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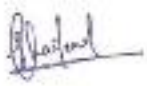

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Impurities →

It can be defined as, impurities in Pharmaceuticals are unwanted chemicals that remain with the active Pharmaceutical ingredients (API's) or develop during formulation or upon aging of both API and formulation.

The presence of these unwanted chemicals even in trace amount may influence the efficacy and safety of Pharmaceutical product.

OR

Impurities are the chemical Substance present with API in a formulation, leads to cause physio-logical changes and also produce adverse effect on therapeutic and pharmacological action of the products.

* Impurities can also be defined as "a foreign particle that affects the purity of a substance.

→ Types of Impurities :-

1. Toxic Impurities :-

foreign particle that bring about adverse or toxic reactions when present in excess beyond their limits

for example :- lead, Arsenic and heavy metals etc.

It must be analysis the qualitative amount of these toxic element is less as per require

2. Activity Depression Impurities :-
Impurities which may not cause toxic effects but bring about deterioration of the activity of chemical.

Example :- Hard Soap containing excess of water.

3. Impurities that Cause incompatibility of active ingredient with other substance or which reduce the properties of active ingredient.

4. Impurities which may lead to technical problems in the applications of the substance.

Example :- Presence of Carbonate in ammonia solutions
presence of KIO_3 in KI.

5. Elemental Impurities :-
Such as excipient cause impurities during manufacturing, as Catalysts for oxidation and hydrolysis.

Example :- Al, As, Sn, Cd, Cr, Cu, Fe, Pb, Hg, Ni, Na, Ca

6. Packaging Material induce impurities :-
leachable and Extractable (L&E) from primary packaging material form reaction products with drug substance or with excipients.

Example :- Alkaline Oxides from glasses (Na_2O, SiO_2, MgO, CaO), diethylhexyl phthalate plasticizer from PVC.

7. Degradation Drug Product :-

for example :- Excipients interaction, which cause decrea
= -e in the shelf-life of drug

8. Impurities which may alter the physical and chemical properties of the substance.

for example :- presence of Phenolic compounds decrease
= Sodium Salicylate.

SOURCE OF IMPURITIES,

- Raw Materials
- Manufacturing Hazards
- Method / Process
  - * Reagents Used
  - * Solvents / Vehicles used
  - * Reagents used to eliminate impurity
  - * Intermediate products
  - * Equipment used
- Atmospheric
- Conditions of Storage
- DELIBERATE ADULTERATI
- Packing Erro

There are Various sources of Impurities in Pharmaceutical Substance are as follows.

1. Raw Materials :-

Pharmaceutical Substances extracted from natural sources or Synthesized from them, that means not 100% pure.

Traces of the elements present in the raw material may get carried to the final preparation.

S. No	Pharmaceutical preparation	Raw Material	Impurities Present.
1	Sodium Compounds	Nacl rock salts	Cl^-, Ca & Mg
2.	Bismuth Compounds	Bismuth Salts	Pb, Cu & Ag
3.	Copper Compounds	Copper turnings	Arsenic & Iron

2. Method / Process of Manufacturing :-

(A) Reagents employed in the manufacturing process :-

Calcium Carbonate Contains 'Soluble Alkali' as impurity.

Anions like Cl^- and SO_4^{-2} are common impurities in many substances because of the uses of HCl and H_2SO_4 in many preparation.

Barium ion may be present as an impurity in H_2O_2 (Hydrogen Peroxide)

(B) Reagents employed to eliminate impurity :-

In some manufacture process certain reagents are used to remove impurities present in the final product these reagents, if not carefully used are liable to get in final product and destroy its properties and actions.

Example :- Barium is used to remove sulphate from potassium bromide, which can be found in (barium) as impurity at the end.

(C) Solvents or Vehicles used in the manufacturing :-

Small amounts of solvents employed in preparation and purification of the product may also result in the contamination of the pharmaceutical substances

for Example :- water is the cheapest solvent which can be the major source of impurities as it contains different types of impurities like Ca_2, Mg_2, NaCl Co_3, Soy in trace amounts.

So, for the formulation of drug, distilled water must be used.

(D) Equipment used in the process of Manufacturing :-

Equipments are made up of basically glass, which metals or their alloys

The material of the equipment may react with the reagents and solvents used in the process of manufacturing and contribute to impurities in the end product

S.No	Material of the Equipment	Impurity
1.	Iron	Arsenic
2.	Galvanized Iron	Zinc
3.	Soda Glass	Alkali
4.	Stream or Water pipe	lead

(E) Intermediates generated during the synthesis :-

Sometimes, an intermediate product formed during the manufacturing process may contaminate the end product.

for example :- Sodium bromide is prepared by reaction of NaOH (Sodium hydroxide) and bromine in slight excess.

$$6NaOH + 3Br_2 \longrightarrow NaBrO_3 + 5NaBr + 3H_2O$$

3. Atmospheric Condition :-

In Atmosphere may gases as dust molecules contain like (Aluminium Oxide, Sulphur, Silica, Soot etc) and some gases like CO_2, SO_3, SO_2, H_2S, they may contaminated the final product during the manufacturing process.

for Example :- Sodium hydroxide readily absorbs atmospheric CO_2, when exposed to atmosphere.

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

4. Condition of Storage :-

Storage conditions determine the efficacy and stability of the product Requirements of storage differ from one drug to the other.

Careless Storage of the product leads to change in P'ceutical behaviour as well as Contamination the preparations, decrease shelf-life of the product.

Raw material should be stored & cared properly to avoid contact with the filthy matter like paint, dust particles, microorganisms may affect the final produ

To resist and avoid the Contamination of final preparation, novel packing techniques are used to inhibit Contamination of the product.

5. Packing Errors :-

Pharmaceutical products having same physical appearances i.e, size, shape, colour, if packed in same type of containers may leads to mislabeling of the product and cause packing errors.

6. Deliberate adulteration :-

Substitution of a pure product Spurious cheap, inferior, defective or toxic substance is termed as adulteration can be prevented by storing away from harmful substances separately from purified substances

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* NOTE :- "Manufacturing Hazards"

Hazardous and toxic substance such as dust, balats, fuel or chemical present in the work place are capable of causing harm to the pharmaceutical products.

The manufacturer should provide analytical procedure to limit such impurities.

for example :- Eye ointment packed in metal tubes made up of tin, aluminium generally get contaminated due to the extrusion of metal particles from the packing material.

GENOTOXIC IMPURITIES

The property of chemical agents that damages the genetic information within a cell using mutations, which may lead to Cancer.

"All mutagens are genotoxic, whereas not all genotoxic substances are mutagenic".

* A five-class System for Categorizing Genotoxic impurities :-

1. CLASS$_1$:- "Impurities Known to be genotoxic and Carcinogenic"

It Includes Known animal Carcinogens with reliable data for a genotoxic mechanism, and human Carcinogens.

The genotoxic nature of the impurity is demonstrate using publish data on the chemical structure.

2. CLASS$_2$:- "Impurities known to be genotoxic, but with unknown carcinogenic potential".

It Includes impurities with demonstrated mutagenicity based on testing of the Impurity in Conventional genotoxicity test.

3. CLASS$_3$:- "Impurities that have an altering structure unrelated to the structure of the APIs and of unknown genotoxic (mutagenic) potential".

It includes impurities with functional moieties that can be linked to genotoxicity based on structure.

These moieties have not been tested as isolated compounds and are identified based on chemistry and using SAR.

4. CLASS$_4$:- "Impurities with an alter altering structure related to the API and impurities that contain an altering functional moiety that is shared with the structure of the API".

5. CLASS$_5$:- "No altering structure or indication of genotoxic potential".

- Reference :-

Ali Mohammed, "Textbook of Pharmaceutical chemistry (Inorganic), published by CBS publisher pvt. Ltd. 1st edition.