Text Book of

PHARMACEUTICAL CHEMISTRY

- Dr. Bhawna Sharma
- Dr. Upendra Kumar Sharma

Himalaya Publishing House

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PHARMACEUTICAL CHEMISTRY

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PREFACE

The present book "Textbook of Pharmaceutical Chemistry" has been written with the aim to cover the new syllabus framed by Pharmacy Council of India (PCI), 2020 for Diploma course in Pharmacy in the Gazette of India, Extraordinary No. 435, Part-III, Section-4.

The book has been divided into thirteen chapters; comprehensively describe all aspects of the subject as mentioned in the syllabus. Every medicinal compounds included in this book are discussed under chemical name, properties, pharmaceutical uses, storage and stability, marketed preparations, dosage form, officials etc. This book also consists of Inorganic Pharmaceutical Chemistry, Impurities in Pharmaceuticals, Volumetric and Gravimetric Analysis, and Introduction to Nomenclature of Organic Chemical systems.

This book will be beneficial to First Year students, teaching faculties and pharmacists in hospitals as well as medical representatives who want to update their knowledge. At the end of each chapter, exercises have been given that will help the students to evaluate their studies.

We express our sincere gratitude to Himalaya Publishing House Pvt. Ltd. and their eminent dedicated editorial, production and response division team who have brought out this book in a record time period.

We also express our deep sense of gratitude towards our parents and friends. Without their support and encouragement, this book could not have taken shape.

We will be highly obliged to all faculties and students who will point out our mistakes that have escaped our attention.

We shall gratefully acknowledge constructive suggestions, feedback, comments and criticisms, as they will help in further improvement for next edition of the book.

Dr. Bhawna Sharma
Dr. Upendra Kumar Sharma

SYLLABUS

AS PER PCI CURRICULUM
FOR D.PHARMA
Pharmaceutical Chemistry (Course Code: ER20-12T)

Unit 1:
Introduction to Pharmaceutical Chemistry: Scope and objectives.
Sources and Types of Errors: Accuracy, precision, significant figures.
Impurities in Pharmaceuticals: Source and effect of impurities in pharmacopoeial substances, importance of limit test, Principle and procedures of limit tests for chlorides, sulphates, iron, heavy metals and arsenic.

Unit 2:
Volumetric Analysis: Fundamentals of volumetric analysis, acid-base titration, non-aqueous titration, precipitation titration, complexometric titration, redox titration.
Gravimetric Analysis: Principle and method.

Unit 3:
Inorganic Pharmaceuticals: Pharmaceutical formulations, market preparations, storage conditions and uses of:

- **Haematinics:** Ferrous sulphate, Ferrous fumarate, Ferric ammonium citrate, Ferrous ascorbate, Carbonyl iron.
- **Gastrointestinal Agents:** Antacids: Aluminium hydroxide gel, Magnesium hydroxide, Magaldrate, Sodium bicarbonate, Calcium Carbonate, Acidifying agents, Adsorbents, Protectives, Cathartics.
- **Topical Agents:** Silver Nitrate, Ionic Silver, Chlorhexidine Gluconate, Hydrogen peroxide, Boric acid, Bleaching powder, Potassium permanganate.
- **Dental Products:** Calcium carbonate, Sodium fluoride, Denture cleaners, Denture adhesives, Mouthwashes.
- **Medicinal Gases:** Carbon dioxide, Nitrous oxide, Oxygen.

Unit 4:
Introduction to nomenclature of organic chemical systems with particular reference to heterocyclic compounds containing up to three rings.

Unit 5:
Drugs Acting on Central Nervous System

- **Anaesthetics:** Thiopental Sodium*, Ketamine Hydrochloride*, Propofol
- **Sedatives and Hypnotics:** Diazepam*, Alprazolam*, Nitrazepam, Phenobarbital*
- **Antipsychotics:** Chlorpromazine Hydrochloride*, Haloperidol*, Risperidone*, Sulpiride*, Olanzapine, Quetiapine, Lurasidone
- **Anticonvulsants:** Phenytoin*, Carbamazepine*, Clonazepam, Valproic Acid*, Gabapentin*, Topiramate, Vigabatrin, Lamotrigine
- **Anti-depressants:** Amitriptyline Hydrochloride*, Imipramine Hydrochloride*, Fluoxetine*, Venlafaxine, Duloxetine, Sertraline, Citalopram, Escitalopram, Fluvoxamine, Paroxetine

Unit 6:
Drugs Acting on Autonomic Nervous System

- **Sympathomimetic Agents:** Direct Acting: Norepinephrine*, Epinephrine, Phenylephrine, Dopamine*, Terbutaline, Salbutamol (Albuterol), Naphazoline*, Tetrahydrozoline. Indirect Acting Agents: Hydroxy Amphetamine, Pseudoephedrine. Agents with Mixed Mechanism: Ephedrine, Metaraminol.

- **Adrenergic Antagonists**: Alpha-adrenergic Blockers: Tolazoline, Phentolamine Phenoxybenzamine, Prazosin. Beta Adrenergic Blockers: Propranolol*, Atenolol*, Carvedilol.
- **Cholinergic Drugs and Related Agents:** Direct Acting Agents: Acetylcholine*, Carbachol and Pilocarpine. Cholinesterase Inhibitors: Neostigmine*, Edrophonium Chloride, Tacrine Hydrochloride, Pralidoxime Chloride, Echothiopate Iodide.
- **Cholinergic Blocking Agents:** Atropine Sulphate*, Ipratropium Bromide.
- **Synthetic Cholinergic Blocking Agents:** Tropicamide, Cyclopentolate Hydrochloride, Clidinium Bromide, Dicyclomine Hydrochloride*.

Unit 7:
Drugs Acting on Cardiovascular System

- **Antiarrhythmic Drugs:** Quinidine Sulphate, Procainamide Hydrochloride, Verapamil, Phenytoin Sodium*, Lidocaine Hydrochloride, Lorcainide Hydrochloride, Amiodarone and Sotalol.
- **Anti-hypertensive Agents**: Propranolol*, Captopril*, Ramipril, Methyldopate Hydrochloride, Clonidine Hydrochloride, Hydralazine Hydrochloride, Nifedipine.
- **Antianginal Agents:** Isosorbide Dinitrate.

Unit 8:
Diuretics: Acetazolamide, Frusemide*, Bumetanide, Chlorthalidone, Benzthiazide, Metolazone, Xipamide, Spironolactone

Unit 9:
Hypoglycemic Agents: Insulin and Its Preparations, Metformin*, Glibenclamide*, Glimepiride, Pioglitazone, Repaglinide, Gliflozins, Gliptins

Unit 10:

- Analgesic and Anti-inflammatory Agents: Morphine Analogues, Narcotic Antagonists; Non-steroidal Anti-inflammatory Agents (NSAIDs) – Aspirin*, Diclofenac, Ibuprofen*, Piroxicam, Celecoxib, Mefenamic Acid, Paracetamol*, Aceclofenac.

Unit 11:
Anti-infective Agents

- **Antifungal Agents:** Amphotericin-B, Griseofulvin, Miconazole, Ketoconazole*, Itraconazole, Fluconazole*, Naftifine Hydrochloride.
- **Urinary Tract Anti-infective Agents:** Norfloxacin, Ciprofloxacin, Ofloxacin*, Moxifloxacin.
- **Anti-tubercular Agents:** INH*, Ethambutol, Para Amino Salicylic Acid, Pyrazinamide, Rifampicin, Bedaquiline, Delamanid, Pretomanid*.
- **Antiviral Agents:** Amantadine Hydrochloride, Idoxuridine, Acyclovir*, Foscarnet, Zidovudine, Ribavirin, Remdesivir, Favipiravir.
- **Antimalarials:** Quinine Sulphate, Chloroquine Phosphate*, Primaquine Phosphate, Mefloquine*, Cycloguanil, Pyrimethamine, Artemisinin.
- **Sulfonamides:** Sulfanilamide, Sulfadiazine, Sulfametho xazole, Sulfacetamide*, Mafenide Acetate, Cotrimoxazole, Dapsone*.

Unit 12:
Antibiotics: Penicillin G, Amoxicillin*, Cloxacillin, Streptomycin, Tetracyclines: Doxycycline, Minocycline.
Macrolides: Erythromycin, Azithromycin, Miscellaneous: Chloramphenicol*, Clindamycin.

Unit 13:
Anti-neoplastic Agents: Cyclophosphamide*, Busulfan, Mercaptopurine, Fluorouracil*, Methotrexate, Dactinomycin, Doxorubicin Hydrochloride, Vinblastine Sulphate, Cisplatin*, Dromostanolone Propionate.

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1 INTRODUCTION TO PHARMACEUTICAL CHEMISTRY

STRUCTURE

OBJECTIVES

Introduction to Pharmaceutical Chemistry: Scope and Objectives

Sources and Types of Errors: Accuracy, Precision, Significant Figures

Impurities in Pharmaceuticals: Source and Effect of Impurities in Pharmacopoeial Substances, Importance of Limit Test, Principle and Procedures of Limit Tests for Chlorides, Sulphates, Iron, Heavy Metals and Arsenic.

1.1 INTRODUCTION

Pharmaceutical chemistry is the study of synthetic organic chemistry; the goal is to obtain new chemical molecules that can be used to find new pharmaceuticals or to improve the existing drug structures, hence increasing the chemical drug range. This discipline mainly involves the synthesis of biologically active substances. It includes major branches of chemistry particularly organic chemistry, inorganic chemistry, analytical chemistry, medicinal chemistry, physical chemistry, etc.

The aim of pharmaceutical chemistry is to produce new chemical entities that could enable the discovery of new pharmaceuticals or optimize already known drug structures, to make them suitable for therapeutic use. It involves synthetic and computational aspects of the study of existing drugs and agents in development in relation to their bioactivities (biological activities and

properties), i.e., understanding their structure-activity relationships (SAR). Pharmaceutical Chemistry focuses on quality aspects of medicines and aims to assure fitness for purpose of medicinal products.

Pharmacopoeia

Pharmacopoeia is an official publication containing a list of drugs, chemicals, and medicinal preparations as well as involving directions of compound identification with their effects and directions for their use.

The word Pharmacopoeia means is "to make a drug". This is derives from the ancient Greek word (pharmakon – drug), followed by the verb-stem (poi-make) and finally the abstract noun ending (-ia).

Pharmacopoeia contains a detailed written study of a single specialized subject which is called monograph. A monograph contains the name of the ingredient, the definition, preparation, storage, packaging, and labeling requirements; and the specifications. The specification contains a series of tests, procedures for the tests, and acceptance criteria. Most of the countries have their own Pharmacopoeias.

Lists of Pharmacopoeia are:

- United States Pharmacopoeia
- British Pharmacopoeia
- European Pharmacopoeia
- International Pharmacopoeia
- Japanese Pharmacopoeia
- Indian Pharmacopoeia
- Chinese Pharmacopoeia
- Others Pharmacopoeia

Official Substances

Official drug or substance, which is listed and described in the current issue of the pharmacopoeia of a country, and officially used for therapeutic purposes, is called an official substance.

Monograph

The descriptive material related to any drug or preparation included in the pharmacopoeia is known as the monograph. Generally the monograph of a crude drug includes the following information on the drugs: Official title, synonym, definition, rubric, description, and special conditions of collection or preparation for the market, identity tests, and tests for adulterants, method of assay, storage requirements, and amount of foreign organic matters, uses and doses.

1.2 SCOPE OF PHARMACEUTICAL CHEMISTRY

Scope of pharmaceutical chemistry is enormously involved in the research and development of new medicines for pharmaceutical companies. One can also enter in the field of teaching after

completing master in Pharmacy and M.Sc. Pharmaceuticals by giving exams like SLET, NET GPAT, etc. Opting for a Ph.D. is another option available for graduate students. Pharmaceutical chemistry has good scope at present and is expected to be progressed in upcoming years as medico companies are increasing in numbers.

The field of Pharmaceutical Chemistry has the scope in the R&D in the pharma companies and the Clinical Trials Unit. It is the most important branch of pharmacy and has scope in the research and development in the pharma companies and the clinical trials unit. Obtaining a degree in pharmaceutical chemistry, individuals can work in a variety of fields, including:

- Health Centers
- Drug Control Administration
- Manufacturing
- Medical Dispensing Stores
- Pharmaceutical Companies
- Product Marketing
- Research
- Teaching after qualifying some exams like NET, SLET, etc.

1.3 SOURCES AND TYPES OF ERRORS

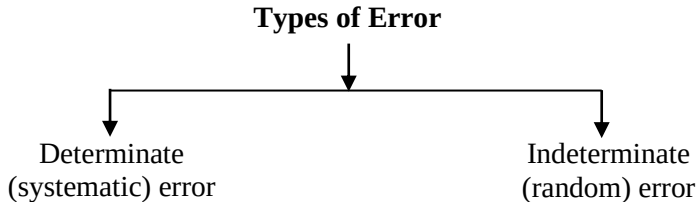
Analytical Chemistry is determined on the basis of accuracy, reliability and reproducibility. Hence, every measurement has a certain degree of variability that is called an error. In analytical chemistry, error is the difference between the experimental mean value and a true value.

Sources of Error: Every measurement, irrespective of how accurate we think it is, contains some inaccuracy due to the method we used to take it.

- Sample preparations
- Error by analyst
- Equipment problem
- Calibration
- Reporting error
- Calculation error
- Error in method selection
- Sampling error
- Laboratory environment
- Error during transport

1.3.1 Classification of Errors

Errors can be classified into two types – determinate and indeterminate errors. Determinate errors are again classified into instrumental errors, personal errors, errors of method, additive and proportional errors. Indeterminate errors are accidental or random errors that cannot be neglected but minimized by calibrating instruments.



1. Instrumental error
2. Personal errors
3. Errors of method
4. Additive and proportional errors

1. Determinate (Systematic) Errors

Systematic or determinate errors are also known and controllable errors, caused by improper functioning of the instrument or analyst, defects in the analytical method, etc. Determinate errors are known and avoidable, and composed of two parts that have a constant value or a proportionate value. The systematic errors are categorized as:

(i) Instrumental or Reagent Errors

Instrumental errors occur due to faulty and uncalibrated instruments or reagent containing impurities. The various factors which cause errors are:

Examples:

- By the use of non-ideal instrument behavior like faulty calibrations, or under inappropriate conditions.
- Uncalibrated volumetric equipment, such as burettes, pipettes, and volumetric flasks, generally deliver or contain volumes slightly different from those indicated by their graduations.
- Use of uncalibrated pH meters, single pan electric balances, UV Spectrophotometers, potentiometers, etc.
- Some electronic instruments can be influenced by temperature, pH and noise, and leads to systematic errors.
- By attack of foreign materials upon glassware.

These errors can be avoided by using calibrated weights, glassware and pure reagents.

(ii) Operational or Personal Errors

Errors occur during operations in which the individual analyst is responsible and are not connected with the method or procedure is called as personal errors. They are exclusively caused due to transfers of solution, effervescence, incomplete drying, underweighing of precipitates, overweighing of precipitates, insufficient cooling of precipitates, etc.

Examples:

- Error occurred due to underwashing or overwashing of precipitate.
- Error occurred due to ignition of the precipitates at inappropriate temperature.
- Error occurred due to insufficient cooling of crucibles before weighing.
- Error caused due to allowing hygroscopic materials to absorb moisture before or during weighing.
- Reagents containing impurities used during procedures cause error.
- Person incapable of view changes sharply in visual titrations which may result in slight overstepping of the endpoint.
- Errors in calculations.

(iii) Errors of Method

In analytical chemistry, sometimes due to improper sampling and incompleteness of a reaction usually lead to serious errors. Errors built in a method are usually difficult to detect. Therefore, these errors are usually the most difficult to identify and correct. A few typical examples invariably encountered in titrimetric and gravimetric analysis are listed below:

Examples: A few typical examples invariably encountered in titrimetric and gravimetric analysis are:

- Errors occurred due to insolubility of precipitates, co-precipitates, post-precipitates, decomposition and volatilization.
- The errors that introduced by non-ideal chemical or physical behavior of the reagents and reactions on which an analysis is based often leads to systematic method errors.
- Undesirable introduction of ‘foreign substances’ caused by the action of reagents on either porcelain or glass apparatus.

(iv) Additive or Proportional Errors

The extent of proportional error depends upon the quantity of the constituent. For example, impurity present in a standard substance produces a wrong value for the normality of a standard solution.

- Additive or Proportional errors decrease or increase in proportion to the size of the sample. A usual cause of proportional errors is the presence of interfering contaminants in the sample.

- This kind of error is independent of the amount of the constituent present in the determination, e.g., loss in weight of a crucible adds error to the weight of precipitate ignited in it.
- Absolute error can be increased while handling with large samples. However, the relative error would remain more or less constant if the sample is perfectly homogenous.

2. Random or Indeterminate Errors

A random error occurs accidentally or randomly, therefore, called as indeterminate or accidental or random error. The analyst has no control over these errors.

- It follows a random distribution and a mathematical law of probability can be applied.
- These errors are accidental in nature, and lead to both high and low results with equal probability.
- Sequential measurements made by the same observer under identical conditions produce slight variations in the results.
- These errors cannot be removed or corrected, and are the ultimate limitation on the measurement. These can be treated by statistics. Repeated measurements of the same variable can have the effect of reducing their importance.

1.3.2 Accuracy

Accuracy is defined as how close a measurement is to the correct or accepted value of the quantity being measured. It is the ability of the instrument to measure the correct value or the closeness of the measured value to a standard or true value.

Types of Accuracy

Accuracy has been classified into three categories:

- **Point Accuracy:** It is the accuracy of the instrument only at the particular point on its scale. It does not give any information about the general accuracy of the instrument.
- **Accuracy as Percentage of True Value:** Percentage of true value is when the accuracy of the instrument is determined by identifying the measured value regarding their true value.
- **Accuracy as Percentage of Scale Range:** Percentage of scale range determines the accuracy of a measurement.

1.3.3 Precision

Precision is defined as the reproducibility of a result or measurement. In other words, precision refers to the closeness of a series of measurements to one another. This term explains how invariable the measurements when experiment is repeated. The repeated measurements decrease the random errors. The precision is independent of accuracy.

For example, if any given substance weighed five times and the result was 5.2 kg each time, then the measurement is very precise but not necessarily accurate. Precision is independent of accuracy.

The accuracy and precision differentiation from one another that reflects how close a measurement to an accepted value (or a known value) whereas precision reflects how reproducible the measurements are. Accuracy and precision are independent of each other.

1.3.4 Significant Figures

Significant figures are essential concepts in analytical chemistry that helps the analyst in the processing of data. Significant figures are digits that are necessary to express the result of a measurement to the precision with which measurement is made.

Digits that generate from measurement are written such that the last digit only is subject to uncertainty, e.g., four significant figures means that three are known and the last one is uncertain. Zeros within the number are significant, and a zero at the end of a number, if included, is counted as a significant figure. For example, in 3575 cm, there are four significant figures, and in 0.743, there are three significant figures.

Significant Figures Rules

There are some specific rules that should be followed to measure the significant figures of a calculated measurement. These are the significant figures rules that govern the determination of significant figures:

1. All non-zero digits are significant. For example, in 8575 cm, there are four significant figures, and in 0.443, there are three significant figures.
2. When in any digit zero precedes the non-zero digit, then it is not significant. The preceding zero indicates the location of the decimal point. In 0.007, there is only one and the number 0.00532 has three figures.
3. When in any digit there is a zero between two non-zero digits, then it is also a significant figure. For example, 6.3006 have five significant figures.
4. When in any digit zeroes occur at the end or on the right side of the number, then it is also significant. For example, 0.600 has three significant figures.
5. Counting the number of objects. For example, 3 apples and 20 mangoes have infinite figures as these are inexact numbers.

Exact Numbers

Exact numbers are usually defined numbers or it is the result of a count. It is a value that is known with complete certainty. In other words, an exact number has zero uncertainty and an infinite number of significant figures. An exact number cannot be reduced or simplified.

For example, 1 foot = 12 inches. There are exactly 12 inches in one foot. Therefore, if a number is exact, it does neither affect the accuracy of a calculation nor the precision of the expression. Another example of this are defined numbers – a dozen is described as 12 objects, and a pound is described as 16 ounces, number of centimeters in one inch, number of people in a room, etc.

- The number 1.4589 (five significant figures) is multiplied by 1.2 (two significant figures). The product, which is equal to 1.75068, would be reported as 1.8 (two significant figures).
- The number 1.4589 (five significant figures) is divided by 1.2 (two significant figures). The dividend, which is equal to 1.21575, would be reported as 1.2 (two significant figures).

  The addition of 5.789 (four significant figures) to 105 (three significant figures) would be reported as 111.

Rules for Calculation of Significant Figures

Addition and Subtraction:

In mathematical calculations involving significant figures, the answer is expressed in such a way that it displays the reliability of the least precise operation. For addition and subtraction, look at the right of the decimal point of the numbers only. Here is what to do: The following rules have to be used for addition and subtraction:

- First count the number of significant figures in the decimal portion of each number in the given problem. (The digits to the left of the decimal place are not used to determine the number of decimal places in the final answer.)
- Add or subtract in the normal way.
- Answer round off to the least number of places in the decimal portion of any number in the problem.

For example, for addition of 1.3 and 5.71, it is observed that the first number stops its significant figures in the tenth's column, while the second number stops its significant figures in the hundredth's column. Therefore, limit the answer to the tenth's column, i.e., 1.2 + 5.71 = 6.91 (limit the final answer to the tenth's column 6.9). Here, drop the last digit, i.e., 1 because it is not significant to the final answer.

Multiplication and Division:

For multiplication and division, following rule applies:

- The answer should not contain a greater number of significant figures.
- The least number of significant figures in any number of the problem determines the number of significant figures in the answer.

Examples:

1. 2.3 × 2.42

   The answer to this problem would be 5.6 (which were rounded from the calculator reading of 5.566). 2.3 have two significant figures while 2.42 have three. Two significant figures are less precise than three. So, the answer has two significant figures.

2. 1.4589 × 1.2

   The number 1.4589 (five significant figures) is multiplied by 1.2 (two significant figures). The product, which is equal to 1.75068, would be reported as 1.8 (two significant figures).

Rules for Rounding Numbers

From various measurements, all numbers are significant. However, performing calculations often results in non-significant digits. There is a need to remove these non-significant digits by rounding off numbers. There are certain rules for rounding off numbers.

- If the first non-significant digit is less than 5, then the least significant digit remains unchanged. For example, 12.4 are rounded to 12.
- If the first non-significant digit is greater than 5, then the least significant digit is incremented by 1. Example, 12.6 is rounded to 13.
- If the first non-significant digit is 5, then the least significant digit can either be incremented or left unchanged.
- If the digit to be dropped is 5, and if any digit following it is not zero, then the last remaining digit is increased by one. For example, 12.51 are rounded to 13.
- If the digit to be dropped is 5 and followed only by zeroes, then the last remaining digit is increased by one if it is odd, but left as it is if even. For example, 11.5 are rounded to 12 and 12.5 is rounded to 12. This rule means that if the digit to be dropped is 5 followed only by zeroes, then the result is always rounded to the even digit. The rationale is to avoid bias in rounding: half of the time we round up, half the time we round down.

Example 1:

Suppose to round 62.5347 to four significant figures. Look at the fifth figure. It is a 4, a number less than 5. Therefore, you will simply drop every figure after the fourth, and the original number rounds off to 62.53.

Example 2:

Round 3.78721 to three significant figures. Look at the fourth figure. It is 7, a number greater than 5. So, you round the original number up to 3.79.

1.4 IMPURITIES IN PHARMACEUTICALS

Impurities

Pharmaceutical impurities are the undesirable elements or substances that remain with active pharmaceutical ingredients (APIs) or which develop during formulation. These unwanted chemicals or elements observed in drug substances may arise during synthesis or may be developed from sources such as starting materials, intermediates, reagents, solvents, catalysts, and reaction by-products during drug product development.

Sources of Impurities in Pharmaceuticals

The various sources of impurity in pharmaceutical products are — reagents, heavy metals, ligands, catalysts, other materials like filter aids, charcoal, degraded end products obtained during or after manufacturing of bulk drugs from hydrolysis, photolytic cleavage, oxidative degradation and de-carboxylation.

The presence of the unwanted chemicals, even in small amount, may affect the quality, safety and efficacy (QSE), of the pharmaceutical products.

According to ICH guidelines, impurities in the drug substance produced by chemical synthesis can broadly be classified into following three categories:

- Organic Impurities (Process and Drug related)
- Inorganic Impurities
- Residual Solvents

1.4.1 Classification of Sources of Impurities

The different sources of impurities in pharmaceuticals are listed below:

1. Raw Materials

Pharmaceutical substances are produced by isolation from natural sources and also synthesized by using chemicals as starting material. Impurities in the raw ingredients may contaminate the end product during the manufacturing process.

Practically, mixtures of closely related substances occur together, e.g., barium and magnesium impurities are found in calcium minerals, zinc accompanies with magnesium or iron compounds, and aluminum ores are usually accompanied by alkali and alkaline earth compounds.

Sodium chloride prepared from rock salt is contaminated with small amounts of calcium and magnesium chloride. Therefore, sodium chloride prepared from rock salt will contain traces of calcium and magnesium compounds.

Rock salt → Calcium Sulphate ($CaSO_4$) + Magnesium Chloride ($MgCl_{12}$) = NaCl prepared

2. Process of Manufacturing

Manufacturing process may introduce new impurities into the final product due to contamination with reagents, catalysts and solvents employed at various steps in manufacturing process. The new impurities may also arise from the reaction vessels and reaction intermediates.

Many drugs and chemicals (usually organic) are manufactured from different raw materials by using different methods or processes.

(a) Reagents Used in the Manufacturing Process:

- Calcium carbonate is synthesized by the reaction of a soluble calcium salt with a soluble sodium carbonate (Na_2CO_3). Therefore, Calcium carbonate ($CaCO_3$) is exposed to contain impurities of soluble alkali.

$$CaCl_2 + Na_2CO_3 \rightarrow CaCO_3 \downarrow + 2NaCl$$

- When hydrogen peroxide is used as reagent in the chemical synthesis, it can contaminate the final product because of the presence of barium ion as an impurity in hydrogen peroxide.
- Anions such as Cl^- and $SO4^{-2}$ are the common impurities present in many substances because HCl and H_2SO_4 are frequently used in manufacturing process.

(b) Reagents Added to Remove Other Impurities:

Potassium bromide contains small amount of barium, which is added in the manufacturing process to remove excess of sulphate.

(c) Solvents:

Various solvents used in the preparation and purification may also result in the contamination of the pharmaceutical substances. Water is the popular solvent available and is used quite frequently in the preparation and can be the major source of impurities, e.g.,

- Softened water contains Na^+ and Cl^- ions as impurity.
- Demineralized water has pyrogens, bacterias and organic impurities.
- Tap water contain impurities of Ca^{2+}, Mg^{2+}, Na^+, Cl^- , CO_3^{-2} and SO_4^{-2} in trace amounts.

(d) Reaction Vessels:

- Certain solvents and reagents used in the process may react with the metals of reaction vessels, leading to their corrosion and passing traces of metal impurities into the solution and contaminate the final product.
- Glassware may give traces of alkali to the solvent.
- Lead (Pb) may be found as impurity in commercial sulphuric acid which has been manufactured by lead chamber process.

(e) Intermediates:

During the manufacturing process, some intermediates are formed. Sometimes, these intermediates may carry impurity to the final product.

- By the reaction of sodium hydroxide and bromine, sodium bromide is prepared.

$$6NaOH + 3Br_2 \rightarrow \underset{\text{Sodium bromide}}{NaBrO_3} + 5NaBr + 3H_2O$$

In the above reaction, first an intermediate sodium bromate is formed and then it may reduce to sodium bromide by heating the residue (obtained by evaporating the solution to dryness) with charcoal.

$$\underset{\text{Sodium bromate}}{NaBrO_3} + 3C \rightarrow \underset{\text{Sodium bromide}}{NaBr} + 3CO$$

If the intermediate (sodium bromate) is not completely converted to the sodium bromide, then it is likely to be present as an impurity in the final product.

- Potassium iodide is prepared by reacting Iodine with Potassium hydroxide.

$$6KOH + 3I_2 \rightarrow 5KI + KIO_3 + 3H_2O$$

The resulting solution is first evaporated and then heated with charcoal.

$$KIO_3 + 3C \rightarrow KI + 3CO$$

In this reaction if the intermediate product (KIO_3) is not completely converted into KI, then it may act as an impurity in the final product.

(f) Atmospheric Impurity during the Manufacturing Process:

The atmosphere dust particle may contain aluminium oxide, sulphur, silica, porcelain, soot, etc., and some gases like carbon dioxide, sulphur dioxide, arsine and hydrogen sulphide. These traces of impurities may contaminate the final product during the manufacturing process.

- Sometimes, substances such as sodium hydroxide readily absorb atmospheric CO_2 when exposed to atmosphere.

$$2NaOH + CO_2 \rightarrow Na_2CO_3 + H_2O$$

- Calcium hydroxide solutions can absorb carbon dioxide from the atmosphere to form calcium carbonate.

$$Ca(OH)_2 + CO_2 \rightarrow CaCO_3 + H_2O$$

3. Manufacturing Hazards

Certain manufacturing hazards can lead to product contamination. The various manufacturing hazards are:

(a) Contamination from the Particulate Matter:

- The unwanted particulate matter may arise by a number of ways, such as an accidental inclusion of dirt or glass, porcelain, plastic or metallic fragments from sieves, granulating, tabletting and filling machines or from product containers.
- Ware and tare of equipment or improper cleaning of equipment may also cause particulate contamination.

(b) Cross-contamination of the Product:

- The handling of powders, granules and tablets in large bulk creates air-borne dust, which leads to cross-contamination of the product.
- Cross-contamination is hazardous, especially in case of steroidal and other synthetic hormones. Therefore, it should be carefully controlled.
- Certain protection such as use of face mask and special extraction equipment can minimize these undesirable contaminations.

(c) Microbial Contamination:

- Many parenteral and ophthalmic preparations are sensitive to contamination by microbes from the atmosphere. During manufacturing of these products, sterility testing is done and it provides an adequate control for microbial contaminations in such preparations.
- Many liquid preparations and creams are liable to bacterial and fungal contamination. Microbial contamination can be controlled by adding suitable antimicrobial and antifungal agents.

(d) Errors in the Manufacturing Process:

- Sometimes, errors arise from incomplete solution of a solute in a liquid preparation and must be detected readily by the normal analytical control procedures.

- An appropriate examination on the efficiency of mixing, filling, tabletting, sterilization, etc. should be exercised in order to obtain a product of maximum purity and desired quality.
- Minor errors arise if the manufacturing tolerance for the quantity of active ingredient in the product has been wide.

(e) Errors in the Packaging:

- Preparations that are same in appearance such as tablets of same size, shape, color, etc. packed in similar containers can result in mislabeling of either or both of the products.
- Suitable care should be taken to avoid the handling of such products in the close proximity.
- Inappropriate labeling or destruction of stock of unused labels also constitutes a major packaging hazard.

4. Instability of the Product

(a) Changes in Physical Properties:

During storage of pharmaceutical products, some changes in physical properties may occur like changes in crystal size, shape, sedimentation, agglomeration and caking of the suspended particles. These physical changes affect the physical appearance as well as therapeutic efficacy of pharmaceutical product.

(b) Chemical Instability:

- Various pharmaceutical products undergo chemical decomposition in inadequate storage conditions. This chemical decomposition is often catalyzed by light, traces of acid or alkali, traces of metallic impurities, air oxidation, carbon dioxide and water vapours.
- The photosensitive substances should be protected from light by storing them in darkened glass or metal containers thereby inhibiting photochemical decomposition.
- The products that are susceptible to oxidation by air or attack by moisture should be stored in sealed containers.

(c) Temperature:

- Chemical and physical changes may occur in the substances if not stored at proper temperature.
- The temperature sensitive substances should store in a condition that protect them from undesirable decomposition.

(d) Reaction with Container Material:

- Certain preparations are susceptible to reaction with metal surfaces such as salicylic acid.
- Atropine sulphate injection must be packed in glass ampoules which comply with the test of hydrolytic resistance. Therefore, such preparations must not be packed in containers made from soda glass.
- Plastic containers give undesirable additives, such as plasticizers, particularly in the presence of non-aqueous solvents.

1.4.2 Importance of Limit Test

Limit Test:

Limit test is described as quantitative or semi-quantitative test designed to identify and control small amount of impurities which are likely to be present in the substance. Limit test is mainly carried out to determine the inorganic impurities present in the substance and compare it with standard to find out:

- the harmful amount of impurities
- the avoidable/unavoidable amount of impurities

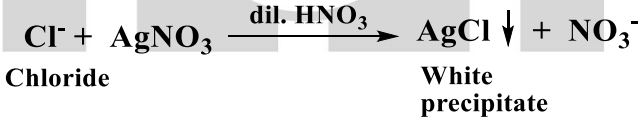
Specificity of the Test:

Any test applied as a limit test necessarily gives some form of selective reaction with the impurity. Various tests are used for the detection of inorganic impurities in official inorganic substances are based upon the separations involved in inorganic qualitative analysis. These tests may be performed in order to exclude one specific impurity, but highly specific tests are not always the best; a less specific test, which limits several likely impurities. At the same time, these tests are advantageous, and in fact, can often be accomplished.

1.4.3 Limit Test for Chlorides

Principle:

This test is based upon the chemical reaction between silver nitrate and soluble chlorides in the presence of dilute nitric acid to form opalescence of silver chloride. Appearance of opalescence is then compared with the standard solution. If the opalescence in the sample is less than the standard, it passes the test. If it is more than the standard, it fails the test.



Procedure: Limit Test for Chlorides:

Test Solution	Standard Solution
1. Specified quantity of sample is dissolved in water (10 ml) or solution is prepared as directed in the pharmacopoeia and transferred in Nessler cylinder.	1. Take 1 ml of 0.05845% w/v solution of sodium chloride in Nessler cylinder.
2. Add 10 ml of dilute nitric acid.	2. Add 10 ml of nitric acid.
3. Diluted to 50 ml with water in Nessler cylinder.	3. Diluted to 50 ml with water in Nessler cylinder.
4. Add 1 ml of $AgNO_3$ solution.	4. Add 1 ml of $AgNO_3$ solution.
5. Stirred immediately with glass rod.	5. Stirred immediately with glass rod.
6. Keep aside for 5 minutes.	6. Keep aside for 5 minutes.
7. Observe the Opalescence/Turbidity.	7. Observe the Opalescence/Turbidity.

Observation:

Observe the opalescence produce in sample solution. It should not be greater than standard solution. If opalescence produces in sample solution is less than the standard solution, then the sample will pass the limit test of chloride and *vice versa*.

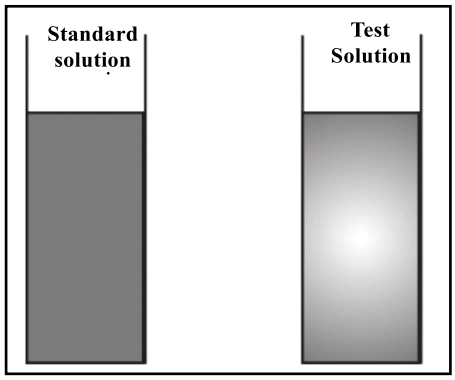


Fig. 1.1: Limit test for Chloride

Reasons:

Nitric acid is added in the limit test of chloride to make solution acidic and help silver chloride precipitate to make solution turbid at the end of process.

1.4.4 Limit Test for Sulphates

Principle:

Limit test for sulphate is based on the reaction between soluble sulphate and barium chloride in the presence of dilute hydrochloric acid to form barium sulphate which appears as solid particles (turbidity) in the solution. Compare the turbidity produced by a given amount of the sample with a reference turbidity obtained from standard solution.

$$\underset{\text{Sulphate}}{SO_4^{-2}} + BaCl_2 \xrightarrow{\text{dil. HCl}} \underset{\text{White precipitate}}{BaSO_4\downarrow} + 2Cl^-$$

Procedure: Limit Test for Sulphates:

Test Sample	Standard Turbidity
1. Specific quantity of compound is dissolved in water or solution is prepared as directed in the pharmacopoeia and transferred in Nessler cylinder.	1. Take 1 ml of 0.1089% w/v solution of potassium sulphate in Nessler cylinder.
2. Add 2 ml of dilute hydrochloric acid.	2. Add 2 ml of dilute hydrochloric acid.
3. Diluted to 45 ml with water.	3. Dilute to 45 ml with water.
4. Add 5 ml of barium sulphate reagent.	4. Add 5 ml of barium sulphate reagent.
5. Stirred immediately with glass rod.	5. Stirred immediately with glass rod.
6. Allow to stand for 5 minutes.	6. Allow to stand for 5 minutes.
7. Observe the Turbidity.	7. Observe the Turbidity.

Observation:

Compare the turbidity produce in sample solution. It should not be greater than standard solution. If turbidity produced in sample solution is less than the standard solution, the sample will pass the limit test of sulphate and *vice versa*.