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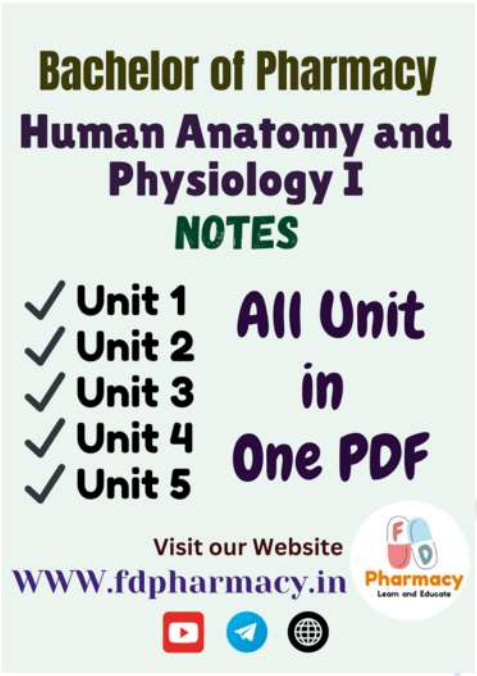
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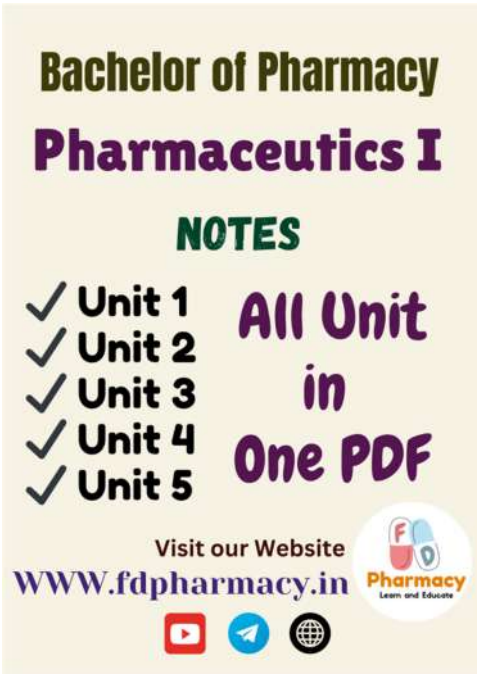
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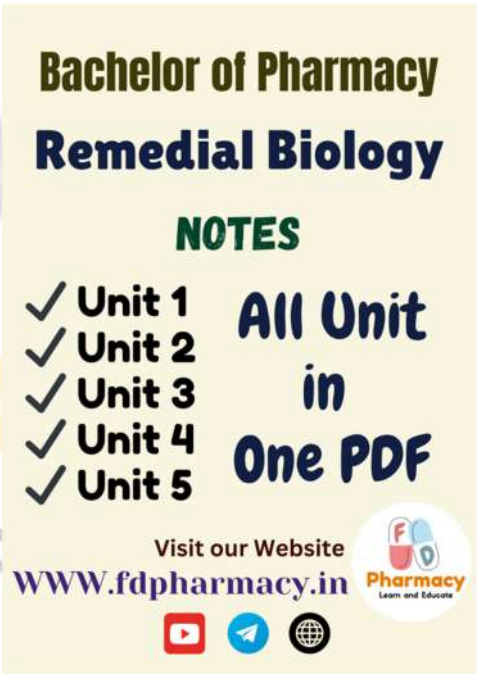
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PHARMACEUTICAL INORGANIC CHEMISTRY

UNIT 1

TOPIC :

- **Impurities in pharmaceutical substances :** History of Pharmacopoeia,
  Sources and types of impurities, principle involved in the limit test for
  Chloride, Sulphate, Iron, Arsenic, Lead and Heavy metals, modified limit test for Chloride and Sulphate
- **General methods of preparation,** assay for the compounds superscripted with asterisk (*), properties and medicinal uses of inorganic compounds belonging to the following classes

Impurities in Pharmaceutical Substance

- Pharmaceutical Inorganic Chemistry is a branch of chemistry that deals with inorganic compounds and their application in pharmacy and medicine. It includes the study of elements and inorganic compounds used as:

  - **Active pharmaceutical ingredients (API)**
  - **Excipients (additives)**
  - **Analytical reagents**
  - **Disinfectants, antiseptics, radiopharmaceuticals, etc.**

Pharmacopoeia

A pharmacopoeia is an official book published by a government or medical authority that contains:

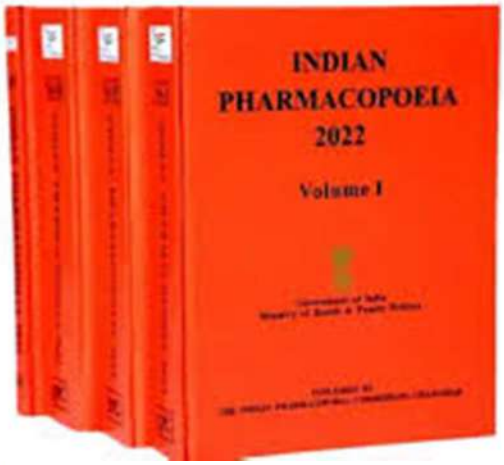
- Standards for the identity, purity, strength, and quality of drugs.
- Formulas, dosage forms, methods of preparation, and tests.
- It is used by pharmacists, chemists, and manufacturers to ensure safe and effective medicines.
- The term "pharmacopoeia" comes from the Greek words:
  - “Pharmakon” = drug or medicine
  - “Poiein” = to make or prepare
- It means “to make drugs” or “drug preparation manual”.
- It is also known as Compendia

History of Pharmacopoeia

- **Old Times (Ancient History):**
  - Medicines were written on clay tablets in Babylon and papyrus in Egypt.
  - Ebers Papyrus (1500 BC) is one of the oldest medical records.
- **Greek and Roman Time:**
  - Dioscorides (a Greek doctor) wrote a book called *De Materia Medica* about plants and medicines.
  - Galen (a Roman doctor) made many medicine mixtures called **Galenicals**.
- **First Official Book – 1498:**
  - *Antidotarium Florentinum* was printed in Italy – this was the first official pharmacopoeia.
- **1546 – Germany:**
  - *Dispensatorium* was written by Valerius Cordus. It became an official medicine book in Germany.
- **1618 – England:**
  - *London Pharmacopoeia* was published by the Royal College of Physicians to make drug standards in London.
- **1820 – United States:**
  - The first U.S. Pharmacopoeia (USP) was printed by doctors to make standard rules for medicines.
- **1864 – British Pharmacopoeia (BP):**
  - Combined all regional books of England into one national standard book.
- **1955 – Indian Pharmacopoeia (IP):**
  - First Indian Pharmacopoeia was published.
  - It is updated regularly by the Indian Pharmacopoeia **Commission (IPC)**.
- **1964 – European Pharmacopoeia (Ph. Eur.):**
  - A common book made for European countries to follow the same drug standards.

Indian Pharmacopoeia (I.P.)

- Indian Pharmacopoeia ia an official document meant for overall quality control and assurance of pharmaceutical product marketed in India by way of contributing to their safety & affordability.
- The Indian Pharmacopoeia is published by the Indian Pharmacopoeia Commission (IPC) on the behalf of the Ministry of Health and Family Welfare, Government of India.
- The Indian Pharmacopoeia is being produced to fulfil the requirement in the Drug & Cosmectics Rules, 1945 of standard of drugs produced in India



Editions of Indian Pharmacopoeia

S.No.of Edition	Year of Publication	Year of Addendum Released
First	1955	1960
Second	1966	1975
Third	1985	1989,1991
Fourth	1996	2000,2002,2005
Fifth	2007	2008
Sixth	2010	2012
Seventh	2014	2015
Eighth	2018	2019

Impurities

- An impurity is any unwanted chemical substance that is present within a pharmaceutical product or active pharmaceutical ingredient (API), which may affect its safety, efficacy, or stability.

Types of Impurities:

1. Organic Impurities:

→ These are impurities that come from the drug's starting materials, intermediates, or by-products during synthesis.

Examples:

- Unreacted starting materials
- By-products
- Degradation products

2. Inorganic Impurities:

→ These are impurities that come from inorganic sources, like reagents, catalysts, or raw materials used during manufacturing.

Examples:

- Heavy metals (like lead, mercury)
- Residual salts
- Filter aids or charcoal

3. Residual Solvents:

→ These are volatile solvents used during the manufacturing process that are not completely removed from the final product.

Examples:

- Ethanol
- Methanol
- Acetone

Sources of Impurities

1. Raw Materials Used in Manufacturing:

→ Impurities may be present in the starting materials, such as active pharmaceutical ingredients (APIs) and excipients.
→ Poor-quality raw materials may carry chemical contaminants or unwanted by-products.

Example:
Impure solvents or unpurified APIs.

2. Reagents and Catalysts:

- Chemical reactions used in drug synthesis often require reagents and catalysts.
- Traces of these materials may remain in the final product if not properly removed.

Example:
Residual metals like platinum, palladium, or zinc.

3. Solvents:

- Organic or inorganic solvents are used to dissolve or extract substances.
- If not fully evaporated, they remain as residual solvents in the final product.

Example:
Remaining methanol, ethanol, or acetone.

4. Manufacturing Process:

- Impurities may be formed as by-products or intermediates during synthesis.
- Improper temperature, pH, or mixing can lead to formation of unwanted chemicals.

Example:
Unreacted intermediates or side-reaction products.

5. Packaging Materials:

- Drug containers or packaging can interact chemically with the product.
- Plastic containers, rubber stoppers, or metal foils may leach chemicals into the medicine.

Example:
Phthalates from plastic bottles, lead from caps.

Limit tests

→ Quantitive tests intended for identifying and controlling small quanties of impurities which may occer in a substance are termed as limit test

→ Limit test used for :-

- Finding out the quantity of harmful impurities
- Finding out the quantity of avoidable impurities

Limit Test for Chloride

Chloride

→ This test is carried out for identifying the chloride ions present in a standard solution

Principal

- The limit test for chloride is based on a reaction that occurs between silver nitrate and soluble chloride which is insoluable in dilute nitric acid.
- The test solution appears turbid due to the formation of silver chloride in the presence of dilute nitric acid . Amount of chloride present in the test samples influences the degree of turbidity.
- Test solution is compared with the standard solution.
- By viewing transversly through both the solution against a black background in nessler's cylinder is compared the samples passes the limit test if the test solution is less turbid than the standard solution and fails in vice versa condition.

Procedure

- In this limit test a standard solution and test solution is prepared and then the appearance of there two solution is compared
  Test solution :- 1.0 gm of sample is accurately weighted and transferred to nessler cylinder dislove in 10 ml distill water . 1 ml of

nitric acid is added to this sol and volume up to 50 ml with distill water . 1 ml of silver nitrate be added to the solution stirring for 5 min after which turbidity develop

- Specified substance (1gm) + 10 ml of water + 1 ml of nitric acid + water up to 50 ml + 1 ml silver nitrate turbidity

Standard solution :- 1 ml of 0.01 m Hcl is mixed with 1 ml of nitric acid in nessler cylinder B and volume up to 50 ml with distill water . 1 ml of silver nitrate solution which produce turbidity after 5 min

- The sample passes the limit test if it is less turbid than the standard solution

Limit Test for Sulphate

Sulphate

→ This test is carried out for controlling the sulphate impurity in inorganic substance

Principle

- In the limit test for sulphate, barium chloride reacts with soluable sulphate in the presence of dilute Hcl solution . The resulting turbid solution is compared with the standard solution of acceptable limit.
- The barium sulphate reagent contain barium chloride , sulphate free alcohol, and potassium sulphate

Procedure

❖ **Test solution :-** 1 gm of sulphate is weighted and 2 ml of Hcl is added to 45ml of solution. 5 ml of $BaSo_4$ reagent is added to prepare the solution

❖ **Standard Solution :** 1 ml of 0.1089 % w/v solution of K_2So_4 is weighted and treated with 2ml of Hcl . This solution is diluated up to 45 ml .At the last the standard solution is prepared by adding 5 ml of $BaSo_4$ reagent

The limit test of sulphate is passes if it is less turbid than the standard solution

Limit Test for Iron

Iron

→ This test is carried out for controlling the iron impurities in inorganic sunstance

Principle

- The limit test for iron relies on the reaction in which iron reacts with thioglycollic acid in a solution. With ammonium citrate buffer
- It results in the formation of a purple colour solution due to the formation of mercaptoacetate
- This purple colour is compared with the standard colour containing a known amount of iron

Procedure

- **Test solution :-** 40 ml of water is added to the sampleand treated with 2 ml of 20% w/v citric acid .Then 2 drop of thioglucollic acid is added the solution is mixed made alkaline with ammonia , and volume made up to 50 ml . Then the solution is allowed to stand for 5 min so that a colour develop which is viewed vertically & compared with the standard solution
- **Standard solution :-** 40 ml of water is added to 2 ml of standard solution of iron .Then 2 ml of 20 % w/v citric acid and 2 drop of

thioglycollic acid is added to the solution the solution is made alkaline with ammonium and volume is made up to 50 ml .The solution is allowed to stand for 5 min so that a colour develop which is viwed vertically and compared with the test solution

When the colour of both the solution is compared the intensity of the colour of the test solution should be less than that of standard solution

Limit Test for Arsenic

Arsenic

→ This test is carried out for controlling the arsenic impurities on inorganic substance

Principal

- The limit test for arsenic is based on the reaction in which arsenic is converted in arsine (AsH_3) by undergoing reduction with zinc and hydrochloric acid. The use of Stannated hydrochloric acis is prescribed in the I.P

$$\underset{\text{Arsenic Acid}}{H_3Aso_4} \longrightarrow \underset{\text{Arseneous Acid}}{H_3Aso_3}$$

$$H_2Aso_3 + 6H_2 \longrightarrow \underset{\text{Arsine}}{AsH_3 \uparrow} + 3H_2O$$

- When arsine comes in contact with dry paper daturated with mercuric chloride | bomide it produce a yellow or brown stain

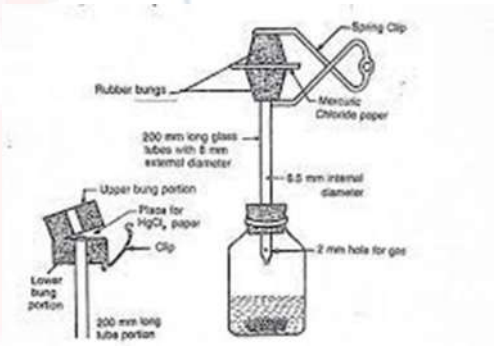
$$2AsH_3 + Hgcl_2 \longrightarrow Hg \begin{matrix} \nearrow AgH_2 \\ \searrow AgH_2 \end{matrix} + 2Hcl$$

- The intensity of the colour produce is proportional to the amount of arenic present, if the diameter of the paper exposed to arsine os constant
- The test solution of the sample is compared with the standard solution with known amount of arsenic

- The strain are the compared in natural light

Procedure

- **Test solution :** The test solution is prepared as directed in the monograph and placed in the generator bottle 5 ml of 1m potassium iodide, 5ml of stannous chloride acid solution and 10gm of zinc AsT are added to the test solution
- A test paper of mercuric chloride is placed in the rubber slit and the bottle is immediately stopped . The reaction is allowed to continus for 40 min at above 40°c.



. Apparatus used for arsenic limit test; on the left is an alternative device for securing mercuric chloride paper.

- **Standard solution :** 0.33 gm of arsenic triocide is dissolved in 5 ml of 2m NaOH solution and volume is made up to 250 ml with water 1ml of this solotion is further diluted with distilled water up to 100 ml

The stain produced by the test sample passes the test if the stain produced by it is less intense than that of the standard solution

Limit Test for Lead

Lead

Principle

→ The Limit Test for Lead is based on the formation of a colored complex between lead ions (Pb^{2+}) and dithizone (diphenylthiocarbazone) in an alkaline medium.

- Lead-dithizone complex is violet in color and extracted in chloroform.
- The intensity of violet color in the test solution is compared with a standard lead solution.

Procedure

Test Solution Preparation:

- Dissolve the sample in water or specified solvent.
- Add ammonium citrate, hydroxylamine hydrochloride, ammonia, and acetic acid.
- Transfer the mixture into a separating funnel.
- Add 5 mL of dithizone solution in chloroform.
- Shake well for 4 minutes.
- Collect the chloroform (lower) layer for observation.

Standard Solution Preparation:

- Prepare a solution with a known quantity of lead standard solution (e.g., 1 mL of 1 ppm Pb solution).
- Add same reagents: ammonium citrate, hydroxylamine hydrochloride, ammonia, acetic acid.
- Treat the solution the same way as the test solution (add dithizone, shake, collect chloroform layer).

Observation

- Compare the color of the chloroform layer from both solutions.
- Pass: If the test solution is not more intensely colored than the standard.
- Fail: If the test solution shows deeper violet color, lead content exceeds the permissible limit.

Limit Test for Heavy Metal

Heavy Metals

→ This limit test is carried out for determining the content of metallic impurities coloured by sulphide ion , under specific condition

Principle

- Limit test for heavy metals are based on the reaction between a solution of a heavy metals and a saturated solution of H_2S in an acidic medium
- A reddish / black colour resulted is compared with the standard solution of lead nitrate solution

Procedure

- **Test solution :-** 25 ml of test solution is prepared in a 50 ml of nessler cylinder and ph is adjusted between 3-4 using dilute acetic acid or dilute ammonia solution , After PH adjustment the solution is diluted up to 35 ml with water
- **Standars solution :-** 2 ml of standard lead solution is prepared out in a 50 ml nessler cylinder and diluted up to 25 ml with water. The pH is adjusted between 3-4 using dilute acetic acid pr dilute ammonia solution After pH adjustment the solution is diluted u to 35 ml with water

After that

10 ml of freshly prepared hydrogen sulphide solution is added into both the cylinder containing standard solution and test solution and diluted up to 50 ml with Water .After dilution the solution is krpt aside over a white surface for 5 min and viewed down wards the test solution colour is lighter than the standars solution colour

Modified Limit Tests for Chlorides and Sulphates

→ Normally a sample substance is weighed in specified amount and dissolved in distilled water and the volume is made up to the 50 ml mark in a Nessler cylinder for the limit tests for chlorides and sulphates. However, the nature of sample varies depending upon its physicochemical characteristics. Thus, few modifications are suggested in the limit tests of such samples.

- ❖ Alkaline nature of sample: To be dissolved in dilute acid (HNO_3 or HCI, respectively) instead of distilled water.
- ❖ Water insoluble samples (e.g., light kaolin, magnesium trisilicate etc.) are generally boiled with the corresponding acid and distilled water (to get extracted) and filtered (as insoluble matter modifies the opalescence). The filtrate is used for the test.
- ❖ Samples which react with nitric acid (for limit test of chloride): Samples like MgO, $MgCO_3$, Ca(OH), etc., are to be dissolved in acetic acid for making sample solution.
- ❖ In case of metallic salts of organic acids (e.g., sodium benzoate, sodium salicylate etc.): The free acid gets liberated on shaking with the mineral acid prescribed in the limit test. The filtrate is employed for the limit test.
- ❖ Samples which are reducing agents (e.g., hypo-phosphorous acid): Such sample can react with silver nitrate reagent in the test for

chlorides and therefore should be pre-oxidized by boiling with nitric acid before carrying the limit test.

- Colored samples: Samples like $KMnO_4$ are pre-reduced by boiling with alcohol prior to the test; while other colored substances like crystal violet, malachite green are carbonized to ash prior to the test and the ash is extracted with distilled water, filtered and the filtrate is used as the sample.