📚 B. Pharmacy 1st Semester - Pharmaceutical Inorganic Chemistry

🔬 UNIT - 1: IMPURITIES IN PHARMACEUTICAL SUBSTANCES

📋 POINTS TO BE COVERED IN THIS TOPIC

➡ History of Pharmacopoeia
➡ Sources and Types of Impurities
➡ Chloride Limit Test
➡ Sulphate Limit Test
➡ Iron Limit Test
➡ Arsenic Limit Test
➡ Lead Limit Test
➡ Heavy Metals Limit Test
➡ Modified Limit Test for Chloride and Sulphate

📖 HISTORY OF PHARMACOPOEIA

🏛️ PHARMACOPOEIA

The term "pharmacopoeia" originates from ancient Greek, where "pharmacon" means drug and "poeia" means to make. A pharmacopoeia represents a legally binding collection prepared by national or regional authorities, containing comprehensive lists of medicinal substances, crude drugs, and formulas for preparing pharmaceutical preparations from these substances.

📚 CONTENTS OF PHARMACOPOEIA

The pharmacopoeia serves as a complete reference document containing the following essential information:

- List of drugs and other related pharmaceutical substances
- Sources and origins of medicinal compounds
- Detailed descriptions and characteristics
- Standardized tests and analytical procedures
- Formulas for preparation and manufacturing processes
- Therapeutic uses and applications
- Recommended doses and dosage guidelines
- Proper storage conditions and requirements

🌍 DIFFERENT TYPES OF PHARMACOPOEIAS

Various countries and regions maintain their own pharmacopoeial standards to ensure drug quality and safety:

- United States Pharmacopoeia (USP)
- Indian Pharmacopoeia (IP)
- British Pharmacopoeia (BP)
- German Pharmacopoeia (Ph. Eur.)
- Mexican Pharmacopoeia
- French Pharmacopoeia
- Japanese Pharmacopoeia (JP)

IN INDIAN PHARMACOPOEIA

The Indian Pharmacopoeia Commission operates as an autonomous institution under the Ministry of Health and Family Welfare, Government of India. This commission establishes comprehensive standards for all drugs manufactured, sold, and consumed within India, ensuring public health and safety through rigorous quality control measures.

Edition	Year	Supplements/Addendum
1st Edition	1955	Supplement 1960
2nd Edition	1966	Supplement 1975, Addendum 1989
3rd Edition	1985	Addendum 1989, Addendum 1991
4th Edition	1996	Addendum 2000, Vet supplement 2000, Addendum 2002, Addendum 2005
5th Edition	2007	Addendum 2008
6th Edition	2010	Addendum 2012
7th Edition	2014	Addendum 2015, Addendum 2016
8th Edition	2018	Addendum 2019

✨ SALIENT FEATURES OF INDIAN PHARMACOPOEIA EDITIONS

🥇 First Edition (1955)

The inaugural edition of the Indian Pharmacopoeia established the foundation for pharmaceutical standards in India. It covered 986 comprehensive monographs, presenting all titles in Latin language following international conventions. The weight and measurement systems were standardized to the metric system while doses were expressed in both metric and English systems for broader accessibility. The edition featured abbreviated titles for convenience and used descriptive terms for solubility rather than exact numerical values.

🥈 Second Edition (1966)

This edition marked a significant transition by changing monograph titles from Latin to English, making the content more accessible to Indian practitioners. Solubility was now expressed precisely in parts of solvent per unit part of solute. The edition expanded with 93 new monographs and incorporated advanced analytical techniques. The sterility test underwent modification to detect fungal contamination, enhancing safety standards.

🥉 Third Edition (1985)

A major expansion occurred with 260 new monographs added and 450 existing ones amended. Revolutionary analytical techniques including flame photometry, electrophoresis, and fluorometry were introduced. The concept of dissolution testing was implemented for the first time. Microbial limit tests became mandatory for liquid preparations, and gas-liquid chromatography gained official recognition. Viscosity determination methods were modified to incorporate the Ostwald viscometer.

🏅 Fourth Edition (1996)

This comprehensive edition contained 1149 monographs and 123 appendices distributed across two volumes. Computer-generated structural formulae replaced hand-drawn diagrams. Infrared and ultraviolet absorption spectrophotometric tests were added for drug identification. The edition included 294 new monographs while removing 110 outdated ones. High-Pressure Liquid Chromatography (HPLC) became an official analytical method, and bacterial endotoxin tests were introduced. A veterinary supplement containing 208 monographs and four appendices was also published.

🏅 Fifth Edition (2007)

The fifth edition was presented in three well-organized volumes. Volume one contained general notices, IPC structure, and acknowledgements. Volumes two and three included general monographs covering dosage forms, drug substances, and pharmaceutical aids, providing comprehensive coverage of pharmaceutical materials.

🏆 Sixth Edition (2010)

This edition maintained the three-volume structure with improved organization. Volume one contained notices, preface, IPC structure, and general chapters. Volume two covered monographs from A to M, while volume three covered N to Z. The microbial contamination chapter received significant updates, and a new chapter on liposomal products was added to address emerging pharmaceutical technologies.

💎 Seventh Edition (2014)

Published in four comprehensive volumes, this edition contained 2567 monographs, including 577 completely new entries. For the first time, 19 radiopharmaceutical monographs were introduced, reflecting advances in nuclear medicine. The edition included 10 antibiotic monographs, 31 herbal monographs, 5 vaccines and immunosera for human use, 6 insulin products, and 7 biotechnological products, along with 19 new general chapters.

👑 Eighth Edition (2018)

The latest edition significantly expanded the use of chromatographic methods to provide greater specificity in assays and better assessment of impurities in ingredients and products. Pyrogen tests were replaced by Bacterial Endotoxin Tests (BET) in parenteral preparations and other monographs. The edition included 53 new Fixed-Dose Combination (FDC) monographs, with 25 being unique to the Indian Pharmacopoeia. General chapters on volumetric glassware, conductivity, dissolution test, disintegration test, and dimensions of hard gelatin capsule shells were revised. Guidelines for maintenance, identification, preservation, and disposal of microorganisms were also updated.

🧪 SOURCES AND TYPES OF IMPURITIES

⚠️ IMPURITY

An impurity refers to the presence of unwanted foreign particles other than the active pharmaceutical ingredient, which may or may not be toxic and is found in pharmaceutical substances. These impurities can significantly affect drug safety, efficacy, and stability, making their identification and control crucial in pharmaceutical manufacturing.

🔍 SOURCES OF IMPURITY

Pharmaceutical substances can become contaminated through various sources during manufacturing, storage, and handling processes:

🏭 Raw Materials Employed in Manufacture

Raw materials used in pharmaceutical manufacturing often contain inherent impurities from their natural sources or previous processing steps. It becomes essential to employ pure chemicals and substances as starting materials to minimize contamination. Natural minerals and extracted compounds frequently carry trace impurities that can affect the final product quality.

⚗️ Reagents Employed in Manufacturing Process

When reagents used during manufacturing processes are not completely removed through washing or purification steps, they may remain as residual impurities in the final product. Complete removal of processing reagents requires thorough washing procedures and effective purification techniques.

💧 Solvents

Water serves as the most common solvent in large-scale pharmaceutical manufacturing. Impure water can introduce trace impurities including sodium, calcium, magnesium, carbonate, chloride, and sulfate ions into the final product. These impurities can be effectively avoided by using purified water that meets pharmacopoeial standards.

🔧 Action of Reagents on Reaction Vessels

Reaction vessels used in manufacturing processes may be constructed from various metals including iron, cast iron, galvanized iron, copper, silver, aluminum, nickel, zinc, and lead. Chemical reactions between reagents and vessel materials can introduce metallic impurities into pharmaceutical products.

🌬️ Atmospheric Contamination During Manufacturing

The manufacturing environment may introduce atmospheric contaminants including dust particles containing sulfur, aluminum oxide, silica, and soot. Gaseous contaminants such as carbon dioxide, sulfur dioxide, arsine, and hydrogen sulfide can also contaminate pharmaceutical products during open processing steps.

🧪 LIMIT TEST

A limit test is defined as a quantitative or semi-quantitative analytical procedure designed to identify and control small quantities of impurities that are likely to be present in pharmaceutical substances. These tests establish maximum acceptable limits for specific impurities, ensuring product safety and quality.

🧂 LIMIT TEST OF CHLORIDE

🔬 PRINCIPLE

The limit test for chloride is based on the chemical reaction between soluble chloride ions and silver nitrate in the presence of dilute nitric acid. This reaction forms silver chloride, which appears as solid particles creating opalescence in the solution. The intensity of opalescence is directly proportional to the chloride concentration present in the test substance.

Chemical Reaction: $Cl^- + AgNO_3 \rightarrow AgCl + NO_3^-$

📝 PROCEDURE

Test Sample	**Standard Compound**
Specific weight of compound dissolved in water or solution prepared as per pharmacopoeia and transferred to Nessler cylinder	1 ml of 0.05845% W/V sodium chloride solution in Nessler cylinder
Add 1 ml nitric acid	Add 1 ml nitric acid
Dilute to 50 ml in Nessler cylinder	Dilute to 50 ml in Nessler cylinder
Add 1 ml $AgNO_3$ solution	Add 1 ml $AgNO_3$ solution
Keep aside for 5 minutes	Keep aside for 5 minutes
Observe opalescence/turbidity	Observe opalescence/turbidity

👁️ OBSERVATION

The opalescence produced in the sample solution should not exceed that produced in the standard solution. If the opalescence in the sample solution is less than the standard solution, the sample passes the chloride limit test. Conversely, if the sample shows greater opalescence, it fails the test.

REASONS

Nitric acid is added to make the solution acidic, which helps silver chloride precipitate effectively and creates visible turbidity at the end of the process. The acidic environment prevents interference from other anions that might otherwise react with silver nitrate.

LIMIT TEST OF SULPHATE

PRINCIPLE

The limit test for sulfate operates on the reaction between soluble sulfate ions and barium chloride in the presence of dilute hydrochloric acid to form barium sulfate. This compound appears as solid particles creating turbidity in the solution. The turbidity produced is compared with a standard solution to determine compliance.

The barium sulfate reagent contains barium chloride, sulfate-free alcohol, and a small amount of potassium sulfate. Alcohol prevents supersaturation and promotes more uniform turbidity development, ensuring accurate and reproducible results.

Chemical Reaction: $SO_4^{2-} + BaCl_2 \rightarrow BaSO_4 + 2Cl^-$

OBSERVATION

The opalescence produced in the sample solution should not exceed that produced in the standard solution. If the opalescence in the sample solution is less than the standard solution, the sample passes the sulfate limit test. Greater opalescence indicates failure to meet the specified limits.

🧐 REASONS

Hydrochloric acid creates an acidic environment that facilitates optimal precipitation conditions. Potassium sulfate increases test sensitivity by providing ionic concentration in the reagent. Alcohol prevents supersaturation, ensuring uniform and consistent turbidity development for accurate comparison.

🧪 LIMIT TEST OF IRON

🔬 PRINCIPLE

The limit test for iron is based on the reaction of iron in ammoniacal solution with thioglycolic acid in the presence of citric acid to form iron thioglycolate, which exhibits a pale pink to deep reddish-purple color. Ferric ions are reduced to ferrous ions by thioglycolic acid, and the resulting compound is ferrous thioglycolate.

Citric acid forms a soluble complex with iron, preventing its precipitation by ammonia as ferrous hydroxide. Color development occurs only in alkaline conditions. The color results from coordination compound formation - ferrous thioglycolate - which remains stable in the absence of air but fades when exposed to air due to oxidation. Therefore, color comparison must be performed immediately after the specified development time.

Chemical Reaction: Fe^{3+} + Thioglycolic acid + NH_3 → Fe-thioglycolate complex (purple color)

👁️ OBSERVATION

The purple color produced in the sample solution should not exceed that produced in the standard solution. If the purple color in the sample solution is less intense than the standard solution, the sample passes the iron limit test. Greater color intensity indicates excessive iron content.

🧐 REASONS

Citric acid prevents iron precipitation by ammonia through complex formation. Thioglycolic acid facilitates the reduction of ferric ions to ferrous ions. Ammonia creates the alkaline environment necessary for color development and complex formation.

🧪 LIMIT TEST OF ARSENIC

🔬 PRINCIPLE

The principle is based on the Gutzeit Test, wherein all arsenic present is converted into arsine gas (AsH_3) through reduction with zinc and hydrochloric acid. The limit test for arsenic relies on the reaction of arsenic gas with hydrogen ions to form a yellow stain on mercuric chloride paper in the presence of reducing agents like potassium iodide.

The stain intensity is proportional to the arsenic amount present in the sample. This stain is compared with that produced from a known arsenic amount. The Indian Pharmacopoeia prescribes limits for arsenic presence (not more than 2 ppm) as an impurity in various pharmaceutical substances. The apparatus used for arsenic limit testing is called the Gutzeit apparatus.

Chemical Reaction: $As + Zn + HCl \rightarrow AsH_3 + ZnCl_2 + H_2$

👁️ OBSERVATION

If the sample shows a stain of lesser intensity than the standard stain, the sample passes the arsenic limit test as per Indian Pharmacopoeia specifications. Greater stain intensity indicates excessive arsenic content requiring rejection.

🏗️ GUTZEIT TEST APPARATUS

The Gutzeit apparatus consists of a specialized setup designed for arsine gas generation and detection. The apparatus includes reaction vessels, gas delivery tubes, and mercuric chloride papers positioned to capture and react with evolved arsine gas.

🧐 REASONS

Stannous chloride ensures complete arsine evolution from the sample. Zinc, potassium iodide, and stannous chloride function as reducing agents in the reaction. Hydrochloric acid provides the acidic environment necessary for the reduction reaction. Lead acetate pledgets or papers trap any hydrogen sulfide that may evolve along with arsine, preventing interference.

🧪 LIMIT TEST OF LEAD

🔬 PRINCIPLE

The limit test for lead is based on the chemical reaction between lead and diphenyl thiocarbazone (dithizone) in alkaline solution to form lead dithizone, which exhibits a red color. Pure dithizone appears green, while lead dithizone formed is violet. The net resultant color of the solution becomes red due to this color combination.

To avoid interference from other metals and optimize pH conditions, reagents including ammonium citrate, potassium cyanide (KCN), and hydroxylamine hydrochloride ($NH_2OH \cdot HCl$) are employed in the testing procedure.

Chemical Reaction: Pb^{2+} + Dithizone (alkaline medium) → Lead dithizone complex (red color)

👁️ OBSERVATION

The color intensity of the complex depends directly on the lead amount present in the solution. The color produced in the sample solution should not exceed that produced in the standard solution. Greater color intensity indicates excessive lead content beyond acceptable limits.

🧪 LIMIT TEST OF HEAVY METALS

🔬 PRINCIPLE

The limit test for heavy metals is based on the reaction of metallic impurities with hydrogen sulfide in acidic medium. The reaction products are sulfides of respective metals. In acidic media, these reactions produce reddish or black colors with hydrogen sulfide, which are compared with standard lead nitrate solution.

Metallic impurities in pharmaceutical substances are expressed as parts of lead per million parts of the substance. The usual limit according to the Indian Pharmacopoeia is 20 ppm. Metals that respond to this test include lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum.

Chemical Reaction: Metal^{2+} + H_2S → Metal sulfide (brownish/black color) + H^+

OBSERVATION

The color produced in the sample solution should not exceed that produced in the standard solution. If the color produced in the sample solution is less than the standard solution, the sample passes the heavy metals limit test. Greater color intensity indicates failure to meet specifications.

MODIFIED LIMIT TEST FOR CHLORIDE

PRINCIPLE

In modified chloride limit tests, precipitation measurement is used to determine concentration. In the presence of dilute nitric acid, chlorides precipitate when silver nitrate reacts with soluble chloride to produce silver chloride, appearing as solid particles in solution. The turbidity intensity depends on the chloride amount present in the test substance.

PROCEDURE

The chloride limit test has been modified in the context of standard solution preparation. Previously, chlorine solution was prepared by dissolving sodium chloride, but this has been modified by substituting hydrochloric acid for sodium chloride.

Modified Chemical Reaction: $HCl + AgNO_3 \rightarrow AgCl + HNO_3$

👁 CONCLUSION

When the opalescence produced in the sample solution is lower than that produced in the standard solution, the sample passes the chloride limitation test. This modification provides improved accuracy and reproducibility in chloride determination.

🔄 MODIFIED LIMIT TEST FOR SULFATE

🔬 PRINCIPLE

The modified limit test for sulfates uses precipitation as its fundamental principle. Sulfate ions react with barium chloride in the presence of hydrochloric acid, causing only sulfate to precipitate while other acid radicals do not react with barium chloride, as hydrochloric acid prevents reactions of different acid radicals with barium chloride.

Chemical Reaction: $SO_4^{2-} + BaCl_2\ (HCl) \rightarrow BaSO_4 + 2Cl^-$

🧪 REAGENT PREPARATIONS

Barium Sulfate Reagent

Prepare 0.05 M barium chloride solution by dissolving 12 grams of barium chloride in 1000 ml of water. Add 55 ml water, 20 ml alcohol, and 5 ml of 0.0181% w/v potassium sulfate solution to 15 ml of the prepared solution. Make up the volume to 100 ml.

Standard Potassium Sulfate Solution

Accurately weigh 0.1089 g of K_2SO_4 and make up the volume to 100 ml with water.

🧪 TEST SOLUTION

- **Sodium Chloride:** Dissolve 2 grams of sodium chloride in 20 ml of water
- **Sodium Bicarbonate:** Dissolve 2 grams of sodium bicarbonate in small quantities of water

📝 PROCEDURE

Limit tests for sulfate have undergone extensive modification, eliminating the need for complex barium sulfate reagents. The method still uses alcohol and barium chloride for turbidity comparison, providing improved accuracy and simplified procedures.

📚 CONCLUSION

The study of impurities in pharmaceutical substances represents a critical aspect of pharmaceutical quality control. Understanding the history and evolution of pharmacopoeias provides insight into the development of standardized testing procedures. The various sources of impurities highlight the importance of controlling manufacturing conditions and raw material quality.

Limit tests for chloride, sulfate, iron, arsenic, lead, and heavy metals provide essential tools for ensuring pharmaceutical safety and efficacy. The modified limit tests represent improvements in analytical methodology, offering enhanced accuracy and simplified procedures for routine quality control operations.

These analytical procedures form the foundation of pharmaceutical quality assurance, ensuring that medicines meet safety standards and provide therapeutic benefits without harmful impurities. Continued development and refinement of these methods contribute to the advancement of pharmaceutical science and public health protection.