IMPURITIES

The impurities in drug are unwanted chemicals that remain with the Active pharmaceutical Ingredients (API), developed during formulation and upon ageing of API/drug products. The presence of these unwanted chemicals even in trace amount may influence the efficacy and safety of pharmaceutical products.

The control of pharmaceutical impurities is currently a critical issue to the pharmaceutical industry. The International Conference on Harmonization (ICH) has formulated a workable guideline regarding the control of impurities.

According to ICH, an impurity in a drug substance is defined as "any component of the new drug substance that is not the chemical entity defined as the new drug substance".

CLASSIFICATION OF IMPURITIES

A. According to ICH guidelines, impurities associated with API's are classified into:
    1. Organic Impurities
    2. Inorganic impurities
    3. Residual solvents
B. United States Pharmacopoeia (USP):
    1. Impurities in Official Articles
    2. Ordinary Impurities
    3. Organic volatile Impurities

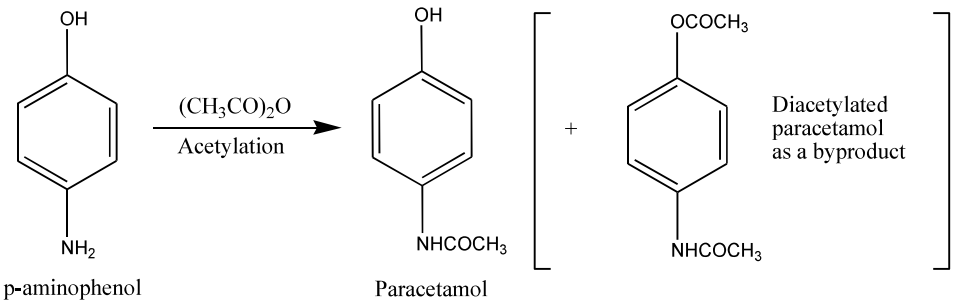
1. Organic Impurities

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.

a) By-product Impurities:

In synthetic chemistry getting a single and product with 100% yield is very rare as there is always a chance of some by-product with desired end product



p-aminophenol Paracetamol

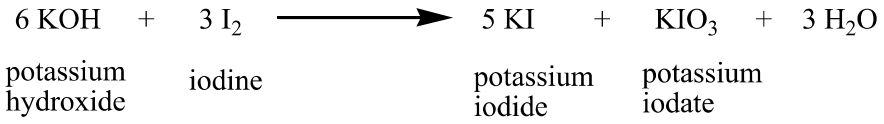
b) Degradation products:

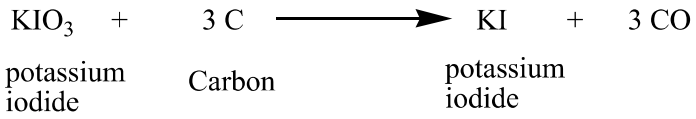
Degradation products resulting from storage of formulation to different dosage forms or aging are common impurities in the medicines.

For e.g. Degradation of penicillin and cephalosporin, Penicillin reacts with moisture to form Penillic acid, Penicilloaldehyde and Penicillamine etc.

c) Intermediate Products:

These products from within the reaction and sometimes those intermediates do not get converted into the product and remains as such as the impurity with the end product.





d) Reagents, ligands and catalysts:

These are the chemicals used to carry out various reactions, these impurities are less commonly found in API's. However, in some cases they may produce a problem as impurities.

e) Enantiomeric Impurities:

Sterioisomers (enantiomers and diastereoisomers) are related products similar to drug substance, which may also act as impurity.

For e.g. (R)- and (S)- naproxen are enantiomers. (*S*)-naproxen is used to treat arthritis pain, but (*R*)-naproxen causes liver poisoning.

2. Inorganic Impurities

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

a) Reagents, ligands and catalysts:

The precipitation of calcium carbonate is washed to remove excess of Na_2CO_3 and $CaCl_2$. If the precipitate is not properly washed, it may remain as an impurity.

b) 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 avoided by using demineralized water and glass-lined reactors.

c) 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

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

Class II Solvents: methyl chloride, methanol, pyridine, toluene, acetonitrile,Most commonly used

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.

b) Elemental impurities:

Brought about as excipient impurities or during manufacturing as catalyst for oxidation and hydrolysis.Eg 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. Eg Alkaline oxide from glass (Na_2O, SiO_2,MgO, CaO).

EFFECT OF IMPURITIES

- Impurities which are toxic can be injurious when present above certain limit.
- Impurities can cause incompatibility with other substances.
- Impurities may cause a change in physical and chemical properties of substances.
- Impurities present in large proportion that the active strength of the substance get lower, its therapeutic effect gets decrease.
- Impurities though harmless in nature may cause change in odour, color, taste etc.
- Impurities may decrease the shelf life of the product.

SOURCES OF IMPURITIES

- A compound is said to be impure if it is having foreign matter i.e. impurities.The substance employed in the pharmaceutical field must be almost pure so that they can be used safely.
- A list of the possible impurities can be readily complied from knowledge of the raw material used for method of manufacture and the stability of the product.The type and amount of impurities present in the chemical or pharmaceutical substance depends upon several factors.
- There are several sources of impurities in pharmaceutical substance:

1. Raw materials employed in manufacturing:

If impurities are present in the raw material (ores, metals etc.) which are used in the preparation of pharmaceutical chemicals then these may be carried through during the manufacturing process to the final product. Thus final compound may be contaminated with these impurities.

Examples:

a) Zinc sulphate is prepared by either zinc oxide or zinc metal with sulphuric acid.

$$Zn + H_2SO_4 \longrightarrow ZnSO_4 + H_2$$

$$ZnO + H_2SO_4 \longrightarrow ZnSO_4 + H_2O$$

Both zinc and zinc oxide contain aluminium (Al), copper (Cu), magnesium (Mg), manganese (Mn), nickel (Ni), arsenic (As) and iron (Fe) as impurities.

b) Copper sulphate may be prepared by the action of sulphuric acid on copper turnings.

$$Cu + 2H_2SO_4 \longrightarrow CuSO_4 + 2H_2O + SO_2$$

Copper turnings may contain iron and arsenic as impurities.

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.Examples:

a) Ammoniated mercury may be prepared by adding a solution of mercuric chloride to dilute ammonia solution.

$$HgCl_2 + 2NH_4OH \longrightarrow NH_2HgCl + NH_4Cl + 2H_2O$$

(Soluble) (Soluble) (ppt) (Soluble)

The NH_2HgCl (ammoniated mercury precipitate) completely washed to remove ammonium hydroxide. If it is not removed completely by washing with water, the final product may contain ammonium hydroxide as impurity.

b) When calcium chloride is react with sodium carbonate precipitated calcium carbonate is formed.

$$CaCl_2 + Na_2CO_3 \longrightarrow CaCO_3 + 2NaCl$$

(Soluble) (Soluble) (ppt) (Soluble)

The precipitate of calcium carbonate is washed to excess of sodium carbonate and calcium chloride.

3. Intermediate products in the manufacturing process:

There are some intermediates which are produced during the manufacturing process. Sometimes, these intermediates may be carried by the final product.

Examples:

- 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 to dryness and heated with charcoal.

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

Potassium iodide so formed is an intermediate product and if it not converted into potassium iodide, it may be present as impurity in the final product.

4. Defects in manufacturing process:

Defects such as imperfect mixing, incompleteness of reaction, non-adherence to proper temperature, pressure, pH or reaction condition etc. may results in the production of chemical compounds with impurities in them.

Examples:

- Method of manufacturing zinc oxide involves heating metallic zinc to bright redness in a current of air. The vapors of the metal burn to form zinc oxide which is collected as a fine white powder

$$2Zn + O2 \longrightarrow 2ZnO$$

If zinc metal is not completely converted into zinc oxide (due to lesser heat or air) a small amount of zinc metal may still remains as impurity in final product

5. Solvents:

Water is a cheapest solvent and is commonly used especially in the manufacturing of inorganic chemicals.

Tap water contains chloride, sulphate, bicarbonate, magnesium, and calcium etc as impurities though in very small amounts. Hence traces of such impurities may still remain in final products, to remove these impurities from water either distilled water or deionized water should be used.

6. Action of solvent and reagent on reacting vessel:

Some reagent and solvent may react with the container in which they are stored or processed.

Example:

- Strong acid leads out alkali from borosilicate glass, copper and zinc vessels react with slightly acidic substance etc. hence a great care must be taken in selection of suitable vessels for manufacturing process or for the purpose of storage.

7. Atmospheric contamination:

In industrial areas, atmosphere is contaminated with dust particles (aluminium oxide, silica glass particles, porcelain particles, plastic fragments, etc.) and some gases like hydrogen sulphide, sulphur dioxide and black smoke. During the manufacture or purification of pharmaceutical products, these impurities enter the final products as impurities.

Example:

- Sodium hydroxide absorbs atmospheric carbon dioxide (contamination) to form sodium carbonate and bicarbonate.

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

Therefore, NaOH should not be exposed to atmosphere for a long time during its manufacturing.

8. Defective storage of final products:

Some pharmaceutical chemicals undergo chemical decomposition if these are not properly stored, may also change their physicochemical properties.

Example:

- When ferrous sulphate is exposed to moist air ferric sulphate is formed.
- Potassium iodide gets liquefied if it is exposed to moist air for a long time.