large no.of inorganic chemicals and their preparations find application in the practice of dental and oral disorders
  - **Dental products include-**
  - ✓ **Anti-caries agents**
  - ✓ **Cleaning agents/ Dentifrices**
  - ✓ **Polishing Agents**
  - ✓ **Desensitizing agents**
  - ✓ **Oral antiseptics and astringents**
  - ✓ **Mouthwashes**
  - ✓ **Cements and Fillers**

Tooth



- Tooth consists of 3 layers

1. Dentine- It surrounds the pulp cavity and extends throughout the entire portion of tooth. 75% mineral
2. Cementum- It is the layer covering the portion of the lying buried in the gum
3. Enamel- white, hard material covering the portion of tooth projecting above the gum.98% mineral-hardest part of the body

- Vit A , C and D are necessary for proper tooth formation.
- Vit A deficiency causes hypoplastic enamel (imperfectlycalcified)
- Vit C deficiency affects calcification of dentine
- Vit D is important for absorption of Calcium from GIT and proper deposition of calcium and phosphorus in tooth

Anti caries Agents

- Dental caries or tooth decay is caused by acid produced by the action of microorganism or carbohydrates- involving decalcification of tooth accompanied by foul odour.
- Exact cause and mechanism not known
- Proposed mechanism-

1. Dental caries starts on the surface of the teeth
2. Acids produced by bacterial metabolism of fermenting carbohydrates act on teeth and produce lesions where bacteria get localised.
3. Demineralisation of enamel takes place (which initially appears as a white , chalky area and eventually becomes brown or yellow)

Dental caries if not treated , then micro-organisms may invade the pulp causing inflammation and infection

Prevention of dental caries

- Maintaining dental hygeine with the help of dentrifices- Dentrifices enhance removal of dental plaque and stains
- Flossing and brushing regularly
- Administration of Fluoride

(Anti caries agents- Sodium Fluoride, Stannous Fluoride, Sodium Monofluorophosphate U.S.P)

Role of Fluoride

- Role of fluoride in preventing dental caries is well accepted.
- Administration of traces of fluoride having salts or their use topically to the teeth have reported encouraging results
- Fluoride ion is a trace element which occurs in the body.

- Water fluoridation as well as topical fluoride applications (e.g. fluoridated toothpaste or varnish) appears to prevent caries, primarily on permanent dentition.
- Topical fluoride sustains the fluoride levels in the oral cavity and helps to prevent caries, with reduced systemic availability.
- Fluoride can affect both the inorganic tooth structure & the bacterial metabolism in plaque, several

- The main in organic constituent of tooth and bone is hydroxy apatite (HAP).
- Hydroxy apatite on addition of fluorine results in the formation of flour apatite (FAP) or fluoridated hydroxy apatite because not all the hydroxyl groups are replaced by fluorides.
- A pure fluorapatite crystal would contain 38,000 ppm F but enamel form a fluoridated area contain only 500 to 2000 ppm.
- This leads to speculation on several possible mechanims of action of systemically ingested fluoride improved crystalinity, the void theory, FAP V/s HAP solubility in acid & improved tooth morphology

Proposed Mechanism of action of fluorides

- **Reduced enamel solubility**-decreased solubility of fluoridated enamel is that fluorapatite (with a solubility product constant of 10-60) is less soluble than hydroxyapatite
- **Improved crystallinity**- Fluoride increasesthe crystal size and produces less strain in crystal lattice.
- **Promotion of reminerlization**- Dissolved enamel Minerals of tooth enamel are continuously inexchange with the minerals of saliva and thusthe balance is maintained. This Equilibrium can get disturbed with the organic acidproduced by the metabolism of fermentable carbohydrates by the microorganism. Thisleads to drop in PH. of the plaque on the enamel surface and in the sub surface.Minerals, particularly calcium and phosphate leave the dissolved enamel in their ionic form an entrace the plaque fluid. This process iscalled deminerilization this get reverrse with the factor like fluoride and is terms remineriliz ation.

- **Lower free surface energy**- void in the crystals decreases the stability and increases chemical reactivity. If fluoride fills these void in the hydroxy apetite crystals it will attain stable from with formation of more and stronger hydrogen bonds. Greater stability will leads to lower solubility and hence greater resistance to dissolution in acids.
- **Desorption of protein and bacteria**
- **Reduced cariogenic flora** - . fluoride is a potent suppressor of the bacterial growth because it oxidizes the thiol group present in bacteria thus inhibiting bacterial matabolism. The concentration of fluoride above 2 ppm in solution progressively decrease the transport of uptake of glucose into Cells of streptococci and also reduces ATP synthesis.(Anti bacterial action)

  The primary assumption in this theory is that dental caries results from a specific pathogen, S. mutans. Thus the elimination or reduction of this pathogen with provide a lasting cariostatic effect.
- **Inhibition of bacterial enzymes systems**-Fluoride has enolase inhibition effect and it also inhibits glucose transport, enolase is a metallo enzyme that requires adjavalent cation for tis activity., fluoride due to its increased reactivity forms a complex with this cation. Thus inhibiting the enzyme. It also inhibits non-metallo enzyme like phosphatage thus leading to reduce acid production

Monographs of Sodium Fluoride

Title: Sodium Fluoride
Molecular formula: NaF
Mol. Wt.: 42.0
Standard: Sodium Fluoride contains not less than 98.5 per cent and not more than 100.5 per cent of NaF, calculated on the dried basis.
Category. Preventive for dental caries.
Description. A white powder or colourless crystals.
Identification

A. Dissolve 2.5 g in sufficient carbon dioxide free water without heating to produce 100 ml (solution A). To 2 ml of solution A add 0.5 ml of calcium chloride solution; a gelatinous white precipitate is produced which dissolves on adding 5 ml of ferric chloride solution.
B. Add about 4 mg to a mixture of 0.1 ml of alizarin red S solution and 0.1 ml of zirconyl nitrate solution and mix; the colour changes to yellow.
C. Gives reaction A of sodium salts

Test: Appearance of solution (clear and colourless) , Acidity or alkalinity, Chlorides (NMT 250 ppm), Fluorosilicate (Absent) , Sulphates (NMT 10 ppm) , Loss on drying (NMT 0.5 %)

Preparation:

By passing hydrogen fluoride into solution of sodium carbonate.

$$\underset{\text{Sodium carbonate}}{Na_2CO_3} + \underset{\text{Hydrogen Fluoride}}{2HF} \longrightarrow \underset{\text{Sodium fluoride}}{2NaF} + CO_2 + H_2O$$

Assay: Non aqueous titration with perchloric acid using crystal violet solution as indicator, until a green colour is produced.

Storage. Store protected from moisture.

USES

- 2 % aqueous solution is used topically for treatment of caries.
- Component of various anti-caries toothpastes

Dentifrices

- Dentifrice is a material which is used for cleaning of teeth and adjacent gums.
- The cleaning is dependent on abrasive property and the rubbing force used.
- They may be applied as pastes or powders with the help of fingers or toothbrush.
- Flavors and colors are usually added to dentifrice formulations to improve their acceptance

- Dentifrices are agents used along with a toothbrush to clean and polish natural teeth. They are supplied in paste, powder, gel or liquid form. The most essential dentifrice recommended by dentists is toothpaste which is used in conjunction with a toothbrush to help remove food debris and dental plaque.
- A good cleaning agent must remove stains from teeth and to achieve this suitable abrasiveness in essential.
- The main drawback is that it will not be able to clean surfaces inside cavities and cervices between teeth.

Types of Dentifrices

- **Toothpaste**-Toothpaste is a dentifrice used in conjunction with a toothbrush to help maintain oral hygiene. The essential components are an abrasive, binder, surfactant and humectant. Other ingredients are also used. The main purpose of the paste is to help remove debris and plaque with some marketed to serve accessory functions such as breath freshening and teeth whitening.
- **Toothpowder**-Tooth powder is an alternative to toothpaste. It comes in both fluoride and non-fluoride versions.

- **Mouthwash**-Mouthwashes come in a variety of compositions, many claiming to kill bacteria that make up plaque or to freshen breath.In their basic form, they are usually recommended for use after brushing but some manufacturers recommend pre-brush rinsing. Dental research has recommended that mouthwash should be used as an aid to brushing rather than a replacement, because the sticky resistant nature of plaque prevents it from being actively removed by chemicals alone, and physical detachment of the sticky proteins is required.
- Tooth soap-Tooth soap cleans gums as well as fissures and pits in teeth using soap. The soap helps remove oils, residue and other contaminants. It is available in hard, liquid and gel.

The functions of toothpaste in conjunction with tooth brushing are:

- ✓Minimizing plaque build up
- ✓Anti-caries action
- ✓Removal of stains
- ✓Mouth freshening/odorising

Examples of dentifrices

- Calcium carbonate
- Dibasic calcium phosphate
- Calcium phosphate
- Sodium metaphosphate
- Pumice

Monograph
Calcium carbonate

Synonym :Precipitated Chalk

Molecular Formula: $CaCO_3$

Molecular weight: 100.1

Standard: Calcium Carbonate contains not less than 98.0 per cent andnot more than 100.5 per cent of CaC03, calculated on the dried basis

Dose. 1 to 5 g.

Description. A fine, white, microcrystalline powder.

Tests:

Substances insoluble in acetic acid: NMT 10mg

Arsenic: NMT 4 ppm

Heavy metals: NMT 20 ppm (Method A)

Barium

Iron: NMT 200 ppm

Chloride: NMT 250 ppm

Sulphates: NMT 0.3 %

Loss on drying: NMT 2 %

Preparation:

Prepared by passing Carbon dioxide gas through lime water.

$$Ca(OH)_2 + CO_2$$

Calcium Hydroxide

$$CaCO_3 + H_2O$$

Calcium Carbonate

Assay: Complexometric titration
Titrant: 0.05 M Disodium edetate
Indicator: Calcon mixture
End point: Pink to full blue colour

- **Calcium phosphate**: Also known as tribasic calcium phosphate/tricalcium phosphate

Synonym: Calcium Hydroxide Phosphate; Calcium Phosphate

Tribasic Calcium Phosphate consists mainly of tricalcium diorthophosphate together with calcium phosphates of more acidic or basic character

Tribasic Calcium Phosphate contains not less than 90.0 per cent and not more than 100.5 per cent of calcium phosphates, calculated as Ca3(P04)2

Category. Pharmaceutical aid (excipient).

Description. Awhite, amorphous powder; odourless or almost odourless.

- **Dibasic Calcium Phosphate**:

Synonym: Calcium Hydrogen Phosphate

CaHP04 Mol. Wt. 136.1 (anhydrous)

CaHP04,2H20 Mol. Wt. 172.1 (dihydrate)

Dibasic Calcium Phosphate is anhydrous or contains two molecules of water of hydration.

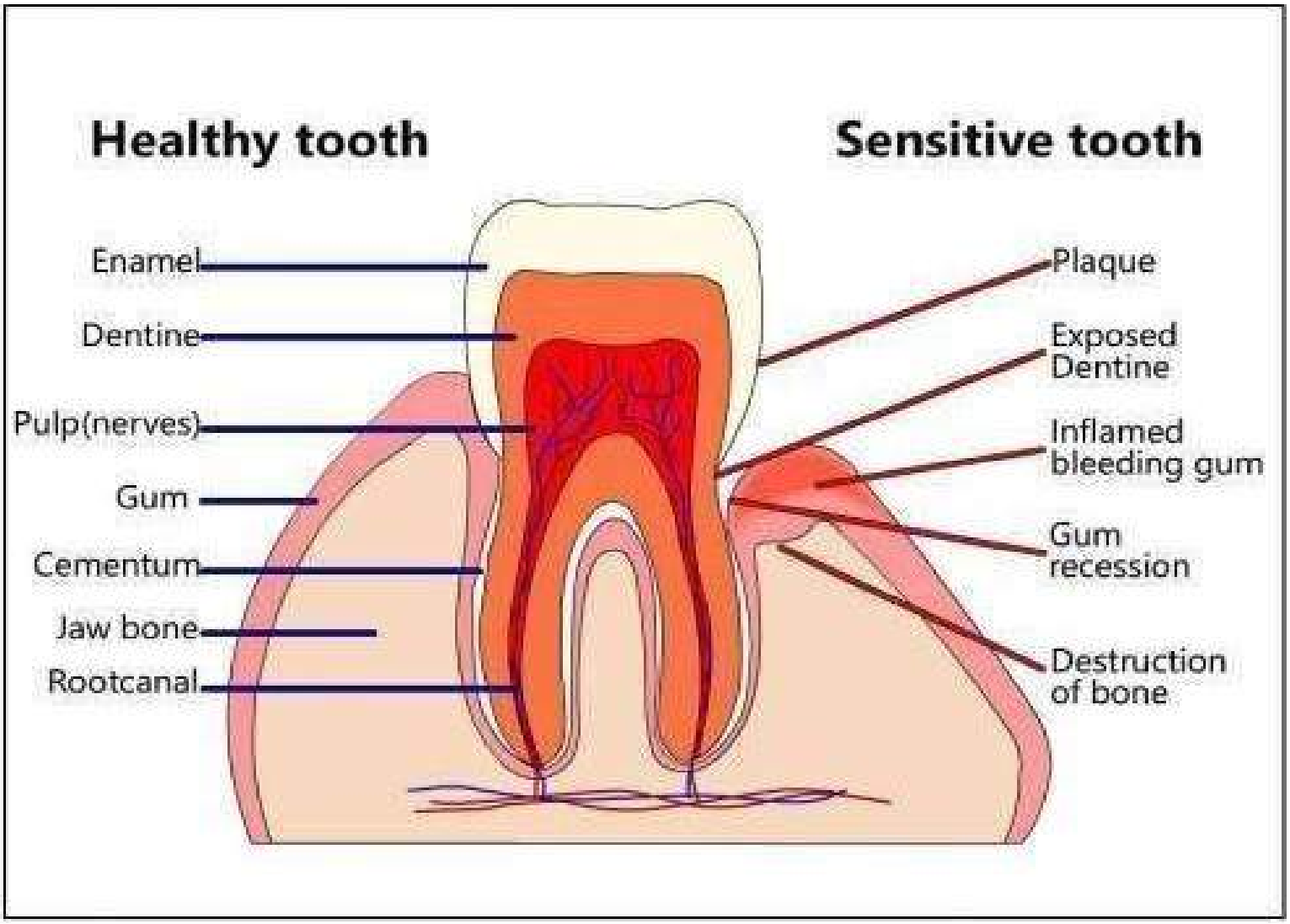
Dibasic Calcium Phosphate contains not less than 98.0 per cent and not more than 105.0 per cent ofCaHP04(for anhydrous material) or ofCaHP$0_{4,}2H_20$ (for the dihydrate).

AGENTS	MATERIAL USED	FUNCTIONS
1.Polishing/Abrasives agents	Calcium carbonate Dicalcium phosphate dihydrate Alumina Silica	These agents have a mild abrasive action, which aids in eliminating plaque and removing stains from tooth surface.
2.Binding/Thickening agents	Water soluble agents a. Alginates b. Sodium carboxymethyl celluose Water insoluble a. Magnesium aluminium silicate b.Colloidal silica c.Sodium magnesium silicate	Agents which controls stability and consistency of a tooth paste.
3. Detergent/Surfactans	Sodium lauryl surface	Produce the foam which aids in the removal of food debris and also despersion of product within mouth.
4. Humectants	Sorbitol Glycerin Polyethylene glycol	Aids in reducing loss of moisture from toothpaste.

5. Flavouring agents	Peppermint oil Spearmint oil Oil of wintergreen	They render the product pleasant to use and leaves a fresh taste in mouth after use.
6. Sweeteners and Coloring agents	Saccharin	Sweetener
7. Antibacterial agents	Ticlosan Delmopinol Metallic ions Zinc citrase trihydrate	
8. Anticalculus agents	Pyrophosphate Zinc citrate Zinc chloride Gantrez acid(copolymer of methyl vinyl ether and maleic anhydride)	Anticalculus agents are mostly designed to inhibit the mineralization of plaque. They are also known as crystal growth inhibitors.
9. Anticaries agents	Sodium monoflurophosphate Sodium flouride Stannous flouride	
10. Diesensitizing agents	Sodium flouride Potassium nitrate Strontium chloride	

Desensitizing agents

- DENTIN HYPERSENSITIVITY is characterized by short sharp pain arising from exposed dentin in response to stimuli—typically thermal, evaporative, tactile, osmotic or chemical—that cannot be ascribed to any other dental defect or disease.
- Dentine hypersensitivity is sensation felt when the nerves inside the dentin are exposed to the environment
- The sensation can range from irritation all the way to intense, shooting pain.
- This sensitivity can be caused by several factors, including wear , decaying teeth or exposed tooth roots.


Healthy tooth
Sensitive tooth
Enamel
Dentine
Pulp(nerves)
Gum
Cementum
Jaw bone
Rootcanal
Plaque
Exposed Dentine
Inflamed bleeding gum
Gum recession
Destruction of bone

Causes of sensitivity

- Gastroesophageal reflux disease (GERD)
- Conditions in which person frequently vomits. I.e. Gatrioparesis or bulimia
- Gum recession
- Tooth decay
- Injured tooth
- Broken tooth
- Chipped tooth
- Worn down fillings /crowns

  Sometimes, it is temporary following dental treatments such as filling, crowning and bleaching

Zinc oxide eugenol cement

- Zinc oxide eugenol (ZOE) is a material created by the combination of zinc oxide and eugenol contained in oil of cloves.
- An acid-base reaction takes place with the formation of zinc eugenolate chelate. The reaction is catalysed by water and is accelerated by the presence of metal salts.
- It has anaesthetic, anti-bacterial properties.

Composition of ZOE

Component	Approximate w/w %	Function
Solids		
Zinc Oxide	69 %	Principal ingredient
White Rosin	29.3%	Reduce brittleness of set cement and maintain homogeneity
Zinc acetate	1.0%	Accelerator, improve strength
Zinc stearate	0.7%	Accelerator, plasticizer
Liquids		
Eugenol	85%	Reacts with ZnO, act as anaesthetic
Olive Oil	15%	Plasticizer

Classification of Zinc oxide Eugenol (ZOE)

- Type –I ZOE: for temporary cementation
- Type –II ZOE: for permanent cementation
- Type III ZOE: for temporary filling and thermal base
- Type IV ZOE: cavity liner

Uses:

1. **ZOE can be used as a dental filling material or dental cement in dentistry.**
   It is often used in dentistry when the decay is very deep or very close to the nerve or pulp chamber. Because the tissue inside the tooth, i.e. the pulp, reacts badly to the drilling stimulus (heat and vibration), it frequently becomes severely inflamed and precipitates a condition called **acute or chronic pulpitis**. (This condition usually leads to severe chronic tooth sensitivity or actual toothache and can then only be treated with the removal of the nerve (pulp) called root canal therapy.)
2. The placement of a ZOE "temporary" for a few to several days prior to the placement of the final filling can help to sedate the pulp.
3. ZOE is used in mucostatic in a technique of taking impressions of gum and teeth
4. It is used as **pulp capping agent**.
5. Commonly used as cavity liner under dental amalgams or as temporary filling material.

Important Questions

- Discuss the role of fluoride in Dental caries
- Define Dentifrices, Anti-caries agents, Desensitizing agents with examples.
- Monograph- Calcium carbonate, Sodium Fluoride, Zinc Eugenol cement
- What are dental products? Discuss their composition and role.
- What are anti caries agents? Discuss in detail.

Title	SODIUM	POTASSIUM	CALCIUM	MAGNESIUM
Atomic formula	Na^{+1}	K^{+1}	Ca^{+2}	Mg^{+2}
Atomic Weight	22.9	39.10	40.08	24.31
Daily Requirements	3 to 5 gms	1.5 to 4.5g	400mg	350 mg
Description	White crystalline Odourless	pale yellow, silvery white	Pale yellow, powder Odourless	Silvery white Odourless Crystal
Source	* Table salt * Salted Nuts * Cheese * Bread & rolls * Soups	* Milk * Cerals * Vegetables * Meat	* Milk * Spinach * Greenleafy Vegetables * fruits * Nuts * Mulberry etc..	* Cerals * Vegetables * Milk * Meat * egg
Solubility	In water only	In water only	In water only	Water only

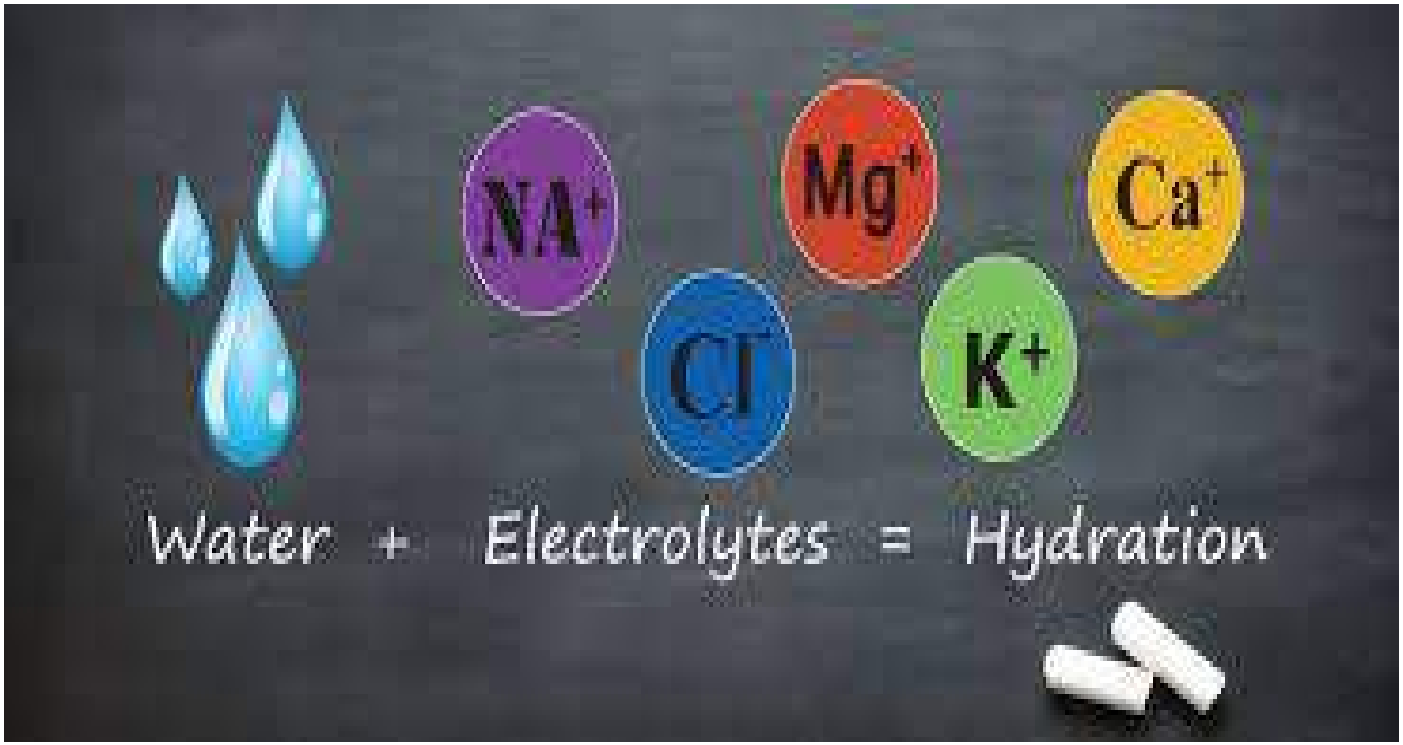
Title	CHLORIDE	PHOSPHATE	BICARBONATES	SULPHATES
Atomic formula	Cl^-	$H_2PO_4^-$	HCO_3^-	SO_4^-
Atomic Weight	35.45	30.97	12.01	32.06
Daily Requirement	5 to 10g	400 mg	1.2 to 1.4 mg	1.2 to 1.5g
pH	-	7.4	Below 7.25	7.20
Category	Electrolyte	Electrolyte	Electrolyte	Electrolyte
Description	Yellow colour liquid form	Odourless blue Colour	Odourless red to yellow	Odourless, white Solid-form
Source	* Table salt * White bread * Banana * Yogurt * Orange Juice	* Milk * Egg * Nuts * Meat	O_2 (oxygen) CO_2 (Carbondioxide) Atmosphere gases	* Green leafy * Vegetables * Egg * Meat
-Hypo	* Dizziness * Weakness	Renal table disease consuming large	Buffers Cannot Maintai-n	It doesn't Maintain acid-base equillibrium
		-Amount of acids	* Acidity ↑ses our body	Buffers Cannot be form

		U	body	form
Hyper	* Renal failure * Vomiting	* Osteo calcia * Renal Rickets	They can be caused many disease & CO_2 ↑ses	They can be over maintain acid-Base Equilibrium
Uses	Replacement therapy	Replacement therapy	Replacement therapy	Amino acids → Metaboli-sm Replacement therapy
functions	* Regulating the acid- * Base equilibrium * Transmission of * Nerve impulse	* prepare Calcium Metabolism * Glucose, hexosel get Metabolised * phosphorylation	* Maintain of an acid - Base equilibrium * Buffer system bicar - bonate causes * Blood pH to go below 7·25	* Metabolism of Aminoacids * Determination Mechanism * Tissue respiration * Oxidised to sulphate ions
storage	Store in a cool & dry place.	store in a cool & dry temp. well closed Containers	store in a cool & dry temp	store in a container & close well

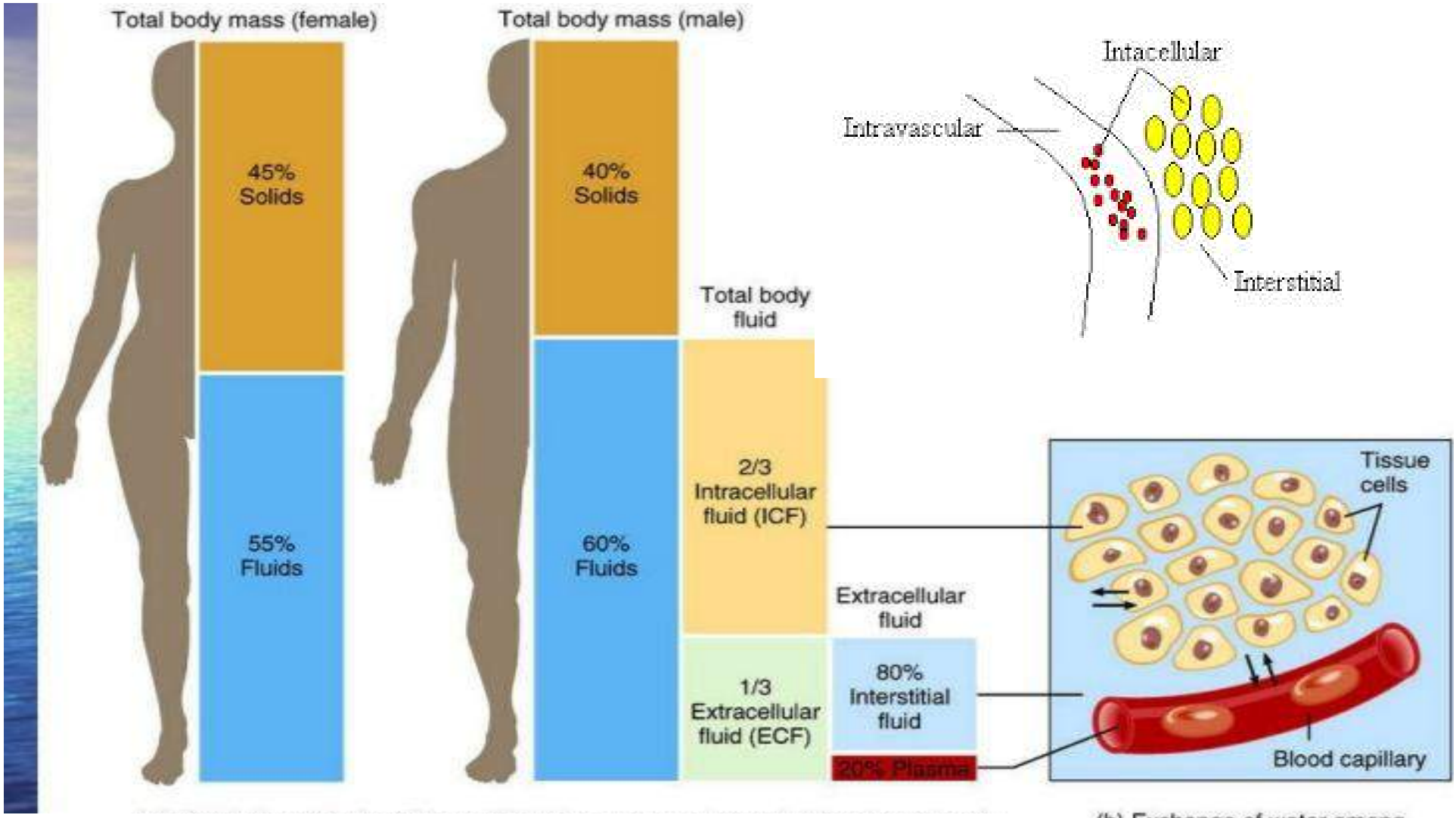
Hyper	* Renal failure * vomiting * Cusing syndrome * Brain damages.	Muscle disfunction dehydration	Bone disorder	Muscle disfunction & Irregularity
Hypo	Dizziness Weakness	Muscle contraction Vomiting diarrohea	Bone disfunction	Bone formation not occur
Uses	Replacement therapy	Replacement therapy	Replacement therapy	Replacement therapy
Function	* Regulating the body in acid-base equillibrium * protecting the body against Excessive fluids loss * Transmission of Nerve impalse	Contraction of muscle Transmission of Nerve impulse Maintaining the Composition TO regulate pH	* Irregulated by parathyroid hormone : Calcitonin * Hardening of a bone * Coagulation of Blood.	* Activate the enzymes * carbohydrates protein metabolism * Neural transmission * Myocardial function * Neuromuscular function
Storage	Moistured less Container & dry Containes are used	Dry containes at a temp. particular	Moistured less Containes are in a dry Container well closed	Store in a well closed containers

Major Intra & Extracellular

ELECTROLYTES



Major extra and intracellular ELECTROLYTES



(b) Exchange of water among body fluid compartments

- Chemical substance dissolved in body fluid can be categorized into:

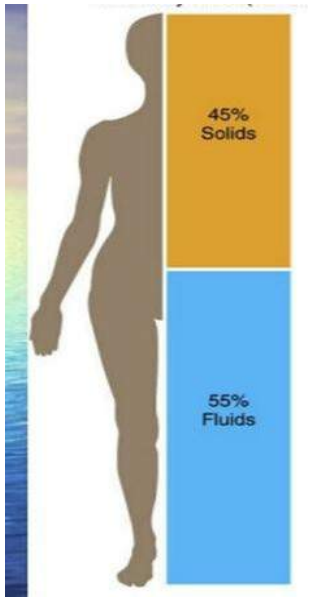
A. Non-electrolytes: Organic molecules, Do not generate ions in solution form.

e.g., Glucose, Urea, Creatine etc

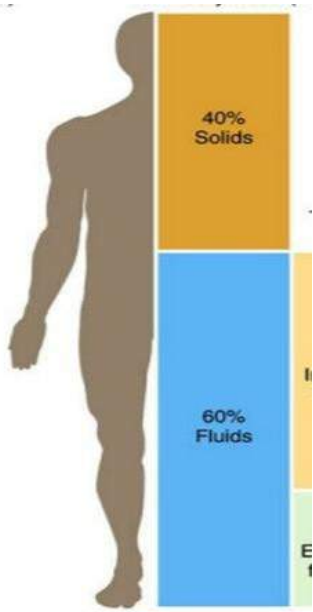
B. Electrolytes: Mostly inorganic substances, Dissociates into ions (+ve/-ve) in the body fluid.

e.g., Acids, Bases, Salts, few organic molecules like Citric acid, Lactic acid, Oxaloacetic acid etc

Body: "Both are necessary to perform physiological functions"!



Body water – *Dissolved* Necessary Elements



Substance Required

To:

Metabolize Nutrients & Drugs

Generate Energy

Maintain & Mfg. Body Components

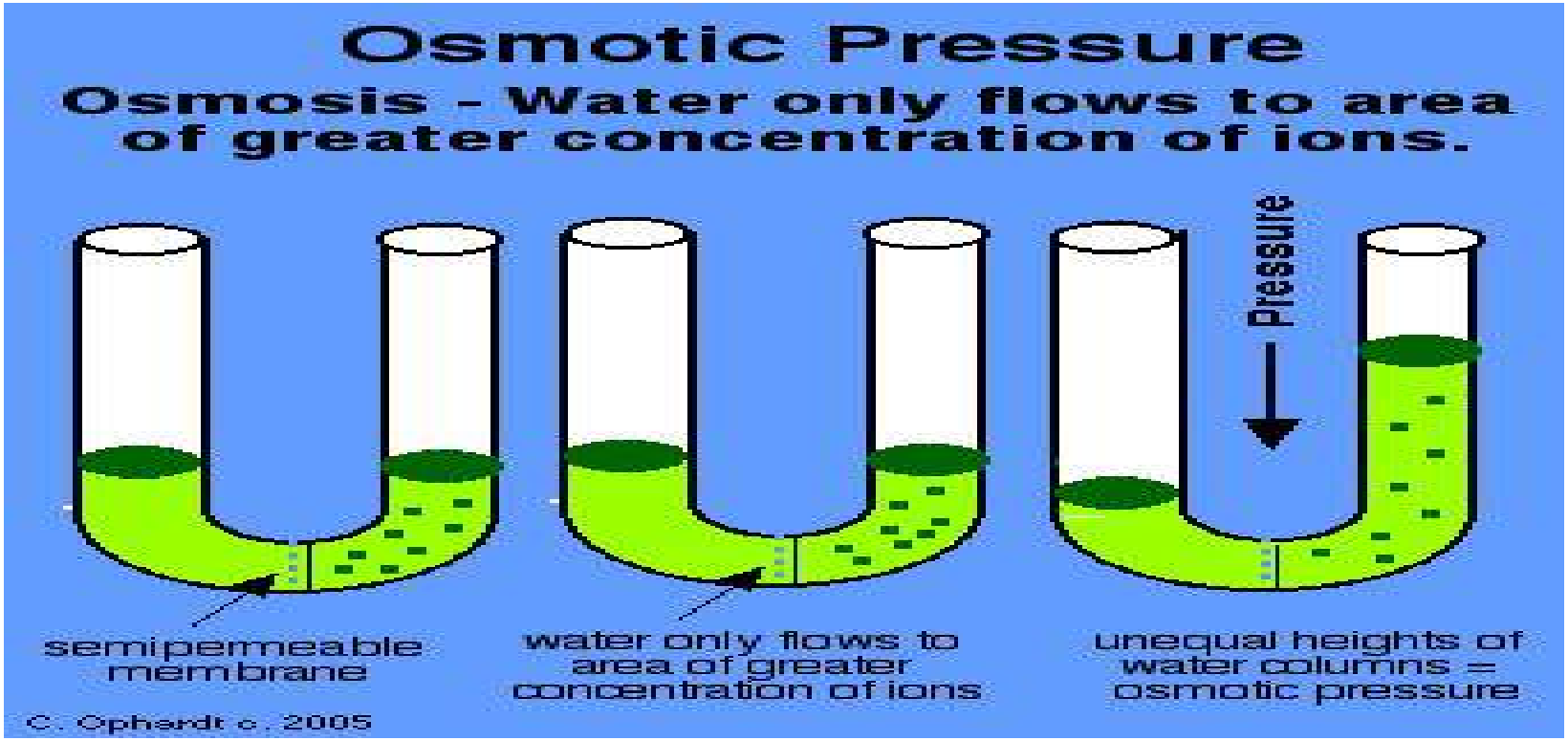
Eliminate:

by-products & waste

Internal Homeostasis (ionic, osmotic, pH balance)

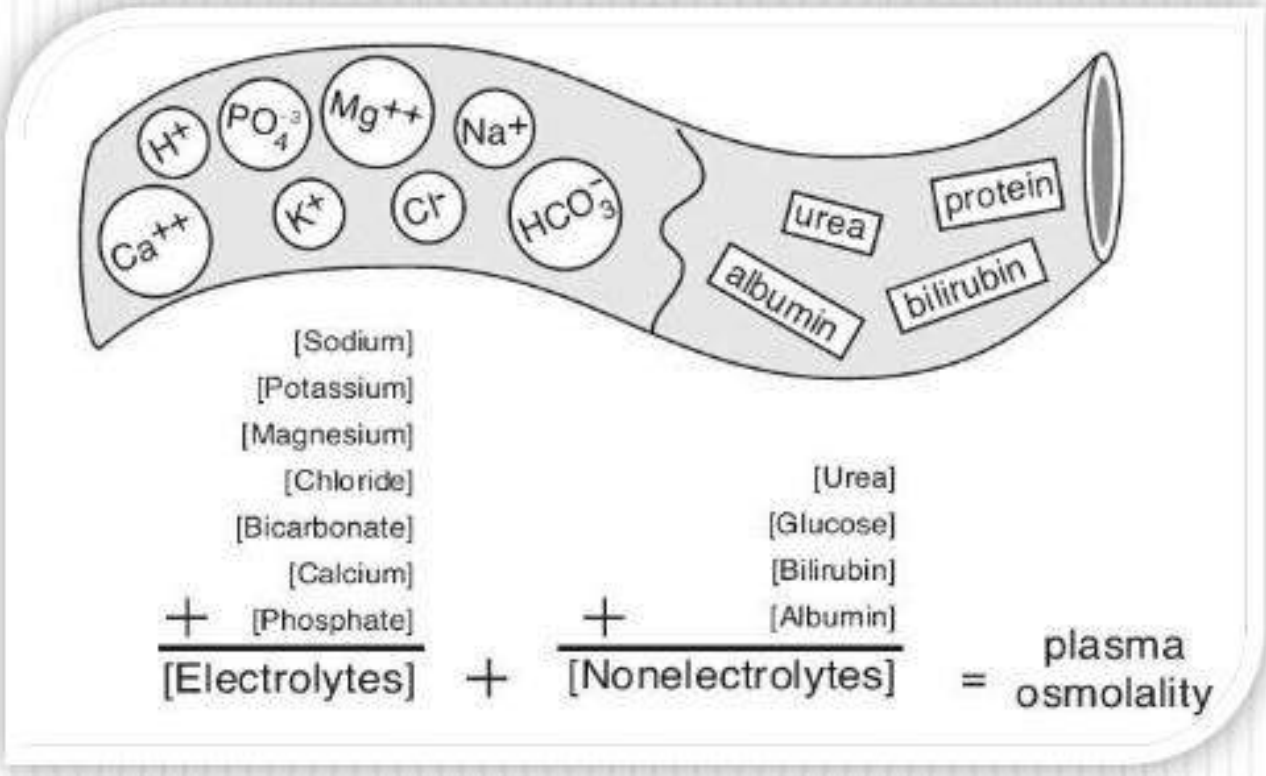
Definitions:

- Osmotic Pressure: concentration of electrolytes (dissolved ions) in each compartment that creates the osmotic pressure that holds water in the appropriate space.

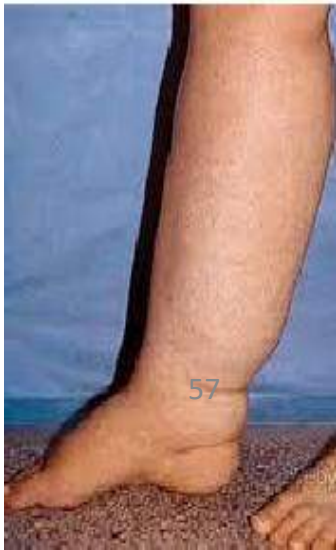


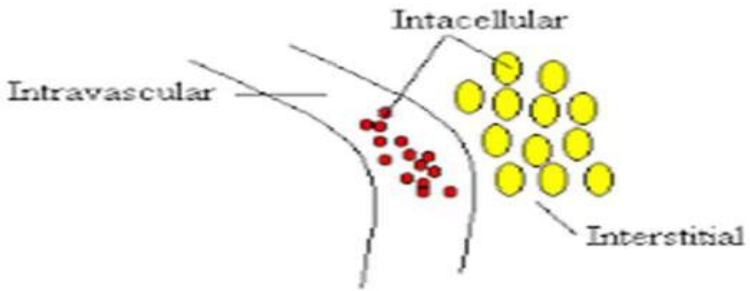
Osmolality

- is the number of particles (mmol) contained in one liter of water, so measured in mmol/L.
- i.e. it is the concentration by number

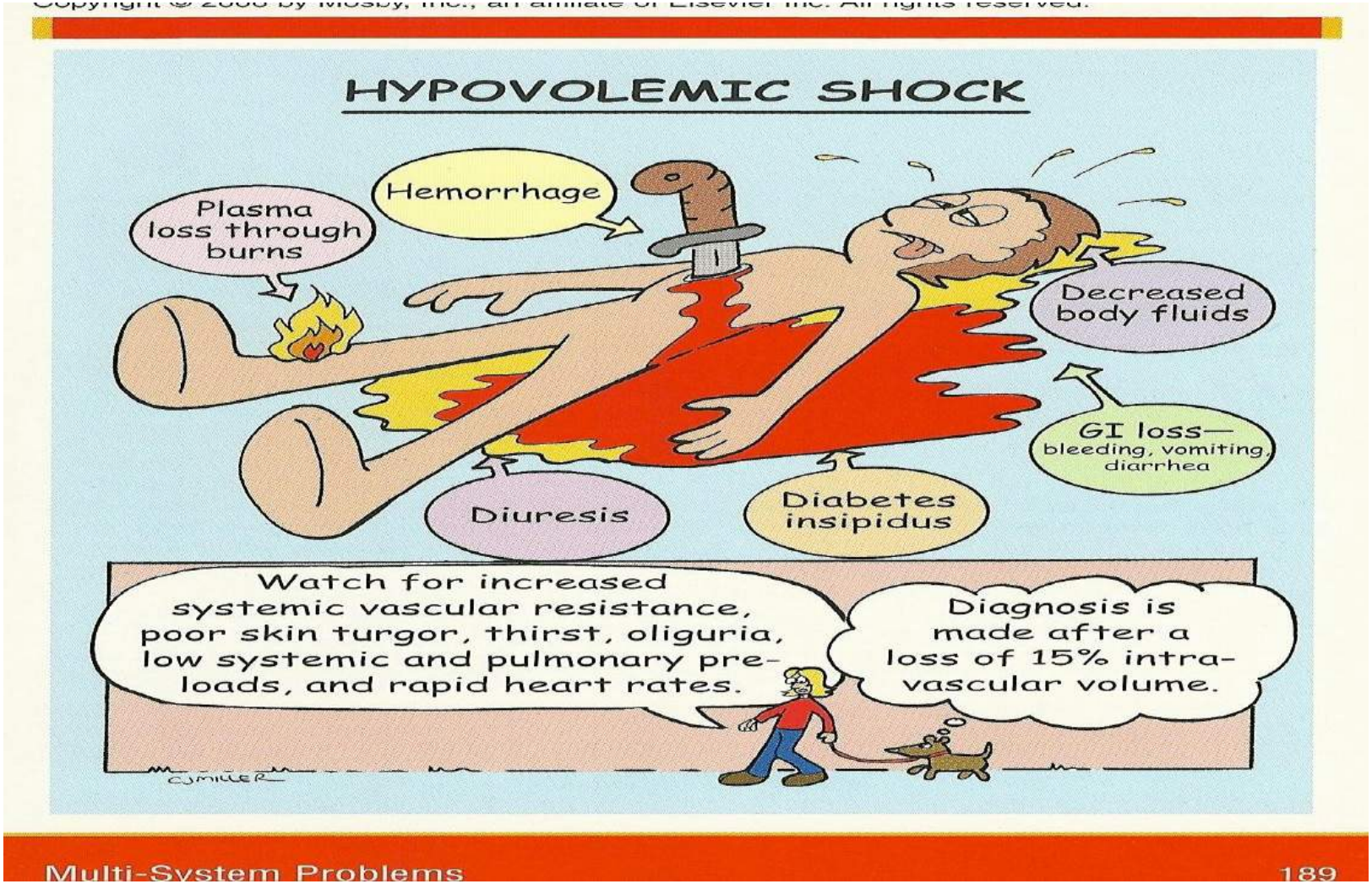


- Dehydration: state in which water volume is low in all 3 compartments (Intracellular, interstitial & plasma fluid).
- Edema: State in which fluid accumulates in the interstitial space due to low Oncotic (Protein) pressure.



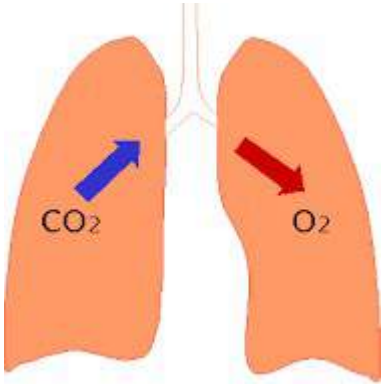


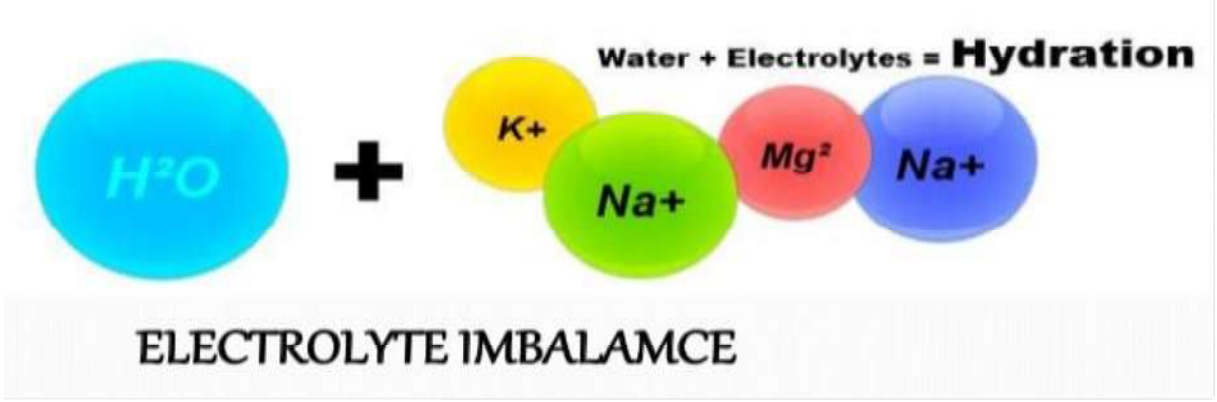
- Hypovolemia: State in which intravascular volume is low.



Salt & water balance:

- Oral intake of fluid & electrolytes
- Evaporation of solute – free water across the skin and lungs.
- Excretion of water & electrolytes through the kidneys : □ output – antidiuretic hormone (ADH) & aldosterone.





- The fluid in each compartment is ionically balanced.
- Body has the capacity to adjust slight variations in electrolytic concentration of the fluid compartments.
- If concentration of electrolytes changes – water will migrate across the cell membrane to reestablish Osmotic equilibrium.

Replacement Therapy

- When body itself fails to correct an electrolyte imbalance.

Products:

- Electrolytes
- Acids & Bases
- Blood Products
- Carbohydrates
- Amino acids
- Proteins

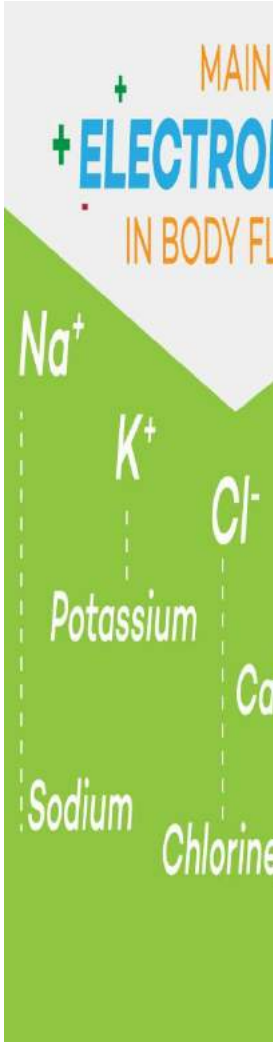
Electrolytes

- Mineral salts (inorganic compounds) are necessary within the body for all body process.
- They are usually required in small quantities.
- Main elements:

Calcium & Phosphorus: bone & teeth

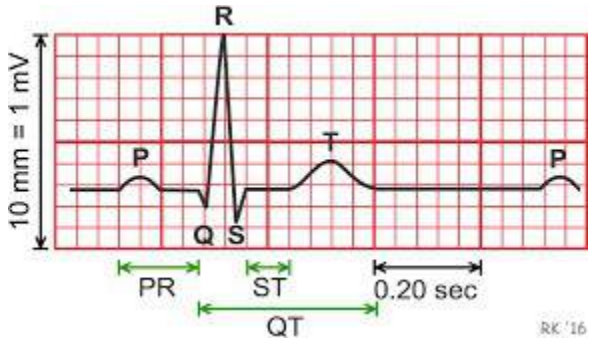
Iron: haemoglobin - convey oxygen & CO2.

Na & K: Transmission of nerve impulses & contraction of muscles



Important Functions:

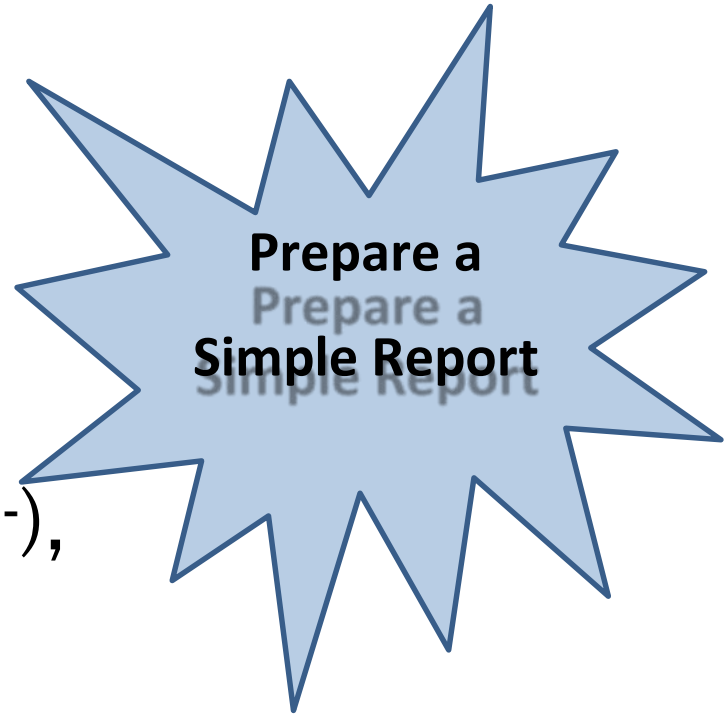
- Control of osmosis of water between body compartments.
- Maintain the acid-base balance required for normal cellular activates.
- Help to generate action potentials & graded potentials.
- Help to control secretion of some hormones (e.g., Aldosterone, Thyroid hormones) and neurotransmitters.



Major Physiological Ions

- **Nature/Properties**
- **Important Role/Major Physiological role**
- ⇅s

Sodium (Na^+),
Chloride (Cl^-),
Potassium (K^+),
Calcium (Ca^{2+}),
Magnesium (Mg^{2+}),
Phosphate ($H_2PO_4^-$,HPO_4^{2-},PO_4^{3-}),
Bicarbonate (HCO_3^-)



Electrolytes used in the Replacement Therapy

- In a healthy person, at least 70 liters of fluids are exchanged (secreted and reabsorbed) across the walls of the intestines per day.
- The brain, heart, kidney, and virtually every other vital organ depend on these fluids to function.
- As the body takes in the water and salts it needs, it loses or excretes those it does not need through urine, stools, and sweat.
- Thus, the secretion and absorption rates are kept in balance.

- In various condition like prolonged fever, sever vomiting or diarrhea creates a tremendous outpouring of water (heavy loss of water) & electrolytes (body salts) state of dehydration and impairs the capacity to reabsorb the fluid & electrolytes in our system.
- To compensate this loss, Electrolyte Replacement Therapy / Oral Rehydration Therapy is required.

"Replace what it Lost" Dr. Perla D. Santos

- 2 types of solutions used

1. A solution for rapid initial replacement:

Name	Concentration Range
Sodium	130 – 150 mEq/L
Chlorine	98 – 110 mEq/L
Potassium	4 – 12 mEq/L
Bicarbonate	28 – 55 mEq/L
Calcium	3 -5 mEq/L
Magnesium	3 mEq/L

These electrolyte concentrations thus closely resemble with the electrolyte concentrations found in extracellular fluids!

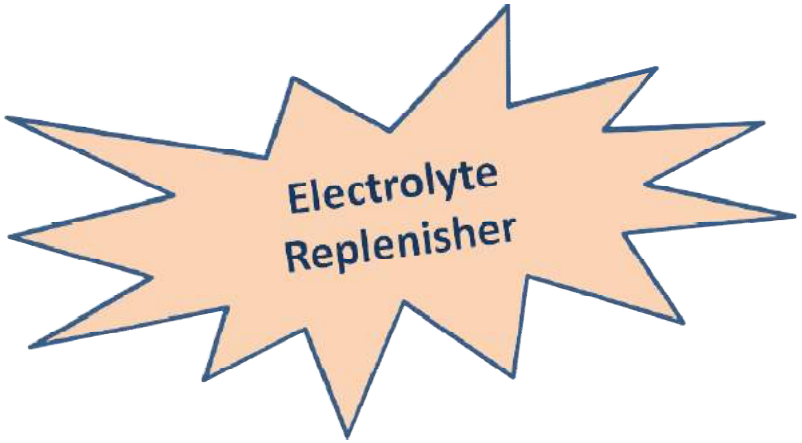
Name	mOsm/Litre
Sodium	75
Potssium	20
Dextrose	75
Chloride	65
Citrate	10
Toal osmolarity in approx. 200ml water	245

2. A solution for subsequent replacement:

Name	Concentration Range
Sodium	40 – 120 mEq/L
Chlorine	30 – 105 mEq/L
Potassium	16 – 35mEq/L
Bicarbonate	16 – 53 mEq/L
Calcium	10 - 15 mEq/L
Magnesium	03 - 06 mEq/L
Phosphorus	0 – 13 mEq/L

Properties, Preparation, Assay & Uses of

- Sodium Chloride
- Potassium chloride
- Calcium gluconate
- Calcium chloride

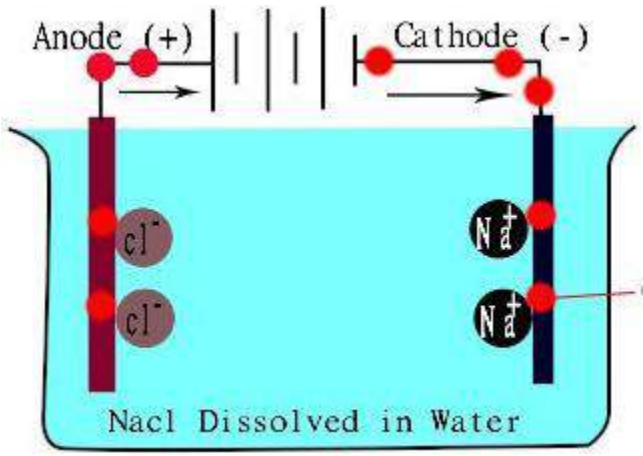


Sodium Chloride (NaCl)

- Sodium chloride is an ionic compound
- It is commonly called as table salt, halite or common salt (99.5% NaCl).
- It is the salt which is mainly responsible for the salinity of the seawater and for the extracellular fluid which is present in many multi-cellular organisms.
- It finds its application from household, medicines to industrial processes.
- Sea water is a major source of this salt.

Properties: NaCl

- It is easily soluble in water and partially in glycerine & alcohol.
- They are white crystals which does not have an odour but possess a taste.
- In its aqueous state NaCl acts as a good conductor of electricity due to the free movement of the ions.
- M.P. 801^{o}C



Preparation of Sodium Chloride:

- 1 mol of sodium bicarbonate reacts with 1 mol of hydrochloric acid to generate 1 mol of salt, 1 mol of water, and/or 1 mol of carbon dioxide.

$$NaHCO_3 + HCl_{(aq)} \rightarrow NaCl_{(aq)} + H_2O_{(aq)} + CO_2$$

Procedure:

- Accurately weigh 5 g of NaHCO3 into evaporating dish.
- Add 5 to 6 mL of distilled water to the dish to wet the bicarbonate. Cover the dish with a watch glass.
- Move the watch glass aside slightly and add, in small portions, about 6 mL of concentrated hydrochloric acid from a 10 mL graduated cylinder.
- After the addition of 6 mL of acid, continue adding acid only as long as CO2 (gas) continues to be evolved.
- Remove the watch glass and evaporate to dryness over a water bath.
- Allow the dish to cool, weigh & collect it out the crystals of NaCl.

- Assay: It is analysed by Precipitation Titration (Mohr's method)

$$NaCl + AgNO_3 \rightarrow AgCl + NaNO_3$$

Sodium chloride reacts with silver nitrate solution using potassium chromate as an indicator

$$2\,AgNO_3 + K_2CrO_4 \rightarrow Ag_2CrO_4 + 2KNO_3$$

Reddish brown coloured

silver chromate

Uses:

- Normal saline (0.9%) that has the same osmotic pressure (isotonic) as body fluids.
- Wet dressings
- Hypotonic solution – when patient unable to take fluid & nutrients orally.
- Hypertonic solution/injections: patients suffers from excessive loss of sodium (1.6% w/v of NaCl).

Potassium Chloride (KCl)

- Colourless, odourless white granular powder or crystals.
- It has a saline taste and is stable in air.
- Soluble in water and insoluble in alcohol.

Assay: It is analysed by Precipitation Titration (Mohr's method)

$$KCl + AgNO_3 \rightarrow AgCl + KNO_3$$

- KCl reacts with silver nitrate solution using potassium chromate as an indicator

$$2\,AgNO_3 + K_2CrO_4 \rightarrow Ag_2CrO_4 + 2KNO_3$$

Reddish brown coloured

silver chromate

Preparation:

Method 1: Potassium chloride can be prepared by treating potassium hydroxide (KOH) or other potassium bases (potassium carbonate, potassium sulphat) with hydrochloric acid:

$$KOH + HCl \rightarrow KCl + H_2O$$

- This conversion is an acid-base neutralization reaction.
- The resulting salt can then be purified by recrystallization.

Method 2:

- By allowing potassium to burn in the presence of chlorine gas (exothermic reaction)

$$2\ K + Cl_2 \rightarrow 2\ KCl$$

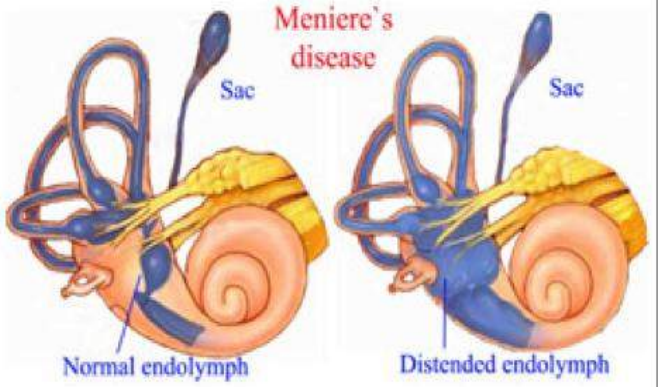
Uses of KCl

- Potassium replacement (hypokalemia or hypochloremic alkalosis condition).
- As an isotonic solution – alone

Or Mixed with NaCl or 5% dextrose solution

- Paralysis
- Menier's syndrome
- Digitalis intoxication

Note: cautiously given in heart & renal diseases.



Calcium Gluconate

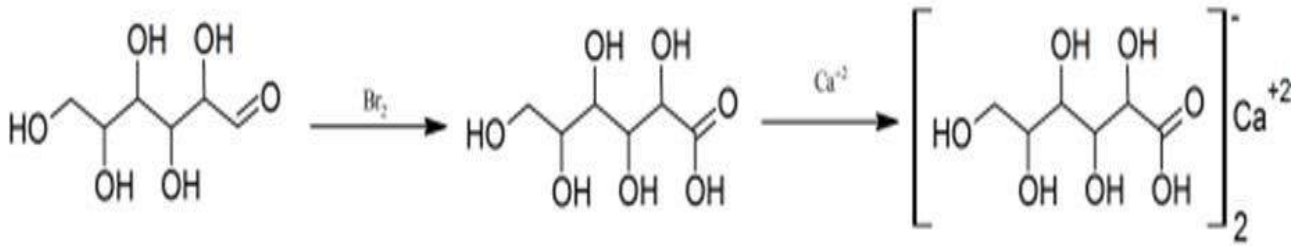
- It appears odourless, tasteless, white crystalline granules or powder.
- Soluble in water and insoluble in alcohol & other organic solvents.
- Its solution remains neutral to litmus.
- Decomposed by dilute mineral acids (HCl) into Gluconic acid and Calcium chloride of the mineral acid used.

Assay: By Complexometric Titration

- An accurate weighed sample is dissolved in small quantity of water, acidified with dil. HCL.
- To the above solution add 1.0 N NaOH solution, murexide indicator and a solution of naphthol green and titrate against Disodium EDTA (Ethylenediamintetraacetic acid) until deep blue colour develops.

Uses: Orally, I.V. or I.M. in the treatment of Hypocalcaemia or in calcium deficiency.

Note:Calcium gluconate injection represents 92 – 103% of calcium gluconate with a pH between 6 - 8.2.



Preparation of calcium gluconate

- To a 200 g of anhydrous glucose in 1000 ml of water, 200 g of bromine are gradually added.
- After the reaction is over the excess of bromine is boiled off and the golden-yellow solution is cooled and the volume measured.
- Add lead carbonate to the above solution - lead gluconate is then formed and this prevents the lead bromide from crystallizing out.
- The resulting mixture is concentrated and allowed to stand in the ice box for 24 hours, after which the lead bromide is filtered off and washed with a little ice-cold water.
- In the presence of silver oxide or silver carbonate, and hydrogen sulfide is passed in to remove minute amounts of lead and silver ions in solution.
- Gluconic acid, is boiled with an excess of calcium carbonate. After cooling, and filtering off the excess of carbonate.
- Filter & concentrate the solution of calcium gluconate.

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CALCIUM CHLORIDE

$CaCl_2 \cdot 2H_2O$ 147.01
Calcium chloride, dihydrate.

Calcium Chloride contains an amount of $CaCl_2$ equivalent to not less than 99.0 percent and not more than 107.0 percent of $CaCl_2 \cdot 2H_2O$.

Preparation: Calcium chloride is mainly produced by reacting limestone ($CaCO_3$) with hydrochloric acid (HCl).

$$CaCO_3 + 2\ HCl \rightarrow CaCl_2 + CO_2 + H_2O$$

It is also produced as a major by-product during manufacture of soda ash (Na_2CO_3) by the Solvay process, in which limestone is reacted with NaCl solution.

Assay—

Transfer about 1 g of Calcium Chloride, accurately weighed, to a 250-mL beaker, and dissolve in a mixture of water and 3 N hydrochloric acid (100:5). Transfer the solution to a 250-mL volumetric flask, dilute with water to volume, and mix. Pipet 50 mL of the solution into a suitable container, add 100 mL of water, 15 mL of 1 N sodium hydroxide, and 300 mg of hydroxy naphthol blue, and titrate with 0.05 M edetate disodium VS until the solution is DEEP BLUE in color. Each mL of 0.05 M edetate disodium is equivalent to 7.351 mg of $CaCl_2 \cdot 2H_2O$.

Packaging and storage— Preserve in tight containers.

Labeling— Where Calcium Chloride is intended for use in hemodialysis, it is so labeled.

Uses:

Calcium chloride has several similar uses as sodium chloride, and it is used as a food additive, food preservative, for de-icing roads in winter, and as brine in refrigeration plants. It is also used as a swimming pool chemical, in water treatment plants, and for desiccating purposes. It also has applications in metallurgy, oil-well drilling, and rubber, paper, dye and paint industries.

PHYSIOLOGICAL ACID-BASE BALANCE

- Electrolytes also play an important role in regulating body's acid-base balance
- Body fluids contain balanced quantities of acids & bases.

Acidity of the solution: No of [H^+] present in fluid/solution - ECF

Sources: [H^+]

- Food
- Cellular metabolism of Glucose, Fatty acids, & Amino acids etc
- Reabsorption

- Biochemical reactions: Very sensitive to change in pH (acidity/alkalinity)

e.g., enzyme Pepsin in the stomach– helps in digestion of dietary proteins at low pH.

enzyme Ptyalin in saliva – helps in digests carbohydrates at pH between 5.4 - 7.5.

Body Fluid	pH value
Urine	4.5 – 08
Blood	7.4 – 7.5
Gastric juice	1.5 – 3.5
Saliva	5.4 – 7.5
Bile	6.0 -8.5

Kidney – removes excess acid – make urine acidic

Metabolic activity – Produces acid/bases - Alter the blood pH

Buffer Systems

Acids-bases are continually taken into & formed by the body, the pH of fluids inside & outside cells remain fairly constant because of the presence of 'BUFFER SYSTEMS'.

- Consists of a weak acid & the salt of that acid

Functions:

- to convert strong acids or bases into weak acids or bases.
- to prevent drastic change in pH of the blood.

Note: However, it will be effective only if excess acid/alkali excreted out by lungs and/or kidneys.

Types of Buffer systems:

- **Carbonic Acid (H_2CO_3) – Bicarbonate (HCO_3^-) Buffer System**
- **Phosphate ($H_2PO_4^-$, HPO_4^{2-}, PO_4^{3-}) Buffer System**
- **Protein (Hemoglobin/HbH) Buffer System**

Carbonic Acid (H_2CO_3) – Bicarbonate (HCO_3^-) Buffer System

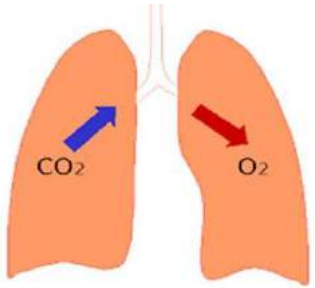
- Major buffer of metabolic acid/base present in Plasma & Kidneys.
- Regulates blood pH

Some CO_2, the end product of cellular metabolism, is carried to the lungs for elimination, and the rest dissolves in body fluids, forming carbonic acid that dissociates to produce bicarbonate (HCO_3^-) and hydronium (H_3O^+) ions.

More of the HCO_3^- is supplied by the kidneys.

$$CO_2 + H_2O \leftrightarrow H_2CO_3$$

$$H_2CO_3 + H_2O \leftrightarrow H_3O^+ + HCO_3^-$$



Regulation of blood pH

- The lungs and kidneys play important role in regulating blood pH.
- The lungs regulate pH through retention or elimination of CO_2 by changing the rate and volume of ventilation.
- The kidneys regulate pH by excreting acid, primarily in the ammonium ion (NH_4^+), and by reclaiming HCO_3^- from the glomerular filtrate (and adding it back to the blood).

Phosphate Buffer System

- The phosphate buffer system ($HPO_4^{2-}/H_2PO_4^-$) plays a role in plasma and erythrocytes.
- $H_2PO_4^- + H_2O \leftrightarrow H_3O^+ + HPO_4^{2-}$
- Any acid reacts with monohydrogen phosphate to form dihydrogen phosphate

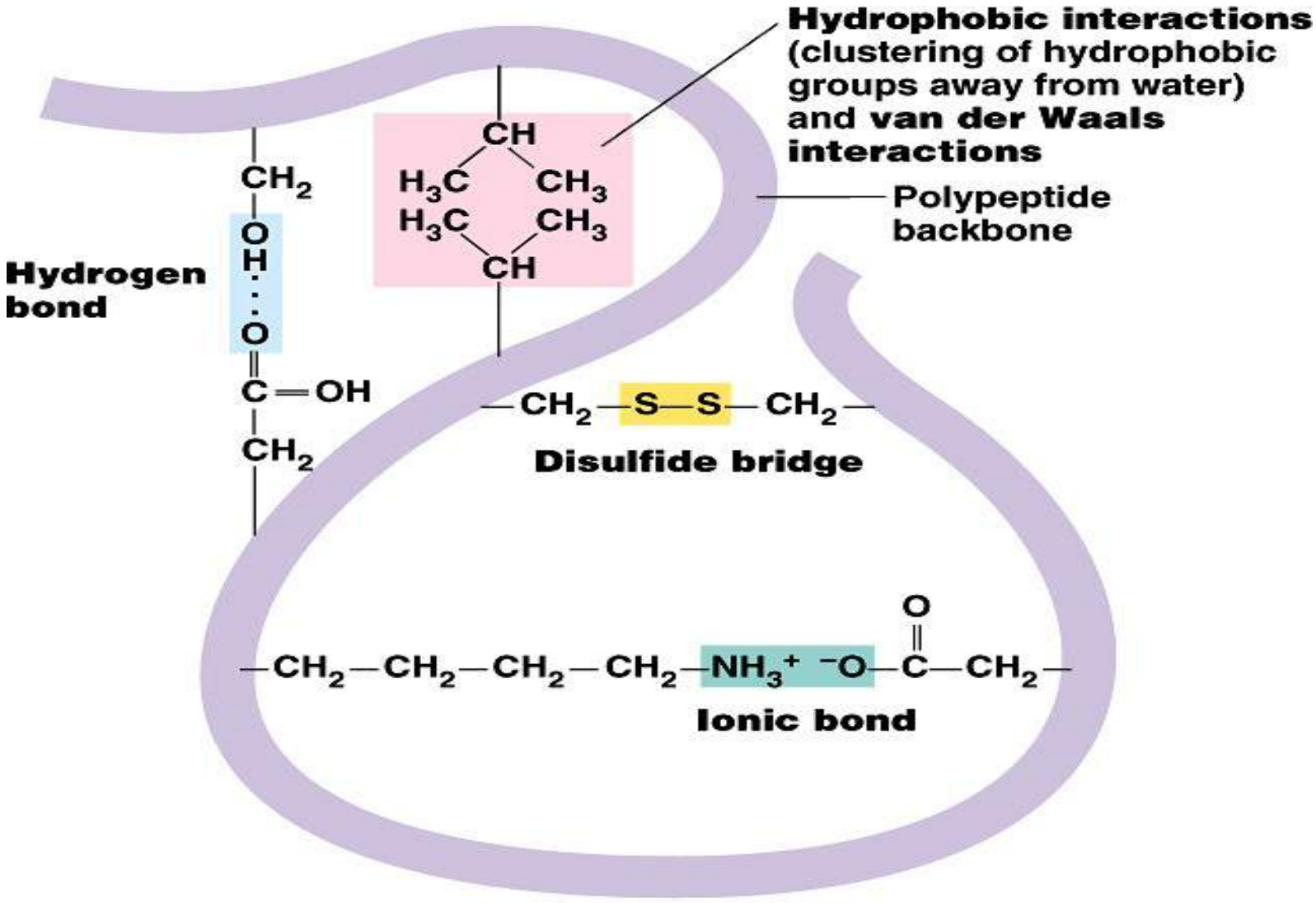
dihydrogen phosphate monohydrogen phosphate

- $H_2PO_4^- + H_2O \leftarrow HPO_4^{2-} + H_3O^+$
- The base is neutralized by dihydrogen phosphate

dihydrogen phosphate monohydrogen phosphate

- $H_2PO_4^- + OH^- \rightarrow HPO_4^{2-} + H_3O^+$

Protein Buffer System



Proteins act as a third type of blood buffer

- Proteins contain – COO^- groups, which, like acetate ions (CH_3COO^-), can act as proton acceptors.
- Proteins also contain – NH_3^+ groups, which, like ammonium ions (NH_4^+), can donate protons.
- If acid comes into blood, hydronium ions can be neutralized by the – COO^- groups
- $- COO^- + H_3O^+ \rightarrow - COOH + H_2O$
- If base is added, it can be neutralized by the – NH_3^+ groups
- $- NH_3^+ + OH^- \rightarrow - NH_2 + H_2O$

Limit Test:

Semiquantitative or quantitative test that is designed to identify and to control the amount of impurities present in the given sample when compared to standard solution according to Indianpharmacoepoeia.

Limit Test for chlorides:

Reactions:

test: $Cl^- + AgNO_3 \xrightarrow{dil\ HNO_3} AgCl\downarrow + NO_3$

(ppt)

Soluble chlorides — Silver nitrate — Silver chloride (insoluble) — Nitrate

Standard:

$NaCl + AgNO_3 \xrightarrow{dil.\ HNO_3} AgCl\downarrow + NaNO_3$

Sodium chloride — Silver nitrate

Test	Standard
10 gm + 10ml dil HNO_3 ↓ 50ml with distilled water ↓ 1 ml of $AgNO_3$ ↓ Stir it well ↓ Observe turbidity.	1 ml of 0.05845 % w/v of Nacl ↓ 1ml of 0.01N Hcl 10 ml of dil. HNO_3 ↓ 1 ml of $AgNO_3$ ↓ Stir it well ↓ Observe turbidity.

Limit Test For Sulphates

Reactions:

test: $SO_4^{-2} + BaCl_2 \xrightarrow{dil.\ HCl} BaSO_4\downarrow + 2HCl$

Soluble Sulphates — Barium chloride — Barium sulphate — hydrochloric acid.

Standard:

$H_2SO_4 + BaCl_2 \xrightarrow{dil\ HCl} BaSO_4\downarrow + 2HCl$.

Sulphuric acid — Barium sulphate

$K_2SO_4 + BaCl_2 \xrightarrow{dil\ HCl} BaSO_4\downarrow + 2KCl$

Composition & Uses of Basa, reagent:

15ml of 0.5% W/v of $BaCl_2$ => Used as precipitating agent
20ml of sulphate free ethanol => Used as
5ml of 0.1089% W/v K_2SO_4 =>
Distilled water to make 100 ml.

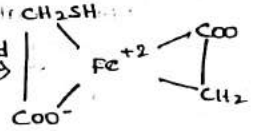
Test	Standard
1 gm of sample solution + 10ml of H_2O	2ml of 0.1089% W/v of K_2SO_4
↓	↓
2ml of dil HCl	2ml of dil HCl
↓	↓
Make up the volume	Make up the volume
↓	↓
5ml of Basa, reagent	5ml of Basa, reagent
↓	↓
Stir it well	Stir it well
↓	↓
Observe the turbidity	Observe the turbidity

Limit Test for Iron

Main reagent: thioglycolic acid.

$Fe^{3+} + 2$ CH_2SH / $COOH$ (thioglycolic acid) $\longrightarrow Fe^{+2} + 2$ CH_2SH / $COOH$ (Citric acid, NH_3)

ferric → ferrous



ferrous thio glycolate compound.

* **NH_3 - maintain alkaline medium**
Test for iron - purple colour.

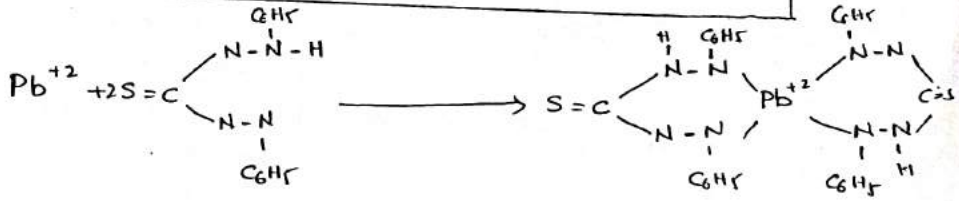
Preparation of standard Iron solution:

Reagent used is ferric ammonium sulphate
0.173 gm of ferric ammonium sulphate
+
15ml of HCl
↓
1000ml with distilled water
0.02mg Iron is present.

Test Solution	Standard Solution
1 gm of sample + H_2O	2ml of standard iron solution
2ml of 20% W/v citric acid	↓
↓	2ml of 20% w/v citric acid
2 drops of thioglycolic acid and add of NH_3 maintain alkaline pH	↓
↓	2 drops of thioglycolic acid by adding NH_3 to maintain alkaline pH
make upto 50ml of H_2O	↓
↓	Make the volume to 50ml
Stir it well	↓
↓	Stir it well
Observe the colour intensity.	↓
	Observe the colour intensity

Limit Test for Lead

Main Reagent : Diphenyl thiocarbazone
Colour : Violet or reddish purple.



Dithizone (diphenyl thiocarbazone)

Lead dithizone complex

Test Solution:

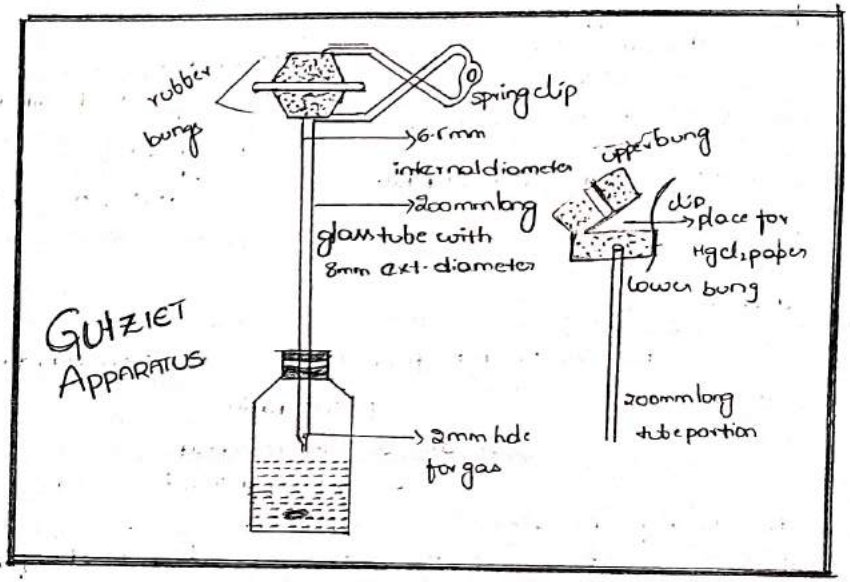
Sample + 6ml of ammonium citrate, 2ml of KCN; 2ml of H_2HCl } take into separating funnel
↓
2 drops of phenol red (indicator)
↓
add NH_3 solution
↓
extracted with 5ml of portions of dithizone choloform
↓
add 30% of 1% HNO_3 - shake for 30sec
↓

Standard Solution:

2ml (or) 5ml of lead nitrate solution is used.

Limit Test Of Arsenic

Apparatus used	- Guitzet apparatus
Main reagent	- Arsenic acid
colour	- yellow colour stain
Precipitating agent	- Mercury chloride paper



Arsenic + acid ⟶ arsenic acid $\xrightarrow[\text{agents}]{\text{reducing}}$ arsenious acid

(Zn, HCl, $SnCl_2$, KI)

+ Nascent hydrogen ⟶ arsine gas ⟶ $HgCl_2$ paper

↓

yellow colour stain

Reactions:

$$H_3ASO_4 \xrightarrow[KI]{SnCl_2/} H_3ASO_3$$

(pentavalent) trivalent

$$H_3ASO_3 + 3H_2 \longrightarrow ASH_3 + 3H_2O$$

trivalent arsine gas

$$2ASH_3 + HgCl_2 \xrightarrow{Zn} Hg\begin{matrix}ASH_2\\ASH_2\end{matrix} + 2HCl$$

mercuric arsinate complex

Test Solution	Standard solution
Sample solution + 5ml of IM KI stannous chloride ↓ 10gm of zinc ↓ $HgCl_2$ paper in ↓ 40 min → time required ↓ 30-40°C - temperature ↓ observe the colour intensity	0.132g of As_2O_3 (arsenic thioxide) ↓ dissolved in 5ml of NaOH solution ↓ diluted to 250ml ↓ take 1 ml → dilute to 100ml with distilled water ↓ 40 min at 30-40°C ↓ observe the colour intensity

MISCELLANEOUS COMPOUNDS

♦ **OVERVIEW** ♦

- **Expectorant : Introduction, Classification of expectorants, Ammonium chloride and Potassium iodide.**
- **Emetics : Introduction, Classification of emetics, Copper sulphate and Antimony potassium tartrate.**
- **Haematinics : Introduction, Iron as a haematinics, Physiological functions of iron, Iron preparations, Ferrous sulphate, Ferrous gluconate.**
- **Poison and Antidotes : Introduction, Mechanism of action, Classification of antidotes, Sodium thiosulphate, Sodium nitrite, Activated charcoal.**

9.1 EXPECTORANT

9.1.1 Introduction

Expectorants are the drugs that help in removing sputum and other material from the respiratory tract (lungs, bronchi and trachea) either by increasing bronchial secretion/ fluidity or reducing the viscosity/thickness which facilitates its removal by coughing. However the exact machanism is not known. They are used in the treatment of various cough (chesty, wet, productive or phlegmy coughs) which typically occur with a cold.

Expectorants

↓

Increases bronchial secretion/ fluidity

or

Reduces the viscosity/ thickness

↓

Stimulation of machno or chemoreceptor
(throat, respiratory passage or stretch receptors in lungs)

↓

Cough

↓

Removal of sputum

Examples of inorganic expectorant are ammonium chloride, potassium iodide, sodium iodide and related substances. If the patient is sensitive or the dose of expectorant is high enough, it may induce vomiting. It is advisable to give the doses of expectorant that could be tolerated (by the patient) along with other pharmaceutical aid and cough suppressant.

9.1.2 Classification of Expectorants

Based on the mechanism of action expectorant can be classified into two categories :

1. **Sedative expectorant :**

These expectorants are stomach irritant it produces its effect through stimulation of gastric reflexes. This reflexes ultimately enhance the bronchial secretion. It is usually bitter in nature.

Examples : For sedative expectorant : Ammonium chloride, Potassium iodide, Antimony potassium tartrate, sodium Citrate or acetate.

2. **Stimulant Expectorant :**

These expectorants produces their effect by stimulation of the secretary cells of the respiratory tract directly or indirectly. Since, these drugs stimulates the secretion, more fluid gets produced in respiratory tract and sputum is diluted.

Examples : For stimulant Expectorant :-Eucalyptus, lemon, Active constituents of oil like terpine hydrate, anethole.

AMMONIUM CHLORIDE (I.P., B.P., U.S.P.)

Chemical formula : NH_4Cl

Molecular weight : 53.49 g/mole

Category : Expectorant

Synonym : Sal ammoniac

It is having not less than 99.5 per cent of ammonium chloride, calculated with reference to substance dried over silica gel for four hours.

Preparation :

I. It is commercially prepared by nuetralizing ammonia with HCl. The solution is evaporated till crude crystalline mass of ammonium chloride is obtained.

$$NH_3 + HCl \rightarrow NH_4Cl$$

The crude crystalline mass of ammonium chloride is purified either by crystallisation or sublimation.

II. It can also be prepared by heating ammonium sulphate with sodium chloride.

$$2NaCl + (NH_4)_2SO_4 \longrightarrow 2NH_3 + 2HCl + Na_2SO_4$$

$$NH_3 + HCl \longrightarrow NH_4Cl$$

III. It can be prepared by treating ammonical gas liquor with lime and liberated ammonia is passed in to hydrochloric acid solution. The crude crystalline mass of ammonium chloride is obtained which is known as **sal ammoniac**.

Properties :

1. It is white fine crystalline or coarse crystalline powder.
2. It is odourless and having a cooling saline taste.
3. It is slightly hygroscopic in nature.
4. It is soluble in water and glycerol.
5. Freshly prepared aqueous solution is nuetral to litmus but on standing it undergoes hydrolysis become acidic.

$$NH_4Cl + H_2O \rightarrow NH_4OH + H_3O^+ + Cl^-$$

Identification test : It gives the reactions of ammonium and chlorides.

Test for purity : It is tested for As, Fe, heavy metal, loss on drying, sulphated ash and pH of a 5% w/v solution is between 4.5 and 6.0.

Assay : Ammonium chloride was previously assayed by Volhard's method.

This method was designed by Volhard in 1874 for estimation of silver in dilutie nitric acid by titrating against standard thiocyanate solution in the presence of ferric salt as indicator. But later it is extended to the estimation of chloride and bromide.

Principle : Ammonium chloride forms acidic solution when dissolved in water. To an aqueous solution of ammonium chloride, nitric acid, nitrobenzene, and known excess amount of 0.1N silver nitrate is added and shaken vigrously. Silver chloride is precipitated and is coagulated by nitrobenzene, this prevent the silver chloride from reacting with ammonium thiocyanate in the subsequent titration. Finally, it is titrated with standard 0.1M ammonium thiocyanate using ferric ammonium sulphate as an indicator.

$$NH_4Cl + AgNO_3 \longrightarrow AgCl\downarrow + NH_4NO_3$$

$$NH_4SCN + AgNO_3 \longrightarrow AgSCN + NH_4NO_3$$

Factor : Each ml of 0.1N $AgNO_3$ is equivalent to 0.005349 g of NH_4Cl.

Now ammonium chloride is assayed by acid base titration method (Formal titration).

In this titration, ammonium chloride undergoes hydrolysis to form ammonium hydroxide and hydrochloric acid. This reaction is facilitated by the addition of formaldehyde, as it fixes ammonia by forming hexamine. Now this can be titrated with alkali without interference using phenolpthalein as an indicator.

$$NH_4Cl + H_2O \longrightarrow NH_4OH + HCl$$

$$NH_4OH + CH_2O \longrightarrow C_6H_{12}N_4 + H_2O$$

Hexamine Hexamine

The formaldehyde is added to the ammonium chloride, to impart acidic properties to the compound and then it can be titrated with standard alkali.

Factor : Each ml of 0.1N NaOH is equivalent to 0.005349 g of NH_4Cl.

Uses :

1. It is used as a mild expectorant.
2. It maintains acid-base equilibrium of body fluid.

Storage : It is stored in well closed containers.

POTASSIUM IODIDE (B.P., U.S.P.)

Chemical formula : KI

Molecular weight : 166 g/mole

Category : Expectorant

It is having not less than 99.0 per cent of KI, calculated with reference to the substance dried to a constant weight at 105°C.

Preparation :

I. **Industrial method :** It can be prepared by the action of iodine on moist iron filling to form ferro-ferric iodide. Which then gets decomposed with potassium carbonate.

$$Fe + I_2 \longrightarrow FeI_2 \cdot 2FeI_3$$

$$FeI_2 \cdot 2FeI_3 + 4K_2CO_3 \longrightarrow 8KI + FeO \cdot Fe_2O_3 + 4CO_2$$

Ferroso-ferric oxide is filtered out. The filterate is concentrated to get KI. It may be purified by recrystallisation.

II. It can also be prepared by treating a hot solution of potassium hydroxide with I_2 in slight excess to form a mixture of potassium iodide and potassium iodate.

$$6KOH + 3I_2 \longrightarrow 5KI + KIO_3 + 3H_2O$$

The solution is concentrated and treated with excess of charcoal powder followed by evaporating the mixture to dryness followed by ignition. The charcoal reduces iodate to iodine, thus utilising the total iodine to get the potassium iodide.

$$KIO_3 + 3C \longrightarrow KI + 3CO$$

Properties :

1. It occurs as colourless, transparent or opaque crystal or a white granular powder.
2. It is odourless, saline and bitter in taste.
3. It is deliquescent in moist air.
4. It is soluble in water, glycerine, alcohol and acetone.

Identification : It gives reactions of potassium and iodide.

Test for purity : It is tested for As, Ca, Ba, sulphate, alkalinity, iodate, cyanide, and heavy metals.

Assay :

The assay of potassium iodide is based on iodometry method.

In this titration, hydrochloric acid is added to the potassium iodide solution and the solution is titrated with 0.05M potassium iodate using chloroform as an indicator. Iodine is liberated from KI in presence of acid. The liberated iodine is converted in to iodine monochloride with more of potassium iodate in presence of acid. The titration is continued until the violet colour disappear in the chloroform layer (chloroform is heavier than water, it sinks to the bottom of the flask and appear bright. Free iodine being more soluble in chloroform, dissolve and colour the chloroform layer bright violet)

$$KIO_3 + 5KI + 6HCl \longrightarrow 6KCl + 3I_2 + 3H_2O$$

$$KIO_3 + 2I_2 + 6HCl \longrightarrow KCl + 5ICl + 3H_2O$$

In this titration, starch cannot be used as an indicator because starch will be hydrolysed by high concentration of the acid.

Factor : Each ml of 0.05N potassium iodate is equivalent to 0.0166 g of KI.

Storage : It should be stored in a well closed containers.

Uses :

1. It is used internally for supplying iodine for treatment of thyroid deficiency.
2. It can also be used as expectorant in cough mixture and saline diuretic.
3. It has mild antifungal activity.

9.2 EMETICS

Emetics are the agents which causes vomiting, it gives rise to forced regurgitation (emesis) by which the contents of the stomach get expelled through oral cavity.

They may act directly on the gastrointestinal tract bringing about emesis through local irritation effect (e.g. ammonium carbonate, ipecacuanha) or indirectly through their effect on the vomiting centre or chemoreceptor trigger zone postremal area near the medulla (i.e. centrally acting emetics).

It is mainly used in the treatment of poisoning cases. Emetics are sometimes added in cough preparations in low doses to stimulate flow of respiratory tract secretion. Example : Copper sulphate, Antimony potassium tartrate.

Emetics should not be used in the following conditions :

- In corrosive poisoning - Acid and alkaline.
- In CNS stimulant poisoning.
- To unconsious patients.

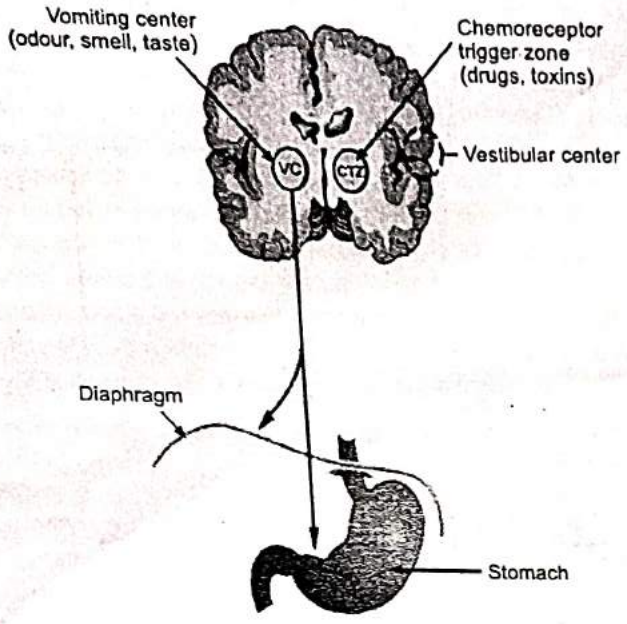


Fig. 9.1

Based on machanism of action, it can be classified in two types :

1. **Local acting emetics :** It act by local irritation of gastric mucosa.
   Examples : ammonium bicarbonate, Ipacacuhana
2. **Centraly acting emetics :** It act directly to Chemoreceptor Trigger Zone (CTZ) in the floor of IVth ventricle in medulla. e.g Apomorphine, Morphine

COPPER SULPHATE

Chemical formula : $CuSO_4 \cdot 5H_2O$

Molecular weight : 249.7 g/mole

Category : Emetic

Synonyms : Cupric sulphate, Blue vitriol

It contains not less than 98.5 per cent and not more than 101 per cent of $CuSO_4 \cdot 5H_2O$.

Preparation :

It is prepared by treating granulated copper in the presence of air with sulphuric acid. The oxygen of air assist the reaction. The solution is filtered and evaporated to crystallisation, crystals of copper sulphate separates out.

$$2Cu + 2H_2SO_4 + O_2 \longrightarrow 2CuSO_4 + 2H_2O$$

It is also prepared by roasting copper containing sulphide ore in presence of air or by heating copper in a furnace with sulphur. The mixture of copper sulphate and CuO formed and is treated with dilute sulphuric acid. The resulting solution is filtered, concentrated and copper sulphate crystal separates out.

Properties :

(1) It exist in the form of deep blue, tridinic crystals of the pentahydrate or as blue crystalline granules or powder.

(2) It is soluble in water, boiling water and insoluble in alcohol.

(3) Its aqueous solution is acidic to litmus paper and form blue green colour.

(4) At higher temperature it decomposes in to SO_2, oxygen, and black cupric oxide.

$$2CuSO_4 \longrightarrow CuO + 2SO_2 + O_2$$

Identification : It gives reactions of copper and sulphate.

Test for purity : It has to be tested for lead, zinc, Fe, As, acidity and clarity of solution.

Assay : The assay of copper sulphate can be performed by iodometry titration method.

An accurately weighed quantity of copper sulphate is dissolved in water and treated with excess of potassium iodide in presence of acetic acid. Cupric iodide is first formed in presence of acetic acid.

$$CuSO_4 + 2KI \longrightarrow K_2SO_4 + CUI_2$$

Cupric iodide is unstable and decomposes to cuprous iodide and free iodine.

$$CuI_2 \longrightarrow Cu_2I_2 + I_2$$

This reaction is reversible, the backward reaction may occur. The liberated free iodine is titrated with standard 0.1N sodium thiosulphate solution using starch as an indicator. The titration is continued until faint blue colour persists. 2 g of potassium thiocyanate is added toward the end point. This converts the small quantity of cuprous iodide in to cuprous thiocyanate and prevent the backward reaction. The tiration is continued until the blue colour disappears.

$$I_2 + 2Na_2S_2O_3 \longrightarrow Na_2S_4O_6 + 2NaI$$

$$Cu_2I_2 + KCNS \longrightarrow 2CuCNS + 2KI$$

Factor : Each ml of 0.1N sodium thiosulphate is equivalent to 0.02497 g of $CuSO_4 \cdot 5H_2O$.

Storage : It should be protected from air, heat and moisture.

Uses :

(1) It is used as emetic in dose of 300 mg in 30 ml water .

(2) It is considered to be chemical antidote in phosphorus poisoning.

(3) It is externally used as an astringent and as a fungicide.

ANTIMONY POTASSIUM TARTRATE (B.P., U.S.P.)

Chemical formula : $C_4H_4KO_7Sb$

Molecular weight : 333.93 g/mole

Category : Emetic

Synonym : Tarter emetic

It contains 99.0 to 103.0 per cent of $C_4H_4KO_7Sb$.

Preparation :

It is prepared by mixing 5 parts of antimony trioxide with 6 parts of potassium hydrogen tartrate in a fine paste. This paste is kept aside for a day. It is then boiled with water for fifteen minutes with constant stirring. The liquid is filtered hot and the filtrate is left for crystallisation. The crystals are collected and dried at atmospheric temperature.

$$KHC_4H_6O_6 + Sb_2O_3 \longrightarrow C_4H_4KO_7Sb + H_2O$$

Properties :

1. It occur as colourless crystals.
2. On exposure to air crystals effloresces.
3. It is odourless and sweet in taste.
4. It is soluble in water and insoluble in alcohol.

Identification : It gives reactions of potassium and antimony.

Test for purity : It has to be tested for lead, As, acidity and alkalinity.

Storage : It should be stored in a well closed containers.

Uses : It is used as emetic because of its irritant action on gastric mucosa.

9.3 HAEMATINICS

9.3.1 Introduction

Vitamins and minerals such as iron, copper, cobalt, vitamins A, B12, B6, C, E, riboflavin, nicotinic acid and various haemopoietic factors (erythropoietin, colony-stimulating factors, CSFs etc.) are essential for normal production of blood cells. The process of blood cellular components formation is called haematopoiesis. The main components of the haemopoietic systems are the blood, bone marrow, lymph nodes and thymus, with the kidney, liver and spleen as important accessory organs. All cellular blood components are derived from haematopoietic stem cells. Among the several nutrients required for haematopoiesis, the most important nutrients are iron, B_{12} and folic acid. Deficiency of any of these substances may be associated with defective erythropoiesis, anaemia and associated morbidity.

Iron has several vital functions in the body. It participates in a wide variety of metabo processes, including oxygen transport, DNA synthesis, and electron transport. Iron required for the production of red blood cells (a process known as erythropoiesis), and it is also part of haeemoglobin (that is the pigment of the red blood cells) that binds to the oxygen and thus facilitates its transport from the lungs via the arteries to all cells throughout the body. About 70% of iron in the body is bound to haemoglobin in red blood cells. The rest is bound to other proteins (transferrin in blood or ferritin in bone marrow) or stored in other body tissues. When red blood cells die, their iron is released and carried by transferrin to the bone marrow and to other organs such as the liver and spleen. In the bone marrow, iron is stored and used as needed to make new red blood cells. Once the oxygen is delivered the iron (as part of haemoglobin) binds the carbon dioxide which is then transported back to the lung from where it gets exhaled. Iron is also involved in the conversion of blood sugar to energy.

Vitamin B_{12} and folic acid are essential for DNA synthesis and cell proliferation. The main manifestation of vitamin B_{12} or folate deficiency is megaloblastic haemopoiesis in which there is marked disorder of eration and defective erythropoiesis. The principal cause of vitamin B_{12} deficiency is decrease absorption of the vitamin due to either to lack of intrinsic factor or to condition which interfere with its absorption in the ileum.

Haematinics are the substances required in the formation of blood, and are used in the treatment of anaemia. The main haematinics are Iron, Vitamin B_{12} and folic acid.

Its deficiency can lead to anaemia. In cases of haematinic deficiency, haematinics can be administered as medicines, in order to increase the haemoglobin content of the blood.

The normal range for haemoglobin is : For men, 13.5 to 17.5 grams per deciliter. For women, 12.0 to 15.5 grams per deciliter.

9.3.2 Iron as a Haematinics

The body of a 70 kg man contain about 4 g of iron, 65% of which circulates in the blood as haemoglobin. About one half of the remainder is stored in liver, spleen and bone marrow as ferritin and haemosidern. The iron in these molecules is available for fresh haemoglobin synthesis. The rest, which is not available for haemoglobin synthesis, is present in myoglobin, cytochromes and various enzymes.

Physiological functions of iron :

1. The primary function of iron is to form haemoglobin.
2. It is necessary for the formation and maturation of RBC.
3. It s responsible for the transport of oxygen in the form of oxyhaemoglobin.
4. Cytochrome is an iron containing enzyme. It is concerned with the oxidation of metabolites in the cell.

5. Myoglobin of muscle is an iron containing chromoprotein. It combines with O_2 and acts as an oxygen store for muscle.
6. The chromatin of the nucleus contains iron and thus helps in the functioning of nuclei.

Iron Absorption :

The site of iron absorption is the duodenum and upper jejunum of intestine.

In diet usualy iron present in two forms – haeme and Non haem/ Inorganic

- Haem form – minor form of dietary Iron but absorbed better without any transporter.
- Inorganic form whiich is present most abundantly in diet as ferric form but absorbs lesser extent. It get converted to ferrous form in Intestine for absorption and it needs transporter namely Divalent metal transporter (DMT1) and Ferroportin (FP).

When body doesn't have enough of the mineral iron , it results in iron deficiency anemia. It is the most common type of anemia, and it occurs when level of red blood cells (RBCs) in blood is lower than normal. This protein is responsible for carrying oxygen to our body's tissues, which is essential for tissues and muscles to function effectively. When there is not enough iron in blood stream, the rest of body can't get the amount of oxygen it needs.

9.3.3 Causes for Iron Deficiency Anemia

Iron deficiency is the most common cause of anemia. There are many reasons why a person might become deficient in iron. These include :

(i) Inadequate iron intake : Eating too little iron over an extended amount of time can cause a iron deficiency inour body. Foods such as meat, eggs, and some green leafy vegetables are high in iron. Iron is essential during times of rapid growth and development, pregnant women and young children may need even more iron rich food in their diet.

(ii) Pregnancy or blood loss due to menstruation : The most common causes of iron deficiency anemia are heavy menstrual bleeding and blood loss during childbirth.

(iii) Internal bleeding : Certain medical conditions can cause internal bleeding, which can lead to iron deficiency anemia. Examples include an ulcer in stomach, polyps in the colon or intestines, or colon cancer. Regular use of pain relievers, such as aspirin, can also cause bleeding in the stomach.

(iv) Inability to absorb iron : Certain disorders or surgeries that affect the intestines can also interfere with how your body absorbs iron. Even if you get enough iron in your diet, celiac disease or intestinal surgery, such as gastric bypass, may limit the amount of iron your body can absorb.

9.3.4 Iron Preparations

1. Oral preparations :

- Ferrous sulphate
- Ferrous gluconate
- Ferrous Fumarate

Adverse effects of oral iron therapy : Epigastric pain, Heart burn,Vomiting, Staining of teeth Metallic taste, Constipation.

2. Parenteral preparations :

Injectables are recommended when oral is not tolerated, failure to absorb iron, or in case of severe deficiency with chronic bleeding.

Examples : Iron Dextran, Iron sorbital citric acid complex

Adverse effects of Injectables : Pain, swelling, or redness at the injection site may occur, fever, headche, joint pains, metallic taste in mouth.

FERROUS SULPHATE (I.P., B.P.)

Chemical formula : $FeSO_4 \cdot 7H_2O$

Molecular weight : 278.0 g/mole

Category : Haematinics

Synonym : Green vitriol

It contains not less than 98.0 per cent and not more than 103.3 per cent of $FeSO_4 \cdot 7H_2O$.

Preparation :

It is obtained by dissolving Fe, FeO or $FeCO_3$ in excess of dilute H_2SO_4. After the effervescence ceases, the liquid is filtered, concentrated and cooled. The green crystal of Ferrous sulphates are formed which is separated by filtration and dried at room temperature.

$$Fe + H_2SO_4 \longrightarrow FeSO_4 + H_2\uparrow$$

$$FeO + H_2SO_4 \longrightarrow FeSO_4 + H_2O$$

$$FeCO_3 + H_2SO_4 \longrightarrow FeSO_4 + H_2O + CO_2$$

Ferrous sulphate forms pale green, monoclinic prism of heptahydrante, $FeSO_4 \cdot 7H_2O$.

Properties :

(1) It is light green coloured crystalline solid highly soluble in water.

(2) It is an efflorescent compound and when exposed to air for long time is oxidized to give brown colour of ferric salt.

(3) Ferrous sulphate when heated, decomposes to yield ferric oxide, sulphur oxide, and sulphuric acid

$$2(FeSO_4 \cdot 7H_2O) \longrightarrow Fe_2O_3 + SO_2 + H_2SO_4 + 13H_2O$$

Identification :

It gives reactions which are characteristic of iron and sulphate.

Test for purity :

It has to be tested for acidity, arsenic, copper, heavy metals and basic sulphates.

Assay :

It is assayed by cerrimetric method of titration in which ferrous sulphate is titrated against 0.1 M cerric ammonium sulphate. Cerric ammonium sulphate acts as an oxidizing agent which oxidizes the ferrous sulphate into ferric sulphate and itself gets reduced into cerrous sulphate and ammonium sulphate in presence dilute sulphuric acid. Ferroin is used as an internal indicator.

At the end point the red colour changes to light blue colour

$$2\,[Ce(SO_4)_2,\ 2(NH_4)_2SO_4] + 2\,FeSO_4 \longrightarrow Fe_2(SO_4)_3 + 4(NH_4)_2SO_4 + Ce_2(SO_4)_3$$

Cerric ammonium sulphate	Ferrous Sulphate	Ferric Sulphate	Ammonium Sulphate	Cerrous Sulphate

Factor : Each ml of 0.1 N cerric ammonium sulphate is equivalent to 0.0278 g of Ferrous Sulphate.

Storage : It should be stored in a well closed containers.

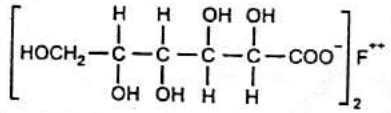
Uses : It used as a haematinic i.e., it promote the formation of haemoglobin in anaemias caused due to iron deficiency.

FERROUS GLUCONATE (I.P., B.P.)

Chemical formula : $C_{12}H_{22}FeO_{14} \cdot 2H_2O$

Molecular weight : 482.2 g/mole

Category : Haematinics



It is having not less than 95 per cent of $C_{12}H_{22}FeO_{14} \cdot 2H_2O$ which is calculated with reference to the substance dried at 105°C for 5 hours.

Preparation :

The preparation of ferrous gluconate involves two steps :

Step 1 : Preparation of gluconic acid

Gluconic acid is prepared by oxidation of glucose.

$$C_6H_{12}O_6 \xrightarrow{[O]} CH_2OH(CHOH)_4COOH$$

Gluconic acid

Step 2 : Preparation of ferrous gluconate :

In this step, gluconic acid is treated with barium chloride solution which is then treated with ferrous sulphate solution. Barium sulphate precipitates out and is removed by fiteration. Filtrate is evaporated and cooled, ferrous gluconate crytallises out from filtrate. ferrous gluconate is having two molecules of water of crystallisation.

$$FeSO_4 + [CH_2OH(CHOH)_4COO]_2Ba \longrightarrow [CH_2OH(CHOH)_4COO]_2Fe{\cdot}2H_2O + BaSO_4(ppt)$$

Properties :

(1) It is a fine yellowish-grey or pale greenish-yellow powder or granules having a slight odour resembling that of burnt sugar.

(2) It is soluble with slight heating in water and practically insoluble in ethanol.

Identification :

It gives reactions which are characteristic of ferrous ion and gluconic acid.

Test for purity :

It has to be tested for acidity, arsenic, barium, heavy metals, ferric, chloride, sulphates, oxalic acid, dextrose, sucrose and loss on drying.

Note : Ferrous gluconate has to be tested for ferric because a ferrous compound if kept open, it gets oxidised in to ferric by the oxygen or air.

Storage : It should be stored in a well closed containers, which are protected from light.

Uses :

If it finds use as a haematinic, it is regarded to cause less side effect than other ferrous salt including ferrous sulphate.

VITAMIN – B_{12} AS A HAEMATINICS

Daily Requirement : 1 – 3 mcg (Pregnancy and Lactation 3 – 5 mcg)

Preparations :

Cyanocobalamin

Hydroxocobalamin

Methylcobalamin

Uses of vitamin B_{12} :

1. Treatment and prophylaxis of vitamin B_{12} deficiency (megaloblastic anemia).

2. Vitamin B_{12} injection in pernicious anemia (condition where vitamin B_{12} is not absorbed from the stomach).

FOLIC ACID AS A HAEMATINICS

Daily requirement : 0.2 mg per day (0.8 mg in pregnancy and lactation)

Preparations

- Folic acid
- Folinic acid : active form of folic acid

Therapeutic uses :

- Megaloblastic anemias due to folic acid deficiency
- As supplement during pregnancy
- To prevent deficiency : Malabsorption syndromes,

Antiepileptic therapy,

Methotrexate toxicity.

9.4 ANTIDOTES

According to WHO "Antidotes are defined as a therapeutic substances used to counteract the toxic actions of a specified xenobiotics".

An antidote is an agent which counteracts a poison. In the treatment of acute poisoning most patients require only supportive and symptomatic therapy. The active removal of poisons from the stomach by gastric lavage or emesis induction is done by the administration of substances like activated charcoal by mouth to reduce the absorption.

9.4.1 Mechanism of Action of Antidotes

Antidotes act by different mechanism. The mechanisms of action of antidotes are given below :

(1) Complex formation.
(2) Metabolic conversion.
(3) Prevention of toxic metabolite formation.
(4) By changing the physio-chemical nature of toxicant.

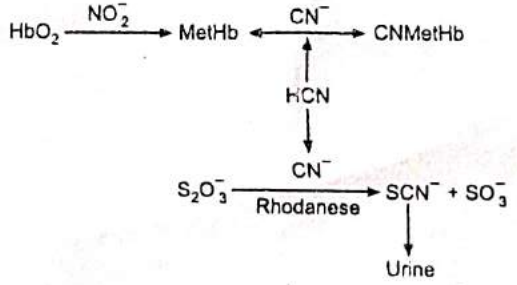
Depending on their action, antidotes are classified as :

1. Chemical Antidotes : Chemical antidotes are the agents interacts with a poison and changes its chemical nature to form a harmless substance. For example, sodium thiosulphate which changes toxic cyanide to the non-toxic thiocyanate; sodium calcium edetate chelates agents used for heavy metal poison.

2. Physiological Antidotes : Physiological antidotes acts by producing the effect opposite to that of poison. Sodium nitrite is a physiological antidote which converts haemoglobin into methaemoglobin into order bind with cyanide

Both Sodium nitrite and Sodium thiosulphate are used in conjunction with each other in cyanide poisoning.

Mode of action : Sodium nitrite and Sodium thiosulphate are administered sequentially in cyanide poisoning, as their combined effects are synergistic compared to either agent alone. Cyanide exerts its toxicity by combining with the cytochrome oxidase enzymes containing iron in the ferric state, to which cyanide has a great affinity and subsequently interrupting cellular respiration. In the presence of sodium nitrites, haemoglobin is converted to methaemoglobin. This complex has a higher binding affinity for cyanide than the cytochrome oxidase complex and removes cyanide from the cytochrome oxidase forming cyano-methaemoglobin regenerating cytochrome function. The resultant cyano-methaemoglobin in the presence of sodium thiosulphate is converted by rhodanase to thiocyanate, which is renally excreted. The methaemoglobin is then reduced via methaemoglobin reductase to haemoglobin.



(3) Mechanical Antidotes : Mechanical antidotes which prevent the absorption of poison into the body.

For example : Activated charcoal

Mode of action : Activated charcoal absorbs the poison prior to absorption across intestinal wall. This ensures a very high adsorptive capacity for a wide range of compounds which are often encountered in accidental and deliberate poisonings. When administered orally, activated charcoal minimises the extent of systemic absorption of the poison in the gastrointestinal tract by adsorbing the toxin onto itself, thereby reducing or preventing

systemic toxicity. Activated charcoal is contraindicated when corrosive agents have been ingested.

9.4.2 Classification of Antidotes

Antidotes are classified based on their mode of action.

Antidotes

Physiological Antidotes	Mechanical Antidotes	Chemical Antidotes
Act by producing the effect opposite of that of poison.	It prevents the absorption of poison into the body.	It acts by combining with the poision and thus changes the chemical nature of the poison.
Example : Sodium nitrite converts haemoglobin into methaemoglobin into order to bind with cyanide.	Example : Activated charcoal absorbs the poison prior to the absorption across the intestinal wall.	Example : Sodium thiosulphate which changes toxic cyanide to the non-toxic thiocyanate.

SODIUM THIOSULPHATE

Chemical formula : $Na_2S_2O_3 \cdot 5H_2O$

Molecular weight : 248.17 g/mole

Category : Antioxidant, sequestrant, antidote to cyanide poisoning

Synonym : Sodium hyposulfite

I. **Preparation :**

Preparation of sodium thiosulphate consists of three steps :

It is commonly prepared from sodium carbonate, sulphur dioxide and sulphur.

Step 1 : Preparation of sodium bisulphite.

Sodium carbonate is reacted with sulphur dioxide in presence of water to sodium bisulphite.

$$Na_2CO_3 + SO_2 + H_2O \longrightarrow 2NaHSO_3 + CO_2$$

Sodium carbonate Sodium bisulphite

Step 2 : Preparation of sodium sulphite

Sodium bisulphite is again treated with sodium carbonate to give sodium sulphite.

$$2NaHSO_3 + Na_2CO_3 \longrightarrow 2Na_2SO_3 + CO_2 + H_2O$$

Step 3 : Preparation of sodium thiosulphate

Sodium sulphite obtained in the previous steps is boiled with powdered sulphur to give sodium thiosulphate

$$Na_2SO_3 + S \longrightarrow Na_2S_2O_3$$

The resulting solution is subjected to evaporation and centrifugation to get the crystals of sodium thiosulphate.

II. Sodium thiosulphate can also be prepared by reacting sodium hydrosulphide with sodium bisulphite.

$$NaHS + NaHSO_3 \longrightarrow Na_2S_2O_3 + H_2O$$

Properties :

1. It is coarse and crystalline powder.
2. It is colourless, odorless and alkaline in taste.
3. It is soluble in water and practically insoluble in alcohol.
4. It is deliquescent in moist air.

Identification :

It gives reactions of sodium and thiosulphate.

Test for purity :

It has to be tested for arsenic heavy metal, calcium, chloride, sulphate, sulphite and sulphide.

Assay : The assay of sodium thiosulphate is based on iodimetric titration.

Dissolve about 0.8 g of the dried sodium thiosulphate was accurately weighed and dissolved in about 30 ml of water and titrate with 0.1 N iodine solution using starch as the indicator. 3 ml starch solution is added towards the end point. The approach of end point can be recognised by yellow colour of iodine, which gets discharged by shaking for few seconds.

$$2Na_2S_2O_3 + I_2 \longrightarrow Na_2S_4O_6 + 2NaI$$

Factor : Each ml of 0.1 N iodine is equivalent to 0.02482 mg of $Na_2S_2O_3$.

Storage : It should be stored in a well closed containers.

Uses :

1. It is used as antidote in cyanide poisoning.
2. It is used in the treatment of skin infection such as dermatophytosis.

Impurities

* **Impurities :-**

A compound is said to be impure if it is having "foriegn matter", i.e impurities.

Sources of Impurities :-

① **Raw materials :-**

Impurities known to be associated with these chemicals may be carried through the manufacturing process and contaminate the final compound. for Example, rock salt contains small amounts of 'Calcium sulphate & 'Mgso4' mg Cl$_2$', so that sodium chloride prepared from this source will almost certainly contains traces of Calcium & mg compounds.

Impurities such as arsenic, pb heavy metals etc.. are present in raw materials & hence are found in substances ∴ Becomes necessary to use pure chemicals & substances as raw materials for the manufacturing process.

Ex:-1 :- Copper sulphate may be prepared by the action of sulphuric acid on copper turnings.

$$Cu + 2H_2SO_4 \rightarrow CuSO_4 + 2H_2O + SO_2$$

Cu turnings are known to have 'iron & Arsenic' as impurities these impurities may be present in negligible quantities. If appreciable Quantities are present in the raw materials they may enter the final products ($CuSO_4 \cdot 5H_2O$)" due to this I.P discribes limit of tolerence for arsenic as impurity to be not more than 8 parts per million in 'Cu sulphate'. similarly, it prescribes a limit for iron as impurity.

* Reagents used in manufacturing process :—

If Reagents used in the manufacturing process are not completely removed by washing these may find entry into the final products.

Ex:-1 :— Ammoniated Hg may be prepared by adding a solution of mercuric chloride to dilute Ammonia solution.

$$HgCl_2 + 2NH_4OH \longrightarrow NH_2HgCl + NH_4Cl + 2H_2O$$

(Soluble) (Soluble) (Ammoniated Hg ppt) (Soluble)

The ppt of Ammoniated mercury (final product) contains Ammonium hydroxide ∴ this ppt is washed with cold water to remove ammonium hydroxide. If it is not removed completely by washing with water, the final product may contain is it ammonium hydroxide as impurity.

* Intermediate products :—

There are some intermediates which are produced during the manufacturing process, sometimes these intermediate may be carried through to the final product.

Ex:- potassium Iodide is prepared by reacting iodine with KOH

$$6KOH + 3I_2 \longrightarrow 5KI + KIO_3 + 3H_2O$$

The resulting solution is first evaporated to dryness & then heated with charcoal

$$KIO_3 + 3C \longrightarrow KI + 3CO$$

If the intermediate product KIO_3 is not completely converted into KI, then it may be carried through to the final product as an Impurity.

* Manufacturing Hazards :-

Even in a well-run manufacturing house, certain hazards exist which can give rise to product contamination.

(a) particulate contaminations :-

The presence of unwanted particulate matter can arise in a number of ways like accidental inclusion of dirt, or glass, porcelain, metallic & plastic fragments from sieves, granulating, tabletting & filling machines or even from product containers.

(b) process errors :- The limits of mechanical efficiency of "mixing, filling, tabletting, sterilising" & other equipment can lead to minor variation & very occasionally gross error.

⇒ Special care is essential to avoid mixing & "filling errors in the preparation of low dosage (5mg & less) forms, such as tablets & capsules of highly potent medicaments & analytical standards etc".

(c) Cross-contamination :- Manufactures of penicilin preparations in the United states are required by the "food & drugs administration (FDA)" to institute adequate control of the manufacture, handling, storage of drugs.

⇒ the applications of special limit test places a check on contamination By "pencillin of other products manufactured on the same premises".

(d) Microbial contamination :- A few materials are self-sterilising, But many products capable of antibacterial antifungal agents if microbiological spoilage of the product is to be Completely avoi-ded.

* Atmospheric contaminations :-

In Industrial areas, atmosphere is contaminated with dust particles AlOH, silica glass particles, porcelain particles plastic fragments etc... & some gases like hydrogen sulphide, SO_2 & black smooke.

Ex:- Sodium hydroxide absorbs atmospheric CO_2

$$2NaOH + CO_2 \longrightarrow Na_2CO_3 + H_2O$$

B/z of this reaⁿ, NaOH should not be Exposed for a long duration during it's manufacture. B/c of this reason, I.P has prescribed that sodium OH shouldn't contain more than 3% of Na_2CO_3

* Purification of Impurities :-

(a) Washing :- When water soluble substances have to be washed away & a water insoluble substance is needed.

Ex:- the prepared Chalk Obtained from required to have not < 97% of $CaCO_3$ on dry basis while basis ppt $CaCO_3$ as water insoluble subs is required to have not < 98.5% of $CaCO_3$

(b) Drying :- Inorganic chemicals may be generally dried in air, Special precautions have to be taken to exclude dust. When anhydrous Chemicals are required (or) Expensive chemicals are manufactured on a small scale, needs care & precaution performed under Vaccum.

(c) Recrystallization :- It has been the most common method for purifying soluble salts.

(d) Sublimation :- The application of this method of purification has been applicable to a very few substance e.g :- Arsenic trioxide, Iodine, $HgCl$, mercurious Chloride & Sublimated Sulphur.

* ~~purification Test Methods~~ :- Test for purity

* Description :-

1. Colour, Odour, Taste :- When other tests for purity are not available, then the tests of Odour, colour etc..

2. Solubility :- Solubility of the substances in diff solvents, determining of melting & Boiling points for organic substances, Optical rotation for optically active sub & refractive index for liquids, have been some reliable values, which can reveal the purity of substances.

3. Humidity :- Estimation of the moisture (or) humidity content of some crude drugs provide valuable information about the conditions of their storage & in turn about their therapeutic potency.

4. Ash :- Determination of ash in crude vegetable drugs, Organic compounds & some inorganic compounds, serves a good indication about the extent of impurities of heavy metals (or) minerals in nature.

5. Water insoluble Ash :- A substance which in the pure state gives a clear solution with a given solvent produces a turbid soluble in the presence of insoluble impurities.

* Acidity, alkalinity & pH :-

Substances prepared from chemical rean which are involving acids & alkalies often have considerable amounts of the acid (or) alkali as an impurity. Hence the tests for acidity, alkalinity have been of a great help for determining the extent of the impurity. Further, solution of certain substances are having a definite pH, at a given conc. The presence of impurity, will cause a change in the pH.

* Anions & Cations :- Many synthetic drugs, both inorganic & Organic may be prepared using strong acids like HCl, NO_3 etc... The presence of Chloride & sulphate ion have been common. Tests for these ions (anions) are usually carried out especially in testing synthetic Organic compounds.

* Arsenic :- The Arsenic content may be Expressed in parts per millions (P.P.M) Monographs on many substances are not including any test for arsenic, because of the advanced method in preparing acids.

⇒ (i) Size and frequency of the dose

(ii) difficulty of removing it from the substance during processing Barium sulfate is administered in dose up to 130g at a time & hence must not contain arsenic more than 1 P.P.M

Monograph

- Monograph is a complete description of a specific pharmaceutical which includes the following:-

1) **Title** :- The title is stated in English and refers to official name of compound. The synonyms are given as sub-titles.
eg. Title - Calcium carbonate synonym - precipitated chalk
Title - Sodium chloride synonym - common salt
Title - Sodium thiosulphate synonym - Hypo.

2) **Formula wt./ Molecular wt** :- The title is followed by chemical formula & molecular weight. eg., $MgCl_2 \cdot 6H_2O$, mol. wt. 202.
- For compounds with indefinite composition, we can't give mol. wt. & formula. eg Ferric ammonium citrate.

3) **Category** :- This describes the therapeutic / pharmacological / pharmaceutical application of the compound.
eg. antacid, laxative etc.

4) **Dose** :- are the quantities for the guidance of prescriber of the physician to have the desired therapeutic effects in adults. eg. $CaCO_3$ ⇒ 1-5 g.

5) **Description** :- This gives a physical description of the substances like state, nature, odour, colour, taste etc.
eg. $CaCO_3$ ⇒ fine, white, powder, odourless, tasteless.

6) **Solubility**:- This gives the information regarding the solubility of a compound.
eg. hot / boiling water, alcohol, glycerol / solvent ether.

Term	Solvent / 1 part of solute
very soluble	< 1 part
Freely soluble	1-10 parts
soluble	10-30 parts
sparingly soluble	30-100 parts
	... parts

7) Star
8) Ide
9) pH
10) Li
11) As
12) S
13) Th
Ap
Ap
Ap

7) Standard :- It is an important part of monograph, which specifies the quantitative purity of title compound, where compound is of definite composition.
eg. KBr is having not less than 98% of KBr calculated to dried substance.

8) Identification :- This usually involves specific chemical test / tests for identifying the substance. commonly used tests are colour reactions, precipitating agents etc.
eg. phenol + $FeCl_3$ solution gives violet colour.

9) pH :- The pH values given in the monograph are for the guidance of manufacturing pharmacist to develop various dosage forms.
eg. Calcium amino salicylate 2% w/v solution gives pH 6-8.

10) Limits for Impurities :- For different chemicals different limit tests have been included, as also different amounts of impurities
eg. acidity, alkalinity, pH, arsenic, chloride etc.

11) Assay :- It is a step-by-step description of a chemical analytical method for the active substance.
eg. titrimetry or Gravimetry is used for most inorganic compounds.

12) Storage - These directions are useful in preserving the activity of the chemical. This includes:
a) well-closed containers - for stable substances to protect from dust, dirt, insects etc.
b) Tightly-closed containers - for atmospheric sensitive substances. eg. reducing agents, hygroscopic sub
c) Light-resistant containers - For light-sensitive substances.
d) cool-place - For Thermosensitive compounds

13) The General notices & monographs are followed by Appendices section
Appendix-1 → describes apparatus used in different tests.
Appendix-3 → describes various chemical tests & assays.
Appendix-5 → some physical tests & determinations like loss on drying, pH determination, M.P. etc.
[illegible] involving cleaning Glassware

* HISTORY OF PHARMACOPIA

pharmacopia :—

pharmacopia means direction & requirements to "Prepare a drug (or) medicine (or) chemical substances" (or) pharmaceutical. list of medicinal drugs & their effects.

⇒ pharmacopia is a greek word derived from.

pharmakon → a drug, poicin → to make

⇒ It is published by Authority (rights to make decision) is the pharmacopia is the legislation of a country (law making)

* It sets (or) maintain standard, Quality of drug

pharmacopia → British (B.P) → published in "1864"
→ Indian (I.P) → published in "1955"
→ United states (USP) → "15th dec. 1820"

→ I.P has "7 editions"

Edition	Year	Supplementary (or) Addrendum Addition
I	1955	1960
II	1966	1975
III	1985	1985, 1991
IV	1996	2000, 2000 (Veternary), 2002, 2005
V	2007	2008
VI	2010	2012
VII	2014	2016, 2015

CONTENTS IN BRITISH PHARMACOPIA

Contents of Volume - I

* Notice
* Preface
* British pharmacopia Commission
* Introduction → Addition, Omissions, Technical changes
* General Notices
* Monographs → medicinal & pharmaceutical substances (A-P)

CONTENTS of Volume - II

* Notice
* General Notices

Monographs → medicinal & pharmaceutical substance

Contents in volume - III :-

* Notices
* General Notices
* Monographs
  ↓
formulated preparations
1. General Monographs
2. Specific "
3. Blood related products
4. Immunological "
5. Surgical materials

Contents of volume - IV

* Notices * General Notices
* Infrared Reference spectra

Appendics
↓
Contents of the application

CONTENTS IN INDIAN PHAMACOPIA

Contents in Volume - I

* Legal Notices
* Preface
* Acknowledgement
* Introduction
5. General Notices
* Monographs [A-P]

Contents in volume - II

* Monographs [Q-Z]
* Appendices
* Contents of Appendices
* Index

CONTENTS IN UNITED STATES PHARMACOPIA

CONTENTS

* People
* Preamble
* Admissions
* Notices
* Monographs
* General chapters
* Reagents
* Tables
* packing & storage
* USP Reference Standards
* clarity of solution
* Identification
* Melting Range
*

Contents in European pharmacopiea :-

* General Notices
* Methods of Analysis apparatus physical & physychochemical method
* Identification
* Limit tests
* Assays
* Biological tests
* Biological Assays
* Methods of the pharmacognosy
* pharmaceutical technical procedures
* Materials used for the manufacture of containers
* Reagents & standadard's

Monographs in Indian pharmacopia :-

(1) Title :- The title is stated in English and refers to the official name of the compound sometimes sub titles are given Eg :- "Calcium Carbonate" called as precipitated chalk

2. formula weight & molecular weight :-
following the title has been the chemical formula of the pure compound, with its molecular weight E.g :- "$MgCl_2 \cdot 6H_2O$" mol. wt 202.30

3. Category :- This describes the therapeutic or pharmacologic application of the compound. Some main categories for inorganic pharmaceuticals mentioned in the pharmacopia include composition "haematinic ; antacid, laxative ; pharmaceutical aid."

4. Dose :- are the quantities for the guidance of the prescriber or the physician to achieve the desired therapeutic effects in adults. Eg :- "$CaCO_3$ dose 1 to dosage strength."

5. Description :- this gives a physical description of the substance like crystalline (or) amorphous, nature, colour, odour, taste etc...
Eg :- $CaCO_3$ fine, white microcrystalline powder, odourless, tasteless

6. Solubility :- This usually given in water, sometimes in hot (or) boiling water, in alcohol, in glycerol, in solvent ether & sometime in other organic solvents, acids (or) alkali.

Descriptive Terms	Relative Quantities of solvent for 1 part of solute
Very soluble	less than 1 part
freely "	from 1 to 10 parts
Soluble	from 10 to 30 parts
Sparingly soluble	from 30 to 100 parts
Slightly soluble	from 100 to 1000 "
Very slightly soluble	from 1000 to 10,000 parts
Practically insoluble	more than 10,000 parts

7. Standard :- It is an important part of monograph, which specifies the quantitative purity of the title compound
Eg :- ① pottassium bromide is having not less than "98.0 % of KBr" Calculated with reference to the dried substance.

8. Identification :- This usually involve specific chemical test (or) tests for identifying the substance.
" phenol + $FeCl_3$ solution gives Voilet colour "

9. PH :- The pH value is the guidance of manufacturing pharmacist to develop various dosage forms & to avoid physiological complications
E.g :- "Calcium amino salicylate"

10. Limit for impurities :- for different chemicals different limit tests have been included as also different amounts of such impurities permissible for that chemical.

(11) Assay :- It is a step by-step description of a chemical analytical method for the active substance.

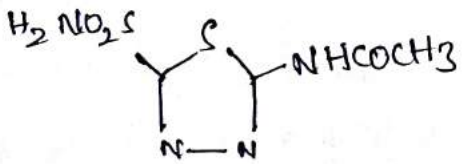
(12) Storage :- These directions are useful in preserving the activity of the chemical. Eg :- ferrous fumarate → store in a light resistant container

Cool	Cool	Room temperature	Warm	Excessive Heat
Any temperature not exceeding 8°C & usually b/w 2° & 8°C	Any temperature b/w 8° & 25°C	Temperature prevailing in working area	Any temperature b/w 20° & 40°C	Any temperature above 40°C

* Packaging storage and Labelling :-

In general labelling of drugs and pharmaceuticals is governed by drugs and cosmetics Act. In certain cases, additional information which must be stated on label is mentioned in the monograph.

Example of Monograph in (I.P) :-



Mol. wt. 222.24

$C_4H_6N_4O_3S_2$

Category :- Carbonic anhydrase inhibitor

Dose :- Initial dose 0.5g : subsequent doses, 0.25g every six hours

Description :- White or yellowish-white, crystalline powder odourless, tasteless

solubility :- Very slightly soluble in water, slightly soluble in alcohol ; practically insoluble in chloroform & in solvent ether.

* Standards :- Acetazolamide is N [5-sulphamoyl-1-1-3,4 thiadiazol 2-yl) acetamide. It contains not less than 98.0% & not more than 102.0% of $C_4H_6N_4O_3S_2$.

* Identification :- Titurate about 0.5g with 5 ml of water, made alkaline with 1ml of N sodium hydroxide ; add about 0.2g of zinc powder & 0.5 ml of Hcl acid mix well, H_2SO_4 by its characteristic Order.

* Light absorption :- weigh accurately about 0.2g & dissolve in 200 ml of boiling water, dilute to 900 ml with water, cool & add sufficient water to produce 1000.0 ml.

* Silver-precipitating substances :- Mix 5g with 250 ml of alcohol add 125 ml of water, 10 ml of nitric acid & 5 ml of 0.1N silver nitrate Stir it for 30 minutes & ammonium thiocyanate is required

* Heavy metals :- Not more than 20 % per million determined by method c, on 1.0g of dissolved in a mixture of 10 ml of N sodium hydroxide & 15 ml of water.

* Water :- Not more than 0.5% w/w

* Sulphated ash :- Not more than 0.1 %

* Assay :- weigh accurately about 0.4g & dissolve in 90ml of dimethyl - formamide. Titrate with 0.1 N tetrabutylammonium hydroxide, determining the end-point

* STORAGE :- Store in well-closed containers

PHARMACOPOEIA

USP

Indian pharmacopoeia	British pharmacopoeia	European pharmacopoeia
Volume -1 :- * legal notices * Preface * Acknowlegments * Introduction * general notices * Monographs (A-P) Volume -2 :- * Monographs (Q-Z) * Appendices * contents of Appendix * Index	1. general content Volume - I * Notices * preface * British pharmacopoeia commission * Introduction, omissions technical changes in the title * General notices * Monographs * Medicinal and pharmaceutical substances Volume -2 * Notices * General notices * Monographs medicinal and pharmaceutical substance Volume -3 * Notices * General Notices * Monographs * General monographs * specific monographs * Blood related products * Immunological products * Radiopharmaceutical Preparations * surgical materials * Homoeopathic Preparations Volume - IV :- * Notices * General Notices * Infrared reference spectra	(1). General notices (2). Methods of analysis * Apparatus * physical & physiochemical methods * Identification * Limit tests * Assays * Biological tests * Biological assays * Methods of pharmacognosy * pharmaceutical technical procedures (3). Materials used for the manufacture of containers and containers * Materials used for the manufacture of containers (4). Reagents * Reagents standard solutions, buffer solution * volumetric analysis (5). general texts * statistical analysis of results of biological assays and tests. * Residual solvents * Alcholimetric solvents * Assays of interaction * Table of physical Characstics of radionuclides mentioned in the european pharmacopia MONOGRAPS MONOGRAPS ON DOSAGE FORMS INDEX

Pharmacopoeia:-

It is a book of directions and requirement for the preparation of medicine, It is generally published by an authority Thus pharmacopoeia is a legislation of a country which sets standards and obligatory quality includes for drugs, raw materials used to prepare them and various pharmaceutical preparations. These regulations are presented separately in general and specific articles.

History of pharmacopoeia:-

Pharmacopoeia is derived from greek word pharmakon, a drug, or medicine and poieo; to make.

The first british pharmacopoeia (B.P) was established in 1864. It was include Monographs on benzoic acid, gallic acid, tartaric acid, tannic acid, camphor, lactose, sucrose and seven alkaloids along with their salts.

The USP was released on 15 December 1820

Indian Pharmacopoeia:-

* The first edition of indian pharmacopoeia of india 1955
* It was having a large no. of crude drugs and their preparations
* The third edition of the I.P published in 1985
* Addendum I to third edition has been published in 1989.
* The addendum I to the pharmacopoeia of India 1985 amends the indian pharmacopoeia 1985 and constitutes a part of Indian pharmacopoeia.

Indian pharmacopoeia, 1996, 2 volumes, 1182 p.:-

* The latest edition of indian pharmacopoeia was established 1996.
* The new edition, which supersedes the 1985 edition and its addenda, includes many new drugs and their dosage forms
* The contents are accommodated in two volumes as was the case with the earlier edition. It contains 1149 monographs and 123 appendices

Monograph:-

It is a complete description of specific pharmaceutical, which include nomenclature, classification, physical characteristics, dosage, purity, limits of impurities, Identification, assays and condition for storage.

Pharmacopocial monographs have been organised as described below:-

(1) Title:-

The title is stated in english and refers to the official name of the compound. some time subtitles are given

Eg:- calcium carbonate can also be called precipated chalk.
Milk of magnesia was called Magnesium hydroxide mixture

(2) Formula weight & molecular weight:-

* Following the title has been the chemical formula of the pure compound with its molecular weight

Eg:- $MgCl_2, 6H_2O$ Mol. wt. 202.30 ; $KMnO_4$ Mol. wt 158.03 etc.

* These two items are not given, provided the constituent chemistry is not known or the compound is of indefinite composition.

Eg:- iron ammonium citrate. formula and mol.wt not given

(3) category:-

* This describes the therapeutic (or) pharmacological (or) pharmaceutical application of the compound
* Some main categories for inorganic pharmaceuticals include. haematinic, antacid, laxative, astringent etc.

(4) Dose:-

* are the quantities for the guidance for the prescribers (or) physician to achieve the desired therapeutic effects in adults

Eg:- $CaCO_3$ dose 1 to 5 gm.

(5) Description:-

* This gives a physical description of the substance like crystalline amorphous nature, colour, odour, taste etc.

Eg:- $CaCO_3$ fine white microcrystalline powder, odourless tasteless.

(6) Solubility :-

* solubility is described in popular terms, which are defined in the pharmacopoeia under general notices.
* This is usually given in water, sometimes in hot (or) boiling water in alcohol, in glycerol, in solvent ethers and some time in other organic solvents, acids, (or) alkalis

Description terms	Relative quantities of solvent for 1 part of solute
Very soluble	less than 1 part
Freely soluble	From 1 to 10 parts
soluble	from 10 to 30 parts
Sparingly soluble	from 30 to 100 parts
slightly soluble	from 100 to 1000 parts
Very slightly soluble	from 1000 to 10,000 parts
Practically insoluble	More than 10,000 parts

(7) standard :-

* It is a part (Important) of monograph, which specifies the quantitative purity of the title compound where the compound is of definite composition
Eg :- pottasium bromide as having not less than 98.0 %. of KBr calculated with reference to the dried substance.

(8) Identification :-

* It is usually involves chemical test (or) tests for identifying the substance
* colour reactions, precipitating tests, and gas evolving reactions are commonly used for inorganic pharmaceuticals.

Eg :- phenol.

Phenol + $FeCl_3$ gives "violet colour"

(9) pH :-

* The pH valves given in the monograph are for the guidance of manufacturing pharmacist to develop various dosage forms to avoid physiological complications

Ex :- calcium amino salicylate 2 % w/v gives pH 6-8

(10) Limits for impurities!-

* For different chemical different limit tests have bee included as also different amounts of such impurities permissible for that chemical.
* They are various tests!- acidity (or) alkalinity, pH, specific impurities
* Limit tests for impurities are generally represented in parts per million by weight or as a percentage.

Assay!-

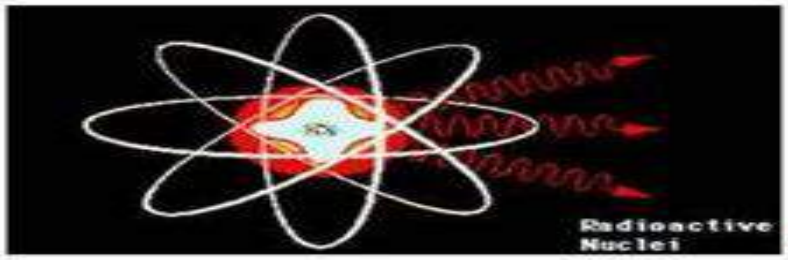
* It is a step-by-step of a chemical analytical method for the active substance.
* For most inorganic pharmaceuticals, titrimetric and gravimetric methods are used.

(12) Storage!-

* This is the last item under the monograph.
* These directions are useful in preserving the activity of the chemical.
* For inorganic pharmaceuticals, the pharmacopica uses these terms

(a) Well closed containers
(b) tightly closed containers (eg:- reducing agents, strong base)
(c) light-resistant containers.
(d) cool-place.
(e) single-dose containers.

Eg!- Ferrous fumarate - store in light resistant containers



RADIOPHARMACEUTICALS

Questions

1. Write a short note on radiopharmaceuticals/What are radiopharmaceuticals? Enumerate units of radioactivity.
2. Properties of alpha, beta and gamma rays/Note on behavioural properties of different radiations.
3. Define half life, radioisotopes.
4. Give an account of clinical applications of radiopharmaceuticals/Applications of radiopharmaceuticals in medicine. Give a brief account on the therapeutic and diagnostic applications of inorganic radiopharmaceuticals.
5. Give an account of precautions to be taken while handling and storage of radiopharmaceuticals or note on handling and storage of radioactive materials.
6. Discuss about measurement of radioactivity or S.N on GM counter. Explain working of GM counter or Note on scintillation counter. Write a note on GM counter. Give preparation, properties and uses of Barium sulphate.
7. Give uses of Sodium iodide [131], Iron [59 Fe], Cyanocobalamine [57 Co]/study of sodium iodide as radioisotope.

WHAT ARE RADIOACTIVE SUBSTANCES????

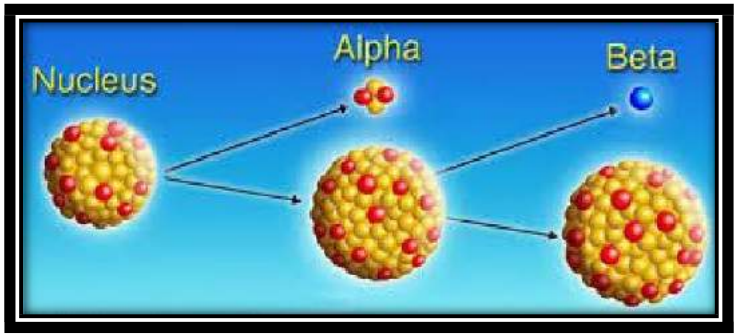
- ✓ Radioactive substances have a property of emitting rays or particles which affect the photographic plate. Forty radioactive elements are known which are arranged as Uranium series, Thorium series and Actinium series.

- ✓ The elements are known as radioactive because they are unstable and undergo decomposition along with emission of radiations or rays.

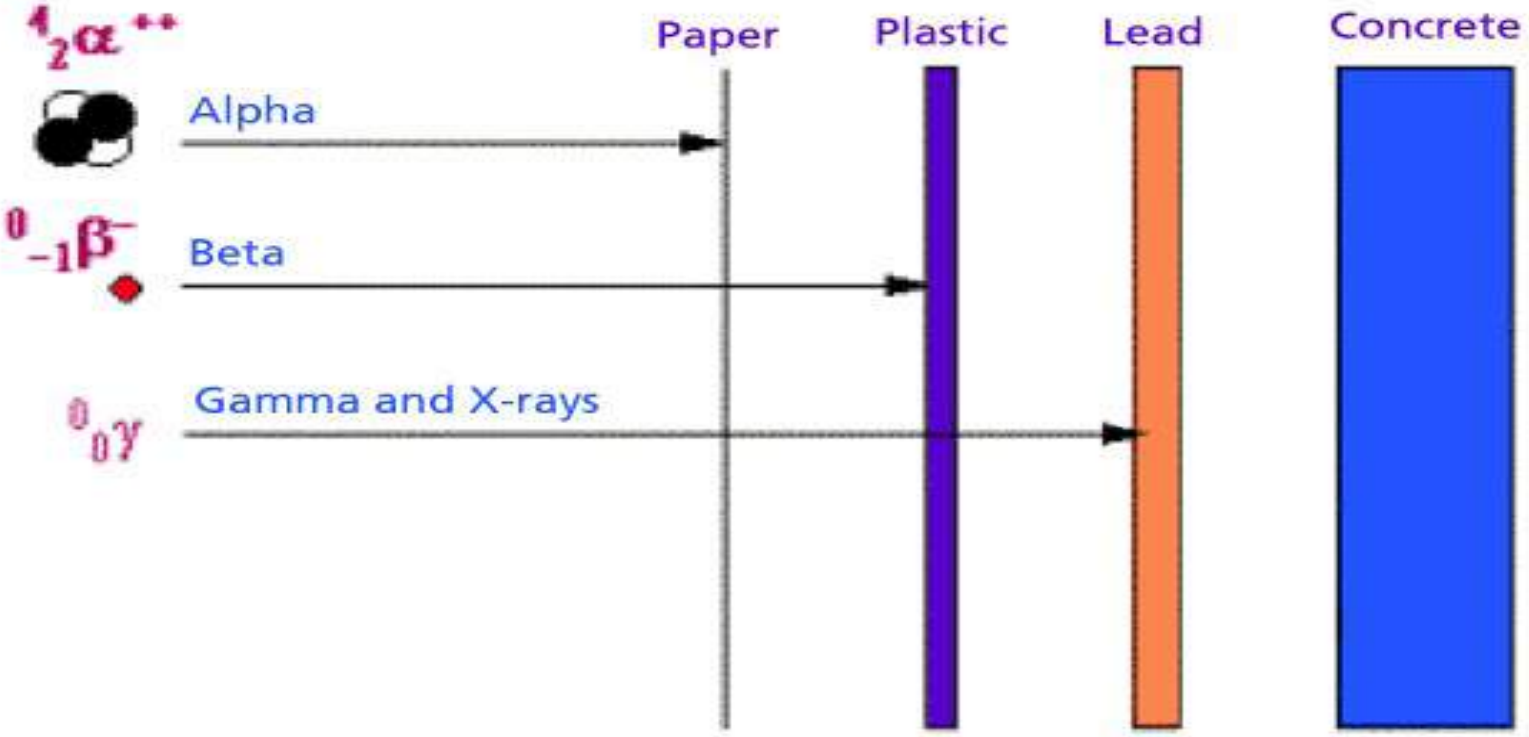
- ✓ The radiations or rays which are emitted are following:
  - ❑ Alpha rays
  - ❑ Beta rays
  - ❑ Gamma rays

- ✓ **Any nucleotide which is not radioactive in nature is regarded as stable. To be stable, a nuclide may possess appropriate energy.**

- ✓ **Those nuclides which undergo spontaneous nuclear change so as to attain stability by emitting radiations are called as radionuclides or radioisotopes.**



Penetrating Distances



Alpha rays

- These rays or particles have low penetrating power.
- They have positive charge and can be detected by a strong magnetic field.
- They carry **two positive charge**.
- They have a mass of **4 amu** (atomic mass unit)
- Heavy metals have capacity to emit such type of rays.
- All alpha particles are having the same energy.
- The penetrating power of alpha rays is less as compared to other emissions.

- **Because of low penetrating power of alpha particles, elements which emit alpha rays do not find use in biological applications because they cannot penetrate tissue.**

- $^{226}_{88}Ra \longrightarrow {}^{222}_{86}Rn + {}^{4}_{2}He$

Beta Rays:

- These have 2 types:

1. Electrically positively charged particles which are called 'positrons'
2. Electrically negatively charged particles which are called 'Negatrons'

- They have greater penetrating power than that of alpha rays.
- Beta particles have negligible mass.
- These particles are usually accompanied by gamma radiation. Beta particles have less ionizing power than alpha particles.

Gamma rays:

- These have been more penetrating than alpha and beta rays.
- They are having the same character as that of very short electromagnetic waves called X-rays.
- **They have no mass or charge.**
- Gamma rays are produced during disintegration of radioactive substances along with **beta radiation** and during nuclear fission.
- They are uncharged and have poor ionizing power.

Type of radiation emitted & symbol	Nature of the radiation formation, structure, relative mass, electric charge	Penetrating power (and speed), and what will block it (more dense material, more radiation is absorbed BUT smaller mass or charge of particle, more penetrating)	Ionising power - the ability to remove electrons from atoms to form positive ions, the process is called ionisation
Alpha particle radiation	**a helium nucleus of 2 protons and 2 neutrons, mass = 4, charge = +2, is expelled at high speed from the nucleus**	**Low penetration**, slowest speed ,biggest mass and charge, stopped by a few cm of air or thin sheet of paper	**Very high ionising power**, the biggest mass and charge of the three radiation's, the biggest 'punch' in ripping off electrons from molecules, other ions are formed
Beta particle	**high kinetic energy electrons**	**Moderate penetration**	**Moderate ionizing power**
Gamma	**Very high frequency electromagnetic radiation mass = 0, charge = 0, gamma emission often accompanies beta decay**	**Very highly penetrating**	**The lowest ionising power**

What are isotopes??

Types of Radionucleotides

1) Natural radionucleotides:

They include about 40 high atomic weight elements such as Uranium 238, Radium 226, which may be alpha, beta, or gamma emitters and also some moderate weight elements such as Potassium 40, Rubidium 87.

2) Artificial Radionucleotides

What are radiopharmaceuticals? Enumerate units of radioactivity.

❖ **Units of radioactivity**

1. **Curie (c) : Defined as quantity of any radioactive substance which undergoes the same number of disintegrations in unit time as of 1 g of radium and is equal to 3.7 x10^{10} disintegrations per second.**

2. **Roentgen: it is the unit of exposure 1R= 2.58 x 10^{-4} coulomb kg^{-1}**

3. **RAD: it is the unit of absorbed dose. Pharmaceutical dosage forms are described in RAD units.**

4. **REM: I t is unit of dose equivalent.**

5. **Exposure rate constant**

6. **RBE (Relative biological effectiveness): shows effect of radiation, alpha, beta and gamma on the biological system.**

Production of Radioisotopes:

They are produced as:

1) Reactor irradiation: Reactor is having an arrangement of fissionable material in a moderator, which slows down the fast neutrons to thermal energies. The fissionable material like uranium is taken in the form of rods which are arranged in a lattice pattern and hence the neutron flux is maximum in the centre where there is most uranium. A heavy water moderated reactor using enriched uranium is having a maximum flux of 10^{14} neutrons cm^{-2} s^{-1}

2) Cyclotron irradiation: While the reactors are able to produce a flux of neutrons and gamma rays, accelerating mechanisms can use many other types of bombarding particles which have been charged particles. They can be accelerated to high velocities so as to overcome the repulsive forces of the nucleus. The beam of energetic particles has been small and targets for irradiation have to be put in this beam. The number of samples that can be irradiated at a time has been limited and the yields has been low. But on the other hand many isotopes which otherwise cannot be produced in a reactor could be produced in a cyclotron.

Q: Note on handling and storage of radiopharmaceuticals

- Great care needs to be taken in handling and storage of radioactive materials for protecting people and personnel who handle it, from the harmful radiation they emit.
- Certain precautions have to be taken while working with detectors, tracer equipment, radio assay manufacturing or handling of radioactive materials.

- In order to have protection from hazards of radiation, radioactive materials must be stored in an area not frequently visited by people.
- **Shielding** may be required.
- Thick glass or Perspex containers provide sufficient shielding.
- To protect from gamma rays (high penetration power), **lead shielding** has to be used.
- The storage area must be regularly checked for radioactivity.

RADIOACTIVE LIQUIDS.

- Working area should not get contaminated with radioactive material.

- If radioactive liquid is to be handled, it must be carried in **trays with absorbent tissue paper**, so that any spillage will get absorbed by the paper.

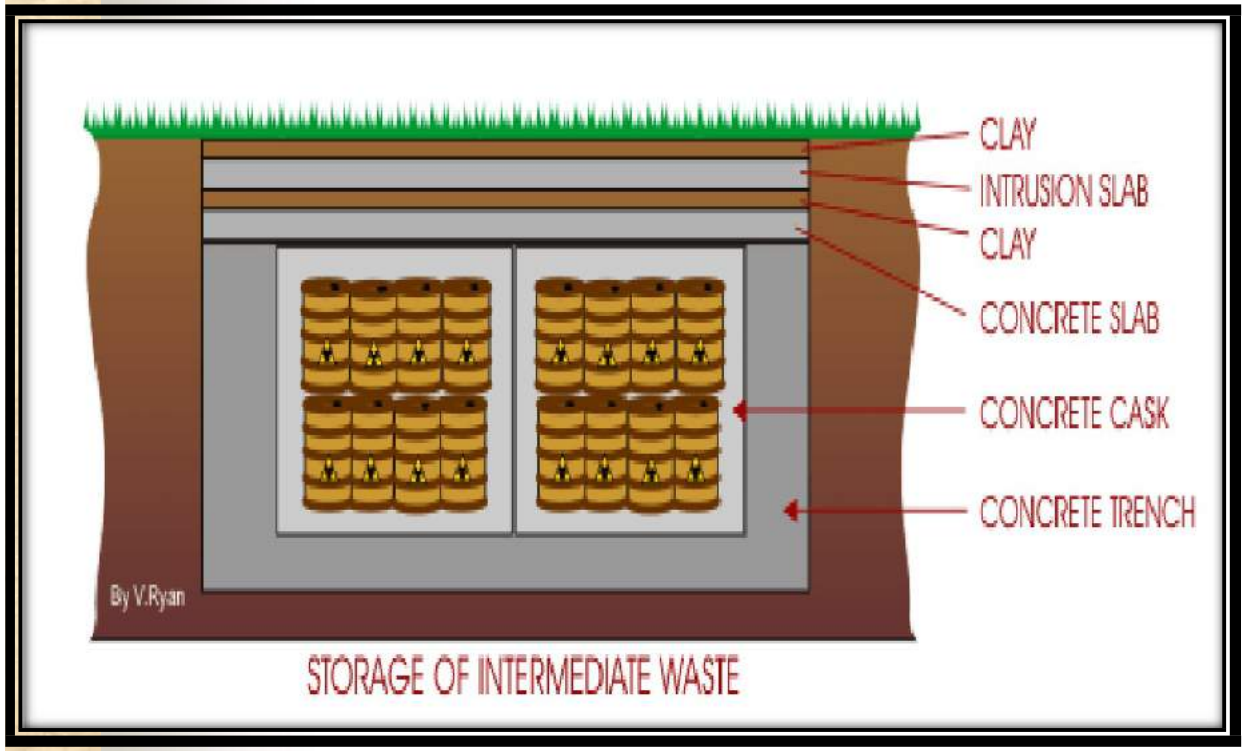
- **Rubber gloves** have to be used when working with radioactive liquids.
- **Pipettes** operated by mouth should never be used.
- Waste of radioactive material has to be stored till its activity becomes low and then only it should be disposed.

PRECAUTIONS While handling and storage of radioactive substances:

1. One should not touch the radioactive emitter with hand but it should be handled by means of **forceps.**
2. **Smoking, eating and drinking activities** should not be handled in laboratory where radioactive material is handled.
3. Sufficient protective clothing and shielding have to be used while handling of materials.
4. Radioactive materials have to be stored in suitable labelled containers, covered (shielded by lead bricks) and preferably in a remote corner.
5. Areas where radioactive materials are stored should be monitored and tested for radioactivity regularly.
6. **Disposal of radioactive materials should be carried out with great care.**

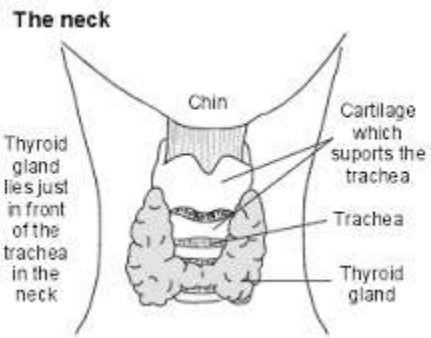
Strict requirements are prescribed by the department of Atomic energy (DAE) for the establishment of a radioactive facility in the hospital or pharmacy.

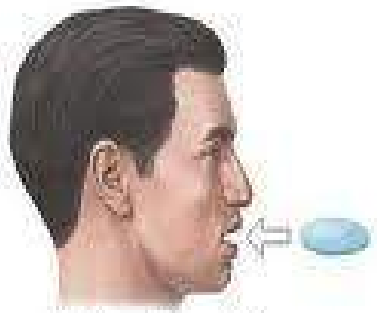
These include specifications for premises, storage space, working area, disposal protocol, training of personnel, periodic check on contamination or leakage.

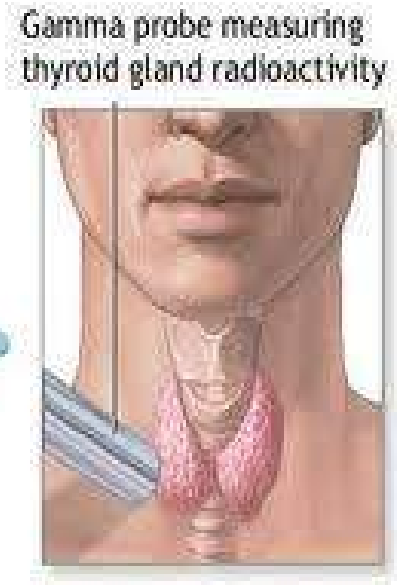


Give uses of Sodium iodide I-131

- Used as a **diagnostic aid** for studying the functioning of the **thyroid gland**.
- Used in ~~scanning the thyroid for determin~~ing the **size, position and possible tumour location.**
- **Used in the treatment of severe cardiac disease (Sodium iodide I-131), which reduces work load on heart.**
- **Radioactive iodine in thyroid carcinoma (cancer): The isotope is used most frequently after the surgical removal of cancer to treat any residual tumour tissues.**







Iron 59:

- ✓ Iron 59 is a beta and gamma emitting isotope.
- ✓ Used in diagnosis to study the iron metabolism and to study the red blood cell formation.
- ✓ The preparation is administered orally for studying the absorption of iron from GIT.
- ✓ Administered I.V to study incorporation of iron in formation of red blood cells.
- ✓ Used to study the formation and destruction of spleen, liver etc. from outside the body.

Applications of Radioisotopes

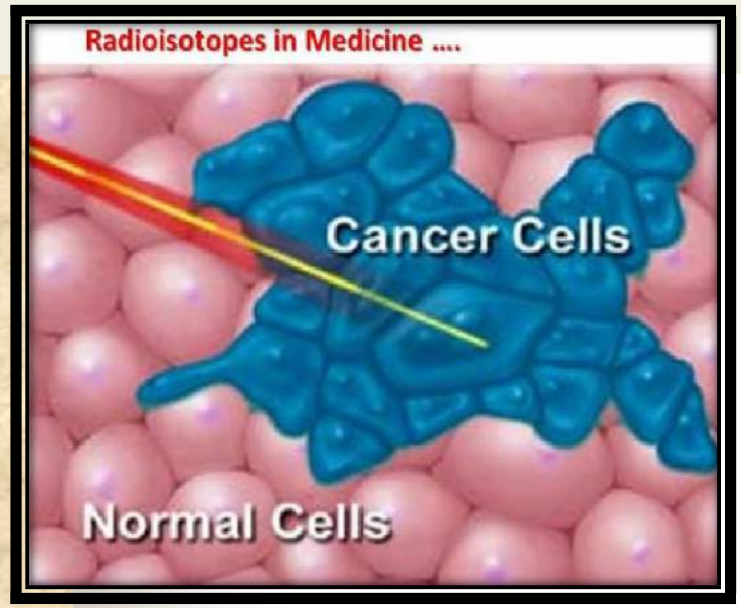
They find use in medicine in 4 different ways:

1. **Radioisotopes in Therapy (Emitted radiations used to destroy cells in condition like cancer)**

2. **Radioisotopes in Diagnosis (Radioactive tracers)**

3. **Research (Biological and medicinal studies by use of radioactive isotopes as tracers)**

4. **Sterilization (For sterilization of pharmaceuticals and surgical instruments)**



Applications:

Diagnostic applications: Radiopharmaceuticals are developed based on the ADME (absorption, distribution, metabolism, excretion) properties of the body. By administering a radiopharmaceutical to a patient, images of the targeted site can be produced by a gamma camera. The images can then be analyzed by the nuclear medicine doctor to detect any medical problems. Radiopharmaceuticals are most widely used to detect various forms of cancer. Depending on the site for diagnosis there is a specified route of administration.

Therapeutic use of Radiopharmaceuticals: Radioactivity can be used in medicine and pharmacy in different areas, the first being radiology, in which an external source of radioactivity passes through a patient and radiation is absorbed by more dense tissues and not by less dense tissues and an image is ultimately formed. The second is radiation therapy, which treats for tumors using an external source of radiation to try and ablate a tumor. This requires lots of radiation in very high doses. Nuclear medicine uses an internal source of radiation to be detected externally, unlike the two previously mentioned. A patient is injected with a radiopharmaceutical, which has a radioactive component that decays and a pharmaceutical component which takes it a desired organ.

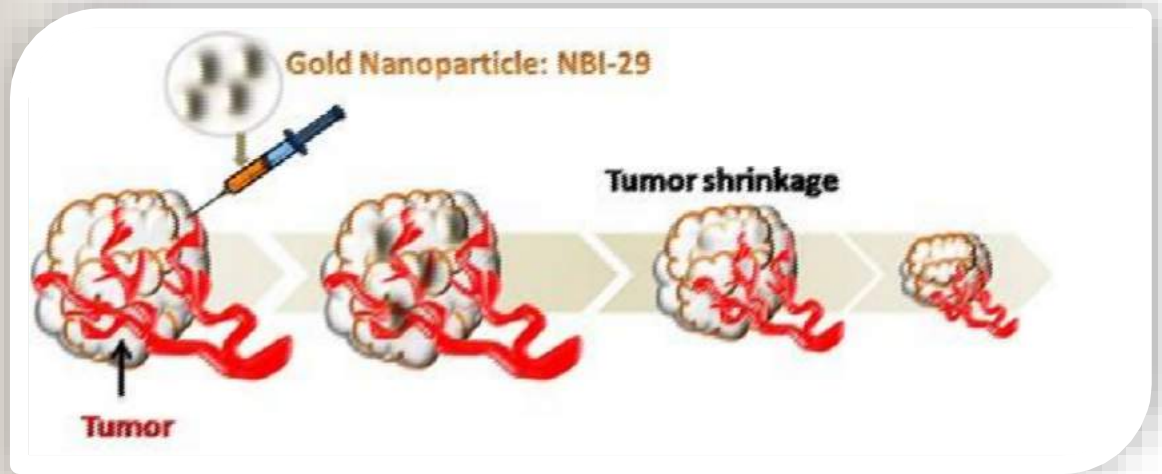
Radiopharmaceuticals can be used to destroy malfunctioning cells. This method of therapy is called radiotherapy. It can be used for both benign and malignant cancers. In order to destroy the diseased tissue, a radionuclide has to emit beta, alpha, or low energy conversion electron emitters. Beta radiation is effective for large tumors and alpha radiation is effective for smaller tumors.

I) In therapeutics:

- ✓ The therapeutically used radioisotopes have been found to depend mainly on their ability to **ionize atoms**.
- ✓ The energy measurement involved in radiation and resulting in ionization may be expressed in millions of electron volts called MeV.
- ✓ **The strength of alpha, beta and gamma rays in expressed in MeV.**
- ✓ All radiations bring about ionization of atoms in their paths.
- ✓ The radiation of short wavelength (gamma rays) is having high penetrating power than long wavelength (beta rays).
- ✓ **The greater the MeV of the rays, the more destructive it becomes to the surrounding tissues.**
- ✓ **RADIOPHARMACEUTICALS CAN DESTROY MALFUNCTIONING CELLS.**
- ✓ This method of therapy is called **radiotherapy**. It can be used for both benign and malignant cancers.

Examples:

- Gold (^{198} Au) is used in treatment of abdominal and pleural effusions associated with malignant tumours. It is given in the form of colloidal gold suspension.
- Gold (^{198} Au) also used in treatment of carcinoma of uterus and urinary bladder.
- Cobalt labelled cyanocobalamine (vitamin B12) is used in diagnosis of pernicious anaemia.
- **Sodium iodide** preparation finds use in treatment of **thyroid disorders**.
- **Calcium** is used to study bone structure and in **carcinoma of bone**.
- Strontium 90 is used in diagnosis of superficial carcinomas.



- ✓ Radioisotopes may be used internally or externally.
- ✓ If the radioisotope are used externally or used as implants in sealed capsule in a tissue, the dose could be terminated by removal or sources.
- ✓ If they are given internally, as unsealed sources, the dose cannot be stopped by the removal of the source.
- ✓ The total dose in therapeutic applications may be calculated on the basis of effective half life of the isotope, concentration of the isotope and the type and energy of the radiation emitted.

In diagnosis:

- **Radioactive tracers find use in medicine for diagnostic purposes.**

1. Labelled cyanocobalamine finds use for measuring the **glomerular filtration rate**.
2. **Ferric citrate injection** finds use for the diagnosis of **haematological disorders.**
3. Colloidal gold injection is used diagnostically to study blood circulation in liver.
4. **Sodium iodide injection** finds use in diagnosis of **proper functioning of thyroid gland**.
5. **Sodium iodohippurate** injection finds use in the study of **renal function**.
6. Sodium rose Bengal injection finds use as diagnostic agent to test liver function.

III) In research:

Excellent biological and medicinal studies have been carried out with radioactive isotopes as tracers.

IV) Sterilization:

- Excellent use is being made of the radiation constantly available from some strong radiation source for sterilizing **pharmaceuticals in their final packed containers** and **surgical instruments in hospitals**.
- No heat or chemical gets involved.
- Thermolabile substances like vitamins, hormones antibiotics can be safely sterilized.
- Finds use in sterilization of pharmaceuticals.

Calcium (Ca-44 and Ca-45)	**The radioactive calcium has been used to study bone structure and in treatment of carcinoma of bone.**
Strontium -90	**Used in the radiotherapy of superficial carcinomas.**
Cyanocobalamine (Co-57)	Used in the diagnosis of pernicious anaemia.
Calcium -47	It is having half life of 4.7 days. It is used in calcium absorption studies.
Cyanocobalamine (Co-60 Solution USP)	Used to study absorption and deposition of vitamin B12 in normal individuals.
Gold (Au-198) solution	Finds use in estimation of reticuloendothelial activity.
Iron (Fe-59)	Finds use in research studies about utilization and absorption of Iron salts.

Measurement of Radioactivity

To measure the radiations of alpha, beta and gamma particles, many techniques involving detection and counting of individual particles or photons are used.

The method selected for the measurement of radioactivity depends upon the extent of energy dissipation and penetrability of radiation.

Gas ionization devices:

1) **Ionization chambers**
2) **Proportional counters**
3) **Geiger Muller counters**
4) **Scintillation Counters**
5) **Autoradiography**
6) **Solid state detectors**

1) Ionisation Chambers:

- They are available in various shapes and sizes.
- An ionization chamber consists of a chambers filled with gas and fitted with two electrodes kept at different electrical potentials and a measuring device to indicate the flow of electric current
- Radiation brings about ionization of gas molecules or ions which cause emission of electrons which in turn reveals the changes in electrical potential.

2) Proportional counters:

- They are modified ionization chambers in which an applied potential ionization of primary electrons causes production of more free electrons which gets carried to the anode.
- For each primary electron liberated, much more additional electrons get liberated, the current pulse through electrical circuit is greatly amplified.
- The voltage range over which the gas amplification (ionization) occurs is called the proportional region, and the counters working in this region are called Proportional counters.

3) Geiger-Muller Counter

- These are most popular **radiation detectors**.
- They do not need the use of high gain amplifier.
- **They can detect alpha, beta and gamma radiations.**

- **Geiger-Muller counter is having ionizing gas and is also having a quenching vapour whose functions are:**

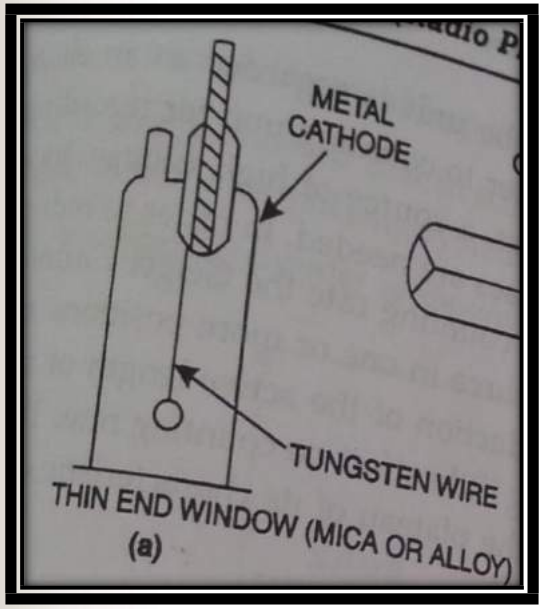
1. To prevent the spurious pulses that may get produced due to the positive ions (cations) reaching the cathode (- electrode).
2. To absorb the photons emitted by excited atoms and molecules returning to their ground state.

- **Chlorine and bromine** are generally used as quenching agent.
- **Ethyl alcohol and ethyl formate** are used as organic quenching agents.
- The filling gas pressure has been much below the atmospheric pressure to avoid use of high operating voltages.

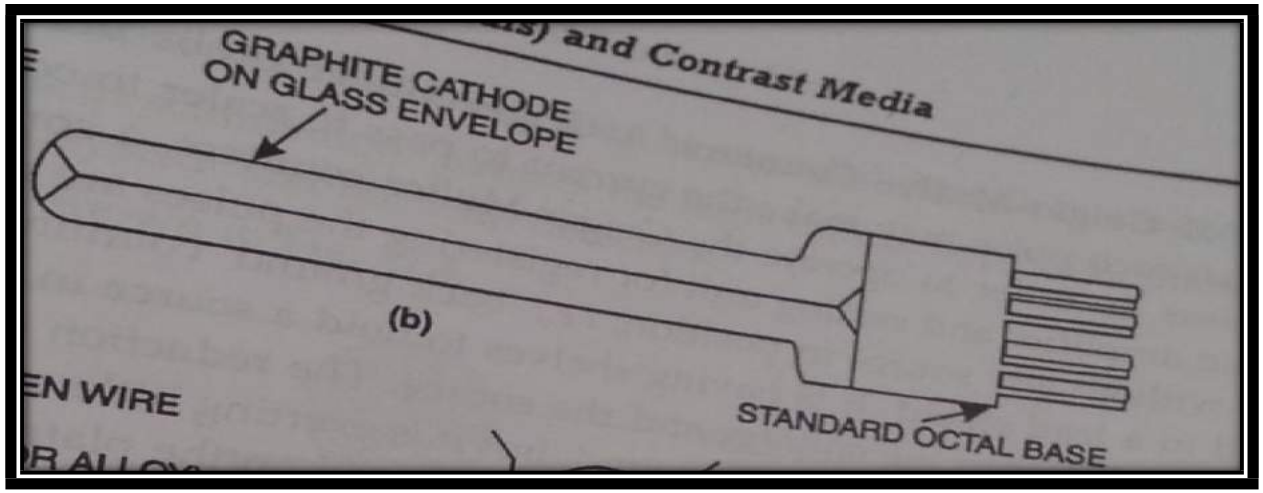
Construction:

- A GM Counter possesses a cylindrical cathode (- electrode) , which is usually 1-2 cm in diameter, along the centre of which is a **wire anode** (+ electrode) .
- The space is filled with a special gas mixture which gets readily ionized together, with a small proportion of quenching vapour.

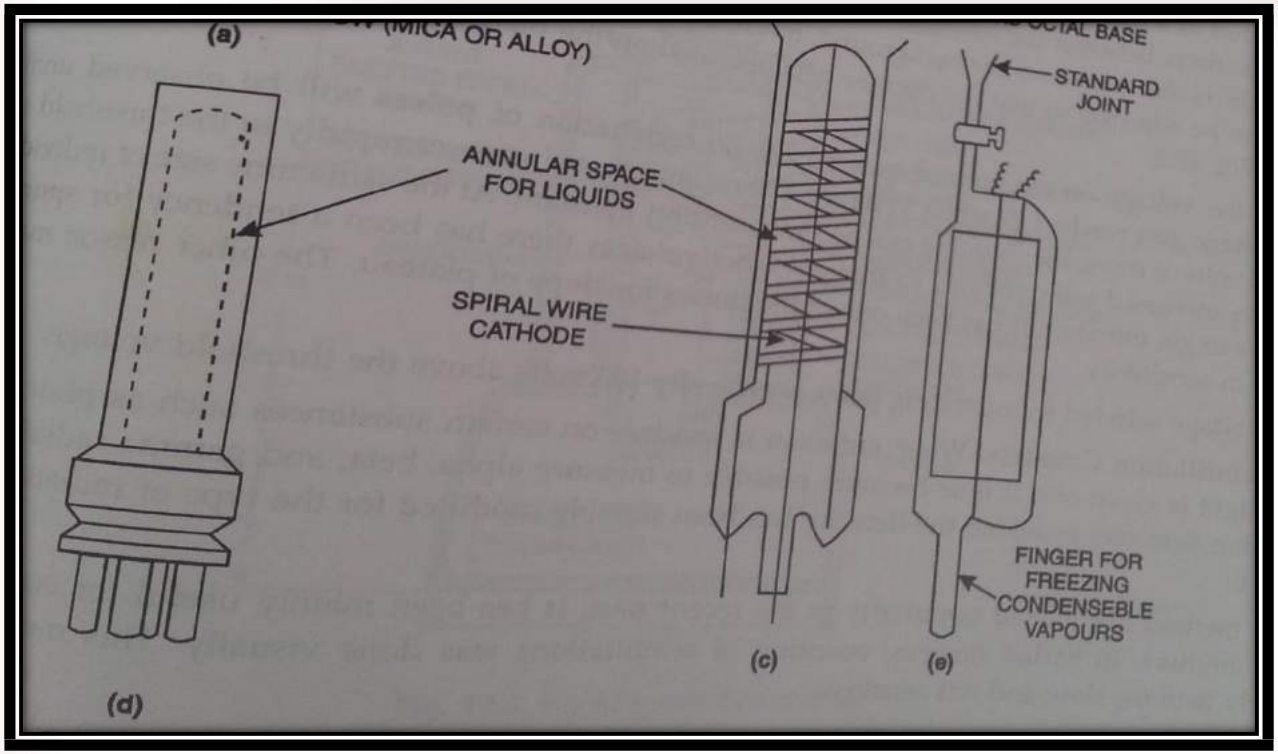
- **For solid radioactive sources**:
  - ✓ For solid radioactive sources, the end window type GM counter has been the most popular.
  - ✓ The window has been made of an **aluminium alloy, mica or a thin glass bubble**.



- ✓ In order to count the medium and high energy beta particles and for gamma counting, thin glass walled counters may be used.
- ✓ They are normally 1 cm in diameter and having a glass wall of 20 – 40 mg cm^{-2} thickness.
- ✓ The tube is coated on the inside to form the cathode.



For radioactive liquid sources:



It is having a capacity of 10 cm^3 in annular space. In such a counter 10 cm^3 of 3 % solution of Uranium salt gives nearly 10,000 counts per minute.

❑ Operation:

- ✓ When ionizing radiation such as alpha, beta or gamma particle enters the tube, it can ionize some of the gas molecules in the tube.
- ✓ From these ionized atoms, an electron is knocked out of the atom and so the remaining atom is positively charged.
- ✓ The high voltage in the tube produces an electric field inside the tube.
- ✓ The electrons that were knocked out of the atom are attracted to the positive electrode (anode) and the positively charged ions are attracted to the negative electrode (cathode)
- ✓ This produces a pulse of current in the wires connecting the electrodes an this pulse is counted.
- ✓ After the pulse is counted, the charged ions become neutralized and the Geiger counter is ready to record another pulse.
- ✓ In order for the Geiger tube to restore itself quickly to its original state after radiation has entered, a gas is added to the tube.

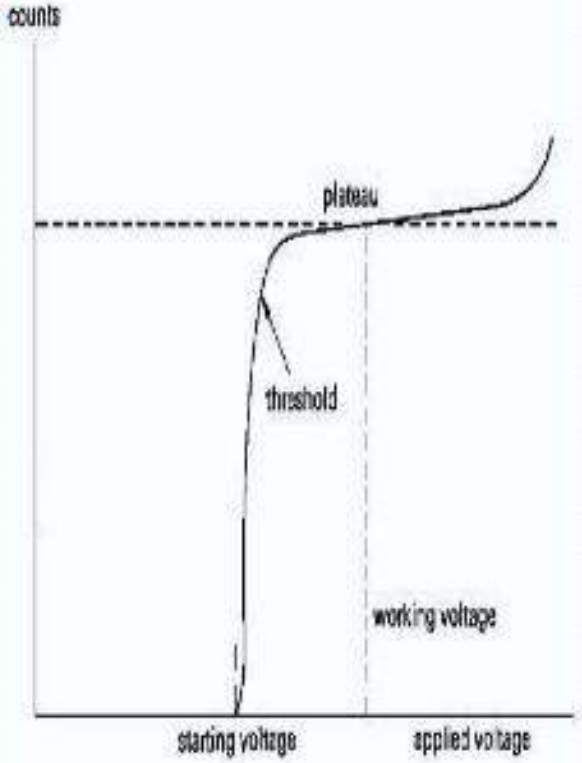
- ✓ For proper use of the Geiger counter, one must have appropriate voltage across the electrodes.
- ✓ If the voltage is too low, the electric field in the tube is too weak to cause a current pulse. If the voltage is too high, the tube will undergo continuous discharge and it will be damaged.
- ✓ For low voltages, no counts are recorded. This is because the electric field is too weak for even one pulse to be recorded. As the voltage is increased, one obtains a counting rate.
- ✓ The voltage at which the GM tube just begins to count is called the stating potential. The counting rate quickly rises as the voltage is increased.
- ✓ The rise is so fast that the graph looks like a step potential.
- ✓ After the quick rise, the counting rate levels 0.This range of voltages is termed as pleateau region.
- ✓ Eventually the voltage becomes too high and we have continuous discharge.
- ✓ The threshold voltage is the voltage where the plateau region begins. Proper operation is when the voltage is in the plateau region of the curve.
- ✓ For best operation, voltage should be selected fairly close to the threshold voltage.

Characteristics of gm counter

- The rate of counting is recorded as function of voltage . A graph between voltage and rate of counting is called ***characteristic curve of counter***

- *When voltage is low counter operates in **ionization chamber** region where there is no gas amplification. The voltage pulse will be small and no counts will be recorded*
- *unless the voltage exceeds v_s the **threshold voltage** .*

- *As voltage increases over v_s counting rate increases as gas amplification sets in and output pulse size increases. This is region of **proportional counter** where more and more low energetic particles are counted until point C is reached . From this point onwards counting rate become constant. The flat region CD is called **plateau of counter**.*



Scintillation counters: (For gamma counting)

- ✓ When radiation is incident on certain substances such as phosphor, a flash of light is given out. It thus becomes possible to measure alpha, beta and gamma radiations by scintillation detectors provided the detector has been suitably modified for the type of radiation to be measured.
- ✓ The scintillation counter consists of a cell, a photomultiplier tube which is coupled with phosphor or fluorescent material to convert scintillation into electrical pulses, amplifier and scaler

Radio-opaque contrast media

- Radio-opaque substances are those compounds (both inorganic and organic) which are having the property of casting a shadow on X-ray films.
- These compounds have the ability to stop the passage of X-rays and appear opaque on X-ray examination.

- **BARIUM SULPHATE**

Formula: $BaSO_4$

Preparation:

1. For pharmaceutical purposes, Barium sulphate is prepared by treating an aqueous solution containing Barium ions with a solution containing sulphate ions.

$$Ba(OH)_2 + H_2SO_4 \longrightarrow BaSO_4 + 2H_2O$$

$$BaCl_2 + H_2SO_4 \longrightarrow BaSO_4 + 2HCl$$

The precipitated salt is washed, dried and screened.

2. It is also prepared by the action of dilute H_2SO_4 on BaS

$$BaS + H_2SO_4 \longrightarrow BaSO_4 + H_2S$$

Properties:

- Heavy
- Fine white bulky powder
- Odourless
- Tasteless
- Free from grittiness
- Insoluble in water
- It may be solubilized by fusing with alkali carbonates.

Uses:

- It is used as a diagnostic drug which is used medicinally in X ray examination.
- It is administered by enema before X ray examination in the form of Barium meal to make intestinal tract opaque to X rays, so that it can be photographed.

Thank You

13. Define emetics with examples.
14. Give the chemical formula and medicinal use of sodium metabisulphite.
15. Define expectorant and emetics. Give examples.
16. Give reasons : (a) Potassium iodide is used in the assay of copper sulphate
    (b) HCHO used in the assay of Ammonium chloride.
17. What are expectorants? Give an example.
18. Write pharmaceutical uses of activated charcoal and sodium thiosulphate.
19. Write the pharmaceutical importance of Bentonite powder.
20. Give the composition and uses of bentonite.
21. Define antidotes with examples.
22. Write the molecular formula and medicinal uses of sodium thiosulphate.
23. What is Haematinics. Give examples.
24. What are antidotes? Give the method of preparation and importance of activated charcoal.
25. Write the synonym for ferrous sulphate and copper sulphate.

❑❑❑

UNIT V

Chapter...10

RADIO-PHARMACEUTICALS

• OVERVIEW •

- **Introduction.**
- **Radioactivity : Radioactive isotope, Radioactive decay (Alpha, beta particles and gamma rays), Unit of radioactivity, Half life of radioactive isotopes.**
- **Detection and measurement of radiation : Ionization chamber, Proportional counter, Geiger-Muller counter, Scintillation counters, Semiconductor detectors, Photographic plate method.**
- **Handling and storage of radiopharmaceuticals.**
- **Radiopharmaceuticals : Sodium iodide – I^{131} solution and capsule.**
- **Radio opaque contrast media : Barium sulphate.**
- **Therapeutic applications of radiopharmaceuticals.**

10.1 INTRODUCTION

Many heavy metals which are unstable in nature, undergoes spontaneous decomposition accompanied by emission of radiation or rays namely alpha, beta and gamma rays termed as radioactive substances.

The natural radioactivity was first observed in 1867 by Niepce de saint- Victor who noticed fogging in silver chloride emulsion while working with uranium salts and attributed this effect as luminescence phenomena. While performing similar phosphorescence experiments in 1896, Antoine Henri Bequerel noted that uranium emitted penetrating rays that were similar to X-rays. Now he credited as the discoverer of radioactivity. Complete phenomenon of radiactivity was truly recognised. In 1998 when Marie and Pierre Curie discovered that this emission were originated from the unstable elements radium, and polonium.

The substances like uranium, thorium, radium and their compounds which emit such radiations are called as **Radioactive substances** and the phenomenon of spontaneous and continuous emission of such radiations is called as **Radioactivity**.

10.2 RADIOACTIVE ISOTOPE

Radioactive isotope is also called as radioisotope, radionuclide or radioactive nuclide.

It is known that every atom of an element is composed of nucleus containing protons and neutrons, surrounded by electrons. If the atom is electrically neutral then the number of protons in nucleus is same as that of electrons. It is known that number of proton in the nucleus is equal to atomic number which determines its properties. The atomic number of the atom is characteristic of that element. Various atomic species are known as nuclides and are represented by the symbol e.g. $^{12}_{6}C$ where superscripts is the mass number and subscript is the atomic number. *Nuclides having same number of protons but different number of neutrons are termed as isotopes or The isotopes have same atomic number but different mass number or atomic weight.*

Example 1 :

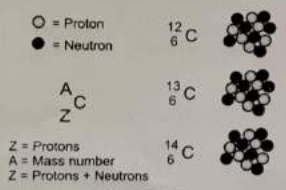


Fig. 10.1 (a)

Example 2 :

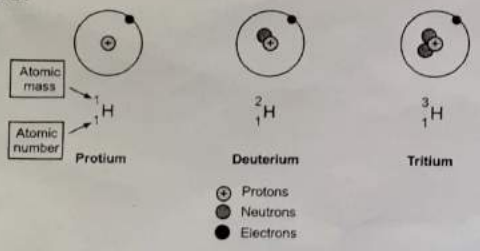


Fig. 10.1 (b)

Isotopes of particular element have same chemical and physical properties with a difference in the kinetics or rates of reactions as it depends upon mass. Every chemical element has one or more radioactive isotopes. Some radioactive isotopes are found

naturally in elements but large number of unstable isotopes are produced synthetically. The unstable nuclei are usually produced by bombardment of atomic nuclei with neutrons or electrons to produce unstable nuclei of the same element or a different element (radionuclides).

There are two types of isotopes found in nature :

1. The stable isotopes (nuclide) which do not decompose to other isotopic form of the element.
2. The unstable or radioactive isotopes (radionuclide) which decomposes or decay by emitting the nuclear particles in to other isotope or different elements. The decomposition is characteristic of each isotope and it continues till stable isotopic level is acheived.

Radioisotopes are widely used in medicine, industry and scientific research, and new applications for their uses are constantly being developed.

10.3 RADIOACTIVE DECAY

Radioactive decay (also known as *nuclear decay* or *radioactivity*) is the process by which an unstable atomic nucleus loses energy (in terms of mass in its rest frame) by emitting radiation, such as an alpha particle, beta particle and gamma ray.

The radioactive disintegration is independent of extra-nuclear condition like temperature, pressure, and the state of chemical combination of the disintegrated atom. Each radionuclide disintegrates at a characteristic rate depending on the number of atoms (and hence on the weight) of radionuclide present, by the emission of a particular particle or electromagnetic radiation of characteristic energy.

The number of decay events –dN expected to occur in a small interval of time dt (rate of decay) is proportional to the number of atoms present *N*, that is

$$\frac{-dN}{dt} \propto N$$

Particular radionuclides decay at different rates, so each has its own decay constant λ.

The expected decay – dN/N is proportional to an increment of time, dt :

$$\boxed{-\frac{dN}{N} = \lambda\, dt}$$

The negative sign indicates that N decreases as time increases, as the decay events follow one after another. The above equation can be rearranged as

$$N(t) = N_0\, e^{-\lambda t}$$

where, N_0 is the initial quantity of the substance.

N(t) is the quantity that still remains and has not yet decayed after a time (t).

Radioactive decay rates are normally and most frequently stated in terms of their half-life. The term half-life is defined as the time it takes for one-half of the atoms of a radioactive material to disintegrate. Each time the half-life of a radioactive material occurs, the amount of the radioactive material decreases to half of the original value.

That means : $\frac{N(t)}{N_0} = \frac{1}{2}$

$$\frac{1}{2} = e^{-\lambda t_{1/2}}$$

$$\log \frac{1}{2} = \log e^{-\lambda t_{1/2}}$$

$$\log \frac{1}{2} = -0.4343\ \lambda t_{1/2}$$

$$0.3010 = 0.4343\ \lambda t_{1/2}$$

$$t_{1/2} = 0.693/\lambda$$

λ is disintegration constant in unit of sec^{-1}.

The half-life is

- Independent of the physical state (solid, liquid, gas), temperature, pressure, the chemical compound in which the nucleus finds itself, and essentially any other outside influence.
- It is independent of the chemistry of the atomic surface, and independent of the ordinary physical factors of the outside world.
- The only thing which can alter the half-life is direct nuclear interaction with a particle from outside, e.g., a high energy collision in an accelerator.
- It varies depending on the atom type and isotope.
- The half-life of a given nuclear species is related to its radiation risk.
- Half life for various radioactive elements varies considerably.

Table 10.1 : Half life of various radioactive elements

Radioisotope	Half-life
Polonium-215	0.0018 seconds
Bismuth-212	60.5 seconds
Sodium-24	15 hours
Iodine-131	8.04 days
Cobalt-60	5.26 years
Radium-226	1600 years
Uranium-238	4.5 billion years

Unit of Radioactivity :

The original unit for measuring the amount of radioactivity was the ***curie*** *(Ci)*–first defined to correspond to one gram of radium-226 and more recently defined as :

1 curie = 3.7×10^{10} radioactive decays per second.

In the International System of Units (SI) the curie has been replaced by the ***becquerel*** (Bq), where

1 becquerel = 1 radioactive decay per second = 2.703×10^{-11} Ci.

Roentgen (γ) is unit of X-radiation or gamma radiation. It measures the ionization effect of X-radiation or gamma radiation and its damaging effect on biological matter.

Approximately 1γ is equivalent to about 930 erg/g tissue of water.

The **RAD** (Radiation Absorbed Dose) is another unit of measuring the radiation absorbed and is defined as the quantity of radiation which releases or absorbs 100 erg/g of a specified medium.

Relative Biological Effectiveness (RBE) : It measures the capacity of a specific ionizing radiation to produce a specific biological effect, expressed relative to a reference radiation. This unit expresses the relative effect of radiation α, β, γ on biological system.

REM : Derived from the phrase *Roentgen Equivalent Man*. It refers to the unit of dose equivalent. The dose in REM has been equal to the dose in RADs multiplied by quality factor and the distribution factor.

Exposure rate constant : It refers to the dose rate in roentgens per hour at 1 m distance from 1 curie. It is about one tenth the dose at a distance of 1 foot from 1 curie.

The properties of radiation :

The radiations emitted by radioactive substance are :

- Alpha (α) particles
- Beta (β) particles
- Gamma (γ) radiation

The most important particulate radiations are α and β radiations.

(a) Alpha particles :

Alpha radiation occurs when an atom undergoes radioactive decay, giving off a particle (called an alpha particle) consisting of two protons and two neutrons (essentially the nucleus of a helium-4 atom), changing the originating atom to one of an element with an atomic number 2 less and atomic weight 4 less than it started with. Due to their charge and mass, alpha particles interact strongly with matter, and only travel a few centimeters in air. Their penetrating power is least as compared to other emissions. Because of low penetrating

power of alpha particles, element which emits these do not find any use in biological applications as it cannot penetrate tissue. if an alpha emitting substance is ingested in food or air can causing serious cell damage. Alpha particles are effected by strong magnetic field.

Example : The decay of Uranium 238

$$^{238}_{92}U \longrightarrow {}^{234}_{90}Th + {}^{4}_{2}\alpha$$

(b) Beta particles :

Beta particles can be described as electron of nuclear energy. These are of two types :

(i) Electrically positive particles (Positrons).

(ii) Electrically negative particles (Negatrons).

Beta radiation have greater penetrating power than that of alpha rays because beta particles are having negligible mass about 1/1836 that of hydrogen ion. As these radiations are lighter, they travel with the velocity little less than that of light. They can penetrate an aluminium sheet up to 3mm thick. These particles are usually accompanied by gamma radiation. Beta particles have less ionising power than alpha particles. These particles are effected by strong magnetic field. It can penetrate skin a few centimeters, number of isotopes emitting beta particles are useful in biological applications because of their high penetration power. They can penetrate tissue.

The emission of beta particles from an element does not alter the atomic mass, but alters the atomic number and is converted to element with next highest atomic number.

Example :

$$^{14}_{6}C \longrightarrow {}^{14}_{7}N + {}^{0}_{-1}e\ (\beta \text{ emission})$$

Carbon-14 (radioactive) — Nitrogen-14 (stable) — Beta particle

Beta particles are sometimes refered as Negatrons, which are emitted by unstable nuclei, in which the neutrons /proton ratio exceeds the stability limit. In such cases, neutrons are converted in to protons with beta emission.

$$_0n^1 \rightarrow {}_0p^1 + \beta^-$$

There is another type of beta emission which are called as positrons (β^+). These are not very common and as they are short lived they do not find application in biological field.

(c) Gamma radiation :

Gamma radiation have more penetrating power than alpha and beta. It does not consist of any particles, instead consisting of a photon of energy being emitted from an unstable nucleus. They have no mass or charge and thus are not effected by electric or magnetic field. They do not have mass and charge but have very high energy and thus have excellent

penetrating power. Only a very thick lead sheet or concrete shield can protect from gamma radiations. They have properties of both wave and particle. They are having the same character as that of short electromagnetic waves of X-rays. As gamma rays are uncharged, they have poor ionising power but they can interact with molecules and atoms in specific media and can produce ions and free radicals by dislodging electrons from orbitals. The applications of gamma radiation are much the same as those of X-rays, both in medicine and in industry. In medicine, gamma ray sources are used for cancer treatment and for diagnostic purposes.

10.4 DETECTION AND MEASUREMENT OF RADIATION

The radiations (mainly alpha and beta radiations) are high speed charged particles which can be deflected by electric and magnetic fields, can penetrate matters and ionize matter (for example, gases) through which they pass and cause certain substances to emit flashes of light (scintillation), and blacken a photographic plate. These properties of radiation are utilised in their detection and measurement, the ionising effect in ionisation chambers and geiger-muller counter, the scintillation effect in scintillation counter and the photographic effect in autoradiography.

1. Ionization chamber :

The ionization chamber is the simplest of all gas filled radiation detectors. The detector of these type makes use of electric conductivity of a gas that has been partially ionized by radiation passing through it. This is carried out in ionization chamber. These chambers are of various shapes and sizes. The chamber is filled with gas and fitted with two electrodes kept at different electrical potentials (50 to 100 volts).

This instrument works on the principle that as radiation passes through air or a specific gas, ionization of the molecules in the air occur. When a voltage potential is applied between the electrodes to create an electric field in the filled gas, the positive ions will be attracted to the negative side of the detector (the cathode) and the free electrons will travel to the positive side (the anode). These charges are collected by the anode and cathode which then form a very small current in the wires going to the detector. By placing a very sensitive current measuring device between the wires from the cathode and anode, the small current measured and displayed as a signal. The more radiation which enters the chamber, the more current displayed by the instrument. Thus, the ionization current produced is proportional to the initial energy of the incident particle. Due to this reason, this can be used to distinguish between a low energy particle and a high energy particle.

It is widely used for the detection and measurement of certain types of ionizing radiation; X-rays, gamma rays and beta particles.

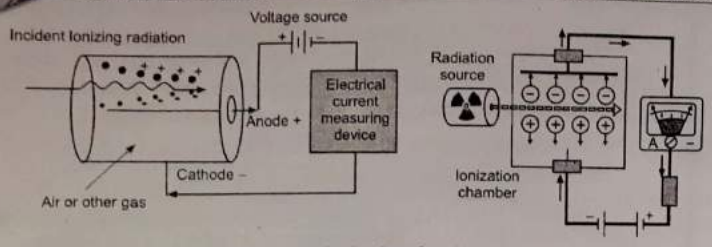


Fig. 10.2 : Ionization chamber

2. Proportional counter :

It is modified ionization method. These counters are photon counting devices, meaning that the detection of each photon results in a discrete signal in the associated electronics. A typical counter, for example as shown, consists of a gas-filled chamber fitted with one or more X-ray transparent windows. Photons penetrate the window and pass into the gas inside where interactions with the gas atoms result in the creation of a number of ion pairs (electrons and partially ionised gas atoms). Anodes in the detector volume are held at a positive potential with respect to the rest of the detector. The anodes are usually thin metal wires, and their electric field causes the electrons to move towards the anodes where the field strength is highest. The energy of the electrons increases, and collisions with other gas atoms cause further ionisation producing more electrons. These secondary electrons themselves drift and acquire enough energy to cause further ionisation (and electrons), and so a large cloud of electrons arrives at the anode in a process known as an avalanche. The quantity of charge produced in the avalanche is great enough to be detectable in an amplifier connected to the anode.

3. Geiger – Muller counter :

A Geiger counter (Geiger-Muller tube) is a device used for the detection and measurement of all types of radiation : alpha, beta and gamma radiation.

It consist of a cylinder of stainless steel or glass coated with silver on the innerside which act as cathode. A fine metal wire is mounted coaxially inside the tube as anode. The space in the chamber is filled with a mixture of argon which provides ionizable subtance and some heavier gas such as alcohol, methane, etc. Radiation enters the tube through a thin section of outer wall called as window. It causes atoms of gas to ionise. A high voltage (800 - 1300 V) is maintained between the electrodes. Due to ionization of gas the positive ions will be attracted to the negative side of the detector (the cathode) and the free electrons will travel to the positive side (the anode). These charges are collected by the anode and cathode. The passage of these ions through the tube constitute a flow of current which is recorded by device known as the 'scalar' which shows total number of pulses.

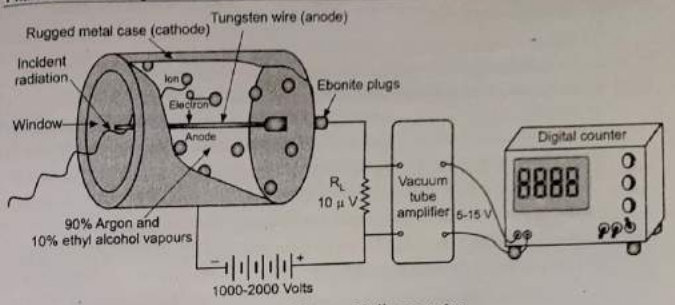


Fig. 10.3 : Geiger – Muller counter

4. Scintillation Counters :

Alpha, beta and gamma radiations can be detected by scintillation counters.

It is an instrument for detecting and measuring ionising radiation by using the excitation effect of incident radiation on a scintillator material, and detecting the resultant light pulses. It consists of a scintillator which generates photons in response to incident radiation and a sensitive Photomultiplier Tube (PMT) which converts the light to an electrical signal and electronics to process this signal.

This detector works on the principles that when ionising radiation strikes certain substances like phosphorous or a flurogenic material, a flash of light is given out. This flash is collected by photomultiplier tube which produces electric impulse. This impulse on further amplification is recorded by the scalar.

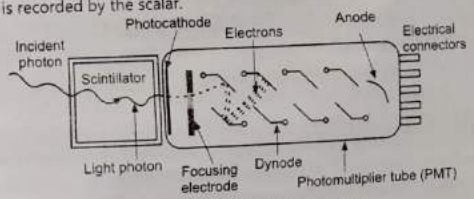


Fig. 10.4 : Scintillation Counters

5. Semiconductor Detectors :

Semiconductors are of several types. It used for the detection and measurement of X-rays and gamma rays. In these detectors, the charge carriers produced by ionizing radiation, are electron hole pair (and not ion-pairs). These travel towards the positive electrode with high velocity.

6. Autoradiography :

This technique is mainly used for detecting gamma radiation in physiological studies of plants and animals. This method involves the administering of radioactive substance, to say an animal and after sufficient time of lapse for localisation, the tissue is removed, embedded in paraffin, cut in to thin sections by microtome and the section kept in contact with photographic emulsion in a dark room. The radioactive atoms (present in the cut section) are emitting particles which darken photographic emulsion. After sufficient time of exposure, the emulsion has been developed and fixed.

Handling and Storage of Radioactive Materials :

Great care has to be taken in handling and storage of radioactive material for protecting people and personnel who handle it :

1. The working areas should not get contaminated with radioactive material.
2. If the radioactive liquid has to be handled, it must be carried in trays having absorbent tissue paper so that any spillage will get absorbed by paper.
3. Rubber gloves have to be used when working with radioactive liquids.
4. Pipettes operated by mouth should never be employed.
5. Smoking, eating, drinking activities are prohibited in the area of radioactive work.
6. The radioactive emitter should be handled with forceps and never by hand.
7. Sufficient shielding device should be used.
8. Radioactive materials have to be stored in suitable labeled containers, shielding by bricks and preferably in a remote corner.
9. Great care has to be applied for disposal of radioactive materials.
10. A regular monitoring of radioactivity should be done in area where radioactive material is stored.
11. The waste radioactive materials have to be stored till the activity becomes low before its disposal.

10.5 RADIOPHARMACEUTICALS

Radiopharmaceuticals are unique medicinal formulations containing radioisotopes which are used in major clinical areas for diagnosis and/or therapy. It exhibits spontaneous disintegration of unstable nuclei with emission of nuclear paticles or photon and includes any non-radioactive reagent kit or nuclide that is intended to be used in the preparation of any such substance.

Nearly 95% of radiopharmaceuticals are used for diagnostic purposes and/or monitoring various disease states whereas remaining 5% is used for therapy.

In imaging, the unique properties of γ-rays emitted from the radioactive isotopes allow the radiopharmaceutical to be traced or their distribution in target tissue imaged non-invasively, thus providing functional information of the target tissue or organ.

e.g. Tc-99 m diphosphonates for bone imaging procedures.

Tc-99 m macroaggregated albumin for lung imaging procedures.

Tl-201 thallous chloride for myocardial perfusion imaging procedures.

In a diagnostic nuclear medicine procedure the radiopharmaceuticals administered to the patient most often by I.V. injection, although sometime by oral inhalation or other routes. The localisation dispositon and/or clearence of radiopharmaceuticals is then determined by detection of radiation with sophosticated instrument termed a gamma camera. The type of radiation detected is gamma, and the data executed by the detector will be an image or picture.

In therapy, the β-ray energy from the radioisotope is delivered to the target tissue partially or completely to destroy the diseased tissue. The radiopharmaceuticals intended for use in the treatment of various disease states use relatively large radiation to cause localized radiation damage.

e.g. I-131 sodium iodide is used for treatment of hyperthyroidism or thyroid cancer.

One of the more recent dovelopments in oncologic medicine is the use of monoclonal antibodies leveled with a gamma – emitting radionuclide for diagonostic imaging and a beta emitting radionuclide for subsequent therapy .

Radiopharmaceuticals are unlike conventional pharmaceuticals in many aspects :

1. The most striking feature is the property of the radionuclide, which disintegrates or decays with time, often resulting in a limited shelf life of the product.
2. In contrast to traditional drugs, it lack of distinct pharmacological effects.
3. Radiopharmaceuticals typically are employed as tracers of physiological functions.
4. Their small amounts of mass produce negligible effects on biological processes, while their radiodioactivity allows non-invasive external monitoring or targated therapeutic irradiation.

Nature of Radiopharmaceuticals :

- Few radiopharmaceuticals are available in its salt form e.g. I-131 sodium iodide, Tl-201 thallous chloride.
- Most of the radiopharmaceuticals consist of radioactive atoms attached to or incorporated in to other chemical compound that serve to carry the radioactive atoms to intended tissues or organs.

- Some of the radiopharmaceuticals may be available as final or ready to use dosage form. Because of their short half lives, however, most of the radiopharmaceuticals require preparation of the final product on-site before administration to the patient on the day of use. This is accomplished most frequently with aid of non-radioactive reagent kit and radioactivity obtained from radionuclide generator. The radionuclide generator most often employed is technetium generator.

Hence, the oncept of "Hospital Radiopharmacy" unit to prepare radiopharmaceuticals has become a practice in Nuclear Medicine departments in hospitals. At the hospital radiopharmacy, a trained radiopharmacist prepares the various radiopharmaceutical formulations, tests each formulation for its quality (quality control). The formulations are then provides to nuclear medicine physician for administration into the patient for investigation or for therapy.

The use of radioactive material necessitates careful and safe handling of these products by trained and authorized personnel, in approved/authorized laboratory facility as per the guide lines of Atomic Energy Regulatory Board (AERB) of India.

10.5.1 Radioactive Pharmaceutical Preparations

Radiopharmaceuticals are unique medicinal formulations containing radioisotopes which are used in major clinical areas for diagnosis and/or therapy. These are more or less like pharmaceutical praparation (solution and injection etc) with all the usual control for such preparation.

A radioactive pharmaceutical preparation is named by one of these method : Sodium radio-iodide injection or sodium iodide I-131 solution or sodium iodide I-131 capsules. The I.P. does not include any radioactive pharmaceutical preparation. However B.P and U.S.P includes radioactive pharmaceutical preparation.

SODIUM IODIDE - I^{131} SOLUTION (B.P., U.S.P.)

This is a solution of carrier free ^{131}I-labelled sodium iodide in dilute sodium thiosulphate.

Structure : Na-I^{131}.

Sodium iodide I-131 Solution (U.S.P.) :

Sodium iodide I-131 solution should not contain less than 90% but not more than 110% of the labelled amount of iodine-131 as iodide which is expressed in microcuries or millicuries at the time indicated in the labelling.

Sodium iodide solution is suitable for either oral or intravenous administration and having radioactive I-131 which is processed in the form of sodium iodide. It is produced from the products of uranium fission or the neutron bombardment of tellurium until it becomes essentially carrier free and is having only minute amount of naturally occurring iodine -127 B.P. It is also having sodium thiosulphate or some other suitable reducing agents.

Sodium iodide I-131 capsules (U.S.P.) :

Sodium iodide I-131 capsules are prepared by evaporating an alcoholic solution of sodium radioiodide directly on the wall of the capsules or on the inert capsule filling material.

Properties :

I^{131} is a β-γ emitting radionuclide, of half-life 8.04 days. This solution is clear and colourless, but over the period of time both the solution and glass may darken due to the effects of radiation. For injection, a suitable preservative such as benzyl alcohol is added. A reducing agents such as sodium thiosulphate is added to the solution to prevent the oxidation of sodium iodide in aqueous solution.

Test for Radioachemical Purity :

The test for radiochemical purity is designed to prove that all the radioactivity of the solution is due to iodide ion not to iodate ion. This can be done by showing the radioactive part of a paper chromatogram prepared from the solution coincides with the position of the iodide ion and that the site of iodate ion is inactive.

Radioactive Assay :

The activity of a suitably diluted sample having an activity of about 0.1 μCi may be measured with a scintillation counter which has been calibrated with a standardized solution of Sodium iodide I^{131}.

A standard ion chamber is a convenient instrument for the assay of I^{131}-labelled radiopharmaceuticals. The ion current of this instrument is known for a given activity of I-131.

Precautions to be taken in the handling of the sodium iodide I-131

Sodium Iodide-I^{131} solution emits radiation and must be handled with safety measures to minimize inadvertent radiation exposure to clinical personnel and patients. The precautions to be taken in the handling of the Radiopharmaceuticals are :

(i) Radiopharmaceuticals should be used only by or under the direction of physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides. The radiopharmaceuticals are needed to be used very carefully.

(ii) Wear waterproof gloves during the entire sodium iodide I-131 solution handling and administration procedure.

(iii) Maintain adequate shielding during the radiation emitting life of the product.

(iv) Measure the patient dose using a suitable radioactivity calibration system immediately prior to administration.

Packaging and Storage :

The solution has to be prepared in single dose or multiple dose containers that have been previously treated to prevent absorbtion. It has been recommended that containers used to handle sodium iodide I-131 solution should be first of all rinsed with a solution having approximately 0.8% of sodium bisulphite and 0.25% of sodium iodide and then with water until the last rinsing has been neutral to litmus.

Other requirement regarding labelling and expiration date :

Labeling : Label the Capsules to include the following : the date of calibration; the amount of ^{131}I as iodide expressed in megabecquerels (microcuries or millicuries) per Capsule at the time of calibration; a statement of whether the contents are intended for diagnostic or therapeutic use; the expiration date; and the statement "Caution–Radioactive Material." The labeling indicates that in making dosage calculations, correction is to be made for radioactive decay, and also indicates that the radioactive half-life of I-131 is 8.04 days.

Contraindications :

(1) Vomiting and diarrhoea represent contraindications to the use of radioiodide.

(2) Therapeutic doses of Sodium Iodide I^{131} may cause fetal harm when administered to a pregnant woman.

(3) Therapeutic doses of Sodium Iodide I^{131} are contraindicated in women who are pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazards to the fetus.

Uses :

1. It is used as a diagnostic aid for studying the functioning of the thyroid gland and in scanning the thyroid for determining size, position and possible tumor location.
2. Sodium iodide I^{131} is also used therapeutically for destroying tissue or at least to alter the function of the tissue cells. It is used in the treatment of hyperthyroidism, thyroid carcinoma and severe cardiac disease.

Dose :

It is administered orally. In calculating the dose to be administered, the rate of radioactive decay must be taken in to account. The following are indicative of the dose required;

(i) For the investigation of thyroid function : 5 to 50 microcuries.

(ii) For the treatment of thyrotoxicosis : 5 to 15 millicuries.

(iii) For the ablation of thyroid function : 25 to 50 millicuries.

(iv) For the treatment of carcinoma of the thyroid - 60 to 100 millicuries.

SODIUM IODIDE-I^{131} INJECTION (B.P.)

This is carrier free ^{131}I-labelled sodium iodide in sterlised isotonic solution containing phosphate buffer and sodium thiosulphate, pH 7.0- 8.0.

Test for radioachemical purity : Same as Sodium iodide- I131 solution, B.P.

Radioactive assay : Same as Sodium iodide-I^{131} solution, B.P.

Dose and usage : Same as Sodium iodide-I^{131} solution, B.P. except that it is administered by intravenous injection.

10.5.2 Radio Opaque Contrast Media

Radiopaque Contrast Media (ROCM) are diagnostic drugs used for the enhancement of radiographic (X-ray) examinations. Radio-opaque substances are those compound, both inorganic or organic , that have the property of casting a shadow on X-ray films. These substances has the ability to stop the passage of X-rays and hence appear opaque on X-ray examination. Such compounds and their preparations are called as X-ray contrast media.

Inorganic compounds like barium sulphate and some bismuth compounds are useful as radio-opaque contrast media for diagnostic use. These are administered either ways (i) orally or intravenously or (ii) by retrograde i.e. by mechanical means, backwardly for various diagnostic purposes. These compounds are useful for examination of gastrointestinal tract, kidney (urography) liver (cholecystography), gall bladder and bile duct, blood vessel of heart (angiography and cardiography) etc.

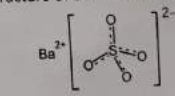
BARIUM SULPHATE

Chemical Formula : $BaSO_4$

Molecular weight : 233.43 g/mol

Category : Diagnostic agents

Structure : It is a salt composed of the barium cation (Ba^{2+}) and the sulphate anion (SO_4^{2-}), in which sulphur is attached to four oxygen atoms. The barium metal is in the +2 oxidation state. The chemical structure of barium sulfate is shown below :



Occurrence : Barium sulfate occurs naturally as the mineral barite, which is widely found and used as the major source of barium and other barium compounds.

Preparation : Barium sulphate is obtained in commercial amounts from the mineral barite, after mining and processing. The processing of the impure barite involves heating it with coke (carbon) to form the water-soluble barium sulfide (BaS), which is then separated

from the impurities and reacted with sulfuric acid to give the pure barium sulfate product :

$$BaS + H_2SO_4 \rightarrow BaSO_4 + H_2S$$

Another method to obtain pure barium sulphate is by reacting barium carbonate or barium chloride with sulfuric acid.

$$BaCl_2 + H_2SO_4 \rightarrow BaSO_4 + HCl$$

Properties :

1. Pure barium sulphate is found as white, odorless powder or small crystals.
2. Barium sulphate is known for its poor solubility in water. It is also insoluble in alcohols, and soluble in concentrated acids. It reacts violently with aluminum powder. Barium sulfate has several medical and radioimaging uses due to its water insolubility and radio-opaque properties.

Storage : It is stored in a well closed container.

Uses : Barium sulphate is widely used as a radio-opaque agent or X-ray contrast agent to diagnose gastrointestinal medical conditions. It is administered by enema before x-ray examination in the form barium meal to make the intestine tract opaque to X-rays, so that it could be photographed.

10.6 THERAPEUTIC APPLICATIONS OF RADIOPHARMACEUTICALS

The application of radiopharmaceuticals is divided into two major areas, diagnostic and therapeutic, the diagnostic side is well established. In therapeutic use of radioisotopes, the radiation emitted produces destructive effect on existing cells and prevents the formation of new cells and tissues. For this reason, the radioisotope therapy is used only in those diseased condition in which extensive cellular metabolic malfunction exist.

Some important radioisotopes used in medicines are :

1. **Calcium (^{44}Ca and ^{45}Ca) :** The radioactive calcium has been used to study bone structure and in the treatment of carcinoma of bone.
2. **Calcium (^{47}Ca) :** It is having half-life of 4.7 days. In the form of its chloride. It is used in calcium absorption studies.
3. **Carbon (^{14}C) :** It is a pure beta-emitter, having half-life of 5600 years. This rays are so soft that it can be shielded out even by paper. This isotope is most widely used in various studies, for example, in reaction mechanism, metabolism of carbohydrates and fats, drug excretion, decomposition of pharmaceutical products.
4. **Cobalt (^{60}Co) :** It emits beta and gamma rays. It is used in therapy where X-rays are used. It is used in the determination of vitamin B_{12} in the culture media. The metallic source like wire, seeds, or needles are implanted in the body cavities or directly in the tumor tissue for the treatment of advanced stages of cancer of mouth vagina, uterus etc. It is also used for the sterlisation for surgical materials and dressings by its gamma radiation.

5. **Cyanocobalamine Co-57 :** The half-life of cyanocobalmine – 57 is 270 days. This is used in the diagnosis of pernicious anemia. It used in investigation of the absorbtion and metabolism of cyanocobalamine.
6. **Cyanocobalamine Co-58 :** It is used in measurement of glomerular filtration rate. It used in investigation of the absorbtion and metabolism of cyanocobalamine.
7. **Cyanocobalamine Co-60 :** It is used for the determination of vitamin B_{12} in the culture media, food stuffs and pharmaceutical products.
8. **Strontium-90 :** It is a pure beta emitter. It is considered as one of the most dangerous isotopes formed during the fission of uranium in atomic bomb blasts due to its long half-life of 28 years. It is used for the radiotherapy of superficial carcinoma.
9. **Gold (Au^{198}) solution :** It emits beta particles and gamma rays and has half-life of 2.7 days. It used as a neoplastic suppressant. Used diagnostically to study blood circulation in liver and to treat myelogenous leukemia.
10. **Hydrogen (H^2 and H^3) :** The dueterium (H^2) and tritium (H^3) are useful in determining total body water.
11. **Iron (Fe^{55} and Fe^{59}) :** It emits beta particles and high energy gamma rays. The half-life of Fe^{59} is 45 days. It is used in research studies about utilisation and absorbtion of iron salt. It is used to measure the red cell life span.
12. **Sodium chromate (Cr^{51}) solution :** It is radioactive chromium-51 ion in the form of $Na_2Cr^{51}O_4$ It has half-life of 26.5 days. It is used to study red cell volume and its survival time.
13. **Sodium iodide (I^{131}) :** It is a radioactive isotope of iodine-131 in the form of iodide-131. It emits beta and gamma rays. It has half-life of 8 days. It is mainly used as diagnostic and therapeutic agents in thyroid related disease, used in the treatment of carcinoma of thyroid.
14. **Sodium phosphate (P^{32}) solution :** It emits beta particles. The radioactive isotope of P^{32} is in the form of sodium acid phosphate ($NaH_2P^{32}O_4$). It has half-life of 14.3 days. It is used in the treatment of polycythemia to decrease the rate of formation of the erythrocytes. It is also used in the treatment of chronic granulocytic luekemia.
15. **Ferric citrate(Fe^{59}) :** It used for diagnostic investigation of haematological disorders.
16. **Nitrogen (N^{13} and N^{15}) :** It useful in investigation of amino acid and protein metabolism.
17. **Sodium (Na^{22} and Na^{24}) :** It is employed in the estimation of extracellular fluid, blood circulation rate, studies in cells permeability, excretion and distribution of water etc.