

**SHREE H. N. SHUKLA INSTITUTE OF  
PHARMACEUTICAL EDUCATION AND  
RESEARCH**



**B.PHRAM**

(SEMESTER -I)

**SUBJECT NAME: PHARMACEUTICAL ANALYSIS -I**

**SUBJECT CODE: BP102TP**

**UNIT 2 (b): NON-AQUEOUS TITRATION**

## Content

**Non-aqueous titration-** Solvents, acidimetry and alkalimetry titration and estimation of sodium benzoate and Ephedrine HCl.

Non-aqueous titrations are the titrations in which estimation of weakly acidic or basic substances are carried out using non-aqueous solvents to get sharp end point.

### 1) Arrhenius Concept:

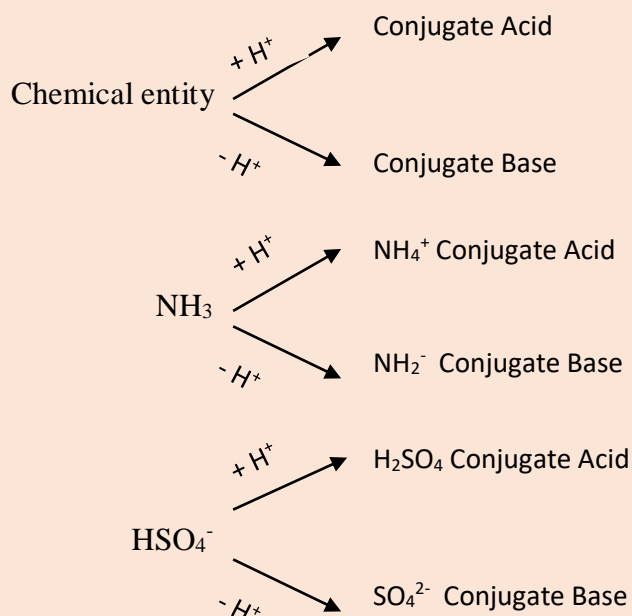
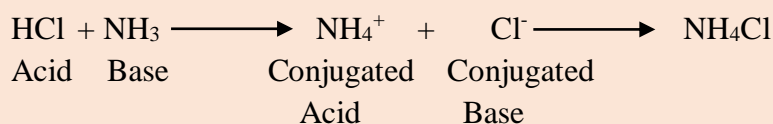
Acid gives proton ( $H^+$  ion) in water.

Base gives  $OH^-$  ions when dissolved in water. This concept is used for only aqueous solution & not applicable when non-aqueous solvent is used.

### 2) Bronsted-Lawry Concept:

Proton donor – Acid

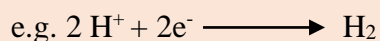
Proton acceptor – Base



### 3) Lewis Concept

Electron acceptor – Acids

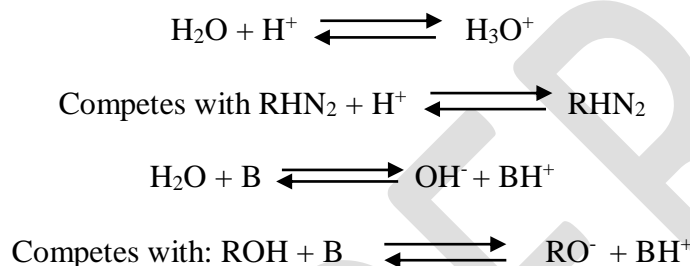
Electron Donor – Bases



**Why non-aqueous titration is used?**

- 1) Reactants are insoluble in water
- 2) Reactants are reactive in water
- 3) Reactants are very weak acid and weak bases in nature. (100 % dissociation will not be achieved.)

If aqueous solvent is used for detection of weak acidic or weak basic drug, water behaves as a both a weak acid and weak base. Thus, in that case, water compete with very weak acid or base drug and interferes in proton donation and acceptance, as shown below:



This makes the endpoint detection relatively more difficult. That's why very weak acid/base can't be titrated in water. Most of drugs are weak acids ( $\text{pK}_a > 7$ ) or weak bases ( $\text{pK}_a < 7$ ) and rule is estimated that acids with  $\text{pK}_a > 7$  and bases with  $\text{pK}_a < 7$  cannot be determined accurately in aqueous solution.

In short, these compounds have two major problems in quantitative assays.

- I. Its weak reactivity
- II. Poor solubility in aqueous medium.

Substances which give poor end points due to being weak acid and base, when being titrated in non-aqueous solution, it gives satisfactory endpoint.

Reaction occurring during non-aqueous acid-base titration can also be explained by Bronsted – Lowry theory of acids and bases.

**SOLVENTS:**

Solvent used in non-aqueous titrations play an important role.

Solvents should be non-toxic for its wide use and it should be liquid at the time of analysis.

Organic solvents are used as a non-aqueous solvent but mainly dependent on three characteristics/properties.

- Self –dissociation,
- Dielectric constant &
- Acid- base Character

**1. Capability of self-dissociation**

Depending on dissociation property, non-aqueous solvents are classified into two groups

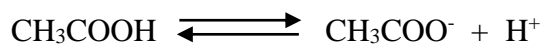
- I. Dissociating solvents
- II. Non-dissociating solvents

- **Dissociating Solvents:** Ethanol dissociates to give ethoxide ion.

Ethanol dissociates to give ethoxide ion.



Acetic acid gives acetate ion



} Gives proton upon dissociation  
Here,  $\text{H}^+$  represents the Solvated proton.

Some solvents dissociates without the production of solvated protons.

e.g. Acetic anhydride



- **Non-dissociating solvents:** These solvents may dissociate, but it is not usually detectable.

For example- Ethers & Hydrocarbons

## 2. Dielectric constant

It is defines as ability of substance to insulate charges from each other. Generally +ve and –ve charges are separated and thus electrical field generated.

As dielectric constant is higher, less energy require to separate ions means it will easy to dissolve the ions.

## 3. Acid-base characters

The non-aqueous solvents can be classified based on its proton-donor acceptor properties.

Non-aqueous solvents are classified into four groups

- I. Aprotic solvents
- II. Protophilic solvents
- III. Protogenic solvents
- IV. Amphiprotic solvents

### **Aprotic solvents:**

They are chemically neutral and unreactive under the conditions employed. They possess low dielectric constant.

They do not cause ionization of solutes and do not undergo reactions with acids and bases.

They frequently used to dilute reaction mixtures while taking no part in overall process.

**Examples:**  $\text{CCl}_4$ , Benzene, Hexane, Toluene

### Protophilic solvents:

They are basic in nature. They possess high affinity for protons. They are used to dissolve acidic analyte because acid dissociates in base.

**Examples:** Ammonia, Amines, Ketones, Ethylene diamine & Dimethyl formamide.

When weak acidic drug is used with protophilic (basic) solvents, they increase strength of acidic drugs and become comparable to those of strong acids. This is known as levelling effect.

### Protogenic solvents:

They are acidic in nature and readily donate protons. They are used to dissolve basic analyte.

They have a high dielectric constant.

**Examples:** Hydrogen Fluoride, Sulphuric acid & Glacial Acetic acid

Because of their strength and ability to donate protons, they enhance the strength of weak bases like ephedrine hydrochloride, imipramine hydrochloride; meclizine hydrochloride, morphine hydrochloride, pethidine hydrochloride, propranolol hydrochloride etc.

### Amphiprotic solvents:

They consist of liquids such as water, alcohol and weak organic acids.

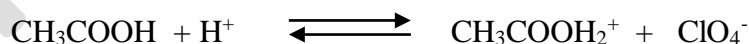
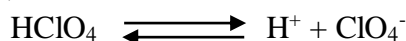
They are slightly ionized and combine both protogenic and protophilic properties and being able to donate and accept protons.

**Examples:** Acetic acid (Ethanoic acid), Alcohols and Water

Ethanoic acid has acidic properties and upon dissociation it gives protons.



However in presence of perchloric acid, acetic acid acts as a **base** and combining with  $\text{H}^+$  obtained from perchloric acid, it will be converted into acetonium ion (Onium ion).



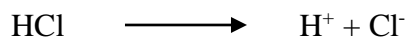
Acetonium ion

The  $\text{CH}_3\text{COOH}_2^+$  ion can readily give up its proton to react with base and therefore a solution of perchloric acid in glacial acetic acid behaves as a strong acidic solution.

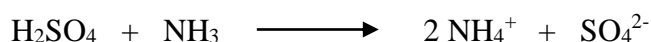
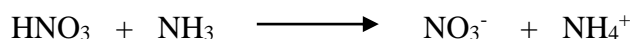
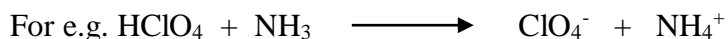
**Levelling Effect:** The acidity of the weak acids can be enhanced using basic solvents because the basic solvent has higher affinity to take up protons from acids. So, acetic acid behaves as a strong acid in ammonia solution.

Similarly, the basicity of the weak bases can be enhanced in the presence of acidic solvent. This is called the levelling effect of the solvent.

**Case 1 (Strong acids):** When strong acid like HCl is added in water, it will ionize completely.

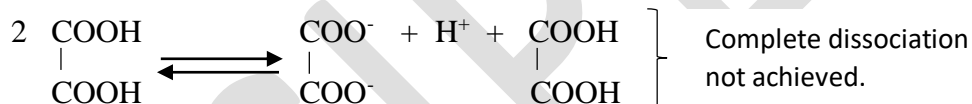


In case of strong acid, they will obviously dissociates in aqueous as well as non-aqueous solvents.



In **non-aqueous basic solvent**, these different acids have same degree of dissociation because basic solvent have tendency to take up protons from these acids.

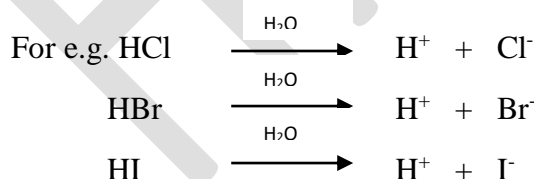
**Case 2 (Weak acids):** But weak acid like oxalic acid do not ionize completely in water. Liquid  $\text{NH}_3$  is a base (protophilic solvent) and tendency to accept proton is high. Therefore if  $\text{NH}_3$  is used as a solvent, it will completely dissociates such compounds which are not able to dissolve in aqueous solvent.



Therefore in case of weak acid, it will only ionized in protophilic (Basic) solvent because these type of non-aqueous solvents increases the strength of the acidic drugs. In such cases, weak acids become comparable of those of strong acid. This effect is known as **levelling effect**.

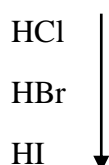
### Differentiating Effect:

HCl, HBr and HI are strong acids and completely dissociates in water as well as protophilic solvents and their degree of dissociation are same.



But in glacial acetic acid, different acids have different degree of dissociation because in acidic solvent acidic drugs cannot be dissociates equally it depends on its acidity.

Degree of dissociation of these acids increases in following order when it is added in glacial acetic acid. This effect is known as differentiating effect.



**FREQUENTLY USED SOLVENT:**

A very large number of inorganic and organic solvents have been used for non-aqueous determinations.

Few have been used more frequently than all.

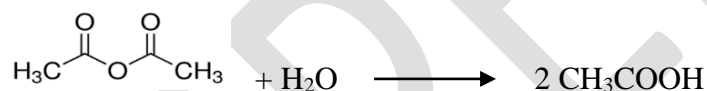
Some are of them discussed below.

**1. Glacial acetic acid (protogenic, Amphiprotic)**

Glacial acetic acid is most frequently used solvent.

Before use, it is advisable to check water content, which may be between 0.1 % to 1.0 %.

In case, the water content is more than the recommended amount, acetic anhydride is added which convert water into acid.



The acid may be used by itself or in conjugation with other solvents.

e.g. Acetic anhydride

Acetonitrile

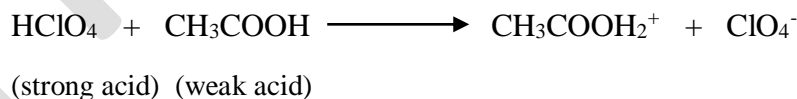
Nitromethane

In Glacial acetic acid, bases (weak or strong) will completely ionized.

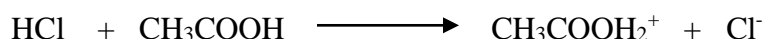
While mineral acids are not completely ionized in acetic acid, their strengths are different.

Glacial acetic acid is a levelling solvent for the weak bases compound and differentiating solvent for acidic compound.

When  $\text{HClO}_4$  will dissolve in the solvent, following reactions takes place.



While  $\text{HCl}$  reacts with solvent Glacial acetic acid, following reaction takes place

**2. Acetonitrile**

It is aprotic solvent and used to dilute reaction mixtures.

Acetonitrile is frequently used with other solvents, such as chloroform and phenol and especially with ethanoic acid.

### 3. Alcohols (Amphiprotic solvents)

Salts of organic acids, especially of soaps are best determined in mixture of glycols and alcohols or mixture of glycols and hydrocarbons.

The most common combinations are ethylene glycol with propane-2-ol or butan-1-ol.

### 4. Dioxan (ether, Aprotic solvent)

It does not act as levelling solvent. It is used in place of glacial acetic acid when mixture of substances are to be quantified.

Separate end points are detected with this solvent.

### 5. Dimethylformamide (Protophilic)

This solvent is used in titration between benzoic acid and amide.

## INDICATORS FOR NON-AQUEOUS TITRATION

Ostwald and Resonance (Quinonoid) theory also applied to non-aqueous titration. But their colour changes at the end point vary from titration to titration as they depend on nature of titrant.

By simple titration, correct end point can be obtained. The colour corresponding to the correct end point may be established by carrying out a potentiometric titration, while simultaneously observe the colour change of the indicator.

### Examples:

1. **Crystal violet:** 0.5 % w/v solution in glacial acetic acid. Colour change: Violet through blue-Green – Greenish yellow.

This indicator is used in reaction Pyridine titrated with perchloric acid.

2. **Methyl Red:** 0.2 % w/v solution in dioxin. Colour change: Yellow to Red
3. **1-Naphthol benzene:** 0.2 % w/v solution in acetic acid. Colour change: yellow to green.

This indicator gives sharp end point in nitromethane containing ethanoic anhydride for titrations of weak bases against perchloric acid.

4. **Quinaldine Red:** 0.1 % w/v solution in ethanol. Colour change: purple red to pale green. It is used for drug determination in dimethylformamide solution.
5. **Thymol Blue:** 0.2 % w/v solution in methanol. Colour change: yellow to blue. It is used for acidic substances in dimethylformamide solution.

### TITRANTS:

1. **Perchloric acid 0.1 M (in glacial acetic acid)**



8.5 ml perchloric acid in 500 ml glacial acetic acid + 25 ml of acetic anhydride up to 1000 ml.

**2. Perchloric acid in Dioxane 0.1 M**

8.5 ml of perchloric acid in sufficient dioxane to make 1000 ml.

**3. Lithium methoxide 0.1 M**

0.7 gm lithium metal in 150 ml methyl alcohol + 850 ml toluene

**4. Sodium methoxide 0.1 M**

2.5 g sodium metal in 150 ml methanol and make the volume up to 1000 ml with toluene.

### ACIDIMETRY AND ALKALIMETRY TITRATION

**Acidimetry:** It is used for quantitative estimation of basic drugs.

Titrant used in acidimetry is acidic in nature. e.g.  $\text{HClO}_4$  (perchloric acid). Protogenic solvents are used. e.g. glacial acetic acid.

Samples which can be determined by acidimetry are: Ephedrine,  
Morphine,  
Acyclovir,  
Adrenaline,  
Caffeine etc.

**Indicator:** Crystal violet (0.5 % in acetic acid)

**Colour change:** From violet to light green.

**Alkalimetry:** It is used for quantitative estimation of weak acidic drugs.

Titrant used in alkalimetry is basic/alkaline in nature. E.g.  $\text{CH}_3\text{ONa}$  (sodium methoxide).

Protophilic solvents are used. e.g. Dimethylformamide.

Samples which can be determined by Alkalimetry are: Nalidixic acid  
Acetazolamide  
Fluorouracil  
Allopurinol  
Mercaptopurine etc.

**Indicator:** Thymol Blue (0.5 % in methanol)

**Colour change:** From Pink to Blue

## ESTIMATION OF EPHEDRINE HCl

### Principle:

During non-aqueous titration of Ephedrine HCl the chloride ion behaves as a weak proton acceptor (weak basic drug).

In this titration, it is replaced as acetate ion by adding Mercuric Acetate in Glacial acetic acid. A titration is performed against perchloric acid using crystal violet as an indicator.

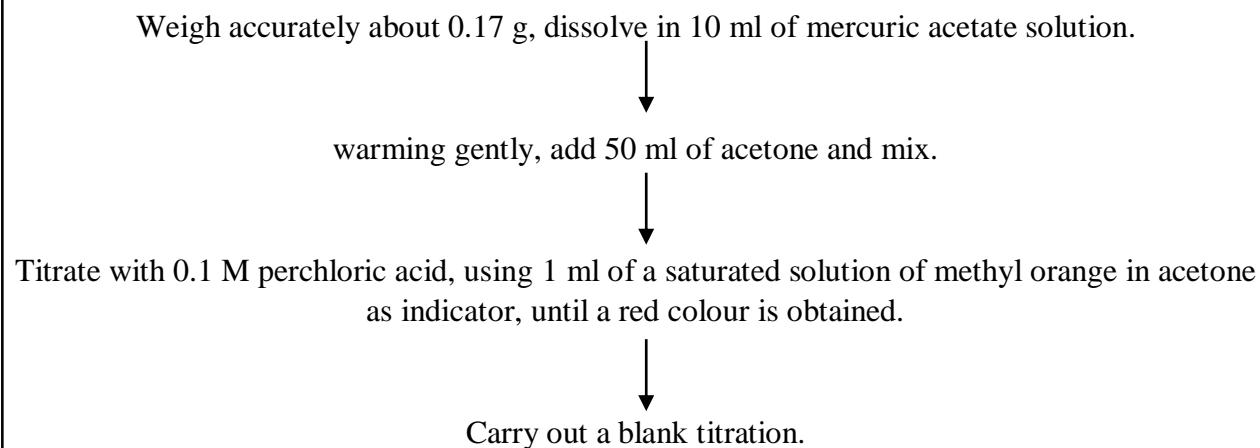
### Procedure:

**Preparation of 0.1M solution of HClO<sub>4</sub> and its standardization:** Dissolve 8.5 ml of 72 % HClO<sub>4</sub> 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 hours.

Acetic anhydride absorbed all the water from HClO<sub>4</sub> and glacial acetic acid and renders the solution virtually anhydrous. HClO<sub>4</sub> must be well diluted with glacial acetic acid before adding acetic anhydride because reaction between HClO<sub>4</sub> and acetic anhydride is explosive.

**Standardization of HClO<sub>4</sub>:** 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 M HClO<sub>4</sub>. The colour changes from blue to blue green.

### Assay Procedure:



A blank titration is performed and this volume is subtracted from the volume of perchloric acid needed by the sample.

**Factor:** Each ml of 0.1 M perchloric acid  $\cong$  0.02017 gm of ephedrine hydrochloride.

### Calculations:

$$\% \text{ Ephedrine Hydrochloride} = \frac{X \text{ ml} \times \text{Molarity (Calculated)} \times 0.02017 \times 100}{M \text{ (Given)} \times \text{wt. of sample (in gm)}}$$

## ESTIMATION OF SODIUM BENZOATE

### Principle:

Sodium benzoate is estimated by non-aqueous titration where it is dissolved in anhydrous glacial acetic acid which enhances the strength of weak base sodium benzoate. This solution is titrated with 0.1 M Perchloric acid using 1-naphtholbenzein as an indicator.

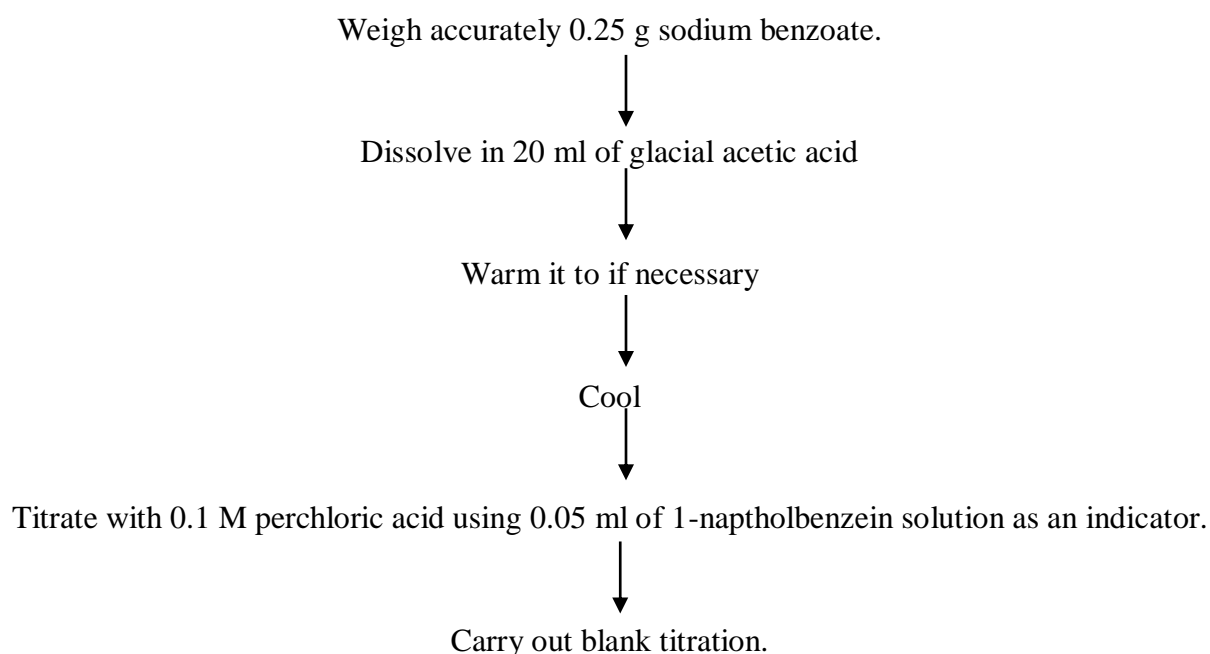
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### Assay Procedure:



**Factor:** 1 ml of 0.1 M perchloric acid is equivalent to 0.01441 g of C<sub>7</sub>H<sub>5</sub>NaO<sub>2</sub>.

$$\% \text{ Sodium Benzoate} = \frac{X \text{ ml} \times \text{Molarity (Calculated)} \times 0.01441 \times 100}{M \text{ (Given)} \times \text{wt. of sample (in gm)}}$$