PHARMACEUTICAL ANALYSIS

UNIT I

INTRODUCTION Pharmaceutical analysis is a branch of practical chemistry that involves a series of process for identification, determination, quantification and purification of a substance, separation of the components of a solution or mixture, or determination of structure of chemical compounds.

The substance may be a single compound or a mixture of compounds and it may be in any of the dosage form. The substance used as pharmaceuticals are animals, plants, microorganisms, minerals and various synthetic products.

The sample to be analysed is called as analyse and on the basis of size of sample, they can be classified as macro(0.1 g or more), semi micro (0.01 g to 0.1 g), micro(0.001 g to 0.01 g), sub micro (0.0001 g to 0.001 g), ultramicro (below 10-4 g), trace analysis(100 to 10000 ppm). Among all, the semi micro analysis is widely used.

TYPES There are main two types of chemical analysis. 1. Qualitative (identification) 2. Quantitative (estimation)

1. Qualitative analysis is performed to establish composition of natural/synthetic substances. These tests are performed to indicate whether the substance or compound is present in the sample or not. Various qualitative tests are detection of evolved gas, formation of precipitates, limit tests, colour change reactions, melting point and boiling point test etc.

2. Quantitative analytical techniques are mainly used to quantify any compound or substance in the sample. These techniques are based in

(a) the quantitative performance of suitable chemical reaction and either measuring the amount of reagent added to complete the reaction or measuring the amount of reaction product obtained,

(b) the charatristic movement of a substance through a defined medium under controlled conditions,

(c) electrical measurement,

(d) measurement of some spectroscopic properties of the compound.

Various types of Qualitative analysis: 1.Chemical methods a) volumetric or titrimetric methods b) gravimetric methods c) gasometric analysis 2.Electrical methods 3.Instrumental methods 4.Biological and microbiological

1. Chemical methods a)Titrimetric or volumetric method It involves reaction of substance to be determined with an appropriate reagent as a standard solution, and volume of solution required to complete the reaction is determined. Volumetric methods require simple and less apparatus and they are susceptible of high accuracy. Various types of titrimetric methods are:

i)Acid-base titrations (neutralization reactions)

ii)Complexometric titrations

iii)Precipitation titrations

iv)Oxidation reduction titrations

v)Non aqueous titrations

b) Gravimetric methods In gravimetric analysis, a substance to be determined is converted into an insoluble precipitate in the purest form, which is then collected and weighed. It is the time consuming process. In electrogravimetry, electrolysis of the sample is carried out on the electrodes is weighed after drying. Thermogravimetry (TG) records the change in

weight, differential thermal analysis (DTA) records the difference in temperature between test substance and an inert reference material, differential scanning calorimetry (DSC) records the energy needed to establish a zero temperature difference between a test substance and reference material.

c) Gasometric analysis Gasometry involves measurement of the volume of gas evolved or absorbed in a chemical reaction. Some of the gases which are analysed by Gasometry are CO2 , N2O,cyclopropane, amyl nitrate, ethylene, N2, helium etc.

2. Electrical methods Electrical methods of analysis involve the measurement of electric current, voltage or resistance in relation to the concentration of some species in the solution. Electrical methods of analysis include: (a)Potentiometry (b)Conductometry (c)Polarography (d)Voltametry (e)Amperometry

Potentiometry measures electrical potential of an electrode in equilibrium with an ion to be determined. Conductometry measures electrical conductivity of an electrode with a reference electrode while Polarography, Voltametry and Amperometry measures electrical current at a micro-electrode.

3. Instrumental methods of analysis Instrumental method involves measurement of some physical properties of the compound or a substance. These methods are employed for determination of minor or trace concentration of element in the sample.

Instrumental methods are preferred due to their selectivity, high speed, accuracy and simplicity of analysis. Any change in the properties of the system are detected by measurement of absorbance, specific rotation, refractive index, migration difference, charge to mass ratio etc.

Spectroscopic methods of analysis depend upon measurement of the amount of radiant energy of a particular wavelength emitted by the sample. Methods which include absorption of radiation are ultra violet, visible, infra red, atomic absorption, nuclear magnetic resonance spectroscopy etc.

Emission methods involve heating or electrical treatment of the sample so that the atoms are raised to the excited state to emit the energy and the intensity of this energy is measured.

Emission methods include emission spectroscopy, flame photometry, flourimetry etc. Chromatographic techniques and electrophoretic methods are separation methods for the mixure of compounds, but also applied for identification of compounds of mixures.

Various chromatographic techniques are GC, HPLC, TLC, HPTLC, PC etc. Mass spectrometry involves vaporization of material using a high vaccum and the vapour is bombarded by a high energy electron beam. Vapour molecules undergo fragmentation to produce ions of varying size. These ions are differentiated by accelerating them in electrical field and then deflecting them in a magnetic field. Each kind of ion gives a peak in the mass spectrum.

4. Biological and microbiological methods Biological methods are used when potency of a drug or its derivative cannot be properly determined by any physical or chemical methods. They are called bio-assays.

Microbiological methods are used to observe potency of antibiotic or anti-microbial agents. In antimicrobial assay, inhibition of growth of bacteria of the sample is compared with that of the standard antibiotic. These methods include cup plate method and turbidimetric analysis.

APPLICATIONS Manufacturing industries require both qualitative and quantitative analysis to ensure that their raw materials meet certain specifications, and to check the quality of final product. Raw materials are to be checked to ensure that the essential components are present within the

predetermined range of composition and there are not any unusual substances present which might upset the manufacturing process or it may appear as a harmful impurity in the final product.

In the development of new products which contains mixtures other then the pure material, it is necessary to ascertain composition of mixture which shows the optimum characteristics for which the material has been developed.

Geographical surveys require analysis to determine the composition of soil sample and numerous rock samples collected from the field.

Most of the industrial processes give rise to pollutants which may cause health related problems. So quantitative analysis of air, water and soil sample should be carried out to determine the level of pollution and to establish the safe limits for pollutants.

Standards can be divided into two types:

➢ Primary standard

➢ Secondary standard

Primary standard

A primary standard is a chemical or reagent which has certain properties such as-

(a) It is extremely pure – A primary standard material should be extremely pure which means that it should be a chemical of high grade of purity, preferably 99.98%. In a pahramceutical analysis laboratory we come across chemicals of different grade of purity. If we check the label we will notice a number with percentage termed as purity. So when a chemical has purity of 99.98% or more it is a suitable material to be used as primary standard.

(b) It is highly stable – It should be highly stable which means it usually does not react easily when kept in its pure form or it should have very low reactivity. This is important because if a reagent reacts easily with atmospheric oxygen or water or changes its property over time then it is unreliable and such a unstable and unreliable chemicals can never be used as standard.

(c) It is anhydrous- It should be anhydrous which means that it does not contain any water molecule in its molecular structure. For example, in a pharmaceutical analysis laboratory we come across same chemical with different number of water molecules attached with it e.g. magnesium sulphate (MgSO4), which is also called Epsom salt. The Epsom salt which is found in drug store is a chemical with formula MgSO4.7H2O. Therefore if we want to prepare a primary standard of magnesium sulphate we should purchase an anhydrous MgSO4 preferably an analytical reagent grade chemical and with purity greater than 99.98%.

(d) It is less hygroscopic in nature- The chemical preferably should be less hygroscopic i.e. on opening the container it should not absorb water molecules from atmosphere.

(e) It has very high molecular weight- It has very high molecular weight compared to its other similar forms. For example Epsom salt. Take 1 gram of MgSO4 for making a primary standard and name it as salt A. Now take 1 gram of MgSO4.7H2O for common uses and name it as salt B.

Now if we compare the actual weight (Molecular weight) of magnesium sulphate to make a standard solution for both chemicals then it is found that-

MgSO4	108
MgSO4.7H2O	234

In first case, molecule of salt A the weight of actual $MgSO_4$ will be 108 atomic mass unit. But in second case, molecule of salt B the weight of actual $MgSO_4$ will be 108 out of its total weight of 234 atomic mass unit.

108 gram salt A ($MgSO_4$) will give 108 gram of $MgSO_4$

So, 1 gram $MgSO_4$ salt will give = 108/108 = 1 gram of $MgSO_4$

But 234 gram salt B ($MgSO_4.7H_2O$) will give 108 gram of $MgSO_4$

So, 1 gram $MgSO_4.7H_2O$ salt will give = 108/234 = 0.461 gram of $MgSO_4$

Therefore if by mistake we make a standard out of salt B, actually we are taking 0.461 gram of $MgSO_4$ and calculating it as 1 gram. So with this faulty standard estimation of $MgSO_4$ in other unknown solution will give less result than the actual concentration. Hence it is important that primary standards must be anhydrous and of high molecular weight.

(f) It can be weighed easily – It can be weighed easily because it is so pure that its weight is in fact a true representative of number of moles present in its actual weight.

(g) It should be ready to use and available

(h) It should be preferably non toxic

(i) It should not be expensive

Uses – Primary standard is used to standardize a volumetric solution i.e. they are used for standardization of titration of solutions. It can be used for titration of acids as well as bases. In a pharmaceutical analysis laboratory, for acid titration the most common basic chemical standard is sodium carbonate (Na_2CO_3), (TRIS) Trisaminomethane [$(CH_2OH)_3CNH_2$] etc. For base titration, potassium hydrogen phthalate [(KHP): $KHC_8H_4O_4$] etc. For redox titration, potassium dichromate ($K_2Cr_2O_7$) & Sodium oxalate ($Na_2C_2O_4$) are very often used as primary standard.

– The primary standard is used for calibration of secondary standard or for method validation using a specific method.

Secondary standard

A secondary standard is involved in preparation of reagents and kits or laboratories responsible for producing quality control material for other laboratories. They use primary standard as the primary calibrator or primary reference material. Secondary standard is used for the purpose of calibration of control material in laboratory for analysis of unknown concentration of a substance. So basically, secondary standard serves the purpose of external quality control for laboratories. So it is essential that the secondary standard must first be standardized against the primary standard.

For preparation of secondary standard solution, aqueous solution must be of high grade purity. It must be deionized, if water is used as aqueous solvent. A secondary standard is a chemical or reagent which has certain properties such as

(a) The purity of secondary standard is less than primary standard

(b) Secondary standard is less stable and more reactive than primary standard

(c) The secondary standard solution remains stable for a long time

(d) Secondary standard is titrated against primary standard

Example – 1: Anhydrous sodium hydroxide (NaOH). It is extremely hygroscopic. As soon as the bottle is opened, NaOH absorbs moisture from atmosphere and it becomes moist. Lets do it practically, take an analytical balance and place a Petridish and make its weight as zero (Tare). Now open the NaOH bottle and place little NaOH crystal on the petridish and note the weight. Now keep the glass windows of the analytical balance open for few minutes and notice the gradual increase in its weight. This is because the NaOH crystals absorb water molecule from air.

Example – 2: Potassium permanganate ($KMnO_4$) very often used as secondary standard. It is a good oxidizing agent, that's why reactive and hence less stable. Its own oxidized product manganese oxide (MnO_2) contaminates the content. Hence it is unsuitable for being a primary standard.

Secondary standard is used as a calibrator by smaller laboratories involved in actual analysis of unknown samples.

Calibration

Calibration means to check whether an instrument is working properly or not i.e. the instrument is giving correct measurement or not. Calibration and standardization are synonyms of each other but in case of solution we use the word standardization and in case of instruments we use the calibration . This is the process by which we compare the measurements by a standard or an instrument (primary) with another standard or an instrument (secondary). By doing so, we try to eliminate any variation or difference in measurement by the secondary standard or an instrument.

SOURCES OF IMPURITIES:

Impurities can originate from several sources

1. Crystallization-related impurities
2. Stereochemistry-related impurities
3. Residual solvents
4. Synthetic intermediates and by-products
5. Formulation-related impurities
6. Impurities arising during storage
7. Method related impurity
8. Mutual interaction amongst ingredients
9. Functional group-related typical degradation

a. Crystallization-related impurities

Based on the realization that the nature of structure adopted by a given compound upon crystallization could exert a profound effect on the solid-state properties of that system, the pharmaceutical industry is required to take a strong interest in polymorphism and solvatomorphism as per the regulations laid down by the regulatory authorities. Polymorphism is the term used to indicate crystal system where substances can exist in different crystal packing arrangements, all of which have the same elemental composition. Whereas, when the substance exists in different crystal packing arrangements, with a different elemental composition, the phenomenon is known as Solvatomorphism.

b. Stereochemistry-related impurities

It is important to look for stereochemistry related compounds; that is, those compounds that have similar chemical structure but different spatial orientation, these compounds can be considered as impurities in the API's. Chiral molecules are frequently called enantiomers. The single enantiomeric form of chiral drug is now considered as an improved chemical entity that may offer a better pharmacological profile and an increased therapeutic index with a more favorable adverse reaction profile. However, the pharmacokinetic profile of levofloxacin (S-isomeric form) and ofloxacin (R-isomeric form) are comparable, suggesting the lack of advantages of single isomer in this regard. The prominent single isomer drugs, which are being marketed, include levofloxacin (S-ofloxacin), lavalbuterol (R-albuterol) and esomeprazole (S- omeprazole).

c. Residual solvents

Residual solvents are organic volatile chemicals used during the manufacturing process or generated during the production. Some solvents that are known to cause toxicity should be avoided in the production of bulk

drugs. Depending on the possible risk to human health, residual solvents are divided into three classes.

Class I: benzene (2 ppm limit), carbon tetrachloride (4 ppm limit), methylene chloride (600 ppm), methanol (3000 ppm, pyridine (200 ppm), toluene (890 ppm) should be avoided.

Class II: N, N dimethyl formamide (880 ppm), acetonitrile (410 ppm).

Class III: acetic acid, ethanol, acetone has permitted daily exposure of 50 mg or less per day, as per the ICH guidelines.

A selective gas chromatography (GC) method has been developed to determine the purity of acetone, dichloromethane, methanol and toluene. Using this method, the main contaminants of each organic solvent can be quantified. Moreover, the developed method allows the simultaneous determination of ethanol, isopropanol, chloroform, benzene, acetone, dichloromethane, methanol and toluene with propionitrile as the internal standard.

d. Synthetic intermediates and by-products

Impurities in pharmaceutical compounds or a new chemical entity (NCE) can originate during the synthetic process from raw materials, intermediates and/or by-product. For example, impurity profiling of ecstasy tablets by GC-MS and MDMA samples, produced impurities in intermediates via reductive amination route.

e. Formulation-related impurities

Many impurities in a drug product can originate from excipients used to formulate a drug substance. In addition, a drug substance is subjected to a variety of conditions in the process of formulation that can cause its degradation or have other undesirable reactions. If the source is from an excipient, variability from lot to lot may make a marginal product,

unacceptable for reliability. Solutions and suspensions are inherently prone to degradation due to hydrolysis or Solvolysis.

Fluocinonide Topical Solution USP, 0.05%, in 60-mL bottles, was recalled in the United States because of degradation/impurities leading to sub- potency.

In general, liquid dosage forms are susceptible to both degradation and microbiological contamination. In this regard, water content, pH of the solution/suspension, compatibility of anions and cations, mutual interactions of ingredients, and the primary container are critical factors.

Microbiological growth resulting from the growth of bacteria, fungi, and yeast in a humid and warm environment may results in unsuitability of an oral liquid product for safe human consumption. Microbial contamination may occur during the shelf life and subsequent consumer-use of a multiple-dose product, either due to inappropriate use of certain preservatives in the preparations, or because of the semi-permeable nature of primary containers.

PREPARATION AND STANDARDIZATION OF VARIOUS MOLAR SOLUTIONS.

1. Oxalic acid (COOH)2

Oxalic acid is available in pure state and its standard solutions can, therefore, be prepared by the direct method.

Eq. wt. of hydrated oxalic acid ($C_2H_2O_4.2H_2O$), being 63 its 0.1N solution would contain 6.3 gm/litre, and 0.05 N solution would contain 3.15 gm/litre. These standard solutions are employed to find the strength of solutions of alkalies (NaOH and KOH) whose standard solutions cannot be prepared by the direct method.

PRINCIPLE – REDOX TITRATION

KMnO4, potassium permanganate is a strong oxidizing agent. Oxalic acid is oxidized by potassium permanganate in acidic solution to produce CO2 and H2O

2KMnO4 + 3 H2SO4 + 5 (COOH)2 2MnSO4 + K2SO4 +10 CO2 + 8H2O

HCl cannot be used in place of sulphuric acid as it readily get oxidized to chlorine in presence of KMnO4

Preparation Of 0.1N Oxalic Acid Solution

Weigh accurately 6.3 gm of oxalic acid & dissolve in distilled water & finally make up the volume to one liter in a volumetric flask.

Standardization Of 0.1 N Oxalic Acid

- Clean and dry al the glasswares as per standard laboratory procedure.

- Take 20 ml of prepared oxalic acid in a conical flask

- Add 5 ml of sulphuric acid , and warm at 70 0C

- Rinse the burrete with distilled water and pre rinse with the portion of potassium permanganate soln.

- Start the titration with 0.1N KMnO4 until the end point.

- End point is the appearance of pink colour that persists for more than 30 seconds.

- Record the reading repeat the titration 3 times to get th precise values.

f. Impurities arising during storage

A number of impurities can originate during storage or shipment of drug products. It is essential to carry out stability studies to predict, evaluate, and ensure drug product safety.

g. Method related impurity

A known impurity, 1-(2, 6-dichlorophenyl) indolin-2-one is formed in the production of a parenteral dosage form of diclofenac sodium, if it is terminally sterilized by autoclave. The conditions of the autoclave method enforce the intramolecular cyclic reaction of diclofenac sodium forming an indolinone derivative and sodium hydroxide. The formation of this impurity has been found to depend on initial pH of the formulation.

h. Mutual interaction amongst ingredients

Most vitamins are very labile and on aging they create a problem of instability in different dosage forms, especially in liquid dosage forms. Degradation of vitamins does not give toxic impurities; however, potency of active ingredients drops below Pharmacopoeial specifications. Because of mutual interaction, the presence of nicotinamide in a formulation containing four vitamins (nicotinamide, pyridoxine, riboflavin, and thiamine) can cause the degradation of thiamine to a sub-standard level within a one year shelf life of vitamin B-complex injections.

i. Functional group-related typical degradation

Ester hydrolysis can be explained with a few drugs aspirin, benzocaine, cefotaxime, ethyl paraben and cefpodoxime proxetil. Hydrolysis is the common phenomenon for ester type of drugs, especially in liquid dosage forms benzylpenicillin, oxazepam and lincomycin. Oxidative degradation of drugs like hydrocortisone, methotrexate,hydroxyl group directly bonded to an aromatic ring (phenol derivatives such as catecholamines and morphine), conjugated dienes (vitamin A and unsaturated free fatty acids), heterocyclic aromatic rings, nitroso and nitrite derivatives and aldehydes (especially flavorings) are all susceptible to oxidative degradation.

In mazipredone, the hydrolytic and oxidative degradation pathway in 0.1 mol/Lt hydrochloric acid and sodium hydroxide at 800C were studied. Ergometrine, nifedipine, nitroprusside, riboflavin and phenothiazines are

very liable to photo-oxidation. In susceptible compounds, photochemical energy creates free radical intermediates, which can perpetuate chain reactions. Most compounds will degrade as solutions when exposed to high-energy UV exposures. Fluroquinolone antibiotics are also found to be susceptible to photolytic cleavage.

In ciprofloxacin eye drop preparation (0.3%), sunlight induces photo cleavage reaction producing ethylenediamine analog of ciprofloxacin.

Decarboxylation of some dissolved carboxylic acids, such as p-aminosalycylic acid, shows the loss of carbon dioxide from the carboxyl group when heated. An example of decarboxylation is the photoreaction of rufloxacin. As seen earlier, impurities in drug products can come from the drug or from excipients or can be brought into the system through an in process step by contact with the packaging material.

For most drugs, the reactive species consist of: 1. Water (can hydrolyze some drugs or affect the dosage form performance) 2. Small electrophiles (like aldehydes and carboxylic acid derivatives) 3. Peroxides (can oxidize some drugs) 4. Metals (can catalyze oxidation of drugs and the degradation pathway) 5. Leachable or Extractable (can come from glass, rubber stoppers, and plastic packaging materials. Metal oxides such as NaO2, SiO2, CaO, MgO, are the major components leached/extracted from glass).

Generally most synthetic materials contain leachable oligomers/monomers, vulcanizing agents, accelerators, plasticizers and antioxidants. Some examples of leachable / extractable from synthetic materials include styrene from polystyrene, diethylhexylphalate (DEHP, plasticizer in PVC), dioctyltin isooctylmercaptoacetate (stabilizer for PVC), zinc stearate (stabilizer in PVC and polypropylene), 2-mercaptobenzothiazole (accelerator in rubber stopper) and furfural from rayon.

ACID BASE TITRATION

Titrant: solution of a known concentration, which is added to another solution whose concentration has to be determined.

Titrand or analyte: the solution whose concentration has to be determined.

Equivalence point: point in titration at which the amount of titrant added is just enough to completely neutralize the analyte solution. *At the equivalence point in an acid-base titration, moles of base = moles of acid and the solution only contains salt and water.*

Acid-base titrations are monitored by the change of pH as titration progresses

Indicator: It is a weak acid or base that is added to the analyte solution, and it changes color when the equivalence point is reached i.e. the point at which the amount of titrant added is just enough to completely neutralize the analyte solution. The point at which the indicator changes color is called the endpoint. So the addition of an indicator to the analyte solution helps us to visually spot the equivalence point in an acid-base titration.

Endpoint: refers to the point at which the indicator changes color in an acid-base titration.

What is a titration curve?

A titration curve is the plot of the pH of the analyte solution versus the volume of the titrant added as the titration progresses.

1) Titration of a strong acid with a strong base

Suppose our analyte is hydrochloric acid HCl (strong acid) and the titrant is sodium hydroxide NaOH (strong base). If we start plotting the pH of the analyte against the volume of NaOH that we are adding from the burette.

Point 1: No NaOH added yet, so the pH of the analyte is low (it predominantly contains H3O+ from dissociation of HCl).

Point 2: This is the pH recorded at a time point just before complete neutralization takes place.

Point 3: This is the equivalence point (halfway up the steep curve). At this point, moles of NaOH added = moles of HCl in the analyte. At this point, H3O+ ions are completely neutralized by OH- ions. The solution only has salt (NaCl) and water and therefore the pH is neutral i.e. pH = 7.

Point 4: Addition of NaOH continues, pH starts becoming basic because HCl has been completely neutralized and now excess of OH- ions are present in the solution (from dissociation of NaOH).

2) Titration of a weak acid with a strong base

Let's assume our analyte is acetic acid CH3COOH (weak acid) and the titrant is sodium hydroxide NaOH (strong base). If we start plotting the pH

of the analyte against the volume of NaOH that we are adding from the burette, we will get a titration curve as shown below.

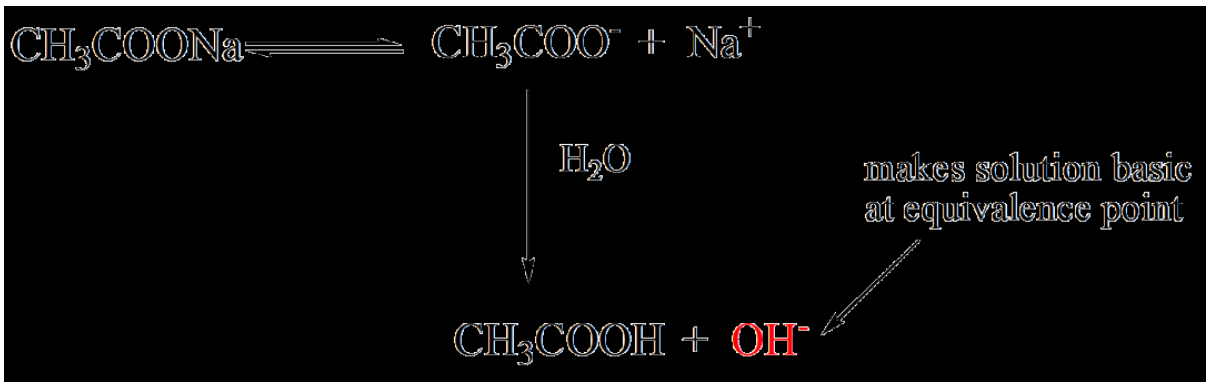
Point 1: No NaOH added yet, so the pH of the analyte is low (it predominantly contains H3O+ from dissociation of CH3 COOH). But acetic acid is a weak acid, so the starting pH is higher than what we noticed in case 1 where we had a strong acid (HCl).

As NaOH is added dropwise, H3O+ slowly starts getting consumed by OH- (produced by dissociation of NaOH). But analyte is still acidic due to predominance of H3O+

Point 2: This is the pH recorded at a time point just before complete neutralization takes place.

Point 3: This is the equivalence point (halfway up the steep curve). At this point, moles of NaOH added = moles of CH3COOH in the analyte. The H3O+ are completely neutralized by OH- ions. The solution contains only CH3COONa salt and H2O

As you can see from the above equation, at the equivalence point the solution contains CH3COONa salt. This dissociates into acetate ions CH3COO- and sodium ions Na-. As you will recall from the discussion of strong/ weak acids in the beginning of this tutorial, CH3COO- is the conjugate base of the weak acid CH3COOH. So CH3COO- is relatively a strong base (weak acid CH3COOH has a strong conjugate base), and will thus react with H2O to produce hydroxide ions (OH-) thus increasing the pH to ~ 9 at the equivalence point.



Point 4: Beyond the equivalence point (when sodium hydroxide is in excess) the curve is identical to HCl-NaOH titration curve.

3) Titration of a strong acid with a weak base

Suppose our analyte is hydrochloric acid HCl (strong acid) and the titrant is ammonia NH3 (weak base). If we start plotting the pH of the analyte against the volume of NH3 that we are adding from the burette

Point 1: No NH3 added yet, so the pH of the analyte is low (it predominantly contains H3O+ from dissociation of HCl).

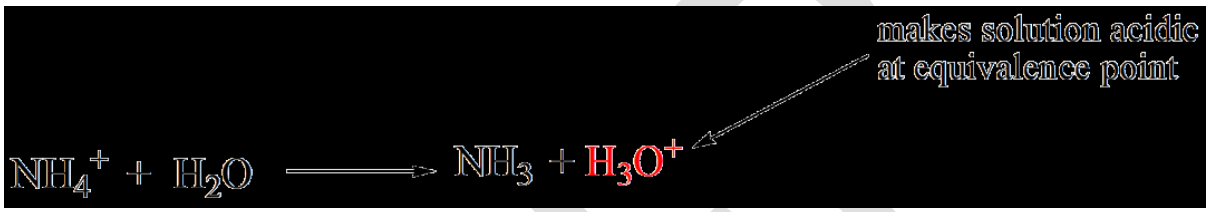
As NH3is added dropwise, H3O+ slowly starts getting consumed by NH3. Analyte is still acidic due to predominance of H3O+ ions.

Point 2: This is the pH recorded at a time point just before complete neutralization takes place.

Point 3: This is the equivalence point (halfway up the steep curve). At this point, moles of NH3 added = moles of HCl in the analyte. The H3O+ are completely neutralized by NH3 . *In the case of a weak base versus a strong*

acid, the pH is not neutral at the equivalence point. The solution is in fact acidic (pH ~ 5.5) at the equivalence point. Let's rationalize this.

At the equivalence point, the solution only has ammonium ions NH4+ and chloride ions Cl-. But again if you recall, the ammonium ion NH4+ is the conjugate acid of the weak base NH3. So NH4+ is a relatively strong acid (weak base NH3 has a strong conjugate acid), and thus NH4+ will react with H2O to produce hydronium ions making the solution acidic.



Point 4: After the equivalence point, NH3 addition continues and is in excess, so the pH increases. NH3 is a weak base so the pH is above 7, but is lower than what we saw with a strong base NaOH (case 1).

4) Titration of a weak base with a weak acid

Suppose our analyte is NH3 (weak base) and the titrant is acetic acid CH3COOH (weak acid). If we start plotting the pH of the analyte against the volume of acetic acid that we are adding from the burette, we will get a titration curve.

If you notice there isn't any steep bit in this plot. There is just what we call a 'point of inflexion' at the equivalence point. Lack of any steep change in pH throughout the titration renders titration of a weak base versus a weak acid difficult, and not much information can be extracted from such a curve.

To summarize

In an acid-base titration, a known volume of either the acid or the base (of unknown concentration) is placed in a conical flask.

The second reagent (of known concentration) is placed in a burette.

The reagent from the burette is slowly added to the reagent in the conical flask.

A titration curve is a plot showing the change in pH of the solution in the conical flask as the reagent is added from the burette.

A titration curve can be used to determine:

1) The equivalence point of an acid-base reaction (the point at which the amounts of acid and of base are just sufficient to cause complete neutralization).

2) The pH of the solution at equivalence point is dependent on the strength of the acid and strength of the base used in the titration.

-- For strong acid-strong base titration, pH = 7 at equivalence point -- For weak acid-strong base titration, pH > 7 at equivalence point -- For strong acid-weak base titration, pH < 7 at equivalence point.

UNIT II

Ostwald's theory and Quinonoid Theory

There are two theories to explain the function of acid-base indicators.

1. Ostwald's theory

2.Quinonoid Theory

Ostwald's theory : This theory was proposed by Ostwald's in 1891. It is based on Arrhenius theory.

Quinonoid Theory : According to this theory the colour change of an acid-base indicator arises as a result of structural change.

There are two theories to explain the function of acid-base indicators.

1. Ostwald's theory

This theory was proposed by Ostwald's in 1891. It is based on Arrhenius theory. According to this theory, the acid-base indicator is either a weak acid

or a weak base. They are partially ionised in solution. The ionised and unionised forms have different colours. The indicator exists predominantly in one of the two forms depending on the nature of the medium and hence there is colour change when the nature of the medium changes. Phenolphthalein is a weak acid and it is partially ionised in solutions.

HPh (Unionised form (colourless) < -- -- -- > H+ + Ph - (ionised form (pink))

In acidic medium, excess H+ ions are present which suppress the dissociation of HpH due to common ion effect. Hence the indicator exists predominantly in unionised form and it is colourless. In alkaline medium, the OH- ion neutralises H+ ion to form water. Consequently the dissociation of HpH is favoured and the indicator is predominantly in the ionised form and it is pink in colour.

Methyl orange is a weak base and its ionisation can be written as

MeOH (Unionised form (yellow)) < -- -- -- > Me+ + OH- (ionised form (pink))

In the presence of a base excess OH- ions suppress the dissociation of MeOH due to common ion effect. Hence in basic medium, the indicator is mostly in unionised form which is yellow.

In acidic solution the H+ ions combine with OH- ions to form unionised water. Hence in acidic solution, the indicator is mostly in ionised form and has pink colour.

This theory also explains why phenolphthalein is not a suitable indicator in the titration of a strong acid against a weak base. The reason is the OH- ions produced by the weak base at the end point is too low to cause the ionisation of phenolphthalein. Hence, the pink colour does not appear exactly at the equivalence point. The pink colour appears only after a sufficient excess of the weak base is added.

For a similar reason, methyl orange is not a suitable indicator in the titration of a strong base against a weak acid. The weak acid does not furnish

sufficient H+ ions to shift the equilibrium towards the right. A sufficient excess of the weak acid has to be added to get the colour change.

Quinonoid Theory

According to this theory the colour change of an acid-base indicator arises as a result of structural change. It is supposed that an indicator exists as an equilibrium mixture of two tautomeric forms namely, benzenoid and quinonoid forms.

One form exists in acidic solution and the other form in basic solution. At least one of the tautomers is a weak acid or a weak base. The two forms possess two different colours and as the pH of the solution containing the indicator is changed, the solution shows a change of colour. The colour change is due to the fact that one tautomer changes over to the other.

Acidimetry in Non-Aqueous Titrations

In order to perform feasible titrations of weak bases, the solvent system should be selected

specifically in such a fashion so as to eliminate as far as possible the competing reaction of water

for the proton besides enhancing the strength of the basic species.

Titration of Weak Bases by Non Aqueous Titration

Following points should be considered: -

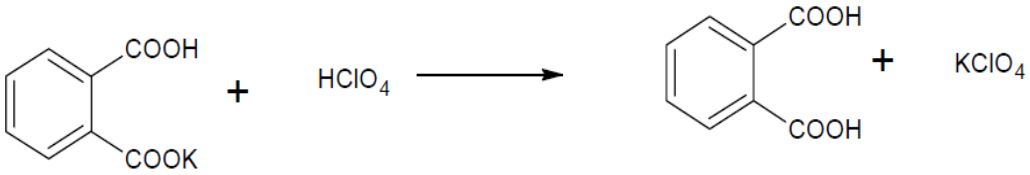
1. Titrant used.
2. Preparation of 0.1N ($HClO_4$) and it standardization.
3. Solvent used.
4. Practical examples of weak bases along with indicators.
5. Typical example of assay of weakly basic substance e.g. ephedrine .

Titrant used: Solution of $HClO_4$ in either glacial acetic acid or dioxane solution is used for titration

of weak bases. Generally HClO4 with a normality of 0.1N to 0.05N is used.

Preparation of 0.1N solution of HClO4 and its standardization: Dissolve 8.5 ml of 72% HClO4 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 HClO4 and glacial acetic acid and renders the solution virtually anhydrous. HClO4 must be well diluted with glacial acetic acid before adding acetic anhydride because reaction between HClO4 and acetic anhydride is explosive.

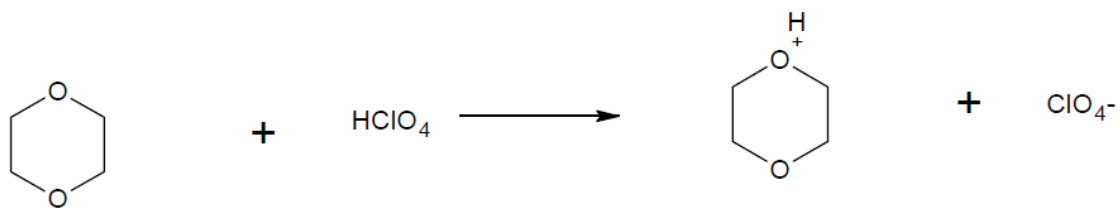
1. Standardization of the above prepared 0.1N HClO4 with A.R. Grade Potassium acid Phthalate.



1 ml of 0.1N HClO4 = 0.020414 gms of 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 HClO4. The colour changes from blue to blue green.

2. Solution in HClO4 in dioxane may be the 2nd titrant, which could be used. It is standardize in the same manner as acetous perchloric acid. High quality dioxane must be used otherwise titrant will become dark. Dioxane can be purified by passing resin or by shaking it with asbestos and then filter it.



Solvent used : Glacial acetic acid alone or sometimes in combination with some aprotic solvents is often used. The other solvents are CHCl3, benzene, chloro benzene, acetic anhydride and various combinations of these sometime glycohydrocarbon mixtures are also used.

Indicators used: Crystal violet 0.05% w/v in glacial acetic acid, methyl red 0.1% w/v in anhydrous methanol, oracet blue 0.5% w/v in glacial acetic acid.

Practical Examples of Weak Bases: It includes adrenaline acid tartarate, erythromycin strerate, metronidazol tartrate methyldopa, noradrenaline, orphenadrine citrate, prochlorperazine maleate etc.

Asssay of Adrenaline: In general, the reaction-taking place between a primary amine and perchloric acid may be expressed as follows:

$R.NH2 + HClO4 \rightarrow [R.NH3] + + ClO4-$

Hence, 183.2 g of $C9H13NO3 \equiv HClO4 \equiv H \equiv 1000$ ml N or 0.01832 g of $C9H13NO3 \equiv 1$ ml of 0.1 N $HClO4$

Procedure: Weigh accurately about 0.3 g of sample into a 250 ml conical flask; add Glacial acetic acid (50 ml), warm gently, if necessary. Cool and titrate with 0.1 N perchloric acid using crystal violet or oracet blue B as indicator.

Alkalimetry in Non-Aqueous Titrations

A plethora of weakly acidic pharmaceutical substances may be titrated effectively by making use of a suitable non-aqueous solvent with a sharp end-point. The wide spectrum of such organic compounds include: anhydride, acids, amino acids, acid halides, enols (viz., barbiturates),

xanthenes, sulphonamides, phenols, imides and lastly the organic salts of inorganic acids.

However, a weak inorganic acid e.g., boric acid, can be estimated conveniently employing ethylenediamine as the non-aqueous solvent.

Preparation of 0.1 N Potassium Methoxide in Toluene-Methanol:

Material Required: Absolute methanol, dry toluene, Potassium metal.

Procedure: Add into a dry flask, a mixture of methanol (40 ml) and dry toluene (50 ml) and cover it loosely. Carefully add freshly cut pieces of potassium metal (5.6 gm) to the above mixture gradually with constant shaking. After complete dissolution of potassium metal, add enough absolute methanol to yield a clear solution. Toluene 50 ml is added with constant shaking until the mixture turns hazy in appearance. The process is repeated by the alternate addition of methanol and benzene until 1 litre of solution is obtained, taking care to add a minimum volume of methanol to give a visible clear solution.

Preparation of 0.1 N Sodium Methoxide: It is prepared exactly in a similar manner as for 0.1 N Potassium Methoxide, using 2.3g of freshly cut sodium in place of potassium.

Preparation of 0.1 N Lithium Methoxide: It is prepared as for 0.1 N Potassium Methoxide, but using 0.7 g of lithium in place of potassium.

Standardization of 0.1 N Methoxide Solution

Material Required: Dimethylformamide (DMF): 10 ml; thymol blue (0.3% in MeOH); 0.1 N lithium methoxide in toluene methanol; benzoic acid: 0.6 g.

Procedure: Transfer 10 ml of DMF in a conical flask and add to it 3 to 4 drops of thymol blue and first neutralize the acidic impurities present in DMF by titrating with 0.1 N lithium methoxide in toluene-methanol. Quickly introduce 0.06g of benzoic acid and titrate immediately with methoxide in toluene-methanol.

Caution: Care must be taken to avoid contamination of neutralized liquid with atmospheric carbon dioxide.

Equations: The various equations involved in the above operations are summarized as stated below:

(i) $Na + CH_3OH \rightarrow CH_3ONa + H\uparrow$

Interaction between sodium metal and methanol is an exothermic reaction and hence, special care must be taken while adding the metal into the dry solvent in small lots at intervals with adequate cooling so as to keep the reaction well under control.

(ii) $H_2O + CH_3ONa \rightarrow CH_3OH + NaOH$

$H_2CO_3 + 2CH_3ONa \rightarrow 2CH_3OH + Na_2CO_3$

The clear solution of sodium methoxide must be kept away from moisture and atmospheric CO_2 as far as possible so as to avoid the above two chemical reactions that might ultimately result into the formation of turbidity.

(iii) $C_6H_5COOH + H—CON(CH_3)_2 \leftrightarrow HCON+H(CH_3)_2+C_6H_5COO$ - ------1

DMF

$CH_3ONa \leftrightarrow CH_3O^- + Na^+$ ----------2

$HCON+H(CH_3)_2 + CH_3O^- \rightarrow HCON(CH_3)_2 + CH_3OH$ ----------3

Summing up: $C_6H_5COOH + CH_3ONa \rightarrow C_6H_5COONa + CH_3OH$

Step 1: It shows the solution of benzoic acid (primary standard) in DMF,

Step 2: It depicts ionization of sodium methoxide,

Step 3: It illustrates the interaction between the solvated proton and the methylated ion.

In summing up, the net reaction between the water in the solvent (DMF) and the titrant is equivalent to the volume of sodium methoxide consumed by DMF or may be considered as a blank determination.

N/10 KOH in Methanol

Dissolve 5.6 gm of anhydrous KOH in 1000 ml of anhydrous methanol. This titrant is not as powerful as others. Its main disadvantage is that it reacts with acidic functional groups and produces a molecule of water, which would affect the sensitivity of titration.

Standardisation: All these titrants are usually standardized against standard benzoic acid ARGrade. A sufficient amount of benzoic acid which would give a titrate value of 20-30 ml is transferred in a dry flask and dissolved in 25 ml dimethylformamide, 2-3 drops of 0.5% thymol blue indicator in dry methanol is added to the solution. A blank titration is also per formed in the solvent to account acidic impurity in dimethylformamide and the correction is made accordingly.

Assay of Ethosuximide

Materials Required: Ethosuximide: 0.2 g ; dimethylformamide : 50 ml ; azo-violet (0.1 % w/v in DMF) : 2 drops ; sodium methoxide 0.1 N.

Procedure: Weigh accurately about 0.2 g of the sample, dissolve in 50 ml of dimethylformamide, add 2 drops of azo-violet solution and titrate with 0.1 N sodium methoxide to a deep blue end point, taking precautions to prevent absorption of atmospheric carbon dioxide. Perform a blank determination and make any necessary correction.

Each ml of 0.1 N sodium methoxide is equivalent to 0.01412 g of $C_7H_{11}NO_2$.

Calculations:

Therefore, 141.17 g $C_7H_{11}NO_2 \equiv NaOMe \equiv H \equiv 1000$ ml N0.01417 g $C_7H_{11}NO_2 \equiv 1$ ml 0.1 N NaOMe

Non Aqueous Titration Theory

The need for non aqueous titration arises because water can behave as a weak base and a weak acid as well, and can hence compete in proton acceptance or proton donation with other weak acids and bases dissolved in it.

The procedure of non aqueous titration is very useful because it satisfies two different requirements, namely – suitable titration of very weak acids or

bases along with providing a solvent with an ability to dissolve organic compounds.

An example of a reaction in which water is not a suitable solvent is the reaction given by:

R-NH2 + H+ = R-NH3+

which is competed with in an aqueous solvent by the reaction given by:

H2O + H+ =H3O+

This type of competition provided by water towards weak bases or weak acids makes it difficult to detect the end point of the titration. Therefore, these substances which have very sharp end points when titrated in aqueous solutions due to their weakly basic or weakly acidic nature generally need to be titrated in non aqueous solvents.

Many reactions which occur in non aqueous titration procedures can be explained via the Bronsted-Lowry Theory and its definition of acids and bases. Basically, acids can be thought of as proton donors, whereas bases can be thought of as proton acceptors.

It can also be noted that potentially acidic substances can behave as acids only when a base (to which a proton can be donated) is present. The converse of this statement also holds true, i.e. potentially basic substances can behave as bases only when an acid (from which a proton can be accepted) is present.

Types of Non Aqueous Solvents

Typically, there exist four types of solvents used in the non aqueous titration of a given analyte. These are:

- • **Aprotic Solvents –** these solvents are neutral in charge and are chemically inert. They also generally have a low dielectric constant. Examples of these types of solvents include chloroform and benzene.

- • **Protophilic Solvents –** these solvents have a basic character and tend to react with the acids they come in contact with, leading to the formation of solvated protons. Examples of protophilic solvents are ammonia and pyridine.
- • **Protogenic Solvents –** these solvents have a more acidic character and tend to have a leveling effect on the bases they come in contact with. Examples of protogenic solvents used in non aqueous titration are sulfuric acid and acetic acid.
- • **Amphiprotic Solvents –** these solvents have properties which are protophilic as well as protogenic. Examples of these types of solvents are acetic acid and alcohols.

Thus, the solvents typically used in non aqueous titrations are described above. The end points of these titrations can also be accurately measured using potentiometric titration procedures.

UNIT III

DIAZOTISATION TITRATION

INTRODCTION

The process of forming diazonium compounds or salts is called *diazotation*, *diazoniation*, or *diazotization*

Diazonium compounds or **diazonium salts** are a group of organic compounds sharing a common functional group with the characteristic structure of R-N2+ X- where R can be any organic residue such alkyl or aryl and X is an inorganic or organic anion such as a halogen.

The reaction was discovered by **Peter Griess** in 1858, who subsequently discovered several reactions of the new compound. This method is first used in the determination of dyes.

Diazonium salts have been developed as important intermediates in the organic synthesis of dyes

Diazotization titrations are carried out for the estimation of drugs containing primary aromatic amino group.

Several drugs contain either primary aromatic amino group or they can be converted to have such groups by simple reaction like hydrolysis or reduction.

An primary aromatic amine reacts with nitrous acid produced by the reaction of sodium nitrite in acidic medium to form diazonium salt.

The reaction is quantitative under the controlled conditions of temp. (approx 150C) and the end point can be detected when a small quantity of excess nitrous acid present at the end point gives colour change with indicator or by electromerically.

It uses the titrant- Sodium Nitrite hence method is *Sodium Nitrite Titration / Nitrite Titration*

CONDITION FOR DIAZOTIZATION

RATE OF TITRATION

Different amino compound react with HONO a t different rates

$NaNO_2$ added from the burette needs time to react with amino group accumulating in the solution

Amines are classified as rapidly, slowly diazotisable depending on the rate of conversion into azo compounds.

TEMPERATURE

The diazonium compounds formed are unstable and readily decompose at elevated temperature

This can lead to side reaction and give wrong result .

To eliminate this problem, this titration is carried out at low temperature (0-50 C).

Optimum temperature for most amine is 10-150 C, when they form relatively stable diazo compounds.

PRINCIPLE

The first involved is addition of sodium nitrite to hydrochloric acid cause formation of nitrous acid

$NaNO2 + HCl \; HONO + NaCl$

This nitrous acid diazotises the aromatic amino group

$R - NH2 + NaNO2 + HCl \; R - N+ \equiv N - Cl- + NaCl$

After the end point , excess nitrous acid formed is shown by instant formation of blue colour with starch iodide paper.

$KI + HCl \; HI+ KCl$

$NaNO2 + HCl \; HNO2 + NaCl$

$2HI + 2HONO \; I2\uparrow + 2NO + 2H2O$

Starch iodide paper is prepared by immersing a filter paper in starch mucilage and potassium iodide solution

The iodine formed reacts with starch mucilage to give the blue colour.

$I2$ + Starch blue color (end point)

The end point can also be end point and potentiometric technique.

Method:

Weigh accurately 0.5 g sulphonamide add to it 20 ml of hydrochloric acid and 50 ml water, stirr, dissolve and cool to 150c. Immerse the electrode in the solution and apply the voltage of about 50 mV. Place burette tip just below the solution to eliminate oxidation of sodium nitrite. Stirr it gently & maintain the temp below 150c.

This method is suitable for most of the pharmacopoeial sulphonamides & its preparations as well as the drugs which contains primary aromatic amines.

The reaction with sulphonamide can be shown as,

Slow diazotisable compounds include compounds that contain sulpha groups, nitrous oxide group, or carboxylic group in aromatic ring or besides aromatic ring

Eg: isomeric nitro aniline, sulphanilic acid and anthranilic acid

Fast diazotisable compounds do not contain any substituent group other than amino group but some times they may contain –CH3 or –OH group along with NH2 group.

Eg : aniline, toluidine and aminophenol

Adding KBr to the solution can increase the rate of titration.

TYPES OF DIAZOTISATION TITRATIONS

DIRECT TITRATIONS

These are carried out by treating 1 mole of the drug with 3 moles of acid solution.

Ice can be used to lower the temperature to about 0-5°c. 0.1M sodium nitrite is added in small amounts and titration is carried out.

The end point is determined by any one of the techniques as said before.

REVERSE METHOD

In this method a solution of amine and sodium nitrite are run into a solution of acid.

This method is used when the diazonium salts are insoluble.

Eg: naphtylamine sulphonic acids form insoluble diaonium salts due to formation of zwitter ions.

SPECIAL METHOD

Aminophenol are readily oxidized by nitrous acid to quinones

For such substances , the titration is carried out in the presence of copper sulphate which forms diazo-oxide

These diazo-oxides are more stable and undergo coupling reaction.

APPLICATIONS

The first use of diazonium salts was to produce water-fast dyed fabrics.

A more common process uses a paper coated with diazo.

It is also applicable in nano technology.

It is also used in the preparation of hydrocarbons, aryl halide, aryl cyanide and aryl hydrazines.

It is used in the assay of sulpha drugs like dapsone, sulphonamides, sulphacetamide sodium, sulphadiazine, sulphamethazole, sulphadoxine, sulphamethoxazole & sulphaphenazone etc.

It is also used in the assay of various drugs like benzocaine, procainamide, procaine, suramin, sodium amino salicylate, primaquine sulphate etc.,

Precipitation Titration

A special type of titremetric procedure involves the formation of precipitates during the course of titration. The titrant react with the analyte forming an insoluble material and the titration continues till the very last amount of analyte is consumed. The first drop of titrant in excess will react with an indicator resulting in a color change and announcing the termination of the titration.

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

Characteristics of Precipitation Titration

They are fast and the stoichiometry is known and reproducibile, (no secondary

reactions of interference.) They are complete or can be quantified depending on the amount of solubility product (in general a precipitation titration is considered complete when Kps < 10-8)

An indicator can be used to find the equivalence point or titration end point which, for this type of titration, corresponds to when precipitation of the analyte under analysis is complete

Principle of Precipitation Titration

The main principle of the precipitation titrations is that the quantity of the added precipitating reagent or precipitant is equivalent to the substance being precipitated.

Methods of Precipitation Titration

According to end point detection method, three main procedures are widely used depending on the type of application. These are:

- Mohr Method
- Volhard Method
- Fajans Method

Mohr Method :

Karl Friedrich Mohr (1806-1879)

This method utilizes chromate as an indicator. Chromate forms a precipitate with Ag+ but this precipitate has a greater solubility than that of AgCl, for example.

Therefore, AgCl is formed first and after all Cl- is consumed, the first drop of Ag+ in excess will react with the chromate indicator giving a reddish precipitate.

$2\ Ag^+ + CrO_4^{2-} \rightarrow Ag_2CrO_4$

In this method, neutral medium should be used since, in alkaline solutions, silver will react with the hydroxide ions forming AgOH. In acidic solutions, chromate will be converted to dichromate. Therefore, the pH of solution

should be kept at about 7. There is always some error in this method because a dilule chromate solution is used due to the intense color of the indicator.This will require additional amount of Ag+ for the Ag2CrO4 to form.

Volhard Method:

Jacob Volhard (1834-1910)

This is an indirect method for chloride determination where an excess amount of standard Ag+ is added to the chloride solution containing Fe3+ as an indicator. The excess Ag+ is then titrated with standard SCN- solution untill a red color is obtained which results from the reaction:

$Fe^{3+} + SCN^- \rightarrow Fe(SCN)^{2+}$

The indicator system is very sensitive and usually good results are obtained. The medium should be acidic to avoid the formation of Fe(OH)3

However, the use of acidic medium together with added SCN- titrant increase the solubility of the precipitate leading to significant errors.

Fajans Method :

Kazimierz Fajans (1887-1975)

Fluorescein and its derivatives are adsorbed to the surface of colloidal AgCl. After all chloride is used, the first drop of Ag+ will react with fluorescein (FI-) forming a reddish color.

$Ag^+ + FI^- \rightarrow AgF$

Among these methods, the Volhard Method is widely used because we can detect the end point of precepitation titration very well.

Limitations of Precipitation Titration

A few number of ions such as halide ions (Cl-, Br-, l-) can be titrated by precipitation method.

Co-precipitation may be occurred.

It is very difficult to detect the end point.

How to overcome the problems of precipitation Titration?

In the assay of substances which react with nitrate but which can't be determined by direct titration with silver nitrate solution.

Excess standard silver nitrate solution is added together with concentrated nitric acid and the excess silver nitrate titrated with 0.1N ammonium thiocynate solution. (This is called Volhard Method)

In the case of chlorides it is usually filtering off the AgCl or to coagulate the precipitate by means of nitrobenzene, which is non-toxic, because AgCl reacts slowly with ammonium thiocyanate.

This makes the end points rather that since involves the production of red iron (III).Thiocyanate complex with the thiocyanate

Indicator of Precipitation Titration

Potassium Chromate (K_2CrO_4)

Silver Chromate (Ag_2CrO_4)

GRAVIMETRIC ANALYSIS

Gravimetric methods are quantitative methods that are based on measuring the mass of a pure compound to which the analyte is chemically related. Since weight can be measured with greater accuracy than almost any other fundamental property, gravimetric analysis is potentially one of the most accurate classes of analytical methods. However it is lengthy and tedious as a result, only a very few gravimetric methods are currently used.

There are three fundamental types of gravimetric analysis.

➢ In precipitation gravimetry, which is our subject in this unit, the analyte is separated from a solution of the sample as a precipitate and is converted to a compound of known composition that can be weighed.

➢ In volatilization gravimetry, the analyte is separated from other constituents of a sample by conversion to a gas. The weight of this gas then serves as a measure of the analyte concentration.

➢ In electrogravimetry, the analyte is separated by deposition on an electrode by an electrical current. The mass of this product then provides a measure of the analyte concentration.

In precipitation gravimetry, the analyte is converted to a sparingly soluble precipitate. This precipitate is then filtered, washed free of impurities, converted to a product of known composition by suitable heat treatment, and weighed.

ADVANTAGES

- ➢ To measure the purity.
- ➢ Most accurate analytical technique.
- ➢ It is an ABSOLUTE method.
- ➢ Precise methods of macro quantitative analysis.
- ➢ Possible sources of errors can be checked.

COPRECIPITATION

This is anything unwanted which precipitates with the analyte during precipitation. Coprecipitation occurs to some degree in every gravimetric analysis (especially barium sulfate and those involving hydrous oxides). You cannot avoid it all what you can do is minimize it by careful precipitation and thorough washing:

1- Surface adsorption

Here unwanted material is adsorbed onto the surface of the precipitate. Digestion of a precipitate reduces the amount of surface area and hence the

area available for surface adsorption. Washing can also remove surface material.

2- Occlusion

This is a type of coprecipitation in which impurities are trapped within the growing crystal and it can be reduced by digestion and reprecipitation .

POSTPRECIPITATION

Sometimes a precipitate standing in contact with the mother liquor becomes contaminated by the precipitation of an impurity on top of the desired precipitate .To reduce postprecipitation filter as soon as the precipitation is complete and avoid digestion .

Precipitating Agents :

Ideally a gravimetric precipitating agent should react specifically or at least selectively with the analyte. Specific reagents which are rare, react only with a single chemical species. Selective reagents which are more common, react with a limited number of species. In addition to specificity and selectivity, the ideal precipitating reagent would react with analyte to give a precipitate that has the preferred requirements which have been previously discussed.

Inorganic precipitating agents :

e.g. S2-, CO32-, PO43- ...etc are usually not compared to the organic precipitants but it give precipitates with well known formula.

Organic precipitating agents :

The organic precipitants such as dimethglyoxime and 8-hydroxyquinoline are more selective than inorganic precipitants . They produce with the analyte less soluble precipitate (small Ksp). They also have high molecular weight so that the weighing error is redued . The disadvantage of organic precipitants is that they usually form with the analyte a precipitate of unknown formula , therefore the precipitate is burned to the metal oxide .

Calculation of Results from Gravimetric Data:

The results of a gravimetric analysis are generally computed from two experimental measurements : the weight of sample and the weight of a known composition precipitate

The precipitate we weigh is usually in a different form than the analyte whose weight we wish to find . The principles of converting the weight of one substance to that of another depend on using the stoichiometric mole relationships. We introduced the gravimetric factor(GF), which represents the weight of analyte per unit weight of precipitate.

ESTIMATION OF BARIUM SULPHATE

A certain barium halide exists as the hydrated salt BaX2.2H2O . where X is the halogen. The barium content of the salt can be determined by gravimetric methods. A sample of the halide (0.2650 g) was dissolved in water (200 mL) and excess sulfuric acid added. The mixture was then heated and held at boiling for 45 minutes. The precipitate (barium sulfate , mw = 233.3) was filtered off, washed and dried. Mass of precipitate obtained = 0.2533 g. Determine the identity of X.

The precipitate is barium sulfate . The first stage is to determine the number of moles of barium sulfate produced, this will, in turn give us the number of moles of barium in the original sample.

Number of moles of Ba = Wt. of BaSO4 ppt. / mw of BaSO4 = 0.2533 / 233.3 = 1.09 x10-3

This is the number of moles of barium present in the precipitate and, therefore, the number of moles of barium in the original sample. Given the formula of the halide, (i.e. it contains one barium per formula unit), this must also be the number of moles of the halide.