Program	:	B. Pharmacy
Semester	:	1st
Subject /Course	:	Pharmaceutical Analysis-I/ B. Pharmacy
Subject/Course ID	:	Pharmaceutical Analysis- I/ BP102T
Module No.	:	02
Module Title	:	Non-Aqueous Titration
Course coordinator	:	Mrs. Manpreet Kaur
Mobile No.	:	9592378971
Email id	:	manipreet663@gmail.com

Learning Outcome of Module-2

LO	Learning Outcome (LO)	Course Outcome Code
LO1	To gain knowledge about concept of non-aqueous titration	BP102.2
LO2	To understand the physiochemical techniques of analysis.	BP102.2
LO3	To gain knowledge about Acid base theories, indicator	BP102.2
LO4	To understand the types of acid base titration	BP102.2

Module Content Table

Topic
• Concepts of non-aqueous titration. • Determination of the endpoint in non-aqueous titrations, Types of non-aqueous titrations, Determination of various drugs • Acid base theories, • indicator Acid base titration: Theories of acid base indicators, • Classification of acid base titrations and theory involved in titrations of strong, weak, and very weak acids and bases, neutralization curves.

NON AQUEOUS TITRATIONS

INTRODUCTION

Non-aqueous titration is the titration of substance dissolved in solvent other than water. Non-aqueous titrations are those in which the titrations of weakly acidic or basic substances are carried out using non-aqueous solvents so as to get sharp end point. Most of the titrations are performed in the aqueous media, means water is used as solvent. There may be difficulty if reactant is insoluble in water or reactant is reactive with water or the analyte (sample) is either too weak acid or too weak base. Those too weak acids or bases can't be titrated in aqueous solution due to the amphoteric behavior of water (i.e water can react as an acid on titration with a base and act as a base on titration with acid). So water will compete with the sample if it is weak acid or weak base. The simple solution for this problem is to replace water as solvent with another non aqueous solvent, so this type of titration is named *"Non Aqueous Titrations"*.

Advantages of Non-aqueous Titrations

Non- aqueous titration has following advantages -

- It is useful for the titrations of very weak acids or bases.
- Many organic acids which are not soluble in water can be dissolved in non-aqueous solvents. Thus, titration of these organic acids is very easy.
- It can be used for titration of mixture of acids as well.
- These titrations show sharp end point with internal indicator.
- It is simple, qualitative and selective method.
- It is a highly accurate method.
- Preferably non-aqueous titration is used for biological matters.
- It is very important in pharmacopoeial assays.

Applications of Non-aqueous Titration

Non-aqueous titration has various uses in numerous fields. Specially, in medicinal field non-aqueous titration is very useful. We have listed here few applications of non-aqueous titration -

- Non – aqueous titration is used to know the purity of assays.
- It is used for determination of concentration expressions.
- It is used in determination of hydrophobic compounds, phenobarbitone, diuretics, steroids.
- It is used in the determination of composition of antitubercular drugs and adrenergic drugs.

Disadvantages of Non-aqueous Titration

Non – aqueous titration has following disadvantages -

- Solvents used in non-aqueous titration are not stable compared to aqueous solvents.
- In non-aqueous titration, non-aqueous solvents are required calibration after every use.
- In non-aqueous titrations temperature corrections are necessary.

Reasons for Non aqueous titrations:

- The reactant is insoluble in water.
- The reactant is reactive with water.
- The sample is too weak acid or too weak base.

Theory of Non Aqueous Titrations:

The acidity of weak acids can be enhanced in presence of a basic solvent, this because basic solvent has a higher affinity to take up protons from the acid. So acetic acid behaves as a strong acid in ammonia solution (basic solvent). Also the basicity of weak bases can be enhanced in presence of acidic solvent. This is called the **leveling effect** of the solvent.

By using this concept, the strength of weak acidic or weak basic drugs can be enhanced by dissolving it in the appropriate solvent to enhance its strength and then can be titrated by acid-base titration (non aqueous titration).

Moisture should be avoided in non aqueous titration to increase the sharpness of the end point; also temperature should be kept constant during titration due to higher coefficients of expansion of organic solvents.

Determination of the endpoint in non-aqueous titrations:

In non-aqueous titrations there are two methods are used to determine the endpoint: the potentiometric method and the indicator method.

- **Potentiometric method:**

It is a method an endpoint is determined by using the reference electrode and indicator electrode. As a reference electrode, a saturated calomel electrode is used, and as an indicator electrode glass electrode is used

Indicator method:

In this method, different indicators are used to detect the endpoint. They are employed in the sample solution before the reaction begins.

Bronsted Lowery theory

The Bronsted Lowery theory of acid and bases can be applied equally well to reactions occurring during acid base titrations in non-aqueous solvents. This is because this approach considers an acid as any substance, which will tend to donate a proton, and a base as any substance, which will accept a proton. Substances which give poor end points due to being weak acids or bases in aqueous solution will frequently give far more satisfactory end point when titrations are carried out in non-aqueous media. An additional advantage is that many substances, which are insoluble in water, are sufficiently soluble in organic solvents to permit their titrations in these non-aqueous media.

In the Bronsted lowery theory, any acid, (HB) is considered to dissociate in solution to give a proton (H^+) and a conjugate base (B^-) :- where as any base (B) will combine with a proton to produce a conjugate acid (HB^+) :

$$HB \leftrightarrow H^+ + B^-$$

$$B + H^+ \leftrightarrow HB^+$$

The ability of substances to act as acids or bases will very much depend on the choice of solvent system.

Types of non-aqueous solvents used in non-aqueous titration

Following four types of solvents are used to dissolve analytes in non-aqueous titrations –

- Protogenic Solvents
- Protophilic Solvents
- Amphiprotic Solvents
- Aprotic Solvent

Protogenic solvents:

These are acidic solvents and used to enhance the basicity of weak bases.

Examples: Glacial acetic acid. (Anhydrous/water-free acetic acid is sometimes called glacial acetic acid because it solidifies just below room temperature, at 16.7°C. Acetic acid can be concentrated by dripping the impure compound over a "stalactite" of glacial (frozen) acetic acid.

Protophilic solvents:

These are basic solvent and used to enhance the acidity of weak acids. Example: Pyridine, Ethylenediamine and Dimethylformamide (DMF)

Amphiprotic solvents:

These solvents behave as acid as well as base depending on the substance dissolved in it. They can accept or donate protons.

Examples: Alcohol.

Aprotic solvents:

These solvents neither accept proton nor donate proton. They are used in dissolving the drugs especially those are insoluble in water. Examples: Benzene, Carbon tetrachloride.

Selection of solvent:

The selection of solvent in non aqueous titration based on:

Solubility of drug:

The weak acidic or basic drug should be soluble in the solvent which at the same time must be miscible with the titrant.

Nature of drug:

The solvent is used according to the nature of drug, whether it is weak acid or weak base.

Unreactivity:

The solvent should be unreacted with the drug.

Some Examples of Non-Aqueous Solvents

A very large number of inorganic solvents have been used for non-aqueous titrations, but a few have been used more frequently than others. Some of the most widely applied solvents systems are discussed below. In all instances pure, dry analytical reagent quality solvent should be used to assist in obtaining sharp end points.

Glacial Ethanoic (Acetic) Acid:

Glacial ethanoic acid is the most frequently used non-aqueous solvent. Before it is used it is advisable to check the water content. This may be between 0.1% and 1.0%. *Acetonitrile:* Acetonitrile (methyl cyanide, cyanomethane) is frequently used with other solvents such as chloroformand phenol and especiallywith ethanoic acid. It enables very sharp end points to be obtained in the titration of metal ethanoates when titrated with perchloric acid.

Alcohol:

Salt of organic acids, especially of soaps are best determined in mixtures of glycols and alcohols or mixtures of glycols and hydrocarbons. The most common combinations are ethylene glycol (dihydroxyethane) with propan-2-ol or butan-1-ol. The combinations provide admirable solvents for both the polar and non-polar ends of the molecules.

Dioxane:

Dioxane is another popular solvent, which is often used in place of glacial ethanoic acid when mixtures of substances are to be quantified. Unlike ethanoic acid, dioxane is not a leveling solvent and separate end points are normally possible, corresponding to the individual components in the mixtures.

Dimethylformamide:

Dimethylformamide (DMF) is a protophillic solvent, which is frequently employed for titrations between, for instance, benzoic acid and amides, although end points may sometimes be difficult to obtain.

TYPES OF NON AQUEOUS TITRATIONS:

Acidimetry

It involves the quantitative determination of weak bases by non aqueous titration.

Alkalimetry

It involves the quantitative determination of weak acids by non aqueous titration

Details	Acidimetry	Alkalimetry
Samples:	Basic drugs such as: Ephedrine, Adrenaline, Caffeine, Acyclovir.	Acidic drugs such as: Nalidixic acid, Flurouracil.
Solvent:	Protogenic solvents such as: glacial acetic acid	Protophilic solvents such as: DMF
Titrant:	Perchloric acid $HClO_4$	Sodium methoxide.
Indicator:	Crystal violet (0.5% in glacial acetic acid) Color change from violet to yellowish green.	Thymol blue (0.5 % in methanol) Color change from pink to blue

INDICATORS

The ionized and unionized or the different resonant forms of indicators are apply equally well for non-aqueous titrations but their colour changes at the end point vary from titration to titrations, as they depend on the nature of the titrant. The colour corresponding to the correct end point may be established by carrying out a potentiometric titration while simultaneously observing the colour change of the indicator.

The majority of non-aqueous titrations are carried out using a fairly limited range of indicators here are some typical example.

1. **Crystal Violet:** Used as 0.5% w/v solution in glacial acetic acid. Its colour change is from violet through blue followed by green, then to greenish yellow, in reactions in which bases such as pyridine are titrated with perchloric acid.
2. **Methyl Red:** Used as a 0.2% w/v solution in dioxane with a yellow to red colour change.
3. **Naphthol Benzein:** When employed as a 0.2% w/v solution in ethanoic acid gives a yellow to green colour change. It gives sharp end points in nitro methane containing ethanoic anhydride for titration of weak bases against perchloric acid.
4. **Quenaldine Red:** Used as an indicator for drug determinations in dimethylformamide solution.

A 0.1% w/v solution in ethanol gives a colour change from purple red to pale green.

5. **Thymol Blue:** Used extensively as an indicator for titrations of substances acting as acids in dimethyl formamide solution. A 0.2% w/v solution in methanol gives a sharp colour change from yellow to blue at the end point.

Table: Acidimetric Assays: Non-aqueous Titrations different Indicators

S. No.	Name of Substance	Indicator Employed
1.	Amantadine hydrochloride	Crystal violet
2.	Chlorpromazine hydrochloride	Methyl orange
3.	Clonidine hydrochloride	α -Naphthol benzein
4.	Cyproheptadiene.HCl	Crystal violet

5.	Dehydroemetine.HCl	Crystal violet
6.	Ephedrine hydrochloride	Crystal violet
7.	Imipramine hydrochloride	Crystal violet
8.	Isoprenaline hydrochloride	Crystal violet
9.	Lignocaine hydrochloride	Crystal violet
10.	Morphine hydrochloride	Crystal violet
11.	Morphine sulphate	Crystal violet
12.	Phenylephrine hydrochloride	Crystal violet
13.	Phenytoin sodium	α -Naphthol benzein
14.	Promethazine hydrochloride	Methyl orange
15.	Thiabendazole	Crystal violet

Table: Alkalimetric Assays: Non-aqueous Titrations different Indicators

S. No.	**Name of Substance**	**Indicator Employed**
1.	Acetazolamide	Potentiometric determination
2.	Bendrofluazide	Azo violet
3.	Allopurinol	Thymol blue
4.	Mercaptopurine	Thymol blue
5.	Amylobarbitone	Quinaldine Red
6.	Nalidixic acid	Thymolphthalein

DETERMINATION OF VARIOUS DRUGS

Assay of Nitrazepam

Preparation of 0.1N solution of HClO4 and its standardization:

Dissolve 8.5 ml of 72% $HClO_4$ in about 900 ml glacial acetic acid with constant stirring, add about 30 ml acetic anhydride and make up the volume (1000 ml) with glacial acetic acid and keep the mixture for 24 hour.

Acetic anhydride absorbed all the water from $HClO_4$ and glacial acetic acid and renders the solution virtually anhydrous. $HClO_4$ must be well diluted with glacial acetic acid before adding acetic anhydride because reaction between $HClO_4$ and acetic anhydride is explosive.

Standardization of the above prepared 0.1N $HClO_4$ with Potassium acid Phthalate

To 500 mg of potassium acid phthalate add 25 ml of glacial acetic acid and add few drops of 5% w/v crystal violet in glacial acetic acid as indicator.

This solution is titrated with 0.1 $HClO_4$. The colour changes from blue to blue green.

1 ml of 0.1N HClO4 = 0.020414 gms of potassium acid Phthalate.

Determination of Nitrazepam:

Weigh accurately about 0.25 g, dissolve in 50 ml of *acetic anhydride.*

Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically.

Carry out a blank titration also.

1 ml of *0.1 M perchloric acid* is equivalent to 0.02813 g of $C_{15}H_{11}N_3O_3$

Assay of Chlorpromazine

Preparation of 0.1N solution of HClO4 and its standardization:

Dissolve 8.5 ml of 72% $HClO_4$ in about 900 ml glacial acetic acid with constant stirring, add about 30 ml acetic anhydride and make up the volume (1000 ml) with glacial acetic acid and keep the mixture for 24 hour.

Acetic anhydride absorbed all the water from $HClO_4$ and glacial acetic acid and renders the solution virtually anhydrous. $HClO_4$ must be well diluted with glacial acetic acid before adding acetic anhydride because reaction between $HClO_4$ and acetic anhydride is explosive.

Standardization of the above prepared 0.1N $HClO_4$ with Potassium acid Phthalate

To 500 mg of potassium acid phthalate add 25 ml of glacial acetic acid and add few drops of 5% w/v crystal violet in glacial acetic acid as indicator.

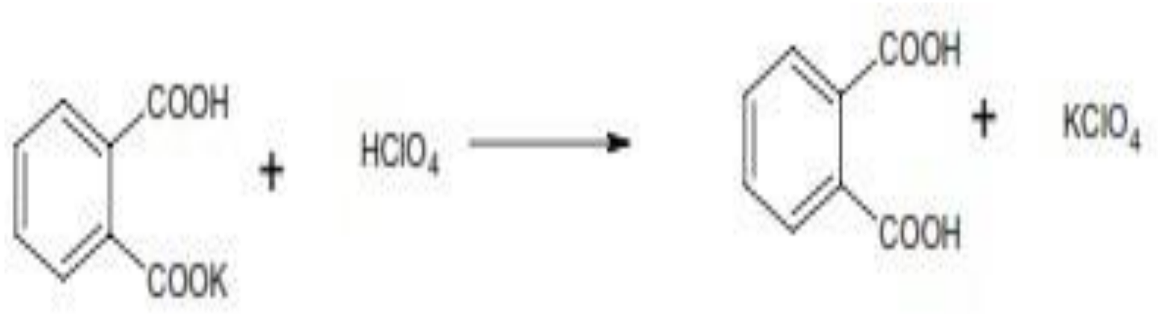
This solution is titrated with 0.1 $HClO_4$. The colour changes from blue to blue green.

1 ml of 0.1N HClO4 = 0.020414 gms of potassium acid Phthalate.

Determination of Chlorpromazine:

Weigh accurately about 0.6 g, dissolve in 200 ml of *acetone* and add 15 ml of *mercuric acetate solution*.

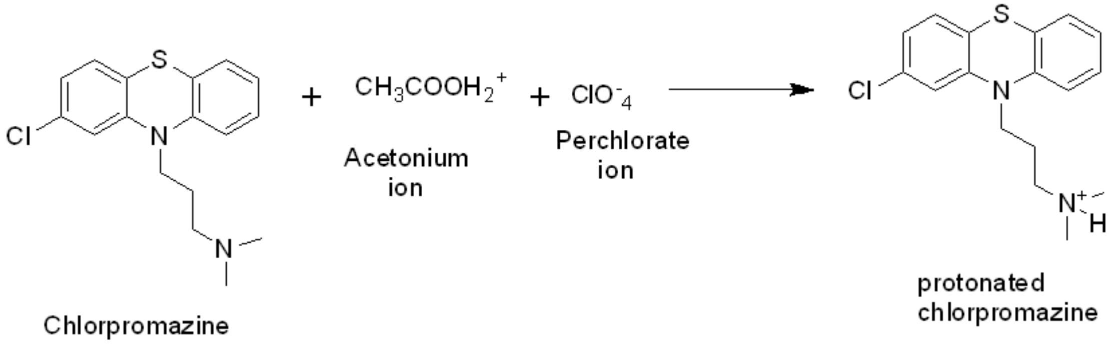
Titrate with *0.1 M perchloric acid*, using a saturated solution of methyl orange in acetone as indicator.



Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.03553 g of C17H19Cl N_2S,HCl.

$$HClO_4 + CH_3COOH \rightleftharpoons CH_3COOH^{+}_{2} + ClO^{-}_{4}$$



INTRODUCTION

- Acids and bases are everywhere. Some foods contain acid, like the citric acid in Lemons and the lactic acid in dairy.
- Cleaning products like bleach and ammonia are bases. Chemicals that are acidic orBasic are an important part of chemistry.
- Several different theories explain what composes an acid and a base.
- The first scientific definition of an acid was proposed by the French chemist Antoine Lavoisier in the eighteenth century.
- He proposed that acids contained oxygen, although he did not know the dual Composition of acids such as hydrochloric acid (HCI).
- Over the years, much more accurate definitions of acids and bases have been created.
- Acid-base titrations are based on the neutralization reaction between the analyte and an acidic or basic titrant.
- These most commonly use a pH meter, or a conductance meter to determine the Endpoint. In our experiments we will use a pH indicator to detect the endpoint of the Reaction.
- Neutralization is a chemical reaction, also called a water forming reaction, in which an acid and a base or alkali (soluble base) react and produce a salt and water:

$$\text{Acid} + \text{Base} \longrightarrow \text{Salt} + \text{Water}$$

THEORY OF ACID-BASE

Several models have been developed to classify, rationalize and predict the reactivity of Acid-base pairs (or donor-acceptor pairs).

1. **Arrhenius Model or Water theory –** acids give hydrogen ions in aqueous solution and bases give hydroxide in aqueous solution.
2. **Brønsted-Lowry Model –** acids are hydrogen ion donors and bases are hydrogen ion acceptors.
3. **Lewis Model –** acids are electron pair acceptors and bases are electron-pair donors.
4. **Electrophile-Nucleophile Model –** acids are electrophilic reagents and bases are Nucleophilic reagents.
5. **Lux-Flood Model –** acids are oxide (O_2^-) acceptors and bases are oxide donors.

6. **Usanovich Model –** an acid-base reaction is a reaction leading to formation of a salt.

Arrhenius Theory

- The Swedish chemist Svante Arrhenius published his theory of acids and bases in 1887. It can be simply explained by these two points:
- Arrhenius Acids and Bases

a) An acid is a substance which dissociates in water to produce one or more hydrogen a ions (H+).

b) A base is a substance which dissociates in water to produce one or more hydroxide ions (OH).

- Based on this definition, you can see that Arrhenius acids must be soluble in water. Arrhenius acid-base reactions can be summarized with three generic equations:

1. An acid will dissociate in water producing hydrogen ions.

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

2. A base (usually containing a metal) will dissociate in water to product hydroxide Ions

$$MOH \longrightarrow M^+ + OH^-$$

3. Acids and bases will neutralize each other when mixed. They produce water and an Ionic salt, neither of which are acidic or basic

$$HA_{(aq)} + MOH_{(aq)} \longrightarrow H2O_{(l)} + MA_{(aq)}$$

- The Arrhenius theory is simple and useful. It explains many properties and reactions of acids and bases.
- For instance, mixing hydrochloric acid (HCl) with sodium hydroxide (NaOH) results in a neutral solution containing table salt (NaCl).

Disadvantage of Arrhenius Theory

1. Unable to explain the reaction of acid and base in non aqueous media.
2. Unable to explain the mechanism of Amphotric substances (Na_2HPO_4, $NaHCO_3$)

Bronsted-Lowry Theory / Proton Theory

In 1923 Bronsted and Lowry proposed an extension of Arrhenius theory that could describe how acids and bases not in solution reacted. Bronsted-Lowry Acids and Bases are

- An acid is a substance from which a proton (H+ ion) can be removed. Essentially, an acid donates protons to bases.
- A base is a substance to which a proton (H+) can be added. Essentially, a base accepts protons from acids.
- Acids that can donate only one proton are monoprotic, and acids that can donate more than one proton are polyprotic.

The following reactions demonstrate the behavior of Bronsted-Lowry acids and bases.

- An acid (in this case, hydrochloric acid) will donate a proton to a base (in this case Water is the base). The acid loses its proton and the base gains it.

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

- Water is not necessary. In this case, hydrochloric acid is still the acid, but ammonia act as base.

$$HCl + NH \longrightarrow Cl + NH_4^+$$

- The same reaction is happening, but now in reverse. What was once an acid is Base (HCl Cl) and what was once a base is now an acid ($NH_3 \rightarrow NH_4^+$).This Concept is called conjugates, and it will be explained in more detail later.

$$Cl+NH_4 \longrightarrow HCl+NH_3$$

- Two examples of acids (HCI and H_3O^+) mixing with bases (NaOH and OH) to form neutral substances (NaCl and H_2O).

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

$$H_3O^+ + OH \longrightarrow 2H_2O$$

- A base (sodium hydroxide) will accept a proton from an acid (ammonia). A neutral substance is produced (water), which is not necessarily a part of every reaction. Compare this reaction to the second one. Ammonia was a base, and now it is an acid. This concept, called amphoterism.

$$NaOH+NH_3 \longrightarrow Na^+ + H_20 + NH_2^+$$

Advantage of Bronsted-Lowry Theory

1. It explains the Behavior of Amphiprotic substance.
2. Show the strong relation between acid and base regardless the type of solvent.

Disadvantage of Bronsted-Lowry Theory

1. Unable to interpretation of acidic and basic Character for some substances which cant' interpret with Arrhenius else.
2. It does not hold good for non-protonic solvents, for instance: BF_3, $POCl_3$ and SO_2.

Amphoterism and Water

Substances capable of acting as either an acid or a base areamphoteric. Water is the most important amphoteric substance. It can ionize into hydroxide (OH , a base) or hydronium (H3O, an acid). By doing so, water is

1. Increasing the H^+ or OH^- concentration (Arrhenius),
2. Donating or accepting a proton (Bronsted-Lowry), and
3. Accepting or donating an electron pair (Lewis).

Water will dissociate very slightly it can be explained by following equations

Acid Base Titration

The presence of hydrogen ions indicates an acid, whereas the presence of hydroxide

Ions indicates a base. Being neutral, water dissociates into both equally.

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

The following equation is more accurate-hydrogen ions do not exist in water because they bond to form hydronium.

$$2H_2O + H_3O^+ + OH^-$$

Ammonia

- Another common example of an amphoteric substance is ammonia. Ammonia is a normally a base, but in some reactions it can act like an acid.
- Ammonia's amphoteric properties are not often seen because ammonia typically acts like a base.
- Water, on the other hand, is completely neutral, so its acid and base behaviors are both observed commonly.
- Ammonia acts as a base. It accepts a proton to form ammonium.

$$NH_3 + HCl \rightarrow NH_4^- + Cl^-$$

- Ammonia also acts as an acid. Here, it donates a proton to form amide.

$$Li_3N + 2NH_3 + 3L^{i+} + 3NH_2$$

Lewis Theory / Electronic Theory

- The Lewis definition is the most general theory, having no requirements for solubility or protons.

Lewis Acids and Bases

1. A Lewis acid accepts a pair of lone pair / nonbonding electrons to form a coordinate Bond. It is an electron-pair acceptor. Examples include:
    - Boron and Aluminium halides like boron trifluoride, BF_3, aluminum, Chloride, $AlCl_3$,
    - Metal ions e.g. $A1^{3+}$
    - Transition metals e.g. Cu_{2+}
    - H^+
    - Silicon compounds
    - SO_3

2.A Lewis base donates a lone pair/ non bonding electrons to form a coordinate covalent bond. It is an electron-pair donor. Examples include:

- NH_3
- OH^-
- H_3O-
- CI^-, F^-, I^-, Br^-
- O_2
- NH_2^-

2. Lewis acids and bases react to create an adduct, a compound in which the acid base have bonded by sharing the electron pair.
3. Lewis acid/base reactions are different from redox reactions because there is no change in oxidation state.
4. The following reaction shows a Lewis base (NH) donating an electron Lewis acid (H^+) to form an adduct (NH_4^+).

Advantage of Lewis theory

- The ability to explain major of organic reaction.
- First time described the hydrogen free substance as acid. (BF_3)

Disadvantage of Lewis theory

Limited only with compound donor pair electron (must have O, N, or S).

Usanovich Theory

Usanovich (1934) modified the Lewis concept of acid and base by removing the restriction of either donation or acceptance of the electron pair in a more generalized fashion. According to this model,

Acid: It is a chemical species that reacts with a base thereby giving up cations or accepting anions or electrons.

Base: It is a chemical species that reacts with an acid thereby giving up anions or electrons combines with cations.

- Unlike Arrhenius, Lowry-Bronsted and Lewis acids and bases, the Usanovich’s Concept in a much broader sense includes all the oxidizing agents as acids and the Reducing agents as bases,

$$\underset{\text{Base}}{Fe^{2+}} \longleftrightarrow \underset{\text{Acid}}{Fe^{3+} + e^{-}}$$

- In the Iron (II)-Iron (III) system, the ferric ion (III) acts as an oxidizing agent and is an acid, while the ferrous íon (II) acts as a reducing agent and is a base.

$$\underset{\text{Base}}{Ce^{3+}} \longleftrightarrow \underset{\text{Acid}}{Ce^{4+} + e^{-}}$$

- Similarly, in the Cerous (III)-Ceric (IV) system, the ceric ion (IV) behaves as an Oxidizing agent and acts as an acid; while the cerous ion (I) behaves as a reducing Agents and acts as a base.

Lux-Flood concept

- The concept of acid-base reactions with respect to the oxide ion was first introduced by Lux (1929) and supported by Flood (1947).
- Acording to the Lux-Flood concept an acid is the oxide-ion acceptor while a base Is the oxíde donor

$$MgO + SiO_2 \longrightarrow MgSiO_3$$

$$CaO + SO_3 \longrightarrow CaSO_4$$

- In the above reactions both MgO and CaO are the oxide ion donor and hence act as bases, whereas SiO_2 and SO_3 are the oxide-ion acceptor and hence act as acids.
- Ultimately, the Lux-Flood acid and base react to form magnesium silicate ($MgSiO_3$) and calcium sulphate ($CaSO_4$) salts respectively.

OVERVIEW OF ACID BASE THEORY

	Arrhenius	Bronsted	Lewis	Usanovich	Lux-Flood Concept
Media	Aqueous	All	All	All	All
Acid	Liberate H^+	Give proton	Receive pair of elecrons	give cation accept anions	Oxide ion acceptor
Base	Liberate OH^+	Receive proton	Donate pair of elecrons	give anions or combine with cations	Oxide donor
Neutral	Salt + Water	Transport proton from acid to base	Formation of coordinate bonds		
Amphotric	-	Give or receive proton			

Hard and Soft Acids and Bases

- In 1963 Ralph Pearson proposed an advanced qualitative concept known as hard soft Acid Base principle, later made quantitative with help of Robert Pare in 1984.
- According his postulate the strong acids and bases are generally more reactive than weak acids and bases.
- However, the direction of the reaction and the stability of the products often depends on another quality is known as the hardness or softness of the acid and bases.

Soft Acids

- For soft acids, the electron-pair acceptor atoms are large, have a low positive charge density, and contain unshared pairs of electrons in their valence shells.
- The unshared pairs of electrons are in the p or d orbitals. Also, soft acids have a high polarizability and a low electronegativity.
- In organic chemistry, the soft acids usually include only the halogens, phosphorus and sulfur compounds.

Hard Acids

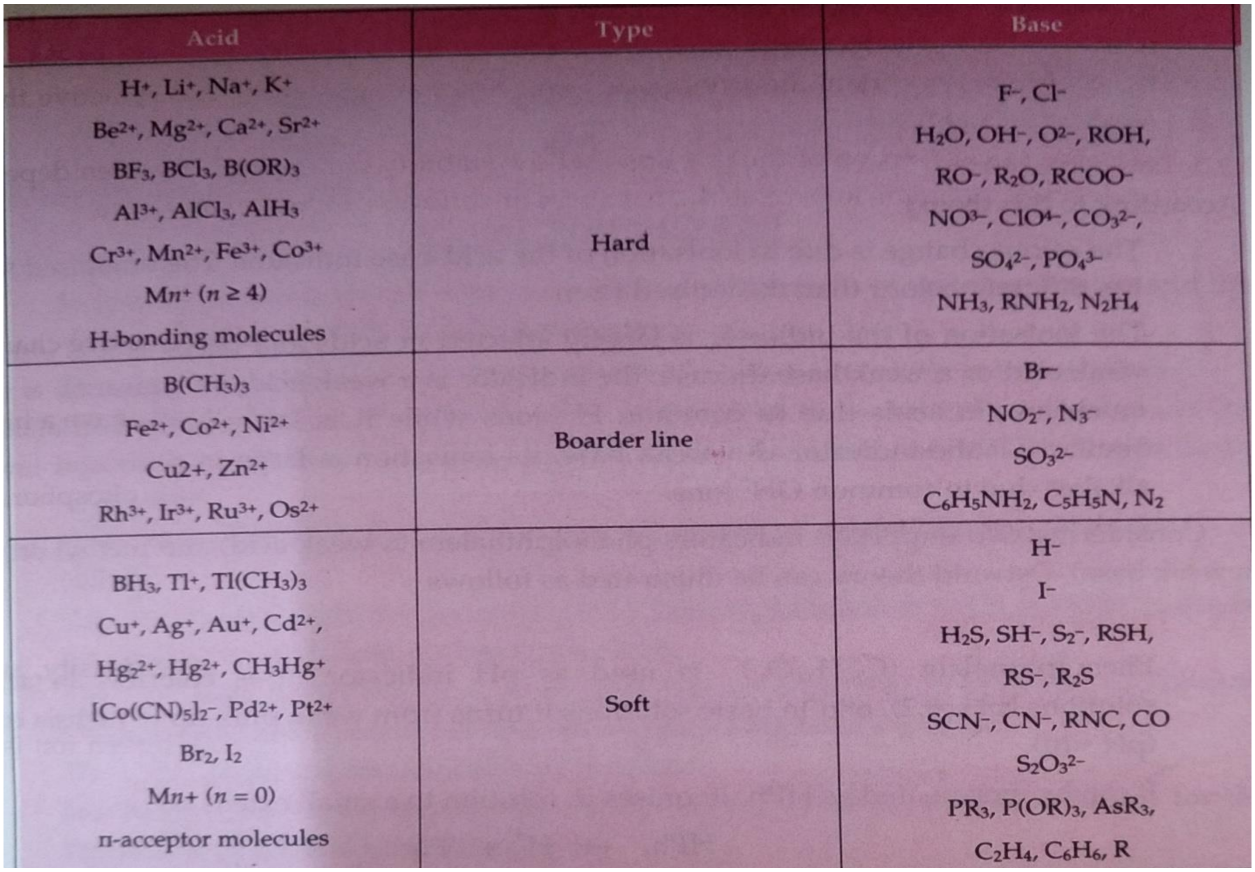
- Hard acids, the acceptor atoms are small, have a high positive charge density, and contain no unshared pairs of electrons in their valence shells.
- They have a low polarizability and a high electronegativity. The hydrogen ion is a good example of a hard acid.

Soft Bases

- Soft bases, the donor atoms hold their valence electrons loosely.
- They have high polarizability, low negative charge density, and low Electronegativity.
- Common soft bases are the cyanide (CN) and iodide (I^-) ions.

Hard Bases

- Hard bases, the donor atoms are small, have a high negative charge density, and hold their valence electrons tightly.
- They have a low polarizability and a high electronegativity.
- The hydroxide ion is a good example of a hard base.



Acid	Type	Base
H^+, Li^+, Na^+, K^+ Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+} BF_3, BCl_3, $B(OR)_3$ Al^{3+}, $AlCl_3$, AlH_3 Cr^{3+}, Mn^{2+}, Fe^{3+}, Co^{3+} Mn^+ ($n \geq 4$) H-bonding molecules	Hard	F^-, Cl^- H_2O, OH^-, O^{2-}, ROH, RO^-, R_2O, $RCOO^-$ NO^{3-}, ClO^{4-}, CO_3^{2-}, SO_4^{2-}, PO_4^{3-} NH_3, RNH_2, N_2H_4
$B(CH_3)_3$ Fe^{2+}, Co^{2+}, Ni^{2+} Cu2+, Zn^{2+} Rh^{3+}, Ir^{3+}, Ru^{3+}, Os^{2+}	Boarder line	Br^- NO_2^-, N_3^- SO_3^{2-} $C_6H_5NH_2$, C_5H_5N, N_2
BH_3, Tl^+, $Tl(CH_3)_3$ Cu^+, Ag^+, Au^+, Cd^{2+}, Hg_2^{2+}, Hg^{2+}, CH_3Hg^+ $[Co(CN)_5]_2^-$, Pd^{2+}, Pt^{2+} Br_2, I_2 Mn+ ($n = 0$) п-acceptor molecules	Soft	H^- I^- H_2S, SH^-, S_2^-, RSH, RS^-, R_2S SCN^-, CN^-, RNC, CO $S_2O_3^{2-}$ PR_3, $P(OR)_3$, AsR_3, C_2H_4, C_6H_6, R

THEORY OF INDICATORS

- An indicator is a substance which is used to determine the end point in a titration Acid-base titrations, organic substances (weak acids or weak bases) are generally used as indicators. They change their colour within a certain pH range.
- Acid-base titrations depend on the neutralization between an acid and a base when mixed in solution.
- In addition to the sample, an appropriate indicator 18 added to the titration chamber, reflecting the pH range of the equivalence point.
- The acid-base indicator indicates the endpoint of the titration by changing color. The endpoint and the equivalence point are not exactly the same because the equivalence point is determined by the stoichiometry of the reaction while the endpoint is just the color change from the indicator.
- Thus, a careful selection of the indicator will reduce the indicator error.
- Two theories have been proposed to explain the change of colour of acid-base indicators with change in pH.

1. Ostwald's theory

2 Quinonoid theory

Ostwald's theory

According to this theory

A. The colour change is due to ionisation of the acid-base indicator. The unionised form has different colour than the ionised form.

B. The ionisation of the indicator is largely affected in acids and bases as it is either Weak acid or a weak base. In case, the indicator is a weak acid, its ionisation is much low in acids due to common H^+ ions while it is fairly ionised in alkalies. Similarly if the indicator is a weak base, its ionisation is large in acids and low in alkalies due to common OH ions.

Considering two important indicators phenolphthalein (a weak acid) and methyl orange (a weak base), Ostwald theory can be illustrated as follows

a. Phenolphthalein:

- Phenolphthalein ($C_{20}H_{14}O_4$) is used as pH indicator. It is colorless in acidic solutions (pH<8.2), and in basic solutions it turns from weak pink up to fuchsia color (pH10).
- It can be represented as HPh. It ionises in solution to a small extent as:

$$\underset{\text{Colourless}}{HPh} \longleftrightarrow \underset{\text{Pink}}{H^+ + Ph^-}$$

Applying law of mass action

$$K= [H^+][Ph^-]/[HpH]$$

- The undissociated molecules of phenolphthalein are colourless while Ph- ions are pink in colour.
- In presence of an acid the ionisation of HPh is practically negligible as the equilibrium shifts to left hand side due to high concentration of H ions.
- Thus, the solution would remain colourless.
- On addition of alkali, hydrogen ions are removed by OH ions in the form of water molecules and the equilibrium shifts to right hand side.
- Thus, the concentration of Ph- ions increases in solution and they impart pink colour to the solution.

Methyl orange:

- It is a very weak base and can be represented as MeOH. It is ionized in solution to give Me^+ and OH^- ions.

$$\underset{\text{Yellow}}{MeOH} \longleftrightarrow \underset{\text{Red}}{Me^+ + OH^-}$$

Applying law of mass action,

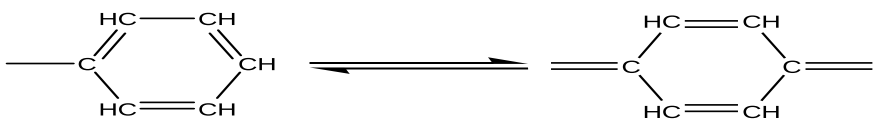
$$K= [Me^+][OH^-]/[MeOH]$$

- In presence of an acid, OH ions are removed in the form of water molecules and the above equilibrium shifts to right hand side.
- Thus, sufficient Me^+ ions are produced which impart red colour to the solution.
- On addition of alkali, the concentration of OH” ions increases in the solution and the equilibrium shifts to left hand side, ie, the ionisation of MeOH is practically negligible.
- Thus, the solution acquires the colour of unionised methyl orange molecules, i.e., Yellow.
- This theory also explains the reason why phenolphthalein is not a suitable indicator for titrating a weak base against strong acid.
- The OH^- ions furnished by a weak base are not sufficient to shift the equilibrium towards right hand side considerably, ie., pH is not reached to 8.3.
- Thus, the solution does not attain pink colour.
- Similarly, it can be explained why methyl orange is not a suitable indicator for the titration of weak acid with strong base.

Quinonoid theory

According to this theory:

i) The acid-base indicators exist in two tautomeric forms having different structures. Two forms are in equilibrium. One form is termed benzenoid form and the other quinonoid form.

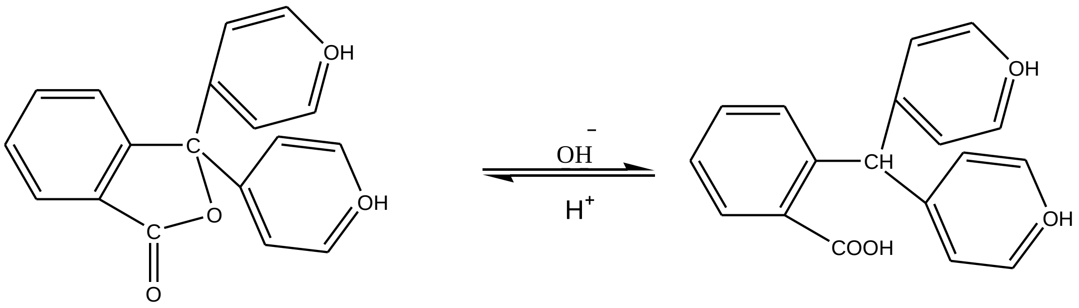


ii) Two forms have different colors. The color change in due to the Interconversation of one tautomeric form into other.

iii) One form mainly exists in acidic medium and the other in alkaline medium. Thus, during titration medium changes from acidic to alkaline or vice versa. The change in pH converts one tautomeric form into other and thus, the colour changes occurs.

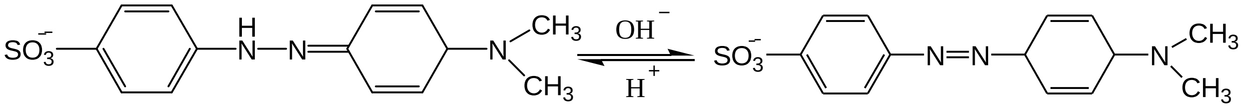
Phenolphthalein

Phenolphthalein has benziod form in acidic medium and thus, it is colourless while it has quinonoid form in alkaline mediumwhich has pink colour



Methyl Orange

Methyl Orange has quinonoid form in acidic solution and benzenoid form in alkaline solution. The colour of benzenoid form is yellow while that of quinonoid form is red.



Quinonoid form The colour change

INDICATORS USED FOR VARIOUS TITRATIONS

Strong Acid against a Strong Base

- Let us consider the titration of HCl and NaOH.
- The pH value of different stages of titration shows that, at first the pH changes very slowly and rise to only about 4.
- Further addition of very small amount as 0.01 mL of the alkai raises the pH value by about 3 units to pH 7.
- The acidis completely neutralized. Further of about 0.01mL of 0.1 M NaOH will amount to adding hydrogen ionand the pH value will jumps to about 9.
- Thus near the ed point there is a rapid increase of pH from about 4 to 9.
- An indicator is suitable only if it undergoes a change of colour at the pH near the end point.
- Thus the indicators like methyl orange, methyl red and phenolphthalein can shows the colour change in the pH range 4 to 10.
- Thus, in strong acid- strong base titration, any one of the above indicator can be used .

Weak acid against Strong base

- Let us consider the titration of acetic acid against NaOH.
- The titration shoes the end point lies between pH 8 to 10.
- This is due to the hydrolysis of sodium acetate formed. Hence phenolphthalein is a suitable indicator as its pH range is 8-9.8.
- However, methyl orange is not suitable as its pH range is 3.1 to 4.5.

Strong acid against Weak base

Strong Acids	Strong Bases	Weak Acids	Weak Bases
HCl	NaOH	Acetic acid	Ammonia
HNO_3	KOH	Hydrocyanic acid	Magnesium hydroxide
HBr	Etc	HF	Pyridine
H_2SO_4		Oxalic acid	Sodium Carbonate
HI		Ethanoic acid	Potassium Carbonate
$HClO_4$		etc	Etc

- Let us conider the titration of Ammonum hydroxide against HCl.
- Due to the hydrolysis of salt ,NH_4Cl formed during the reaction, the pH lies in the acid range
- Thus,the pH at the endpoint lies in the range of 6 to 4.
- Thus, methyl orange is a suitable indicator while phenolphthalein is not suitable.

TYPES OF ACID BASE TITRATION

These are normal titration between acid and base dissolved in water. Hence the name aqueous titration.

Strong Acid V/S Strong Base

- Here are strong acid reacts with a strong alkali to form salt and water.
- The reaction of this type is swift and also complete. The reaction happens in stoichiometric means, ie, each molecule of acid reacts with the corresponding molecule or the base.
- At the end of the reaction, no molecule of acid or base exists as every molecule in the reaction has completely reacted to form a salt.
- Hence the endpoint or equivalence point is precise and sharp.
- Example or these types of acids are HCI, H_2SO_4, HNO_3, HBr, $HCIO_4$ (perchloric acid),H_3PO_4, etc.
- The exemples or strong bases are NaOH, $MgOH_2$, Al_2OH_2, etc.
- Either the known quantity of acid is taken in burette to react with an unknown quantity of strong base in the flask.
- The pH at the end point is neutral i.e. 7. So the indicator changing their colour around pH 7 are used here.

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

Strong Acid V/S Weak Base

- Here a strong base reacts with weak add to form salt and water.
- But since the reaction uses a strong acid, the pH at the endpoint will be towards acidic, ie, below 7.

$$HCl + NH_4OH \longrightarrow NH_4Cl + H2O.$$

- Here the salt formed NH4Cl is slightly acidic. So indicators changing color at lower pH's are employed.
- During the reaction, a known concentration of strong acid is taken in a burette and allowed to react drop by drop with the base in a beaker.

Weak Acid V/S Strong Base

- Here the reaction happens between a weak acid and strong base.
- The weak acid is taken in a beaker and known quantity of strong base is dropped from a burrete till the endpoint.

$$H_2CO_3 + NaOH \rightarrow Na_2CO_3 + H_2O$$

- The salt formed is slightly basic, so the pH at the end point is above 7. The indicator used is one with a change in color at higher pH.

Weak Acid V/S Weak Base

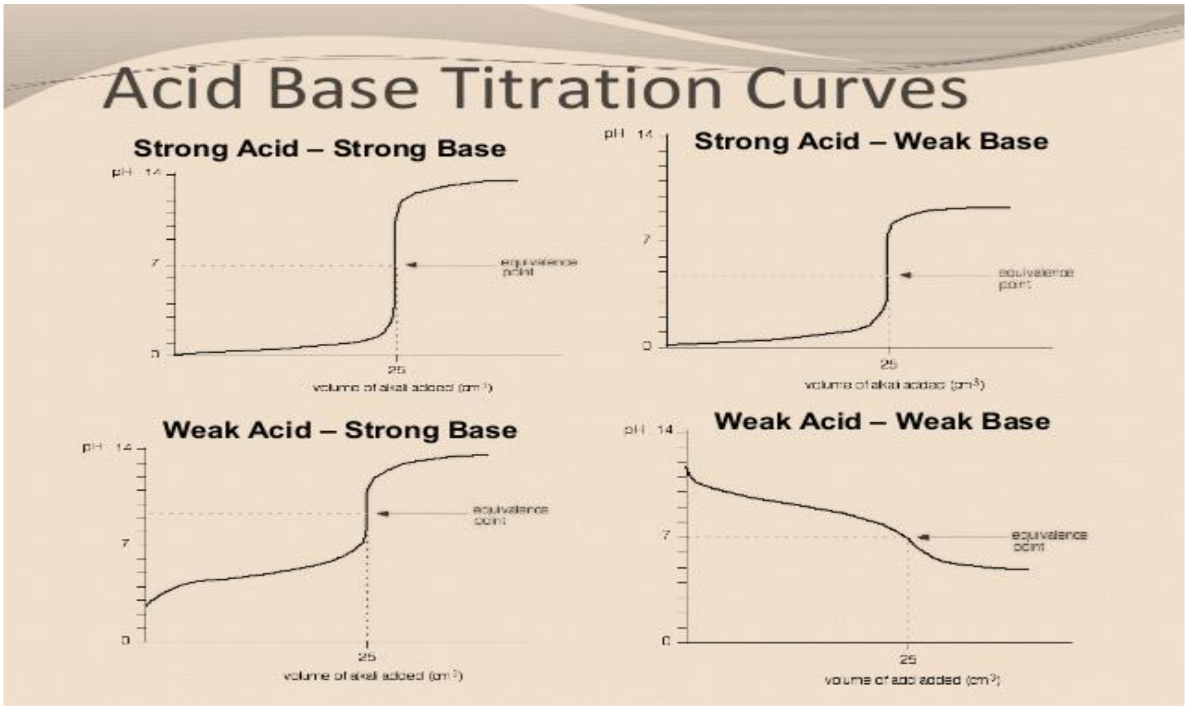
- Here both acid and base are weak.
- So mostly they are avoided due to imprecise endpoints.
- At the endpoint, the pH will be seven theoretically.
- But cannot be measured precisely like that in strong acid and strong base case.
- An extra amount of titrant is needed to reach the endpoint due to the imprecise reaction.

$$H_2CO_3 + NH_4OH \longrightarrow NH_4OH + H_2O$$

- The endpoint is neutral as the salt is neutral but due t excess titrant added the could be in favor of it.

Non aqueous titration

- These are conventional methods of Non aqueous titration.
- Here instead of water as solvent glacial acetic acid is used to make the reactants.
- Since many drugs are water insoluble and slightly acidic or basic, they are analysed by non-aqueous titration.
- They are extensively used for quality control and analysis of drugs.



Acid Base Titration Curves

Strong Acid – Strong Base

Strong Acid – Weak Base

Weak Acid – Strong Base

Weak Acid – Weak Base

IMPORTANT QUESTIONS

Short answer questions

1. Give reasons why you go to Non-Aqueous titration.
2. Write the Advantage of NAT.
3. Name the solvents used in NAT.
4. Define Leveling effect.
5. What are the precautions for the preparation of 0.1N perchloric acid?
6. Name the titrant used in alkalimetry in NAT.
7. Name the indicators used in acidimetry and alkalimetry in NAT.
8. What is acid base titration and classify?
9. Name the theories of acid base indicator.
10. Define Lewis acid and base?
11. Give advantage and disadvantage of Lewis theory?
12. Give the examples of indicators used in acid base titration.

Long answer questions

1. Explain the types of solvent used in NAT?
2. Write a note on solvent, titrant and indicator used in the determination of weak base in NAT?
3. Explain the solvent, titrant and indicator used in alkalimetry in NAT?
4. Explain the theories of indicators.
5. Explain in detail types of acid base titration