Program	B. Pharmacy
Semester	1st
Subject /Course	Pharmaceutical Inorganic and Analytical Chemistry
Subject/Course ID	Pharmaceutical Inorganic and Analytical Chemistry/BP106T
Module No.	01
Module Title	Introduction to pharmaceutical analysis, Errors, Impurities
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LO	Particular
1.	To explain the basic concept of pharmaceutical analysis, methods of expressing concentrations of solutions and role of primary and secondary standards.
2.	To differentiate between various types of sources of errors and how to minimize them.
3.	To Interpret concept of accuracy, precision and significant figures in calculations and analytical measurements.
4.	Describe and perform identification of pharmaceutical impurities limit test according to pharmaceutical standards.

Module Content Table

Sr. no.	Topic
1.	**Introduction to pharmaceutical analysis** Different techniques of analysis, Methods of expressing strength of solutions, Primary and secondary standards with examples
2.	**Errors** Sources of errors, types of errors, methods of minimizing errors, accuracy, precision and significant figures.
3.	**Impurities** Definition, types, contents and regulatory importance. Sources and types of impurities in Pharmaceuticals, limit tests for chloride, sulphate, iron, arsenic, lead, heavy metals, and modified limit test for chloride and sulphate.

Introduction to Pharmaceutical analysis

Pharmaceutical analysis is a branch of practical chemistry that involves a series of process for identification, determination, quantification and purification of a substance, separation of the components of a solution or mixture, or determination of structure of chemical compounds.

The substance may be a single compound or a mixture of compounds and it may be in any of the dosage form. The substance used as pharmaceuticals are animals, plants, microorganisms, minerals and various synthetic products.

The different pharmaceutical agents are as follows:

- Plants
- Microorganisms
- Minerals
- Synthetic compounds

Pharmaceutical analysis is traditionally defined as analytical chemistry dealing with drugs both as bulk drug substances and as pharmaceutical products (formulations). However, in academia, as well as in the pharmaceutical industry, other branches of analytical chemistry are also involved, *viz.* bioanalytical chemistry, drug metabolism studies and analytical biotechnology. The development of drugs in the pharmaceutical industry is a long-term process, often taking more than a decade from the start of a research project to the appearance of a drug on the market. That process involves several decision points, such as the choice of the candidate drug after the preclinical screening phase, the investigational new drug (IND) application before testing the compound for the first time in man, and finally the new drug application (NDA) which summarizes the data obtained from all the studies needed for marketing approval of the drug as a medicine. In all these steps, especially the IND and NDA, the amount of data generated is enormous. Analytical chemists take part in many of the studies that constitute this documentation. Substance quality and its specifications are based on substance analysis, and that knowledge is later used for quality control during full-scale production. Product analysis involves dealing with the various formulations and starts after the IND has been approved. The results from such work lead to specifications that form the basis for the quality control of the product. For both substances and formulations there is an increasing interest in the introduction of process analytical chemistry.

The sample to be analysed is called as analyse.

- Quality control and quality assurance

- Chromatographic techniques
- Quantitative and qualitative analysis
- Validation methods
- Stoichiometry between reactants & products

Scope of Pharmaceutical Analysis

Quality control: People specialized in pharmaceutical analysis are indispensable to the manufacturing, quality control and analytical manifestations of the industry. They ensure the quality of raw materials, intermediate and final products. They can work in quality control department which oversees the purity, qualitative aspects and the matching of the stringent regulatory limits required by a finished product.

Research: Research and development have huge implications on the results of the analysis and detection of new compounds. More and more companies are stressing on a separate analytical R&D department.

Identification of compounds: To detect the presence or absence of one or more components present in the drug.

Determination of impurities: To determine the amount of impurities or foreign particle present in the compound.

Diagnosis: Different disease can be diagnosed by pharmaceutical analysis techniques like HIV is diagnosed by ELISA.

Food industry: Different kind of preservatives, coloring, flavoring and sweetening agents are used in packed food which can be natural or synthetic chemical ingredients so these would be analyze qualitatively and quantitatively.

Types of Pharmaceutical Analysis:

Pharmaceutical analysis is a branch of pharmaceutical science that deals with the identification, determination, separation, and quantification of chemical substances used in medicines and pharmaceutical formulations. It includes the study of analytical methods used to ensure the quality, purity, safety, and efficacy of drugs and pharmaceutical products.

Pharmaceutical analysis plays an important role in drug development, manufacturing, quality control, and regulatory compliance.

Based upon the determination type, there are mainly two types of analytical methods. They are as follows:

1. Qualitative analysis

2. Quantitative analysis

1. Qualitative analysis: - This method is used for the identification of the chemical compounds. Qualitative analysis is performed to establish composition of natural/synthetic substances. These tests are performed to indicate whether the substance or compound is present in the sample or not. Various qualitative method tests are detection of evolved gas, formation of precipitates, limit tests, colour change reactions, melting point and boiling point test etc.

2. Quantitative analysis: - This method is used for the determination of the amount of the sample. Quantitative analytical techniques are mainly used to quantify any compound or substance in the sample. There are various methods to find out the quantity of a substance in a product like:

a. the quantitative performance of suitable chemical reaction and either measuring the amount of reagent added to complete the reaction or measuring the amount of reaction product obtained,

b. the characteristic movement of a substance through a defined medium under controlled conditions

Various types of Qualitative analysis:

1. Chemical methods

- volumetric or titrimetric methods
- gravimetric methods
- gasometric analysis

2. Electrical methods

3. Instrumental methods

4. Biological and microbiological

1. Chemical methods

a) Titrimetric or volumetric method: It involves reaction of substance to be determined with an appropriate reagent as a standard solution, and volume of solution required to complete the reaction is determined. Volumetric methods require simple and less apparatus and they are susceptible of high accuracy. Various types of titrimetric methods are:

i)Acid-base titrations (neutralization reactions)

ii)Complexometric titrations

iii)Precipitation titrations

iv)Oxidation reduction titrations

v)Non aqueous titrations

b) Gravimetric methods: In gravimetric analysis, a substance to be determined is converted into an insoluble precipitate in the purest form, which is then collected and weighed. It is the time-consuming process. In electrogravimetry, electrolysis of the sample is carried out on the electrodes is weighed after drying. Thermogravimetry (TG) records the change in weight, differential thermal analysis (DTA) records the difference in temperature between test substance and an inert reference material, differential scanning calorimetry (DSC) records the energy needed to establish a zero-temperature difference between a test substance and reference material.

c) **Gasometric analysis:** Gasometry involves measurement of the volume of gas evolved or absorbed in a chemical reaction. Some of the gases which are analysed by Gasometry are CO_2, N_2O, cyclopropane, amyl nitrate, ethylene, N_2, helium etc.

2. Electrical methods: Electrical methods of analysis involve the measurement of electric current, voltage or resistance in relation to the concentration of some species in the solution. Electrical methods of analysis include:

Potentiometry: Potentiometry measures electrical potential of an electrode in equilibrium with an ion to be determined.

Conductometry: Conductometry measures electrical conductivity of an electrode with a reference electrode

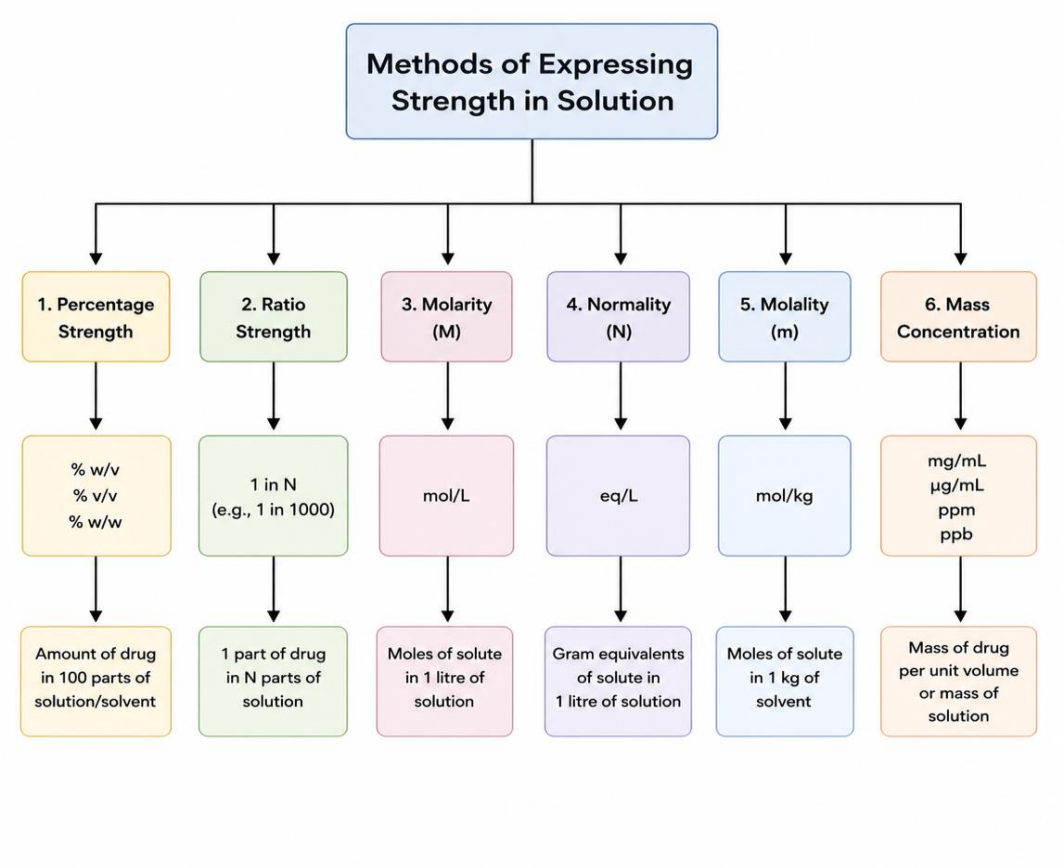
Polarography: Measures electrical current at a microelectrode.

3. Instrumental methods of analysis: Instrumental method involves measurement of some physical properties of the compound or a substance. These methods are employed for determination of minor or trace concentration of element in the sample. Instrumental methods are preferred due to their selectivity, high speed, accuracy and simplicity of analysis. Any change in the properties of the system are detected by measurement of absorbance, specific rotation, refractive index, migration difference, charge to mass ratio etc.

Methods which include absorption of radiation are ultra violet, visible, infra-red, atomic absorption, nuclear magnetic resonance spectroscopy and chromatographic techniques are GC, HPLC, TLC, HPTLC etc.

4. Biological and microbiological methods: Biological methods are used when potency of a drug or its derivative cannot be properly determined by any physical or chemical methods. They are called bio-assays. Microbiological methods are used to observe potency of antibiotic or anti- microbial agents. In antimicrobial assay, inhibition of growth of bacteria of the sample is compared with that of the standard antibiotic. These methods include cup plate method and turbidimetric analysis.

Methods of Expressing Strength In Solution



In pharmaceutical analysis, the strength of a solution means the amount of solute (drug/substance) present in a given amount of solvent or solution or Concentration of solution is the amount of solute dissolved in a known amount of the solvent or solution. Different methods are used to express concentration depending on the type of analysis and accuracy required.

1. Percentage: It refers to the amount of the solute per 100 parts of the solution. It can also be called as parts per hundred (pph). It can be expressed by any of following four methods:

Weight to weight percent % w/w = Wt. of solute/ Wt. of solution x 10

Weight to volume percent % w/v = Wt. of solute/volume of solution x 100

Volume to Volume percent % v/v = Volume of solute/volume of solution x 100

Example: 5% w/v glucose = 5 g glucose in 100 mL solution.

2. Parts per million (ppm) and parts per billion (ppb): When a solute is present in trace quantities, it is convenient to express the concentration in parts per million and parts per billion. It is the number of parts of solute per million (10^1) or per billion (10^9) parts of the solution. It is independent of the temperature.

Ppm = mass of solute component/Total mass of solution x 10^1

PPb = Mass of solute component/ Total mass of solution x 10^9

3. Normality: It is defined as the number of gram equivalents (equivalent weight in grams) of a solute present per litre of the solution. Unit of normality is gram equivalents litre^{-1}. Normality changes with temperature since it involves volume. When a solution is diluted times, its normality also decreases by times. Solutions in term of normality generally expressed as,

Normality= Gram equivalent of solute/Volume of solution

(* 1 equivalent = 1000 mill equivalent or meq.)

(N = Normal solution; 5N = Penta normal, 10N = Deca normal; N/2 = semi normal N/10 = Deci normal; N/5 = Penta normal N/100 or 0.01N = cent normal, N/1000 or 0.001 = milli normal)

4. Molarity: The number of moles of solute per liter of solution OR the molar concentration of a solution usually expressed as the number of moles of solute per liter of solution. Solutions labelled with the molar concentration are denoted with a capital M.

Molarity (M) = Mole of solute/ Volume of solution in litres

5. Molality: The number of moles of solute per kilogram of solvent. It is important the mass

of solvent is used and not the mass of the solution. Solutions labelled with molal concentration are denoted with a lower-case m.

$$m = \text{Mass of solvent in kg} / \text{Moles of solute}$$

6. Mass Concentration: It expresses the mass of solute present per unit volume of solution.

Common units:

- mg/mL
- µg/mL
- ppm
- ppb

Primary and Secondary Standards

A standard substance is a pure and stable compound used for the preparation or standardization of solutions in analytical chemistry.

Analytical chemistry deals with the identification, separation, and quantitative determination of chemical substances. For accurate chemical analysis, solutions of known concentration are required. These solutions are prepared using highly pure chemicals called standard substances. Standard substances play a very important role in volumetric analysis, titration, pharmaceutical analysis, quality control testing, and laboratory research. They help in determining the exact concentration of unknown solutions accurately and precisely.

A standard substance is a chemical substance having definite composition, high purity, and stability, which is used for the preparation or standardization of a standard solution. These substances ensure reliability and accuracy in analytical procedures.

In volumetric analysis, a solution of known concentration is allowed to react with a solution of unknown concentration. The accuracy of this analysis mainly depends upon the quality and purity of the standard substance used.

An ideal standard substance should possess the following properties:

- It should be highly pure.

- It should be chemically stable.
- It should not absorb moisture from air.
- It should not react with atmospheric gases.
- It should have high molecular weight.
- It should be easily soluble in suitable solvent.
- It should react completely according to the chemical equation.

Depending upon their purity and method of use, standard substances are classified into two main types:

1. **Primary Standard Substances**
2. **Secondary Standard Substances**

1. Primary Standard Substances: A primary standard substance is a highly pure, stable, non-hygroscopic chemical substance that can be weighed directly to prepare a solution of accurately known concentration. Primary standards are used for the preparation of standard solutions and for the standardization of secondary standard solutions.

Primary standard should have following properties:

(a) Extremely pure: A primary standard material should be extremely pure which means that it should be a chemical of high grade of purity, preferably 99.98%. In a pharmaceutical analysis laboratory, we come across chemicals of different grade of purity. Presence of impurities changes the actual weight of active substance. This leads to inaccurate concentration and analytical errors

(b) Highly stable: It should be highly stable which means it usually does not react easily when kept in its pure form or it should have very low reactivity. This is important because if a reagent reacts easily with atmospheric oxygen or water or changes its property over time then it is unreliable and such as unstable and unreliable chemicals can never be used as standard.

(c) Anhydrous: It should be anhydrous which means that it does not contain any water molecule in its molecular structure. For example, in a pharmaceutical analysis laboratory we come across same chemical with different number of water molecules attached with it e.g. magnesium sulphate ($MgSO_4$), which is also called Epsom salt. The Epsom salt which is found

in drug store is a chemical with formula MgSO4.7H2O. Therefore, if we want to prepare a primary standard of magnesium sulphate, anhydrous MgSO4 preferably an analytical reagent.

(d) Non-Hygroscopic: The chemical preferably should be less hygroscopic i.e. on opening the container it should not absorb water molecules from atmosphere. Moisture absorption increases the weight of substance and produces weighing errors. Sodium hydroxide absorbs moisture and therefore cannot be used as a primary standard.

(e) Solubility: The substance should dissolve completely in water or suitable solvent. Solubility prevents incomplete reaction and produces homogeneous solution. For eg. Oxalic acid dissolves easily in water. Undissolved particles do not participate completely in reaction, causing titration error.

(f) Chemical Stability: The chemical composition should remain constant during storage and use. It ensures concentration remains unchanged over long time. For eg. Benzoic acid is chemically stable. Unstable substances decompose slowly and alter the concentration of solution.

Examples of primary standards:

1. Sodium carbonate

- **Chemical Formula:** Na_2CO_3
- **Type of Titration:** Acid-base titration
- **Used For:** Standardization of Hydrochloric acid and Sulfuric acid
- **Characteristics:** Highly pure, stable, non-hygroscopic, high molecular weight

Reaction:

$Na_2CO_3 + 2HCl \rightarrow 2NaCl + H_2O + CO_2$

2. Oxalic acid

- **Chemical Formula:** $H_2C_2O_4 \cdot 2H_2O$
- **Type of Titration:** Redox titration
- **Used For:** Standardization of Potassium permanganate
- **Characteristics:** Pure crystalline form, stable, easily soluble in water

Reaction:

$2KMnO_4 + 5H_2C_2O_4 + 3H_2SO_4 \rightarrow K_2SO_4 + 2MnSO_4 + 10CO_2 + 8H_2O_2$

3. Potassium dichromate

- **Chemical Formula:** $K_2Cr_2O_7$
- **Type of Titration:** Redox titration
- **Used For:** Standardization of reducing agents and ferrous salts
- **Characteristics:** Highly stable, pure, non-hygroscopic, high molecular weight

Reaction:

$K_2Cr_2O_7 + 6Fe^{2+} + 14H^+ \rightarrow 2Cr^{3+} + 6Fe^{3+} + 7H_2O$

4. Benzoic acid

- **Chemical Formula:** C_6H_5COOH
- **Type of Titration:** Acid-base titration
- **Used For:** Standardization of Sodium hydroxide
- **Characteristics:** Stable, pure crystalline solid, non-hygroscopic

5. Arsenic trioxide

- **Chemical Formula:** As_2O_3
- **Type of Titration:** Redox titration
- **Used For:** Standardization of Iodine solution
- **Characteristics:** High purity, stable composition

6. Sodium oxalate

- **Chemical Formula:** $Na_2C_2O_4$
- **Type of Titration:** Redox titration
- **Used For:** Standardization of Potassium permanganate
- **Characteristics:** Stable, pure, non-hygroscopic

7. Potassium hydrogen phthalate (KHP)

- **Chemical Formula:** $KHC_8H_4O_4$
- **Type of Titration:** Acid-base titration
- **Used For:** Standardization of Sodium hydroxide
- **Characteristics:** Stable, high molecular weight, available in pure form

Secondary Standard Substances

Secondary standards are substances whose solutions cannot be prepared accurately by direct weighing because they lack one or more properties of primary standards.

A secondary standard is involved in preparation of reagents and kits or laboratories responsible for producing quality control material for other laboratories. They use primary standard as the primary calibrator or primary reference material. Secondary standard is used for the purpose of calibration of control material in laboratory for analysis of unknown concentration of a substance. So basically, secondary standard serves the purpose of external quality control for laboratories. So, it is essential that the secondary standard must first be standardized against the primary standard. For preparation of secondary standard solution, aqueous solution must be of high-grade purity. It must be deionized, if water is used as aqueous solvent.

A secondary standard is a chemical or reagent which has certain properties such as:

(a) The purity of secondary standard is less than primary standard

(b) Secondary standard is less stable and more reactive than primary standard

(c) The secondary standard solution remains stable for a long time

(d) Secondary standard is titrated against primary standard

Example: **1. Anhydrous sodium hydroxide (NaOH):** It is extremely hygroscopic. On opening the container NaOH absorbs moisture from atmosphere and it becomes moist. There is gradual increase in molecular weight of NaOH after absorbing the moisture.

2. Potassium permanganate (KMnO4): Very often used as secondary standard. It is a good oxidizing agent, that's why reactive and hence less stable. Its own oxidized product manganese oxide (MnO2) contaminates the content.

Examples of secondary standards used for titrations:

1. Hydrochloric acid

- **Chemical Formula:** HCl
- **Type of Titration:** Acid-base titration
- **Standardized Against:** Sodium carbonate
- **Characteristic:** It is Volatile and concentration changes on storage.

2. Sodium hydroxide

- **Chemical Formula:** NaOH
- **Type of Titration:** Acid-base titration
- **Standardized Against:** Oxalic acid or Potassium hydrogen phthalate
- **Characteristic:** Hygroscopic and absorbs carbon dioxide from air.

3. Potassium permanganate

- **Chemical Formula:** $KMnO_4$
- **Type of Titration:** Redox titration
- **Standardized Against:** Oxalic acid or Sodium oxalate
- **Characteristic:** Decomposes slowly during storage and may contain impurities.

4. Silver nitrate

- **Chemical Formula:** $AgNO_3$
- **Type of Titration:** Precipitation titration
- **Standardized Against:** Sodium chloride
- **Characteristic:** Decomposes in light and may lose stability.

ERRORS

Error is the difference between the true result (or accepted true result) and the measured result. If the error in an analysis is large, serious consequences may result. As reliability, reproducibility and accuracy are the basis of analytical chemistry.

$$\text{Error} = \text{Observed value} - \text{True value}$$

Errors may occur due to limitations of instruments, personal mistakes, environmental conditions, or chemical methods used during analysis.

CLASSIFICATION OF ERRORS

The numerous uncertainties usually encountered in a chemical analysis give rise to a host of 'errors' that may be broadly categorized into *two* heads, namely:

1. Determinate (systematic) Errors, and
2. Indeterminate (random) Errors.

1. Determinate Errors

Determinate errors are the errors that occur in a definite direction and have identifiable causes. These errors are also called systematic errors because they occur repeatedly in the same manner during an experiment. They may either increase or decrease the analytical result consistently.

Characteristics of Determinate Errors

- Occur in a definite direction
- Reproducible
- Have known causes
- Can be detected and corrected
- Affect accuracy of analysis

The most important errors belonging to this particular class are:

1. Personal errors: Personal errors occur because of mistakes or carelessness on the part of the analyst during analysis. These errors may arise from incorrect observation of the meniscus, parallax error while reading measurements, improper handling of apparatus, or incorrect interpretation of colour change at the endpoint of titration. Personal errors can be minimized by careful observation and proper laboratory techniques.

2. Method errors: Method errors arise due to limitations or imperfections in the analytical procedure or chemical method used. These errors may occur because of incomplete chemical reactions, side reactions, instability of reaction products, or improper indicator selection. Method errors affect the accuracy of the analysis and are often difficult to eliminate completely.

3. Reagent errors: Reagent errors occur due to impurities present in reagents, chemicals, or solvents used during analysis. Contaminated distilled water, impure chemicals, or incorrectly prepared solutions may produce inaccurate analytical results. The use of high-purity reagents and proper storage conditions helps in minimizing reagent errors.

4. Instrumental Errors: These are invariably caused due to faulty and uncalibrated instruments, such as: pH meters, single pan electric balances, uv-spectrophotometers, potentiometers etc.

5. Environmental errors: Environmental errors are caused by surrounding laboratory conditions that affect analytical measurements. Factors such as temperature changes, humidity, dust particles, air currents, vibrations, and exposure to light may influence experimental results. Sensitive instruments and chemicals are especially affected by environmental conditions. Maintaining controlled laboratory conditions helps reduce these errors.

6. Additive Errors: It has been observed that the additive errors are independent of the quantum of the substances actually present in the assay.

Examples: (*i*) Errors caused due to weights,

(*ii*) Loss in weight of a crucible in which a precipitate is incenerated.

2. INDETERMINATE (RANDOM) ERRORS

As the name suggests, indeterminate errors cannot be pin-pointed to any specific well-defined reasons. They are usually manifested due to the minute variations which take place inadvertently in several successive measurements performed by the same analyst, using utmost care, under almost identical experimental parameters. These errors are mostly random in nature and ultimately give rise to high as well as low results with equal probability. They can neither be corrected nor eliminated, and therefore, form the **'ultimate limitation'** on the specific measurements. It has been observed that by performing repeated measurement of the same

variable, the subsequent statistical treatment of the results would have a positive impact of **'reducing their importance'** to a considerable extent.

Indeterminate errors are random errors that occur due to uncontrollable variations in experimental conditions. These errors do not occur in a fixed direction and may either increase or decrease the analytical result randomly. Indeterminate errors mainly affect the precision of analytical results and cannot be completely eliminated, although they can be minimized.

The different sources and explanations of indeterminate errors are given below:

1. Temperature Variations: Small fluctuations in laboratory temperature may affect the volume, density, solubility, and reaction rate of chemicals during analysis. Expansion or contraction of liquids due to temperature changes can cause slight variations in measurements. Sensitive analytical instruments may also respond differently at different temperatures.

2. Humidity Variations: Changes in atmospheric humidity can affect hygroscopic substances and sensitive weighing procedures. Some chemicals absorb moisture from air, causing slight increases in weight and producing random variations in analytical results.

3. Air Currents: Air movement inside the laboratory can affect analytical balances and other sensitive instruments. Even slight air currents may cause fluctuations in balance readings and influence precise measurements during weighing.

4. Electrical Fluctuations: Minor changes in electrical supply may affect electronic instruments such as pH meters, spectrophotometers, and digital balances. These fluctuations may produce slight random variations in readings.

5. Mechanical Vibrations: Vibrations from nearby equipment, movement of people, or laboratory machinery can disturb sensitive instruments and weighing balances. This may result in small unpredictable variations in measurements.

6. Observational Variations: Indeterminate errors may arise due to small unavoidable differences in observation by the analyst. Slight variation in judging colour change at the endpoint, reading the meniscus, or recording measurements can cause random errors.

7. Instrument Sensitivity Limitations: Every analytical instrument has a limited sensitivity and precision. Small fluctuations in readings occur naturally due to limitations in the measuring capability of instruments.

8. Minor Variations in Sample Handling: Small unavoidable differences during pipetting, transfer of solutions, washing of apparatus, or mixing of solutions may produce random variations in analytical results.

Characteristics of Indeterminate Errors

- Occur randomly and unpredictably
- Have no fixed direction
- May increase or decrease results
- Usually small in magnitude
- Affect precision rather than accuracy
- Cannot be completely eliminated

Sources of Errors:

In the process of measurement, the errors are bound to occur. If the sources of errors are known, then the efforts can be made to reduce the errors and partly to eliminate them. The various possible sources of errors are:

- Faculty design of instrument which directly leads to the serious measurement errors.
- Due to insufficient knowledge of the quantity to be measured and design conditions can cause error.
- For the instrument frequent maintenance is necessary. If such maintenance is not done then error may occur.
- If there are irregularities in quantity to be measured or sudden change in the parameters to be measured then error may exist.
- The unskilled operator of the instrument can cause serious error.
- The certain limitations while designing the instrument can cause error.
- Loading effect i.e. improper way of using instrument can cause error (weighing).

- The effects of environmental condition, temperature changes also can cause the errors. Proper care taken considering the sources of errors can help to reduce the percentage of errors and to improve the accuracy of measurement.

Methods of Minimizing Errors

Errors are unavoidable in pharmaceutical and analytical work, but they can be minimized by following proper procedures, maintaining instruments carefully, and performing experiments with accuracy and precision. Minimizing errors is important to obtain reliable, accurate, and reproducible results. Different methods are used to reduce determinate (systematic) and indeterminate (random) errors during analysis.

1. Proper Calibration of Instruments

Analytical instruments such as balances, burettes, pipettes, pH meters, spectrophotometers, and thermometers should be calibrated regularly. Calibration ensures that the instrument gives correct readings according to standard values. Uncalibrated instruments may produce systematic errors and lead to inaccurate results. Before starting an experiment, instruments should be checked with standard reference materials.

2. Use of Standard and Pure Reagents

Impure chemicals and contaminated reagents can introduce significant errors in analysis. Therefore, analytical grade reagents and standard solutions should always be used. Solutions should be prepared carefully using accurate weighing and measuring techniques. Freshly prepared reagents help in avoiding decomposition-related errors.

3. Correct Sampling Techniques

A sample should represent the entire bulk material properly. Improper sampling can produce inaccurate results even if the analytical method is correct. Clean and dry containers should be used for sample collection, and contamination must be avoided during handling and storage.

4. Maintaining Proper Environmental Conditions

Environmental factors such as temperature, humidity, pressure, dust, and vibrations may affect analytical measurements. For example, temperature changes can alter solution volume and

instrument sensitivity. Experiments should therefore be performed under controlled laboratory conditions to reduce environmental errors.

5. Careful Observation and Handling

Human carelessness is a major source of experimental errors. Errors can be minimized by careful reading of measurements, proper handling of apparatus, and following the procedure accurately. The analyst should avoid parallax error while reading burettes and measuring cylinders by taking readings at eye level.

6. Repetition of Experiments

Performing experiments repeatedly helps in minimizing random errors. Multiple observations are taken and the average value is calculated to obtain more reliable results. Repetition increases precision and helps identify abnormal readings or outliers.

7. Proper Cleaning of Apparatus

Dirty glassware and instruments can contaminate samples and affect results. All apparatus should be cleaned thoroughly before and after use. Burettes, pipettes, and flasks should be rinsed with distilled water and sometimes with the solution to be used in the experiment.

8. Following Standard Operating Procedures (SOPs)

Standard Operating Procedures provide step-by-step instructions for performing analytical work. Following SOPs ensures uniformity and reduces operational mistakes. Proper documentation and adherence to laboratory guidelines help in maintaining accuracy and reproducibility.

9. Training and Skill Development of Analysts

Well-trained analysts are less likely to make operational mistakes. Proper knowledge of analytical techniques, instrument handling, and safety procedures helps in minimizing personal errors. Regular training programs improve laboratory efficiency and analytical performance.

10. Use of Blank and Control Experiments

Blank experiments are performed without the analyte to detect impurities or interference from reagents and apparatus. Control experiments using standard samples help in comparing and validating results. These methods help identify hidden systematic errors.

11. Proper Storage of Chemicals and Samples

Chemicals and samples should be stored under recommended conditions to prevent decomposition, evaporation, or contamination. Exposure to moisture, heat, or light may alter the composition of chemicals and affect analytical results.

12. Regular Maintenance of Instruments

Routine servicing and maintenance of instruments help ensure smooth functioning and accurate measurements. Worn-out parts, leakage, or damaged components should be repaired or replaced immediately to avoid instrumental errors.

Minimization of errors is essential in pharmaceutical and analytical chemistry to obtain accurate and dependable results. Errors can be reduced by proper calibration, careful handling, maintaining controlled conditions, repeating experiments, and following standard procedures. Although errors cannot be completely eliminated, systematic efforts and good laboratory practices greatly improve the accuracy, precision, and reliability of analytical work.

Accuracy, Precision, and Significant Figures

Accurate and precise measurements are essential in pharmaceutical and analytical chemistry because the quality and reliability of analytical results depend upon them. During experiments, measurements are expressed using significant figures to indicate the degree of certainty in the observed values. Accuracy, precision, and significant figures together help in evaluating the reliability and quality of analytical data.

Accuracy

Accuracy refers to the closeness of an experimental value to the true or accepted value. It indicates how correct a measurement is. An analytical method is said to be accurate if it produces results very close to the actual value. Accuracy mainly depends on the absence of

systematic or determinate errors. If systematic errors are present, the measured value deviates from the true value, reducing accuracy.

The accuracy of a determination may be defined as the concordance between the data and the true or most probable value. The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

Factors Affecting Accuracy

- Faulty instrument calibration
- Impure reagents
- Incorrect analytical methods
- Personal errors in observation
- Environmental conditions

Methods to Improve Accuracy

- Use of standard reagents
- Following standard procedures
- Performing blank and control experiments
- Proper calibration of instrument

Expression of Accuracy: Accuracy is often expressed in terms of absolute error and relative error.

Absolute Error: It is the difference between the experimental value and the true value.

$$\text{Absolute Error} = \text{Measured Value} - \text{True Value}$$

Relative Error: It is the ratio of absolute error to the true value.

$$\text{Relative Error} = \text{Absolute Error}/\text{True Value} \times 100$$

For Analytical methods these two are possible ways of determining the accuracy. They are:

1. Absolute method **2. Comparative method**

1. Absolute method: In the absolute method, the accuracy of an analytical method is determined by comparing the obtained experimental result directly with the true or standard value. This method does not require comparison with another analytical procedure. A standard reference material or a sample with known concentration is analyzed, and the obtained result is compared with the actual value. The difference between the measured value and the true

value indicates the accuracy of the method. If the experimental result is very close to the true value, the method is considered accurate.

Example: Suppose the actual concentration of a drug sample is 100 mg/mL and the experimental analysis gives a result of 99.8 mg/mL. Since the obtained value is very close to the true value, the method shows high accuracy.

Advantages of Absolute Method

- Simple and direct method
- Easy interpretation of results
- Does not require another analytical method for comparison
- Useful when standard reference materials are available

Limitations of Absolute Method

- True value may not always be available
- Requires pure standard substances
- Difficult to apply for complex samples

2. Comparative method: In the comparative method, the accuracy of a new analytical method is determined by comparing its results with those obtained from a well-established or official standard method. The same sample is analyzed by both methods, and the results are compared statistically. If both methods give nearly similar results, the new method is considered accurate. This method is commonly used in pharmaceutical analysis when the true value of the sample is unknown.

Example: A newly developed spectrophotometric method for drug analysis is compared with an official pharmacopoeial titration method. If both methods provide nearly identical assay values, the new method is considered accurate.

Advantages of Comparative Method

- Useful when true value is unavailable
- Suitable for complex pharmaceutical samples
- Helps validate newly developed methods
- Widely used in method validation studies

Limitations of Comparative Method

- Requires a reliable reference or official method
- Comparison process may be time-consuming
- Errors in the reference method can affect results

Precision

Precision refers to the closeness of repeated measurements to one another under the same conditions. It indicates the reproducibility or consistency of results. Precision is related mainly to random or indeterminate errors. A method is considered precise when repeated measurements give nearly identical results, even if they are not close to the true value. **For example,** if four measurements of a sample give values 25.1 mL, 25.1 mL, 25.2 mL, and 25.1 mL, the results are highly precise because they are very close to one another.

Precision does not necessarily mean accuracy. Results may be precise but inaccurate if all measurements are consistently away from the true value due to systematic errors.

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

1. Repeatability: Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision. Repeatability should be assessed using:

a) a minimum of 9 determinations covering the specified range for the procedure (e.g., 3 concentrations/3 replicates each); or

b) a minimum of 6 determinations at 100% of the test concentration.

Precision obtained under the same operating conditions over a short time interval.

2. Intermediate precision: Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc. The extent to which intermediate precision should be established depends on the circumstances under which the procedure is

intended to be used. Typical variations to be studied include days, analysts, equipment, etc. It is not considered necessary to study these effects individually. The use of an experimental design (matrix) is encouraged.

Precision obtained within the same laboratory but under different conditions such as different analysts or instruments.

Reproducibility: Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology). Reproducibility is assessed by means of an inter-laboratory trial. Reproducibility should be considered in case of the standardization of an analytical procedure, for instance, for inclusion of procedures in pharmacopoeias.

Precision obtained between different laboratories using the same method.

Example for precision: if in a lab you obtain a weight measurement of 3.2 kg for a given substance, if you weigh a given substance five times, and get 3.2 kg each time, then your measurement is very precise. Precision is independent of accuracy. You can be very precise but inaccurate, as described above. You can also be accurate but imprecise.

Significant Figures

A number is an expression of a quantity. A figure of digit denotes any one of the ten numerals (0,1,2,3,4,5,6,7,8,9). A digit alone or in combination, serves to express a number. A simple way of indicating the probable uncertainty associated with an experimental measurement is to round the result.

A Significant Figure is a digit which denotes the amount of quantity in the place in which it stands. The digit zero is significant figure except when it is the first figure in a number.

Example: Thus, in the quantities 1.2680 gm and 1.0062 gm the zero is significant, but in the quantity 0.0025 kg the zeros are not significant figures; they serve only to locate the decimal point and can be omitted by proper choice of units.

Rules for deciding the number of significant figures in a measured quantity:

(1) All nonzero digits are significant:

1.234 g has 4 significant figures, 1.2 g has 2 significant figures.

(2) Zeroes between nonzero digits are significant:

1002 kg has 4 significant figures, 3.07 mL has 3 significant figures.

(3) Zeroes to the left of the first nonzero digits are not significant; such zeroes merely indicate the position of the decimal point:

0.001° C has only 1 significant figure, 0.012 g has 2 significant figures.

(4) Zeroes to the right of a decimal point in a number are significant:

0.023 mL has 2 significant figures, 0.200 g has 3 significant figures.

(5) When a number ends in zeroes that are not to the right of a decimal point, the zeroes are not necessarily significant: 190 miles may be 2 or 3 significant figures, 50,600 calories may be 3, 4, or 5 significant figures.

Rounding off Rules

When calculations produce more digits than required, rounding off is done according to these rules:

- If the digit to be dropped is less than 5, the previous digit remains unchanged.
- If the digit to be dropped is greater than 5, the previous digit increases by one.
- If the digit is exactly 5 followed by non-zero digits, increase the previous digit by one.

Example:

- 5.43 becomes 5.4
- 7.68 becomes 7.7

Importance of Significant Figures

- Indicate reliability of measurements
- Reflect instrument precision
- Avoid false accuracy
- Improve scientific reporting
- Ensure proper calculation and data interpretation

IMPURITIES

Impurities are unwanted chemicals or foreign materials present in pharmaceutical substances, active pharmaceutical ingredients (APIs), or finished pharmaceutical products. These substances may arise during manufacturing, storage, packaging, or degradation of the drug product. Even small amounts of impurities can affect the safety, efficacy, stability, and quality of pharmaceutical products. Therefore, identification, control, and regulation of impurities are essential parts of pharmaceutical analysis and quality assurance. The study of impurities is important in pharmaceutical chemistry because impurities may reduce therapeutic activity, produce toxic effects, or interfere with analytical procedures. Regulatory authorities have established strict guidelines for monitoring and controlling impurities in drugs.

Impurity is any unwanted substance present in desired substance in less than or near to 5% of desired substance, **e.g.** a pinch of sodium chloride present in 100mg of sugar is known as impurity.

Definition of Impurities: Impurities are any undesired substances present in a drug substance or pharmaceutical product other than the intended active ingredient or excipients.

According to pharmaceutical standards, impurities include:

- Starting materials
- By-products
- Degradation products
- Residual solvents
- Contaminants introduced during manufacturing or storage

Types of Impurities

1. Organic Impurities: Organic impurities arise during the manufacturing process or storage of drug substance i.e., starting material, byproducts, intermediates, degradation products, reagents, catalysts and enantiomeric impurities. Arise during synthesis, purification and storage of drug substances.

a. By Products: Side reactions occurring during synthesis may produce unwanted compounds called by-products. These compounds are different from the desired product and may remain as impurities.

For example, during oxidation or nitration reactions, unwanted side products may form due to uncontrolled reaction conditions. In synthetic chemistry getting a single and product with 100% yield is very rare as there is always a chance of some by-product with desired end product.

b. Starting Materials: Impurities may arise from raw materials used during synthesis. If the starting materials are impure or incompletely purified, traces may remain in the final product. For example, unreacted acids, alcohols, or amines used during synthesis may persist as impurities.

c. Intermediates: Intermediate compounds formed during multistep synthesis may remain in small amounts if the reaction is incomplete. Improper purification can lead to the presence of intermediates in the finished pharmaceutical product.

d. Reagents and Catalysts: Reagents, ligands, or catalysts used during chemical synthesis may react partially or remain unchanged in the final product. Organic reagents used for derivatization or purification may also contribute to impurities.

e. Degradation Products: Many drugs are chemically unstable and undergo decomposition during storage. Heat, moisture, oxygen, and light may produce degradation products that act as organic impurities.

For example: Aspirin hydrolyzes to salicylic acid, Adrenaline oxidizes during exposure to air, Vitamins may undergo photodegradation

2. Inorganic Impurities: Inorganic impurities are non-carbon-containing unwanted substances present in pharmaceutical products, active pharmaceutical ingredients (APIs), excipients, or intermediates. These impurities may arise during the manufacturing process, purification steps, storage, or handling of pharmaceutical substances. Inorganic impurities are generally derived from reagents, catalysts, filter aids, heavy metals, inorganic salts, water, or manufacturing equipment used during production.

a. Heavy Metal Impurities: Heavy metals are toxic metallic impurities that may enter pharmaceutical products from raw materials, catalysts, equipment, or environmental contamination. These metals are harmful even at low concentrations and may produce toxic

effects on the nervous system, liver, kidneys, and blood. **Examples:** Lead, Mercury, Cadmium, Arsenic

b. Residual Catalysts: Residual catalysts are metallic substances remaining after chemical synthesis. These impurities must be controlled because prolonged exposure may produce adverse health effects. **Examples:** Palladium, Platinum, Nickel

c. Inorganic Salts: Inorganic salts may remain after neutralization or purification processes. Excess amounts may affect drug stability and solubility. **Examples:** Sodium chloride, Calcium sulphate, Potassium nitrate

d. Other materials (e.g. filter aids, charcoal): Activated Carbon, Filters and filtering aids such as centrifuge bags are used in drug manufacturing, fibres and black particles in bulk drug manufacturing is essential to avoid.

3. Residual solvents: Solvents are organic volatile chemicals used during the manufacturing process or generated during the production. Residual solvents are classified into three classes **Class I Solvents:** Benzene (1-2 ppm), carbon tetrachloride (1-4 ppm) are avoided because of their carcinogenic and toxic effect

Class II Solvents: methyl chloride, methanol, pyridine, toluene, acetonitrile, Most commonly used

Class III Solvents: acetic acid, acetone, isopropyl alcohol, butanol, ethanol, ethyl acetate permitted daily exposure 50 mg or less per day.

4. Other Impurities

a) Excipient impurities: Excipients such as peroxide, aldehydes, heavy metals, alkaline residue may render as an impurity in final product.

b) Elemental impurities: Brought about as excipient impurities or during manufacturing as catalyst for oxidation and hydrolysis. Example As, Al, Ca, Na, Pb

5. Packing material: Leachable and extractable substances from primary packaging material form reaction products (impurities) with drug substances. Example: Alkaline oxide from glass (Na 2 CaO).

Sources of Impurities

Impurities are unwanted chemicals or foreign substances present in pharmaceutical substances or dosage forms. They may arise during manufacturing, storage, transportation, or handling of drugs. Impurities can affect the quality, stability, efficacy, and safety of pharmaceutical products. Therefore, identification and control of impurities are very important in pharmaceutical analysis. The major sources of impurities along with suitable chemical reactions are discussed below.

1. Impurities Arising from Raw Materials: Raw materials used in pharmaceutical manufacturing may contain impurities due to incomplete purification or contamination during production. Starting materials, intermediates, reagents, and solvents may carry impurities into the final product. For example, sodium chloride prepared from sea water may contain calcium and magnesium salts as impurities.

Example reaction: $CaCl_2 + Na_2CO_3 \rightarrow CaCO_3\downarrow + 2NaCl$

Here, calcium impurity can be removed by precipitation as calcium carbonate.

2. Impurities Due to Manufacturing Process: During synthesis, incomplete reactions or side reactions may produce unwanted by-products. Improper reaction conditions such as temperature, pH, or pressure may increase impurity formation.

Example: Preparation of aspirin from salicylic acid. If the reaction is incomplete, unreacted salicylic acid remains as an impurity in aspirin.

$$C_7H_6O_3 + (CH_3CO)_2O \rightarrow C_9H_8O_4 + CH_3COOH$$

3. Impurities Due to Reagents and Catalysts: Reagents and catalysts used during synthesis may remain in trace amounts in the final product if not removed completely. Metallic catalysts are especially important because of their toxicity.

Example: Hydrogenation reactions using nickel catalyst. Traces of nickel may remain as impurity in the product.

$$C_2H_4 + H_2 \rightarrow NiC_2H_6$$

4. Impurities Due to Residual Solvents: Organic solvents used during extraction, crystallization, or purification may remain in pharmaceutical products after processing. Residual solvents such as methanol, benzene, acetone, or chloroform are harmful above permissible limits.

5. Impurities Due to Water: Water used in manufacturing may contain dissolved salts, microorganisms, or pyrogens. Hard water may introduce calcium and magnesium impurities. Formation of magnesium hydroxide indicates magnesium impurity.

6. Impurities Due to Atmospheric Contamination: Exposure to air, oxygen, carbon dioxide, or moisture may cause degradation of drugs and formation of impurities. Example: Sodium hydroxide absorbs carbon dioxide from air. Thus, sodium carbonate becomes an impurity in sodium hydroxide.

7. Impurities Due to Cross-Contamination: Cross-contamination occurs when traces of one product mix with another product during manufacturing due to improper cleaning of equipment. Though chemical reactions may not always occur, contamination affects product purity and safety.

Example: Penicillin contamination in other antibiotics may cause allergic reactions.

8. Impurities Formed During Storage: Drugs may decompose during storage due to light, heat, moisture, or oxygen, producing degradation products. For example: Aspirin undergoes hydrolysis during storage, Adrenaline undergoes oxidation on exposure to air (the solution becomes pink or brown due to degradation products).

9. **Impurities Due to Containers and Closures:** Containers may react with pharmaceutical products and release contaminants. Alkali released from glass containers. The released alkali may alter pH and stability of preparations. Plastic containers may leach plasticizers and coloring agents into formulations.

10. Impurities Due to Microbial Contamination: Microorganisms may grow in pharmaceutical preparations and produce toxic substances. Fermentation of sugars by microorganisms: Such microbial decomposition spoils pharmaceutical preparations.

11. Impurities Due to Accidental Substitution or Adulteration: Human errors during labelling, weighing, or dispensing may introduce wrong chemicals into formulations. Deliberate adulteration may also reduce product quality. Example: Addition of cheaper substances to pharmaceutical materials for economic benefit.

12. Impurities Due to Transportation and Handling: Improper transportation conditions such as excessive heat, moisture, or sunlight may cause decomposition of drugs and formation of impurities. Vitamin C undergoes oxidation during improper storage.

Contents and Regulatory Importance of Identifying Impurities

Identification and control of impurities are extremely important in pharmaceutical industries because impurities directly affect drug quality and patient safety. Regulatory authorities require strict monitoring of impurities before approval of pharmaceutical products.

1. Ensures Drug Safety

Some impurities may be toxic, mutagenic, teratogenic, or carcinogenic. Even trace quantities of harmful impurities can produce adverse effects in patients. Identification of impurities helps in preventing harmful substances from reaching consumers. **For example:**

- Heavy metals can damage organs.
- Residual solvents may cause toxicity.
- Degradation products may produce allergic reactions.

2. Maintains Drug Efficacy

Impurities may interfere with therapeutic action of drugs and reduce their potency. Decomposition products formed during storage may lower drug effectiveness. **Example:** Hydrolysis of aspirin decreases the amount of active drug available for therapeutic action.

3. Improves Drug Stability

Identification of degradation impurities helps in understanding stability behavior of pharmaceutical products. Stability studies allow manufacturers to determine:

- Shelf life
- Storage conditions
- Packaging requirements

For example, oxidation-sensitive drugs are packed in airtight containers to minimize degradation.

4. Compliance with Regulatory Standards

Regulatory authorities require pharmaceutical manufacturers to identify, quantify, and control impurities according to specified limits. Compliance with these regulations is essential for approval and marketing of drugs. Major regulatory organizations include:

- International Council for Harmonisation
- United States Pharmacopeia
- Food and Drug Administration
- European Medicines Agency
- Central Drugs Standard Control Organization

5. Regulatory Guidelines for Impurities

The International Council for Harmonisation has established important guidelines for impurity control.

ICH Q3A: Deals with impurities in new drug substances.

ICH Q3B: Deals with impurities in new drug products.

ICH Q3C: Deals with residual solvents.

ICH Q3D: Deals with elemental impurities.

6. Supports Quality Assurance and Quality Control

Impurity profiling is an important part of pharmaceutical quality assurance (QA) and quality control (QC). It ensures that pharmaceutical products meet pharmacopeial standards and remain consistent from batch to batch. Analytical techniques commonly used include:

- Chromatography
- Spectroscopy
- Titrimetric
- Electrophoresis

7. Helps in Selection of Packaging and Storage Conditions

Knowledge of impurities and degradation pathways helps in choosing suitable packaging materials and storage conditions. Examples:

- Light-sensitive drugs are packed in amber-colored containers.
- Moisture-sensitive drugs are stored in airtight containers.
- Oxidation-sensitive drugs require inert atmosphere packaging.

8. Prevents Product Recalls and Legal Issues

Failure to control impurities can result in:

- Product recalls
- Regulatory action
- Loss of public trust
- Financial losses
- Legal penalties

Limit tests

Limit test is defined as quantitative or semi quantitative test designed to identify and control small quantities of impurity which is likely to be present in the substance. Limit test is generally carried out to determine the inorganic impurities present in compound. In short, limit test is nothing but to identify the impurities present in the substance and compare it with standard.

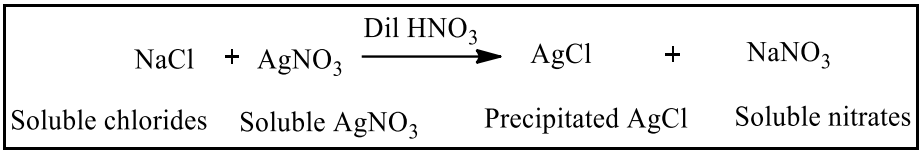
In Chemistry, Limit means a value or amount that is likely to be present in a substance and test means to examine or to investigate. Thus, limit test is nothing but to identify the impurities in the substance and compare it with standard. In general, limit test is defined as quantitative or semi quantitative test designed to identify and control small quantities of impurity which is likely to be present in the substance. Limit test is generally carried out to determine the inorganic impurities present in compound.

- Limit test of chloride is based on the reaction of soluble chloride with silver nitrate in presence of dilute nitric acid to form silver chloride, which appears as solid particles (Opalescence) in the solution.
- Limit test of sulphate is based on the reaction of soluble sulphate with barium chloride in presence of alcohol and potassium sulphate to form barium sulphate, which appears as solid particles (turbidity) in the solution. Here alcohol is added to prevent super saturation.
- Limit test of heavy metals is based on the reaction of metallic impurities with hydrogen sulfide in acidic medium to form colored solution. Metals that response to this test are lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum.
- Limit test of lead is based on the reaction of lead and diphenyl thiocarbazone (dithizone) in alkaline solution to form lead dithizone complex which is read in color. Limit test of Iron is based on the reaction of iron in ammonical solution with thioglycolic acid to form iron thioglycolate which is pink-reddish purple in color.
- Limit test of Arsenic is based on the reaction of arsenic gas with hydrogen ion to form yellow stain on mercuric chloride paper in presence of reducing agents like potassium iodide. It is also called as Gutzeit test and requires special apparatus.

The word Pharmacopoeia is derived from Greek words 'pharmakon' means a drug (both remedy and poison) and 'poiein' means to make or create. Pharmacopoeia is a book containing directions for the identification of samples and the preparation of compound medicines, and published by the authority of a government or a medical or pharmaceutical society. For this reason Pharmacopoeia is a legislation of a nation which sets standards and mandatory quality indices for drugs, raw materials used to prepare them and various pharmaceutical preparations.

Limit test for chloride:

Principle: Limit test for chloride is based on reaction of silver nitrate with soluble chlorides to form precipitate of silver chloride which is insoluble in dilute nitric acid. The extent of precipitate depends upon the amount of silver chloride formed or amount of chloride ions present in the substance. The opalescence produced is compared with standard opalescence from standard solution containing a fixed amount of chloride under same experimental conditions. The opalescence produced by test substance should be less intense than that of standard substance to pass the limit test for chloride.



Procedure: The are the apparatus required to perform limit test such as: Nessler cylinder, glass rod, beaker, dropper, volumetric flask, pipette etc.

For this we have to prepare test and standard solution both.

Test: It is that substance in which we have to identify the impurities.

Standard: Highly pure substance that meets the standards of pharmacopoeia

S. No.	Standard	Test
1.	1ml of 0.0824% *w/v* solution of NaCl is taken in Nessler's Cylinder	Dissolve specific quantity of substances as per I.P monograph in 10 ml of distilled Water
2.	Add 10 ml of Dil. Nitric Acid	Add 10 ml of Dil. Nitric Acid
3.	Make up the volume upto 50 ml with distilled water	Make up the volume upto 50 ml with distilled water
4.	Now add 1 ml of silver nitrate to this solution	Now add 1 ml of silver nitrate to this solution
5.	Stir the solution with glass rod and allow to stand for 5 minutes	Stir the solution with glass rod and allow to stand for 5 minutes

Observation: The opalescence produce in sample solution should not be greater than standard solution. If opalescence produces in sample solution is less than the standard solution, the sample will pass the limit test of chloride and vica-versa.

Role of dilute nitric acid: Nitric acid is added in the limit test of chloride to make solution acidic and helps silver chloride precipitate out and to make solution turbid at the end of process.

Limit test for Sulphate:

Principle: Limit test of sulphate is based on the reaction of soluble sulphate with barium chloride in presence of dilute hydrochloric acid to form barium sulphate which appears as solid particles (turbidity) in the solution. Test solution may contain small amount of potassium sulphate, which increases the sensitivity of test. Any sulphate ion impurity in test substance will produce barium sulphate in excess of already dissolved amount, causing turbidity. To prevent supersaturation of barium sulphate, which may occur, small amount of ethanol is added. The opalescence produced by test substance should be less intense than that of standard substance to pass the limit test for chloride.

$$BaCl_2 + Na_2SO_4 \longrightarrow BaSO_4 + 2NaCl$$

white ppt.

Procedure:

S. No.	Test Solution	Standard Solution
1.	Take 1 ml of Barium Chloride solution (25% w/v) in Nessler Cylinder	Take 1 ml of Barium Chloride solution (25% w/v) in Nessler Cylinder
2.	Now add 1.5 ml of ethanolic sulphate standard solution	Now add 1.5 ml of ethanolic sulphate standard solution in it
3.	Mix well and allow to stand for 1 Minute	Mix well and allow to stand for 1 minute
4.	Add 15 ml solution of sodium bicarbonate in it.	Add 15 ml solution of sulphate standard solution in it
5.	Add 0.15 ml of 5M acetic acid	Add 0.15 ml of 5M acetic acid
6.	Make upto 50 ml with distilled Water	Make upto 50 ml with distilled water
7.	Stir with glass rod and set aside for 5 minutes	Stir with glass rod and set aside for 5 Minutes

Observation: The turbidity produce in sample solution should not be greater than standard solution. If turbidity produces in sample solution is less than the standard solution, the sample will pass the limit test of sulphate and vice versa.

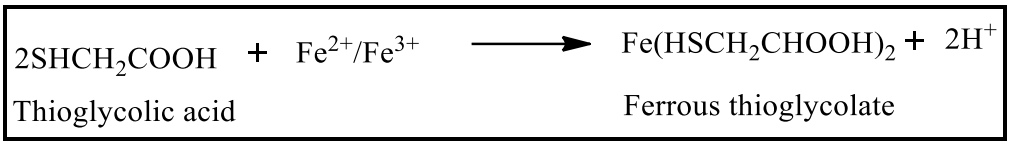
Reasons: Hydrochloric acid helps to make solution acidic. Potassium sulphate is used to increase the sensitivity of the test by giving ionic concentration in the reagent Alcohol helps to prevent super saturation.

Limit test for Iron:

Principle: Limit test for iron is based on reaction of iron in ammonical solution in the presence of citric acid with thioglycolic acid to form ferrous thioglycolate. The ammonical ferrous thioglycolate solution is pink to deep reddish-purple color depending on concentration of iron. The intensity of color is compared with standard intensity obtained from fixed concentration of iron.

Role of citric acid: Iron may be precipitated as ferrous or ferric hydroxide on reaction with ammonia solution. The precipitate may interfere with the intensity of color. Citric acid prevents

the precipitation of iron as hydroxide by forming complex with iron which is not precipitated by ammonia solution.



Procedure:

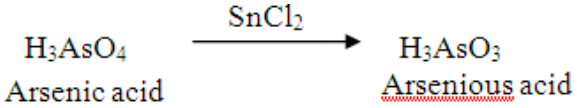
S. No.	Standard Solution	Test Solution
1.	Add 2 ml iron standard solution	Add 1g of sodium chloride
2.	Make upto 40 ml with distilled water	Make upto 40 ml with distilled water
3.	Add 2 ml iron free citric acid solution	Add 2 ml iron free citric acid solution
4.	Add 0.1 ml thioglycolic acid	Add 0.1 ml thioglycolic acid
5.	Add 2-3 drops of ammonia solution	Add 2-3 drops of ammonia solution
6.	Set aside for 5 minutes	Set aside for 5 minutes

Observation: The intensity of the purple color produce in sample solution should not be greater than standard solution. If purple color produces in sample solution is less than the standard solution, the sample will pass the limit test of iron and vice versa.

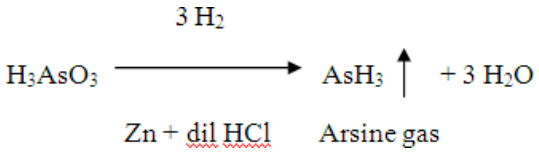
Limit test for Arsenic:

This test is used for identifying and controlling arsenic impurities in substances. Arsenic is well known undesirable and harmful substance present in medicinal substance

Principle: The test is based on the fact that arsenic gets converted into arsenic acid in presence of an acid, which gets reduced by reducing agents (potassium iodide, stannous acid, zinc etc.,) to arsenious acid.

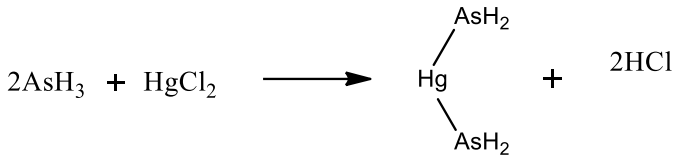


Then ascent hydrogen produced by zinc and dil. HCl reduced this arsenious acid to arsine gas.



This gas is passed over mercuric chloride paper; it produces a strain, which ranges from yellow

to brown. The intensity and length are proportional to amount of arsenic.



Mercuric Arsenide

The stain of the test sample is compared in day light with standard stains produced by known quantity of arsenic in the sample.

Apparatus: A special type of apparatus is used to perform limit test for arsenic.

Gutzeit Apparatus

A: Approximately 60 ml generator bottle with 40 ml indicating line.

B: Glass tube with 6.5 mm inner diameter

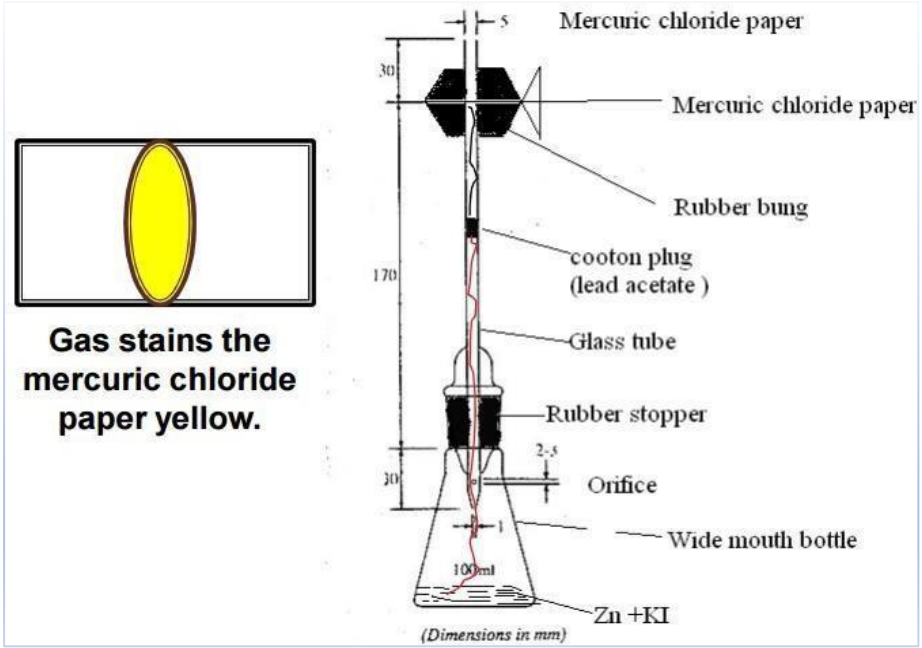
C and D: a ground joint glass tube with 6.5 mm inner diameter and 18 mm outer diameter at the joint. Inner joint and the outer joint form a concentric circle.

E: rubber stopper

F: narrow part of the glass tube B. Glass wool is inserted up to this part.

G: rubber board (Lead acetate cotton plug)

H : clamp



Procedure:

For standard solution: Add 1 gm of potassium iodide AsT and 10 gm of zinc dust AsT in a wide mouthed glass bottle. Then 10 ml of stannated HCl and 1 ml of dilute arsenic solution are added to the above solution. Then add 50 ml of water, glass tube is placed quickly in position. The glass tube is tightly placed with lead acetate cotton wool. The reaction is allowed to takeplacefor45 to 90 minutes. To accurate the reaction the apparatus is kept on hot surface for atleast 10 minutes.

For test solution: Add 1 gm of potassium iodide AsT and 10 gm of zinc dust AsT in a wide mouthed glass bottle. Then 10 ml of stannated HCl and 1 ml of test solution (2.5 gm of ammonium chloride in 50 ml of water) are added to the above solution. Glass tube is placed quickly in position. The glass tube is tightly placed with lead acetate cotton wool. The reaction is allowed to take place for 45 to 90 minutes. To accurate the reaction the apparatus is kept on hot surface for atleast 10 minutes.

Observation:

a. If the test solution shows yellow stain with more intensity then standard – limit test fails.
b. If the test solution shows yellow stain with less intensity then standard – limit test pass.

Reasons for using particular reagents: Stannous chloride is used for complete evolution of arsine Zinc; potassium iodide and stannous chloride is used as a reducing agent Hydrochloric acid is used to make the solution acidic Lead acetate pledger or papers are used to trap any hydrogen sulphide which may be evolved along with arsine.

Limit test for Heavy metals:

The limit test for heavy metals is a semi-quantitative test used to detect and control small amounts of heavy metal impurities present in pharmaceutical substances. Heavy metals such as lead, mercury, bismuth, copper, and cadmium are toxic even in trace quantities and therefore must be controlled within permissible limits.

The test is based on comparison of the colour produced by the test solution with that produced by a standard lead solution under identical conditions.

Lead

Lead is a most undesirable impurity in medical compounds and comes through use of sulphuric acid, lead lined apparatus and glass bottles use for storage of chemicals.

Principle: Limit test of lead is based on the reaction of lead and diphenyl-thiocarbazone (dithizone) in alkaline solution to form lead dithizone complex which is red in color. Dithizone is green in color in chloroform and lead-dithizone complex is violet in color, so the resulting color at the end of process is red.

Procedure:

Test sample	**Standard compound**
A known quantity of sample solution is transferred in a separating funnel	A standard lead solution is prepared equivalent to the amount of lead permitted in the sample under examination
Add 6ml of ammonium citrate	Add 6ml of ammonium citrate
Add 2 ml of potassium cyanide and 2 ml of hydroxylamine hydrochloride	Add 2 ml of potassium cyanide and 2 ml of hydroxylamine hydrochloride
Add 2 drops of phenol red	Add 2 drops of phenol red
Make solution alkaline by adding ammonia solution.	Make solution alkaline by adding ammonia solution.
Extract with 5 ml of dithizone until it becomes green	Extract with 5 ml of dithizone until it becomes Green
Combine dithizone extracts are shaken for 30 mins with 30 ml of nitric acid and the chloroform layer is discarded	Combine dithizone extracts are shaken for 30 mins with 30 ml of nitric acid and the chloroform layer is discarded
To the acid solution add 5 ml of standard dithizone solution	To the acid solution add 5 ml of standard dithizone solution
Add 4 ml of ammonium cyanide	Add 4 ml of ammonium cyanide
Shake for 30 mins	Shake for 30 mins
Observe the color	Observe the color

Observation: The intensity of the color of complex, is depends on the amount of lead in the solution. The color produce in sample solution should not be greater than standard solution. If color produces in sample solution is less than the standard solution, the sample will pass the limit test of lead and vice versa.

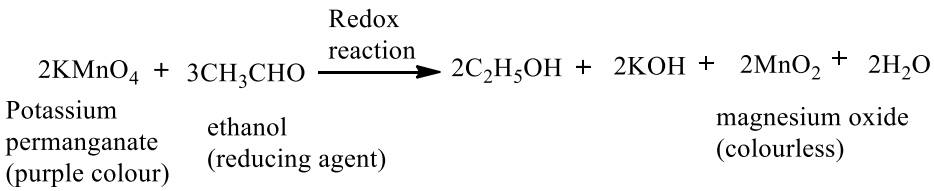
Reasons for using particular reagents:

Ammonium citrate, potassium cyanide, hydroxylamine hydrochloride is used to make pH optimum so interference and influence of other impurities have been eliminated. Phenol red is used as indicator to develop the color at the end of process. Lead present as an impurities in the substance, gets separated by extracting an alkaline solution with a dithizone extraction solution.

Modified Limit test for Chlorides and Sulphate

Modified limit test is performed, if the limit test for a sample (colored compound) cannot be done by normal method. Modified limit tests are performed when the official limit test cannot be carried out directly due to interference caused by coloured substances, insoluble materials, or acidic/basic nature of the sample. In such cases, suitable modifications are made before performing the standard comparison test. For Example: When the sample is coloured compound such as potassium permanganate $KMnO_4$. In this type of test firstly we have convert colored solution to colourless solution so the any type of interference is not created by substance.

Chemical reaction:



✓ How to prepare potassium permanganate?

1.5 mg of potassium permanganate in 50 ml of distilled water with 4ml of ethanol and heat it on a water bath until the color becomes colourless. Filter the solutions for comparing with standards, use 40ml of filtrate and complete the limit test.

Procedure:

S. No.	Standard	Test
1.	1ml of 0.0824% *w/v* solution of NaCl is taken in Nessler's Cylinder	20 ml prepared $KMnO_4$ solution is taken in Nessler's Cylinder
2.	Add 10 ml of Dil. Nitric Acid	Add 10 ml of Dil. Nitric Acid
3.	Make up the volume upto 50 ml with distilled water	Make up the volume upto 50 ml with distilled water
4.	Now add 1 ml of silver nitrate to this solution	Now add 1 ml of silver nitrate to this Solution
5.	Stir the solution with glass rod and allow to stand for 5 minutes	Stir the solution with glass rod and allow to stand for 5 minutes

Observation: The opalescence produced in sample solution should not be greater than standard, if opalescence produces in sample solution is less than the standard solution will pass the limit test for chloride.

Modified Limit test for Sulphates

Principle: Potassium permanganate gives pink color in aqueous solution which interferes with the general limit test. To decolorize potassium permanganate, it is reduced by heating with ethanol, the precipitate formed is removed by filtration. The colourless filtrate obtained is subjected to limit test. Sulphate ions then react with barium chloride to form white turbidity of barium sulphate.

Procedure:

S. No.	Standard	Test
1.	15 ml of sulphate standard (Potassium sulphate) and 15 ml of distilled water is taken in Nessler's Cylinder	20 ml prepared $KMnO_4$ solution is taken in Nessler's Cylinder
2.	Add 2 ml of HCl	Add 2 ml of HCl
3.	Add 5 ml of BaSO4 reagent	Add 5 ml of BaSO4 reagent

4.	Make up the volume upto 50 ml with distilled water	Make up the volume upto 50 ml with distilled water
5.	Stir the solution with glass rod and allow to stand for 5 minutes	Stir the solution with glass rod and allow to stand for 5 minutes

Observation: The opalescence produced in sample solution should not be greater than standard, if opalescence produces in sample solution is less than the standard solution will pass the limit test for sulphate.

Importance

- Ensures purity of potassium permanganate.
- Detects chloride and sulphate impurities.
- Maintains pharmaceutical quality standards.
- Prevents interference in pharmaceutical preparations.
- Ensures compliance with pharmacopeial requirements.

Points to Remember:

- ✓ **Pharmaceutical analysis** deals with identification, estimation, and purity testing of drugs and pharmaceuticals.
- ✓ It ensures the safety, efficacy, quality, and stability of medicines.
- ✓ **Qualitative analysis** identifies substances, while quantitative analysis determines their amount.
- ✓ Common analytical techniques include titrimetry, gravimetry, chromatography, and spectroscopy.
- ✓ Strength of solutions is expressed as % strength, molarity, normality, molality, and ppm.
- ✓ **Primary standards** are pure and stable substances used for preparing standard solutions.
- ✓ **Secondary standards** require standardization before use because they are less stable.
- ✓ **Errors** are differences between true value and observed value in analysis. Errors may be systematic, random, or gross errors. Instrumental, personal, method, and environmental factors are common sources of errors. Errors can be minimized by calibration, proper procedures, and repeated measurements.
- ✓ **Accuracy** indicates closeness to the true value, while precision shows reproducibility.
- ✓ **Significant** figures indicate the precision of analytical measurements.
- ✓ **Impurities** are unwanted substances present in pharmaceutical products. Impurities may be organic, inorganic, residual solvents, or microbial impurities. Sources of impurities include raw materials, manufacturing process, solvents, storage, and containers.
- ✓ **Regulatory authorities** such as the International Council for Harmonisation control impurity limits for drug safety.
- ✓ **Limit tests** are semi-quantitative tests used to detect small amounts of impurities. Chloride test is based on formation of white silver chloride turbidity. Sulphate test is based on formation of white barium sulphate turbidity.
- ✓ Heavy metals produce coloured sulfides in presence of hydrogen sulfide.
- ✓ Arsenic test involves formation of arsine gas and yellow stain on mercuric chloride paper.
- ✓ Lead test uses dithizone reagent to produce coloured complex.
- ✓ **Modified limit tests** are used for coloured substances like potassium permanganate.
- ✓ Pharmaceutical analysis is essential for quality control and regulatory compliance of medicines.

Case Based Learning (CBL)

Case Based Learning – 1: Error in Pharmaceutical Analysis

A pharmaceutical company was analysing sodium hydroxide solution using titration. Two analysts obtained very different results for the same sample. Later, it was found that one burette was not calibrated properly and the NaOH solution had absorbed carbon dioxide from air.

Questions:

1. Identify the types of errors involved in the case.
2. Why is sodium hydroxide considered a secondary standard?
3. Suggest methods to minimize such analytical errors.
4. Differentiate between accuracy and precision in this case.

Case Based Learning – 2: Impurity Detection in Potassium Permanganate

During quality control testing of potassium permanganate, the analyst was unable to perform the normal limit test for chlorides because the purple colour of the sample interfered with turbidity comparison.

Questions:

1. Why does potassium permanganate interfere with the limit test?
2. Which modified limit test is used in this case?
3. What reagent is used for decolourization?
4. Write the reaction involved in reduction of potassium permanganate.
5. Why are modified limit tests important in pharmaceutical analysis?

Problem Based Learning (CBL)

Sulphate Impurity in Calcium Carbonate

During routine quality control testing, a calcium carbonate sample produced excessive white turbidity during sulphate limit testing. The analyst concluded that the sample contained sulphate impurities, possibly introduced during manufacturing using sulphuric acid.

Quiz Questions

1. Which impurity is detected in this test?

   a) Chloride
   c) Iron
   b) Sulphate
   d) Lead

2. Which reagent is used in sulphate limit test?

   a) Silver nitrate
   c) Dithizone
   b) Barium chloride
   d) Thioglycolic acid

3. White turbidity in sulphate test is due to formation of:

   a) AgCl
   c) $BaSO_4$
   b) PbS
   d) $FeSO_4$

4. Which acid is used in sulphate limit test?

   a) Hydrochloric acid
   c) Acetic acid
   b) Nitric acid
   d) Sulphuric acid

5. Excess sulphate impurity may affect:

   a) Drug purity
   c) Taste only
   b) Colour only
   d) Labelling only

Multiple Choice Questions (MCQs):

1. Pharmaceutical analysis mainly deals with:

A) Manufacturing drugs
C) Marketing medicines
B) Testing and identification of drugs
D) Packaging of drugs

Answer: B

2. Which technique is commonly used in pharmaceutical analysis?

A) Titrimetry
C) Spectroscopy
B) Chromatography
D) All of these

Answer: D

3. Quantitative analysis determines:

A) Identity of substance
C) Colour of substance
B) Amount of substance present
D) Odour of substance

Answer: B

4. Qualitative analysis is used to determine:

A) Purity only
C) Identity of chemical constituents
B) Quantity only
D) Cost of drug

Answer: C

5. Which unit expresses concentration as grams of solute in 100 mL solution?

A) ppm
C) Molarity
B) % w/v
D) Normality

Answer: B

6. Molarity is defined as:

A) Gram equivalent per litre
C) Gram per litre
B) Mole of solute per litre of solution
D) Mole per kg solvent

Answer: B

7. Normality is:

A) Mole per litre
C) Gram equivalent weight per litre
B) Gram molecular weight per litre
D) Gram per mL

Answer: C

8. ppm stands for:

A) Parts per million
C) Parts per mole
B) Purity per mass
D) Percent per million

Answer: A

9. A primary standard should be:

A) Hygroscopic
C) Volatile
B) Highly pure
D) Coloured

Answer: B

10. Which is a primary standard?

A) Sodium hydroxide
C) Sodium carbonate
B) Hydrochloric acid
D) Potassium hydroxide

Answer: C

11. Secondary standards are:

A) Highly unstable
C) Never used in titration
B) Standardized against primary standards
D) Insoluble compounds

Answer: B

12. Sodium hydroxide solution is generally a:

A) Primary standard
C) Buffer
B) Secondary standard
D) Solvent

Answer: B

13. Which analytical method involves measurement of light absorption?

A) Gravimetry
C) Titrimetry
B) Spectroscopy
D) Electrolysis

Answer: B

14. Chromatography is mainly used for:

A) Separation of compounds
C) Drying compounds
B) Weighing compounds
D) Heating compounds

Answer: A

15. Random errors are also called:

A) Determinate errors
C) Indeterminate errors
B) Systematic errors
D) Personal errors

Answer: C

16. Systematic errors can be minimized by:

A) Careful calibration
C) Using dirty apparatus
B) Increasing temperature
D) Guessing readings

Answer: A

17. Personal error occurs due to:

A) Faulty instruments
C) Carelessness of analyst
B) Environmental conditions
D) Chemical impurities

Answer: C

18. Instrumental error is caused by:

A) Impure reagent
C) Wrong calculation
B) Faulty apparatus
D) Temperature change

Answer: B

19. Accuracy refers to:

A) Reproducibility of results
C) Speed of analysis
B) Closeness to true value
D) Purity of chemical

Answer: B

20. Precision means:

A) Correctness of result
C) Speed of work
B) Reproducibility of results
D) Number of titrations

Answer: B

21. Significant figures represent:

A) Approximate values
C) Incorrect digits
B) Meaningful digits in measurement
D) Mathematical constants

Answer: B

22. Which is the least precise measurement?

A) 10.00 g
C) 10.000 g
B) 10.0 g
D) 10.0000 g

Answer: B

23. Errors due to environmental conditions are:

A) Gross errors
C) Random errors
B) Personal errors
D) Method errors

Answer: C

24. Replicate analysis helps in:

A) Increasing error
C) Destroying sample
B) Minimizing random error
D) Decreasing purity

Answer: B

25. Impurities are:

A) Desired substances
C) Preservatives
B) Unwanted chemicals present in drug
D) Colouring agents only

Answer: B

26. Impurities in pharmaceuticals may arise from:

A) Manufacturing process
C) Decomposition
B) Storage conditions
D) All of these

Answer: D

27. Which impurity is caused during storage?

A) Residual solvent
C) Catalyst impurity
B) Degradation product
D) Reagent impurity

Answer: B

28. Regulatory importance of impurity testing is related to:

A) Safety and efficacy
C) Brand name
B) Colour of medicine
D) Packaging size

Answer: A

29. Heavy metals in pharmaceuticals are harmful because they are:

A) Nutrients
C) Sweet in taste
B) Toxic
D) Insoluble

Answer: B

30. Limit tests are generally:

A) Quantitative tests
C) Biological tests
B) Semi-quantitative tests
D) Physical tests only

Answer: B

31. The limit test for chloride is based on formation of:

A) Yellow precipitate
C) Blue colour
B) White precipitate of silver chloride
D) Red precipitate

Answer: B

32. Which reagent is used in chloride limit test?

A) Silver nitrate
C) Potassium permanganate
B) Barium chloride
D) Ferric chloride

Answer: A

33. Sulphate limit test involves formation of:

A) Silver sulphate precipitate
C) Iron sulphide precipitate
B) Barium sulphate turbidity
D) Lead sulphate crystals

Answer: B

34. Which reagent is used in sulphate limit test?

A) Sodium hydroxide
C) Hydrochloric acid
B) Barium chloride
D) Nitric acid

Answer: B

35. The iron limit test produces:

A) Purple colour
C) Brown colour complex
B) Green precipitate
D) White precipitate

Answer: C

36. Arsenic limit test is based on formation of:

A) Arsine gas
C) Sulphur dioxide
B) Chlorine gas
D) Carbon dioxide

Answer: A

37. Lead impurities are dangerous because lead is:

A) Volatile
C) Radioactive only
B) Toxic metal
D) Non-reactive

Answer: B

38. Heavy metal limit test commonly uses:

A) Hydrogen sulphide
C) Nitrogen
B) Oxygen
D) Chlorine

Answer: A

39. Turbidity in limit tests is compared with:

A) Blank solution
C) Water
B) Standard solution
D) Acid

Answer: B

40. Modified limit tests are developed to:

A) Increase impurities
C) Reduce testing time only
B) Improve accuracy for colored compound
D) Avoid standards

Answer: B

41. The main purpose of pharmaceutical analysis is:

A) Drug advertisement
C) Reducing tablet size
B) Ensuring quality of drugs
D) Increasing sweetness

Answer: B

42. Gravimetric analysis is based on:

A) Volume measurement
C) Colour change
B) Weight measurement
D) Temperature change

Answer: B

43. Volumetric analysis is also called:

A) Titrimetric analysis
C) Biological analysis
B) Thermal analysis
D) Spectral analysis

Answer: A

44. Which factor affects accuracy?

A) Calibration of apparatus
C) Purity of reagents
B) Analyst skill
D) All of these

Answer: D

45. Which error cannot be completely eliminated?

A) Gross error
C) Instrumental error
B) Random error
D) Personal error

Answer: B

46. Which impurity may come from raw materials?

A) Process impurity
C) Residual impurity
B) Degradation impurity
D) Starting material impurity

Answer: D

47. Significant figures help in:

A) Expressing precision of measurement
C) Changing units
B) Reducing weight
D) Preparing buffers

Answer: A

48. The acceptable level of impurity in pharmaceuticals is controlled by:

A) Regulatory authorities
C) Patients
B) Shopkeepers
D) Advertisers

Answer: A

Short Answer Type Questions (Objective type questions):

1) Define pharmaceutical analysis.
2) List different techniques of pharmaceutical analysis.
3) Define qualitative analysis and quantitative analysis.
4) Define molarity.
5) Define normality.
6) List different methods of expressing strength of solutions.
7) Define primary standard.
8) Give examples of primary standards.
9) Define secondary standard.
10) List the types of analytical errors.
11) Define accuracy.
12) Define precision.
13) Define significant figures.
14) Define impurities.
15) List the types of impurities in pharmaceuticals.
16) State the sources of impurities in pharmaceuticals.
17) Define limit test.
18) Name the reagents used in limit test for chlorides and sulphates.
19) List the limit tests used for pharmaceutical impurities.
20) What is the role of dilute nitric acid in limit test of chloride?

Long Answer Type Questions

1) Explain different types of method for qualitative analysis used in pharmaceutical analysis with suitable examples.
2) Discuss various methods of expressing strength of solutions and their pharmaceutical applications.
3) Analyze the sources and types of errors encountered in pharmaceutical analysis and explain methods used to minimize them.
4) Apply the concepts of accuracy, precision, and significant figures in interpretation of

analytical results.

5) Analyze the sources and types of impurities present in pharmaceutical substances with suitable examples.
6) Evaluate the regulatory importance of impurity profiling in maintaining the quality and safety of pharmaceutical products.
7) Explain the principles, procedures, and reactions involved in limit tests for chlorides and sulphates.
8) Justify the need for modified limit tests for chlorides and sulphates in coloured pharmaceutical substances such as potassium permanganate.