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IMPURITY PROFILE IN PHARMACEUTICS

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ABSTRACT

Impurity has no clear meaning in the pharmaceutical industry. Impurity profiling involves the recognition, structural characterization, and identification and quantification of impurities and decomposition products in bulk medical properties and pharmaceutical preparations. Different forms of contaminants can be detected, identified, and quantified using impurity profiling. Organic, inorganic, and residual solvents are the three types of contaminants that are classified. Intermediates, starting materials, degradation products, reagents, ligands, catalysts, and by products are all examples of organic impurities. Heavy metals, residual solvent, inorganic salt, filter, aids, charcoal, and reagents are examples of inorganic impurities. Various analytical procedures such as UV, HPLC, LC-MS, GC-MS, SCFC, and others can be used to profile pharmaceutical impurities. Starting materials, intermediates, penultimate impurity, by product, and degradation product are all examples of impurities.

KEYWORDS: Impurity, Classification, Identification method, Source, Application.

1. INTRODUCTION

The detection, identification/structure elucidation, and quantitative determination of organic and inorganic impurities, as well as residual solvents in bulk pharmaceuticals and pharmaceutical formulations, is referred to as impurity profiling.[1] The impurity profile of a drug substance is influenced by a number of factors, including the synthetic route, reaction conditions, the source and quality of the starting materials, the reagents and solvents used during the synthesis, the purification steps, crystallisation, distillation, drying, and storage

conditions, and so on. As a result, the impurity profile of a drug substance is a good fingerprint in the hands of drug authorities to indicate the degree and consistency of the bulk drug substance's manufacturing process: even tiny changes in the above-mentioned criteria can create huge changes in the impurity profile.[2] Impurity profiling, also known as characterization, is a broad term that refers to any materials analysis process that uses macroscopic techniques such as mechanical testing, thermal analysis, and density calculations on scales ranging from angstroms to centimetres, such as imaging coarse grain structures in metals and determining the impurity level in any pharmaceutical drug using new techniques and methodologies. a) UV Spectroscopy, b) IR Spectroscopy, c) Mass Spectrometry (MS), d) Nuclear Magnetic Resonance (NMR), and e) HPLC Methods.[3]

Any industry's main task is to generate high-quality products, which necessitates stringent quality control checks to ensure that each industry's output remains of high quality and purity. The purity of any product is dependent on the raw components, production method, crystallisation, and purifying processes. Analytical chemistry, which is linked to industrial development concepts, evolves with time. The various pharmacopoeias specify stringent purity and impurity criteria. Modern separation methods have progressed because they can simultaneously separate and quantify components, making impurity separation and characterization easier.[4] The British Pharmacopoeia (BP), the United States Pharmacopoeia (USP), and the Indian Pharmacopoeia (IP) are gradually adopting restrictions to permissible amounts of contaminants contained in APIs or formulations .The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has also published guidelines for the validation of methods for analysing impurities in new drug substances, products, residual solvents, and microbiological impurities in new drug substances, products.[5]

Need for impurity profile

Analyse the presence of contaminants in the raw materials used for production is a prerequisite for carrying out any formulation's production process. API solubility may be hindered by several contaminants. The presence of these undesirable compounds or chemicals may impact drug safety parameters by causing adverse drug reactions or toxicities in the body, jeopardising API safety and efficacy.[6]

Guidelines on impurity

Drug Applications (NDA) or Abbreviated New Drug Application (ANDA) with the types of material that should be included in their submissions, as well as assisting FDA reviewers and field investigators in their consistent interpretation and implementation of rules.[7]

The various regulatory guidelines regarding impurities are as follows[7]

1. ICH guidelines “stability testing of new drug substances and products"- Q1A
2. ICH guidelines “Impurities in New Drug Substances”- Q3A
3. ICH guidelines “Impurities in New Drug Products”- Q3B
4. ICH guidelines “Impurities: Guidelines for residual solvents”- Q3C
5. US-FDA guidelines “NDAs -Impurities in New Drug Substances”
6. US-FDA guidelines “ANDAs – Impurities in New Drug Substances”
7. Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia.

ICH Limits

Various regulatory bodies, including the International Conference of Harmonization [ICH], the United States Food and Drug Administration (USFDA), the Canadian Drug and Health Agency, and others, have established various impurity requirements. With novel approaches to quantitation and certification, impurities in new drug substances and drug products are detected and estimated. Regulatory criteria for identifying, quantifying, and controlling contaminants in pharmacological compounds and their formulations are becoming increasingly clear, thanks in part to the International Conference on Harmonization (ICH). Identification of impurities below 0.1 percent threshold is not considered necessary, according to the ICH guideline on impurities in new medicinal products, unless potential impurities are judged to be extremely strong or harmful. The maximum daily dose qualification criteria to be considered, according to the ICH, is 2g/day, 0.1mg per day intake (whichever is lower)>2g/day, 0.05 percent.

Qualification

Qualification is the process of collecting and analysing data to determine the biological safety of a single impurity or a specific impurity profile at the prescribed level(s). The application should explain why impurity acceptability standards should be established, taking into account safety concerns. A novel drug substance's amount of any impurity that has been thoroughly investigated in safety and/or clinical investigations is termed qualified.

In animal and/or human investigations, impurities that are also major metabolites are normally deemed qualified. A study of the actual amount of impurity delivered in earlier relevant safety studies can also justify a level of qualifying impurity higher than that present in a new medicinal ingredient.[8]

Specification: Impurity restrictions should be included in the specifications for a new pharmacological substance. Impurities likely to emerge in commercial products can be predicted using stability studies, chemical development studies, and routine batch analyses.
A justification for including or excluding contaminants from the requirements should be provided. A discussion of the impurity profiles seen in the safety and clinical development batches, as well as the impurity profile of material made using the proposed commercial procedure, should be included in this reasoning.[9]

2. Classification

Impurities are classified into various categories upon their origin, composition type and biological safety.

As per USP

The impurities can be classified as Impurities in official literature / publication, Ordinary impurities and Organic volatile impurities.

1. Impurities in Official Articles.
2. Ordinary Impurities.
3. Organic Volatile Impurities.

As per ICH guidelines

In the chemical synthesis, impurities produced can be classified into Organic impurities, Inorganic impurities and Residual solvent a single end product with a 100 percent yield is extremely rare; by-products are always a possibility.

2.1 Organic impurities (Process and Drug Related)

Organic impurity might emerge during the manufacturing process and/or storage of the drug substance. They might be identified or unidentified, volatile or non-volatile. This type of impurity includes- intermediate, starting material, degradation product, reagents, ligands and catalyst used at different stages of synthesis of API and drug products.

a. Starting materials: This type of impurity could be critical in generating the next step's starting material. However, although the final product is rinsed with solvents in multistep synthesis, there is a chance that residues of the initial material will be present.

Example: There is a limit test for p aminophenol in paracetamol bulk, which might represent a beginning material for one manufacturer or an intermediate for another as an impurity in the next step.[1]

b. By-products: In synthetic organic chemistry, obtaining. The most prevalent process contaminants in medications are by-products from side reactions**.** (10) Side reactions such as incomplete reactions, overreactions, isomerization, dimerization, rearrangement, and undesirable reactions involving starting materials or intermediates and chemical reagents or catalysts can all result in by-products.

c. Intermediates: Intermediates are compounds created during the production of a desired material or as part of the production or synthesis of drug material**.**

d. Degradation product: Product deterioration occurs throughout the manufacturing process, storage, dosage form formulation [12], and ageing. Penicillin and cephalosporin are two authoritative examples of contaminants from breakdown products**.** (4)

e. Reagent, ligands and catalyst: These compounds are less common in APIs, although they can cause problems as contaminants in some situations. The presence of some compounds, such as trimethylamine, has also been discovered to have a degradative effect on the product. Under rapid stability testing, ampicillin trihydrate samples with triethylamine level of 2000 ppm to 4000 ppm (measured by visual colour method developed by Gist-Brocades, Delft, and Holland) were found to. When the triethylamine content reached 7000 ppm, however, the product began to degrade**.** (11 be stable).

2.2 Inorganic impurities (Reagent, ligand, catalyst)

Inorganic impurities may also be derived from the manufacturing processes used for bulk drugs. They are present mainly include heavy metals, residual solvents, inorganic salts, filter aids, charcoal, reagent, ligands and catalyst.

a. Heavy Metals: The reactors (if stainless steel reactors are utilised), where acidification or acid hydrolysis takes place, and the water used in the operations are the principal sources of

heavy metals. Heavy metal contaminants can be easily avoided by employing demineralized water and glass-lined reactors**.**[11]

b. Reagent, Ligand and Catalyst[12]**:** Although these contaminants are uncommon, they might cause problems in particular processes if manufacturers do not take adequate precautions throughout production.

c. Other materials: In bulk medicine manufacturing processes, filters or filtering aids such as centrifuge bags are commonly utilised, as is activated carbon in many circumstances. To avoid these impurities, constant monitoring of fibres and black particles in bulk pharmaceuticals is required.[9]

2.3 Residual solvent (Volatile solvent)

Residual solvents are organic or inorganic liquids used during the process of manufacturing of drug substance. Some solvent are very toxic and it is very difficult to remove the solvent completely by work process. Some solvent are very toxic and it is very difficult to remove the solvent solvents completely by work process. Depending on the possible risk to human health, residual solvent can be classified into three classes.

a. Class 1 Solvent (Solvents to be avoided): Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.[13] These solvents should be avoided in the pharmaceutical products because they are known as carcinogenic solvent**.**

Example: Solvents like benzene (2 ppm limit) and carbon tetrachloride (4 ppm limit) need to be averted.[14]

b. Class 2 Solvent (Solvents to be limited): Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities**.**[13] These solvents are also harmful or dangerous to pharmaceutical products.**[5]**

Example: Methylene chloride (600 ppm limit), methanol (3000 ppm limit), pyridine (200 ppm limit), toluene (890 ppm limit) and acetonitrile (410 ppm limit) are the most commonly used solvents.[14]

c. Class 3 Solvent (Solvents with low toxic potential): Low toxic potential to man; no health-based exposure limit needed.[9] These types of solvents are less toxic than class one and class two solvents. As per ICH guidelines they are found negative in genotoxic studies.[5]

Example: Acetic acid, acetone, isopropyl alcohol, butanol, ethanol and ethyl acetate have permitted day by day exposures of 50 mg or much less per day.[14]

3. Identification method

3.1 Spectroscopic method

a. Ultraviolet[15]: Ultraviolet radiation is a type of electromagnetic radiation. It is the study of UV absorption in the 200-400nm region. This absorption is unique and is dependent on the type of electron present.

UV spectroscopy terminology

Chromophore: The nucleus or any covalently bonded group responsible for the absorption of light radiation.

Auxochrome: Colour enhancing group is another name for it. These are co-ordinately saturated or unsaturated groups that do not absorb radiations on their own, but when present along the path of a Chromophore, they increase the Chromophore's absorbing characteristics.

b. Infrared spectrophotometry: Infrared spectrophotometry can provide detailed information on certain functional groups, allowing for measurement and selectivity. Low level delectability, on the other hand, is typically a problem that necessitates more complicated measures to solve.[16]

c. NMR: Nuclear magnetic resonance spectroscopy (NMR spectroscopy) offers fairly structural information about a molecule and is a very valuable approach for characterisation of molecules. Pollutants; nonetheless, its utility as a purifier is limited. Because of the cost and schedule constraints, a quantitative strategy was chosen considerations.[16]

d. MS: Over the last several decades, has had an increasingly significant impact on the pharmaceutical development process. The design and efficiency of interfaces, which are directly related to separation techniques using Mass Spectrometers (MS), have gained new identification for monitoring, characterising, optimising, and quantifying active pharmaceutical compounds present in the core of pharmaceutical products or formulations.[17]

3.2 Separation method

A. TLC: Because of its ease of use, cost-effectiveness, good sensitivity, separation speed, and ability to examine many samples simultaneously, thin-layer chromatography (TLC) is a commonly used separation technique. TLC is critical in the early stages of drug development, when knowledge about contaminants and degradants in the drug substance and drug product is scarce**.**[1]

B. HPLC: In today's world, high-pressure liquid chromatography is commonly referred to as high performance liquid chromatography. Both of these words can be shortened as HPLC, and chromatographers use them interchangeably. The use of a range of detectors, including as fluorescence, electrometric, MS, and others, has greatly expanded the uses of this technology for pharmaceutical chemists**.**[16]

C. HPTLC: HPTLC is a more advanced version of TLC with higher separation efficiency and detection limitations. HPTLC is the only chromatographic method that allows you to see your results as an image. Other benefits include simplicity, parallel sample analysis, low costs, quick findings, and the ability to detect many components.

The HPTLC approach may help to reduce the danger of harmful organic effluents being exposed to humans and greatly lessen the challenges associated with their disposal. With developments in the introduction of densitometers as detection equipment and stationary phases, HPTLC is still finding its way into pharmaceutical analysis.[18]

D. GC: The gas chromatography (GC) method is a dynamic method for separating and detecting volatile organic molecules in a mixture. Gaseous solutes are phased between an inert gas mobile phase and a stationary solid or liquid phase. Modern capillary column gas chromatographs can separate a large number of volatile components, allowing for identification via retention characteristics and detection at ppm levels utilising a variety of detectors**.**[3]

E. Supercritical fluid chromatography: It is an analytical scale that is utilised. It's a hybrid of HPLC and GC. It's crucial for high-molecular chiral separation and analysis. It can be used with a flame ionisation detector that is universal. The principle is based on the concept of a supercritical fluid. It's a material that can be either a liquid or a gas and can exist in a state above critical temperature or pressure where gases and liquids can coexist**.**[15]

Capillary electrophoresis

The following are some of the electrophoresis methods that have been developed in conjunction with chromatography.[19]

• Capillary zone electrophoresis.

• Capillary gel electrophoresis.

• Micellar eletrokinetic capillary chromatography.

• Capillary electro chromatography.

• Capillary isoelectric focusing.

• Capillary isotachophoresis

3.3 Isolation method

Isolation of contaminants is frequently required. Isolation of impurities is avoided when instrumental procedures are utilised since it directly characterises the contaminants.

Prior to characterisation, contaminants are usually isolated using chromatographic and non-chromatographic procedures. A chromatographic reactor is a device that uses an analytical-scale column as both a flow through reactor and a separation medium for the reactant(s) and product (s).[19]

3.4 Hyphenated method/ Characterization method

1. GC-MS

It was the first hyphenated method for identifying organic volatile contaminants and residual solvents in a sample, and it is still used today. While GC can separate volatile and semi-volatile impurities, it cannot identify them, whereas MS can identify impurities by providing structural information at the molecular level but cannot separate them. As a result, immediately after the introduction of GC, these two approaches were combined.[10]

2. LC-MS

It's a hybrid technology that combines the separation power of HPLC with the detection capability of mass spectrometry, and it's become quite popular with the development of the thermal spray and particle beam interfaces. For example, using a combination of ammonium acetate and methanol as the mobile phase, researchers investigated 10-methoxy-1, 6-dimethylergoline-8-methanol, 5-bromonicotinic acid ester (Nicergoline) and related compounds.[20]

3. LC-NMR[15]

It's a new technology that combines NMR and HPLC.

For example, LC-NMR has been used to analyse pharmaceutical metabolites.

Impurities in vestipitant can be identified by LC-NMR.

GC-MS, LC-MS, LC-MS-MS, and LC-NMR are the most widely used hyphenated techniques for drug impurity profiling.

3.5 Reference standard method

The main goal is to make the complete life cycle, qualification, and governance of reference standards used in the development and control of new pharmaceuticals more transparent. Reference standards are the benchmarks for assessing medicine safety for patient consumption and serve as the foundation for evaluating both process and product performance.[7]

4. Source

4.1 Formulation related: Interactions with excipients used to create a pharmacological product can result in a variety of contaminants in the finished product.

a. Dosage form related: Liquid dosage forms, in general, are highly vulnerable to both deterioration and microbial contamination. Water content, pH of solution, and mutual interaction of component and primary container are all important factors in this regard.[11]

b. Method related: If a parenteral dosage form of diclofenac sodium is terminally sterilised by autoclave, a recognised contaminant, 1-(2, 6-dichlorophenyl) indolin-2-one, is produced.[22] The autoclave method's conditions (i.e., 123 + 2 o C) force diclofenac sodium to undergo an intramolecular cyclic reaction that produces an indolinone derivative and sodium hydroxide. It has been discovered that the production of this impurity is influenced by the formulation's initial PH.[21]

c. Environmental related

Humidity: Humidity is harmful to both bulk powder and prepared solid dose forms for hygroscopic products. Examples include aspirin and ranitidine.

Light especially UV light: Several investigations have indicated that ergometrine and methyl ergometrine injections are unstable in tropical circumstances like sunshine and heat, and that

many field samples contain very low levels of active component. Only 50% of the marketed samples of ergometrine injections tested met the active component level requirements.90 percent to 110 percent of the reported content is the BP/USP limit. Ergometrine injections prepared to order when placed in direct sunshine for 42 hours, (0.2mg/mL) showed practically complete deterioration.

Temperature: Many APIs are susceptible to heat and tropical climates. Vitamins, for example, are extremely heat-sensitive medicinal components, and degradation usually results in potency loss in vitamin products, particularly in liquid forms.

4.2 Synthetic intermediate and by product

Raw ingredients, intermediates, and/or by-products can all contribute to impurities in medicinal compounds or novel chemical entities (NCEs). Impurity profiling of, for example, GC-MS analysis of ecstasy pills and MDMA samples produced via the reductive animation technique, impurities in intermediates**.**[5]

4.3 Impurities arising during storage

Impurities are frequently produced during the storage of medicinal products. The shelf life of a drug product can decline over time, resulting in the formation of various compounds. Polymorphism occurs from time to time, resulting in a decrease in pharmacological activity. A variety of contaminants can develop during the storage or transportation of pharmaceuticals. Stability studies are critical for predicting, evaluating, and ensuring drug product safety**.**[21]

4.4 Stereochemistry related impurity

Impurities can be caused by the stereochemistry of APIs. In general, a single enantiomeric version of an API is seen to be a superior chemical entity than other enantiomers or racemic mixtures, as it may have better pharmacological efficacy and a higher therapeutic index. E.g. the S-conformation of ofloxacin (levofloxacin), the R-conformation of albuterol (lavalbuterol), the S-conformation of omeprazole (esomeprazole), and the R-conformation of esomeprazole (esomeprazole).[6]

4.5 Functional group related

a. Oxidative degradation: Organic molecules with hydroxyl groups, conjugated dienes, heterocyclic aromatic rings, nitro so and nitrile derivatives, as well as aldehydes, are all

susceptible to oxidative destruction. Several organic products Catecholamine, for example, is a medicinally important hydroxyl molecule. Morphine, Ergometrine, Nifedipine, Nitroprusside, and Phenothiazine are some of the most commonly prescribed pain relievers. Photo-oxidation is a process that occurs when something is exposed to light.

Some substances, for example, under the conjugated dienes class, Vitamin A and Unsaturated Free Acid show when exposed to light, the material will oxidise. Methotrexate, a substance similar to hydrocortisone, When exposed to light, they will also show oxidation. The neurotransmitter epinephrine goes through a transformation. Oxidation results in the formation of adrenochrome, a colour molecule**.**[22]

b. Ester hydrolysis: Ester hydrolysis occurs in drugs such as aspirin, benzocaine, cefoxime, cocaine, and ethyl paraben**.**

c. Hydrolysis: Drugs such benzyl penicillin, barbital, and chloramphenicol are commonly hydrolysed**.**

d. Photolytic cleavage: Pharmaceutical products are exposed to light in a variety of ways, including when they are created as solids or solutions and when they are packed. In addition, it is periodically exposed to light in pharmacies or hospitals while awaiting use, or it is held by the consumer while awaiting use.[22]

e. Decarboxylation: When heated, some dissolved carboxylic acids, such as p-amino salicylic acid, release CO2**.**

5. Application

There are numerous applications in the fields of drug design and monitoring the quality, stability, and safety of pharmaceutical substances, whether synthesised, extracted from natural materials, or produced through recombinant technologies**.**[9]

Alkaloids, amines, amino acids, analgesics, antibacterial, anticonvulsants, antidepressants, tranquillizers, antineoplastic agents, local anaesthetics, macromolecules, steroids, and other medications are among the applications**.**[16]

CONCLUSION

Impurities in drug substance and drug product are discussed in this review. Pharmaceutical impurity profiles are becoming increasingly important, and medication safety is garnering more and more attention in the literature. There are also regulations in this paper that set the impurity threshold level, and different countries have their own pharmacopoeias that specify the impurity level and isolate them. This article discusses the different types of impurities and the numerous procedures for isolating and characterising them, as well as the various analytical techniques for determining, identifying, and qualifying impurities, as well as key considerations to consider while preparing bulk pharmaceuticals.

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