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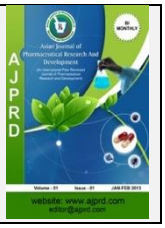

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Review Article

A Review on Impurity Profiling In Pharmaceutical Substances

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A B S T R A C T

The term "impurity profiling" describes a group of analytical techniques aimed at detecting, identifying, and quantifying residual solvents and organic and inorganic impurities in bulk medications and pharmaceutical formulations. This is the main objective of contemporary drug analysis since it is the most effective method of characterizing the stability and quality of pharmaceutical formulations and bulk drugs. To monitor them, certain analytical methods have to be developed. Even in cases where synthesis, formulation, or production procedures are improved, new purities may emerge from changes made to them. The International Conference on Harmonization (ICH), the US Food and Drug Administration (FDA), and other regulatory organizations are closely monitoring the identification of contaminants in Active Pharmaceutical Ingredients (APIs) and the requirements for their purity. In addition to degraded end products obtained during manufacture, pharmaceutical goods may contain impurities from a range of sources, such as ligands, heavy metals (HMs), catalysts, reagents, and other components like filter aids and similar compounds. The permissible quantities of pollutants found in APIs or formulations are progressively being limited by a number of pharmacopoeias, including the American, British, and Indian pharmacopoeias. Pharmaceutical contaminants are separated and analyzedby employingvarious techniques, that includes infrared spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry, ultracold extraction column chromatography, and ultraviolet spectrometry. For impurity profiling, this is the hyphenated method that is most frequently employed.

Keywords: Characterization, identification, impurities, NMR, chromatography, Ultraviolet Spectrometry

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INTRODUCTION

The term "impurity" refers to any material that exists with the original medicine, like starting material, intermediates, or substances generated as a result of side reactions. The presence of these undesirable substances, even in minute doses, may affect the safety and efficacy of pharmacological medications. The identification and number of impurities in pharmaceuticals, or impurity profiling, is currently receiving significant attention from regulatory bodies. By using analytical, spectroscopic, and chromatographic techniques wisely, a general plan is established for the determination of the impurity of bulk medicinal compounds. A drug compound's impurity profile addresses the various standards that need to be achieved.

The number of contaminants that are allowed to be present in APIs or formulations are increasingly being limited by several pharmacopoeias, like the American "Pharmacopoeia (USP), Indian Pharmacopoeia (IP), and British Pharmacopoeia (BP). Guidelines for validating approaches for evaluating impurities present in innovative drug substances, residual solvents,

products, and microbiological contaminants have also been released by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use" (ICH) (1).

IMPURITY PROFILING

The term impurity profiling lacks a specific definition. An explanation of the impurities found in the substance under examination is provided by impurity profiling. Additionally, it calculates how much of certain contaminants are actually present in the medication. A material under investigation's impurity profile is an inventory or explanation of the widest range of known or unknown contaminants that could be present in every API sample made using a certain controlled production method.Both qualitative and quantitative information about contaminants must be included in the impurity profile.(2).

Need for Impurity profiling:

Any formulation's production process must include an analysis of the contaminants present in the raw materials utilized for formulation. These contaminants could affect how soluble APIs are. The presence of these undesirable compounds or substances may also have an impact on a drug's safety parameters by causing toxicities in the body or unfavorable drug responses, which compromises the safety as well as effectiveness of APIs. (3).

ICH limits of impurities:

Numerous regulatory bodies, including the United States Food and Drug Administration (USFDA), the Canadian Drug and Health Agency, the ICH, and others, have provided different impurity criteria. Novel pharmacological substances and therapeutic products are subjected to the identification and quantification of impurities using innovative ways to qualify. Regulatory standards for the detection, quantification, and management of contaminants in pharmaceutical substances and their formulation are being more precisely specified, particularly with the aid of ICH.ICH has released guidelines that must be used for the validation of techniques for the analysis of impurities in innovative drug substances, residual solvents, products, as well as microbiological impurities. Based on the ICH guidelines, if an impurity's concentration is <0.1%, it is not required to identify it unless it is expected to be extremely strong and hazardous. Limits for inorganic impurities, residual solvents, and organic contaminants should all be included in APIs.The ICH has established the following impurity limits: Impurities should be present at less than 0.1percent or 1mg/day intake, whichever is lower when the dosage is <2gm/day. Impurities should make up less than 0.05 percent of the total intake when the dose exceeds 2 grams per day (4).

Sources of impurities:

Impurities from diverse sources might be present in formulations. Sources of impurities include:

(i) API-related impurities, which may arise through crystallization, stereochemistry, or the functional group of the APIs;

(ii) Chemicals, reagents, as well as catalysts utilized "in synthesis; intermediates and by-products; degradation products; impurities associated with method conditions and formulations; and other process-related impurities

(iii) Stability-related impurities include API deterioration" and interactions with formulation excipients. (5).

Common Terms of Impurities:

The ICH and other regulatory agencies refer to the impurities by the following terms:

1. **Intermediate**: The substances generated either as a byproduct of the synthesis process or during the production of the desired"material.
2. **Penultimate Intermediate:**It is the last substance in the chain of synthesis before the last desired compound is produced.
3. **By-products:**The" substance generated during the reaction that isn't one of the necessary intermediates. These can be caused by a variety of unwanted interactions between chemical reagents or catalysts and starting materials or intermediates, as well as by overreaction, incomplete reactions, demonization, and rearrangement.
4. **Transformation Products:**They have to do with products that can arise in a reaction, both theoretical and nontheorized. Though more is known about these reaction products, they are comparable to by-products.
5. **Interaction Products:**These compounds result from the intentional or unintentional interaction of the different substances.
6. **Related Products:**They may even have biological activity and are chemically comparable to pharmacological substances.
7. **Degradation Products:**They are created when an external substance, such as heat, light, or moisture, breaks down the active component or another material of "interest (6).

CLASSIFICATION OF IMPURITY:

United States Pharmacopoeia (USP):

USP states that impurities are divided into 3 categories.

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

The ICH Terminology:

The following three categories broadly describe impurities in pharmacological substances made by chemical synthesis, according to ICH "guidelines:

Organic Impurities (Process as well as drug-related)
Inorganic Impurities (Reagent, ligands, catalysts)
Residual Solvents (Volatile solvents) (7).

ORGANIC IMPURITY:

These kinds of impurities develop when the" drug material is being manufactured or is being stored. The following sub-impurities are among "them.

Starting Materials or Intermediate Impurities:

If adequate precautions are not taken at each stage of the multistep" production of therapeutic products, such contaminants are common in nearly all APIs. Even though solvents are always used to wash the final products, producers

may not be as careful about impurities as they should be and there may be residue from unreacted beginning constituents.

By-products:
Obtaining "a single end product with complete yield is" extremely uncommon in synthetic organic chemistry; instead, byproducts may occasionally be present besides the desired end product.

Degradation Products:
When bulk pharmaceuticals are being manufactured, the ultimate product may also degrade, forming impurities. This typically arises from inappropriate storage of formulations (8).

Other Types of Organic Impurities:

A. Synthesis Related Impurities:
During the synthetic process, a new chemical entity is created from a source material, solvent, intermediate, and byproduct. If an impurity is present in any of the substances involved in the reaction, even in trace amounts, during the synthesis process, the result will be a final product contaminated with one or more undesired elements. Consequently, each phase of the synthesis process must be performed with the highest precision to minimize any impurities.

B. Formulation Related Impurities:
Drug substances are exposed to a range of circumstances, which might cause them to degrade or respond in different ways. Hydrolysis is a common cause of deterioration in solutions and suspensions. In addition to adding impurities, the water employed in the formulation creates an environment favorable for hydrolysis as well as"catalysis (9).

Factors Affecting On Formulation Related Impurities:

a. Environment related:
I. Exposed to adverse temperature: Heat-labile substances or those that exist in tropical" climates cause the active ingredients to break down and impurities to develop.
II. Exposed to light: Exposure of photosensitive materials to light or ultraviolet light, results in degradation and impurities.
III. Humidity: Bulkpowder as well as formulations with solid dosage forms may suffer "as a result.

b. Formation of impurities on ageing:
Mutual interaction: The mutual interaction between the constituents in a formulation" results in the production of "impurities.

C. Functional Group Related Impurities:
a) Ester hydrolysis: Ester hydrolysis occurs in the case of drugs like aspirin, benzocaine, cefoxime, cocaine, and ethyl paraben.
b) Oxidative degradation: Drugs like" methotrexate, hydrocortisone, nitroso/nitrile derivatives, and heterocyclic aromatic rings (10).

INORGANIC IMPURITY:

The manufacturing procedures that are utilized in the formulation of bulk drugs also yield inorganic contaminants. Usually, they can be recognized as well as identified.

a. Reagent, Ligands and Catalysts:
Extremely rare occasions when these contaminants exist. A problem may arise if a production technique is not followed correctly.

b. Heavy Metals:
Water is typically utilized in a variety of production processes where acid hydrolysis or acidification occurs. These processes are the primary source of HMs, includingMg, Ar, Cr, Na, Cd, and Mn. HM contaminants can be effectively mitigated by the application of glass-lined reactors and demineralized water.

c. Other Materials (Filter Aids, Charcoal):
Activated carbon, which serves as a source of contaminants, is commonly utilized in conjunction with filters or filtering aids like centrifuge bags in bulk drug manufacturing plants. Consequently, it is imperative to routinely inspect bulk medications for fibers and black particles to prevent "contamination (11).

1. Residual Solvents:
Residual solvents refer to organic or inorganic liquids utilized in" production procedure. Complete removal of these solvents through the work-up process is quite challenging. When producing bulk pharmaceuticals, certain solvents that are known to be harmful must be avoided (12).

2. Formation of related impurities (Impurities in drug product):

Inert components utilized in the formulation of a pharmacological agent may lead to various impurities in the therapeutic product. A pharmaceutical compound undergoes several conditions during formulation that may lead to degradation or other adverse effects. Hydrolysis has the ability to cause degradation in solutions and suspensions. In addition to adding its own contaminants, the water employed in the formulation may also create an ideal environment for hydrolysis and catalysis. It is feasible for other solvents that may be employed to have similar effects. The contaminants associated with the formulation could be categorized as follows:

- Method related
- The following are the main environmental elements that are related to the environment and can lower stability:

I. Humidity
II. Light-especially UV light
III. Exposures to adverse temperatures

Method related:
If terminal autoclaving is used to sterilize diclofenac sodium, a recognized impurity known "as 1-(2, 6-diclorophenyl) indolin-2-one is generated throughout the production process. The autoclave method's requirement of 123+2°C for the intramolecular cyclic reaction of diclofenac sodium to create the indolinone derivative and sodium hydroxide was followed. It has been discovered that the initial pH of formulation affects the production of this"impurity. The ampoule's final product has an impurity concentration that surpasses the BP's raw material limit.

Environmental related:

The following are the main environmental elements that can lower stability:

Exposures to adverse temperatures: Numerous APIs exhibit heat- or tropical-temperature sensitivity. For instance, vitamins lose efficacy in vitamin products due to deterioration, especially in liquid formulations, as they are highly heat-sensitive medicinal compounds.

Light-especially UV light: According to a number of studies, ergometrine, and methyl ergometrine injection are unstable in tropical environments with high light and heat levels, and many field samples contain very little active component. The level of active ingredient in only fifty percent of the commercially available "samples of ergometrine injections that were tested met the BP/USP threshold of 90percent to 110percent of the" declared quantity. The ergometrine injection, which was produced to order and had 0.2 mg/mL, nearly completely degraded after 42 hours in the sun.

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

Dosage form related:

Pharmaceutical firms do pre-formulation research, that includes stability assessments, prior to product introduction; however, dosage form complications that impact medicine stability frequently necessitate recalls of products. Due to sub-potency brought on by impurities and degradation, the 60 mL bottles of "Fluocinonide Topical Solution USP, 0.05% (Teva Pharmaceuticals USA, Inc., Sellersville, Pennsylvania) were recalled in the US.Liquid dosage formulations are generally prone to deterioration and microbial impurities. The presence of water, the solution or suspension's pH, the compatibility of anions as well as cations, the interactions among constituents, and the principal container are all critical aspects in this context. In a warm, humid environment, the growth of yeast, bacteria, and fungi can cause microbiological development that can result in the production of oral liquid products that are unsafe for human ingestion. Microbial impurities can occur when users store and utilize multiple-dose products because the primary containers are semipermeable or because certain preservatives were not employed correctly in the "preparations. (13).

General Scheme For Drug Impurity Profiling:

Using a thin-layer, high-performance liquid, or gas chromatogram, the" impurities are first identified as part of the impurity profiling procedure. Acquiring standard impurity samples (final synthesis intermediate, predicted side reaction products, degradation products, if any), from synthetic organic chemists. The most sensible method for figuring out the structure of an impurity in the event that standard samples fail to identify it is to examine the UV spectra, which are simple to obtain in HPLC cases using a diode-array detector and quantify using a densitometer. In rare instances, if one has experience in the drug's manufacturing, one may be able to determine the impurity's structure using NMR spectrum data martial23, 24. If there is not enough information from the UV spectrum to do an impurity profile, the next step is to obtain the mass spectrum of impurity. The principal drawback of this approach is the volatility of contaminants and issues related to thermal stability. Derivatization processes are frequently utilized in GC/MS analysis, yet their utilization presents challenges since their buyingproducts can be mistaken for contaminants. The subsequent phase in the impurity profiling process involves synthesizing the material (impurity standard) according to the prescribed structure (14).

Acceptance Criteria for Impurities:

The specification for newly synthesized drug compounds must have acceptance criteria for impurities. Contaminant prediction in commercial products can be achieved by stability studies, routine batch analyses, andchemical development studies. A description "of the impurity profiles found in the batches that were analyzed and an assessment of the impurity profile of the material made using the suggested commercial process must be involved in the rationale for including/excluding impurities from the specification. The quantitation or detection limit of analytical"techniques must align with the regulatory threshold for potent impurities that may induce dangerous or unexpected pharmacological effects. A descriptive label appropriate for qualitative examination must be provided in the specification of unknown contaminants. A universal acceptance threshold for any unidentified impurity should not exceed 0.1%. Acceptance criteria must be formulated on the basis of data obtained from actual batches of drug substance, considering its stability attributes and allowing for adequate flexibility to address standard manufacturing and analytical variability. Significant variations in impurity levels across batches might indicate that the process of production of medicinal ingredients is inadequately controlled as well as validated, even in the anticipation of standard manufacturing variations.Limits for total impurities, organic impurities, residual solvents, and inorganic impurities must all be involved in the acceptance criteria. Furthermore, all specified identifiable impurities, all defined unidentified impurities at or exceeding 0.1%, and any unnamed impurities with a threshold not exceeding 0.1% must be listed (15).

ANALYTICAL METHOD DEVELOPMENT:

At different phases of the research process, meaningful as well as reliable analytical data must be generated for new drug development.

a) Selection of sample sets for the development of analytical methods

b) Screening of the phases and conditions of chromatography, usually with the use of the gradient elution linear solvent-strength model

c) Optimization of the process for changing characteristics related to robustness and "toughness (16).

1. Reference standard method:

The primary objective is to explain the whole life cycle, certification, and governance of reference standards utilized in the development and regulation of new pharmaceuticals. Reference standards serve as benchmarks for assessing the safety of medicine for patient consumption and establish the basis for evaluating both process and product performance. These requirements apply not only to the active substances in

dosage forms but also" to excipients, starting materials, degradation products, impurities, and process intermediates (17).

1. Spectroscopic methods:

Impurities are often markedby employing spectroscopic approacheslike IR, MS, NMR, UV, and Raman (18).

2. Separation methods:

For the purpose of separating contaminants and degradation products, techniques such as "capillary electrophoresis (CE), gas chromatography (GC), supercritical fluid chromatography (SFC), chiral separations, TLC, HPTLC, and HPLC are" frequently employed (19).

Isolation methods:

Isolating impurities is typically required. Nevertheless, because instrumental approaches directly identify impurities, the isolation of impurities can be avoided when employing these techniques. Chromatographic and non-chromatographic methods are typically employed to isolate impurities before characterizing them. The utilization of an analytical-scale column as both a flow-through reactor and a medium for the separation "of reactants and/or products is referred to as a 'chromatographic reactor.'The kinetics of solution-phase hydrolysis for the prodrug Aprepitant (EmendTM), fosaprepitantdimeglumine, had beenexplored"by employing an HPLC chromatographic reactor approach.Ofloratidine was identified as an impurity in loratidine; celecoxib and amikacin are two further examples. The following is a list of techniques for isolating contaminants.

- Solid-phase extraction methods
- Column chromatography
- Flash chromatography
- Liquid-liquid extraction methods
- Supercritical fluid extraction
- Accelerated solvent extraction methods
- TLC
- GC
- Supercritical fluid chromatography (SFC) (20-22)
- HPLC
- HPTLC
- Capillary electrophoresis (CE)

Characterization methods:

It takes extremely sophisticated tools, that include MS coupled to a GC or HPLC, to detect tiny components (drugs, impurities, degradation products, and metabolites) in a range of matrices. Different techniques are used to characterize impurities. These strategies include the following: NMR is a potent analytical tool for structural elucidation because of its capacity to reveal details about the precise stereochemistry and bonding structure of compounds of medicinal interest.

NMR:

A conventional mixture of actual materials comprising both monomers as well as dimers was employed to validate the capability of the diffusion coefficient determination to differentiate between monomeric and dimeric substances. Regretfully, in comparison to other analytical methods, NMR has historically been regarded as a less sensitive approach. In comparison to MS, which takes less than 1 mg of sample, conventional NMR requires samples of approximately 10 mg (23).

MS:

In recent decades, it has increasingly influenced the pharmaceutical development process. Advancements in the design and functionality of interfaces linking separation approaches to MS have enabled new opportunities for the observation, characterization, as well "as quantification of drug-related compounds in active pharmaceutical ingredients as well as pharmaceutical formulations. Consideration" should be given to orthogonal coupling of chromatographic techniques, like HPLC-TLC as well as"HPLC-CE, or the integration of chromatographic separations with information-dense spectroscopic approaches, like HPLC-MS or HPLC-NMR if" a singular approach fails to deliver the necessary selectivity. This should be regarded solely as a development tool, not for everyday "quality control applications (24).

Hyphenated Methods:

- LC-MS-MS
- GC-MS
- HPLC-DAD-NMR-MS
- HPLC-DAD-MS
- LC-MS

Determining" which of the numerous possible impurities are actually formed during the production process and which occur under certain storage circumstances is a common goal for research on impurities related to both process and product deterioration (25).

VALIDATION OF IMPURITY PROFILING

In the actual world, the validation procedure is to test the technique and establish the bounds of permissible variability for the necessary circumstances for the method to be executed. Validation is defined as "the process of providing documented evidence that the method does what it is intended to do" by the United States Pharmacopoeia. It is imperative to commence the validation process with a well carefully planned validation plan in place to test the technique and acceptance criteria. In order to meet compliance requirements, the created method for impurity profiling must be verified. Assay validation performance parameters encompass specificity, accuracy, limit of quantitation, precision, linearity, range, and robustness. Furthermore, analysts are advised to assess the stability of the sample solution and conduct a suitable system-suitability test to confirm that the instruments used for the analysis are operating correctly (26).

APPLICATIONS

The fields "of drug design and quality, stability, along safety monitoring of pharmaceutical compounds—whether synthesized, derived from natural materials, or created through recombinant"approaches—have seen a great deal of application. Applications encompass anticonvulsants, amino acids, alkaloids, amines, antibacterials, analgesics, tranquilizers, steroids, antineoplastic drugs, macromolecules, and numerous other substances.

The synthesis of pharmacological compounds and the production of dosage forms both benefit greatly from impurity profiling, which can yield vital information on toxicity, safety, and different limits of detection (27).

CONCLUSION

A substance under investigation's impurity profile provides the most comprehensive account of the impurities that are present in it. The quality standards for producers are established by guidelines for impurity levels in pharmacological substances as well as products. The most important thing is to demonstrate the qualification of a new chemical entity's impurity profiling. It is imperative that pharmaceutical analysts carefully consider their analytical methodology when dealing with substances that have a qualifying level of 0.1% or lower. Using very selective methods, such as hyphenated procedures, may be important, especially during the development stages. To make sure that the contaminants present in the batches being utilized in safety studies are given the proper consideration, development scientists should understand the significance of qualifying impurity profiles. The topic of impurity identification and quantitation has advanced, starting with limit testing. To obtain and assess data proving biological safety, impurity characterization, and isolation are necessary. This demonstrates the significance and extent of drug impurity profiling in scientific investigations.

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