Pharmaceutical Analysis Unit 2 :
Acid-Base and Non-Aqueous Titrations

Chapter 1: Acid-Base Titration Fundamentals

Introduction to Titration

Titration is a laboratory technique used to determine the unknown concentration of a solution. It involves a controlled chemical reaction between a solution of known concentration (the titrant) and a solution of unknown concentration (the titrant or analyte) until the reaction is complete. This process helps us find out exactly how much of a substance is present in a sample.

Key Terms in Titration:

- **Titrant:** This is a solution with a **known concentration**. It is typically added from a burette during titration.
- **Titrand (Analyte):** This is the solution with an **unknown concentration** that you want to determine. It is usually placed in a conical flask.
- **Indicator:** This is a special substance added to the titrant in the conical flask. Its purpose is to help identify when the reaction is complete by changing color.
- **End Point:** This is the point in the titration where the indicator changes color, signalling that the reaction is visually complete.
- **Equivalence Point:** This is the theoretical point where the moles of titrant added are exactly equal to the moles of the analyte (the substance in the unknown solution). The end point, identified by the indicator, should ideally be very close to the equivalence point.

Principle of Acid-Base Titration:

Acid-base titration, also known as **neutralisation titration**, is based on the chemical reaction between an acid and a base. In this reaction, an acid reacts with a base to form a salt and water. The main principle is to determine the unknown concentration of an acid or base using a solution of a known concentration of the other. It is a type of quantitative analysis.

For example, when hydrochloric acid (HCl) reacts with sodium hydroxide ($NaOH$), they form sodium chloride ($NaCl$) and water (H_2O). HCl (Acid) + $NaOH$ (Base) → $NaCl$ (Salt) + H_2O (Water)

Advantages of Acid-Base Titration:

- The reaction between an acid and a base is typically **fast and almost instantaneous**.
- It is usually a **single reaction without side reactions**, making it straightforward.
- The reaction almost always goes to **completion**.
- The reaction is **stoichiometric**, meaning the reactants combine in fixed, simple whole-number ratios.

Acidimetry and Alkalimetry:

These are specific types of acid-base titrations:

- **Acidimetry:** This involves using a standard **acid** solution to determine the unknown concentration of a basic solution.
- **Alkalimetry:** This involves using a standard **base** (or alkali) solution to determine the unknown concentration of an acidic solution.

Theories of Acids and Bases

Several theories help explain what makes a substance an acid or a base.

1. Arrhenius Theory (H^+ and OH^-):

Proposed in 1884, this theory defines acids and bases based on their behaviour in water.

- **Acids:** Substances that ionise (partially or completely) in water to produce **hydrogen ions (H^+)**, which associate with water to form hydronium ions (H_3O^+). For example, HCl in water produces H^+ ions.
- **Bases:** Substances that ionise in water to produce **hydroxyl ions (OH^-)**. For example, NaOH in water produces OH^- ions.
- **Neutralisation Reaction:** According to Arrhenius, an acid and a base react to form salt and water. The key reaction is $H^+ + OH^- \rightarrow H_2O$.

Limitations of Arrhenius Theory:

- This theory defines acids and bases only in an **aqueous (water) medium**.
- It doesn't explain the behaviour of substances that act as acids or bases but do not produce H^+ or OH^- ions (like CO_2, SO_2).
- It doesn't cover conjugate acid-base pairs.

2. Bronsted-Lowry Theory (Taking and Giving Protons):

Proposed independently in 1923, this theory offers a more generalised definition, independent of the solvent.

- **Acids (Proton Donors):** A substance that can **donate a proton (H^+)**.
- **Bases (Proton Acceptors):** A substance that can **accept a proton (H^+)**.

In a Bronsted-Lowry reaction, a proton is transferred from an acid to a base. This creates a conjugate acid-base pair. For example, if an acid (HA) donates a proton, it forms its conjugate base (A^-). If a base (B) accepts a proton, it forms its conjugate acid (BH^+). Water can act as both an acid and a base, making it **amphoteric**.

3. Lewis Theory (Taking and Giving Electrons):

Also introduced in 1923, the Lewis theory broadens the definition even further, focusing on electron pairs.

- **Acids (Electron Pair Acceptors):** Substances that can **accept a lone pair of electrons**. These are also known as electrophiles.
- **Bases (Electron Pair Donors):** Substances that have a **self-tendency to donate a lone pair of electrons**. These are also known as nucleophiles.

For example, Ammonia (NH_3) is a Lewis base because it can donate its lone pair of electrons. Aluminium Chloride ($AlCl_3$) is a Lewis acid because it can accept an electron pair. Water is also considered a Lewis base. This theory explains acid-base reactions in systems where H^+ or OH^- are not involved.

Summary of Acid-Base Theories:

Theory	Acid	Base
Arrhenius	Hydrogen ion donor	Hydroxide ion donor
Bronsted-Lowry	Proton donor	Proton acceptor
Lewis	Electron pair acceptor	Electron pair donor

Law of Mass Action

The Law of Mass Action was proposed in 1867. It states that the **rate of a chemical reaction is proportional to the active masses (concentrations) of the reacting substances**. For reversible reactions at equilibrium, the ratio of the product of concentrations of products to the product of concentrations of reactants, each raised to the power of their stoichiometric coefficients, is a constant known as the **equilibrium constant (K)**. This law helps predict the behaviour of solutions in dynamic equilibrium.

Role of Solvents

Solvents play a crucial role in acid-base chemistry, influencing the dissociation of acids and bases.

Water as a Solvent: Water is the most common solvent in aqueous acid-base titrations. It shows **amphiprotic properties**, meaning it can act as both an acid and a base depending on the substance dissolved in it.

Characteristics of Solvents: The suitability of a solvent for analysis depends on properties such as:

- **Self-dissociation:** Solvents can dissociate to some extent. For example, ethanol can self-dissociate to ethoxide ions and H^+.
- **Dielectric Constant:** This property indicates a solvent's ability to separate ions. Solvents with a higher dielectric constant (like water) can easily dissolve polar ionic solutes, leading to complete dissociation.
- **Acid-Base Character:** Solvents are classified based on their proton donor-acceptor properties.

Classification of Solvents based on Acid-Base Character:

- **Protogenic Solvents (Acidic):** These solvents are acidic in nature and can donate protons. They have a relatively high dielectric constant and are ionised. Examples include acetic acid, formic acid, and propionic acid. Used to enhance the basicity of weak bases.
- **Protophilic Solvents (Basic):** These solvents are basic in nature and can accept protons. They react with acids to form solvated protons and have a high dielectric constant. Examples include pyridine, dimethylformamide (DMF), and ethylenediamine. Used to enhance the acidity of weak acids.

- **Aprotic Solvents:** These solvents cannot donate or accept hydrogen ions (protons). Both acidic and basic properties are entirely absent. They are neutral and are used for neutral substances. Examples include hexane and carbon tetrachloride.
- **Amphiprotic Solvents:** These solvents possess both protogenic (acidic) and protophilic (basic) properties. They can both donate and accept protons. Examples include water and ethanol.

Relative Strength of Acids and Bases

According to the Bronsted-Lowry theory, the **relative strength of acids and bases** at equilibrium depends on the ability of a base to accept a proton from an acid. The dissociation constant (Ka for acids, Kb for bases) is closely related to the strength.

Common Ion Effect: The common ion effect describes what happens when a **strong electrolyte** (which fully dissociates) is added to a solution containing a **weak electrolyte** (which only partially dissociates) with a common ion. The addition of the common ion from the strong electrolyte suppresses the dissociation of the weak electrolyte. This shifts the equilibrium of the weak electrolyte's dissociation backward, reducing the concentration of its ions.

For example, adding sodium acetate (CH3COONa, a strong electrolyte) to acetic acid (CH3COOH, a weak electrolyte) will suppress the dissociation of acetic acid because both produce acetate ions (CH3COO-).

pH and pOH

pH: pH is a numerical scale (typically 0-14) used to indicate the **acidity or alkalinity (basicity)** of an aqueous solution. It is defined as the negative logarithm (base 10) of the hydrogen ion (H+) concentration.

- Solutions with a pH less than 7 are **acidic**.
- Solutions with a pH greater than 7 are **alkaline** (basic).
- A solution with a pH of 7 is **neutral**.

pOH: pOH is a measure of the **hydroxyl ion (OH-) concentration** or basicity. It is derived from pH measurements and is the negative logarithm (base 10) of the hydroxide ion concentration. The relationship between pH and pOH in water at 25°C is: **pH + pOH = 14**.

Ionic Product of Water (Kw): Water undergoes a slight self-ionisation (auto-ionisation) into hydronium (H3O+) and hydroxide (OH-) ions. H2O + H2O ⇌ H3O+ + OH- The equilibrium constant for this reaction is called the **ionic product of water (Kw)**. At 25°C, Kw is 1 x 10^-14. In pure, neutral water at 25°C, the concentrations of H3O+ and OH- are both 1.0 x 10^-7 mol/litre, which results in a pH of 7.

Hydrolysis of Salts

A salt is formed when an acid reacts with a base. The pH of the salt solution depends on the strength of the acid and base from which it was formed.

- **Neutral Salts:** Formed from the reaction of a **strong acid and a strong base**. These salts typically have a pH of 7 (e.g., NaCl, KNO3). Their cations and anions have a slight tendency to react with water, so they are considered neutral.

- **Acidic Salts:** Formed from the reaction of a **strong acid and a weak base**. The solution formed will be acidic, with a pH less than 7. For example, ammonium chloride (NH_4Cl) is an acidic salt formed from HCl (strong acid) and NH_4OH (weak base).
- **Basic Salts:** Formed from the reaction of a **weak acid and a strong base**. The solution formed will be basic, with a pH greater than 7. For example, sodium acetate (CH_3COONa) is a basic salt formed from CH_3COOH (weak acid) and NaOH (strong base).

Henderson-Hesselbalch Equation

This equation is frequently used to relate the pH of a solution of a weak acid to its acid dissociation constant (pKa) and the degree of ionisation. It is crucial for understanding and calculating the pH of buffer solutions.

For a weak acid (HA) and its conjugate base (A-): **pH = pKa + log ([Salt] / [Acid])** Or, **pH = pKa - log ([HA] / [A-])**

Similarly, for a weak base and its conjugate acid: **pOH = pKb + log ([Salt] / [Base])**

This equation assumes that the acid is essentially unionised and the base comes from the dissolved salt.

Buffer Solutions

Definition and Function: Buffers are solutions that **resist significant changes in pH** when small amounts of acid, base, or water are added. They are typically made by mixing a weak acid with its conjugate base (as a salt) or a weak base with its conjugate acid (as a salt).

How Buffers Work:

- If a small amount of **acid (H+)** is added to an acidic buffer, the conjugate base in the buffer reacts with the H+ ions, converting them into the weak acid, thereby preventing a drastic drop in pH.
- If a small amount of **base (OH-)** is added, the weak acid in the buffer reacts with the OH- ions, converting them into water and the conjugate base, thus preventing a drastic increase in pH.

Types of Buffer Solutions:

- **Acidic Buffer Solution:** Made by mixing a **weak acid** with the **salt of its conjugate base**. For example, acetic acid (CH_3COOH) and sodium acetate (CH_3COONa). These solutions have a pH less than 7.
- **Basic Buffer Solution:** Made by mixing a **weak base** with the **salt of its conjugate acid**. For example, ammonia (NH_3) and ammonium chloride (NH_4Cl). These solutions have a pH greater than 7.

Buffer Calculations: The Henderson-Hesselbalch equation is used to calculate the pH of buffer solutions.

- For acidic buffers: pH = pKa - log ([HA] / [A-])

- For basic buffers: pOH = pKb - log ([Base] / [Salt])

A buffer works best when the concentrations of the acid and conjugate base (or base and conjugate acid) are equal, in which case pH = pKa (or pOH = pKb). Buffers generally work well within a 10:1 ratio of acid to conjugate base.

Chapter 2: Acid-Base Titration Types and Indicators

Types of Acid-Base Titrations

Acid-base titrations are broadly classified into four main categories based on the strengths of the acid and base involved.

1. Strong Acid with Strong Base Titration:

- **Reactants:** Both the acid and the base dissociate completely in water. Examples: Hydrochloric acid (HCl) with Sodium hydroxide (NaOH).
- **Reaction:** HCl (Strong Acid) + NaOH (Strong Base) → NaCl (Neutral Salt) + H2O.
- **Neutralisation Curve:** The pH starts very low (acidic), rises slowly, then **sharply changes around the equivalence point (pH 7)**, and then rises slowly again (basic).
- **Equivalence Point:** The equivalence point occurs at **pH 7**.
- **Indicators:** Indicators that change color in the pH range of 3 to 10.5 can be used. Common examples include Phenolphthalein, Methyl orange, Methyl red, Bromothymol blue, and Phenol red.

2. Weak Acid with Strong Base Titration:

- **Reactants:** A weak acid (partially dissociates) and a strong base (completely dissociates). Examples: Acetic acid (CH3COOH) with Sodium hydroxide (NaOH).
- **Reaction:** CH3COOH (Weak Acid) + NaOH (Strong Base) → CH3COONa (Basic Salt) + H2O.
- **Neutralisation Curve:** The pH starts higher than for a strong acid, rises slowly, undergoes a sharp change, and then rises slowly again. The equivalence point occurs at a pH greater than 7 due to the hydrolysis of the basic salt formed.
- **Equivalence Point:** The equivalence point occurs at **pH greater than 7** (e.g., pH 8.72 for 0.1 N CH3COOH with 0.1 N NaOH).
- **Indicators:** Indicators that change color in the basic pH range are suitable. Examples include Phenolphthalein, Thymolphthalein, and Thymol Blue.

3. Weak Base with Strong Acid Titration:

- **Reactants:** A weak base (partially dissociates) and a strong acid (completely dissociates). Examples: Ammonia (NH4OH) with Hydrochloric acid (HCl).
- **Reaction:** NH4OH (Weak Base) + HCl (Strong Acid) → NH4Cl (Acidic Salt) + H2O.
- **Neutralisation Curve:** The pH starts high (basic), decreases slowly, then sharply drops around the equivalence point, and continues to drop slowly (acidic). The equivalence point occurs at a pH less than 7 due to the hydrolysis of the acidic salt formed.
- **Equivalence Point:** The equivalence point occurs at **pH less than 7** (e.g., pH 5.28 for 0.1 M NH4OH with 0.1 M HCl).
- **Indicators:** Indicators that change color in the acidic pH range are suitable. Examples include Methyl orange, Methyl red, Bromophenol, and Bromocresol green.

4. Weak Acid with Weak Base Titration:

- **Reactants:** Both the acid and the base partially dissociate. Examples: Acetic acid (CH_3COOH) with Ammonia (NH_4OH).
- **Reaction:** CH_3COOH (Weak Acid) + NH_4OH (Weak Base) → CH_3COONH_4 (Neutral Salt, if $K_a \approx K_b$) + H_2O.
- **Neutralisation Curve:** The pH change around the equivalence point is very small and less sharp. This makes it difficult to pinpoint the end point accurately using ordinary indicators.
- **Equivalence Point:** The equivalence point's pH depends on the relative strengths (dissociation constants) of the weak acid and weak base:
    - If $K_a = K_b$, then pH = 7 (neutral salt).
    - If $K_a > K_b$, then pH < 7 (acidic salt).
    - If $K_a < K_b$, then pH > 7 (basic salt).
- **Indicators:** Often, **mixed indicators** are used for these titrations due to the narrow pH range at the end point.

Neutralisation Curves

Neutralisation curves are graphs that plot the **pH of the analyte** against the **volume of titrant added** during a titration. These curves are essential for understanding the mechanism of the neutralisation process and for selecting appropriate indicators. The sharpest change in pH usually occurs near the equivalence point, which is where the indicator should change color.

Theories of Indicators

Definition of an Indicator: An indicator is a substance that **exhibits a colour change at a specific stage of a chemical reaction**, typically near the equivalence point of a titration. Acid-base indicators are usually weak organic acids or bases that have different colours in their ionised (conjugate base/acid) and unionised forms.

1. Ostwald's Theory: According to this theory, indicators are either weak organic acids or weak organic bases. The colour change is due to the difference in colour between the ionised and unionised forms of the indicator.

- **Acidic Indicator (HIn):** In an acidic solution, the indicator remains largely in its unionised form (HIn), which has one colour. In an alkaline (basic) solution, it dissociates to its ionised form (In^-), which has a different colour. HIn (colour A) $\rightleftharpoons$ H^+ + In^- (colour B) In acidic solutions, H^+ concentration is high, suppressing dissociation (common ion effect), so colour A predominates. In basic solutions, H^+ is low (reacts with OH^-), promoting dissociation, so colour B predominates.
- **Basic Indicator (InOH):** In an alkaline solution, the indicator remains largely in its unionised form (InOH), which has one colour. In an acidic solution, it dissociates to its ionised form (In^+), which has a different colour. InOH (colour A) $\rightleftharpoons$ In^+ (colour B) + OH^- In basic solutions, OH^- concentration is high, suppressing dissociation, so colour A predominates. In acidic solutions, OH^- is low, promoting dissociation, so colour B predominates.

2. Resonance Theory: This theory explains that acid-base indicators are organic compounds that exist in two tautomeric forms (structural isomers that can interconvert), such as **benzenoid** and **quinonoid** forms. These forms have different electronic structures and therefore absorb light differently, resulting in different colours.

- The colour change of an indicator depends on the change in its electronic structure due to the pH of the solution.
- For example, Phenolphthalein exists in a colourless benzenoid form in acidic medium and a pink quinonoid form in alkaline medium.
- Methyl Orange is red in acidic benzenoid form and yellow in alkaline quinonoid form.

Acid-Base Indicators

The choice of indicator is critical for accurate titration results and depends on the pH range over which the indicator changes colour. This range should ideally fall within the steep portion of the titration curve, near the equivalence point.

Commonly Used Indicators in Acid-Base Titrations:

Indicator	pH Range	Colour in Acidic Solution	Colour in Alkaline Solution
Methyl Orange	2.9-4.6	Red	Orange
Methyl Red	4.2-6.3	Red	Yellow
Bromothymol Blue	6.0-7.6	Yellow	Blue
Phenolphthalein	8.3-10.0	Colourless	Pink
Thymolphthalein	9.3-10.5	Colourless	Pink
Quinaldine Red	1.4-3.2	Colourless	Red
Bromocresol Green	3.6-5.2	Yellow	Blue
Neutral Red	6.8-8.0	Red	Orange
Phenol Red	6.8-8.4	Yellow	Red

Specific Indicator Recommendations for Different Titration Types:

- **Strong Acid with Strong Base:** Methyl orange, Methyl red, Phenolphthalein, Bromothymol Blue.
- **Weak Acid with Strong Base:** Phenolphthalein, Thymolphthalein, Thymol Blue.
- **Strong Acid with Weak Base:** Methyl orange, Methyl red, Bromophenol, Bromocresol green.
- **Weak Acid with Weak Base:** Mixed indicators are often used.

Mixed Indicators

For titrations involving a weak acid and a weak base, the pH change at the equivalence point is very narrow (less than two pH units). This makes it difficult for ordinary single indicators to give a sharp and accurate end point. **Mixed indicators** are used to overcome this problem. They are combinations of two or more indicators with close pK values that give a sharper colour change over a narrow pH range. For example, a mixture of Methyl green and Phenolphthalein changes colour from grey to pale blue at pH 8.4-8.8. Another example is Thymol blue and cresol red, which changes from yellow to violet at pH 8.

Chapter 3: Non-Aqueous Titrations

Introduction to Non-Aqueous Titration

Definition: Non-aqueous titration is a type of titration where the analytes are dissolved in **solvents other than water** (non-aqueous solvents). This method is primarily used for the titration of weak acids and weak bases.

Why Non-Aqueous Titration? Non-aqueous titrations are necessary in several situations:

- **Insolubility in Water:** When the reactant compound or drug is **insoluble in water**, a non-aqueous solvent is essential to dissolve it for titration. Many drugs, for example, are insoluble in water.
- **Reactivity with Water:** If the reactant or sample is **reactive with water** and its chemical composition changes when dissolved in water, then non-aqueous titration prevents this unwanted reaction.
- **Weak Acids and Bases:** Water is an amphiprotic solvent, meaning it can act as both a weak acid and a weak base. This property makes it compete with very weak acids or bases, making it difficult to titrate them accurately in aqueous solutions. Non-aqueous solvents can enhance the acidity or basicity of these weak substances, leading to a sharper end point.

Types of Solvents in Non-Aqueous Titration

Non-aqueous solvents are classified based on their proton donor-acceptor abilities:

1. Protogenic Solvents (Acidic Solvents):

- These solvents are **acidic in nature** and are strong proton donors. They enhance the basicity of weak bases.
- Examples: **Glacial acetic acid** (anhydrous acetic acid, which is free from water content and solidifies at 16.7°C), formic acid, propionic acid.
- They are used for titrating weak bases.

2. Protophilic Solvents (Basic Solvents):

- These solvents are **basic in nature** and are strong proton acceptors. They enhance the acidity of weak acids.
- Examples: **Pyridine**, Ethylenediamine, **Dimethylformamide (DMF)**.
- They are used for titrating weak acids.

3. Amphiprotic Solvents:

- These solvents can behave as both acids and bases, depending on the substance dissolved in them. They can both donate and accept protons.
- Examples: Alcohols (methanol, ethanol, propanol, butanol), water (though generally avoided in non-aqueous titrations for specific reasons).

4. Aprotic Solvents:

- These solvents are **neutral** and neither accept nor donate protons. They are primarily used for dissolving drugs, especially those that are insoluble in water. They do not enhance the strength of acids or bases.

- Examples: **Benzene**, Carbon tetrachloride, Hexane, Dioxane, Acetonitrile.

Selection of Solvent

Choosing the right non-aqueous solvent is crucial for a successful titration. Key factors include:

- **Solubility:** The weak acidic or basic drug (solute) must be soluble in the chosen solvent.
- **Nature of Drug:** The solvent should be selected according to whether the drug is a weak acid or a weak base, to enhance its strength.
- **Unreactivity:** The solvent should not react with the drug itself.
- **Miscibility with Titrant:** The solvent must be miscible (mixable) with the titrant.

Commonly Used Non-Aqueous Solvents:

- **Glacial acetic acid:** A very common protogenic solvent, often used to titrate weak bases. Water content must be controlled (0.1% to 1.0%).
- **Acetonitrile:** An aprotic solvent, often used with other solvents to achieve sharp end points, especially for metal ethanoates titrated against perchloric acid.
- **Alcohols (Methanol, Ethanol):** Amphiprotic solvents used for both polar and non-polar reactants. They should be free from water.
- **Dimethylformamide (DMF):** A protophilic solvent used for weak acids.

Levelling Effect

The **levelling effect** refers to the phenomenon where the acidity of weak acids (or basicity of weak bases) can be significantly enhanced in the presence of an appropriate solvent.

- A **basic solvent** (protophilic) with a high affinity for protons can cause a weak acid to dissociate completely, making it behave like a strong acid. For example, acetic acid acts as a strong acid in a basic solvent like ammonia.
- Similarly, an **acidic solvent** (protogenic) can cause a weak base to fully accept protons, making it behave like a strong base.

This effect allows for sharp end points in titrations of weak acids and bases that would otherwise be difficult to titrate in water. However, it also means that all acids (or bases) stronger than the conjugate acid (or base) of the solvent will appear to have the same strength.

Differentiating Solvents: These are solvents that do not exhibit a levelling effect. They allow for different degrees of dissociation for various acids or bases, making it possible to distinguish between their strengths. For example, glacial acetic acid can act as a differentiating solvent for bases, as it allows for incomplete dissociation of strong bases, unlike water which would level them.

Acidimetry and Alkalimetry in Non-Aqueous Titration

These are the two main types of non-aqueous titrations:

1. Acidimetry (Non-Aqueous):

- **Purpose:** Quantitative determination of **weak bases**.

- **Principle:** A weak basic sample is dissolved in a **protogenic (acidic) solvent** (like glacial acetic acid) to enhance its basicity. It is then titrated with a **strong acid titrant** (like perchloric acid, $HClO_4$).
- **Samples:** Basic drugs such as Ephedrine, Adrenaline, Caffeine, Acyclovir.
- **Titrant:** Perchloric acid ($HClO_4$).
- **Indicator:** Crystal violet (color change: violet to yellowish-green).

2. Alkalimetry (Non-Aqueous):

- **Purpose:** Quantitative determination of **weak acids**.
- **Principle:** A weak acidic sample is dissolved in a **protophilic (basic) solvent** (like DMF or pyridine) to enhance its acidity. It is then titrated with a **strong base titrant** (like sodium methoxide).
- **Samples:** Acidic drugs such as Nalidixic acid, Fluorouracil, Acetazolamide.
- **Titrant:** Sodium methoxide (CH_3ONa).
- **Indicator:** Thymol blue (color change: pink to blue).

Non-Aqueous Indicators

Indicators used in non-aqueous titrations must also be compatible with the non-aqueous solvent system and show a clear colour change at the equivalence point.

Common Non-Aqueous Indicators:

Indicator	Colour in Acidic Solution	Colour in Alkaline Solution	pH range (approx)
Crystal Violet	Bluish-Green	Violet	0.0-1.0
Methyl Red	Red	Yellow	4.2-6.3
Naphthol Benzein	Yellow	Green	
Quinaldine Red	Purple-Red	Pale-Green	1.4-3.2
Thymol Blue	Pink	Blue	8.0-9.6

- **Crystal Violet:** Used extensively for titrations with perchloric acid. Changes from violet to greenish-yellow.
- **Methyl Red:** Changes from yellow in alkaline medium to red in acidic medium.
- **Naphthol Benzein:** Changes from yellow in alkaline medium to green in acidic medium, useful for titrating weak bases with perchloric acid in nitromethane.
- **Thymol Blue:** Changes from pink in acidic medium to blue in alkaline medium.

Estimation of Sodium Benzoate

Principle: The assay (estimation) of Sodium Benzoate (a weak acid salt) is based on a non-aqueous acid-base titration method. Sodium benzoate reacts with perchloric acid. $C_6H_5COONa + HClO_4 \rightarrow C_6H_5COOH + NaClO_4$

Preparation of Reagents:

- **Preparation of 0.1 N Perchloric Acid ($HClO_4$):**
  - Gradually mix 8.5 mL of perchloric acid to 900 mL of glacial acetic acid with vigorous and continuous stirring.
  - Add 30 mL of acetic anhydride and make up the volume to 1 litre with glacial acetic acid.
  - Allow to stand for 24 hours before use to ensure complete reaction of acetic anhydride with any water present.
  - The normality of $HClO_4$ should be accurately determined.

Procedure:

1. Accurately weigh about 0.25 g of sodium benzoate (analyte/titrand).
2. Dissolve the weighed sample in 20 mL of glacial acetic acid in a conical flask. Warm the solution if necessary to ensure complete dissolution, then cool.
3. Add 2-3 drops of Crystal Violet indicator.
4. Titrate this solution against the standardised 0.1 N perchloric acid (titrant) from a burette.
5. The end point is reached when the colour changes to **bluish-green**.
6. A blank titration (without the sample) is also carried out to minimise errors.

Calculation of Purity: Purity (%) = (Volume of $HClO_4$ x Normality of $HClO_4$ x 0.01441 x 100) / (Weight of Sodium Benzoate in grams x Expected Normality of $HClO_4$) Where 0.01441 g is the weight of sodium benzoate equivalent to 1 mL of 0.1 N $HClO_4$ (Molecular weight of Sodium Benzoate = 149.12 g/mol, so 0.01491 if for 0.1N).

Estimation of Ephedrine HCl

Principle: The assay of Ephedrine HCl (a weak base salt) is also based on a non-aqueous acid-base titration method. Ephedrine HCl reacts with perchloric acid. The weak base (Ephedrine) is protonated in the presence of glacial acetic acid and then reacts with perchloric acid. $HClO_4 + CH_3COOH \rightleftharpoons CH_3COOH_2^+ + ClO_4^-$ (Onium ion formation) $C_{10}H_{15}NO + CH_3COOH \rightleftharpoons C_{10}H_{15}N^+HO + CH_3COO^-$ (Protonated Ephedrine) $CH_3COOH_2^+ + CH_3COO^- \rightleftharpoons 2CH_3COOH$

Preparation of Reagents:

- **Preparation of 0.1 N Perchloric Acid ($HClO_4$):** (Same as for Sodium Benzoate estimation)
  - Mix 8.5 mL of perchloric acid with 900 mL of glacial acetic acid, add 30 mL of acetic anhydride, and make up to 1 litre with glacial acetic acid. Let stand for 24 hours.

Procedure:

1. Accurately weigh about 0.5 g of Ephedrine HCl (analyte/titrand).
2. Dissolve the weighed sample in 25 mL of glacial acetic acid in a conical flask. Add 10 mL of mercuric acetate solution and shake well.
3. Add 2-3 drops of Crystal Violet indicator.
4. Titrate this solution against the standardised 0.1 N perchloric acid (titrant).
5. The end point is reached when the colour changes to **bluish-green** (or light green).

Calculation of Purity: Purity (%) = (Volume of $HClO_4$ x Normality of $HClO_4$ x 0.02017 x 100) / (Weight of Ephedrine HCl in grams) Where 0.02017 g is the weight of Ephedrine HCl equivalent to 1 mL of 0.1 N $HClO_4$.

📌 Frequently Asked Questions (FAQs) on Pharmaceutical Analysis

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1. What is acid-base titration and its underlying principle?

Acid-base titration (neutralisation titration) is a **quantitative analytical technique** used to determine the unknown concentration of an acid or base.

- **Principle:** Based on a **neutralisation reaction** between an acid and a base → forms salt + water.
- A **titrant** (known concentration) is added from a burette to a **titrand/analyte** (unknown concentration) until the reaction is complete.
- **Endpoint:** Shown by a colour change due to an indicator.
- Features: Reaction is **fast, stoichiometric, and goes to completion**.

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2. How are acid-base indicators classified and what theories explain their function?

Indicators are weak organic acids or bases that change colour near the endpoint.

Theories of indicator action:

- 🔹 **Ostwald's Theory:** Indicators exist in **unionised** and **ionised** forms, each having different colours.
    - Example: **Phenolphthalein** – colourless in acidic (unionised), pink in basic (ionised).
- 🔹 **Quinonoid (Resonance) Theory:** Indicators show colour due to equilibrium between **Benzenoid** (acidic, colourless) and **Quinonoid** (basic, coloured) forms.
    - Example: **Phenolphthalein** – colourless in acid, pink in base.

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3. What are the types of acid-base titrations based on acid and base strength?

Acid-base titrations are classified into **four types**:

1. **Strong Acid vs Strong Base**
    - Equivalence at **pH 7**

- Sharp pH change
- Indicators: **Phenolphthalein, Methyl Orange, Bromothymol Blue**

2. **Weak Acid vs Strong Base**
   - Equivalence at **pH > 7** (basic)
   - Indicator: **Phenolphthalein**
3. **Strong Acid vs Weak Base**
   - Equivalence at **pH < 7** (acidic)
   - Indicators: **Methyl Red, Bromocresol Green**
4. **Weak Acid vs Weak Base**
   - Very small pH inflection near equivalence
   - Difficult to detect endpoint
   - Mixed indicators used

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4. What is the role of solvents in acid-base titrations, particularly non-aqueous titrations?

Role of solvents: Dissolve analytes & allow reactions to occur.

- **Aqueous titrations:** Use water (amphiprotic).
- **Non-aqueous titrations:** Used when analytes are:
  - Insoluble in water
  - Too weak to react in water
  - Reactive with water

Types of solvents:

- Protogenic → acidic, donate protons (e.g., glacial acetic acid)
- Protophilic → basic, accept protons (e.g., pyridine, DMF)

- Amphiprotic → act as both acid & base (e.g., water, ethanol)
- Aprotic → neutral, neither donate nor accept protons (e.g., hexane, CCl_4)

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5. What is the "levelling effect" of solvents in non-aqueous titrations?

The **levelling effect** explains how solvents **enhance the apparent strength of acids or bases**:

- Protophilic solvents make **weak acids** behave like strong acids.
- Protogenic solvents make **weak bases** behave like strong bases.

👉 This effect provides **sharper endpoints** in titrations of weak acids/bases.

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6. What are Acidimetry and Alkalimetry in non-aqueous titrations?

- **Acidimetry (Non-aqueous):**
  - Used to estimate **weak bases** (e.g., Ephedrine, Adrenaline).
  - Titrant: **Perchloric acid ($HClO_4$)** in glacial acetic acid.
  - Indicator: **Crystal Violet** (violet → greenish-yellow).
- **Alkalimetry (Non-aqueous):**
  - Used to estimate **weak acids** (e.g., Nalidixic acid, Acetazolamide).
  - Titrant: **Sodium methoxide (CH_3ONa)** in DMF.
  - Indicators: **Thymol Blue, Thymolphthalein** (colourless → pink or pink → blue).

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7. How is the purity of Sodium Benzoate & Ephedrine HCl estimated using non-aqueous titration?

- **Sodium Benzoate (weak base):**
  - Solvent: Glacial acetic acid
  - Titrant: 0.1N $HClO_4$

- Indicator: Crystal Violet (endpoint: violet → light green)
- Purity formula:

$$\% \text{ Purity } = \frac{\text{Vol. } HClO_4 \times \text{Normality} \times 0.01441 \times 100}{\text{Weight of sample (g)} \times 0.1}$$

- **Ephedrine HCl (weak base):**
  - Solvent: Glacial acetic acid + mercuric acetate
  - Titrant: 0.1N $HClO_4$
  - Indicator: Crystal Violet (endpoint: blue → bluish-green)
  - Purity formula:

$$\% \text{ Purity } = \frac{\text{Vol. } HClO_4 \times \text{Normality} \times 0.02017 \times 100}{\text{Weight of sample (g)} \times 0.1}$$

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8. What is a buffer solution and how does the Henderson-Hasselbalch equation relate?

Buffer solution: A solution of **weak acid + conjugate base** or **weak base + conjugate acid** that resists pH changes.

- **Equation:**

$$pH = pKa + \log\left(\frac{[A^-]}{[HA]}\right)$$

- For basic buffers:

$$pOH = pKb + \log\left(\frac{[Salt]}{[Base]}\right)$$

- Buffers work best when **pH ≈ pKa** and acid/base ratio ≈ 1:1.

👉 These **FAQs on Pharmaceutical Analysis Notes** will help students preparing for **1st semester exams** and **GPAT revision**.

📖 Glossary of Key Terms in Pharmaceutical Analysis

Understanding key terms is essential for mastering **Pharmaceutical Analysis Notes**. Below is a glossary of important concepts related to **acid-base titrations** and **non-aqueous titrations**.

🔹 General Titration Terms

- **Acid-Base Titration (Neutralisation Titration):** A quantitative method to determine the concentration of an acid or base by reacting it with a titrant of known concentration.
- **Titrant:** A solution of known concentration, usually added from a burette, to react with the analyte.
- **Titrand (Analyte):** The solution of unknown concentration placed in a conical flask for analysis.
- **Indicator:** A substance added to the titrand that changes colour near the equivalence point, signalling completion of the titration.
- **End Point:** The stage where the indicator changes colour, visually approximating the equivalence point.
- **Equivalence Point:** The theoretical point where the number of moles of titrant and analyte are chemically equivalent.
- **Neutralisation Curve:** A graph showing the change in pH during an acid-base titration (pH vs. volume of titrant).

🔹 Theories of Acids and Bases

- **Arrhenius Theory:** Acids produce H^+ ions, and bases produce OH^- ions in aqueous solution.
- **Brønsted-Lowry Theory:** Acids donate protons (H^+), and bases accept protons, independent of solvent.
- **Lewis Theory:** Acids accept electron pairs, and bases donate electron pairs.

Chemical Principles

- **Law of Mass Action:** The rate of reaction is proportional to the active masses (concentrations) of reactants, each raised to its stoichiometric coefficient.
- **Buffer Solution:** A solution that resists changes in pH, typically made of a weak acid and its conjugate base or vice versa.
- **Hydrolysis of Salts:** Reaction of salts with water to produce acidic, basic, or neutral solutions.
- **Henderson-Hasselbalch Equation:** Relates pH (or pOH) of a buffer to pKa (or pKb) and the ratio of concentrations of acid/base forms.
- **Common Ion Effect:** Suppression of ionisation of a weak electrolyte when a strong electrolyte with a common ion is present.

Non-Aqueous Titration Terms

- **Non-Aqueous Titration:** A titration carried out in solvents other than water, used for substances insoluble or unstable in water.
- **Protogenic Solvents:** Acidic solvents that donate protons (e.g., glacial acetic acid).
- **Protophilic Solvents:** Basic solvents that accept protons (e.g., pyridine, DMF).
- **Aprotic Solvents:** Neutral solvents that neither donate nor accept protons (e.g., hexane, CCl_4).
- **Amphiprotic Solvents:** Solvents acting as both acid and base (e.g., water, ethanol).
- **Levelling Effect:** A solvent property that makes all strong acids or bases appear equally strong due to complete dissociation.
- **Acidimetry:** Determination of weak bases using a strong acid titrant in non-aqueous media.
- **Alkalimetry:** Determination of weak acids using a strong base titrant in non-aqueous media.

Common Titrants & Indicators

- **Perchloric Acid ($HClO_4$):** A strong acid used in non-aqueous acidimetry.

- **Sodium Methoxide (CH_3ONa):** A strong base used in non-aqueous alkalimetry.
- **Crystal Violet:** An indicator used in non-aqueous titrations, showing a violet to greenish-yellow colour change.

👉 This **glossary of key terms** is particularly helpful for **Pharmaceutical Analysis 1st Semester Notes PDF** and for revising quickly before exams like **GPAT**.