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RESEARCH ARTICLE

A Better Method for Pharmaceutical Quality Control for Impurity Profile Data

Ajay Kumar Shukla, Vimal Kumar Yadav, Vishnu Yadav, Vineet Bharti, Kunal Agam

Institute of Pharmacy, Dr. Rammanohar Lohia Avadh University, Ayodhya, Uttar Pradesh, India

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ABSTRACT

In the pharmaceutical industry, an impurity is any extra organic substance that is not a part of the medicine or component, or any unwanted chemicals that are left over after synthesis. Pharmaceutical contaminants are undesirable materials that are left over or created during the production of medications. The existence and amount of impurities in pharmaceuticals can significantly affect their quality and safety; hence, there is an urgent need for a systematic and comprehensive medication impurity profiling technique. Moreover, industry productivity is under constant pressure to increase. The quality of the medication is being adversely affected by the presence of impurities. Among the various types of contaminants are degradation products, byproducts, penultimate impurities, intermediates, and starter materials. Impurities come in many different forms, including beginning materials, intermediates, penultimate impurities, byproducts, and degradation products. The process of impurity profiling aids in the identification, detection, and measurement of different kinds of impurities as well as residual solvents in pharmaceutical formulations and bulk pharmaceuticals. It is the most effective method for describing the stability and quality of pharmaceutical formulations and bulk medications. This review paper addresses the pharmaceutical impurity profile.

Keywords: Active pharmaceutical ingredients, impurity profile, impurity, pharmaceuticals

INTRODUCTION

Something that taints or causes something else to taint is called an impurity. A substance of interest combined or impregnated with an extraneous or typically inferior component is referred to as an impure substance.[1-3] There are numerous opportunities for contaminants to form during the manufacture of active pharmaceutical ingredients (API).[4] According to the dictionary, an impurity is something that is unclean or causes something else to be unclean. Therefore, an impurity can be defined as "any substance coexisting with the original drug substance (DS), such as starting material or intermediates from reaction or that is formed, due to any chemical interaction or by-products from side reaction," or more succinctly, as "any material that affects the purity of the material of interest," such as an API or DS.[5] The drug's safety is contingent on both the impurities present in the API and its own toxicological characteristics. For this reason, one of the most crucial areas of work in pharmaceutical analysis is the precise evaluation of API impurity profiles. While a drug candidate moves through different stages of development and the process is scaled up, modifications to the synthetic process, such as those involving synthetic routes, reaction conditions, and purification procedures, may occur. These modifications may also raise concerns regarding safety and alter the impurity profile. As a result, impurity profiling becomes a common task that is labor- and time-intensive.[6]

Profile of impurities a collection of analytical procedures known as "impurity profiling" is used to find, identify, clarify the structure of, and quantify organic and inorganic impurities as well as leftover

***Corresponding Author:**
Ajay Kumar Shukla,
E-mail: ashukla1007@gmail.com

solvents in pharmaceutical formulations and bulk pharmaceuticals. The ICH, USFDA, Canadian Drug and Health Agency, and other regulatory bodies are putting a lot of emphasis on the purity standards and the detection of contaminants in APIs.[7] Impurity profile refers to the identification, characterization, and quantification of both known and unknown impurities in novel pharmacological substances.[8] It describes the contaminants found in both the drug's bulk and final form. It aids in the identification and measurement of contaminants found in pharmaceutical formulations or pharmacological substances (API). It lists every conceivable kind of impurity found in pharmaceutical formulations and DSs (API).[9]

CATEGORIZATION OF CONTAMINANTS

The two main categories of pharmaceuticals are drug product (DP), also known as finished pharmaceutical product, and APIs, also known as DS. Pharmacopeia and ICH recommendations are used to classify pharmaceutical impurities.[10]

Typical Names

- Related goods
- Transformation products
- By-products
- Degradation products
- Interaction products
- Intermediates
- Final intermediates

United State Pharmacopeia

Impurities are categorized by the United States Pharmacopeia into three sections: Ordinary impurities, organic volatile impurities, and impurities in official articles.

ICH Terminology

The following three categories broadly describe contaminants in the drug ingredient created by chemical synthesis, according to ICH guidelines:

Remaining solvents; inorganic impurities; and process- and drug-related organic impurities

During the manufacturing process and/or storage of the DS, organic impurities may emerge. These impurities can be volatile or non-volatile, identifiable or unidentified, and they might include starting ingredients, intermediates, and by-products.

Deterioration goods.

SOURCES OF IMPURITIES

Every pharmaceutical drug, regardless of dose type, contains contaminants from different sources from the time that the product is manufactured until it is finished. Two categories of contaminants are present in medications: (1) Impurities connected to the active components in pharmaceuticals; and (2) impurities formed during formulation, as a result of age, or in relation to the prepared forms.[11] Broadly speaking, the different kinds of contaminants that could exist in medicinal materials can originate from the following places:

1. The ingredients that were used raw
2. The manufacturing technique used
3. As a result of the product's instability and
4. As a result of air pollution.[12]

METHOD OF DETECTION OF IMPURITY

When a sample is available, it is crucial to validate it for estimate purposes. According to FDA regulations, an impurity content must be stated if the estimations show that it is more than 0.1%. For the initial characterization of the contaminants, hyphenated procedures such as gas chromatography (GC), mass spectroscopy, liquid chromatography, mass spectrometry, or any number of alternative chromatographic-spectroscopic arrangement are ideal.

a. Methods of spectroscopy
b. Chromatographic techniques
c. The fusion of chromatographic and spectroscopic methods (For example, hyphenated methods).

Highly complex instruments are essential for identifying small components (drugs, contaminants,

degradation products, and metabolites) in a variety of matrices. Examples of these instruments are MS coupled to a GC and high-performance liquid chromatography (HPLC). Several methods are employed to characterize contaminants, including the following ones.

NMR

NMR, or nuclear magnetic resonance, is a potent analytical tool for structural elucidation due to its capacity to reveal details about the precise stereochemistry and bonding structure of compounds of pharmacological relevance. Using a common combination of real materials that included both monomers and dimers, the capacity of NMR-based diffusion coefficient determination to distinguish between non-numeric and dimeric compounds was validated. Regretfully, NMR has a reputation for being a less sensitive method than other analytical techniques. Compared to MS, which requires less than 1 mg of material, conventional NMR requires samples of about 10 mg.

MS

Over the past few decades, mass spectroscopy, or MS, has had an ever-greater impact on the pharmaceutical development process. Novel opportunities for the monitoring, characterization, and quantification of drug-related substances in API and pharmaceutical formulations have been made possible by improvements in the design and functionality of the interfaces that directly connect separation techniques with mass spectrometers. Orthogonal coupling of chromatographic techniques, such as HPLC-TLC and HPLC-capillary electrophoresis, or coupling of chromatographic separations with information-rich spectroscopic methods, such as HPLC-MS or HPLC-NMR, may need to be considered if a single method is unable to provide the required selectivity. Ideally, this would only be necessary as a tool for development rather than for regular quality control use.[13-25]

PHARMACEUTICAL USES

Pharmaceutical compounds, whether synthesized, taken from natural materials, or created through recombinant technologies, have been used for a wide range of purposes, including medication design and quality, stability, and safety monitoring. Applications include: antineoplastic agents, local anesthetics, macromolecules, steroids, analgesics, antimicrobials, anticonvulsants, antidepressants, tranquilizers, and other substances.[26]

SOME SPECIFIC REPORTED CASES

Identification and Structural Characterization of Degradation Products of Linagliptin Using Mass Spectrometry Techniques

Maintaining the purity of API during the pharmaceutical development process is essential to guaranteeing the end product's quality, safety, and efficacy. Throughout the manufacturing process, raw materials, intermediates, reagents, solvents, and degradation products brought on by environmental elements such as heat, light, or moisture can all be sources of impurities in APIs. These contaminants may lessen the medication's therapeutic benefit, cause unwanted side effects, or endanger patients' safety. To discover the breakdown products of linagliptin, this study focuses on forcing the drug to degrade. Liquid chromatography coupled with high-resolution mass spectrometry and UPLC coupled with a single quadrupole detector mass spectrometer were used to identify and characterize the degradation products. According to the findings, linagliptin does not significantly degrade in alkaline, thermolytic, or photolytic environments, but it is especially vulnerable to deterioration in acidic and oxidative (peroxide) circumstances.[27]

In Developing Pharmaceutical DPS, it is Crucial to Ensure that Leachable Impurities Remain at Acceptable Levels

The concentration of these contaminants at particular temperatures and periods can theoretically be predicted by knowing the diffusion and partition coefficients. To investigate the migration of organic

compounds with low-to-high molecular weights from mono-and multilayer polyolefin films into aqueous solutions with different pH values or other polyolefin films, kinetic experiments were conducted in this work. In the next paper, we will talk about how to overestimate these coefficients to take experimental variability into account and how these parameters can be used to forecast the amounts of other substances that leak into aqueous medication formulations from multilayer films.[28]

The Toxicological Analysis of Lead Impurities in Traditional Herbal Medicinal Products

The purpose of the study was to examine lead contaminants in traditional herbal medical products (THMPs) from Polish pharmacies that contained Thymi herba (*Thymus vulgaris* L. and *Thymus zygis* L.). It involved doing an extensive toxicological risk evaluation as well as developing impurity profiles. Based on manufacturer-recommended dosages, lead impurities were found in all samples (2.15–6.99 μg/L), with single-dose levels ranging from 32.25 to 105.01 ng and daily dose levels from 64.50 to 210.00 ng. The results demonstrated that there was no harm to adult health from the THMPs under investigation, in accordance with the ICH Q3D (R1) standards on elemental impurities.[29]

Development of a Stability-indicating Test Technique and Structural Characterization of Enasidenib Degradation Products using LC/Q-TOF-MS

The FDA has approved the medication enasidenib (EDB), an oral selective inhibitor of the mutant isocitrate dehydrogenase-2 enzyme, to treat acute myeloid leukemia. On the other hand, there were no thorough forced degradation studies or stability-indicating assay methods (SIAM) for EDB. In accordance with ICH, Q1A, and Q1B (R2) recommendations, this study profiles EDB degradation under various stress circumstances and develops a validated SIAM to meet these needs.
Numerous stress conditions, including hydrolytic, photolytic, oxidative, and thermal stress, were applied to EDB. An Agilent ZORBAX Eclipse Plus C18 column was used for the HPLC analysis. With a flow rate of 1 mL/min and a detection wavelength of 270 nm, the mobile phase was composed of 0.1% formic acid in Milli-Q water and acetonitrile. The degradation products were identified and characterized using LC/Q-TOF HRMS. This study contributed to the risk assessment of the medication by effectively developing a validated SIAM for EDB, characterizing all degradation products using LC/Q-TOF-HRMS, and discussing possible NDSRI production.[30]

CONCLUSION

The synthesis of DSs and the production of dosage forms both benefit greatly from impurity profiling, which can yield vital information about the toxicity, safety, different detection limits, and quantitation limits of a number of organic and inorganic impurities that are typically present in bulk drugs and completed products. Efficient technique development and procedure validation facilitate the impurity profiling task.

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