Sources of Impurities in Medicinal Agents:

IMPURITY
• A compound is said to be impure if it is having foreign matter. Pure chemical compound refers to that compound which is having no foreign matter i.e., impurities.
• Purification of chemicals is an expensive process, substances should not be purified more than required as it brings about waste of time, material and money.
• Sugarcane, dextrose, inorganic salts 99% purity while many other only are having traces of impurity.
• Pure Relative term Pharmacopoeia of India and BP has been prescribed test for purity.

Impurities commonly found in Medicinal preparations:
1. Activity depressing impurities.
2. Due to colouring or flavouring substances, e.g., Sodium Salicylate.
3. Humidity.
4. Decrease shelf life.
5. Physical and chemical properties.
6. Impurities due to which substances become incompatible.

SOURCES OF IMPURITIES

1. Raw Materials Employed in the Manufacturing of the Pharmaceutical Substance:
Pharmaceutical substances are either isolated from natural sources or synthesized from chemical starting materials. The natural sources include mineral sources, plants, animals and microbes. It is essential to verify the identity of the source material and to establish its quality otherwise impurities associated with the raw materials may be carried through the manufacturing process to contaminate the final product. In nature minerals rarely occurs in a reasonably pure form. Almost always mixtures of closely related substances occur together e.g., aluminum ores are usually accompanied by alkali and alkaline earth compounds, barium and magnesium impurities are found in calcium minerals, zinc accompanies magnesia or iron compounds, lead and heavy metals are found as impurities in many sulphide ores, among the acid radicals or anions, bromides and iodides are often found as impurities in chlorides, bismuth salts contains silver copper and lead as impurities.
Rock salt used for the preparation of sodium chloride is contaminated with small amounts of calcium and magnesium chlorides, so that sodium chloride prepared from rock salt will definitely contain traces of calcium and magnesium compounds impurities.

2. Method of Manufacture: The process or method of manufacture may introduce new impurities into the final product arising due to contamination by reagents, catalysts and solvents employed at various stages of the manufacturing process. The new impurities may also arise from the reaction vessels and reaction intermediates.

3. Reagents employed in the manufacturing process: Calcium carbonate contains ‘soluble alkali’ as impurity which arises from the sodium carbonate (Na₂CO₃) employed in the process. Calcium carbonate is prepared by the interaction of a soluble calcium salt with a soluble carbonate. Therefore, the final product (CaCO₃) is liable to contain small amount of ‘soluble alkali’ as impurities which were not removed by the washing process.

\[
CaCl₂ + Na₂CO₃ → CaCO₃ \downarrow + 2 NaCl
\]
Soluble Soluble Precipitate Soluble
4. **Regents used to eliminate other impurities:** Barium is used in the preparation of potassium bromide to remove sulphate which in turn arise from the bromine used in the process. It is likely that potassium bromide will now be contaminated by traces of barium.

5. **Solvents:** Most of the pharmaceutical substances are prepared in solvated crystalline form. Small amounts of solvents employed in preparation, and purification of reaction intermediates or the final product may also result in the contamination of the pharmaceutical substances. Water is the cheapest solvent available and is used quite frequently in the preparation of inorganic pharmaceuticals. Water can be the major source of impurities as different types of water containing different types and amount of impurities are available. Various types of water which are available are

   (i) **Tap water:** Containing impurities of \( \text{Ca}^{2+}, \text{Mg}^{2+}, \text{Na}^+, \text{Cl}^-, \text{CO}_3^{-2} \) and \( \text{SO}_4^{-2} \) in trace amounts. The use of tap water on large scale will lead to the contamination of the final product with these impurities because the impurities will remain in the product even after washings.

   (ii) **Softened water:** It is almost free from divalent cations (\( \text{Ca}^{2+}, \text{Mg}^{2+} \)) but contains more of \( \text{Na}^+ \) and \( \text{Cl}^- \) ions as impurities because of the usual chemical water softening process. Therefore, the final products obtained using softened water as solvent will not have \( \text{Ca}^{2+} \) and \( \text{Mg}^{2+} \) impurities but still contain \( \text{Na}^+ \) and \( \text{Cl}^- \) impurities.

   (iii) **Demineralized water:** It is prepared by means of ion-exchange and is free from \( \text{Na}^+, \text{Ca}^{2+}, \text{Mg}^{2+}, \text{Cl}^-, \text{SO}_4^{-2} \) and \( \text{CO}_2^{-2} \) etc. It may have pyrogens, bacterias and organic impurities. So, it is a better solvent than tap water or softened water but the economic factors discourage its use on large scale.

   (iv) **Distilled water:** It is free from all organic and inorganic impurities and is therefore the best as a solvent but it is quite expensive. As it is free from all impurities, it does not pass on any impurities to the final products.

6. **Reaction vessels:** The reaction vessels employed in the manufacturing process may be metallic such as copper, iron, cast iron, galvanized iron, silver, aluminium, nickel, zinc and lead. Glass and silica are also used in the construction of the chemical plants but these days many of these are replaced by stainless steel and variety of other alloys. Some solvents and reagents employed in the process may react with the metals of reaction vessels, leading to their corrosion and passing traces of metal impurities into the solution, contaminating the final product. Similarly, glass vessels may give traces of alkali to the solvent. Lead (Pb) may be found as impurity in commercial sulphuric acid which has been manufactured by lead chamber process. Also, substances prepared by same electrolytic process, may contain electrode material as an undesirable impurity e.g., antimony, bismuth etc.

7. **Intermediates:** Sometimes, an intermediate substance produced during the manufacturing process may contaminate the final product e.g., Sodium bromide is prepared by reaction of sodium hydroxide and bromine in slight excess.

   \[
   6\text{NaOH} + 3\text{Br}_2 \rightarrow \text{NaBrO}_3 + 5\text{NaBr} + 3\text{H}_2\text{O}
   \]

   The sodium bromate an intermediate product is reduced to sodium bromide by heating the residue (obtained by evaporating the solution to dryness) with charcoal.

   \[
   \text{NaBrO}_3 + 3\text{C} \rightarrow \text{NaBr} + 3\text{CO}
   \]

   If sodium bromate is not completely converted to the sodium bromide then it is likely to be present as an impurity

8. **Atmospheric contamination during the manufacturing process:** Atmosphere may contain dust aluminum oxide, sulphur, silica, soot etc.) and some gases like carbon dioxide, sulphur dioxide, arsine and hydrogen sulphide. These may contaminate the final product during the manufacturing process. Some substances which are susceptible to action by atmospheric carbon dioxide and water
may get contaminated with them during their preparation e.g., sodium hydroxide readily absorbs atmospheric carbon dioxide when exposed to atmosphere.

\[ 2\text{NaOH} + \text{CO}_2 \rightarrow \text{Na}_2\text{CO}_3 + \text{H}_2\text{O} \]

Calcium hydroxide solutions can absorb carbon dioxide from the atmosphere to form calcium carbonate.

\[ \text{Ca(OH)}_2 + \text{CO}_2 \rightarrow \text{CaCO}_3 + \text{H}_2\text{O} \]

9. Manufacturing hazards: If the manufacturer is able to control and check impurities from the all above mentioned sources there exists certain manufacturing hazards which can lead to product contamination. The various manufacturing hazards can lead to:

(i) Contamination from the particulate matter: The unwanted particulate matter can arise by a number of ways, such as accidental inclusion of dirt or glass, porcelain, plastic or metallic fragments from sieves, granulating, tabletting and filling machines and the product container. The particulate contamination mainly arises from the wear and tear of the equipments. It may also arise from the bulk materials used in the formulation or from dirty or improperly maintained equipments e.g., metal particles found in eye ointments packed in metal tubes made up of tin and aluminium.

(ii) Cross-contamination of the product: This manufacturing hazard has to be considered in the preparation of solid dosage forms. Cross-contamination of product can occur by air-born dust arising out of handling of powders, granules and tablets in bulk. Cross-contamination is dangerous particularly in case of steroidal and other synthetic hormones and therefore, it should be carefully controlled. Precautions, such as use of face mask and special extraction equipment can minimize these undesirable contaminations.

(iii) Contamination by microbes: Many products, like liquid preparations and creams intended for topical applications are liable to contamination by microbes from the atmosphere during manufacturing. For all products intended for parenteral administration and ophthalmic preparations, sterility testing is done and it provides an adequate control for microbial contaminations in such preparations. Microbial contamination can be controlled by adding suitable antimicrobial and antifungal agents.

(iv) Errors in the manufacturing process: Sometimes in a liquid preparation, there is incomplete solution of the solute. This ought to be detected by the normal analytical methods as it can lead to major error. A proper check on the efficiency of mixing, filling, tabletting, sterilization etc. should be exercised in order to obtain a product of maximum purity and desired quality. Special precautions are required to be observed to avoid mixing and filling errors in the preparation of low dosage forms (e ú 5 mg) such as tablets and capsules containing highly potent medicaments.

(v) Errors in the packaging: Similar looking products, such as tablets of the same size, shape and colour, packed in similar containers can result in mislabeling of either or both of the products. Adequate care should be taken to avoid the handling of such products in the close proximity.

10. Instability of the Product:

(A) Chemical instability: Impurities can also arise during storage because of chemical instability of the pharmaceutical substance. Many pharmaceutically important substances undergo chemical decomposition when storage conditions are inadequate. This chemical decomposition is often catalyzed by light, traces of acid or alkali, traces of metallic impurities, air oxidation, carbon dioxide and water vapours. The nature of the decomposition can easily be predicted from the knowledge of chemical properties of the substance. All such decompositions can be minimized or avoided by using proper storage procedures and conditions. The photosensitive substances should be protected from light by storing them in darkened glass or metal containers thereby inhibiting photochemical decomposition. Materials susceptible to oxidation by air or attack by moisture should be stored in sealed containers and if necessary the air from the containers can be displaced.
by an inert gas such as Nitrogen. Oxidation can also be prevented by adding suitable antioxidants which are capable of undergoing oxidation at the expense of the substances.

(B) **Changes in physical properties:** Pharmaceuticals may undergo changes in physical properties during storage. There can be changes in crystal size and shape, sedimentation, agglomeration and caking of the suspended particles. These physical changes are not always avoidable and may result in significant changes in the physical appearance, pharmaceutical and therapeutic effects of the product. Particle size and consequently surface area is a critical factor in determining the bioavailability of the low solubility drug such as griseofulvin. Physical changes such as sedimentation and claying in case of multidose suspension may constitute a safety hazard leading to the possibility of under dosage and later to overdosage of the drugs. Similarly increase in the globule size of the injectable emulsions on storage may lead to fat embolism.

(C) **Reaction with container material:** The possibility of reaction between the container material and the contents cannot be ruled out as it constitutes a safety hazard. Preparations susceptible to reaction with metal surfaces e.g., salicylic acid ointment must not be packed in metal tubes. Solutions of substances which are alkali-sensitive e.g., atropine sulphate injection must be packed in glass ampoules which comply with the test of hydrolytic resistance therefore such preparations must not be packed in containers made from soda glass. Plastic containers and closures must be carefully evaluated because of their tendency to give undesirable additives, such as plasticizers, particularly in the presence of non-aqueous solvents. Plastic containers intended for injectables should be sufficiently translucent to allow visual inspection of the contents and if they are having higher than 500 ml capacity, they must also comply with the test limiting animal toxicity in the cat, ether-soluble extractive and metal additives with special reference to barium and heavy metals like lead, tin and cadmium. Rubber closures are more susceptible to absorb medicaments, antioxidants and bactericides from solution, unless they are appropriately pretreated by immersion in solutions of the concerned compounds.

(D) **Temperature:** The rate of chemical decomposition and physical changes of stored products depends upon the temperature. The susceptible substances may have temperature storage requirements assigned to them in order to protect them against undesirable decomposition.