UNIT –II

NON AQUEOUS TITRATIONS

DEPT – PHARMACEUTICAL CHEMISTRY

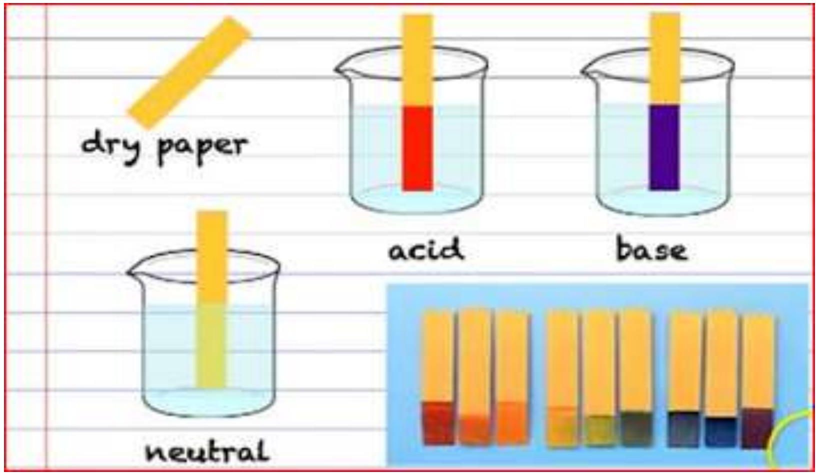
K.K WAGH COLLEGE OF PHARMACY

INTRODUCTION

- **Acids & Bases :General properties**

ACIDS

- Taste sour
- Turn litmus
- React with active metals – Fe, Zn
- React with bases



BASES

- Taste bitter
- Turn litmus
- Feel soapy or slippery (react with fats to make soap)
- React with acids

DEFINITIONS

- Several different theories explain what is an **acid** and a **base.**

Arrehenius(1887)
only in water

- **Acids** – produce H^+ HCl
- **Bases** - produce OH^- NaOH

Bronsted-Lowry
(1923)
any solvent

- **Acids** – donate H^+ HCl
- **Bases** – accept H^+ NH_3

Lewis

- **Acids** – accept e^- pair BF_3
- **Bases** – donate e^- pair $:NH_3$

Strong acids in water

$HCl + H_2O$ -------------> $H3O^+ + Cl^-$

(acid) (base) (conjugate acid) (conjugate base)

weak acids in water

$HCOOH + H_2O$ ←--------> $H_3O^+ + HCOO$

(acid) (base) (conjugate acid) (conjugate base)

weak acids in non aqueous solvents

$HCOOH + CH_3NH_2$ ←-------> $CH_3NH_4^+ + HCOO$

(acid) (base) (conjugate acid) (conjugate base)

It follows from these definitions that an acid may be either:

* an electrically neutral molecule, e.g. HCl, or

* a positively charged cation, e.g. C6H5NH3+, or

* a negatively charged anion, e.g. HSO4-.

A base may be either:

* an electricially neutral molecule, e.g. C6H5NH2, or an anion, e.g. Cl-.

Substances which are potentially acidic can function as acids only in the presence of a base to which they can donate a proton. Conversely basic properties do not become apparent unless an acid also is present

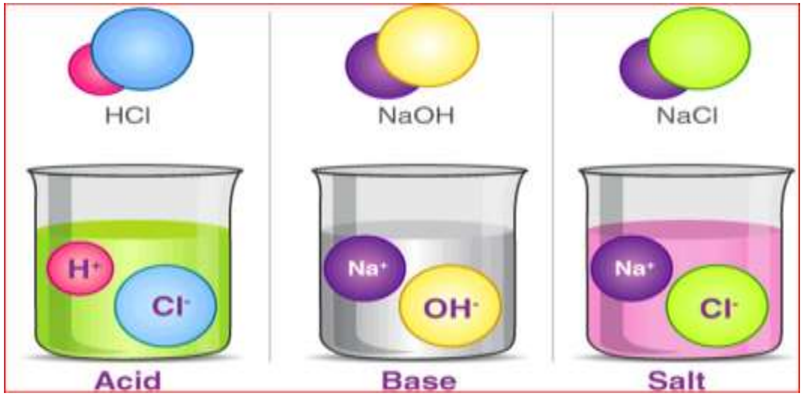
CONJUGATE PAIRS: BRONSTED-LOWRY CONJUGATE PAIRS

- AN **ACID** THAT HAS DONATED ITS PROTON BECOMES A *CONJUGATE BASE*.

HCl Cl^- CH_3COOH CH_3COO^-

- A base that has accepted a proton becomes a *conjugate acid.*

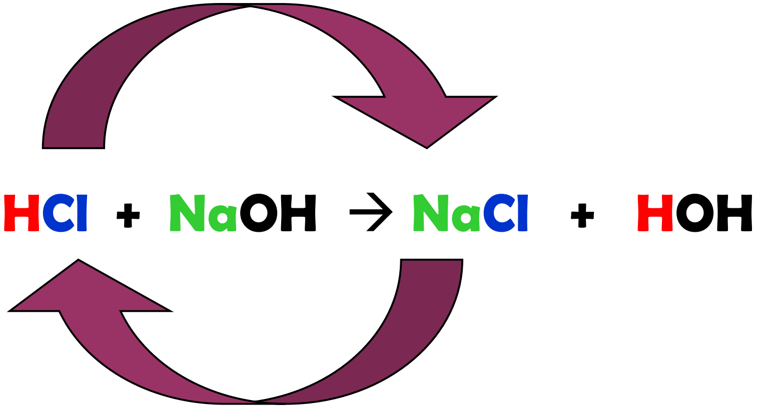
NH_3 NH_4^+ NO_3^- HNO_3



NEUTRALIZATION

In general: Acid + Base → Salt + Water

All neutralization reactions are double displacement reactions.



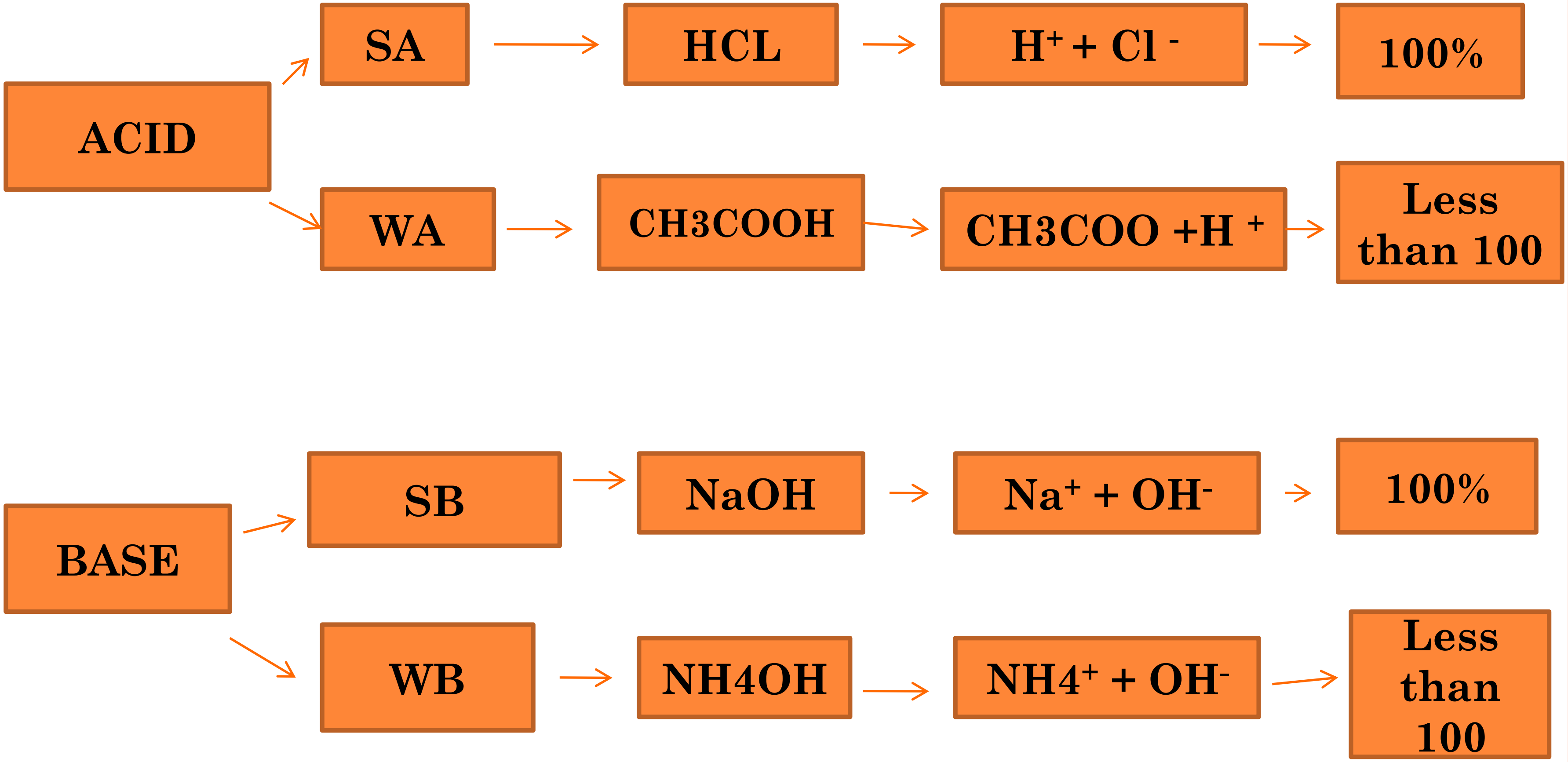
$HCl + NaOH \rightarrow NaCl + HOH$

Introduction

- Non aqueous titration is the titration of **substances dissolved in solvents other than water.**
- It is the most common titrimetric procedure used in pharmacopoeial assays and serves a double purpose:
- **It is suitable for the titration of very weak acids and very weak bases, and**
- **It provides a solvent in which organic compounds are soluble.**
- The most commonly used procedure is the titration of **organic bases with perchloric acid in anhydrous acetic acid.**
- These assays sometimes take some perfecting in terms of being able to judge the endpoint precisely.

Need of Non aqueous titrations

- Often times we need to perform an acid-base titration in non-aqueous solvent due to :
- The analyte is too weak acid or a base to be titrated in H2O.
- Reactants or products are insoluble in H2O.
- Reactants or products react with H2O.
- Titration in H2O doesn’t allow a sharp end point but in a non aqueous solvent with a stronger base than OH-it is possible to get an sharp end point.



ACID → SA → HCL → $H^+ + Cl^-$ → 100%

ACID → WA → CH3COOH → CH3COO +H^+ → Less than 100

BASE → SB → NaOH → $Na^+ + OH^-$ → 100%

BASE → WB → NH4OH → $NH4^+ + OH^-$ → Less than 100

ADVANTAGES OF NON-AQUEOUS TITRATIONS

- Elimination of poor solubility of substances.
- Enhancement of weak reactivity of substances.
- Selective titration by using suitable solvent and titrant of acidic/basic components of physiologically active moiety of a salt.
- Maintenance of speed, precision, accuracy and simplicity at par with classical methods of analysis.

Properties of Non-aqueous Solvent

1. Should be liquid at room temperature.
2. Should not be highly toxic.
3. Should have capability of self dissociation.
4. Should have acid-base character.
5. Should have dielectric constant.
6. Should exert levelling and differentiating effects.

DIFFERENT TYPES OF SOLVENTS

- There are three types of solvents used in non-aqueous titration:

Protophilic Solvents

Solvents which have greater tendency to accept protons,
i.e., **water, alcohol, liquid ammonia**,
etc

Protogenic Solvents

which have the tendency to produce protons,
i.e., water, liquid hydrogen chloride, glacial acetic acid,
etc

Amphiprotic Solvents

a solvent capable of acting as an acid or a base; for example, H_2O

Different Types of Solvents

(A) APROTIC SOLVENTS

- They are essentially **basic in nature** and **normally react with acids to form solvated protons**.
- These solvents are neither accept or donate proton.
- they cannot reacts with analyte.
- These solvents generally used for **titration of weak acids**.
- Low dielectric constant and they are used for dilution.
- Example: Carbon Tetrachloride, Toluene ,Benzene

- **Aprotic solvents** are neutral, chemically inert substances such as benzene and chloroform. They have a low dielectric constant, do not react with either acids or bases and therefore do not favor ionization.
- The fact that picric acid gives a colorless solution in benzene which becomes yellow on adding aniline shows that picric acid is not dissociated in benzene solution and also that in the presence of the base aniline it functions as an acid, the development of yellow color being due to formation of the picrate ion.
- Carbon tetrachloride and toluene come in this group; they possess low dielectric constants, do not cause ionization in solutes and do not undergo reactions with acids and bases.
- Aprotic solvents are frequently used to dilute reaction mixture

(B) PROTOGENIC SOLVENTS:

- They are **acidic in nature and generate the proton H+** ex. sulphuric acid.
- They exert a ‘**levelling effect**’ on increases the basic nature of weak base.
- These solvents are generally used for **titration of weak bases.**
- Weakly basic substances react with protogenic solvents and due to that increse the basicity.
- $\mathbf{HCL \longrightarrow H^{+} + CL^{-}}$
- $\mathbf{CH3COOH \longrightarrow CH3COO^{-} + H^{+}}$
- $\mathbf{H2SO4 \longrightarrow H^{+} + HSO^{4}}$

For example: **Acetic acid**, **sulphuric acid.**

(C)PROTOPHILIC SOLVENTS

- This solvents attracts protons.
- They are basic in nature.

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- $\ddot{N}\ddot{H}^3 \xrightarrow{H^+} NH^4$
- All the protophilic solvents have a lone pairs.
- They increse the acidic nature of weak acid.
- They basic in nature. according to Lewis concept.
- Ex: Amines (ethyle amine),Ammonia.

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- CH2- CH2-CH2-NH2

(D) AMPHIPROTIC SOLVENTS

- They possess **both protophillic and protogenic** characteristics.
- These solvent are **acidic as well as basic in nature.**
- Acetic acid is mostly employed as a solvent for the titration of basic substances and its dissociation can be depicted as shown below:

$$\mathrm{CH3COOH} \rightarrow \mathrm{H^+} + \mathrm{CH3COO^-}$$

- For example: Water, alcohol, acetic acid.

PERCHLORIC ACID

- It is a very strong acid and when it is made to dissolve in acetic acid,
- the latter can behave as a base and forms an 'onium ion' after combining with protons donated by the perchloric acid.

  Thus, we have:

$$\mathrm{HClO4} \rightleftharpoons \mathrm{H^+} + \mathrm{ClO4^-}$$

$$\mathrm{CH3COOH} + \mathrm{H^+} \rightleftharpoons \mathrm{CH3COOH2^+}$$

Onium ion

- As the $\mathrm{CH3COOH2^+}$ ion can instantly donate its proton to a base, therefore, a solution of perchloric acid in glacial acetic acid, behaves as a strongly acidic solution.

Glacial acetic acid

- It is a solvent for base in particular
- The water content should be less than 1%
- Acetic anhydiride is added
- When a weak base, such as pyridine, is dissolved in acetic acid, the acetic acid exerts its levelling effect and enhances the basic properties of the pyridine. It is possible, therefore, to titrate a solution of a weak base in acetic acid with perchloric acid in acetic acid, and obtain a sharp endpoint when attempts to carry out the titration in aqueous solution are unsuccessful.

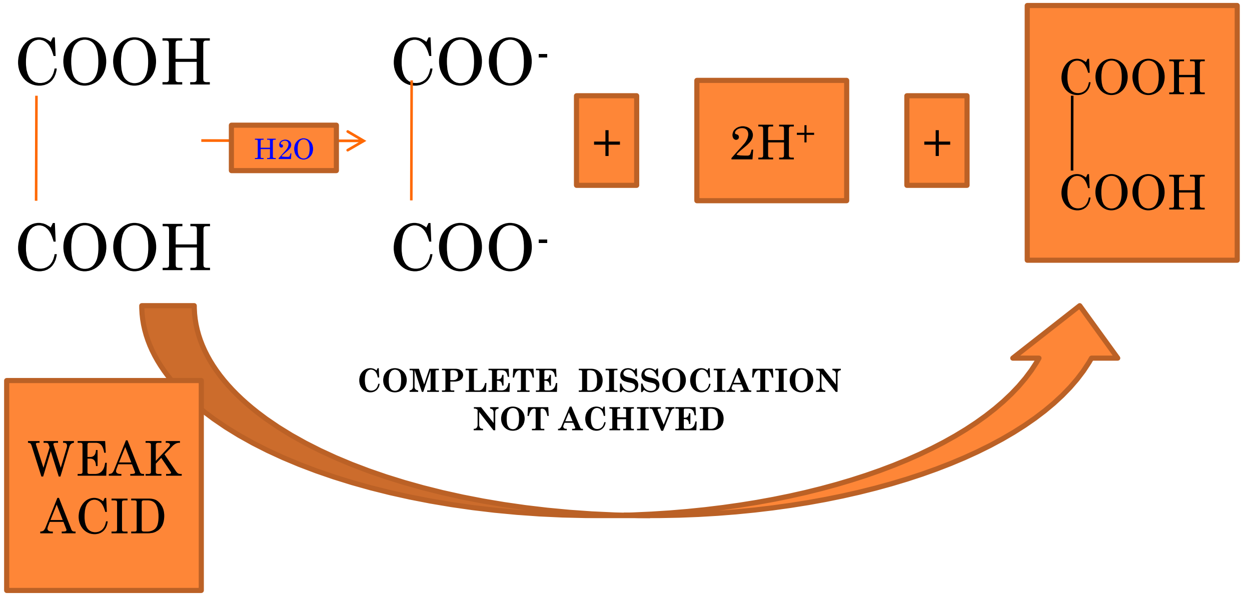
Leveling effect or solvent leveling

- Leveling effect or solvent: leveling refers to the effect of solvent on the properties of acids and bases.
- The strength of a strong acid is limited ("leveled") by the basicity of the solvent. Similarly the strength of a strong base is leveled by the acidity of the solvent.
- When a strong acid is dissolved in water, it reacts with it to form hydronium ion (H_3O^+).[2] An example of this would be the following reaction, where "HA" is the strong acid:
- $HA + H_2O \rightarrow A^- + H_3O^+$
- Any acid that is stronger than H_3O^+ reacts with H_2O to form H_3O^+. Therefore, no acid stronger than H_3O^+ exists in H_2O.
- Similarly, when ammonia is the solvent, the strongest acid is ammonium (NH_4^+), thus HCl and a super acid exert the same acidifying effect.
- The same argument applies to bases. In water, OH^- is the strongest base. Thus, even though sodium amide ($NaNH_2$) is an exceptional base (pKa of NH_3 ~ 33), in water it is only as good as sodium hydroxide.
- On the other hand, $NaNH_2$ is a far more basic reagent in ammonia than is NaOH.

- $HCL \xrightarrow{H2O} H^+ + CL^-$
- $H_2SO^4 \xrightarrow{H2O} 2H^+ + SO4^{2-}$
- $HNO3 \xrightarrow{H2O} H^+ + NO^{3-}$
- $HCLO4 \xrightarrow{H2O} H^+ + CLO^{4-}$

All acts as strong acid in water

STRONG ACIDS



$$\begin{array}{c}COOH\\|\\COOH\end{array} \xrightarrow{H2O} \begin{array}{c}COO^-\\|\\COO^-\end{array} + 2H^+ + \begin{array}{c}COOH\\|\\COOH\end{array}$$

COMPLETE DISSOCIATION NOT ACHIVED

WEAK ACID

DIFFERENTIATING EFFECT

- All acts and bases are dissociates into different degree in differentiating solvent.
- Weak acid acts as a differentiating solvent for acid .
- Weak base acts as a differentiating solvent for bases.
- Three acid (strong acid)

$$\left.\begin{array}{l} \mathrm{HCl} \longrightarrow \mathrm{H^+} + \mathrm{Cl^-} \\ \mathrm{HBr} \longrightarrow \mathrm{H^+} + \mathrm{Br^-} \\ \mathrm{HI} \longrightarrow \mathrm{H^+} + \mathrm{I^-} \end{array}\right\}$$

Acts as a strong acid in water

- Glacial acetic acid is used as a solvent

HCl

HBr

HI

$\uparrow$ Increasing acidity.

Other solvent

- Formic acid: is only used for the titratin of weakest base eg caffeine or urea
- Trifluoroacetic acid: suitable as solvent for weakest base where acetic anhydride cannot be used because of acetylation. But it is expensive solvent.
- Amphipotic basic solvent: eg Ethylendiamine, Butylamine, Benzylamine
- Aprotic basic solvent: Pyridine, Dimethylformamide, Dimethylsulphoxide,

METHODOLOGY FOR NON-AQUEOUS TITRATIONS

For non-aqueous titrations, the following four steps are usually taken into consideration, namely:

(i) Preparation of 0.1 N Perchloric acid.

(ii) Standardization of 0.1 N Perchloric acid.

(iii) Choice of Indicators.

(iv) Effect of Temperature on Assays.

(i) Preparation of 0.1 N Perchloric Acid

Materials Required:

- 8.5 ml of perchloric acid (70.0 to 72.0%)
- 1 litre of glacial acetic acid
- 30 ml of acetic anhydride.

Procedure:

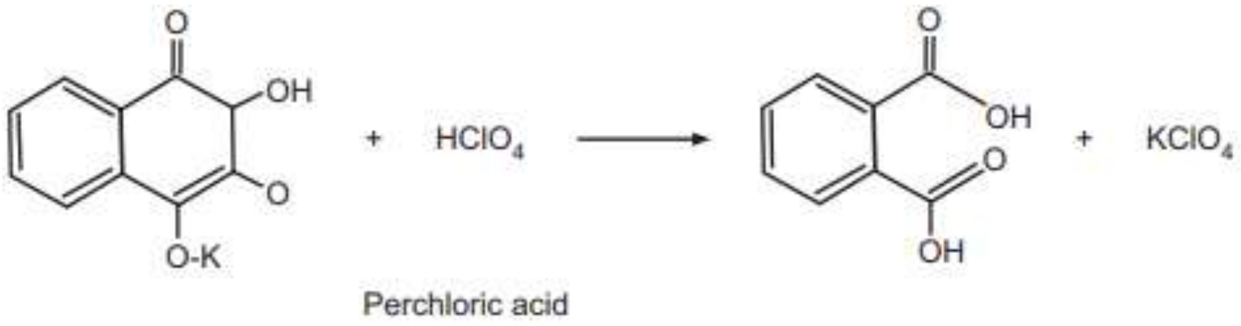
- Gradually mix 8.5 ml of perchloric acid to 900 ml of glacial acetic acid with vigorous and continuous stirring.
- Now add 30 ml acetic anhydride and make up the volume to 1 litre with glacial acetic acid and allow to stand for 24 hours before use.
- The acetic anhydride reacts with the water (approx. 30%) in perchloric acid and some traces in glacial acetic acid thereby making the resulting mixture practically anhydrous.
- Thus we have:

$$\mathbf{H2O + (CH3CO)2\ O \rightarrow 2CH3COOH}$$

Acetic anhydride **Acetic acid**

(ii) Standardization of 0.1 N Perchloric acid.

- Standardization of acid titrant may be carried out with the any substance which is a strong base and which is available in a known purity. Potassium hydrogen phthalate (KHP) is used as a primary standard because of its high purity.



- During titration, crystalline precipitate of KClO4 appears, but this does not interfere with location of end point. Therefore,

204.14 gm C8H5O4K ≡ HClO4 ≡ 1000 ml N

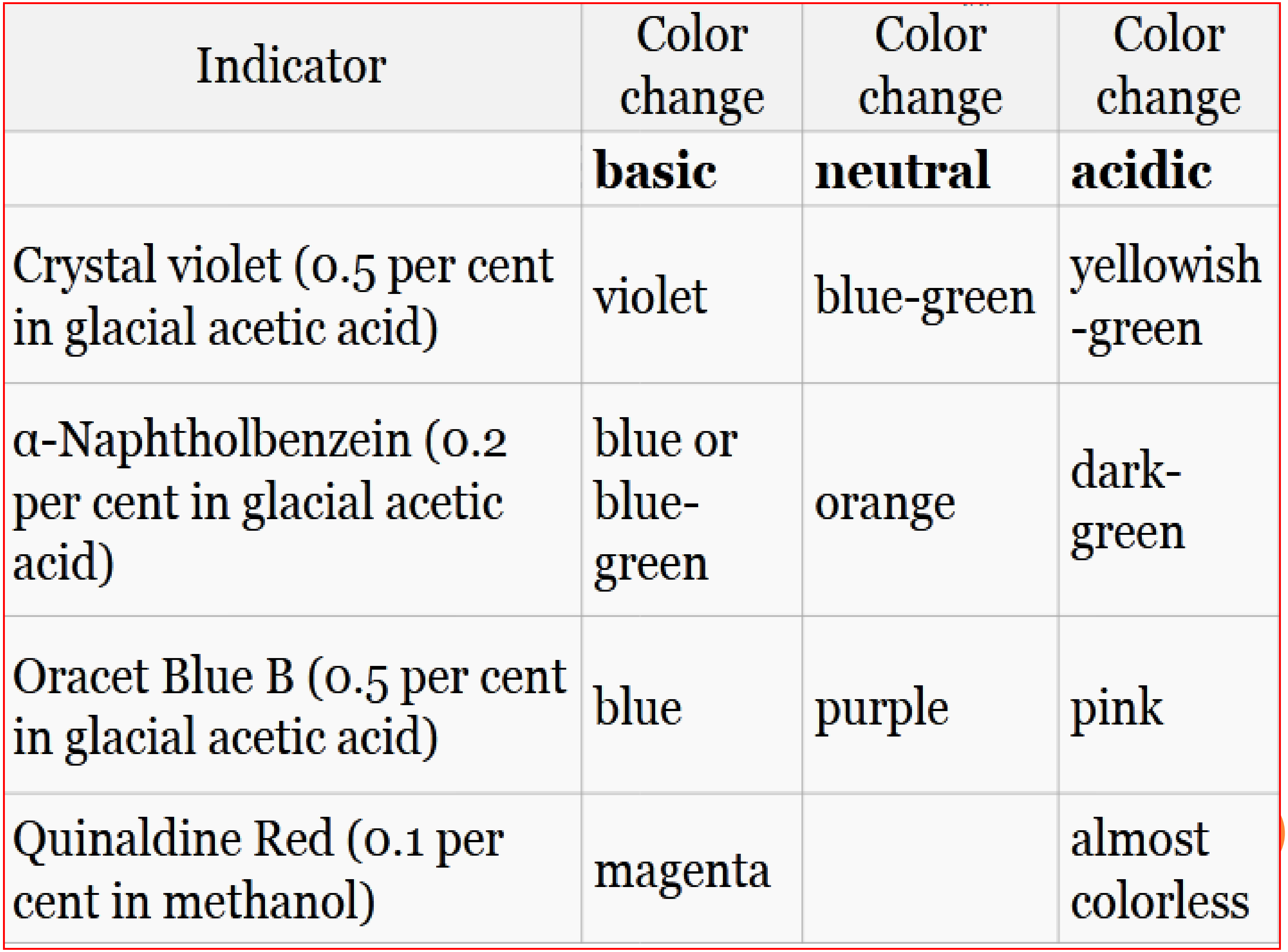
or 0.02041 gm of C8H5O4K ≡ 1 ml of 0.1 N HClO4

Procedure: Weigh accurately about 0.5 gm of potassium hydrogen phthalate in a 100 ml conical flask. Add 25 ml of glacial acetic acid and attach a reflux condenser fitted with a silica-gel drying tube. Warm until the salt gets dissolved completely. Cool and titrate with 0.1 N perchloric acid by making use of either of the following two indicators:

(a) acetous crystal violet - 2 drops, end point Blue to Blue-Green (0.5% w/v).

(b) acetous oracet blue B - 2 drops, end point Blue to Pink

(iii) Choice of Indicators:



Indicator	Color change	Color change	Color change
	basic	**neutral**	**acidic**
Crystal violet (0.5 per cent in glacial acetic acid)	violet	blue-green	yellowish -green
α-Naphtholbenzein (0.2 per cent in glacial acetic acid)	blue or blue-green	orange	dark-green
Oracet Blue B (0.5 per cent in glacial acetic acid)	blue	purple	pink
Quinaldine Red (0.1 per cent in methanol)	magenta		almost colorless

(IV) EFFECT OF TEMPERATURE ON ASSAYS:

- It is always advisable to carry out standardization and titration preferably at the same temperature. In a situation where these temperature parameters cannot be achieved, the volume of titrant may be corrected by the application of the following formula:

$$\mathbf{V_c = V[1 + 0.001\ (t_1 + t_2)]}$$

where, Vc = Corrected volume of titrant,

V = Volume of titrant measured,

t1 = Temperature at which titrant was standardized,

t2 = Temperature at which titration was performed.

TITRANT USED IN NON-AQUEOUS TITRIMETRY

- Acidic titrants:
  - Perchloric acid
  - p- Toluenesulfonic acid,
  - 2,4-Dinitrobenzenesulfonic acid
- Basic titrants
  - Tetrabutylammonium hydroxide
  - Sodium acetate
  - Potassium methoxide
  - Sodium aminoethoxide

ASSAYS BY NON-AQUEOUS TITRATIONS

- Assays of various pharmaceutical substances either in pure form or in dosage form may be assayed successfully by non-aqueous titrations. For the sake of convenience, these typical titrations can be categorized into two broad groups, namely:

(a) **Acidimetry in Non-aqueous Titrations**:

It can be further sub-divided into two heads, namely:

(i) Titration of primary, secondary and tertiary amines.

(ii) Titration of halogen acid salts of bases.

(b) **Alkalimetry in Non-aqueous Titrations**: i.e., titration of acidic substances.

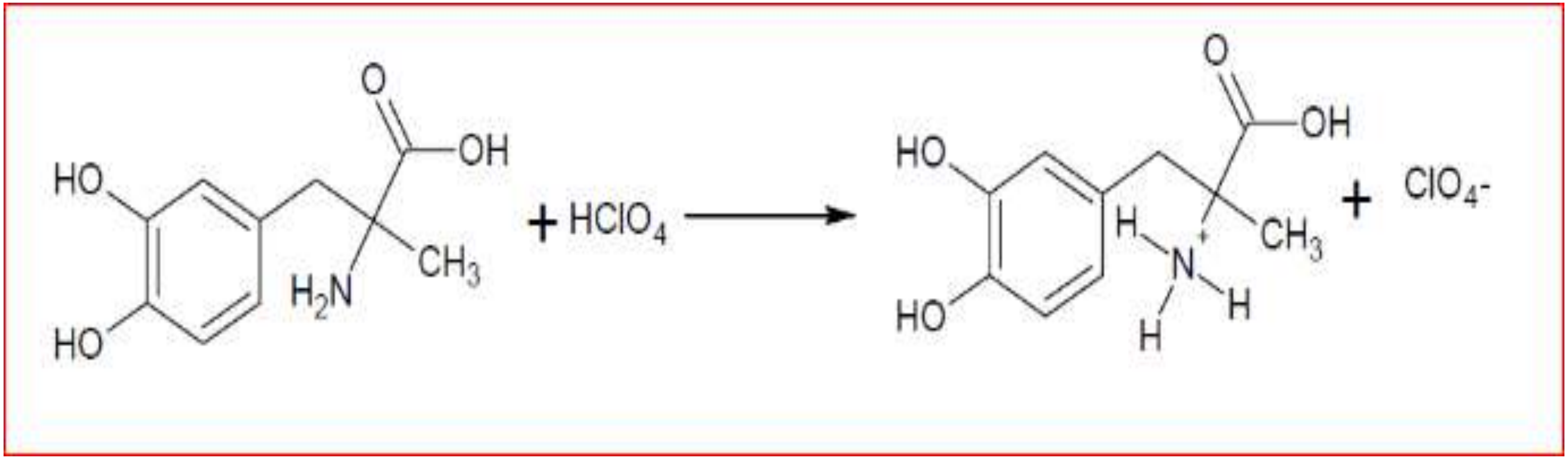
A) ACIDIMETRY IN NON-AQUEOUS TITRATIONS

- 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.

1. TITRATION OF PRIMARY, SECONDARY AND TERTIARY AMINES

Assay of Methlyldopa:

- The specific reaction between methyldopa and perchloric acid is expressed by the



Hence,

211.24 gm of C10H13NO4 ≡ HClO4 ≡ H ≡ 1000 ml N

or 0.02112 gm C10H13NO4 ≡ 1 ml of 0.1 N HClO4

Material Required:

- Methyldopa 0.2 g
- anhydrous formic acid : 15 ml
- glacial acetic acid : 30 ml
- dioxane : 30 ml
- 0.1 N perchloric acid
- crystal violet solution.

Procedure:

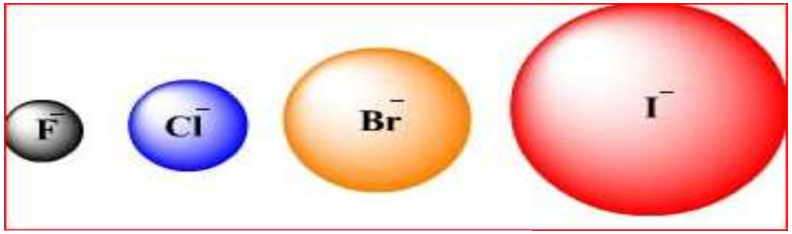
- Weigh accurately about 0.2 g of sample dissolve in a mixture of 15 ml of anhydrous formic acid, 30 ml of glacial acetic acid and 30 ml of dioxane.
- Add 0.1 ml of crystal violet solution and titrate with 0.1 N perchloric acid.
- Perform a blank determination and make any necessary correction.
- Each ml of 0.1 N perchloric acid is equivalent to 0.02112 g of $C_{10}H_{13}NO_4$.

Calculations: The percentage of methyldopa present in the sample is given by :

$$\% \text{ Methyldopa} = \frac{X \text{ ml} \times \text{Normality (Calculated)} \times 0.02112 \times 100}{\text{N(Given)} \times \text{Wt. of sample(in gm)}}$$

2. TITRATION OF HALOGEN ACID SALTS OF BASES

- In general, the halide ions, namely: **chloride, bromide and iodide** are **very weakly basic** in character so much so that they **cannot react quantitatively** with **acetous perchloric acid**.
- In order to overcome this problem, **mercuric acetate** is usually added (it remains undissociated in acetic acid solution) to a halide salt thereby causing **the replacement of halide ion** by an equivalent amount of acetate ion, which serves as **a strong base in acetic acid** as shown below:



$$2R{\cdot}NH_2{\cdot}HCl \rightleftharpoons 2RNH_3^+ + 2Cl^-$$

$$\underset{\text{undissociated}}{(CH_3COO)_2Hg} + 2Cl^- \longrightarrow \underset{\text{undissociated}}{HgCl_2} + 2CH_3COO^-$$

$$2CH_3COOCH_2^+ + 2CH_3COO^- \rightleftharpoons 4\,CH_3COOH$$

B) 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 includes: anhydrides, 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 ethylene diamine as the non-aqueous solvent.

Estimation of Compound by Non-aqueous Titration

Sodium Benzoate I.P.: Weigh accurately about 0.25 gm; dissolve in 20 ml of anhydrous glacial acetic acid, warming to 50°C if necessary, cool.

- Titrate with 0.1 M perchloric acid, using 0.05 ml of 1 naphtholbenzein solution as indicator.
- Carry out a blank titration.
- Factor: 1 ml of 0.1 M perchloric acid is equivalent to 0.01441 gm of C7H5NaO2.

Ephedrine Hydrochloride I.P.:

- Weigh accurately about 0.17 gm, dissolve in 10 ml of mercuric acetate solution, warming gently, and add 50 ml of acetone and mix.
- Titrate with 0.1 M perchloric acid, using 1 ml of a saturated solution of methyl orange in acetone as indicator, until a red colour is obtained.
- Carry out a blank titration.
- Factor: 1 ml of 0.1 M perchloric acid is equivalent to 0.02017 gm of C10H15NO, HCl.

APPLICATIONS OF NON-AQUEOUS TITRATION

1. Determination of weak bases. For example: Weak base antipyrine in water does not give sharp end point but in acetic acid provides end point break.
2. Very weak base e. g. Caffeine give good end point in acetic anhydride.
3. Determination of alkali salts of weak acids.
4. Mixture of bases of different strength can be analyzed by selecting a differentiating solvent for bases. For example: ACN
5. Determination of substances that are not themselves basic. For e. g. Amine salts, dissolved in acetic acid, is treated with an excess of mercurous acetate, the amine is freed and can be titrated as a base with perchloric acid.

6. Imide is moderately strong acid and phenols are weak acids which can be titrated in non-aqueous media.

7. Drugs can be titrated in their dosage form without interference of pharmaceutical adjuncts. Sometimes stearic acid, in tablet formulation is interfering in end point detection consuming base in direct titration and this substance must be removed before an acidic active ingredient is titrated.

8. Percentage of purity is determined by the assays.

9. Used in the determination of the concentration expressions.

10. Used in the determination of hydrophobic compounds, diuretics, steroids, antitubercular drugs, adrenergic drugs, etc.

QUESTION BANK

1. Define Non-aqueous titration. Enlist the different types of solvents used in non-aqueous titration.
2. Define levelling and differentiating solvents.
3. Give the preparation and standardization of 0.1 N Perchloric acid.
4. Explain types of solvents used in non-aqueous titration with suitable examples.
5. Explain levelling and differentiating effects.
6. Give the assay for sodium benzoate by non-aqueous titration.
7. Give the assay for ephedrine HCL by non-aqueous titration.

Thank You…!