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Pharmaceutical Chemistry

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1. Pharmaceutical Impurities

KEY NOTES

Impurities in Pharmaceutical Substances

- It is almost impossible to have completely pure chemical compounds and the pure chemical composition by analysis contains traces of impurities.
- Contamination/Pharmaceutical impurities is Unwanted foreign matter present in a compound that is different from the actual molecular mechanism.
- The compound is naturally unclean if it contains unpleasant external substances which means dirt. Chemical purity is therefore free from external factors.

Pharmaceutical Impurities Sources

- The various sources of pollutants are as follows:
- The range of contaminants that may be present in a particular pharmaceutical product can be easily compiled from the knowledge of the raw materials used, the production process and the stability of the final product.
- Contamination can also result from physical contamination and improper storage conditions. The various sources of impurities are as follows:

Raw materials: Pharmaceuticals are isolated from natural resources or combined with the first chemical impurities.

- Impurities associated with raw materials can be borne by the production process to contaminate the final product.
- Natural resources include mineral resources, plants, animals and bacteria.
- Natural minerals do not usually occur in pure form
- Almost always a combination of closely related things happens together.

Method of manufacture: The process can bring about new impurities. Due to contaminated reagents, catalysts and solvents, response vessels and reactors are employed at various stages:

- Reagents are employed in the production process
- Reagents are used to eliminate other impurities from the solutions
- Intermediates
- Impurities atmospheric pollution during the production process.

Manufacturing hazards: If the manufacturer is able to control and inspect contaminants from all of the above sources there are certain production risks that could lead to product contamination.

- Contamination from particle matter
- The opposite contamination of the product
- Bacterial contamination
- Errors in the production process
- Errors in packaging.

Product instability: Contamination also occurs during storage due to the chemical instability of the pharmaceutical liquid.

Similarly, an increase in globule size of injected emulsions in storage can lead to oil accumulation.

- Chemical instability
- Changes in physical properties
- Containment of container items
- Temperature.

Types of Impurities

Drug contamination can be divided into the following categories:

1. Natural Impurities: This type of contamination in many pharmaceutical chemicals is harmless because it has no significant biological and adverse biological activity at present values. Flexible natural pollutants are residual liquid chemicals produced during drug synthesis or excipient used in the production of drug formulations. A few examples include starting materials, reaction products, intermediates, degradation products, reagents, ligands, and catalysts.

They can be identified or unknown, unstable or inconsistent, and include:

- Initiating things or mediators
- Degrading products
- Reagents, ligands and catalysts
- Enantiomeric contamination.

2. Inorganic Impurities: Inorganic impurities can also be found in production processes that are used for many

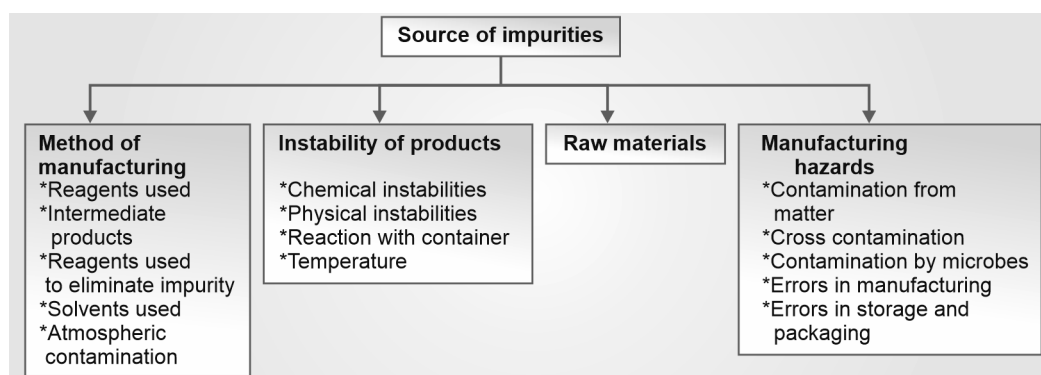


Fig. 1.1: Source of impurities



drugs. These contaminants are usually reagents, ligands, catalysts, heavy or residual metals, inorganic salts, filtration agents, or coal.

They are generally known and identified and include the following:

- Reagents, ligands and catalysts
- Heavy metals
- Other materials (e.g. filtration equipment, coal).

3. Residual Solvents: The third type of contamination in medical treatment is residual solvents. These pollutants are residues of liquid chemicals present in the production process. Liquid chemicals used in pharmaceuticals are classified into three categories according to their toxicity.

- First-line solvents should always be avoided, as they are known to be human carcinogens or harmful to the environment.
- Classic chemicals should be of limited use, as other levels of hazardous toxins may be present.
- Third-party solvents have low levels of toxicity to humans and do not require a limit.

Impurities Effect: We know that almost pure content is hard to find, and a certain amount of pollution is always present in the content. Therefore, contamination in objects can have the following effects:

- Impurities can cause incompatibility with other things.
- Sometimes pollution changes the physical and chemical properties of things.
- Impurities can shorten the shelf-life of items.
- It can change the smell, colour, taste of an object.
- Impurities can cause difficulties during construction and use.
- The effect of treatment may be reduced.
- It shows a toxic effect after a certain period of time.
- Damage to your presence beyond certain limits.

Limit Test

- Limit = Value or potential value for a substance
- Testing = Testing or investigation

Limitations are defined as a limited or limited test designed to identify and control the minimum impurities potential.

Limitations are usually performed to detect the inorganic contaminants present in the compound. In short, a test limit is nothing other than identifying the impurities present in an object and comparing it to the standard.

Importance of limit tests:

- Determining the amount of hazardous waste
- Identifying unavoidable.

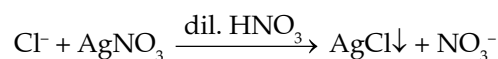
Limit Test of Chloride

The limit test for chloride is based on the reaction between chloride ions in the test compound and silver nitrate in the presence of dilute nitric acid, forming silver chloride (AgCl). Silver chloride appears as a white, opalescent (cloudy) precipitate.

Dilute nitric acid is used to create an acidic medium and helps to prevent interference from other ions or impurities.

The silver chloride precipitate formed is insoluble in dilute nitric acid and is responsible for the opalescence observed in the solution.

Reaction:



Procedure

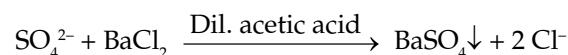
Test	Standard
Take 10 ml of test compound in a Nessler cylinder	Take 10 ml of Std. compound in Nessler cylinder
Add 10 ml of dilute nitric acid	Add 10 ml of dilute nitric acid
Dilute to 50 ml with distilled water	Dilute to 50 ml with distilled water
Add 1.0 ml of 0.1 N silver nitrate compounds	Add 1.0 ml of 0.1 N silver nitrate compounds

Stir and allow to stand for a specified time (usually 5 minutes) and compare the turbidity.

Limit Test of Sulphate

Principle: The limit test for sulphate is based on the reaction between sulphate ions present in the sample and barium chloride in the presence of dilute acetic acid, resulting in the formation of barium sulphate (BaSO₄).

Reaction:



Procedure

Test compound	Standard compound
Move 1.0 ml of a 25.0% w/v compound of barium chloride in a Nessler cylinder	Move 1.0 ml of 25.0% w/v compound of barium chloride in a Nessler cylinder
Add 1.5 ml of ethanolic sulphate standard compound (10 ppm SO ₄ ²⁻), stir and accepted to stand for 1 minute	Add 1.5 ml of ethanolic sulphate standard compound (10 ppm SO ₄ ²⁻), stir and accepted to stand for 1 minute
Dissolve the given sample in 15 ml of water and add 0.15 ml of 5 M acetic acid and pour the compound into a Nessler's cylinder	Mix 15 ml of sulphate standard compound (10 ppm SO ₄ ²⁻) and 0.15 ml of 5 M acetic acid to the Nessler's cylinder
Mix enough water to take 50 ml	Mix enough water to take 50 ml
Stir immediately with a glass rod and allow to stand for 5 minutes and viewed transversely against a dark background	Stir immediately with a glass rod and allow to stand for 5 minutes and viewed transversely against a dark background



Limit Test of Iron

Principle: The limit test for iron is based on the reaction between iron ions present in the sample and thioglycolic acid in the presence of citric acid and an alkaline (ammoniacal) medium.

This reaction forms a purple-coloured complex known as ferrous thioglycolate.

Citric acid acts as a complexing agent to prevent interference from other metals.

The intensity of the purple colour is compared with that of a standard solution containing a known amount of iron.

Reaction



Procedure

Test	Standard
Take 2 ml of given sample of test compound and 20 ml of distilled water in Nessler cylinder	Take 2 ml of given sample of standard compound and 20 ml of distilled water in Nessler cylinder
Add 2 ml 20% iron free citric acid	Add 2 ml 20% iron free citric acid
Add 0.1 ml of thioglycolic acid	Add 0.1 ml of thioglycolic acid
Make the compound basic with iron-free ammonia compound (about 15 ml)	Make the compound alkaline/basic with iron-free ammonia compound (about 15 ml)
Dilute it with 50 ml with distilled water	Dilute it with 50 ml with distilled water

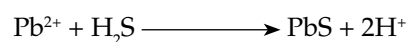
Limit Test of Lead

Principle

- Limit test of lead is depends on the reaction of lead and diphenylthiocarbazon (dithizone) in alkaline compound to form lead dithizone complex which is perused in shading.

- Dithizone is green in shading in chloroform and lead-dithizone complex is violet in shading, so the subsequent shading toward the finish of the procedure is red.

Chemical reaction



Procedure

Test	Standard
A known amount of test compound is moved in a separating funnel	A standard lead compound is readied proportionate to the measure of lead allowed in the sample under assessment
Include 6 ml of ammonium citrate	Include 6 ml of ammonium citrate
Include 2 ml of potassium cyanide and 2 ml of hydroxylamine hydrochloride	Include 2 ml of potassium cyanide and 2 ml of hydroxylamine hydrochloride
Include 2 drops of phenol red	Include 2 drops of phenol red
Make arrangement basic by including ammonia compound	Make arrangement basic by including ammonia compound
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 compound include 5 ml of standard dithizone compound	To the acid compound include 5 ml of standard dithizone compound
Include 4 ml of ammonium cyanide	Include 4 ml of ammonium cyanide
Shake for 30 mins	Shake for 30 mins
Watch the colour	Watch the colour

Limit Test of Arsenic

Principle

- Limit test of arsenic is depends on the reaction of arsenic gas with hydrogen particle to form yellow stain on mercuric chloride paper in nearness of decreasing agents like potassium iodide. It is likewise called Gutzeit test and requires extraordinary mechanical assembly.

- Arsenic, present as arsenic acid in the sample is decreased to arsenious acid by reducing agents like potassium iodide, stannous acid, zinc, hydrochloric acid, etc. Arsenious acid is additionally decreased to arsine (gas) by hydrogen and responds with mercuric chloride paper to give a yellow stain. The depth of yellow stain on mercuric chloride paper will depend upon the nature of arsenic present in the sample.



Chemical reaction



Procedure

<i>Test compound</i>	<i>Standard compound</i>
<p>The test arrangement is set up by dissolving specific amount in water and stannated HCl (arsenic free) and kept in a wide mouthed bottle</p> <p>To this arrangement 1 gm of KI, 5 ml of stannous chloride acid compound and 10 gm of zinc is included (this reagent must be arsenic-free)</p> <p>Set the compound aside for 40 mins and stain got on mercuric chloride paper, is compared with standard compound</p>	<p>A known amount of dilute arsenic compound is kept in a wide- mouthed bottle and rest procedure is followed as described in test compound</p>

IMPORTANT TABLES FOR QUICK REVISION

PHARMACEUTICAL IMPURITIES

Pharmaceutical impurities are substances other than the active pharmaceutical ingredient (API) that are present in a pharmaceutical product. Impurities can be chemical or biological and may affect the safety, efficacy, and

quality of the pharmaceutical product. The presence of impurities is critical for quality control and regulatory compliance, which ensures the safety of the drug for public consumption.

SOURCES OF PHARMACEUTICAL IMPURITIES

<i>Source</i>	<i>Description</i>
Raw materials	Impurities introduced during the synthesis or extraction of active ingredients
Manufacturing process	Contamination during the synthesis, formulation, or packaging of the drug
Storage conditions	Degradation of the API due to improper storage conditions (e.g. moisture, temperature)
Packaging materials	Leachates from packaging materials (e.g. plasticizers or adhesives)
Environmental contaminants	Pollutants from the environment like dust, air, and water that may contaminate the product

TYPES OF PHARMACEUTICAL IMPURITIES

<i>Type of impurity</i>	<i>Description</i>
Organic impurities	By-products from the synthesis of the drug or decomposition of the API, including solvents and degradation products
Inorganic impurities	Metals (e.g. lead, arsenic, mercury), salts, and other inorganic residues that might be present due to manufacturing or contamination
Microbial impurities	Microorganisms (e.g. bacteria, fungi) introduced during manufacturing or improper storage
Residual solvents	Organic solvents used during synthesis and not completely removed during the manufacturing process
Excipients impurities	Impurities introduced from excipients like fillers, binders, stabilizers, or preservatives
Polymorphic impurities	Different crystalline forms of the active pharmaceutical ingredient, which may alter its bioavailability



EFFECTS OF PHARMACEUTICAL IMPURITIES

<i>Effect</i>	<i>Description</i>
Toxicity	Some impurities, especially heavy metals, can cause toxicity or poisoning
Reduced efficacy	Impurities may alter the absorption, distribution, metabolism, and elimination of the drug, leading to reduced therapeutic efficacy
Adverse reactions	Impurities might cause allergic reactions or other undesirable side effects in sensitive individuals
Physical properties	Impurities can affect the physical properties of the drug, such as solubility, stability, and appearance
Regulatory issues	Excessive impurities can lead to noncompliance with regulatory standards and may result in the drug being banned or recalled

Limit Tests for Impurities as per Indian Pharmacopoeia

The Indian Pharmacopoeia (IP) specifies limit tests for various impurities to ensure the quality and safety of pharmaceutical products. These limit tests are essential to check if the level of impurities is within the acceptable range.

Limit Test for Heavy Metals: To detect and limit the presence of heavy metals (such as lead, arsenic, mercury, and iron) in pharmaceutical substances. The limit test for heavy metals is carried out using specific reagents and instruments like the atomic absorption spectrophotometer (AAS) or qualitative precipitation methods.

<i>Heavy metal</i>	<i>IP limit</i>	<i>Test method</i>
Lead (Pb)	2 ppm (parts per million)	Gravimetric/Colorimetric test
Iron (Fe)	0.1% (w/v)	Thiocyanate test or spectrophotometric method
Arsenic (As)	2 ppm	Silver diethyldithiocarbamate test
Mercury (Hg)	1 ppm	Dithizone method or atomic absorption spectrophotometry

Limit Test for Chlorides: To determine the chloride content in pharmaceutical substances. The silver nitrate titration method is used to determine the chloride concentration.

<i>Substance</i>	<i>IP limit</i>	<i>Test method</i>
Chlorides	0.05% (w/v) for most substances	Titration with silver nitrate solution, using potassium chromate as an indicator

Limit Test for Sulfates: To detect and limit the amount of sulfates in pharmaceutical substances. The barium chloride method is commonly used to test for sulfates.

<i>Substance</i>	<i>IP limit</i>	<i>Test method</i>
Sulfates	0.1% (w/v) for most substances	Precipitation of barium sulfate from the sample using barium chloride solution, followed by filtration and weighing

MULTIPLE CHOICE QUESTIONS

- Impurities in pharmaceutical preparation may be due to following source:
 - Raw material
 - Manufacturing process
 - Chemical instability
 - All of the above
- Oxygen requirement in the body can be classified into four major divisions:
 - Anoxic
 - Stagnant
 - Anaemic
 - All of the above



3. Nitrous oxide is:
A. Analgesic B. Anaesthetic
C. Both A and B D. None of the above
4. Temporary hardness of water may be softened by _____.
A. Boiling B. Clarks lime process
C. Deionised water D. All of the above
5. In Bronsted Lowry concept acid is:
A. Proton donor B. Electron donor
C. Proton acceptor D. Electron acceptor
6. Pharmaceutical buffer system could be categorises into:
A. 1 B. 2
C. 3 D. None of the above
7. Which of the following is an example of a strong acid?
A. Hydrochloric acid (HCl)
B. Acetic acid (CH₃COOH)
C. Carbonic acid (H₂CO₃)
D. Hydrocyanic acid (HCN)
8. HSAB categorises acids and bases according to properties:
A. Size B. Charges
C. Polarizability D. All of the above
9. Standard solution in limit test of sulphates is prepared using:
A. Sulphuric acid B. Potassium sulphate
C. Calcium sulphate D. Sodium sulphate
10. Which of the following statement is true:
A. The pharmaceutical product without impurity is not possible.
B. The pharmaceutical product without impurity is possible.
C. Both A and B
D. None of the above
11. Dilute HCl is given as an acidifying agent to treat achlorhydria, it is advised to take slow sips from "Straw" in order to:
A. Avoid damage to teeth
B. Avoid damage to oesophagus
C. Avoid damage to the stomach
D. Avoid damage to the oral cavity
12. Which of the following is a "Strong Base"?
A. NaHCO₃
B. Na₂CO₃
C. NH₄OH
D. C₆H₅NH₂
13. As per Arrhenius concept of acid and base a compound called "Acid" when?
A. It dissociates to form "H⁺ ions"
B. It dissociates to form "OH⁻ ions"
C. It accepts lone pair of electrons
D. It donates lone pair of electrons
14. As per Bronsted Lowry concept of acid-base a "Base" is a:
A. Proton Donor B. Proton acceptor
C. Both A and B D. None of the above
15. Although sodium Bicarbonate is a potent antacid its repeated use is restricted as it causes:
A. Systemic alkalosis
B. Rebound activity
C. Achlorhydrid
D. Peptic ulcer

ANSWER KEY

1. D 2. D 3. C 4. D 5. C 6. B 7. A 8. D 9. B 10. B 11. A 12. B 13. A 14. B
15. A

2. Monographs

Monograph and Its Importance

A monograph is a detailed written description of a particular substance or compound. It provides essential information about the substance, including its identity, chemical structure, physical properties, tests for purity, and methods of assay (measurement of potency).

Importance of Monographs:

- **Standardization:** Monographs provide standardized information about the quality, purity, and strength of a drug.

- **Regulatory compliance:** Monographs are essential for ensuring that a drug complies with regulatory guidelines set by pharmacopoeias, such as the Indian Pharmacopoeia (IP).

- **Quality control:** They contain methods for testing the identity, purity, and potency of pharmaceutical substances, ensuring that products meet the required quality standards.

Guideline for manufacturers: Monographs guide manufacturers in the proper methods of production, testing, and quality control.