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# PHARMACEUTICAL INORGANIC & ANALYTICAL CHEMISTRY

(STRICTLY ACCORDING TO SYLLABUS APPROVED BY PCI FOR B.PHARM COURSE)

For B.PHARM
1st Sem

SHREE SAI PRAKASHAN

UNIT I

Chapter 1

# Introduction to Pharmaceutical Analysis

## INTRODUCTION

### What is Chemistry?

- *Chemistry is known as the central of science*
- *"It is a branch of physical science that studies the composition, structure, properties and changes of matter".*

### Branches of Chemistry

➢ **Physical Chemistry**

- *It is the branch of chemistry concerned with the application of the techniques and theories of physics to the study of chemical systems.*
- *Branches: chemical Kinetics, Electrochemistry, spectroscopy, photochemistry.*

➢ **Inorganic Chemistry**

- *It deals with the synthesis and behaviour of inorganic and organometallic compounds*
- ***Branches :** Bioinorganic, Cluster, Material & Nuclear Chemistry.*

➢ **Organic Chemistry**

- *To study of the structure, properties, and reactions of **organic** compounds and **organic** materials, i.e., matter in its various forms that contain carbon atoms.*
- ***Branches :** Biochemistry, biophysical, Bioorganic, Pharmaceutical, and Medicinal Chemistry.*

## Introduction to Pharmaceutical Analysis

Pharmaceutical analysis is concerned with separation, identification, and determination of the relative amount of the components. It is concerned with chemical characterization. It is used to determine purity commerce safety and quality of drugs.

**It is of 2 type** - Qualitative and Quantitative

**Qualitative analysis** - It is a method of determination of what substance or constituent in an unknown sample called qualitative analysis. At primary level by reaction analysis with reagent yield colour boiling point melting point solubilities refractive index at advanced level for industrial technique.

**Quantitative analysis** - It is a method to determine the quantity of the substance or constituent.

Pharmaceutical analysis is a branch of practical chemistry that deals with the qualitative identification, quantitative determination, separation, purification, and structural characterization of pharmaceutical substances. It encompasses a wide range of physical, chemical, and instrumental techniques used to ensure that drugs and pharmaceutical products meet established standards of identity, purity, potency, safety, and quality.

## Techniques of Pharmaceutical Analysis

| | **Pharmaceutical Analysis**<br>Techniques of analysis | |
|---|---|---|
| | ↓ | |

| **Classical Methods**<br>Chemical / wet techniques | | **Instrumental Methods**<br>Physical-property based |
|---|---|---|

## Classical Methods

| **Titrimetric Analysis**<br>Quantifies an analyte by measuring the volume of a standard reagent needed to reach the end point of a reaction. | | **Gravimetric Analysis**<br>Quantifies an analyte by isolating it as a pure solid (precipitate or residue), drying it, and recording its mass. |
|---|---|---|

## Instrumental Methods

| **Spectroscopic**<br>Light–matter interaction | | **Chromatographic**<br>Separation techniques | | **Electroanalytical**<br>Electrical-property based |
|---|---|---|---|---|

## Spectroscopic Techniques

| | | |
|---|---|---|
| **UV–Visible Spectroscopy**<br>Measures absorption of UV or visible light by a drug solution; used for assay and purity testing. | **Infrared (IR) Spectroscopy**<br>Detects molecular vibrations from IR absorption; used for identification of functional groups. | **Fluorimetry**<br>Measures fluorescence emitted after excitation; highly sensitive for trace-level drug analysis. |
| | | |
| **NMR Spectroscopy**<br>Uses radio-frequency response of nuclei in a magnetic field to elucidate molecular structure. | **Mass Spectrometry**<br>Ionises molecules and sorts ions by mass-to-charge ratio; gives molecular weight and fragments. | **Atomic Absorption (AAS)**<br>Measures light absorbed by free atoms in a flame; used for trace metal estimation in drugs. |

## Chromatographic Techniques

| | |
|---|---|
| **Thin-Layer Chromatography (TLC)**<br>Components separate on a coated plate as a mobile phase rises by capillarity; used for purity and identity checks. | **High-Performance Liquid Chromatography (HPLC)**<br>Liquid mobile phase pumped at high pressure through a packed column; principal technique for drug assay. |
| | |
| **Gas Chromatography (GC)**<br>Volatile analytes carried by an inert gas through a column; used for residual solvents and volatile drugs. | **High-Performance TLC (HPTLC)**<br>Refined TLC with finer sorbent and densitometric scanning for faster, more accurate quantitative results. |

## Electroanalytical Techniques

| | | |
|---|---|---|
| **Potentiometry**<br>Measures potential of an indicator electrode against a reference at near-zero current to find concentration. | **Conductometry**<br>Measures electrical conductance of a solution; commonly used to track ionic changes during a titration. | **Polarography**<br>Records current–voltage curves at a dropping-mercury electrode; quantifies reducible drug species. |

## Scope and Importance

The principal aim of pharmaceutical analysis is to safeguard public health by ensuring that medicines are safe and effective. Analytical methods are used to verify the identity of raw materials, monitor in-process intermediates, evaluate the strength and uniformity of finished products, detect impurities and degradation products, and assess stability under varying storage conditions. Regulatory authorities such as the Indian Pharmacopoeia (IP), United States Pharmacopeia (USP), British Pharmacopoeia (BP), and the International Council for Harmonisation (ICH) prescribe official analytical procedures that must be followed by the pharmaceutical industry to obtain marketing authorization.

## Scope of Pharmaceutical Analysis

Pharmaceutical analysis is a multidisciplinary science that underpins every stage of drug research, development, manufacture, and clinical use. Its scope extends far beyond simple chemical testing and embraces the qualitative, quantitative, and structural evaluation of pharmaceutical substances and products. The principal areas in which pharmaceutical analysis is applied are summarised below.

### 1. Identification and Purity Testing

Confirms the identity of raw materials, active pharmaceutical ingredients (APIs), and excipients, and detects impurities such as related substances, residual solvents, heavy metals, and degradation products as per IP, BP, USP, and ICH guidelines.

### 2. Quantitative Assay of Drugs

Determines the strength or potency of an API in bulk drugs and in finished dosage forms (tablets, capsules, injections, syrups, ointments) to ensure that the labelled claim of the medicine is accurate.

### 3. Quality Control and Quality Assurance

Provides analytical support for in-process control, finished-product release, and batch-to-batch consistency, helping the industry comply with current Good Manufacturing Practices (cGMP) and regulatory standards.

### 4. Stability and Shelf-life Studies

Monitors changes in drug content, appearance, and impurity profile under varying conditions of temperature, humidity, and light, enabling the assignment of expiry date and recommended storage conditions.

### 5. Research, Development, and Formulation

Supports drug discovery, structure elucidation of new molecules, pre-formulation studies, dissolution testing, and the development of validated analytical methods using techniques such as UV, IR, HPLC, GC, NMR, and mass spectrometry.

### 6. Biopharmaceutical and Clinical Analysis

Quantifies drugs and metabolites in biological fluids (blood, plasma, urine) for pharmacokinetic, bioavailability, bioequivalence, and therapeutic drug monitoring studies, and supports forensic and toxicological investigations.

### 7. Detection of Counterfeit and Substandard Drugs

Helps regulatory authorities identify spurious, adulterated, or substandard medicines circulating in the market, thereby protecting public health and reinforcing pharmacovigilance.

**In summary,** the scope of pharmaceutical analysis encompasses the entire life-cycle of a medicine—from raw material to patient—integrating chemistry, instrumentation, statistics, and regulatory science to ensure that every dose delivered is safe, effective, and of reliable quality.

## Methods of Expressing Strength of Solutions

The **strength (or concentration) of a solution** represents the quantity of solute dissolved in a definite quantity of solvent or solution. In pharmaceutical analysis, accurate expression of concentration is fundamental for the preparation of standard solutions, volumetric titrations, dilutions, dosage calculations, and the formulation of dosage forms. Several methods are employed, each suited to a particular type of analytical or pharmaceutical operation.

### 1. Percentage Strength

Percentage expresses the parts of solute present in 100 parts of solution. It is the most commonly used method in pharmacopoeial formulations. There are four forms recognised by the Indian Pharmacopoeia :

**(a) % w/w (weight in weight) :** grams of solute per 100 g of solution.it is used for ointments and semi-solid preparations.

**(b) % w/v (weight in volume) :** grams of solute per 100 mL of solution. It is used for solutions of solids in liquids (e.g., dextrose injection).

**(c) % v/v (volume in volume) :** millilitres of solute per 100 mL of solution. It is used for liquid-in-liquid preparations (e.g., alcohol mixtures).

**(d) % v/w (volume in weight) :** millilitres of solute per 100 g of solution. It is used rarely, for liquids dispersed in solids.

## 2. Molarity (M)

Molarity is the number of moles of solute dissolved per litre of solution. It is widely used in volumetric analysis because it directly relates to stoichiometric calculations.

$$\text{Molarity (M)} = \frac{\text{Weight of solute} \times 1000}{\text{Molecular weight} \times \text{Volume of solution in mL}}$$

Molarity changes slightly with temperature because the volume of the solution expands or contracts on heating or cooling.

## 3. Molality (m)

Molality is the number of moles of solute per kilogram of solvent. Because it is based on the mass of the solvent rather than the volume of the solution, molality is independent of temperature and is preferred in physico-chemical studies involving boiling-point elevation, freezing-point depression, and osmotic pressure.

$$\text{Molality (m)} = \frac{\text{Moles of solute}}{\text{Mass of solvent in kg}}$$

## 4. Normality (N)

Normality represents the number of gram-equivalents of solute per litre of solution. It is the classical method of expressing concentration in titrimetric analysis (acid–base, redox, precipitation, and complexometric titrations).

$$\text{Normality (N)} = \frac{\text{Weight of solute time 1000}}{\text{Equivalent weight} \times \text{Volume in mL}}$$

The relation $\mathbf{N_1V_1 = N_2V_2}$ is used in dilution and titration calculations.

## 5. Formality (F)

Formality is the number of gram-formula weights of solute per litre of solution. It is used for ionic compounds (e.g., NaCl) where the actual molecular species in solution differs from the chemical formula. For non-ionic substances, formality and molarity are numerically equal.

## 6. Mole Fraction (X)

Mole fraction is the ratio of the number of moles of one component to the total number of moles of all components in the solution. It is dimensionless and the sum of mole fractions of all components equals one.

$$X_a = n_a / (n_a + n_e);\ X_a + X_e = 1$$

## 7. Parts per Million (ppm) and Parts per Billion (ppb)

Used to express extremely low (trace) concentrations such as impurities, heavy metals, and residual solvents in drugs. **1 ppm = 1 mg per litre or 1 mg per kg;** ppb is one thousand times smaller. These units are routinely encountered in pharmacopoeial limit tests and environmental analyses.

## 8. Milliequivalent (mEq/L)

A milliequivalent is one-thousandth of a gram-equivalent. The unit mEq/L is widely used in clinical pharmacy and parenteral preparations to express the concentration of electrolytes (e.g., $Na^+$, $K^+$, $Ca^{2+}$, $Cl^-$) in body fluids and intravenous fluids.

## Summary

| Method | Symbol / Unit | Definition |
|---|---|---|
| **Percentage** | % w/w, % w/v, % v/v, % v/w | Parts of solute per 100 parts of solution. |
| **Molarity** | M (mol/L) | Moles of solute per litre of solution. |
| **Molality** | m (mol/kg) | Moles of solute per kilogram of solvent. |
| **Normality** | N (eq/L) | Gram-equivalents of solute per litre of solution. |
| **Formality** | F (formula wt/L) | Gram-formula weights of solute per litre of solution. |
| **Mole fraction** | X (dimensionless) | Ratio of moles of one component to total moles in the solution. |
| **Parts per million / billion** | ppm, ppb | Parts of solute per 106 or 10? parts of solution; used for trace amounts. |
| **Milliequivalent** | mEq/L | Thousandth of a gram-equivalent per litre; common in clinical practice. |

# PRIMARY AND SECONDARY STANDARDS

**Standard Solution :** A standard solution is a solution whose concentration is accurately known.

**Standards are of two types :**

1. Primary Standard
2. Secondary Standard

**1. Primary Standard :** A primary standard is a highly pure, stable, non-hygroscopic substance that can be weighed directly to prepare a standard solution of exact concentration.

## Characteristics of Primary Standards :

- High purity
- Stable in air
- Non-hygroscopic (does not absorb moisture)
- High molecular weight
- Easily soluble in solvent
- Reacts completely in chemical reactions

## Examples of Primary Standards

| Compound | Use |
|---|---|
| Sodium carbonate ($Na_2CO_3$) | Standardization of acids |
| Oxalic acid ($H_2C_2O_4 \cdot 2H_2O$) | Standardization of $KMnO_4$ |
| Potassium dichromate ($K_2Cr_2O_7$) | Oxidation reactions |
| Potassium hydrogen phthalate (KHP) | Standardization of NaOH |
| Borax ($Na_2B_4O_7 \cdot 10H_2O$) | Acid-base titration |

**2. Secondary Standard :** Asecondary standard is a substance whose concentration cannot be prepared accurately by direct weighing and therefore must be standardized using a primary standard.

## Characteristics of Secondary Standards

- Less pure
- Hygroscopic or unstable
- Concentration changes on storage
- Requires frequent standardization

## Examples of Secondary Standards

| Compound | Standardized Against |
|---|---|
| Hydrochloric acid (HCl) | Sodium carbonate |
| Sodium hydroxide (NaOH) | Potassium hydrogen phthalate |
| Potassium permanganate ($KMnO_4$) | Oxalic acid |
| Silver nitrate ($AgNO_3$) | Sodium chloride |
| Sodium thiosulfate ($Na_2S_2O_3$) | Potassium dichromate |

**Difference Between Primary and Secondary Standards**

| Primary Standard | Secondary Standard |
|---|---|
| Highly pure | Less pure |
| Stable | Unstable |
| Non-hygroscopic | Hygroscopic |
| Prepared directly by weighing | Requires standardization |
| Concentration remains constant | Concentration may change |
| Used to standardize other solutions | Used after standardization |

**Example :**

**Primary Standard Example :** Oxalic acid is accurately weighed and dissolved to prepare a standard solution.

**Secondary Standard Example :** $KMnO_4$ solution cannot be prepared accurately directly, so it is standardized using oxalic acid.

## Errors

Analytical chemistry is based on reliability, reproducibility, and accuracy. However, every measurement has some degree of uncertainty called **error.**

**Error may be defined as a deviation from the absolute value or from the true average of a large number of results.** Error is the difference between the experimental value and true value.

The goal of an analytical chemist is to minimize these errors to get the true value or nearest to the true value.

## Types of Errors

(I) Systemic / Determinate / Constant Errors

(II) Random / Indeterminate Errors

**(I) Systemic Errors :** Errors that can be avoided or whose magnitude can be determined are called systemic errors.These errors may be high or low but remain constant.This type of error goes in one direction.

### Causes of Systemic Errors

1. Errors in calibration
2. Operation of measuring instruments
3. Impurities in reagents
4. Biased personal errors:

- Pouring and mixing
- Weighing operation
- Matching colours
- Making calculations/manipulations

**Types of Systemic Errors :** Four type of systemic errors are there -

**1. Operational & Personal Errors :** Errors for which the individual analyst (person) is responsible and are not connected with the method or procedure are called personal errors.

**Examples :**

- Unable to judge colour during titration or chemical tests
- Copying wrong information

These Errors occurring during operation or while following procedure is known as operational error.

**Examples :**

- Transfer of solution
- Incomplete drying
- Underweighing of precipitate
- Overweighing of precipitate
- These errors are physical in nature and occur when the analytical technique is not followed properly.

**2. Instrumental & Reagent Errors :** These errors occur because of instruments or due to reagents having impurities.

**Examples :**

- Uncalibrated burette, pipette, and flask
- Impurities present in reagents may interfere with results

**3. Errors of Method :** These errors occur because of the method or procedure and such type of errors are difficult to correct.

**Examples :**

- In gravimetric analysis, errors occur due to -
  - Insolubility of precipitates
  - Co-precipitation
  - Decomposition
- There may be loss of analyte during sample preparation by volatilization or precipitation.
- These errors occur due to :
  - Failure of reaction

- Side reactions
- Difference between observed endpoint and stoichiometric/equivalence point.

**4. Additive or Proportional Errors :** Additive errordoes not depend on the constituent present.

**Example :**

- Loss in weight of crucible after precipitate ignition.
- These errors are revealed by taking samples of different weights.

**Proportional Errors :** Depend on the amount of constituent.

**Example :**

- Impurities in standard compounds leading to incorrect values for normality or molarity of standard solution.

**(II) Random (Indeterminate) Errors :** Errors occurring accidentally or randomly. Also called random, indeterminate, or accidental errors. The analyst has no control over these errors. They follow random distribution and mathematical laws of probability can be applied.

**Sources of Indeterminate Errors :**

- Limitation of reading balances
- Electrical noise in instruments

**Example :**

- If a balance can measure only up to 0.01 g and you weigh 0.016 g, the value must be rounded.

**Methods of Minimizing Errors :** Only systemic errors can be minimized or reduced.

**1. Calibration of Apparatus :** Calibrate all instruments before use :

- Balance
- Spectrometer
- Burette, etc.

**2. Control Determination :** Standard substances should be used in experiments. Standard materials should be carefully analyzed from National Bureau of Standards.

**3. Blank Determination :** Performed to minimize errors caused by impurities present in vessels or reagents. Blank titration is carried out without sample.

**4. Independent Method of Analysis :** Used to maintain accuracy. Example - Iron(III) determined gravimetrically by precipitation method and titrimetrically by reduction to Iron(II).

**5. Parallel Determination :** Instead of single determination, duplicate or triplicate determinations are carried out to minimize accidental errors.

**Example :**

- HCl used to standardize NaOH solution.
- Precipitation and weighing as silver chloride.

**6. Standard Addition Method :** Generally applied to physicochemical procedures such as :

  - Polarography
  - Spectrophotometry

- It is a type of quantitative analysis where standard is directly added to the analyzed sample.

**7. Internal Standards :** Used in spectroscopic and chromatographic determinations.

**8. Amplification Method :** Used when a very small amount of material is to be measured or analyzed.

**9. Isotopic Dilution :** Used for radioactive isotopes.

**ACCURACY :** Accuracy means degree of closeness between true value and determined value.

*"Accuracy can be defined as concordance between the data and the true or most probable value".* It is how close a measured value is actual.

It measures correctness and closeness of result by comparing it to absolute value. Accuracy denotes agreement of mean experimental value with true value. The difference between mean and true value is called absolute error.

**Methods of Determining Accuracy**

1. Absolute Method
2. Comparative Method

**Absolute Method :** Based on evaluation of concentration/amount using fundamental physical constants or universal quantities.

**Comparative Method :** Involves use of secondary standards.

**PRECISION–[Repeatedly of true value] :** Precision means closeness of repeated measurements to each other.

*"Precision can be defined as concordance of a series of measurements of the same quantity".* The mean or relative mean deviation is a measure of precision.

- Precision represents :
  - Uniformity
  - Repeatability

- Reproducibility

- Precision is usually reported as :
  - Average deviation
  - Standard deviation
  - Range

## Precision Measures

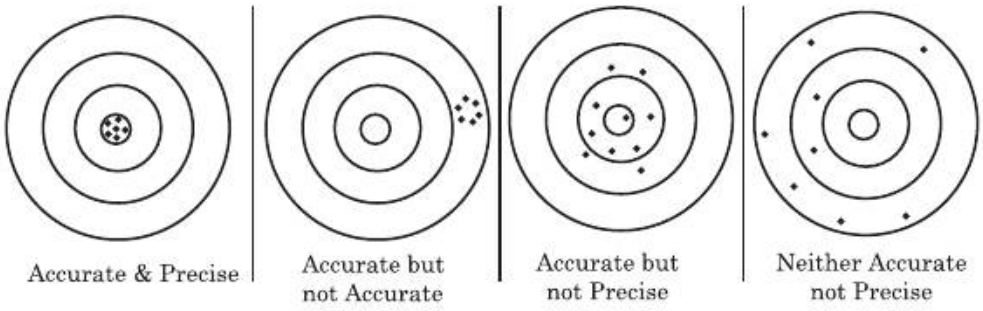
**1. Ruggedness Test :** Degree of reproducibility of test results obtained under different conditions such as :

- Different laboratories
- Different analysts
- Different instruments
- Different time and assay conditions
- Temperature and pressure variations

**2. Mean :** Obtained by adding results of various measurements and dividing by number of measurements.

**3. Median :** Value about which all others are equally distributed.

## Accuracy vs Precision




- Both accuracy and precision should be the goal of any measurement.
- Precision measures agreement among values in a group of data, whereas accuracy measures agreement between data and true value.

## Significant Figures

Accuracy and precision are very important in analytical chemistry.

**Significant Figure :** Number of digits in a figure that express precision of measurement instead of magnitude or "Digits expressing measurement where only the last digit is uncertain are called significant figures."

**Atlantic-Pacific Rule (APR) :** Used to determine significant digits.

## Rule

- If decimal point is absent, zeros on the right side are insignificant.
- If decimal point is present, zeros on the left side are significant.

**General Rules for Significant Figures :**

**1. All Non-Zero Digits are Significant :** Example1234 has 4 significant figures.

**2. Zeros are Significant with Exceptions**

**(a) Leading Zeros :** Zeros before non-zero digits are not significant. Example 0.0042 has 2 significant figures.

**(b) Embedded Zeros :** Zeros between non-zero digits are significant. Example 205.07 has 5 significant figures.

**(c) Trailing Zeros :** Zeros after decimal point are significant.Example2.500 has 4 significant figures.

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