Chapter ... 3

NON-AQUEOUS TITRATIONS

♦ LEARNING OBJECTIVES ♦

- *To describe the necessity of the non-aqueous titrations.*
- *To identify the solvents applicable for non-aqueous titrations.*
- *To describe why the non-aqueous titrations are highly useful for weak acids and bases.*

OUTCOMES

On satisfying the requirements of this course, students will have the knowledge and skills to:

- Requirement of non-aqueous titrations, levelling effects of solvents and nature of the solvents.
- Quantitative analysis of the weak acids and bases by non-aqueous titrations.

3.1 SOLVENTS

Most of the titrations are performed in the aqueous media, means water is used as solvent. There may be difficulty if reactant is insoluble in water or reactant is reactive with water or the analyte (sample) is either too weak acid or too weak base.

Those too weak acids or bases can not be titrated in aqueous solution due to the amphiprotic behaviour of water (i.e. water can react as an acid on titration with a base and act as a base on titration with acid). So water will compete with the sample if it is weak acid or weak base.

The simple solution for this problem is to replace water as solvent with another non-aqueous solvent. So this type of titration is named *"Non-Aqueous Titration"*.

Reasons for Non-aqueous Titrations:

The reactant is insoluble in water: If the reactant compound is insoluble in water, then non-aqueous solvent is mandatory to dissolve the compound.

The reactant is reactive with water: If the reactant is reactive with water and converts its chemical composition when dissolved in water, then also non-aqueous titration method is used.

The sample is too weak acid or too weak base: If the reactant compound is very weak acid or base, then dissociation of the compound will be very less and enough concentration of the ion cannot be achieved and non-aqueous titration is preferred method.

3.2 TYPES OF SOLVENTS IN NON-AQUEOUS TITRATIONS

Protogenic solvents:

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

Examples: Glacial acetic acid. (Anhydrous acetic acid is called glacial acetic acid, it is free from water content and solidifies at 16.7°C).

Protophilic solvents:

These are basic solvents and used to enhance the acidity of weak acids.

Examples: Pyridine, Ethylenediamine and Dimethylformamide (DMF).

Amphoteric solvents:

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

Examples: Alcohols, Ethanol, Methanol.

Aprotic solvents:

These solvents neither accept proton nor donate proton. They are used in dissolving the drugs especially those are insoluble in water.

Examples: Benzene, Carbon tetrachloride.

Selection of solvent:

The selection of solvent in non-aqueous titration is based on:

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

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

Unreactivity: The solvent should be unreacted with the drug.

Selected Examples of Non-Aqueous Solvents:

Many inorganic solvents are used in non-aqueous titrations, but most commonly used solvents are listed below:

1. *Glacial acetic acid (CH_3COOOH):*

It is also known as Glacial ethanoic acid and is most commonly used non-aqueous solvent. Before using glacial acetic acid, water content should be checked and permitted within the range of 0.1% and 1.0%.

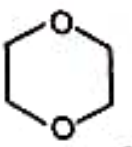
2. *Acetonitrile (CH_3CN):*

It is used with other solvents (chloroform, acetic acid) and enables sharp end points to be obtained in the titration of metal ethanoates when titrated against perchloric acid.

3. *Alcohols (CH_3OH, C_2H_5OH, C_3H_7OH, C_4H_9OH, $HOCH_2CH_2OH$):*

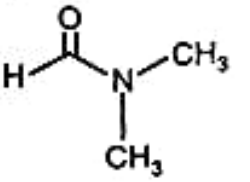
Methanol, ethanol, propanol, butanol and ethylene glycols are used as solvents for both polar and non-polar reactants in non-aqueous titration. All the solvents should be free from water content.

4. *Dioxane:*



Dioxane is also used in non-aqueous titration as a replacement of glacial acetic acid. Dioxane is not a levelling solvent.

5. *Dimethylformamid* (DMF):



DMF is a protophillic solvent and commonly used for titration of amides and benzoic acid in non-aqueous titrations.

3.3 LEVELLING EFFECT

The acidity of weak acids can be enhanced in presence of a basic solvent. This is because basic solvent has a higher affinity to take up protons from the acid. So acetic acid behaves as a strong acid in ammonia solution (basic solvent). Also the basicity of weak bases can be enhanced in presence of acidic solvent. This is called the **levelling effect** of the solvent. By using this concept, the strength of weak acidic or weak basic drugs can be enhanced by dissolving it in the appropriate solvent to enhance its strength and then can be titrated by acid-base titration (non-aqueous titration).

Levelling Effect Reactions:

$$HCl \longrightarrow H^+ + Cl^-$$
$$H_2SO_4 \longrightarrow 2H^+ + SO_4^{2-}$$
$$HNO_3 \longrightarrow H^+ + NO_3^-$$
$$HClO_4 \longrightarrow H^+ + ClO_4^-$$

All acts as strong acid in water and all are actually strong acids.

If we are taking the example of weak acid; then

$C_2O_4H_2 \longrightarrow (COO)_2^{2-} + 2H^+ + C_2O_4H_2$ (Remaining because of incomplete dissociation; when water is used as a solvent).

Now ammonia is used as a solvent; then

$$HCl + NH_3 \longrightarrow NH_4^+ + Cl^-$$
$$H_2SO_4 + 2NH_3 \longrightarrow 2NH_4^+ + SO_4^{2-}$$
$$HNO_3 + NH_3 \longrightarrow NH_4^+ + NO_3^-$$
$$HClO_4 + NH_3 \longrightarrow NH_4^+ + ClO_4^-$$

Again all strong acids act as strong acid in ammonia

and $C_2O_4H_2 + 2NH_3 \longrightarrow (COO)_2^{2-} + 2NH_4^+$ (Weak acid will be completely dissociated and acts as strong acid due to leveling effect).

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

Differentiating Solvents: Degree of dissociation varies for different acids or bases in differentiating solvents; means these types of solvents do not gives levelling effect.

Example: A strong acid acts as a levelling solvent for bases, but a weak acid acts as a differentiating solvent for the acids, because complete dissociation not occurs. Same rule is applicable for strong basic and weak basic solvents.

Differential Effect Reactions:

$$HCl \longrightarrow H^+ + Cl^-$$
$$HBr \longrightarrow H^+ + Br^-$$
$$HI \longrightarrow H^+ + I^-$$

All acts as strong acid in water and all are actually strong acids.

If glacial acetic acid is used as a solvent; then HI will be strongest acid, HBr will be moderate and HCl will be weakest acid amongst all three; and this effect is known as differential effect.

3.4 ACIDIMETRY AND ALKALIMETRY TITRATION

Acidimetry:

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

Alkalimetry:

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

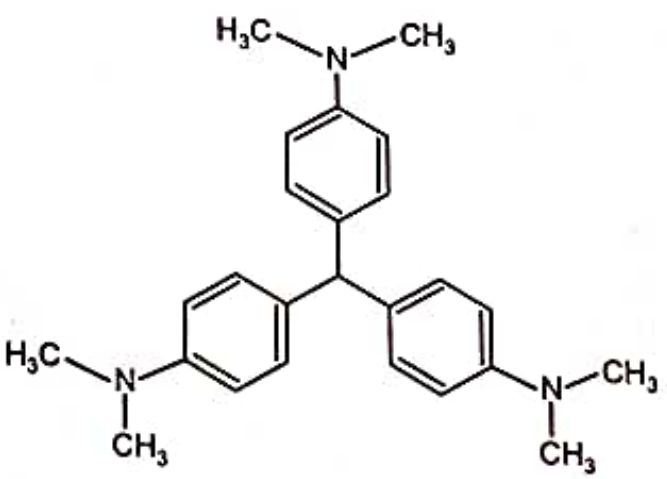
Details	Acidimetry	Alkalimetry
Samples:	Basic drugs such as: Ephedrine, Adrenaline, Caffeine, Acyclovir.	Acidic drugs such as: Nalidixic acid, Flurouracil.
Solvent:	Protogenic solvents such as: glacial acetic acid	Protophilic solvents such as: DMF
Titrant:	Perchloric acid $HClO_4$	Sodium methoxide.
Indicator: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

3.5 INDICATORS

The ionized and non-ionized indicators are used for non-aqueous titrations, but colour changes during the end point vary for different titration, because it is dependent on the nature of the titrant. The resultant colour at the correct end point can be determined by carrying out a potentiometric titration and at the same time observing the colour change of the indicator.

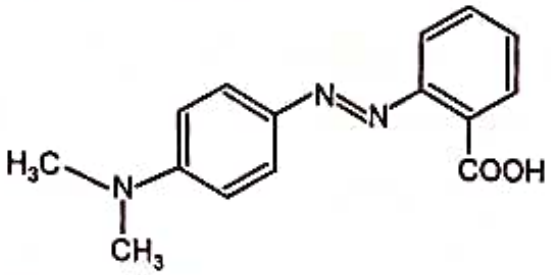
List of commonly used indicators in non-aqueous titrations are given below:

1. *Crystal Violet* (0.5% w/v solution in glacial acetic acid)



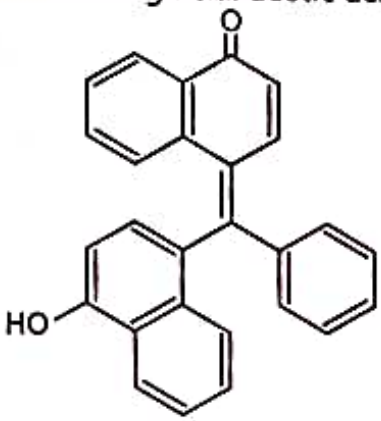
Colour change: Violet through blue followed by green, then to greenish yellow, in reactions in which bases such as pyridine are titrated with perchloric acid.

2. *Methyl Red* (0.2% w/v solution in dioxane)



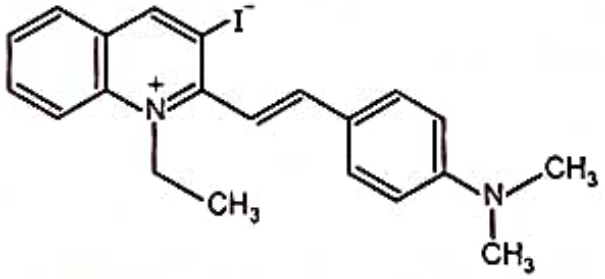
Colour change: Yellow (Alkaline medium) to red (Acidic medium) colour.

3. *Naphthol Benzein* (0.2% w/v solution in glacial acetic acid)



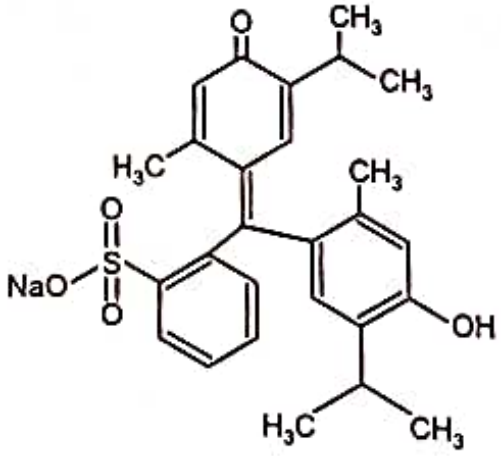
Colour change: Yellow (Alkaline medium) to green (Acidic medium) colour change. It gives sharp end points in nitro methane containing acetic anhydride for titration of weak bases against $HClO_4$.

4. *Quenaldine Red* (0.1% w/v solution in ethanol)



Colour change: Purple red (Acidic medium) to pale green (Alkaline medium).

5. *Thymol Blue* (0.2% w/v solution in methanol)



Colour change: Pink (Acidic medium) to blue (Alkaline medium) at the end point.

Table 3.1 enlists the various cognate determinations using different indicators but employing the same titrant i.e. 0.1 N perchloric acid.

Table 3.1: Acidimetric indicators for non-aqueous titrations

Sr. No.	Name of Substance	Indicator Employed
1.	Amantadine hydrochloride	Crystal violet
2.	Cyproheptadiene HCl	Crystal violet
3.	Dehydroemetine HCl	Crystal violet
4.	Ephedrine hydrochloride	Crystal violet
5.	Imipramine hydrochloride	Crystal violet
6.	Isoprenaline hydrochloride	Crystal violet
7.	Lignocaine hydrochloride	Crystal violet
8.	Morphine hydrochloride	Crystal violet
9.	Morphine sulphate	Crystal violet
10.	Phenylephrine hydrochloride	Crystal violet
11.	Thiabendazole	Crystal violet
12.	Chlorpromazine hydrochloride	Methyl orange
13.	Promethazine hydrochloride	Methyl orange
14.	Clonidine hydrochloride	α-Naphthol benzene
15.	Phenytoin sodium	α-Naphthol benzene

Table 3.2: Alkalimetric indicators for non-aqueous titrations

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

3.6 ESTIMATION OF SODIUM BENZOATE

Principle:

Assay of sodium benzoate is based on non-aqueous acid base titration method.

$$C_7H_5NaO_2 + HClO_4 \longrightarrow C_7H_6O_2 + NaClO_4$$

Preparation of Reagents:

Preparation of 0.1 N $HClO_4$:

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.

Experimental Methodology:

1. Weigh accurately about 0.51 g of potassium hydrogen phthalate in a 100 ml conical flask and add 25 ml of glacial acetic acid and attach a reflux condenser attached with a silica-gel drying tube. Prepared solution is 0.1 N potassium hydrogen phthalate.
2. Warm the conical flask until the salt gets dissolved completely.
3. Cool and titrate with 0.1 N perchloric acid by using acetous crystal violet indicator (2 drops).
4. Colour at the end point will be blue to bluish-green. Calculate the actual normality of $HClO_4$ by using the formula $N_1V_1 = N_2V_2$.
5. Accurately weigh about 0.25 g of sodium benzoate and dissolve in 20 ml of glacial acetic acid, heat the solution at 50°C if required and cool.
6. Titrate the above solution with 0.1 N standardized perchloric acid, using acetous crystal violet indicator (2 drops) solution as indicator.
7. Colour at the end point will be blue to bluish-green.

Calculation:

Each ml of 0.1 N $HClO_4 \equiv 0.01441$ g of $C_7H_5NaO_2$

$$\% \text{ purity of } C_7H_5NaO_2 = \frac{\text{Vol. of } HClO_4 \times \text{Actual normality of } HClO_4 \times 0.01441 \times 100}{\text{Weight of } C_7H_5NaO_2 \text{ (in g)} \times 0.1 \text{ (Expected normality of } HClO_4)}$$

Results:

Percentage purity of the given sample of sodium benzoate was found to be x %.

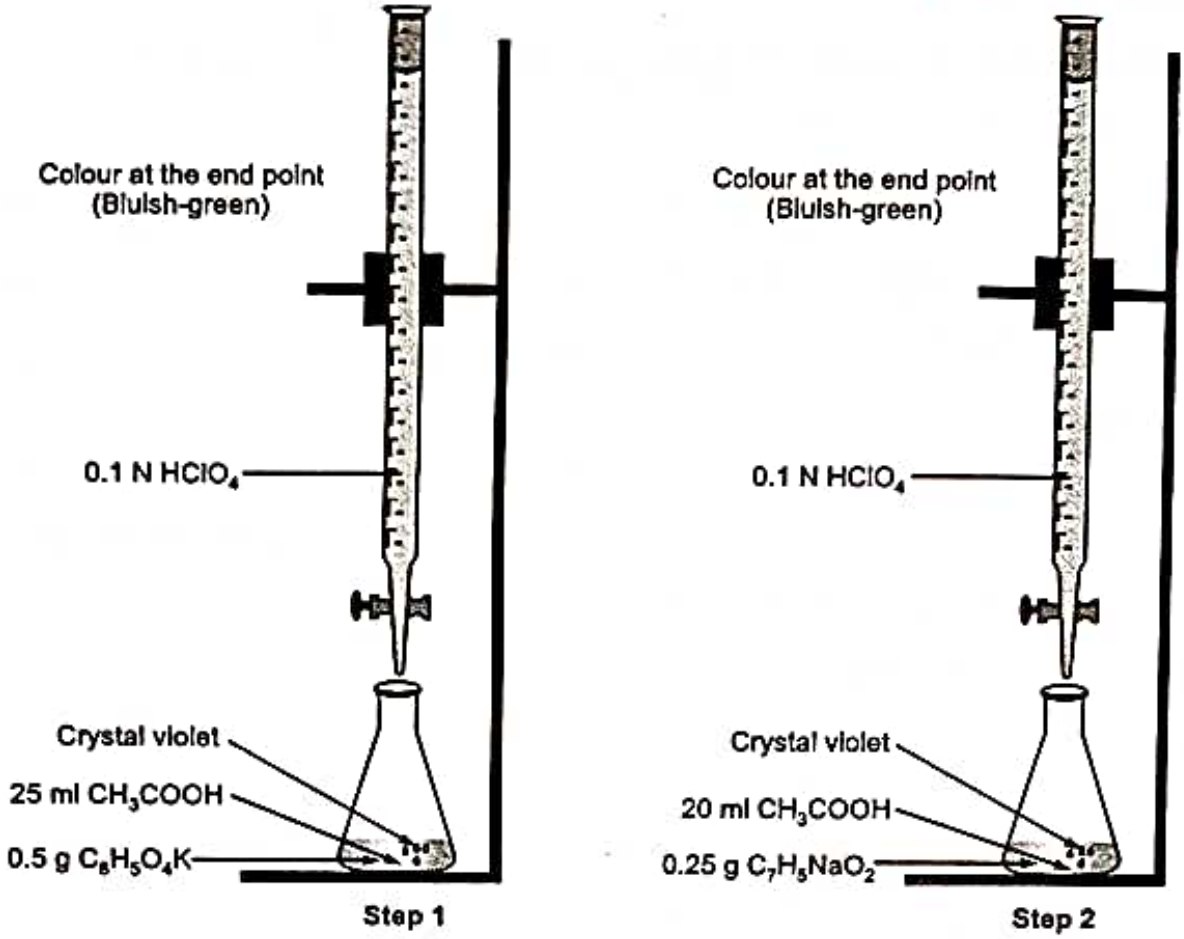


Fig. 3.1: Assay of $C_7H_5NaO_2$

3.7 ESTIMATION OF EPHEDRINE HCl

Principle:

Assay of ephedrine HCl is based on non-aqueous acid base titration method.

$$HClO_4 + CH_3COOH \longleftrightarrow \underset{\text{Onium ion}}{CH_3COOH_2^+} + ClO_4^-$$

$$\underset{\text{Ephedrine}}{C_{10}H_{15}NO} + CH_3COOH \longleftrightarrow \underset{\text{Protonated ephedrine}}{C_{10}H_{15}N^+HO} + CH_3COO^-$$

$$CH_3COOH_2^+ + CH_3COO^- \longleftrightarrow 2CH_3COOH$$

Preparation of Reagents:

Preparation of 0.1 N $HClO_4$:

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 standing for 24 hours before use.

Experimental Methodology:

1. Weigh accurately about 0.5 g of potassium hydrogen phthalate in a 100 ml conical flask and add 25 ml of glacial acetic acid and attach a reflux condenser attached with a silica-gel drying tube.

2. Warm the conical flask until the salt gets dissolved completely.
3. Cool and titrate with 0.1 N perchloric acid by using acetous crystal violet indicator (2 drops).
4. Colour at the end point will be blue to bluish-green.
5. Dissolve 0.5 g ephedrine hydrochloride in glacial acetic acid, add few drops of crystal violet indicator and titrate with standard perchloric acid till the appearance of blue to bluish green.
6. Glacial acetic accepts the proton from perchloric acid to form the onium ions which is the actual titrating species. The onium ions react with acetate ions liberated after protonation of ephedrine hydrochloride.

Calculation:

Each ml of 0.1 N $HClO_4$ ≡ 0.02017 g of $C_{10}H_{15}NO.HCl$

$$\% \text{ purity of } C_{10}H_{15}NO.HCl = \frac{\text{Volume of } HClO_4 \times \text{Actual normality of } HClO_4 \times 0.02017 \times 100}{\text{Weight of } C_{10}H_{15}NO \cdot HCl \text{ (in g)} \times 0.1 \text{ (Expected normality of } HClO_4)}$$

Result:

Percentage purity of the given sample of ephedrine hydrochloride was found to be x %.

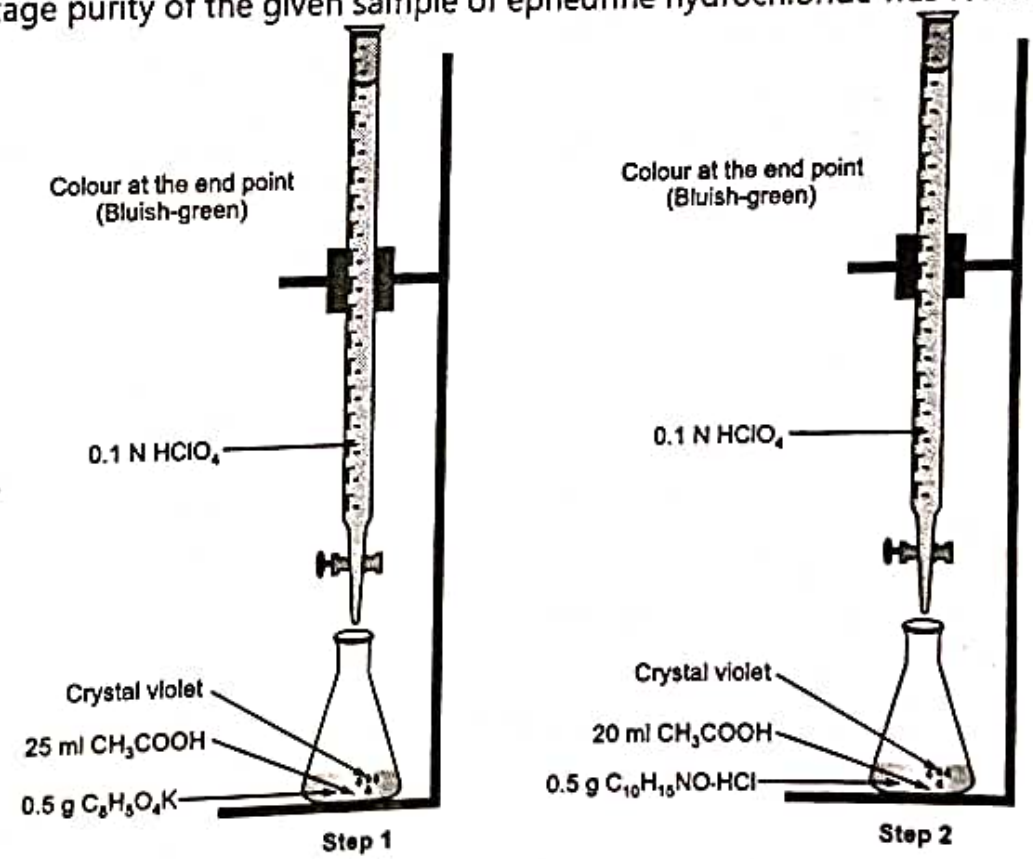


Fig. 3.2: Assay of $C_{10}H_{15}NO.HCl$

QUESTIONS

1. Define non-aqueous titrations?
2. Enlist types of drugs analyzed by non-aqueous titrations.
3. Enlist types of solvents used in non-aqueous titrations.
4. Explain differentiating solvents.

5. Give details about acidimetric and alkalimetric titrations.
6. Give the preparation and standardization method of 0.1 N perchloric acid.
7. What do you understand by levelling effect of solvent?
8. What are the indicators used in non-aqueous titrations?
9. Write a note on estimation of Ephedrine HCl by non-aqueous titrations.
10. Write a note on estimation of sodium benzoate by non-aqueous titrations.

MULTIPLE CHOICE QUESTIONS

1. Which is the valid reason(s) for non-aqueous titrations?
   (a) The reactant is insoluble in water
   (b) The reactant is reactive with water
   (c) The sample is too weak acid or too weak base
   (d) All of the above
2. Solvent as an acid on titration with a base and act as a base on titration with acid is known as .....
   (a) Protogenic (b) Protophilic
   (c) Aprotic (d) Amphoteric
3. Which solvent can be used in non-aqueous titration?
   (a) Acetic acid (b) Galcial acetic acid
   (c) Semi-normal acetic acid (d) All of the above
4. Moisture should be avoided in non-aqueous titration to ..... of the end point.
   (a) Get the rapid end point (b) Increase the sharpness
   (c) Decrease the titration time (d) Increase the pH
5. Which drug can be determined by acidimetric non-aqueous titration?
   (a) Nalidixic acid (b) Flurouracil
   (c) Acyclovir (d) All of the above
6. Which drug can be determined by acidimetric non-aqueous titration?
   (a) Nalidixic acid (b) Amylobarbitone
   (c) Thiabendazole (d) Bendrofluazide
7. Which drug can be determined by alkalimetric non-aqueous titration?
   (a) Thiabendazole (b) Allopurinol
   (c) Caffeine (d) Adrenaline
8. Indicator used in Acidimetric non-aqueous titration is .....
   (a) Thymol blue (b) Iron (II) Salt
   (c) Crystal violet (d) None of the above
9. Which indicator is employed for determination of Acetazolamide?
   (a) Azo violet (b) Thymol blue
   (c) Crystal violet (d) Potentiometric determination
10. Indicator used in Alkalimetric non-aqueous titration is .....
    (a) Thymol blue (b) Iron (II) salt
    (c) Crystal violet (d) All of the above

Answers

1. (d)	2. (d)	3. (b)	4. (b)	5. (c)	6. (c)	7. (c)	8. (c)	9. (d)	10. (a)

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