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IMPURITY PROFILING OF PHARMACEUTICALS – A REVIEW

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ABSTRACT

Impurity is any substance coexisting with the original drug such as starting material or intermediates or that is formed due to any side reaction. Impurity profiling includes identification, structural elucidation and quantification of impurities and degradation products and bulk drug materials and pharmaceutical formulations. The presence of impurities influence the safety and efficacy of pharmaceutical product. So the profiling of impurity is very crucial. Some impurities are unavoidable and will be present in trace amounts hence ICH guidelines and policies establishes the specification limits, evaluation and control of impurities. Validation of analytical process is performed for the identification of impurity to establish a impurity profile of any drug substance. This review focuses on sources of impurities, its classification, various analytical techniques for the identification and quantification of impurities.

KEYWORDS: Impurities, Impurity profiling, Active pharmaceutical ingredient, Efficacy, Evaluation, Validation.

INTRODUCTION

In the pharmaceutical industry, an impurity is considered as any other inorganic or organic material, or residual solvents other than the drug substances or ingredients that arise out of synthesis or unwanted chemicals that remains with the APIs. The presence of these unwanted chemicals even in trace amounts may influence the efficacy and safety of pharmaceutical product.

Impurity profiling has gained importance in modern pharmaceutical analysis due to the fact that identified, potentially toxic impurities are hazardous to health and inorder to increase the safety of drug theraphy, impurity should be identified and determined by selective methods. Impurities in formulated products and APIs are regulated by various authorities such as ICH, USFDA, Canadian drug and health agency that are emphasising the purity requirements and the identification of impurities in API and the drug product are critical in drug development. Organic impurities are often free radicals from by-products, intermediates or degradation products. Inorganic impurities include transition metals, Reagents and ligands. Identification of impurities is done by variety of chromatographic and spectroscopic techniques, either alone or in combination with other techniques.

REGULATORY GUIDELINES ON IMPURITY

International conference on harmonization (ICH) guidance of technical requirements for registration of pharmaceuticals for human use is inscribed by the united states Food and Drug Administration (FDA).

The various regulatory guidelines regarding impurities are as follows

1. ICH Q1A: Stability testing of new dug substances and products.
2. ICH Q3A: Impurities in new drug substances.
3. ICH Q3B: Impurities in new drug products.
4. ICH Q3C: Impurities guidelines for residual solvents.
5. ICH-Q3D: Guidelines for elemental impurities.
6. US-FDA: NDAs –Impurities in new drug substances.
7. US-FDA: ANDAs – Impurities in new drug substances.

Sources of impurities

- Raw materials employed in manufacture.
- Method or the process used in manufacture.
- Chemical processes and the plant materials employed in the processes.
- Storage conditions.
- Decomposition.

Effect of impurities

We know that almost pure substances are difficult to get and some amount of impurity is always present in the material. So the impurities which are present in the substances may have the following effects.

- Impurities may bring about incompatibility with other substances.
- Impurities may lower the shelf life of the substances.
- Impurities may cause difficulties during formulations and use of the substances.
- Sometimes Impurities changes the physical and chemical properties of the substances.
- Therapeutic effect can be decreased.
- Shows toxic effect after a certain period.
- Injurious when present above certain limits.
- It may change odour, colour, taste of the substance.

To prevent these impurities many test such as limit test are carried out to lower the impurities to make the pharmaceuticals more safe.

Classification of impurities

Impurities can be classified into the following categories:

1. Organic impurities (process- and drug-related)
2. Inorganic impurities
3. Residual solvents

1. Organic impurities (process- and drug-related)

Organic impurities can arise during the manufacturing process and/or storage of the drug substance

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands and catalysts

2. Inorganic impurities

Inorganic impurities can result from the manufacturing process.

- Reagents, ligands and catalysts
- Heavy metals or other residual metals

- Inorganic salts
- Other materials (e.g., filter aids, charcoal).

Elemental impurities: Elemental impurities are the traces of metals that can be found in finished drug products.

Elemental impurities Classification

❖ The elements included in ICH 3D guideline have been placed into three classes based on their toxicity (PDE) and likelihood of occurrence in the drug product.

Classes	Included elemental impurities	Include in risk assessment
Class 1	As,Pb,Cd,Hg	Yes
Class2A	V,Mo,Se and Co	Yes
Class2B	Ag,Au,Tl,Pd,Pt,Ir,Os,Rh, and Ru	Yes only if intentionally added
Class 3	Sb,Ba,Li,Cr,Cu,Sn,Ni	Dependent upon route of administration
Class 4	B, Fe,Zn,K,Ca,Na,Mn,Mg,W,Al	No

3. Residual solvents

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance.

Residual solvents classification

Residual solvents are classified according to the risk assessment to human health to 3 main classes.

Solvent	Risk assessment	Example
Class 1	Solvents to be avoided	Benzene (2ppm), Carbon tetra chloride(4ppm), methylene chloride (600ppm), methanol (3000ppm), pyridine (200ppm), toluene (890pm)
Class 2	Solvents to be limited	N,N –dimethyl formamide (880ppm), acetonitrile (410ppm)
Class 3	Solvents with low toxic potential	Acetic acid, ethanol, acetone has permitted daily exposure of ≤ 50 mg /day

REPORTING AND CONTROL OF IMPURITIES

Organic Impurities

- Identify the possible & potential impurities most likely to arise during the synthesis, purification, and storage.
- Stress testing (ICH-Q1A on Stability) used to identify potential impurities arising during storage.

- Any impurity at a level greater than (⎜>) the identification threshold should be identified.
- Any degradation impurity observed in stability studies at a level⎜ greater than (>) the identification threshold should be identified.

Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
≤ 2 gm /day	0.05%	0.10% or 1.0 mg per day intake	0.15% or 1.0 mg per day intake
>2gm /day	0.03%	0.05%	0.05%

Reporting Threshold: A limit above (>) which an impurity should be reported.

Identification Threshold: A limit above (>) which an impurity should be identified.

Qualification Threshold: A limit above (>) which an impurity should be qualified.

Inorganic Impurities

- Inorganic impurities are normally detected and quantified using pharmacopoeia or other appropriate procedures such as sulphated ash/Residue on ignition.
- No heavy metals test is recommended due to no longer available from 1st January 2018.
- Metal used/carryover should be identified and reported as per Residual Solvents.
- The control of residues of the solvents used in the manufacturing process for the new drug substance should be discussed and presented according to the ICH Q3C Guideline for Residual Solvents.

Reporting impurity content of batches

- Quantitative results should be presented numerically, and not in general terms such as "complies", "meets limit" etc.
- Any impurity at a level greater than (>) the reporting threshold should be reported.
- Results should be rounded using conventional rules.
- Impurities should be designated by code number or by an appropriate descriptor, e.g., retention time.
- All impurities at a level greater than (>) the reporting threshold should be summed and reported as total impurities.

Listing of impurities in specifications

Drug substance specification should include (where applicable):

➢ Organic Impurities

- Each specified identified impurity
- Each specified unidentified impurity
- Any unspecified impurity
- Total impurities
  - Inorganic impurities
  - Residual solvents
- Individual impurities with specific acceptance criteria should be included in the specification are referred to as specified impurities.
- Note that specified impurities can be idenetified or unidentified.
- Specified identified impurities should be included along with specified unidentified impurities estimated to be present Individual impurities with specific acceptance criteria should be⎫ included in the specification are referred to as "specified impurities“. Note that specified impurities can be identified or unidentified at a level greater than (>) the identification threshold.
- Specified, unidentified impurities should be referred to by an appropriate descriptive label e.g., “unidentified A", “unidentified with RRT of 0.9”.

Unspecified impurity should be included with the acceptance criterion of not more than (≤) the identification threshold

Qualification of impurities

- Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.
- The level of any impurity present in drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified.
- Impurities that are also significant metabolites present in animal and or human studies are generally considered qualified.

ISOLATION AND CHARACTERISATION

Isolation can be done by various chromatographic techniques. They are as follows :

1. Liquid chromatography
2. Gas chromatography
3. Thin layer chromatography

1. Liquid chromatography

The technique best suited to isolating impurities is preparative liquid chromatography (LC), using low or high-pressure columns. The technique requires loading of a preparative-scale LC column with repeated doses of the sample, and collecting fractions either using known time intervals or mass-based fraction collection (using the mass of the molecule you are collecting). This allows isolation and concentration of sufficient impurity for identification purposes using highly sophisticated techniques,

2. Gas chromatography

This technique is an analytical technique that helps to separate and analyse volatile impurities without their decomposition. It is carried out in a suitable temperature in a glass or metal tubing known as column, which contains liquid or stationary phases, inert gases like helium or unreactive gases like nitrogen used as mobile phase which passes over the stationary phase.

3. Thin layer chromatography

TLC utilizes finely divided adsorbent material which is spread evenly on a suitable support (such as glass, plastic, or aluminium) in thickness ranging between 0.1-0.33 mm. The plate is then placed in a chamber containing the mobile phase which moves up through capillary action. Impurities are separated on this stationary phase based on their adsorptive capacities either by process of adsorption, partition or both.

Hyphenated Techniques

The hyphenated technique is developed from the coupling of a separation technique and an on-line spectroscopic detection technology. Hyphenated techniques combine chromatographic and spectral methods to exploit the advantages of both. Chromatography produces pure or nearly pure fractions of chemical components in a mixture. Spectroscopy produces selective information for identification using standards. Various hyphenated techniques are:

1. LC-MS
2. GC-MS
3. LC-MS-MS
4. HPLC-DAD-MS
5. HPLC-DAD-NMR-MS

1. LC-MS: LC-MS refers to the coupling of an LC with a mass spectrometer (MS) The separated sample emerging from the column can be identified on the basis of its mass spectral data. A switching valve can help make a working combination of the two techniques. A typical automated LC-MS system consists of double three-way diverter in-line with an autosampler, an LC system, and the mass spectrometer. The diverter generally operates as an automatic switching valve to divert undesired portions of the eluate from the LC system to waste before the sample enters the MS.

2. GC-MS: GC-MS is a hyphenated technique developed from the coupling of GC and MS. Compounds that are adequately volatile, small, and stable in high temperature in GC conditions can be easily analyzed by GC-MS. Sometimes, polar compounds, especially those with a number of hydroxyl groups, need to be derivatized for GC-MS analysis. In GC-MS, a sample is injected into the injection port of GC device, vaporized, separated in the GC column, analyzed by MS detector, and recorded.

Applications

- Impurity profiling is applied in the areas of drug designing and in monitoring quality, stability, and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced recombinant methods.

CONCLUSION

In pharmaceuticals impurity profiling increases drug safety. Impurity identification establishes an overall profile of a drug which includes its toxicity and safety limits of quantization and detection. This article provides the detailed information about the impurity introduction, ICH guidelines, sources of impurities, its classification, limits for impurities, recent techniques used in isolation and characterization of impurity and applications of impurity profiling.

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