PHARMACEUTICAL CHEMISTRY

Pharmaceutical Aids and Necessities

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Introduction

These are the chemicals having very little or no therapeutic value but are important in the manufacturing of the various dosage forms such as tablets, ointments, liquid orals and parentrals etc. These compounds are required for such purposes as preservation, stabilization, filtration, excipient, adsorption, acidification, alkalization, suspending, absorption, prevention of oxidation, complexation, colouration etc.

The major areas under which these can be categorised are :

1. Acids and bases
2. Buffers
3. Anti oxidants
4. Solvents-(water)

Acids and Bases

There are various theories of acids and bases (e.g. Arrhenius theory, Bronsted Lowry theory and Lewis theory). These theories are actually different definitions for acids and bases. Since these are only definitions, we cannot say that one theory is more right or wrong than any other and further the use of a particular theory is for a particular chemical situation i.e. whether we are considering ionic reactions in aqueous solution, in non-aqueous solutions or in a fused melt and whether we are measuring the strengths of acids and bases.

In general an acid can be defined as the chemical species, which reacts with bases, gives up cations, or accepts anions or electrons while a base can be considered as any chemical species, which reacts with acids, gives up anions or electrons, or combines with cations.

Arrhenius Concept: Arrhenius introduced one of the first concepts of acids and bases in 1884. He explained acids and bases according to the effect these substances have on water. He defined an acid as any substance which produces hydrogen ions (H^+ or protons) in aqueous solution. The hydrogen ion, is not just a bare proton, it is a proton bonded to a water molecule, H_2O. This results in a hydronium ion, H_3O^+. According to this theory, a strong acid is a substance that completely ionizes in aqueous solution to give hydronium ion, H_3O^+, and an anion.

$$HCl\ (aq) \longrightarrow H^+(aq) + Cl^-$$

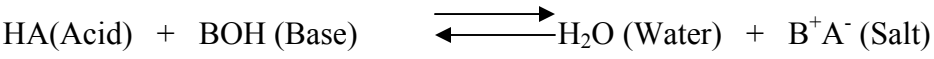
$$H^+ + H_2O \longrightarrow H_3O^+$$

He defined base as any substance which produces hydroxyl ions (OH^-) in an aqueous solution. According to this theory, a strong base is a substance that completely ionizes in aqueous solution to give hydroxyl ion, OH^-, and a cation.

$$KOH\ (aq) \longrightarrow K^+(aq) + OH^-$$

In the above reaction potassium hydroxide, (a strong base) is in an aqueous soluion. This potassium hydroxide ionizes completely and results in hydroxyl ion and a potassium cation. Some other examples of strong bases are: NaOH, LiOH, and $Ca(OH)_2$

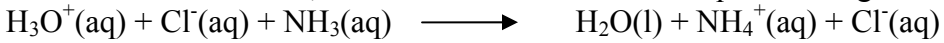
The neutralization reaction thus involves the combination of above two ions (H^+, OH^-) to form water and a salt. This can be represented with the help of following general reaction between an acid (HA) and a base (BOH) :



Limitations:

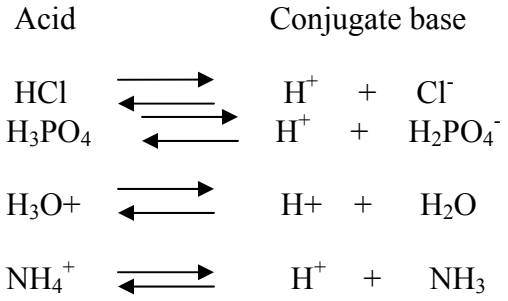
1. It could not explain the acidic character of the substances devoid of hydrogen ions e.g., CO_2 and basic character of the substances devoid of hydroxyl ions e.g., NH_3.
2. The concept can be applied only to aqueous systems.

Bronsted-Lowry Concept : This is one of the most popular concept of acids and bases developed independently by J. N. Bronsted and J. M. Lowry in 1923. They defined acids and bases in terms of proton (H^+) transfer. According to the Bronsted-Lowery concept an acid is any substance that can donate a proton in a proton-transfer reaction to any other substance and a base is any substances that can accept a proton in a proton-transfer reaction from any other substance. Thus, an acid is a proton donor whereas a base is a proton acceptor eg. in the reaction of hydrochloric acid with ammonia, when we write it as an ionic equation we get:

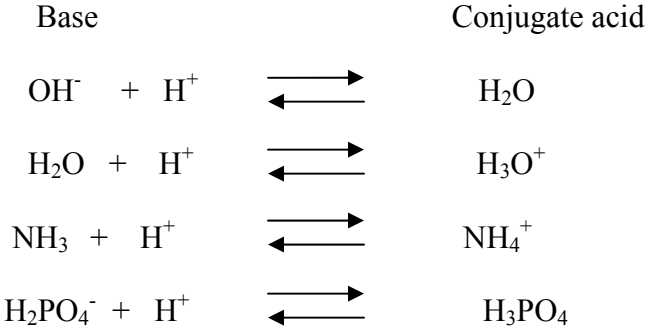


In this reaction in aqueous solution there is a proton transfer from H_3O^+ to NH_3. This results in H_3O^+ losing a (H^+), resulting in H_2O. The NH_3 gains the transferred proton, resulting in NH_4^+. We can call H_3O^+ as the proton donor, or acid and NH_3 the proton acceptor, or base..

In the Bronsted-Lowery concept when an acid donates its proton it forms a conjugate base of the acid e.g.

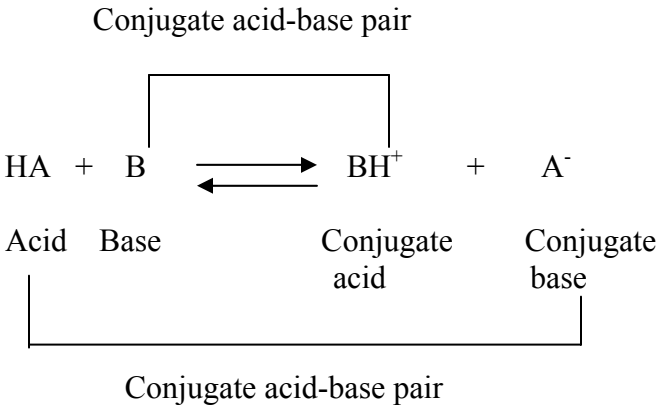


Similarly, when a base accepts a proton it forms a conjugate acid of the base e.g.



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

A complete acid-base reaction thus requires an acid that can donate its proton to a base, thereby producing a conjugate base and conjugate acid, respectively. This can be represented by the following general reaction:



Some examples are:-

Acid		Base		Conjugate Acid		Conjugate Base
HCl	+	H_2O	$\rightleftharpoons$	H_3O^+	+	Cl^-
H_2SO_4	+	OH^-	$\rightleftharpoons$	H_2O	+	HSO_4^-
H_2O	+	NH_3	$\rightleftharpoons$	NH_4^+	+	OH^-
NH_4^+	+	H_2O	$\rightleftharpoons$	H_3O^+	+	NH_3
H_3PO_4	+	OH^-	$\rightleftharpoons$	H_2O	+	$H_2PO_4^-$
H_3O^+	+	OH^-	$\rightleftharpoons$	H_2O	+	H_2O

Water is amphoteric *i.e*. it can act as an acid or a base. A strong acid can readily donate its proton to a base, so its conjugate base must necessarily be weak. In general, strong acids have weak conjugate bases and strong bases have weak conjugate acids.

Limitations:

1. It focuses exclusively on the proton transfer and excludes non-protonated systems.
2. The extent of acidity or basicity of a dissolved substance depends largely on the solvent.

Lewis Concept: In 1923, G. N. Lewis introduced a more generalized concept of acids and bases. According to him, an acid is a substance that can accept a pair of electrons from another substance to form a covalent bond and a base is a substance that can donate a pair of electrons to another substance to form a covalent bond. Thus an acid is an electron pair acceptor whereas a base is an electron pair donor. The product of Lewis acid-base reaction is referred as an adduct, coordinated complex or acid-base complex.

Acid		Base		Adduct
H^+	+	NH_3	$\rightleftharpoons$	$[H:NH_3]^+$
BF_3	+	NH_3	$\rightleftharpoons$	$[BF_3:NH_3]$
Cu^{2+}	+	$4NH_3$	$\rightleftharpoons$	$[Cu(NH_3)_4]^{2+}$

Limitations:

1. Substances that are not normally considered as acids, behave as Lewis acids e.g. BF_3.
2. As the strength of an acid or a base varies with the solvent and also depends upon the type of reaction, there can be no scale of acid or basic strength.

Role of acids and bases in Pharmacy

Acids bases and their reactions play an important role in pharmacy practice. Therapeutically they can be used in the control and adjustment of the pH of the GI tract, body fluids and urine e.g.:

1. Dilute HCl is used in the treatment of achlorhydria (a condition in which stomach is not able to secrete gastric acid) so as to achieve the acidic pH in stomach.
2. Sodium bicarbonate is used as antacid to reduce the acidity because of the increased secretion of gastric acid further it can also be used in the treatment of metabolic acidosis.

The conjugate pairs of acids and bases are used as buffers e.g. buffer acid as a proton donor and buffer base as a proton acceptor.

They are used in various analytical procedures, which involve acid-base titrations (acidimetry and alkalimetry titration) e.g. NaOH can be assayed by its titration with HCl or H_2SO_4. They can also be used in various pharmaceutical preparations and analytical procedures as acidifier or alkalizer to achieve the required pH e.g.

1. In the limit test for iron, ammonia solution is used to obtain an alkaline pH.
2. H_2SO_4 is used to provide acidic pH, in the assays involving use of $KMnO_4$. The acid solution of $KMnO_4$ reacts to reduce the permanganate ion(Mn^{7+}) to the manganous ion (Mn^{2+}) with the evolution of oxygen.

$$2KMnO_4 + 3H_2SO_4 \longrightarrow K_2SO_4 + 2MnSO_4 + 3H_2O + 5[O]$$

Acid base neutralization reactions are used in the conversion of drugs to chemical forms (e.g. Hydrochloride salts, sulphate salts and sodium salts etc.), which are suitable for product formulation.

Uses and Formulation of Acids

1. Boric Acid: H_3BO_3 Mol. Wt. 61.83

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

1.**From Borax:** A hot conc. solution of borax is treated with sulphuric acid or HCl.

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

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.

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

$$Ca_2B_6O_{11} + 2SO_2 + 9H_2O \longrightarrow 2CaSO_3 + 6H_3BO_3$$

Identification Tests: 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.

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 methyl ortho-borate.

$$H_3BO_3 + 3CH_3OH \longrightarrow B(OCH_3)_3\uparrow + 3H_2O$$

2. The dilute solution of boric acid in boiling distilled water (30g in 90ml) 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 1g of boric acid shall dissolve almost completely in 10 ml of boiling ethanol (95%). This test is done to check the absence of metallic borates and insoluble impurities.

Assay: Boric acid is a much weaker acid than carbonic acid or even hydrogen sulphide. The value of pK_a for the ionization of the first proton at 25°C is 9.19. This shows that it is a very weak acid and because of this one does not get accurate results on titrating it with a standard base in aqueous solution. With strong alkalis; it forms salts known as metaborates.

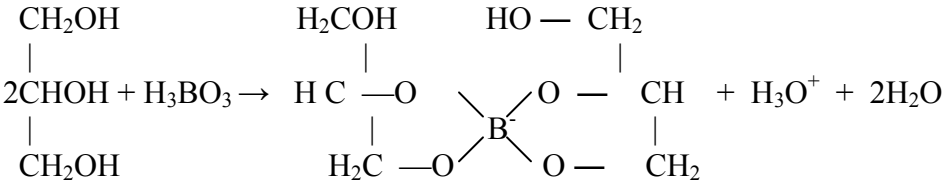
$$H_3BO_3 + NaOH \longrightarrow B(OH)_4^- + Na^+ \longrightarrow NaBO_2 + 2H_2O$$

(Sodium metaborate)

When boric acid is titrated with sodium hydroxide the end point is not sharp due to the excessive hydrolysis of sodium meta-borate formed during titration.

$$NaBO_2 + H_2O \longrightarrow H_3BO_3 + NaOH$$

However, the hydrolysis can be checked by adding polyhydroxy compounds such as glycerol, mannitol and catechol etc. to the titration mixture. These compounds react with meta-borate ion to give complex compounds resulting in the free ionization of boric acid during titration with strong alkali. Thus, the addition of such compounds makes boric acid behave as a strong monobasic acid and the end point can be easily detected.



(Glycerin) (Glyceroboric acid)

Method: About 2g of the sample is weighed accurately and dissolved in a mixture of 50ml of water and 100ml of glycerin, previously neutralized to phenolphthalein solution. Contents are then titrated with 1M sodium hydroxide using phenolphthalein solution as indicator.

Each ml of 1M sodium hydroxide is equivalent to 0.06183g of H_3BO_3.

Uses:

- It is a weak bacteriostatic agent, mainly used as local anti-infective.
- 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.
- It is also added to various dusting powders for its local anti-infective properties.
- It is used to provide acidic media and buffered media for other drugs.
- It is used in different topical medications to maintain an acidic pH in the medium.
- It is used as a buffer to maintain the pH around 6 in various ophthalmic preparations. In these solutions it also helps in the maintenance of isotonicity.
- It is used to prepare Boroglycerin Glycerite ($C_3H_5BO_3$), which is used as a suppository base.

Note: - Due to its toxic effects it is not used in preparations meant for internal use.

2. Hydrochloric Acid : HCl (Concentrated Hydrochloric Acid) Mol. Wt. 36.46

It is also known as chlorhydric acid and muriatic acid and spirit of salt. It contains not less than 35.0 % w/w and not more than 38.0% w/w of HCl.

Preparation:

1.From Sodium Chloride: - It can be prepared by reacting concentrated sulphuric acid with sodium chloride. The weighed amount of salt is taken in the cast-iron pan of a salt cake furnace, now an equal amount of concentrated sulphuric acid is allowed to run over it. Hydrogen chloride gas is evolved. Gently heat the furnace so as to complete the reaction.

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

The pasty mass of byproduct sodium hydrogen sulphate is heated in a muffle furnace to dull redness with the excess of sodium chloride so as to produce more hydrogen chloride, but this time it is mtore impure.

$$NaCl + NaHSO_4 \rightleftharpoons Na_2SO_4 + HCl$$

The hydrogen chloride so obained is passed by a pipeline into the tower containing lumps of coke, down which water falls. The crude concentrated acid is collected ait is contaminated with iron, sulphuric acid, sulphur dioxide, arsenic and other impurities.

2.From hydrogen and chlorine gases: Pure hydrochloric acid can be prepared using hydrogen and chlorine gases produced as by products during electrolysis of brine solution (sodium chloride solution) in the preparation of caustic soda.

In this process the chlorine is burned in large diameter silica tubes in the presence of hydrogen, to give hydrogen chloride, which is then absorbed in water to give hydrochloric acid.

$$H_2 + Cl_2 \longrightarrow 2HCl$$

Identification Tests:

1.Addition of hydrochloric acid to potassium permanganate results in the evolution of chlorine gas.

$$2KMnO_4 + 16HCl \longrightarrow 2MnCl_2 + 2KCl + 5Cl_2\uparrow + 8H_2O$$

In this test the hydrochloric acid is oxidized by potassium permanganate, a strong oxidizing agent, resulting in the evolution of chlorine gas. In the above test the potassium permanganate can be replaced by manganese dioxide.

2.It gives the reactions of chlorides

A. Due to the chloride ion it precipitates the metal ions such as Ag, Pb and Hg (I) in the form of insoluble chlorides of metals.

$$AgNO_3 + HCl \longrightarrow AgCl\downarrow + HNO_3$$

B. It reacts with a mixture of potassium dichromate and sulphuric acid and results in the evolution of chromyl chloride, which turns the colour of the strip moistened with solution of diphenyl carbazide in alcohol to violet red.

$$4Cl^- + Cr_2O_7^{2-} + 6H^+ \longrightarrow 2CrO_2Cl_2\uparrow + 3H_2O$$

Test for purity: It has to be tested for arsenic, heavy metals, bromide and iodide, free chlorine, sulphate, sulphite and residue on evaporation (non-volatile matter).

Test for bromide and iodide: 5 ml of the acid is diluted with 10ml of water and to this 1ml of chloroform is added. Now with constant shaking drop wise chlorinated lime solution is added, the chloroform layer does not become brown or violet.

In this test chlorinated lime act as oxidizing agent and liberates bromine or iodine from bromides or iodides. If any bromine or iodine is formed, it is extracted with chloroform. This changes the colour of chloroform layer.

Test for free chlorine: Take 60ml acid and add 50ml of carbon dioxide free water, then add 1ml of a 10% w/v solution of potassium iodide and 0.5ml of starch solution. The mixture is allowed to stand in the dark for 2 minutes. Any blue colour produced disappears on the addition of 0.2ml of 0.01M sodium thiosulphate.

In the test the free chlorine is detected by the liberation of iodine from potassium iodide. The amount of liberated iodine is detected by sodium thio-sulphate.

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

Starch is added to make adsorption complex with iodine, which is of blue colour.

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

Sodium thiosulphate Sodium tetrathionate

Assay: The assay is based upon acid-base titration. It involves titration of strong acid (HCl) with alkali hydroxide (NaOH) using methylred as indicator.

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

Method: Take about 2g accurately weighed acid is a conical flask. To this add 30ml of water mix the contents and titrate with 1M sodium hydroxide using methyl red solution as indicator.

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

Uses:

- It is mainly used as a pharmaceutical aid more specifically as an acidifying agent.
- Because of its strong acid character it can react with weakly basic organic molecules to form usually water soluble hydrochloride salts for extraction or other separation purposes, e.g. alkaloids, which are usually sparingly soluble in water, can be treated with HCl to form salts which are freely soluble in water.
- Now a days in various acid-base titrations hydrochloric acid is generally preferred to sulphuric acid because with certain indicators it gives a sharper end point.
- In the determination of calcium carbonate and calcium hydroxide sulphuric acid cannot be used because that gives precipitates of sparingly soluble calcium sulphate, while hydrochloric acid gives completely insoluble calcium chloride. For the same reason hydrochloric acid is used in the processes involving the titration of barium-hydroxide. Very dilute hydrochloric acid can be used as gastric acidifier in achlorhydria.

3. Nitric Acid : HNO_3 Mol. Weight 63.01

It contains not less than 69.0 percent and not more than 71.0 percent, by weight of HNO_3.

Preparation:

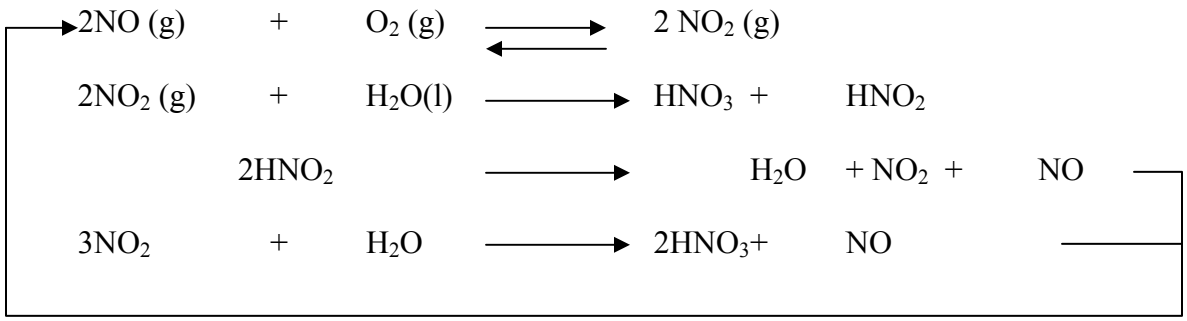
1.From sodium nitrate: In the laboratory, it can be prepared by heating a mixture of sodium nitrate and sulphuric acid.

$$NaNO_3 + H_2SO_4 \longrightarrow NaHSO_4 + HNO_3$$

2.By Ostwald process: The method involves the catalytic oxidation of ammonia to NO, followed by oxidation of NO to NO_2 and conversion of NO_2 with water to HNO_3.

$$4NH_3\,(g) + 5O_2 \xrightarrow[5 \text{ atmospheres, } 850^oC]{\text{Platinum / Rhodium catalyst}} 4NO\,(g) + 6H_2O\,(g)$$

The NO and air (O_2) are cooled and the mixture of gases is absorbed in a counter current of water.



Overall Reaction:

$$NH_3 + 2O_2 \longrightarrow HNO_3 + H_2O$$

This process gives dilute nitric acid (50% – 60% by weight), which is concentrated by distillation till it forms a constant boiling mixture (bp 121^{o}C). This is the ordinary concentrated HNO_3 and is 68% in strength. Fuming HNO_3 (98% HNO_3) can be obtained by distilling this acid with concentrated H_2SO_4. Fuming nitric acid may also be obtained by dissolving excess of NO_2 in concentrateds HNO_3. Crystals of pure HNO_3 may be obtained by cooling fuming HNO_3 in a freezing mixture.

Identification Test:

1.It gives positive tests for nitrate ions. Mix equal volumes of nitric and sulphuric acid. Cool the mixture and slowly add a solution of ferrous sulphate. A brown colour is produced at the junction of two liquids.

$$2HNO_3 + 3H_2SO_4 + 6FeSO_4 \longrightarrow 3Fe_2(SO_4)_3 + 4H_2O + 2\,NO\uparrow$$

$$NO + FeSO_4 \longrightarrow [Fe(NO)]SO_4$$

(Brown ring)

2. When nitric acid is heated with sulphuric acid and metallic copper, brownish red fumes are evolved. In this test nitric acid is decomposed by concentrated sulphuric acid to give

brownish red fumes of NO_2, which intensify on addition of copper turnings in the mixture.

$$4HNO_3 \xrightarrow{\text{Conc. } H_2SO_4} 4NO_2 \uparrow + O_2 \uparrow + 2H_2O$$

2. It gives xanthoproteic test. It produces a yellow stain on animal tissues. This yellow stain is because of nitration of aromatic acids, phenylalanine, tyrosine and tryptophan present in the protein of the skin.

Test for purity: It has to be tested for residue on ignition, chloride, sulphate, iron and heavy metals.

Assay: Its assay is based upon simple acid base titration.

A weighed sample is titrated against 1N sodium hydroxide using methyl red as an indicator.

$$HNO_3 + NaOH \longrightarrow NaNO_3 + H_2O$$

Each ml of 1N NaOH is equivalent to 0.06301 g of HNO_3.

Uses: It is the most important oxoacid of nitrogen. Besides as a useful acidifying agent, it is also used for its oxidizing and nitrating properties. When mixed with conc. H_2SO_4, the nitronium ion NO_2^+ is formed, which is the active species in the nitration of organic compounds. This is an important step in making important nitro compounds. It is an excellent oxidising agent particularly when hot and concentrated.

H^+ ions are oxidising, but the NO_3^- ion is an even stronger oxidising agent in acid solution. Thus metals such as copper and silver, which are insoluble in HCl, dissolve in HNO_3. Non-metals can also be oxidized with nitric acid. This reaction is used to produce sulphuric acid and phosphoric acid by treating elemental sulphur and phosphorous respectively with acid.

It can be used as a source of nitrate ion.

It can be used externally to destroy warts and chancres.

4. Phosphoric acid (Orthophosphoric; Concentrated phosphoric acid): H_3PO_4
Mol. Wt. 98.00

It contains not less than 84.0% w/w and not more than 90.0% w/w of H_3PO_4.

Preparation:

1.By Furnace method :Pure H_3PO_4 can be prepared by this method. Molten phosphorous is burnt in a furnace with air and steam. It results in the formation of P_2O_5 (phosphorous pentoxide) by reaction between P and O_2. This P_2O_5 is immediately hydrolysed by hot water to give liquid phosphoric acid

$$4P + 5O_2 \longrightarrow 2P_2O_5$$

$$P_2O_5 + 3H_2O \longrightarrow 2H_3PO_4$$

The liquid is transferred to a dish and evapourated to syrup. Concentrated acid contains about 85%by weight of H_3PO_4. 100% pure (anhydrous) H_3PO_4 is seldom used, but it can be prepared by evaporation at low pressure.

2.In laboratory it can be prepared by the action of concentrated HNO_3 on phosphorous .

$$P + 5HNO_3 \longrightarrow H_3PO_4 + 5NO_2 + H_2O$$

3. On large scale H_3PO_4 is prepared by digesting crushed mineral phosphate with dilute sulphuric acid.

$$Ca_3(PO_4)_2 + 3H_2SO_4 \rightleftharpoons 3CaSO_4 + 2H_3PO_4$$

The $CaSO_4$ is hydrated to gypsum ($CaSO_4.2H_2O$), which is separated from the solution along with other undissolved matter by filtration. The H_3PO_4 is concentrated by evaporation.

Test for identification:

1. Its aqueous solution is strongly acidic.
2. Its neutralized (neutralization is done with NaOH) aqueous solution gives following reactions of phosphates

$$2NaOH + H_3PO_4 \longrightarrow Na_3PO_4 + 2H_2O$$

a. On adding silver nitrate solution, a light yellow precipitate of silver phosphate (Ag_3PO_4) is formed. (Metaphosphates and pyrophosphates give white precipitates with silver nitrate). The colour of the precipitate is not changed by boiling and they are readily soluble in ammonia solution and in dilute nitric acid.

$$Na_3PO_4 + 3AgNO_3 \rightarrow Ag_3PO_4\downarrow + 3NaNO_3$$
(Yellow ppt)

$$Ag_3PO_4 \rightleftharpoons 3Ag^+ + PO_4^{3-}$$

$$Ag^+ + 2NH_3 \rightleftharpoons [Ag(NH_3)_2]^+$$
(Soluble silver-diamino complex)

b. On adding ammoniacal magnesium sulphate, solution a white crystalline precipitate of magnesium ammonium phosphate is formed.

$$Mg^{2+} + NH_4^+ + PO_4^{3-} \longrightarrow MgNH_4PO_4\downarrow$$
Magnesium Ammonium Phosphate

c. On adding dilute nitric acid and ammonium molybdate solution and warming the solution a bright yellow precipitate of a complex ammonium 12-molybdophosphate is slowly formed.

$$Na_3PO_4 + 3HNO_3 \longrightarrow 3NaNO_3 + H_3PO_4$$

$$H3PO_4 + 12(NH_4)_2MoO_4 + 21HNO_3 \longrightarrow (NH_4)_3[PO_4.MO_{12}O_{36}] + 12H_2O + 21NH_4NO_3$$
Canary yellow ppt.

Test for purity: It has to be tested for clarity and colour of the solution, arsenic, heavy metals, iron, chloride, sulphate, alkali phosphates, aluminium and calcium, hypophosphorous acid and phosphorous acid.

Impurities of calcium, iron and sulphate are usually present in phosphoric acid prepared directly from natural phosphates. As a result of incomplete oxidation, the acid prepared from phosphorous may contain phosphorous acid impurity. Impurities of phosphorous and hypophosphorous acids can be detected with silver nitrate which is reduced to silver by these impurities.

Assay: It contains three replaceable H atoms, and is tribasic. It undergoes stepwise dissociation

$H_3PO_4 \rightleftharpoons H^+ + H_2PO_4^-$ $K_{a1} = 7.5 \times 10^{3-}$ $(pK_{a1} = 2.12)$

$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$ $K_{a2} = 6.2 \times 10^{8-}$ $(pK_{a2} = 7.21)$

$HPO_4^{2-} \rightleftharpoons H^+ + PO_4^{3-}$ $K_{a3} = 1 \times 10^{12-}$ $(pK_{a3} = 12.32)$

The K_a values of the above reactions show the decrease in acid strength with each successive ionization. In the simple ionization process very little of the phosphate trianion, PO_4^{3-} is produced.

The official assay method (as given in IP 1996) includes titration of only the first two protons. The titration is done to the Na_2HPO_4 end point with 1M sodium hydroxide using dilute phenolphthalein solution as indicator.

$$H_3PO_4 + 2NaOH \longrightarrow Na_2HPO_4 + 2H_2O$$

Further in order to get more accurate end point the assay is carried out in the presence of sodium chloride.

Method: Weigh accurately about 1g, add a solution of 10g of sodium chloride in 30 ml of water and titrate with 1M sodium hydroxide using dilute phenolphthalein solution as indicator.

1 ml of 1M sodium hydroxide is equivalent to 0.04900g of H_3PO_4.

Uses:

- It is used as pharmaceutical aid (acidifying agent) but the solubilities of the various phosphate salts produced limits its use as an acidifying agent.
- It is nonvolatile and does not possess oxidizing properties, thus it can be used wherever a non-oxidizing acid is required e.g. in the synthesis of HBr from NaBr and in the synthesis of HI from NaI, it will substitute sulphuric acid which cannot be used because of its oxidizing action.
- On treatment with NaOH it gives mixtures of NaH_2PO_4 and Na_2HPO_4, which are used in the preparation of phosphate buffer system.

5. Sulphuric Acid : H_2SO_4 (Oil of Vitriol) Mol. Wt. – 98.07

It contains not less than 95% and not more than 98%, by weight, of H_2SO_4.

Preparation:

1. **From SO_2**

   Sulphuric acid is commercially the most important acid and is manufactured by two processes, namely chamber process and contact process. Each of the two processes is suited to certain concentration and purity of the product. By chamber process sulphuric acid of about 78% strength can be prepared and by contact process about 100% pure sulphuric acid can be produced.

   A. **Lead chamber process**. It involves oxidation of sulphur dioxide by atmospheric oxygen in the presence of oxides of nitrogen (NO_2) as catalyst. This process is now obsolete.

   B. **Contact process**. It involves the oxidation of sulphur dioxide by air at low temperature (optimum temp is 400 – 450^oC), high pressure (about 1.6 to 1.7 atm), excess of oxygen and presence of catalyst (platinum, ferric oxide or vanadium pentoxide) to give sulphur trioxide, which when dissolved in 98% sulphuric acid gives oleum ($H_2S_2O_7$) which on dilution with water gives sulphuric acid.

$$2SO_2 + O_2 \underset{}{\overset{\text{Catalyst}}{\rightleftharpoons}} 2SO_3$$

$$SO_3 + H_2SO_4\ (98\%) \longrightarrow H_2S_2O_7$$
(Oleum or pyrosulphuric acid)

$$H_2S_2O_7 + H_2O \longrightarrow 2H_2SO_4$$

In the above process the SO_3 can be mixed with water to give H_2SO_4, but the reaction is violent and produces a dense chemical mist which is difficult to condense.

2. **From Sulphur:** On laboratory scale it can be prepared by boiling sulphur with nitric acid.

$$S + 6HNO_3 \xrightarrow{\text{boil}} H_2SO_4 + 6NO_2 + 2H_2O$$

Identification Test :

1. It gives tests for sulphate ion
   a. On treatment with $BaCl_2$ solution, white precipitate is produced which is insoluble in hydrochloric acid and in nitric acid.
      $SO_4^{2-} + BaCl_2 \longrightarrow BaSO_4 + 2Cl^-$
   b. With lead acetate solution, it gives a white precipitate which is soluble in ammonium acetate solution.
      $SO_4^{2-} + (CH_3COO)_2Pb \longrightarrow PbSO_4 \downarrow + 2CH_3COO^-$

Test for purity: It has to be tested for residue on ignition, chloride, arsenic, heavy metals and reducing substance.

Assay: A weighed sample of acid is titrated against 1N sodium hydroxide using methyl orange as an indicator.

The assay is based upon simple acid-base titration method in which strong acid (Sulphuric Acid) is titrated with strong base (sodium hydroxide) in the presence of methyl orange as an indicator.

Each ml of 1N Sodium hydroxide is equivalent to 0.04904g of H_2SO_4.

Uses:

- It is used as a pharmaceutical aid (acidifying agent).
- It is used to form water soluble salts of basic organic drug molecules.
- It can also be used as a dehydrating agent in many reactions such as esterification and nitration where water has to be removed. Sulphuric acid is applied in drying gases which do not react with the acid (e.g. SO_2, Cl_2, HCl etc.)
- In inorganic qualitative analysis, it is used to detect the certain basic radicals such as Barium, Strontium and lead as it forms insoluble sulphates with these basic radicals (sulphate salts of most metals are soluble in water).

  $Ba^{2+} + H_2SO_4 \longrightarrow BaSO_4 \downarrow + 2H^+$

- It is used to sulphonate fatty acids to make detergents.

Uses and Formulation of Bases

1. Strong Ammonia Solution (Ammonium hydroxide, stronger ammonia water): NH_3 Mol. Wt. 17.03

Strong ammonia solution is a solution of NH_3, containing not less than 27.0% and not more than 31.0% (w/w) of NH_3. On exposure to air it loses ammonia rapidly.

Preparation:

1. **From binary metal compounds.** It can be prepared from binary metal compounds such as Mg_3N_2, Ca_3P_2 by the action of water or dilute acids.

   $Mg_3N_2 + 6H_2O \longrightarrow 3Mg(OH)_2 + 2NH_3$

2. **From Nitrogen (Haber Process).** On commercial scale it can be prepared by the Haber process, which involves the direct combination of N_2 and H_2.

   $N_2 + 3H_2 \longrightarrow 2NH_3$

   The reaction is allowed to take place at 450 – 550^oC under a pressure of 100 – 1000 atmosphere.

   At 20^oC and one atmosphere pressure 53.1g NH_3 dissolves in 100g of water. Therefore, its 27.0% solution can be prepared by dilution of the above mentioned solution.

In solution ammonia forms ammonium hydroxide (NH_4OH) and behaves as a weak base.

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

The chemical reactions and various other properties of ammonia solution is due to the presence of NH_3.

Identification Test:

1. Dip a glass rod in hydrochloric acid and bring it near the surface of the NH_3 solution, dense, white fumes are produced. The test is based upon reaction of NH_3 with HCl.

   $$NH_3 \uparrow + HCl \longrightarrow NH_4Cl$$

2. Because of its ability to give hydroxyl ions, aqueous ammonia had basic character and thus turns red litmus blue and phenolphthalein pink.

   $$NH_3\,(aq.) + H_2O \rightleftharpoons NH_4^+ + OH^-$$

3. With Nessler's reagent it gives reddish brown precipitate.

   $$HgCl_2 + 2KI \longrightarrow 2KCl + HgI_2 \downarrow \text{(Red ppt.)}$$

   $$HgI_2 + 2KI \longrightarrow K_2HgI_4$$

   (Nesseler's reagent)

   $$K_2HgI_4 + NH_3{+}3KOH \longrightarrow H_2N \,.\, HgO \,.\, HgI\downarrow + 7KI + 2H_2O$$

Test for purity: It has to be tested for heavy metals, limit of nonvolatile residue and readily oxidisable substances.

Assay: Weigh accurately about 3g in a flask containing 50 ml of 1 N H_2SO_4 and titrate the excess of acid with 1 N NaOH using solution of methyl red as indicator.

Each ml of 1 N H_2SO_4 ≡ 0.01703g of NH_3

Uses:

- It is used as a pharmaceutical aid. Mainly, it is used in making ammonia water by dilution and as a chemical reagent.
- It is a good laboratory reagent. It is used as a base (Bronsted base) to form ammonium salts of acids, and to make certain solutions alkaline e.g. in the limit test for iron.
- It combines with certain cations like Ag^+, Cu^{2+}, Hg^{2+} etc. and forms very stable soluble complex cations.

  $$AgCl + \underset{\text{(Excess)}}{2NH_4OH} \longrightarrow \underset{\substack{\text{(Silverammine Chloride)}\\ \text{Soluble}}}{[Ag(NH_3)_2]Cl} + H_2O$$

- It is also used in preparing ammoniacal silver nitrate solution (Tollen's reagent).

2. Calcium Hydroxide: $Ca(OH)_2$ Mol. Wt. 74.09

It contains not less than 95.0% and not more than 100.5% of $Ca(OH)_2$.

Preparation: From calcium oxide: It is manufactured by the process of slaking from quick lime or calcium oxides (CaO), through the addition of water in limited amounts. The calcium oxide absorbs water and there is evolution of large amount of heat. The CaO lumps swell and disintegrate into a fine powder of $Ca(OH)_2$. The calcium hydroxide so obtained is mixed with excess of water and allowed to settle. The supernatant liquid is decanted and the residue is air dried.

$$CaO + H_2O \longrightarrow Ca(OH)_2$$

Test for Identification:

A. When mixed with from 3 to 4 times its weight of water it forms a smooth magma. The clear supernatant liquid from the magma is alkaline to litmus.

B. Mix 1g with 20 ml of water, and add sufficient 6N acetic acid to make solution. The resulting solution gives following tests for calcium.

1. To 5 ml of above solution add 1 ml of glacial acetic acid and 0.5 ml of potassium ferrocyanide solution. The resulting solution remains clear. On adding about 50 mg of NH_4Cl, a white, crystalline precipitate is formed.

$$2Ca^{++} + K_4Fe(CN)_6 \longrightarrow Ca_2Fe(CN)_6 + 4K^+$$

$$Ca_2Fe(CN)_6 + 2NH_4Cl \longrightarrow (NH_4)_2Ca[Fe(CN)_6]\downarrow + CaCl_2$$

White ppt.

2. Take 5 ml of the prepared solution and add 0.2 ml of a 2% w/v solution of ammonium oxalate, a white precipitate is obtained that is only sparingly soluble in dilute acetic acid but is soluble in hydrochloric acid.

$$(NH^+_4)_2(COO^-)_2 \rightleftharpoons 2NH_4^+ + \begin{matrix} COO^- \\ | \\ COO^- \end{matrix}$$

$$Ca^{2+} + \begin{matrix} COO^- \\ | \\ COO^- \end{matrix} \longrightarrow \begin{matrix} COO \\ | \quad \diagdown \\ COO \quad Ca \end{matrix}$$

(Calcium Oxalate)

$$\begin{matrix} COO \\ | \quad \diagdown \\ COO \quad Ca \end{matrix} + 2HCl \longrightarrow CaCl_2 + \begin{matrix} COOH \\ | \\ COOH \end{matrix}$$

(Oxalic acid)

3. Take 5 ml of the prepared solution, add 5 ml of ammonium carbonate solution; a white precipitate is formed which, after boiling and cooling the mixture, is only sparingly soluble in ammonium chloride solution.

$$Ca^{2+} + (NH_4)_2CO_3 \longrightarrow CaCO_3 \downarrow + 2NH_4^+$$

(White ppt.)

Test for Purity: It is tested for limit of acid – insoluble substances, carbonate, heavy metals, chloride, sulphate, phosphate and limit of magnesium and alkali salts.

Assay: It's assay is based upon the principle of complexometric titrations in which calcium ions form a complex with disodium EDTA. The pH of the solution is adjusted to 12 by using sodium hydroxide.

Method: Weigh accurately about 1.5g of $Ca(OH)_2$ and transfer it to a beaker and gradually add 30 ml of 3N hydrochloric acid. When solution is complete, transfer the solution to a 500 ml volumetric flask, rinse the beaker thoroughly, adding the rinsings to the flask, dilute with water to volume, and mix. Pipette 50 ml of the solution into a suitable container, add 100 ml of water, 15 ml of 1N sodium hydroxide and 300 mg of hydroxynaphthol blue trituration, and titrate the contents with 0.05 M disodium ethylenediaminetetraacetate to a blue end point.

Each ml of 0.05 M disodium ethylenediaminetetraacetate is equivalent to 3.705 mg of $Ca(OH)_2$.

Uses: It is used in various pharmaceutical preparations because of its high hydroxide ion concentration. It is used to prepare calcium soaps of fatty acids, which have emulsifying properties and can be used in the preparation of suspensions or mixing of other ingredients.

It can also be used as a topical astringent and as a fluid electrolyte (as a source of calcium).

It can absorb CO_2; for this property it is used in soda lime (A mixture of calcium hydroxide and sodium hydroxide) to absorb CO_2 from expired air in metabolic function test and in closed circuit anesthetic machine. It is used to prepare bleaching powder and for softening of water.

Available as Calcium hydroxide solution (A solution containing, not less than 140 mg of $Ca(OH)_2$ in each 100 ml). It is prepared by adding 3 g of calcium hydroxide to 1000 ml of purified water. The mixture is agitated repeatedly for a period of one hour. The excess calcium hydroxide is allowed to settle down. The clear supernatant liquid is used.

3. Potassium Hydroxide (Caustic Potash): KOH Mol. Wt. 56.11

It contains not less than 85.0% of total alkali, calculated as KOH, including not more than 3.5% of K_2CO_3 as per USP and not more than 4.0% of K_2CO_3 as per B.P.

Preparation:

(1) By electrolysis of KCl solution: It can be prepared by the electrolysis of KCl solution in a diaphragm cell. The caustic liquor obtained is evapourated and the resulting fused potassium hydroxide is either allowed to solidify and then broken up, or cast into sticks, or made into the more convenient pellets.

$$KCl_{(aq)} \underset{}{\overset{\text{Electrolysis}}{\rightleftharpoons}} K^+ + Cl^-$$

$$H_2O \underset{}{\overset{\text{Electrolysis}}{\rightleftharpoons}} H^+ + OH^-$$

At cathode $2H^+ + 2e^- \longrightarrow H_2$

At Anode $2Cl^- \longrightarrow Cl_2 + 2e^-$

In solution: - $K^+ + OH^- \longrightarrow KOH$

(2) By the action of lime on potassium carbonate

$$Ca(OH)_2 + K_2CO_3 \longrightarrow CaCO_3 + 2KOH$$

(3) It may also be prepared by the action of $Ba(OH)_2$ on potassium sulphate.

$$K_2SO_4 + Ba(OH)_2 \longrightarrow 2KOH + BaSO_4 \downarrow$$

Identification Tests: A Solution (1 in 25) responds to the following tests for potassium.

1. It gives a violet colour to a nonluminous flame, (the presence of small quantities of sodium masks the colour).
2. On adding sodium hydrogen tartrate to the neutral aqueous solution of the compound, a white crystalline precipitate of potassium hydrogen tartrate is produced. The precipitate is soluble in 6N ammonium hydroxide and in solutions of alkali hydroxides and carbonates. Stirring or rubbing the inside of the test tube with a glass rod can accelerate the formation of the precipitate. The addition of a small amount of glacial acetic acid or alcohol also helps precipitation.

   $NaHC_4H_4O_6$ + KOH $\longrightarrow$ $KHC_4H_4O_6$ + NaOH (Sodium hydrogen tartrate) (Potassium hydrogen tartrate)

3. A fairly dilute aqueous solution of potassium hydroxide gives a yellow precipitate of potassium cobaltinitrite, with sodium cobaltinitrite.

   $3KOH + Na_3[CO(NO_2)_6] \longrightarrow K_3[CO(NO_2)_6] + 3NaOH$

   Potassium cobaltinitrite (Yellow ppt.)

4. To the aqueous solution of sample add platinic chloride (Chloroplatinic acid) solution in the presence of hydrochloric acid; a yellow crystalline precipitate of potassium chloroplatinate is formed.

   $H_2PtCl_6 + 2K^+ \longrightarrow K_2[PtCl_6] + 2H^+$

Note: Ammonium salts also give positive responses to all the above precipitation tests for potassium. Therefore, ammonium salts should be removed by ignition, before testing for potassium.

Test for purity: It has to be tested for insoluble substances, heavy metals.

Potassium hydroxide can be adulterated with sodium (in the form of sodium hydroxide). Sodium because of its lower equivalent actually increases the apparent percentage of total alkali. Antimonate test can be done for the detection of significant amounts.

Antimonate Test for the detection of sodium as impurity in potassium compounds. The test is done with aqueous – alcoholic solution of the KOH sample. An alkaline solution of the potassium antimonate gives with sodium salts a white, amorphous precipitate of the sodium antimonite, which rapidly changes to the crystalline pyroantimonate.

$$KSbO_3 \cdot 2H_2O + Na^+ \longrightarrow NaSbO_3 \cdot 3H_2O + K^+$$

Potassium Antimonate Sodium Antimonate

$$2NaSbO_3.3H_2O \xrightarrow{H_2O} Na_2H_2Sb_2O_7 \cdot 6H_2O$$

Crystalline pyroantimonate

The test is of some sensitivity if done in aqueous – alcoholic solution, because, solubility of the pyroantimonate is about 1 in 350 in cold water and it is almost insoluble in alcohol.

Assay: The assay is done by the modified Winkler method, Winkler method is the most satisfactory process for the determination of alkali hydroxide and carbonate when present together.

Method: Dissolve about 1.5 g of potassium hydroxide, accurately weighed in 40 ml of carbon dioxide free water. Cool the content to 15^o, add phenolphthalein and titrate with 1N sulphuric acid. At the discharge of the pink colour of the indicator, record the volume of acid solution required, then add methyl orange and continue the titration to a persistent pink colour.

Each ml of 1N sulphuric acid is equivalent to 56.11 mg of total alkali, calculated as KOH, and each ml of acid consumed in the titration with methyl orange is equivalent to 138.2 mg of K_2CO_3.

In the assay, firstly the hydroxide in the solution is determined by titration with N/1 sulphuric acid, using phenolphthalein as indicator. In the titration to phenolphthalein end point two titrations occur.

$$2KOH + H_2SO_4 \longrightarrow K_2SO_4 + 2H_2O$$

$$2K_2CO_3 + H_2SO_4 \longrightarrow K_2SO_4 + 2KHCO_3$$

The titration is done slowly and with constant shaking, the indicator changes colour before any of the $KHCO_3$ is acted upon by the acid. Methyl orange is now added, and the titration is continued to the pink end-point.

$$2KHCO_3 + H_2SO_4 \longrightarrow K_2SO_4 + CO_2 + H_2O$$

Uses: It is used as a pharmaceutical aid in several pharmaceutical preparations.

Potassium hydroxide is a very strong base. It is mainly used as a base or alkaline reagent. It possess caustic or corrosive effect on tissues, therefore, great care shall be taken while handling potassium hydroxide, as it rapidly destroys tissues. It is used to manufacture the soft soap. In I.P. 1996 the acid value and saponification value of fatty substances are defined in terms of potassium hydroxide. It can be used in place of sodium hydroxide in soda lime as it can absorb CO_2. Its aqueous and alcoholic solutions can be used for titrating acids. In the form of alcoholic solution (alcoholic caustic potash) it can be used in organic chemistry, especially in the elimination of hydrogen halide.

$$C_2H_5Br + KOH\ (Alc) \longrightarrow C_2H_4 + KBr + H_2O$$

It is available as potassium hydroxide and potassium hydroxide solution.

4. Sodium Carbonate: (Carbonic acid disodium salt, Disodium carbonate) Na_2CO_3
Mol. Wt. Anhydrous 105.99 Monohydrate 124.00

Sodium carbonate is anhydrous or contains one molecule of water of hydration. It contains not less than 99.5% and not more than 100.5% of Na_2CO_3 calculated on the anhydrous basis.

Preparation: It exists in various forms, namely anhydrous sodium carbonate Na_2CO_3 (Soda-ash); monohydrate $Na_2CO_3 . H_2O$ (crystal carbonate); heptahydrate $Na_2CO_3 . 7H_2O$ and decahydrate $Na_2CO_3 . 10H_2O$ (washing soda or sal soda).

1. **From Solvay** (**Ammonia Soda) Process**: Most of the Na_2CO_3 is produced synthetically by the solvay (ammonia-soda) process.

   In this process, brine (NaCl), ammonia and carbon dioxide are used as raw materials. The chemical reactions involved are as below:

$$NH_3 + H_2O + CO_2 \longrightarrow NH_4HCO_3$$

$$NaCl + NH_4HCO_3 \longrightarrow NaHCO_3 \downarrow + NH_4Cl$$
(Sodium Bicarbonate)

$$2NaHCO_3 \xrightarrow{150^o} Na_2CO_3 + CO_2 + H_2O$$

$$CaCO_3 \xrightarrow[\text{Lime Kiln}]{1100^oC\ \text{in}} CaO + CO_2$$

$$CaO + H_2O \longrightarrow Ca(OH)_2$$

$$2NH_4Cl + Ca(OH)_2 \longrightarrow 2NH_3 + CaCl_2 + 2H_2O$$

The first stage in the process is to purify saturated brine, and then react it with gaseous ammonia. Now the ammoniated brine is carbonated with CO_2 to form $NaHCO_3$.Because of the common ion effect this $NaHCO_3$ is insoluble in the brine solution and therefore can be filtered off. On heating

to 150°C $NaHCO_3$ is decomposed to anhydrous Na_2CO_3 (called light soda ash because it is fluffy solid with a low packing density of about 0.5g cm^{-3}). CO_2 is removed by heating the solution, and the CO_2 is reused. Limestone ($CaCO_3$) is heated to provide Lime (CaO) and CO_2, which is required in the reaction. On mixing with water lime gives $Ca(OH)_2$ which drives off NH_3 from NH_4Cl.

Thus the materials consumed are NaCl and $CaCO_3$, and there is formation of one useful product, Na_2CO_3, and one by-product, $CaCl_2$. As very small amount of $CaCl_2$ is required so only a small amount is recovered from solution, and the rest is wasted.

2. **From natural deposit**. It can also be obtained from a natural deposit called Trona, (Na_2CO_3 . $NaHCO_3$. $2H_2O$), obtained from dried up lake beds in Egypt. Trona is sometimes called sodium sesquicarbonate and this is converted to sodium carbonate by heating.

$$2(Na_2CO_3 \cdot NaHCO_3 \cdot 2H_2O) \xrightarrow{\text{heat}} 3Na_2CO_3 + CO_2 + 5H_2O$$

3. **By electrolysis of sodium chloride**. It can be prepared by the electrolysis of sodium chloride. By this sodium is produced at cathode and chlorine is formed at anode. Sodium reacts with water and gives sodium hydroxide. This solution on treatment with carbon dioxide gives sodium carbonate.

4. **The monohydrate form of Na_2CO_3** can be prepared by crystallizing a concentrated solution of this salt at a temperature above 35°C. Stirring is done so as to make small crystals. Crystals contain about 15% water of crystallization.

The largest use of Na_2CO_3 is for glass making and for this heavy ash is required which is chemically Na_2CO_3 . H_2O. It can be prepared by recrystallisation of 'light ash' produced in the Solvay process, from hot water.

Identification Tests:

A. A 1 in 10 solution is strongly alkaline to phenolphthalein.

B. It gives tests for sodium and for carbonate.

Tests for Sodium:

1. To the aqueous solution of the compound add potassium carbonate and heat to boiling no precipitate is formed. Now add freshly prepared potassium antimonate solution and heat to boiling. Allow to cool in ice and if necessary scratch the inside of the test tube with a glass rod, a dense, white precipitate is formed.

   Sodium salts give a white amorphous precipitate of sodium antimonate on reaction with alkaline solution of potassium antimonate. The amorphous precipitate immediately changes to crystalline form due to the formation of sodium pyroantimonate.

$$KSbO_3 \cdot 3H_2O + Na^+ \longrightarrow \underset{\text{(Sodium Antimonate)}}{NaSbO_3 \cdot 3H_2O} + K^+$$

$$2NaSbO_3 \cdot 3H_2O \xrightarrow{H_2O} \underset{\text{(Sodiumpyroantimonate)}}{Na_2H_2Sb_2O_7.6H_2O}$$

2. An acidified solution (acidification is done with acetic acid) of the substance on reaction with a large excess of magnesium uranyl acetate solution gives a yellow crystalline precipitate.

$$Na^+ + 3(CH_3COO)_2\,UO_2 + (CH_3COO)_2Mg + CH_3COOH \rightarrow NaMg(UO_2)_3\,(CH_3COO)_9 + H^+$$

(Sodium magnesium uranyl-acetate)

Tests for carbonate:

a. Carbonates and bicarbonates effervesce with acids, evolving a colourless gas, which when passed into calcium hydroxide produces a white precipitate immediately.

$$Na_2CO_3 + 2HCl \longrightarrow H_2CO_3 + 2NaCl$$

$$H_2CO_3 \longrightarrow CO_2 + H_2O$$

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

b. A cold solution of the compound is coloured by phenolphthalein, while a similar solution of bicarbonate remains unchanged or is only slightly coloured.

Test for purity: It has to be tested for water, heavy metals and organic volatile impurities.

Assay : Sodium carbonate is a strong base (its 1M solution has a pH of 11.6). This high alkalinity in solution is because of the hydrolysis of the carbonate anion, which is a strong base, and because of the hydrolysis of bicarbonate ion.

$$CO_3^{2-} + H_2O \rightleftharpoons HCO_3^- + OH^-$$

$$HCO_3^- + H_2O \rightleftharpoons H_2CO_3 + OH^-$$

Thus it can be assayed by titrating its solution with a strong acid such as H_2SO_4, using methyl orange as indicator.

$$Na_2CO_3 + H_2SO_4 \longrightarrow Na_2SO_4 + H_2O + CO_2 \uparrow$$

Method: Transfer the anhydrous sodium carbonate obtained in the test for water to a flask with the aid of 50 ml of water, add methyl orange and titrate with 1N sulphuric acid.

Each ml of 1N sulphuric acid is equivalent to 52.99 mg of Na_2CO_3.

Uses: It is mainly used as a pharmaceutical aid for its basicity, in various pharmaceutical preparations. It is used to form sodium salts of acidic drugs. It is also used in the softening of water. It may also be used in the preparation of carbonates of various metals.

5. Sodium Hydroxide (Caustic Soda) NaOH Mol. Wt. 40.00

It contains not less than 97.0% and not more than 100.5% of total alkali calculated as NaOH.

Preparation:

1. From electrolysis of NaCl: On large scale it is produced by the electrolysis of a concentrated aqueous solution of NaCl (brine) using either a diaphragm cell or a mercury cathode cell. Since chlorine is one of the by products, it may react with NaOH forming NaCl and sodium hypochlorite, therefore to avoid reaction between NaOH and Cl_2 specially designed

electrolytic cells e.g. Nelson cell (or diaphragm cell) and Castner-Kellner cell (or mercury cathode cell) are used.

$$NaCl\ (aq) \rightleftharpoons Na^+ + Cl^-$$

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

A. Reaction in Nelson Cell: -

At Cathode : $2H^+ + 2e^- \longrightarrow H_2$

At Anode : $2Cl^- \longrightarrow Cl_2 + 2e^-$

The solution remained behind contains Na^+ and OH^- and thus about 10-15% NaOH is obtained. It is concentrated under vacuum to 50% when NaCl (being less soluble) is almost separated. The filtrate is evapourated and dry mass is fused and cast into sticks.

B. Mercury Cathode Process: -

$$NaCl\ (aq) \rightleftharpoons Na^+ + Cl^-$$

At Cathode (mercury) : $2Na^+ + 2e^- \longrightarrow 2Na$

$Na + Hg \longrightarrow NaHg$ (Sodium Amalgam)

At Anode (graphite) : $2Cl^- \longrightarrow Cl_2 + 2e^-$

Sodium amalgam is removed from cell. It is then decomposed in a separate cell by water giving NaOH, hydrogen and mercury.

$$Hg_xNa_2 + 2H_2O \longrightarrow 2NaOH + xHg + H_2\uparrow$$

2. From Sodium Carbonate (Causticizing Process): It is an old process. A 10% solution of Na_2CO_3 is heated with a little excess of milk of lime ($Ca(OH)_2$).

$$Na_2CO_3 + Ca(OH)_2 \longrightarrow CaCO_3\downarrow + 2NaOH$$

The sodium hydroxide can be separated by filtration. The filtrate is collected and evapourated to get molten NaOH. This is then converted into sticks, scales, pellets or masses.

Note: Commercial sodium hydroxide, besides other impurities, contains some amount of sodium carbonate due to the absorption of atmospheric CO_2. However it may be purified by dissolving it in alcohol in which impurities including Na_2CO_3 are insoluble. The filtrate may be used as pure NaOH solution or may be evapourated in a silver basin to get solid NaOH.

Test for identification:

1. The pH of its 0.01% w/v solution is not less than 11.0.
2. Its neutralized (neutralization is done with HCl) aqueous solution gives reactions of sodium.

A. To the above solution add 15% w/v solution of potassium carbonate and heat to boiling, no precipitate is produced. Now add few ml of freshly prepared potassium antimonate solution and heat to boiling. Allow to cool in ice and if necessary scratch the inside of the test-tube with a glass rod; a dense white precipitate is formed.

In the above test sodium reacts with potassium antimonate alkaline solution ($KSbO_3.3H_2O$) and gives a white amorphous precipitate of the sodium antimonate, $NaSbO_3.xH_2O$, which immediately changes to the crystalline pyroantimonate, $Na_2H_2Sb_2O_7.6H_2O$.

$$Na^+ + KSbO_3.3H_2O \xrightarrow{H_2O} NaSbO_3.3H_2O\ K^+$$

$$2NaSbO_3.3H_2O \xrightarrow{H_2O} Na_2H_2Sb_2O_7.6H_2O\downarrow$$

Sodium pyroantimonate

B. Acidify the above prepared solution with acetic acid and add a large excess of magnesium uranyl acetate solution, a yellow crystalline precipitate will be produced.

$$Na^+ + 3(CH_3COO)_2UO_2 + (CH_3COO)_2Mg + CH_3COOH \rightarrow NaMg(UO_2)_3\ (CH_3COO)_9 + H^+$$

Sodium Magnesium Uranyl Acetate

Test for purity: It is tested for clarity and colour of solution, arsenic, heavy metals, iron, carbonate, chloride, sulphate and potassium.

Assay: Commercial sodium hydroxide contains soluble carbonate, which are calculated as Na_2CO_3 and are determined in the assay of NaOH. Therefore the assay of NaOH is based upon modified Winkler method which is considered as the most satisfactory method for the determination of alkali hydroxide and carbonate when present together.

The mixture is titrated with a standard solution of HCl or H_2SO_4 by the selective use of indicators. With HCl, the reaction proceeds in the following way:

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

$$Na_2CO_3 + HCl \longrightarrow NaCl + NaHCO_3$$

This $NaHCO_3$ further reacts with HCl.

$$NaHCO_3 + HCl \longrightarrow NaCl + H_2O + CO_2$$

The phenolphthalein is added as first indicator, which loses its colour of alkaline medium when NaOH and half Na_2CO_3 are neutralized. In fact, it does not give colour in $NaHCO_3$ solution.

Now use of methyl orange as second indicator is made which shows the complete neutralization, that is a red colour is obtained at end point.

Method: Weigh accurately about 2g, dissolve it in about 80ml of carbon dioxide free water, add 0.3ml of phenolphthalein solution and titrate with 1M hydrochloric acid. Add 0.3ml of methyl orange solution and continue the titration with 1M hydrochloric acid.

Each ml of 1M HCl used in the 2nd part of the titration is equivalent to 0.1060g of Na_2CO_3.

Each ml of 1M HCl used in the combined titration is equivalent to 0.0400g of total alkali, calculated as NaOH.

Uses:

1. It is the most important alkali used in pharmaceutical industry. It is used for a wide variety of purposes including making many inorganic and organic compounds, neutralizations and making soaps. It is used to make water soluble sodium salts of various organic drugs.
2. It is also used in making soda lime. It is used as a saponifying agent.

3. It is a powerful cautery and breaks down proteins of the skin thereby damage tissues, therefore, it has been used to remove warts.

Buffers

Introduction : Buffers are widely employed in the field of pharmaceutical chemistry and pharmacy. They are used as ingredients in pharmaceutical preparations either to adjust the pH of the preparation to a value required for maximum stability or to maintain the pH within a specified range for optimal physiological activity. Control of pH is an important aspect to be considered for chemical stability and solubility of the drug and for patient comfort. Deviation of pH values may render the pharmacologically active drug ineffective. Many reactions, particularly the biochemical reactions, in the laboratory, are to be carried out at constant pH. For all such above-mentioned purposes we need a solution, which can have constant pH.

A solution whose pH is not altered to any great extent by the addition of small quantities of either an acid (H_3O^+) or a base (OH^-) is called the buffer solution. In other words the buffer system consist of pairs of related chemical compounds which resist large changes in the pH of the system produced by the addition of small amounts of acid or base.

The buffer system is usually composed of one of the following.

1. A weak acid and its salt with a strong base e.g., boric acid and sodium borate.
2. A weak base and its salt with a strong acid e.g., ammonium hydroxide and ammonium chloride.
3. A solution of an amphoteric electrolyte e.g., glycine
4. A concentrated solution of a strong acid e.g., HCl
5. A concentrated solution of strong base e.g., NaOH

The ability of some solutions to resist the changes in pH upon addition of an acid or a base is known as buffer action. e.g., consider a mixture of a weak acid (acetic acid) and its salt with strong base (sodium acetate). The two components together constitute the buffer pair. The two components of the buffer system complement each other. Acetic acid being a weak acid is only slightly dissociated and its dissociation is further suppressed by the common ion (CH_3COO^-) provided by the almost complete dissolution of strong electrolyte, sodium acetate. Thus, the mixture consists of unionized acetic acid molecules as well as acetate and sodium ions.

$$CH_3COO^-Na^+ \longrightarrow CH_3COO^- + Na^+$$

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

If a small quantity of a strong acid is added to this solution, the H^+ ions of it are immediately neutralized by acetate ion to form the very slightly dissociated acetic acid thereby resisting the change in pH.

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

Similarly, when small quantity of a strong base is added, the hydroxide ions of it are neutralized by acetic acid to form water and acetate ion and again there is no change in the pH of the solution. Thus, each component of the buffer system combines with either acid or base to form the other component, thereby resisting the large changes in pH.

Buffer solutions are formulated to produce pH's within particular ranges. The pH of a buffer solution can be determined with the help of buffer equation or Henderson-Hasselbalch equation. The buffer equation for a weak acid and its salt is given by

$$pH = pK_a + \log \{[Salt] / [Acid]\}$$

and that for a weak base and its salt is given by

$$pH = pK_w - pK_b + \log \{[Base] / [Salt]\}$$

The buffer capacity is the measure of the effectiveness of the buffer in controlling the pH of the solution of upon addition of an acid or a base. Buffer capacity (β) is defined as the quantities of acid or base required to alter the pH of 1 litre of a buffer solution by 1 unit. Buffer capacity is also known as buffer coefficient, buffer efficiency or buffer index.

$$\beta = \delta B / \delta pH$$

A buffer solution consisting of a weak acid and its salt has the maximum buffer capacity when $pH = pK_a$, i.e. when there is equal concentration of weak acid and its salt.

Buffer Solutions: According to I.P., buffer solutions have been classified into two categories:

(A) Standard Buffer Solution and (B) Other Buffer Solution

A. Standard buffer solutions: They are the solutions of standard pH. They are used for reference purposes in pH measurement and for carrying out many pharmacopoeial tests which require adjustments to or maintenance of a specified pH.

Standard buffer solutions having pH ranges between 1.2 and 10.0 can be prepared by appropriate combinations of the solutions described below:

1. **Boric acid and potassium chloride, 0.2M:** Dissolve 12.366 g of boric acid and 14.911 g of potassium chloride in water and make up the volume to 1000 ml with water.
2. **Disodium hydrogen phosphate, 0.2M:** Dissolve 71.630 g of disodium hydrogen phosphate in water and make up the volume to 1000 ml with water.
3. **Hydrochloric acid, 0.2M:** Dilute hydrochloric acid with water to contain 7.292 g of HCl in 1000 ml and standardize it.
4. **Potassium chloride, 0.2M:** Dissolve 14.911 g of potassium chloride in water and make up the volume to 1000 ml with water.
5. **Potassium dihydrogen phosphate, 0.2M:** Dissolve 27.218 g of potassium dihydrogen phosphate in water and make up the volume to 1000 ml with water.

6. **Potassium hydrogen phthalate, 0.2M:** Dissolve 40.846 g of potassium hydrogen phthalate in water and make up the volume to 1000ml with water.

7. **Sodium hydroxide, 0.2M:** Dissolve sodium hydroxide in water to produce a 40-60% w/v solution and allow to stand. Siphon off the clear supernatant liquid avoiding absorption of CO_2, dilute with water to contain 8.0 g NaOH in 1000 ml and standardize it.

All the crystalline reagents except boric acid should be dried at 110º-120º for one hour before use. The water used for the preparation of buffer solution should be carbon dioxide-free.

Composition of standard buffer solutions:

1. **Hydrochloric acid buffer:** Transfer 50 ml of the 0.2M potassium chloride to a 200 ml volumetric flask. Add the specified volume of 0.2M hydrochloric acid as given in table below and then make up the volume with water.

pH	0.2M HCl, ml	pH	0.2M HCl, ml	pH	0.2M HCl, ml
1.2	85.0	1.6	32.4	2.0	13.0
1.3	67.2	1.7	26.0	2.1	10.2
1.4	53.2	1.8	20.4	2.2	7.8
1.5	41.4	1.9	16.2		

2. **Acid phthalate buffer:** Transfer 50 ml of the 0.2M potassium hydrogen phthalate to a 200 ml volumetric flask. Add the specified volume of 0.2M hydrochloric acid as given in table below and then make up the volume with water.

pH	0.2M HCl, ml	pH	0.2M HCl, ml	pH	0.2M HCl, ml
2.2	49.5	3.0	22.3	3.8	2.9
2.4	42.2	3.2	15.7	4.0	0.1
2.6	35.4	3.4	10.4		
2.8	28.9	3.6	6.3		

3. **Neutralized phthalate buffer or phthalate buffer:** Transfer 50 ml of the 0.2M potassium hydrogen phthalate to a 200 ml volumetric flask. Add the specified volume of the 0.2M sodium hydroxide as given in the table below and then make up the volume with water.

pH	0.2M NaOH, ml	pH	0.2M NaOH, ml	pH	0.2M NaOH, ml
4.2	3.0	4.8	16.5	5.4	34.1
4.4	6.6	5.0	22.6	5.6	38.8
4.6	11.1	5.2	28.8	5.8	42.3

4. **Phosphate buffer:** Transfer 50 ml of the 0.2M potassium disodium phosphate to a 200 ml volumetric flask. Add the specified volume of 0.2M sodium hydroxide as given in the table below and then make up the volume with water.

pH	0.2M NaOH, ml	pH	0.2M NaOH, ml	pH	0.2M NaOH, ml
5.8	3.6	6.6	16.4	7.4	39.1
6.0	5.6	6.8	22.4	7.6	42.4
6.2	8.1	7.0	29.1	7.8	44.5
6.4	11.6	7.2	34.7	8.0	46.1

5. **Alkaline borate buffer:** Transfer 50 ml of the 0.2M boric acid and potassium chloride to a 200 ml volumetric flask. Add the specified volume of 0.2M sodium hydroxide as given in the table below and then make up the volume with water.

pH	0.2M NaOH, ml	pH	0.2M NaOH, ml	pH	0.2M NaOH, ml
8.0	3.9	8.8	15.8	9.6	36.9
8.2	6.0	9.0	20.8	9.8	40.6
8.4	8.6	9.2	26.4	10.0	43.7
8.6	11.8	9.4	32.1		

The standard pH values given in the tables are reproducible within ± 0.02 unit at 25ºC. The prepared solutions should be stored in glass-stoppered bottles made up of chemically resistant, alkali-free glass and should be used within three months of preparation. If the solution becomes cloudy or shows any other sign of deterioration it should be discarded.

Other buffer solutions: These are actual pharmaceutical buffers, which are used to maintain the pH within the specified limits in pharmaceutical preparations. The I.P.1996 enlists a number of such buffer solutions with their pH value and specified method of preparation. They are

1. Acetate Buffer (pH 2.8)
2. Acetate Buffer (pH 3.4)
3. Acetate Buffer (pH 3.5)
4. Acetate Buffer (pH 3.7)
5. Acetate Buffer (pH 4.0)
6. Acetate Buffer (pH 4.4)
7. Acetate Buffer (pH 4.6)
8. Acetate Buffer (pH 4.7)
9. Acetate Buffer (pH 5.0)
10. Acetate Buffer (pH 5.5)
11. Acetate Buffer (pH 6.0)
12. Acetate Buffer solution
13. Acetic acid–Ammonium Acetate Buffer
14. Acetic–Ammonia Buffer, Ethanolic (pH 3.7)
15. Acetone Solution, Buffered
16. Albumin Phosphate Buffer (pH 7.2)
17. Ammonia–Ammonium Chloride Buffer
18. Ammonia Buffer (pH 9.5)
19. Ammonia Buffer (pH 10.0)
20. Ammonia Buffer (pH 10.9)
21. Barbitone Buffer (pH 7.4)
22. Barbitone Buffer (pH 8.6)
23. Boric Buffer (pH 9.0)
24. Buffer Solution (pH 2.5)
25. Carbonate Buffer (pH 9.7)
26. Chloride Buffer (pH 2.0)
27. Citro-Phosphate Buffer (pH 5.0)

28. Citro-Phosphate Buffer (pH 6.0)
29. Citro-Phosphate Buffer (pH 7.0)
30. Citro-Phosphate Buffer (pH 7.2)
31. Citro-Phosphate Buffer (pH 7.6)
32. Cupric Sulphate Solution, Buffered (pH 4.0)
33. Diethanolamine Buffer (pH 10.0)
34. Glycine Buffer (pH 11.3)
35. Glycine Buffer Solution
36. Imidazole Buffer (pH 6.5)
37. Imidazole Buffer (pH 7.4)
38. Palladium Chloride Solution, Buffered
39. Phosphate Buffer (pH 2.0)
40. Phosphate Buffer (pH 2.5)
41. Phosphate Buffer (pH 3.6)
42. Phosphate Buffer, Mixed (pH 4.0)
43. Phosphate Buffer (pH 4.9)
44. Phosphate Buffer (pH 5.0)
45. Phosphate Buffer, Mixed (pH 5.5)
46. Phosphate Buffer (pH 6.5)
47. Phosphate Buffer, Mixed (pH 6.8)
48. Phosphate Buffer, 0.2M Mixed (pH 6.8)
49. Phosphate Buffer, Mixed (pH 7.0)
50. Phosphate Buffer with Azide, Mixed (pH 7.0)
51. Phosphate Buffer, 0.067M Mixed (pH 7.0)
52. Phosphate Buffer, 0.033M Mixed (pH 7.5)
53. Phosphate Buffer, 0.02M (pH 8.0)
54. Phosphate Buffer, 0.025M Standard
55. Saline, Phosphate-Buffered
56. Saline, Phosphate-Buffered (pH 6.4)
57. Saline, Phosphate-Buffered (pH 7.4)

Selection of pharmaceutical buffer: The selection of a pharmaceutical buffer depends on chemical and pharmacological factors.

Chemical factors are:

1. The buffer system should not react with other chemical ingredients of a pharmaceutical preparation i.e., it should not change the solubility of other ingredients, should not indulge in undesirable acid-base or oxidation-reduction reactions and should not undergo complexation with active components of the pharmaceutical preparation.
2. The buffer system must have reasonable chemical stability. The volatile species such as CO_2 and NH_3 should not be used for the preparation of buffers since their loss will change the pH and will affect the buffer capacity of the system. The basic buffer i.e. a mixture of weak base and its salt can absorb CO_2 from the atmosphere resulting in the lowering of the pH.

3. For an acid buffer, the buffer capacity is maximum when the ratio of concentration of salt/acid is one. In other words when pH = pK_a. So, a pharmaceutical buffer should be selected in which buffer acid is having pK_a near the middle of the desired pH range.

Pharmacological factors are :

1. The buffer system should not be toxic especially when used in preparations intended for internal administration. Toxicity is an important factor and restricts the use of some of the buffer systems e.g., borate buffer systems because of their toxicity are not employed in internal preparations and are mainly used in ophthalmic preparations, and preparations intended for topical application.

2. The buffer system should not affect the therapeutic ability of the active ingredients of the preparation.

3. The buffer system should not support the growth of microorganisms. Many buffer systems are susceptible to microbial growth as they can provide the nutrients for the same. Such systems can be preserved by adding low concentrations of suitable antimicrobial agents.

Antioxidants

Antioxidants are the compounds, which are added to pharmaceutical preparations containing easily oxidizable substances. They prevent oxidation and subsequent deterioration of the formulation. Chemically they are reducing agents which prevent oxidation either by getting oxidise themselve in place of active component as they under go oxidation more readily than the active component or by reducing the already oxidized active component back to the normal oxidation state.

In brief the antioxidant action is based upon oxidation-reduction reaction in which the antioxidant itself gets oxidized. Oxidation-reduction reactions can be considered similar to Bronsted acid-base reactions, as the "conjugate pairs" of oxidised and reduced forms of a chemical compound can be separated from the chemical equation. In redox reaction there is transfer of electrons from one compound to the other, therefore the loss or gain of electrons is used to balance the oxidation states on both sides of the half-reaction e.g. if Ox_A is the oxidised form of compound A and the Red_B is the reduced form of compound B then the half reaction can be written as,

$$Ox_A + e^- \rightleftharpoons Red_A$$

$$Red_B \rightleftharpoons Ox_B + e^-$$

The overall redox reaction can be given by

$$Ox_A + Red_B \rightleftharpoons Red_A + Ox_B$$

It is possible to determine the tendency of a chemical substance to under go oxidation – reduction reaction, this can be done by using electro chemical cells in which the electron transfer takes place through a system of electrodes. The electrical potential developed in the electrochemical cell can be measured by the voltmeter and the electrode potential can be determined by using Nernst equation.

$$E_{cell} = E^o_{cell} - \frac{RT}{} \ln \frac{[Ox]}{}$$

$$nF \qquad [Red]$$

Where, E_{cell} is the potential of the cell in volts,

E^{o}_{cell} is the standard potential.
R is the gas constant.
T is the absolute temperature.
F is the Faraday constant.
n is the no. of electrons transferred and
[Ox]/[Red] is the ratio of concentration of oxidized and reduced forms respectively.

For a cell at 298.73ºK and converting to the logarithms to the base 10, the above equation can be rewritten as,

$$E_{cell} = E^{o}_{cell} - (0.0591/n) \log \{[Ox]/[Red]\}$$

The value of E^{o}_{cell} is determined from a table of standard electrode potentials enlisting the potentials for various half reactions.

Selection Criteria of Antioxidants: Following criteria should be considered while selecting an antioxidant.

1. It should be able to produce desire redox reaction. This can be assessed by using standard electrode potentials and the Nernst equation.
2. It should be physiologically and chemically compatible.
3. It should be physiologically inert.
4. It should be non-toxic both in the reduced and oxidized forms.
5. It should not create any solubility problem for various components of the formulation.
6. It should be effective in low concentration and should provide prolonged stability to the formulation.
7. Utmost care must be taken in selecting antioxidants for formulations containing strong oxidizing agents as very strong reducing agents can form explosive mixtures with very strong oxidizing agents.

Active Component + Antioxidant + Oxidizing Agent

(Reduced form) (Reduced form) (Oxidized form)

↓

Active Component + Antioxidant + Oxidizing Agent
(Reduced Form) (Oxidized Form) (Reduced Form)

1. Hypophosphorous Acid: H_3PO_2 (Phosphinic Acid) Mol. Wt. 66.00

Hypo phosphorous acid contains not less than 30.0 percent and not more than 32.0 percent of H_3PO_2.

Preparation:

From hypophosphite of calcium, barium or potassium. It can be prepared by the reaction of hypophosphite of calcium, barium or potassium with excess of sulphuric acid, oxalic acid and tartaric acid respectively.

$$Ca(H_2PO_2)_2 + H_2SO_4 \longrightarrow 2H_3PO_2 + CaSO_4\downarrow$$

$$Ba(H_2PO_2)_2 + H_2C_2O_4 \longrightarrow 2H_3PO_2 + BaC_2O_4\downarrow$$

(oxalic acid) (Barium oxalate)

$$KH_2PO_2 + C_4H_6O_6 \longrightarrow H_3PO_2 + KHC_4H_4O_6\downarrow$$

(Tartaric acid) (Pot. Bitartrate)

Identification Tests:

1. When strongly heated it evolves spontaneously flammable phosphine.

$$3H_3PO_2 \longrightarrow 2PH_3 + 2H_3PO_3\uparrow$$

In this test the acid on heating is decomposed giving phosphine and phosphorous acid.

2. Its solution gives a white precipitate with mercuric chloride solution. This precipitate becomes grey when an excess of hypophosphite is present.

$$H_2PO_2^- + 4HgCl_2 + 2H_2O \longrightarrow 2Hg_2Cl_2\downarrow + H_3PO_4 + 3H^+ + 4Cl^-$$

$$H_2PO_2^- + 2Hg_2Cl_2\downarrow + 2H_2O \longrightarrow 4Hg\downarrow + H_3PO_4 + 3H^+ + 4Cl^-$$

(Excess) (Metallic Mercury Grey in colour)

In this test the hypo phosphorous acid is acting as strong reducing agent. Thus mercuric chloride is reduced to mercurous chloride and mercury. The acid itself is oxidized to orthophosphoric acid.

3. It's solutions when acidified with sulphuric acid and warmed with cupric sulphate gives a red precipitate.

$$3H_2PO^-_2 + 4Cu^{2+} + 6H_2O \longrightarrow 4CuH\downarrow + 3H_3PO_4 + 5H^+$$

Red ppt.

Test for purity: It is tested for barium, oxalate and heavy metals.

Assay: Hypophosphorous acid is monobasic as it contains only one ionisable hydrogen (one which is bonded to oxygen atom). Its assay is based upon acid base titration, and is done by titrating it with sodium hydroxide using phenolphthalein indicator.

$$H_3PO_2 + NaOH \longrightarrow NaH_2PO_2 + H_2O$$

Method: Take about 7ml of hypophosphorous acid into a tared, glass-stoppered flask and weigh accurately. Dilute with about 25ml of water, add phenolphthalein and titrate with sodium hydroxide.

Each ml of 1N sodium hydroxide is equivalent to 66.00mg of H_3PO_2.

Uses:

1. Hypophosphorous acid and its salts do not show any important pharmacological action therefore they don't have any medicinal use.

2. However it is a very strong reducing agent as the P in it is in the oxidation state (+1). So it is used as antioxidant in Ferrous Iodide Syrup, Hydroiodic Acid Syrup and in Diluted Hydroiodic Acid to prevent the formation of free iodine. In Ferrous Iodide Syrup it also prevents the formation of ferric ions.

3. Its salts (hypophosphites) can be used as preservatives e.g. ammonium hypophosphite can be used as preservative in many preparations.

2. Sulphur Dioxide: SO_2 Atomic wt. 64.06

Sulphur dioxide contains not less than 97.0% by volume of SO_2.

Preparation:

1. **From Sulphur:** It can be manufactured by burning S in air or oxygen.

$$S + O_2 \xrightarrow{} SO_2$$

2. From Metal sulphide: It can be manufactured by roasting various metal sulphide ores (particularly FeS_2 and to a smaller extent CuS and ZnS) with air.

$$4FeS_2 + 11O_2 \longrightarrow 2Fe_2O_3 + 8SO_2 \uparrow$$

$$2ZnS + 3O_2 \longrightarrow 2ZnO + 2SO_2 \uparrow$$

3. By heating copper turnings with conc. H_2SO_4.

$$Cu + H_2SO_4 \text{ (conc.)} \xrightarrow{\Delta} CuSO_4 + SO_2 + 2H_2O$$

4. By the reduction of H_2SO_4 with carbon or sulphur.

$$C + 2H_2SO_4 \longrightarrow CO_2 + 2SO_2 + 2H_2O$$

$$S + 2H_2SO_4 \longrightarrow 3SO_2 + 2H_2O$$

5. On lab scale by the action of mineral acid on sulphites.

$$Na_2SO_3 + 2HCl \longrightarrow 2NaCl + H_2O + SO_2$$

Test for purity: Sulphur dioxide is used most in the form of a gas in pharmaceutical applications. However it is usually packaged under pressure. Hence the following purity tests shall be done in liquid form.

Water : It can be determined by the Karl Fischer Method.

Non-volatile residue: For the determination of the non-volatile residue the weighed sample is allowed to evapourate and any residue obtained is weighed. The weight of the residue should not exceed 7.5mg (0.0025%).

Sulphuric acid: To determine this, the residue obtained in the test for non-volatile residue is mixed with water, and the resulting mixture is titrated with 0.10N sodium hrydroxide. (not more than 1.3ml is required).

Identification tests: On bringing a filter paper previously moistened with acidified potassium dichromate solution, near SO_2, the colour of the paper turns green. In this test SO_2 reduces acidic potassium dichromate to green chromium sulphate [$Cr_2(SO_4)_3$]

$$K_2Cr_2O_7 + H_2SO_4 + 3SO_2 \longrightarrow K_2SO_4 + Cr_2(SO_4)_3 + H_2O$$

Assay: The assay of SO_2 include collection of the measured volume of gaseous SO_2 over mercury. The temperature and pressure is noted. Now excess of 0.1N sodium hydroxide solution is introduced into the air space over mercury. After shaking the contents, the solution is titrated with 0.1N iodine using starch as indicator, appearance of pale blue colour is the end point.

In the assay of SO_2, the sodium hydroxide reacts with SO_2 and forms sodium bisulphite; which is then titrated with I_2.

$$SO_2 + NaOH \longrightarrow NaHSO_3$$

$$HSO_3^- + I_2 + H_2O \longrightarrow SO_4^{2-} + 2I^- + 3H^+$$

Each ml of 0.1N iodine is equivalent to 1.094ml of SO_2 at a temp. of 0º and a pressure of 760mm of mercury.

3. Sodium Bisulphite: $NaHSO_3$ Mol. Wt. 104.06

(Sodium acid sulphite, Sodium Hydrogen Sulphite, Sodium pyrosulphate)

Sodium bisulphite is unstable in the solid state, so the official preparation is a mixture of sodium bisulphite ($NaHSO_3$) and sodium metabisulphite ($Na_2S_2O_5$) in varying proportions. It gives not less than 61.6% and not more than 67.4% SO_2.

Preparation: It is manufactured by passing SO_2 into an aqueous solution of Na_2CO_3 until the solution is saturated.

$$Na_2CO_3 + 2SO_2 + H_2O \longrightarrow 2NaHSO_3 + CO_2 \uparrow$$

Sodium bisulphite can be crystallized from the aqueous solution or precipitated with ethanol.

Identification test: They liberate SO_2 on treatment with dilute acids, which smells like burning sulphur.

$$NaHSO_3 + HCl \longrightarrow NaCl + SO_2 + H_2O$$

This SO_2 reduces acidic $K_2Cr_2O_7$ to green $Cr_2(SO_4)_3$ and acidic $KMnO_4$ to colourless $MnSO_4$.

$$K_2Cr_2O_7 + H_2SO_4 + 3SO_2 \longrightarrow K_2SO_4 + Cr_2(SO_4)_3 + H_2O$$

$$2KMnO_4 + 2H_2O + 5SO_2 \longrightarrow K_2SO_4 + 2MnSO_4 + 2H_2SO_4$$

Test for purity: It has to be tested for arsenic, heavy metals and iron.

Assay: Sodium bisulphite contains S in the (4+) oxidation state and is a moderately strong reducing agent. Its assay is based upon its reaction with I_2, and determination of the remaining I_2 with sodium thiosulphate.

$$NaHSO_3 + I_2 + H_2O \longrightarrow NaHSO_4 + 2HI$$

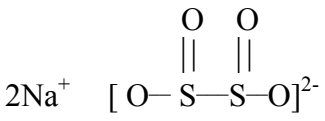
$$2Na_2S_2O_3 + I_2 \longrightarrow Na_2S_4O_6 + 2Na^+ + 2I^-$$

Uses:

1. It is mainly used as an antioxidant. It is used to prevent oxidation of drugs which have phenol or catechol ring to quinones and similar substances.
2. It may also be used to prepare water soluble derivatives of normally insoluble drugs.
3. Reduction of its solution containing SO_2, with Zn dust, or electrolytically give Sodium dithionites. These contain S in the oxidation state (+III).

$$2HSO_3^- + SO_2 \xrightarrow{Zn} \underset{\text{(Dithionite)}}{S_2O_4^{2-}} + SO_3^{2-} + H_2O$$

Structure of sodium dithionite



4. Sodium Metabisulphite Sodium Pyrosulphite Sodium Disulphite: $Na_2S_2O_5$ Mol. Wt. 190.10

Preparation: It can be prepared by saturating a hot concentrated solution of sodium hydroxide with sulphur dioxide and allowing crystallization to occur. Presumably sodium bisulphite ($NaHSO_3$) is first formed, being unstable in the solid state, loses water and the solid sodium metabisulphite separates out.

$$NaOH + SO_2 \longrightarrow NaHSO_3$$

$$2NaHSO_3 \longrightarrow Na_2S_2O_5 + H_2O$$

Identification:

A. Gives reactions of sodium salts.

B. A solution decolourizes iodinated potassium iodide solution and the resulting solution gives the reactions of sulphates.

In this test the sodium metabisulphite reduces molecular I_2 to iodide(I^-), which is colourless, and itself converts to bisulphate.

$$2I_2 + Na_2S_2O_5 + 3H_2O \longrightarrow 4HI + 2NaHSO_4$$

Test for purity: It shall be tested for arsenic, heavy metals, iron and thiosulphate.

Thiosulphate is detected by heating a mixture of sample and hydrochloric acid, appearance of an opalescence or turbidity due to S indicates the presence of thiosulphate.

$$Na_2S_2O_3 + 2HCl \longrightarrow 2NaCl + SO_2 + S + H_2O$$

While in case of sodium metabisulphite

$$Na_2S_2O_5 + 2HCl \longrightarrow 2NaCl + 2SO_2 + H_2O$$

Assay: It contains not less than 95.0% and not more than 100.5% of $Na_2S_2O_5$.

It can be assayed by reducing 0.1M iodine solution (added in excess) in slightly acid solution. The excess of iodine is then determined by titration with sodium thiosulphate.

$$Na_2S_2O_5 + H_2O \longrightarrow 2Na\ H\ SO_3$$

$$2Na\ H\ SO_3 + 2I_2 + 2H_2O \longrightarrow 2Na\ H\ SO_4 + 4HI$$

$$2I_2 + Na_2S_2O_5 + 3H_2O \longrightarrow 4HI + 2NaHSO_4$$

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

Method: Weigh accurately about 0.1g and dissolve in 50.0ml of 0.1M iodine, add 1 ml of hydrochloric acid and titrate the excess of iodine with 0.1M sodium thiosulphate using starch solution added towards the end of the titration as indicator.

Each ml of 0.1M iodine is equivalent to 0.004753g of $Na_2S_2O_3$.

Uses :

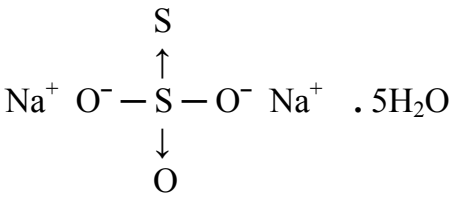
1. It is widely used as an antioxidant and reducing agent in various formulations. It is added to the solutions of drugs that contain the phenol or catechol nucleus to prevent oxidation of these nucleus to quinones and like substances e.g. it is used to stabilize injections containing salts of adrenaline or morphine.
2. When dissolved in water it immediately converts to bisulphite, so, this salt can be used when bisulphite is specified.

$$Na_2S_2O_5 + H_2O \longrightarrow 2NaHSO_3$$

5. Sodium Thiosulphate Sodium Hyposulphite $Na_2S_2O_3 . 5H_2O$ Mol. Wt. 248.17

It is disodium salt of thiosulphuric acid, $H_2S_2O_3$ (a highly unstable oxyacid of sulphur).

In the structure of sodium thiosulphate the sulphur is in two oxidation states. One of the sulphur atom is oxidized and is in a +VI state (due to this it resists further oxidation). The other sulphur atom is in zero oxidation state, therefore it can act as a reducing agent or as an antioxidant.



Preparation:

1. It can be made by boiling sodium sulphite solution with S in absence of air. The unreacted S is removed, filtrate is evapourated to give crystals of sodium thiosulphate.

$$\underset{\text{(Sodium Sulphite)}}{Na_2SO_3} + S \longrightarrow Na_2S_2O_3$$

2. By oxidizing polysulphides with air

$$2Na_2S_3 + 3O_2 \xrightarrow{\text{Heated in air}} 2Na_2S_2O_3 + 2S$$

3. By passing SO_2 gas into Na_2S solution

$$2Na_2S + 3SO_2 \longrightarrow 2Na_2S_2O_3 + S$$

4. By passing SO_2 gas through the concentrate of waste liquor of sodium sulphide which contains Na_2S, Na_2SO_3 and sodium sulphate.

$$Na_2SO_3 + 3SO_2 + 2Na_2S \longrightarrow 3Na_2S_2O_3$$

$$Na_2CO_3 + 4SO_2 + 2Na_2S \longrightarrow 3Na_2S_2O_3 + CO_2$$

Identification:

A. With silver nitrate its aqueous dilute solution gives a white precipitate which quickly becomes yellowish and finally black. Mixing of sodium thiosulphate with solutions containing other metal cation (eg. Ag^+) results in the precipitation of the metal thiosulphate. In acid solution these precipitates may darken due to the formation of the corresponding sulphide (eg. Ag_2S).

$$2AgNO_3 + Na_2S_2O_3 \longrightarrow Ag_2S_2O_3\downarrow + 2NaNO_3$$

$$Ag_2S_2O_3 + H_2O \longrightarrow Ag_2S\downarrow + H_2SO_4$$

B. On adding few drops of iodine to its aqueous solution, the colour of iodine solution is discharged.

The presence of excess of sulphur makes sodium thiosulphate a useful reducing agent. Iodine very rapidly oxidizes thiosulphate ions ($S_2O_3^{2-}$) to tetra thionate ions ($S_4O_6^{2-}$) and the I_2 is reduced to I^- ions (hence colour of iodine is discharged).

$$2Na_2S_2O_3 + I_2 \longrightarrow \underset{\text{(Sodium tetra thionate)}}{Na_2S_4O_6} + 2NaI$$

C. On adding hydrochloric acid to its dilute aqueous solution, a gas is evolved which turns starch iodate paper blue and a precipitate of sulphur is produced.This is because,when treated with dilute acids sodium thiosulphate is converted to thiosulphuric acid which spontaneously decomposes to SO_2 and S. The iodate ions (IO_3^-) oxidize SO_2 and there is liberation of I_2 which combines with starch to give a blue coloured adsorption complex.

a) $Na_2S_2O_3 + 2HCl \longrightarrow 2NaCl + H_2S_2O_3$

$H_2S_2O_3 \longrightarrow H_2O + SO_2 + S$

$Na_2S_2O_3 + 2HCl \longrightarrow 2NaCl + H_2O + SO_2 + S\downarrow$

b) $5SO_2 + 2KIO_3 + 4H_2O \longrightarrow 2KHSO_4 + 3H_2SO_4 + I_2$

c) I_2 + Starch $\longrightarrow$ Blue colour complex

d) Its aqueous solution gives reaction of sodium salts.

Test for purity: It shall be tested for arsenic, chloride, heavy metals, sulphide, sulphate and sulphite and clarity and colour of solution.

Sulphide can be tested by adding sodium nitroprusside solution to the aqueous solution of the sodium thiosulphate. The solution does not become violet.

Assay: It contains not less than 99.0% and not more than 101.0% of $Na_2S_2O_3.5H_2O$.In solution, sodium thiosulphate reacts quantitatively with iodine to form sodium iodide and sodium tetra-thionate. So it can be assayed by titrating its solution with iodine using starch mucilage as indicator. Appearance of blue colour is the end point as iodine gives a deep blue coloured adsorption complex with starch.

$Na_2S_2O_3 + I_2 \longrightarrow Na_2S_4O_6 + 2NaI$

Method: Weigh accurately about 0.5gm, dissolve in 20ml of water and titrate with 0.05ml iodine using starch solution added towards the end of the titration as indicator.

Each ml of 0.05M iodine is equivalent to 0.02482gm of $Na_2S_2O_3.5H_2O$

Uses: The presence of excess of sulphur makes it a useful reducing agent. Thus it reduces halogen.

1. It is mainly used for iodine titrations in volumetric analysis.
2. In conjunction with sodium nitrite it is used as an antidote for cyanide poisoning. It is also used as an effective antidote in mercury, iodine, lead and bismuth poisoning.
3. It is used as an antioxidant but its use as an antioxidant is usually limited to solutions containing iodides. Sometimes in combination with acids (acid causes the precipitation of S and evolution of SO_2) it is used to treat various dermatological problems.
4. It is used as an antichlor eg. in the bleaching operations to destroy any excess Cl_2 . Similarly it is sometimes used to remove the taste from heavily chlorinated drinking water.

6. Sodium Nitrite (Nitrous acid sodium salt): $NaNO_2$ Mol. Wt. 69.00

It contains not less than 97.0% and not more than 101.0% of $NaNO_2$, calculated on the dried basis.

Preparation:

1. It can be prepared by strong heating of sodium nitrate either on its own or with Pb.

$$2NaNO_3 \xrightarrow{\text{Heat } (500^0C)} 2NaNO_2 + O_2$$

$$NaNO_3 + Pb \xrightarrow[\text{Heat } (500^0C)]{} NaNO_2 + PbO$$

2. It can be manufactured by absorbing oxides of nitrogen in Na_2CO_3 solution.

$$Na_2CO_3 + NO_2 + NO \longrightarrow 2NaNO_2 + CO_2$$

3. It can also be made by chemical reduction of $NaNO_3$.

$$2NaNO_3 + C \longrightarrow 2NaNO_2 + CO_2$$

4. More commonly it is made by reduction of sodium nitrate with metallic lead at a lower temperature.

$$NaNO_3 + Pb \longrightarrow NaNO_2 + PbO\downarrow$$

Identification Tests:

a) To the aqueous solution of the sample add 2ml of 15% w/v solution of potassium carbonate. Heat the contents to boiling, no precipitate is produced. Add 4ml of a freshly prepared potassium antimonate solution and heat to boiling. Allow cooling in ice and if necessary scratch the inside of the test tube with a glass rod; a dense, white precipitate is formed.

$$Na^+ + \underset{\text{(Pot. Antimonate)}}{KH_2SbO_4} \longrightarrow \underset{\text{(Sod. Pyroantimonate)}}{NaH_2SbO_4\downarrow} + K^+$$

b) Add a large excess of magnesium uranyl acetate solution to the acidified (with acetic acid) solution of the sample, a yellow, crystalline precipitate is formed.

$$Na^+ + 3UO_2(CH_3COO)_2 + Mg(CH_3COO)_2 + CH_3COOH \longrightarrow \underset{\text{(yellow ppt.)}}{[NaMg(UO_2)_3](CH_3COO)_9\downarrow} + HCl$$

c) Sodium nitrite gives brownish red fumes when treated with diluted mineral acids or acetic acid

Test for purity: It has to be tested for loss on drying, pH, arsenic, lead and heavy metals.

Assay: Take sodium nitrite, accurately weigh and dissolve it in water. Transfer solution into a mixture of potassium permanganate, water and sulphuric acid (Take care that while adding the sodium nitrite solution, the tip of the pipette is beneath the surface of the permanganate mixture). Warm the liquid to 40ºC and allow it to stand for few minutes. Now add oxalic acid. Heat the mixture to about 80ºC and titrate with potassium permanganate.

Each ml of 0.1N potassium permanganate is ≡ 3.450 mg of $NaNO_2$

Note: The nitrite solution must be run into the potassium permanganate solution, and not vice versa, because the acidification of a solution of sodium nitrite results in the production of nitrous acid, which decomposes immediately with loss of oxides of nitrogen. The potassium permanganate already present in the solution prevents this loss by immediately oxidizing nitrous acid.

$$NaNO_2 + H_2SO_4 \longrightarrow HNO_2 + NaHSO_4$$

$$HNO_2 + O \longrightarrow HNO_3$$

Uses:

- Chemically, nitrites can act as both oxidizing and reducing agents. When nitrites acts as a reducing agent then nitrite is oxidized into nitrate.

$$\underset{\text{(N oxidation state +III)}}{3HNO_2} + KClO_3 \longrightarrow \underset{\text{(N oxidation state +V)}}{HNO_3} + KCl$$

- When nitrites react as oxidizing agent then nitrite is reduced into nitric oxide (NO) in acidic solution or molecular nitrogen in neutral to alkaline solution.

$$2HNO_2 + 2KI + H_2SO_4 \longrightarrow I_2 + K_2SO_4 + 2NO$$

$$NaNO_2 + NH_4Cl \longrightarrow NaCl + 2H_2O + N_2\uparrow$$

- It is not used specifically as an antioxidant in pharmaceutical preparations. However it is used as a reducing agent when combined with sodium carbonate. This combination is available in anti-rust tablets which are used to prevent rusting of various surgical instruments.

- Nitrite ions relax the smooth muscles of the blood vessels thus produce vasodilator effect. Instead of sodium nitrite, organic derivatives containing nitrite and nitrate groups eg. Isosorbide dinitrite, are used as coronary vasodilator.

- Sodium nitrite is used as a food additive in cured meats and fish. Here it serves three functions : colour development (reductive decomposition of NO_2^- gives NO, which forms a red complex with hemoglobin and improves the look), flavour production and preservation (NO_2^- ions inhibit the growth of bacteria, particularly Clostridium botulinum). However, the nitrites may react with amines and be converted into potentially carcinogenic nitrosamines ($R_2N\text{-}N{=}0$), it has resulted in a great deal of concern about the safety of using nitrites, and the levels that should be allowed to remain in meat products. Some countries have banned the use of nitrite as a flavouring and colouring agent but they only permit the level necessary as an anti botulinogenic agent.

- It is official in USP as an antidote in the cyanide poisoning where it causes the oxidation of the ferrous (Fe^{2+}) ion of hemoglobin to the ferric ion of methemoglobin, which then binds with the serum cyanide.

- In laboratory it is used to prepare diazo dye or in the detection of primary aromatic amines.

- The NO_2^- ion may act as a chelating ligand.

7. Nitrogen : N_2 Mol. Wt. 28.01

It contains not less than 99.0% by volume of N_2.

Preparation:

1. Can be prepared on lab scale by heating a mixture of NH_4Cl and $NaNO_2$.

$$NH_4Cl + NaNO_2 \longrightarrow [NH_4NO_2] + NaCl$$
$$(\text{Unstable})$$

$$NH_4NO_2 \xrightarrow{\text{Heat}} N_2 + 2H_2O$$

2. By oxidation of ammonia

$$8NH_3 + 3Cl_2 \longrightarrow 6NH_4Cl + N_2$$

$$2NH_3 + 3CuO \longrightarrow 3Cu + N_2 + 3H_2O$$

3. By passing vapours of HNO_3 on strongly heated copper.

$$5Cu + 2HNO_3 \longrightarrow 5CuO + N_2 + H_2O$$

4. By heating ammonium dichromate.

$$(NH_4)_2\,Cr_2O_7 \longrightarrow Cr_2O_3 \downarrow + N_2 + 4H_2O$$

5. Commercially it can be obtained by liquefying air followed by fractional evaporation. By doing this the Nitrogen, having a lower b.p. (77.3º K), boils off more readily than the less volatile oxygen (b.p. 90.04º K).

Identification Tests: Insert a burning wood splinter into a test tube filled with nitrogen. The flame will extinguish, because it is an inert gas and neither burns nor supports the combustion.

Test for purity: It has to be tested for odour and carbon monoxide.

Uses : Because of the inert nature it can be used to prevent the air oxidation of the pharmaceuticals and chemicals, by displacing the air in the containers and in the reacting vessels, eg. It can used to replace air during manufacturing and packaging of parenterals, multivitamin preparation and various oil preparations.

- It is used as a diluent to dilute the action of oxygen before administering later to patient.
- It can also be used in the preparation of ammonia, nitric acid, nitrides, cyanamides and other nitrogen compounds.
- Nitrogen is an essential constituent of all proteins found in animals and plants.
- It is used to provide an inert atmosphere.

Water

It is one of the most widely and abundantly used substances in pharmaceutical manufacturing. It is required for a variety of purposes ranging from manufacturing process to the preparation of the final dosage forms. It is a highly associated liquid having high boiling point (100ºC), a high dielectric constant (at 25ºC dielectric constant of H_2O is 78.5) and a high specific heat (at 14.5ºC specific heat of H_2O is 1 calorie). Its good solubilising capacity for salts is due to high dielectric constant. It is a chemically stable compound. Even at 1700ºC, less than 1% is dissociated into its elements. The k_w for H_2O is 10^{-14}. Despite this relative non reactivity it acts as a solvent.

These days in pharmaceutical systems pharmacists are concerned with dissolution of relatively non polar drugs in aqueous or mixed polar aqueous solvents. Organic compounds having low molecular weight with polar groups capable of making hydrogen bonds with water are soluble in water. Polar groups -OH, -CHO, -COH, -CHOH, $-CH_2OH$, -COOH, $-NO_2$, -CO, $-NH_2$ and $-SO_3H$ increase the solubility of organic compounds in water.

Indian pharmacopoeia prescribes standards for the various types of water to be used in the manufacture of pharmaceutical preparations. The starting material for most forms of water is drinking water. Drinking water itself may be used in the manufacture of drug substances but not in the preparation of dosage forms, or in the preparation of reagents and test solutions.

Official water as given in I.P. 1996: It has been categorized into

a. Purified water
b. Water for injection.
c. Water for injection in bulk.
d. Sterile water for injection.

Purified water: It can be prepared by distillation, by means of ion exchange or by any other suitable method. It is a clear colourless, odorless and tasteless liquid. It contains no added substance.

Test for purity: It has to be tested for acidity or alkalinity, ammonium, calcium and magnesium, heavy metals, chloride, nitrate, sulphate, oxidisable substances and residue on evaporation.

The test for sulphate and chloride is done to ensure almost complete absence of these impurities. Oxidisable matter is detected by boiling the water with very dilute acidified permanganate.

Uses: It is used as pharmaceuticals aid (solvent). It is used in preparation of dosage forms for internal administration. It is not intended for parenteral administration.

Water for injection: It is apyrogenic but not sterile distilled water. It is obtained by distilling potable water or purified water from a neutral glass, quartz or suitable metal still fitted with effective device for preventing the entrainment of droplets. The first portion of the distillate is discarded and remainder is collected. It contains no added substance.

Uses: It is used as a solvent for dissolving or diluting substances. It is also used in the preparation of injectables (injectable preparations in the final container should be made sterile and thereafter protected from microbial contamination).

Water for injection in bulk: It is a clear colourless, odorless, and tasteless liquid .

Test for purity: It complies with the tests given under purified water with an additional test for bacterial endotoxins.

Sterile water for injection: It is water for injection which is sterilized by heat under conditions that ensure that the water remains apyrogenic and is packed in suitable containers so as to permit the withdrawal of a nominal volume (The water for injection shall be sterilised within 12 hours of collection and distributed in sterile containers). It is a clear, colourless and odorless liquid which is stored in single dose container of not larger than one litre capacity.

Test for purity: It has to be tested for clarity and colour, acidity or alkalinity, oxidisable substances, ammonium, calcium and magnesium, heavy metals, chloride, nitrate, sulphate, bacterial endotoxins, sterility, and residue on evaporation.

Uses: It is mainly used as a solvent for injectable preparations such as powders for injection that are distributed dry because of limited stability of their solutions.

Pharmaceutically Acceptable Glass

Greatest attention has to be paid to the containers in which pharmaceuticals are stored or maintained even for short periods of time. The containers are in intimate contact with the pharmaceutical. None of the containers presently available is totally non reactive. Both the chemical and physical characteristic affect the stability of the pharmaceutical, but the physical characteristics are given primary consideration in the selection of a protective container. The most commonly used materials for pharmaceutical containers are glass and plastics. Although challenged by plastics, glass is still the most important material for the containers.

The chemistry of the glass is extremely complicated. It is an amorphous, hard, brittle, transparent, supercooled liquid of infinite viscosity. It is not a true solid. Glass is a generic term used for vitreous silicate materials which are prepaid by fusing a base e.g., Na_2CO_3 and $CaCO_3$, with pure silica. Upon cooling, a clear vitreous mass is formed. This vitreous material does not have a clearly defined melting point and it softens gradually over a temperature range as a result of somewhat haphazard arrangement of the silicon-oxygen bonds. Certain other compounds may be added to vitreous silicates to impart special properties e.g., manganese dioxide is added to hide the blue-green colour of the iron usually present in silica, borates are added to reduce the coefficient of expansion, compounds of alkaline earth metals (e.g., $CaCO_3$, CaO, $BaCO_3$) are added for getting glass a high refractive index, calcium phosphate is added for getting opalescent glass and colouring materials e.g., Fe_2O_3 to get yellow colour, chromic oxide to get green colour, manganese oxide to get purple colour, and cobalt oxide to get blue colour. Potassium is added to get a brown light-resistant glass.

Glass containers must be strong enough so that they can withstand the physical shocks of handling and shipping and the high pressure during the process of autoclaving and sterilisation.

They must also be able to withstand the thermal shock resulting from large temperature changes during processing (i.e. it shall have a low coefficient of thermal expansion). To inspect the contents, the container must be transparent. Keeping them in amber glass containers protects light sensitive preparations.

Advantages of glass containers: Offer transparency, sparkle, easy cleaning, effective closure and reclosure where applicable, high speed handling, good rigidity and stack ability and also the correct type of glass is usually inert.

Disadvantages of glass containers: The two main disadvantages are fragility and heavy weight. These can be partially reduced by surface coatings to increase the surface lubricity and careful design, which includes the avoidance of sharp angles and the use of adequate radii.

As the basic structural network of glass is of silicon oxide tetrahedron, boric oxide will enter into this structure, but most of the other oxides do not. They are only loosely bound and are relatively free to migrate. These loosely bound oxides may be leached into the solution in contact with the glass. The leaching process is accelerated by heat. The leaching may result in rise in pH of the solution because of the hydrolysis of the dissolved oxides. Some of the glass compounds are attacked by solutions and result in removal of glass flakes into the solution. Such problems can be minimized by the proper selection of the glass composition.

The pharmacopoeia specifies the type of glass container to be used for certain materials and include tests for these types of glasses.

Types of glass: On the basis of results from the official tests, U.S.P. classifies glass compounds into four types.
Type I- A borosilicate glass
Type II- A soda lime treated glass
Type-III- A soda lime glass
NP- General purpose soda lime glass not suitable for containers for parentrals

The U.S.P. provides the Powdered Glass test and Water Attack tests for evaluating chemical resistance of glass. These tests measure the amount of alkaline constituents leached from the glass by purified water under controlled elevated temperature conditions. Powdered Glass test is done on ground, sized glass particles, and the Water Attack test is done on whole container.

Type I, III and NP glasses are tested for Powdered Glass test whereas type II glass is tested for Water Attack test.

Type I glass offer maximum chemical resistance while resistances offered by NP glass is least. The selection of the type of glass to be used for various products depends upon the chemical resistance offered by glass.
Type I glass is suitable for all products (buffered and unbuffered aqueous solutions) although SO_2 treatment sometimes is used for even greater resistance to glass leachables.

Type II glass is suitable for buffered aqueous solution with pH below 7 or for a solution which does not react with the glass.

Type III glass is suitable for anhydrous liquids or dry substances.

NP glass is not suitable for parentrals. They are used for tablets, oral solution and suspensions and liquids for external use.

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