

Impurities

Impurities defined as a foreign particle that affects the purity of a substance. Usually, impurities occurring in many pharmaceutical or medicinal preparations may be of the following types.

1. Foreign particle that bring about adverse or toxic reactions when present in excess beyond their limits.

Example: lead, heavy metals, arsenic etc.

2. 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 solution, presence of KIO_3 in KI solution.

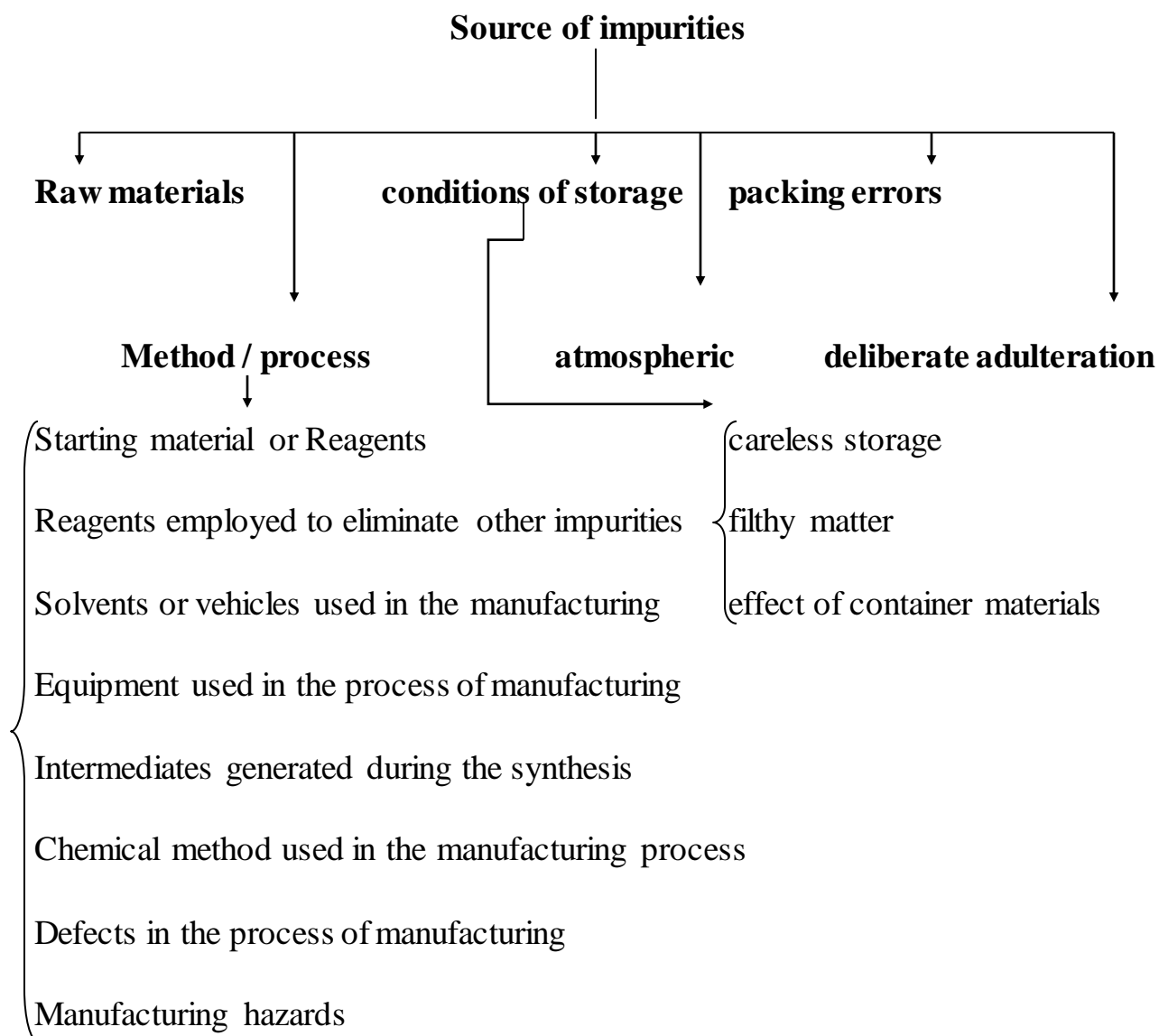
5. Impurities arising due to humidity temperature.

Example: presence of very low amount of moisture may enable substance to get oxidized easily or may reduce its free flowing characteristics.

6. Impurities arising due to colouring and flavoring substances. These impurities can be detected by changes in colour, odour, taste and appearance.

Examples: Presences of phenolic compounds decolourize sodium salicylate, presence of minute quantities of magnesium salt causes dampening of sodium chloride.

7. Impurities which may alter the physical and chemical properties of the substance.
8. Impurities which decrease the shelf – life.



Raw materials:

Generally, most of the raw materials used in the manufacturing of pharmaceutical products are naturally occurring substances. Traces of the elements present in the raw materials may get carried to the final preparation.

Pharmaceutical preparation	Raw materials	Impurities present
Sodium compounds	Sodium chloride rock salt	Chlorides, Ca and Mg
Bismuth compounds	Bismuth salts	Lead, copper, and silver
Copper compounds	Copper turnings	Arsenic and iron
Zinc compound	Zinc metal or zinc oxide	Aluminum, copper, manganese, Mg, arsenic, iron and nickel.

Therefore, proper measures should be taken to ensure the purity of raw materials used in the manufacture.

Method / process of manufacture:

Manufacturing process involves various reactions carried out in single or multiple steps. Starting from the raw materials used, equipment, reactions, intermediates produced, solvents employed to the status of completion of the reaction, every aspect serves as the source of impurity. These are explained as follows.

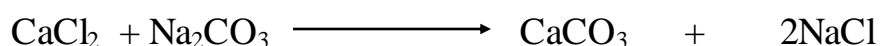
Starting materials or reagents used:

Many reagents are used in the process of manufacturing a product. If the products are not washed properly to remove excess reagents, then these reagents are liable to be carried as impurities to the final preparation.

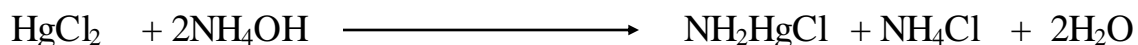
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Examples:

Calcium carbonate is prepared from the reagents calcium chloride and sodium carbonate. Hence, calcium carbonate by this process is associated with alkali (Na_2CO_3) and soluble chlorides. If the CaCO_3 product is not washed properly to remove excess of Na_2CO_3 and chlorides, then they get carried as impurities. Due to this reason, pharmacopeia has prescribed limits for soluble chlorides and alkali for CaCO_3 .



In the synthesis of ammoniated mercury, dilute ammonia solution and mercuric chloride solution are used as reagents. Proper washing of the end product (ammoniated mercury) with cold water renders it completely free from impurities (ammonium hydroxide).



Reagents employed to eliminate other impurities:

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 carried to the end product.

Example:

Barium is employed to remove excess sulphate in the synthesis of potassium bromide. Improper usage results in the presence of very small amounts of barium in the final product.

Solvents or vehicles used in the manufacturing

Water is the most commonly used solvent in many preparations. However, water serves as a source for many impurities.

Type of water	Impurities present
Tap water	Calcium, magnesium, sulphates, chlorides, sodium and carbonates
Softened water	Sodium and chloride
Demineralized water	Organic impurities
Distilled water	No impurities

Tap water is the cheapest solvent available but it contains many impurities. Therefore, washing the final product with tap water leaves it with traces of impurities and sometimes even adding additional impurities. Softened water is prepared by passing tap water through sodium form of zeolite, such that sodium ions from zeolite are exchanged for calcium and magnesium. However, sodium and chlorine may get incorporated into the final preparation.

Demineralized water is prepared by passing tap water through the column of ion – exchange resins. All the impurities present in tap water except organic impurities get eliminated. Therefore, in those preparations where demineralized water has been used, the final product is liable to contain organic impurities.

Distilled water is free from both organic as well inorganic impurities but it is very expensive. Hence, its use is limited.

Equipment used in the process of manufacturing

Equipments or reactions vessels employed in the manufacturing process are made of glass, tuber, 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.

Material of the equipment	Impurity
Iron	Arsenic
Galvanized iron	Zinc
Soda glass	Alkali
Stream or waste pipe	lead

In order to control the impurities arising from chemical reactions between the solvents, reagents or both with the reaction vessel, vessel made from hard inert glass like pyrex – borosilicate glass should be used. However, its high cost limits its use.

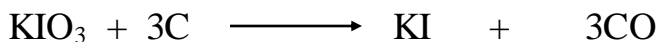
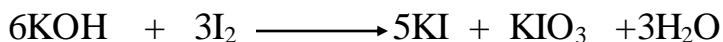
Intermediates generated during the synthesis

Most of the preparations involve generation of intermediates. If these intermediate products are not completely converted into the final product, they get incorporated as impurities.

Example:

In the preparation of potassium iodide (KI) from potassium hydroxide and iodine, potassium iodate (KIO_3) is formed as an intermediate. KIO_3 is evaporated to dryness and the residue obtained is heated with charcoal to get KI. Incomplete or

improper conversion of KIO_3 is liable to be carried as an impurity to the final preparation which is desirable.



Chemical methods used in the manufacturing process:

A substance or a reagent is subjected to a variety of chemical reactions during the manufacturing process. The type of chemical reactions like halogenations, oxidation, reduction, nitration, hydrolysis etc., employed may also contribute to the presence of impurities in the final preparation.

Example:

Potassium iodide is synthesized from kelp (ash of a sea weed). When sea weed containing nitrogenous organic matter is heated at very high temperature in the presence of alkali, cyanides are generated. These cyanides may get incorporated as an impurity.

Defects in the process of manufacturing

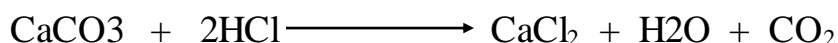
Synthesis of a compound should be carried out under appropriate conditions along with correct measures of preparation. Improper mixing, incompleteness of the reaction, inappropriate temperature, pressure and pH conditions yield compounds with impurities.

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Examples:

Synthesis of calcium chloride involves addition of pure calcium carbonate to slightly excess quantity of dilute hydrochloric acid with continuous stirring followed by filtration and concentration of filtrate to give CaCl_2 crystals.

If the ingredients are not mixed properly or if any amount of HCl passes through the filter or if the concentration is not properly carried out, then it affects the final product.



Manufacturing hazards:

Hazardous and toxic substance such as dust, paints, fuel or chemicals present in the work place are capable of causing harm to the pharmaceutical products. The manufacturer should provide analytical procedure to limit such impurities. The manufacturing errors may go unnoticed. These are typical errors that occur due to microbial contamination, particulate contamination etc. specifications and analytical procedures are employed to estimate the identified or unidentified impurities and also to include limits for impurities.

i. *Arbitrary inclusion of particulate matter:*

The hazardous substance such as dirt, glass, metallic ions, porcelain, plastic fragments found during the operations like granulating, tableting or in equipment like sieves, filling machines, product container etc., may be accidentally introduced into the pharmaceutical products.

Example:

Eye ointments packed in metal tubes made up of tin, aluminum generally get contaminated due to the extrusion of metal particles from the packing material. The extent of contamination depends upon the viscosity of the ointment. As the viscosity of the ointment increases, the extent of extrusion increases.

ii. Arbitrary inclusion of microorganisms:

Almost all the pharmaceutical preparations may undergo microbial contamination during the process of manufacture or during storage. Generally raw materials obtained naturally are more prone to microbial contamination. Therefore to control it, sterility tests should be performed on all the products, mainly upon liquids or creams applied on the mucous membranes or broken skin, ophthalmic and parenteral preparations.

<i>Materials</i>	<i>Free from</i>
Acacia, senna, and tragacanth	Salmonella
Gelatin, pancreatin, starch, cochineal	Salmonella and E.coli
Al(OH) ₃ gel, dried Al(OH) ₃ gel and aluminum phosphate gel	pseudomonas

iii. Cross contamination:

When large quantities of powders, granules and tablets are handled, a substantial amount of air borne dust generates. If it is not properly controlled, it leads to cross contamination of the products.

Precautions

The use of face masks or special equipment help to curb impurities occurring by cross contamination.

Conditions of storage:

Storage conditions determine the efficacy and stability of the product. Requirement of storage differ from one drug to the other. Various factors like material of the container temperature, reactions taking place in the product., affect the final preparation during the storage.

a) Careless storage:

Pharmaceutical preparations behavior when not stored properly.

Example:

Ferrous sulphate should be stored in air tight containers. Improper storage leads to the conversion of soluble ferrous sulphate to insoluble ferric oxide in the presence of air and moisture.

b) Filthy matter:

Dust particles, microorganisms, insect excreta etc., may affect the final preparations. Novel packing techniques available inhibit contamination of the end product, but raw materials are more likely to be attacked by filth during storage.

c) Effect of container materials

Pharmaceutical preparations when stored in inappropriate containers react with the material of the containers undergo deterioration.

Examples:

Salicylic acid reacts with metal tubes, therefore, it should not be stored in metal tubes unless and until they are lacquered internally.

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Atropine sulphate injection should be strictly packed in glass ampoules as it offers hydrolytic resistance.

Therefore, a container should be so selected such that it is suitable for storing the preparation and does not contribute to its degradation.

There are grades of glass containers available.

Type I: it exhibits very high hydrolytic resistance. It is a neutral glass.

Type II: it is formed by the surface treatment of glass and exhibit very high hydrolytic resistance.

Type I and II glasses can be differentiated from each other by crushed glass test.

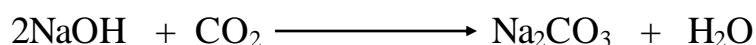
Type III: it possesses very limited hydrolytic resistance.

Aqueous solutions of injections should be stored in either type I or II glass containers while non – aqueous solutions as well as injectable solids are stored in type III glass containers after complying with the test for hydrolytic resistance.

4. Atmospheric / environmental conditions:

Atmospheric conditions during manufacturing process as well as during storage affect the quality of the final preparation.

Example: if sodium hydroxide is exposed to air for very long periods during the process of manufacturing it reacts with carbon dioxide and gets converted to sodium carbonate. This sodium carbonate gets incorporated into NaOH and serves as an impurity.



5. Packing Errors:

Crystal packing of solids may lead to serve reactions which may affect the preparation. Pharmaceutical products having same physical appearance i.e., size, shape, colour, if packed in same type of containers may lead to packaging errors. This leads to mislabeling of the products. Therefore handling similar type of products at the same time should be avoided.

6. Deliberate adulteration or international substitution

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