Ministry of Health of the Russian Federation
Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

GENERAL PHARMACEUTICAL CHEMISTRY

IMPURITIES IN MEDICINES AND THEIR SOURCES.

Lesson 9
IV term

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Discipline

GENERAL PHARMACEUTICAL CHEMISTRY

LESSON №9 Impurities in medicines and their sources.	Purity of medicines. Impurities in medicines and their sources. Impurity isolation methods. Impurity analysis methods.

QUESTIONS FOR THE LESSON

1. What is an impurity?
2. Common terms:
   - Degradation product
   - Enantiomeric impurity
   - Starting material
   - Interaction product
   - Intermediate
   - Penultimate intermediate
   - New drug product
   - New drug substance
   - Identified impurity
   - Potential impurity
   - Total impurity
   - Qualification threshold
   - Specification
3. Different types of impurities
4. Sources of impurities
5. Factors affecting the presence of impurities
6. Acquired impurities
7. Technological impurities:
   - Raw material
   - Intermediates
   - by-products
   - Decomposition products

- Tautomeric impurities

8. Impurity isolation methods
9. Analytical methods
10. Remedies to prevent the impurities in pharmaceutical products

IMPURITY

In general term **impurity** means the unwanted or undesired compound or component in desired product.

International Conference on Harmonization (ICH) defines it for drug substance and drug product as, "***Any component of the new drug substance which is not the chemical entity defined as the new drug substance and any component of the new drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product***".

Regulatory authorities are also emphasizing on not only the purity profile but on impurity profiling (identification, isolation and characterization of impurity) for the licensing purpose and regulatory related issues for particular drug substance and drug product.

Different pharmacopoeias like British Pharmacopoeia (BP), European Pharmacopoeia (EP), Russian Pharmacopoeia, Indian Pharmacopoeia (IP), Japanese Pharmacopoeia (JP) and United States Pharmacopoeia (USP) are also revising their monographs for the drug substances and drug products every year by introducing the limits for the different types of impurities.

The ICH has published the guidelines for the analysis of impurities in new drug substances and drug products. It has also published the guideline for the analytical method validation for the impurity identification and quantification to check the quality of the products.

The sources of impurities are the major concern for any drug manufacturer. Hence the control of these impurities is very critical at the same time very essential too as some times the effect caused by these impurities can be teratogenic, mutagenic or carcinogenic.

COMMON TERMS

Degradation product

A molecule produced by a chemical change in the drug molecule over a period of time and/or by the action of different parameters such as light, temperature, pH, water quality or by reaction with an excipient and/or the immediate container system. It is also called decomposition product.

Enantiomeric impurity

A compound with the same molecular formula as the drug substance that differs in the spatial arrangement of atoms within the molecule and is a non-superimposable mirror image.

Starting material

A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting materials are normally commercially available and of defined chemical and physical properties and structure.

Interaction product

It is a product formed by the interaction of chemicals in reaction mixture either intentionally or unintentionally.

Intermediate

It is a compounds formed during the synthesis of desired product or as a part of synthetic route.

Penultimate intermediate

It is the second last compound in the route of synthesis prior to the production of the final desired product.

New drug product

It is a compounds formed during the synthesis of desired product or as a part of synthetic route.

New drug substance

The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved drug substance.

Identified impurity

An impurity for which; impurity profiling has been performed and the exact structure of the impurity has been explicated.

Potential impurity

An impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the new drug substance that may or may not be harmful.

Total impurity

It is a sum of all type of impurities and it is very important for the quality measurement of drug substance and drug product.

Qualification threshold

A limit above which an impurity should be qualified.

Specification

It is a list of tests with references to their analytical procedures and suitable acceptance criteria. According to the specification a drug substance or drug product should pass the acceptance criteria for its intended use.

DIFFERENT TYPES OF IMPURITIES

According to the definitions of International Council for Harmonization (ICH) impurities are classified into Organic impurity, Inorganic impurity and Residual solvents, as shown in Figure 1.

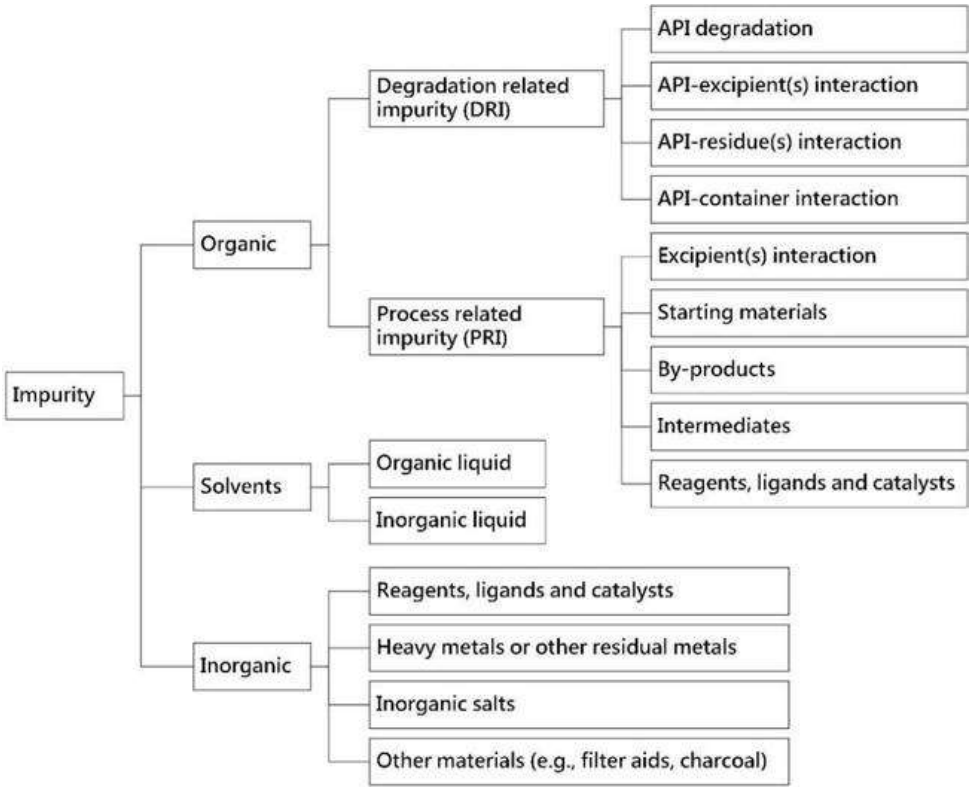


Figure 1. Impurity classification

Even microbiological impurities are also of great importance in especially parental drug formulation and injectables.

Further we can divide these different types of impurities into their subpart on the basis of their identification and chemistry involved in it.

On the basis of their identification

- ✓ Enantiomeric impurity
- ✓ Inorganic impurity
- ✓ Organic impurity
- ✓ Polymorphic impurity
- ✓ Residual solvents

SOURCES OF IMPURITIES

There are number of sources by which impurity can enter in the drug substances or drug products. The different sources of impurities can be listed out with the help of knowledge of the raw material used in manufacturing of product, manufacturing process, storage condition and transportation process. The major reasons for the impurity generation are physical contamination and the storage condition.

The various ***sources*** of impurities in pharmaceutical drug substance and drug product are given below:

Chemical related impurity

- ➢ By products
- ➢ Degradation products
- ➢ Excipient degradation
- ➢ Intermediates
- ➢ Residual solvents
- ➢ Starting material or raw material

Operation related impurity

- ➢ Centrifuging
- ➢ Crystallization
- ➢ Drying of the product by different drying methods
- ➢ Filtration

- Glassware contamination
- Human operation contamination
- In-process operations
- Isolation of products and by products
- Machinery contamination
- Reactor contamination
- Resolution and racemization of chiral molecules
- Solvent extraction
- Stirring
- Transportation of the product

Method parameters related impurity

- Density
- Humidity
- Light intensity especially in the case of light sensitive products
- pH of the reaction mixture
- Pressure of the reactor
- Product contact time
- Stirring time
- Temperature
- Viscosity

Storage and aging related impurity Contamination by

- microbes on long storage
- Different storage condition
- Interaction amongst the components and packaging
- material Light exposure
- Packaging material
- Transportation environment

Functional group related impurity

- Decarboxylation
- Ester hydrolysis

- Hydrolysis
- Oxidative degradation
- Photolytic cleavage

FACTORS AFFECTING THE PRESENCE OF IMPURITIES

Various factors affecting the presence of impurities in a drug can be divided into:

1. Technological factors: the degree of purity of the starting products, temperature, pressure, pH of the medium, solvents, mode and temperature of drying - all these factors can lead to the appearance of impurities that accumulate from one stage to another.
2. The second group of factors affecting the purity is a violation of the conditions and duration of storage, drying, grinding, transportation.
3. The third group of factors is the dust and gas contamination of production facilities of chemical and pharmaceutical enterprises (cross contamination).
4. The fourth group of factors is the contamination of drugs obtained from plant materials with associated natural compounds.

Thus, all pollution factors are divided into

- technological (1 and 4)
- acquired (2. 3.).

ACQUIRED IMPURITIES

Prevention of cross-contamination during production

The possibility of contamination of raw materials must be eliminated. The risk of accidental cross-contamination is increased by the uncontrolled spread of dust, gases, vapours, aerosols or microorganisms present on materials and products, equipment, clothing and human skin and introduced by insects.

The degree of risk depends on the type of contamination and the product affected. The most dangerous contaminants include sensitizers, biological preparations containing live microorganisms, certain hormones, cytotoxins, and potent substances. Contamination is especially dangerous for medicines used for injection or to treat open wounds, as well as those intended for long-term use or high doses.

To prevent cross-contamination, considering the conditions of production, the following measures should be taken:

- reducing the risk of pollution caused by recirculation or re-entry of untreated or insufficiently treated air;

- taking special measures to prevent the formation and spread of dust in case of use in the production of dry materials and products;
- use of specially equipped rooms for weighing raw materials;
- personnel wearing appropriate process clothing and storing protective clothing within product manufacturing areas with a high risk of cross-contamination;
- use of highly effective certified (validated) methods for cleaning equipment and premises;
- control of the absence of residues of the previous product or detergent and marking of equipment indicate the status of cleanliness.

TECHNOLOGICAL IMPURITIES

Any material that may affect the purity of a pharmaceutical substance or finished drug product, is considered an impurity. Impurities occur from a variety of sources, which typically include:

- ✓ the raw material itself
- ✓ intermediate products;
- ✓ by-products;
- ✓ decomposition products;
- ✓ tautomers

Raw material

Substance starting materials are raw materials, intermediates that are used to produce other APIs, and those that are included as an important building block in the formulation. API starting materials are usually described by chemical properties and structure.

System or approach for selecting raw materials:

- A starting material is a compound whose name, chemical structure, chemical and physical characteristics and properties, and impurity profile are clearly defined in the chemical literature.
- The influence of the quality of the starting material on the quality of the pharmaceutical substance has been studied and controlled.
- The starting material is commercially available and is included in the new drug substance as an important structural element.
- The starting material has been characterized, and the stability has been well studied.

Intermediates

Organic compounds formed during the synthesis of a pharmaceutical substance are called intermediates.

Non-reactive intermediates

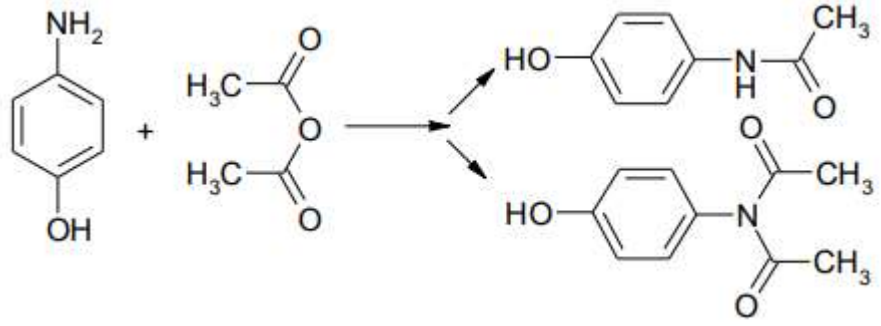
Non-reactive intermediates are impurities that are formed at some intermediate stage of the reaction because of the interaction of reagents. Such impurities remain inactive in later stages.

Reactive intermediates

Reactive intermediates are by-products or impurities resulting from intermediate steps of a reaction that may react with reactants or catalysts used in later steps. They pass to every stage up to the final pharmaceutical substance as reactive intermediates.

by-products

In synthetic organic chemistry, obtaining one 100% pure final product is a rather rare phenomenon. This is because of the conversion of the parent material into by-products, which may result from various side reactions such as incomplete reactions, reaction continuation, isomerization, or undesired reactions between starting materials, intermediates, chemicals or catalysts. For example, in the mass production of paracetamol, it can be formed as a by-product diacetylated paracetamol.



Decomposition products

During the production of drugs, the substance is subjected to various influences, as a result of which decay processes are possible. For example, if heat is used during drying or other steps, it can contribute to the breakdown of thermally labile substances. In solutions and suspensions, the decomposition of a substance is more likely because of hydrolysis or solvolysis processes. Impurities formed during the decomposition or breakdown of the final product during the manufacture of a medicinal product are also called degradation products. This term also includes degradation products resulting from storage, formulation, or aging.

Tautomeric impurities

Tautomers are isomers that coexist in equilibrium. If the tautomer is thermodynamically stable and is the basic form, the other tautomers should be considered as impurities. Tautomers differ in their kinetic and thermodynamic stability, which makes it difficult to determine them, despite the fact that they can be separated, isolated or analyzed. Therefore, the term “tautomer admixture” is used.

IMPURITY ISOLATION METHODS

Generally chemical and instrumental methods are used to isolate this impurity.

Different methods used in the pharmaceutical industries for the isolation are listed below:

- Accelerated solvent extraction
- Column chromatography
- Different types of drying methods like microwave drying, freeze drying, rotary drying, fluid bed drying (FBD), Tray drying, vacuum tray drying, belt drying etc.
- Flash chromatography
- Liquid-liquid extraction
- Preparative liquid chromatography
- Preparative thin layer chromatography (TLC)
- Solid phase extraction
- Supercritical fluid extraction (SFE)

ANALYTICAL METHODS

Once an impurity has been isolated, it is identified and quantified using the following methods:

- Atomic absorption spectroscopy (AAS) (I/Q)
- Capillary electrophoresis (CE) (I/Q)
- Chiral High performance liquid chromatography (C-HPLC) (I/Q)
- Differential scanning calorimeter (DSC) (I/Q)
- Differential thermal analysis (DTA) (I/Q)
- Electron paramagnetic resonance spectroscopy (EPR) (I)
- Elemental analysis (C, H, N, S, O) (I/Q)

- Fluorescence spectroscopy (I)
- Fourier transform infrared spectroscopy (FT-IR) (I)
- Gas chromatography (GC) (I/Q)
- Gas chromatography-Head space analyzer (GC-HS) (I/Q)
- Gas chromatography-Mass spectroscopy (GC-MS) (I/Q)
- Gravimetric analysis (Q)
- High performance liquid chromatography (HPLC) (I/Q)
- High performance thin layer chromatography (HPTLC) (I/Q)
- Inductive coupled plasma (ICP) (I/Q)
- Ion chromatography (IC) (I/Q)
- Liquid chromatography-Mass spectroscopy (LC-MS) (I/Q)
- Nuclear magnetic resonance spectroscopy (NMR) (I)
- Particle size analysis (I/Q)
- Raman spectroscopy (I)
- Supercritical fluid chromatography (SFC) (I/Q)
- Thermo gravimetric analysis (TGA) (Q)
- Ultraviolet visible spectroscopy (UV-Vis) (I/Q)
- Qualitative and volumetric analysis (I/Q)
- X-Ray diffraction (XRD)

REMEDIES TO PREVENT THE IMPURITIES IN PHARMACEUTICAL PRODUCTS

Some of the remedies to prevent the impurities in pharmaceutical products are listed below:

- ✓ Control of critical factors during the manufacturing of any product; which affect the product.
- ✓ Extreme operational care should be taken while handling the equipments, machineries, reactors and other tools that by any mean due to the operational activity, impurity should not be entered into the product.
- ✓ The wet cake should be thoroughly washed to remove all unwanted chemical including the residual solvents.
- ✓ In the specification, maximum possible impurities should be specified with stringent limits for the better quality products.

- ✓ Time to time the specifications of drug substances and drug products should be studied and revised for specific impurity profiling and should be made strict for impurity acceptance criteria.
- ✓ During analytical method development and validation study of any drug substance and drug product, the method parameters should be optimized in such a way that the method can resolve maximum number of impurities which will help the synthetic chemist to improve the synthetic process.
- ✓ Stability study should be carried out methodically and meticulously for the identification of degradation products and to fix the shelf life of drug substances and drug products.
- ✓ Stress study should be performed for any drug substance or drug product to handle the transportation related issues properly.
- ✓ Packaging care should be taken for the moisture/light/environment/stress sensitive materials.
- ✓ Regulatory authorities should become stricter before giving any license or permission for any product to be sold in any regulated market.
- ✓ Before giving any approval for any pharmaceutical product to any company, the authorities should ensure the total compliance of the manufacturing site and product, as this is the matter related to human health and it can not be taken in very casual way.
- ✓ If some of the listed remedies are implemented seriously and strictly, then the pharmaceutical industries can get rid of this burning issue of impurities at major extent.