PHARMACEUTICAL INORGANIC CHEMISTRY- BP104T

UNIT: 1 (IMPURITIES IN PHARMACEUTICAL SUBSTANCES)

CLASS: 3

TOPIC: IMPURITIES IN PHARMACEUTICAL SUBSTANCES

- It is virtually impossible to have absolutely pure chemical compounds and even analytically pure chemical compounds contain minute trace of impurities.
- Impurities: Foreign unwanted matters present in a compound which are differ from the actual molecular formula.
- Chemically a compound is impure if it contains undesirable foreign matter i.e. impurities.
- Thus, chemical purity is freedom from foreign matter.

Impure Chemical Compound:

A compound is said to be impure if it is having foreign matter i.e., Impurities.

Pure Chemical Compound:

A pure chemical compound refers to that compound which is having foreign matter i.e., impurities. Chemical purity means freedom from foreign matter. Analytically 100 % pure substances are not available and traces of impurities must be present. Normally undesirable foreign materials are present in the pharmaceutical substances. Impurity is any material that affects the purity of the material of interest. Presence of Impurities in the pharmaceutical substances may produce toxic effects on the body and may also lower down the active strength of the pharmaceutical substance. Impurities commonly in chemical substances include small quantities of Iron, lead, Arsenic, Chloride and sulphate.

SOURCES OF IMPURITIES

1. The different sources of impurities in pharmaceuticals are listed below:
2. Raw material used in manufacture
3. Reagents used in manufacturing process
4. Method/ process used in manufacture or method of manufacturing
5. Chemical processes used in the manufacture

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6. Atmospheric contamination during the manufacturing process
7. Intermediate products in the manufacturing process
8. Defects in the manufacturing process
9. Manufacturing hazards
10. Inadequate Storage conditions
11. Accidental substitution or deliberate adulteration with spurious or useless materials

1. **Raw materials used in manufacturing:** Impurities known to be associated with these chemicals may be carried through the manufacturing process and contaminate the final product.

Example:

(i) Rock salt is combination of Calcium Sulphate (CaSO4) + Magnesium Chloride (MgCl2). NaCl is prepared from Rock salt which contains small amounts of Calcium sulphate and Magnesium chloride. Thus Sodium chloride prepared from this source will contain traces of Calcium and Magnesium compounds. Impurities such as Arsenic, Lead and Heavy metals are present in raw materials and hence are found in substances. So, it is necessary to use pure chemicals and substances as raw materials for the manufacturing process.

(ii) Copper sulphate may be prepared by the action of sulphuric acid on copper turnings:

$$\mathbf{Cu + 2\ H_2SO_4 \longrightarrow CuSO_4 + 2\ H_2O + SO_2}$$

Copper turnings are known to have Iron and Arsenic as impurities. If Large quantities of impurities are present in the raw material (e.g Copper turnings), they may enter the final product. (CuSO4.5H2O) Due to this I.P. prescribes limit of tolerance for Arsenic as impurity to be not more than 8 parts per million in copper sulphate. Similarly it prescribes a limit of Iron as impurity.

2. **Reagents used in manufacturing process:** If reagents used in the manufacturing process are not completely removed by washing, these may find entry into the final products.

Example: Ammoniated mercury may be prepared by adding a solution of Mercuric chloride to dilute ammonia solution.

$$HgCl_2 + 2NH_4OH \longrightarrow NH_2HgCl + NH_4Cl + 2H_2$$

(Soluble) (Soluble) (Ammoniated mercury ppt)

The precipitate of Ammoniated mercury (Final Product) contains ammonium hydroxide. Thus, this precipitate is washed with cold water to remove ammonium hydroxide. If it is not removed completely by washing with water, the final product may contain in it Ammonium hydroxide as impurity.

3. Method or process used in manufacturing:

- Many drugs and chemicals (usually organic) are manufactured from different raw materials, by using different methods or processes.
- Some impurities are incorporated into the materials during the manufacturing process.
- The type and amount of impurity present in the drug/ chemical varies.
- In certain drugs, a multiple-step-synthesis procedure is used, which produces intermediate compounds.
- The purification of intermediates is also important; otherwise the impurities present in the intermediate will get incorporated in the final product.
- Usually side reactions occur during the synthesis.
- Impurities of the product side reactions also occur in the substances. This may introduce new impurities due to contamination by reagents and solvents at various stages of the process as described below:
  A. Reagents employed in the process
  B. Reagents added to remove other impurities
  C. Solvents
  D. Action of solvents and reagents on reaction vessels.

I. **Reagents employed in the manufacturing process:**

- Soluble alkali in Calcium carbonate arises from sodium carbonate used in the process.

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- Calcium carbonate is obtained by interaction of a soluble calcium salt and a soluble carbonate and therefore the product will contain traces of soluble alkali, which the washing process has failed to remove.

II. **Reagents added to remove other impurities:**

Potassium bromide contains traces of Barium, which is added in the manufacturing process to remove excess of sulphate.

III. **Solvents:** Water is the cheapest solvent available and has been used wherever possible.

Tap Water	It has Ca^{+2} , Mg^{+2} , Na^{+}, Cl^{-} , SO_4^{-2} and CO_3^{-2} as impurities in small amounts
Softened water	It is obtained by allowing the tap water to pass through the sodium form of Zeolite which removes divalent cations like Ca^{+2} and Mg^{+2} from tap water in exchange of sodium. So, softened water contains Na^{+}, Cl^{-} ions as impurity.
De-mineralized water	It is obtained by passing tap water through columns packed with ion exchange resin. The water obtained from this process is free fromCa^{+2}, Mg^{+2} , Na^{+}, Cl^{-} , SO^{-2} and CO^{-2} Thus the final product is free from these impurities. The water obtained from this source may still contain organic impurities and so final product contains organic impurities.
Distilled water	It is considered the best but it is very costly

IV. **Action of solvents and reagents on reaction vessels:** During manufacturing process, some of the solvents and reagent may undergo reaction with metals of reaction vessel and may dissolve these metals, which appear as impurities in the final product.

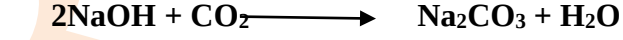
Example: Iron is known to contain Arsenic impurity. The inorganic compounds manufactured in Iron vessel will contain Arsenic and Iron as impurities. Thus IP has prescribed limit test for Arsenic and Iron for most inorganic compounds.

4. Chemical process used in manufacturing:

- For the synthesis of drugs, many chemical reactions such as Nitration, Halogenation, Oxidation, reduction, hydrolysis are involved.
- In these chemical processes, different chemicals are used.
- Tap water is generally used in the various processes and it is often having Cl^- ,Mg^{+2} ,Ca^{+2} ions, which are generally found in the substance which is being manufactured

5. Atmospheric contamination during the manufacturing process:

- In the industrial areas, the atmosphere is contaminated with dust particles and some gases like hydrogen sulphide, Sulphur dioxide, and black smoke.
- During the manufacture or purification of the pharmaceutical products, these impurities enter the final product.
- There are many pharmaceutical products which when manufactured are contaminated with atmospheric CO_2 and water vapour. **Example:** NaOH absorbs atmospheric CO_2.



- Due to this reaction, NaOH should not be kept open for a longer time during its manufacture. Therefore, IP has prescribed that Sodium hydroxide should not contain more than 3% of sodium carbonate

6. Defects in manufacturing process: In many manufacturing processes, there are defects like imperfect mixing, incompleteness, non-adherence to proper temperature, pressure, pH or reaction conditions, which may give chemical compounds with impurities in them.

Example: Zinc oxide may be prepared by heating metallic zinc to bright redness in a current of air. The vapors of Zinc burn to form Zinc oxide which is collected as a fine white powder. But if there is less heat or air or both, zinc metal is not completely converted to zinc oxide. Thus the final product, Zinc oxide may still contain metallic zinc as impurity. So, IP has prescribed a test for Zinc metal in zinc oxide.

7. **Intermediate products in manufacturing process:** There are some intermediates which are produced during the manufacturing process. Sometimes these intermediates may be carried through to the final product as impurity.

Example: Potassium iodide is prepared by reacting Iodine with Potassium hydroxide.

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

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

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

In this process if the intermediate product (KIO3) is not completely converted into KI, then it may be carried through to the final product as an impurity.

8. **Manufacturing hazards:**

A. Particulate contamination:

- The presence of unwanted particulate matter can arise due to dirt, dust, glass, porcelain or plastic fragments from sieves, granulating or tableting machines or from product containers.
- Ware and tare of equipment or improperly cleaned equipment may also cause particulate contamination.
- Clarity of solutions for injection is particularly important.

Example: Metal particles which have been found in eye ointments packed in metal tubes.

B. Process errors: Cross errors arising from incomplete solution of a solute in a liquid preparation must be detected readily by the normal analytical control procedures.

C. Cross contamination: The handling of powders, granules, and tablets in large bulk creates air-borne dust, which leads to cross contamination of the product. So, face masks and special extraction equipment are used to protect operators from harmful effects of drugs.

Example: Penicillin preparation requires special handling during its manufacture.

D. Microbial contamination: Parenteral preparations and ophthalmic preparations require special care against microbial contamination. Many liquid preparations and creams are liable to bacterial and fungal contamination. So care should be taken.

Example: Acacia, senna, tragacanth they should be controlled for Salmonellae.

E. Packing errors: Products of similar appearance such as tablets of same size, shape, color packed in similar containers can constitute a potential source of danger. Improper labeling or destruction of stock of unused labels also constitutes a major packaging hazard

9. **Storage conditions:** The chemical substances when prepared have to be stored in different types of containers depending upon:
    - Nature of the material
    - Batch size
    - Quantity

Many types of materials are used for storage purpose like plastic, polythene, iron vessels, stainless steel and aluminum

Leaching out effect: Alkalis stored in ordinary glass containers extract lead from it which in found as impurity in the final product Strong chemicals react with iron containers and extract iron an impurity in final product.

Inadequate storage and their effects are as follows:

A. Filth: Stored products may become contaminated with dust, bodies of insects, animal and insect excreta.

B. Chemical instability: decomposition because of light, traces of acid or alkali, air oxidation, water vapour, CO_2 and traces of metallic ions. e.g light sensitive materials should be stored in amber colored bottles.

C. Reactions with container materials: Example: salicylic acid ointment must not be stored in metal tubes.

D. Physical changes: The occurrence of changes in the physical form of drug like change in crystal size can lead to change in efficiency of product.

E. Temperature effect: Chemical and physical changes occur if materials are not stored at proper temperature.

10. **Decomposition of product during storage:** Chemical decomposition, analysis or breakdown is the separation of a chemical compound into elements or simpler compounds. It is sometimes defined as the exact opposite of a chemical synthesis. Chemical decomposition is often an undesired chemical reaction. Some substances decompose on storing due to presence of air, light and oxygen. So, the final product is contaminated. Deliquescent substances absorb water from the atmosphere and get liquefied. Decomposition products appear as impurities in the substances.

11. **Accidental substitution or deliberate adulteration with spurious or useless materials:** It is possible to avoid accidental substitution by storing the toxic substances together separately or in a locked cupboard. Many pharmaceutical chemicals are adulterated with cheaper substances. **Example:** The expensive potassium may be adulterated with sodium bromide.

EFFECT OF IMPURITIES: The impurities present in the substances may give following effects:

- Impurities having toxic effects may be injurious to health, if present above certain limits. Traces of impurities may exert a cumulative toxic effect after a certain time.
- Impurities may lower the active strength of the substance.
- Impurity may decrease shelf life of substance.
- Impurity may cause incompatibility with other substances.
- Impurities may cause a physical or chemical change in the properties of the substance, so making the substance medicinally useless.
- May cause change in color, odor and taste.

TYPES OF IMPURITIES

According to ICH guidelines, the impurities are classified into:

1. Organic impurities

2. Inorganic impurities
3. Residual solvents

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

2. **Inorganic impurities:** Inorganic impurities involve reagents, ligands, catalysts, heavy metals, or other residual metals, inorganic salts, filter-aids, charcoal etc.

   A. Heavy metals: The main source of heavy metals is the water used in the processes and the reactors (if stainless steel reactors are used), where acidification and acid hydrolysis take place. May avoid by using demineralized water and glass-lined reactors

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

3. **Residual solvents:** Solvents are organic volatile chemicals used during the manufacturing process or generated during the production. Residual solvents are classified into three classes

   A. Class I Solvents: Benzene (1-2 ppm), carbon tetrachloride (1-4 ppm) are avoided because of their carcinogenic and toxic effect

   B. Class II Solvents: Methyl chloride, methanol, pyridine, toluene, acetonitrile, Most commonly used.

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

4. **Other impurities:**

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

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

C. Packaging material induced impurities: Leachable and extractable substances from primary packaging material form reaction products (impurities) with drug substances. Example: Alkaline oxide from glass (Na_2O, SiO_2, MgO, CaO).

2 MARKS QUESTIONS

1. What is an impurity and classify them?
2. List out the sources of impurities

5 MARKS QUESTIONS

1. Explain briefly the implications of impurities in pharmaceutical substances
2. Define an impurity and explain the types of impurities with suitable examples?

10 MARKS QUESTIONS

1. Write briefly the different sources of impurities present in pharmaceutical substances
2. What are impurities? Explain different sources of impurities with examples?

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