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REVIEW ON IMPURITY PROFILING OF PHARMACEUTICALS

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Abstract:

The International Conference on Harmonisation (ICH), the Food and Drug Administration of the United States (FDA), and the Canadian Drug and Health Agency (CDHA) are among the regulatory agencies that place a strong emphasis on the purity standards and the detection of impurities in active pharmaceutical ingredients (APIs). Reagents, heavy metals, ligands, catalysts, other substances like filter aids, charcoal, and the like, degraded end products obtained during or after manufacturing of bulk drugs from hydrolysis, photolytic cleavage, oxidative degradation, decarboxylation, enantiomeric impurity, and so on are just a few of the different sources of impurity in pharmaceutical products. Limits to permissible levels of impurities present in APIs or formulations are gradually being added by the various pharmacopoeias, including the British, American, andIndian versions.For example, capillary electrophoresis, electron paramagnetic resonance, gas-liquid chromatography, gravimetric analysis, high performance liquid chromatography, solid-phase extraction methods, liquid-liquid extraction methods, UV spectroscopy, infrared spectroscopy, supercritical fluid extraction column chromatography, mass spectrometry, nuclear magnetic resonance (NMR) spectroscopy, and others are used to isolate and characterise impurities in pharmaceuticals. Liquid chromatography (LC)-mass spectroscopy (MS), LCNMR, LC-NMR-MS, gas chromatography-mass spectroscopy (GC-MS), and LC-MS are the hyphenated methods used the most frequently for drug impurity profiling. This highlights the significance and necessity of drug impurity profiling in pharmaceutical research.

Keywords: Characterization, chromatography, identification, impurities.

Introduction:

Impurities found in APIs are of ever-increasing interest. Recent regulatory requirements have made it necessary to have both a purity profile and an impurity profile. In the pharmaceutical industry, an impurity is defined as any additional organic material that results from synthesis or undesirable compounds that are still present in APIs. The impurity may appear during formulation or after both raw APIs and formed APIs have aged in pharmaceutical products. Identification of impurities in APIs such as 1-(1, 2, 3, 5, 6, 7-hexahydro-s-indacen-4-yl)-3-4[1-hydroxy-1-methyl-ethyl]-furan-2-sulphonylurea employing Multidisciplinary method may serve as an effective demonstration of this definition.

Even a little amount of these undesirable compounds can have an impact on the safety and effectiveness of medicinal goods. Regulatory agencies are now paying critical attention to impurity profiling, which involves the identification and quantification of impurities in medications. Limits on Allowable levels of impurities present in the APIs or formulations are gradually being incorporated by the various Pharmacopoeias, including the British Pharmacopoeia (BP), United States Pharmacopoeia (USP), and Indian Pharmacopoeia (IP).

Guidelines for the Validation of Methods for Analysing Impurities in New Drug Substances, Products, Residual Solvents, and Microbiological Impurities have also been issued by the International Conference on Harmonisation of Pharmaceuticals for Human Use Technical Requirements for Registration (ICH).Several articles have provided instructions and suggested methods for isolating and identifying process-related impurities and degradation products using Tandem Mass Spectrometry, Fourier Transform Ion Cyclotron Resonance Mass Spectrometry, High Performance Liquid Chromatography, and Nuclear Magnetic Resonance for pharmaceutical substances. The many impurities that can be found in APIs are described in this article, along with methods for recognising them and potential solutions for dealing with the interferences they can create.

Designation of impurities

Common Impurity Terms

The regulatory agencies and ICH use the words below to describe impurities.

1. Intermediate
2. The last intermediate
3. By-products
4. Product transformations
5. Product interactions
6. Related items
7. Products of degradation

Classification of Impurity

(USP) United States Pharmacopoeia

Impurities are divided into three divisions, according to USP.

1. Defects in official publications
2. Common Impurities
3. Natural Volatile Impure Elements

ICH Terminology Impurities in pharmacological substances created by chemical synthesis can be roughly categorised into the following three

1. Organic impurities (connected to manufacturing and drugs)
2. Inorganic Impurities (Ligands, Reagents, and Catalysts)
3. Volatile solvents (residual solvents) categories, according to ICH recommendations.

1. Organic impurities

These contaminants develop during the drug substance's storage or production processes. The following sub-impurities are among them.

- **Initial Components or Middle Impurities**

Unless sufficient precautions are taken throughout each phase of the multistep manufacturing of the therapeutic product, these types of contaminants are present in practically every API. If the makers are not extremely vigilant about the impurities, even though the finished products are always cleansed with solvents, there is a chance that they may still contain traces of the unreacted beginning materials.

• Substitutes

Receiving a single end product with a full yield in synthetic organic chemistry is extremely uncommon; there is always a potential of receiving byproducts in addition to the desired end product.

• Products of Degradation

During the production of bulk pharmaceuticals, the end product might potentially degrade and produce impurities. This generally happens as a result of incorrect formulation storage.

- **Additional Organic Impurities**

A. Impurities Related to Synthesis: During the synthetic process, a new chemical entity is created from a source material, solvent, intermediate, and by product. If an impurity is present during the synthesis process in even a little or considerable amount in any of the substances involved in the reaction, the end product will be contaminated with one or more undesired materials. Because of this, it is important to take the utmost precautions during each stage of the synthesis process to reduce the level of impurity that may develop.

B. Impurities related to the formulation: Drug substances can degrade or undergo other reactions when they are exposed to a variety of environments. Hydrolysis makes solutions and suspensions susceptible to deterioration. Water utilised in the formulation adds to the product's impurities and creates an Impurities Related to Formulation: Influencing Factors

a. Environmentally relevant

I.Exposed to unfavourable temperature: Materials that are sensitive to heat or tropical climates cause the degradation of active ingredients and the creation of impurities. For instance, heat sensitivity causes vitamin breakdown, which reduces potency.

II.Exposure to light: Photosensitive materials degrade when exposed to light or UV radiation, creating impurities.

III. Humidity: It might be harmful to formulations comprising solid dose form and bulk powder.

b. Impurities that form with age:

Mutual Interaction: When chemicals included in a formula interact, impurities emerge as a result of this mutual interaction.

C. Associated Functional Group Impurities

Ester hydrolysis occurs with drugs such aspirin, benzocaine, Cefoxime, cocaine, and ethyl paraben.Drugs like barbital, chloramphenicol, and benzyl penicillin frequently go through hydrolysis.Drugs like hydrocortisone, methotrexate, heterocyclic aromatic rings, and nitroso/nitrile derivatives are examples of those that oxidatively degrade.

D. Photolytic cleavage: Product exposed to light during manufacture, hospital storage before to use, or consumer storage prior to use.

2. Inorganic impurities

a. Inorganic pollutants are also created by the manufacturing processes used in the manufacture of bulk medications. They are frequently known by name.

These impurities, reagent, ligands, and catalysts, are sporadic. If the production process is not correctly followed, a problem will develop.

b. Heavy Metals: In manufacturing processes where acidification or acid hydrolysis takes place, water is often used as the main supply of heavy metals such Ar, Cd, Cr, Na, Mg, and Mn. By using demineralized water and glass-lined reactors, heavy metal contamination can be easily avoided.

c. Other Materials (Filter Aids, Charcoal): Bulk drug manufacturing facilities frequently use filters or filtering aids like centrifuge bags.

3. Residual solvents

Organic or inorganic liquids used in manufacturing are residual solvents. By using the work-up method, it is quite challenging to entirely eliminate these solvents. In the manufacturing of bulk pharmaceuticals, certain solvents that are known to cause toxicity should be avoided.

4. Impurities in drugs (impurities related to formulation)

A. Inert components employed to create a drug substance can lead to a variety of impurities in the drug product. A drug substance is put to a number of circumstances during formulation that could cause it to degrade or have other negative effects. Hydrolysis may make solutions and suspensions susceptible to deterioration. In addition to adding contaminants of its own, the water employed in the formulation can create an ideal environment for hydrolysis and catalysis. Other solvents that might be used degrade in similar ways. The following categories apply to formulation-related impurities:

• Methodological;

• Environmental

Regulatory guidelines on impurities in an active pharmaceutical ingredient:

The necessity to monitor contaminants in drug products is supported by ethical, financial, and competitive considerations in addition to those relating to safety and efficacy. However, even those who work in the pharmaceutical sciences and industry have differing perspectives on what monitoring contaminants and regulating these impurities mean. To ensure that everyone utilises the same terminology while discussing issues relating to impurities, a uniform nomenclature is required. The International Conference of Harmonisation (ICH) provided the guidance, which was approved by the United States Food and Drug Administration (US FDA). Regulations and industry officials from the European Union (EU), Japan, and the United States collaborated to create the ICH guideline for contaminants in medicines, which has helped to assure.

The deadlines not only help sponsors of New Drug Applications (NDA) or Abbreviated New Drug Applications (ANDA) with the kinds of materials that should be included with their applications, but they also help FDA reviewers and field investigators interpret and apply regulations 1-2 consistently. The various regulatory guidelines for impurities are as follows:

1. "Stability testing of new drug substances and products" according to ICH criteria, Q1A
2. "Impurities in New Drug Substances" ICH guidelines
3. "Impurities in New Drug Products" ICH recommendations, Q3B
4. ICH recommendations "Impurities: Guidelines for residual solvents"- Q3C
5. US-FDA regulations titled "NDAs -Impurities in New Drug Substances"
6. The US-FDA's "ANDAs - Impurities in New Drug Substances" rules.
7. Australian Therapeutic Governance Authority (TGA) regulation guidelines for prescription drugs.

Rationale for Reporting of Impurities in Active Pharmaceutical Ingredient:

A number of variables, including the toxicology of impurities connected to the medicine, the route of administration, the daily dose, the target population, the source of the drug material, and the length of therapy, all must be taken into consideration when establishing limits for acceptable impurities in bulk drugs. Impurities in drug substances must be managed to maintain the safety, efficacy, and quality of API throughout its development and usage as a product, as some of these impurities may possess specific negative toxicological potential. This is the rationale behind placing limitations on the level of impurities.The ICH recommendations state that "The applicant Should summarise the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance on impurities in new drug substances (Q3A). This should be supported.The applicant should also include a summary of the lab tests done to find impurities in novel medicinal compounds. Results from both the development process and the commercial process batches should be included in this summary. It is also important to discuss the studies done to describe the structures of the impurities present above the identification threshold. A summary of laboratory investigations demonstrating the futile effort should be presented when impurity identification is not possible. In general, it is not thought important to identify contaminants that are present at levels lower than the detection threshold. But for the impurities that are predicted to have unusually toxic pharmacological effects, analytical methodology has to be devised. [11]

Characterization of impurities

When an impurity in a medicine is discovered, it is imperative to quantify it. If it is discovered that the impurity present in the Sample is greater than 0.1%, it must be classified in accordance with FDA criteria. The raw material must be characterised if impurities are anticipated, which may be caused by degradation, the production of intermediates, or the development of complexes with excipients. The procedures listed below are used to identify contaminants. [12,13]

- Cite a typical procedure.
- Method of separation.
- Spectroscopic approach.
- Isolation technique.
- Method of characterization

Reference Standard Method

This method's primary goal is to quantify and regulate Reference standards, which are utilised in the development and regulation of new medications. We are aware that the reference Standards gives us access to the fundamental knowledge needed to assess and monitor the performance of bulk drugs, by-products, contaminants, degradation products, excipients, raw materials, and intermediates.

Spectroscopic Methods

Impurities are typically characterised using spectroscopic methods such as UV, IR, MS, NMR, and Raman. ICP MS is now a highly useful tool for locating contaminants. Additionally, it offers a variety of options from several regulatory authorities.

Nuclear Magnetic Resonance (NMR)

This approach gives the necessary details on the particular bond, different structures, and stereochemistry of the targeted chemical entity. It is a crucial analytical tool for illuminating the structure of a pharmaceutical substance of interest.

Mass Spectroscopy (MS)

Mass spectroscopy has long been a crucial tool for characterising contaminants found in medicinal products of desire. Its effectiveness is increased by a recent design development that enables it to work in conjunction with separation procedures. They offer chances for characterising, quantifying, and monitoring desirable pharmacological components in APIs and different formulations. It has a number of benefits, including the need for little sample, speedy results, ability to distinguish between isotopes, The majority of the time, MS can be used in tandem with IR or CC to detect proteins. MS also provides us with compositional information, however it is unable to provide structural details. Nevertheless, the information is sufficient and is frequently discernible.

IR Spectroscopy

Electromagnetic radiation between 500 cm-1 and 4000 cm-1 is applied to the sample. Because of the absorption of energy at a specific wavelength, this radiation affects the molecules' bonds, causing the molecules to stretch or bend. We may learn about various sorts of bonds from the wavelength at which they are absorbed and utilise this information to determine the structure of our sample. They are mostly used to describe solid and semi-solid objects. It offers a substantial or unique fingerprint of each molecule, albeit a bit complex, which can be utilised for sample analysis and identification of contaminants. The benefit is that it may be coupled with other treatments like UV and that the cost is really low.

UV Spectroscopy

UV at a single wavelength does not provide enough data. Nowadays, diode array detectors are utilised to ensure improved selectivity and to obtain the most information possible about molecules .

Separation Methods

It uses a variety of techniques for separation, including thin-layer chromatography, high-pressure liquid chromatography, gas chromatography, capillary electrophoresis, and supercritical fluid chromatography**.**

Thin-Layer Chromatographic (TLC) Method

This approach is the most popular one. It has many benefits and is very simple to use. It requires little money, little effort, and has good sensitivity and simultaneous multi-sample analysis capabilities. When there is very little information available regarding a medicine orany mixture in the first step. because of the development of high-performance TLC, versatile densitometers, and improved TLC plates. Additionally, thin layer chromatography is a vital quantitative analytical method for profiling medication impurities.

Gas Chromatography (GC)

The sample is vaporised in the gas chromatographic process before being injected into the column. Gas Flow is used to move the sample through the column. The stationary phase is a liquid film deposited on a support of fused silica or a packed sorbent, and the solvent is an inert gas. Through the phenomenon of adsorption and partition, the sample in vapour form passes through the column. Due to each component's unique propensity to participate in the adsorption and desorption processes, the components in the sample mixture are separated. Eluting from the column, the separated components are then detected by an appropriate detector.

High-pressure Liquid Chromatography (HPLC)

In essence, HPLC is a better form of column chromatography. A solvent is forced through a column at high pressures of up to 5000 psi rather than being permitted to go through it naturally through gravity. As a result, the separation on the column happens considerably more quickly and consistently. The employment of a range of detectors, including UV, refractive index, fluorescence, electrochemical, MS, NMR, etc., has greatly increased the applications of this technology and increased their effectiveness. The great sensitivity of UV detectors, the availability of a variety of stationary phases, the speed of analysis, and the cost-effectiveness of the LC-UV technique increase the technology's versatility in the field of pharmaceutical analysis. The causes may also be attributed to the fact that the bulk of pharmaceutical chemicals are organic substances, many of which are UV-active. As a result, a UV detector can be used to analyse a variety of substances. To achieve the best separation in LC, a variety of stationary phases, ranging from polar (silica) to non-polar (C18), are available.

Capillary Electrophoresis (CE)

Through the use of an applied potential, a solution containing a mix of components is introduced into a small capillary zone and encouraged to travel through the zone during capillary electrophoresis. Based on the individual mobility of the components under the effect of the electric field, the components in the mixture migrate through the capillary zone at varying rates. As a result, after a predetermined amount of time, the mixture of components is divided into various distinct zones of individual components. The following modes of electrophoresis have been developed in conjunction with chromatography:

Capillary gel electrophoresis and capillary zone electrophoresis are two examples.

• Capillary eletrokinetic chromatography with micelles.

• Electrochromatography in a capillary.

• Isoelectric capillary focusing.

• Isotachophoresis in capillaries.

When only extremely limited numbers of test samples are available, CE is a practical and efficient technique. When compared to other approaches, the resolutions are significantly higher. Less repeatability, however, is this technique's main flaw .

Supercritical Fluid Chromatography

In terms of detection and separations, it differs from GC and HPLC in a few ways. This approach has more room for improvement and is most useful for sample extraction.

Isolation Methods

It is crucial to isolate impurities; yet, if we utilise an instrumental method, the impurities will be directly characterised, preventing their isolation. Normally Several chromatographic and non-chromatographic procedures are utilised before its characterisation. "Chromatographic Reactor" refers to the simultaneous use of an analytical-scale column as a flow-through reactor and as a medium for reactant and product separation. The solution-phase hydrolysis Kinetics of the Aprepitant prodrug, fosaprepitantDimeglumine, were examined using an HPLC, chromatographic reactor method. Ofloratidine was one of several impurities discovered in loratidine , along with celecoxib and amikacin. The following is a list of techniques that can be used to isolate contaminants.

Methods of extraction include liquid-liquid, solid-phase, and accelerated solvent extraction.

Characterization Methods

This makes use of extremely complex equipment, such as the HPLC or the coupling of mass spectroscopy to gas chromatography. They are a crucial tool for locating insignificant components in diverse matrices, such as contaminants, degradation products, and metabolites. They go by the name HYPHENATED METHOD as well. The numerous hyphenated methods used are as follows:

▪ GC-MS.

▪ LC-MS.

▪ LC-DAD-MS.

▪ LC-NMR.

▪ LC-DAD-NMR-MS.

▪ LC-MS-MS

This approach is getting a lot of attention these days because it can be used to solve many different analytical issues. It is being utilised for both quantitative and qualitative investigation of Unknown chemicals in complex goods since it combines separation procedures with spectroscopic approaches .

Applications:

Numerous applications have been sought in the fields of drug design and monitoring pharmaceutical compounds' quality, stability, and safety, regardless of how they were made whether synthetically, by extracting them from natural sources, or by recombinant methodsThe applications cover a variety of medications, including alkaloids, amines, amino acids, analgesics, antibiotics, anticonvulsants, antidepressants, tranquillizers, antineoplastic medicines, local anaesthetics, macromolecules, steroids, and others.[14]

Conclusion:

This review presents an opinion on contaminants in drug substance and drug products. The importance of pharmaceutical impurity profiles is rising, and the public and the media are paying more and more attention to drug safety. This article offers useful details on the different types of impurities and their classification, numerous procedures for isolating and characterising them, analytical techniques for determining their qualifications, and important aspects to take into account while preparing bulk medications. Nowadays, it is a requirement in various pharmacopoeias to know the impurities present in APIs.

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References:

1.Bari, Sanjay B., et al. "Impurity profile: significance in active pharmaceutical ingredient." Eurasian J Anal Chem 2.1 (2007): 32-53.

2.International Conference on Harmonization (2000) Draft Revised Guidance On Impurities In New Drug Substances. Federal Register Q3A(R) 65 (140): 45085.

3.International Conference on Harmonization (2000) Draft Revised Guidance On Impurities In New Drug Products. Federal Register Q3B(R) 65 (139): 44791.

4.International Conference on Harmonization (1997) Impurities, Q3C- Guidelines for Residual Solvents,Q3C. Federal Register 62(247): 67377.

5.International Conference on Harmonization (1999) Specifications, Q6A: Test Procedures and Acceptance Criterial for New Drug Substances and New Drug Products. Chemical substances 65 (146):67488.

6.Venkatesan, P., and K. Valliappan. "Impurity profiling: theory and practice." Journal of pharmaceutical sciences and research 6.7 (2014): 254.

7.Bari S.B., Kadam B.R., Jaiswal Y.S., Shirkhedkar A.A., Impurity profile: Significance in Active Pharmaceutical Ingredients.Eurasian Journal of Analytical Chemistry, 2007; 2(1):32-53.

8.Federal Register, International Conferences on Harmonization. Impurities in New Medicinal Products,3AQ12a, 1996: 95-105.

9.Patil, Poonam P., Veena S. Kasture, and K. Vanitha Prakash. "Impurity profiling emerging trends in quality control of pharmaceuticals." Int J Pharm Chem 5.1 (2015): 1-10.

10.ICH Guidelines, Q3A (R2), Impurities in New Drug Substances, October 25, 2006.

11.Ayre, A., et al. "Impurity profiling of pharmaceuticals." Adv Res Pharm Biol 1.2 (2011): 76-90.

12.Nath, Dipankar, and Bidhya Sharma. "Impurity Profiling-A Significant Approach in Pharmaceuticals." Current Pharmaceutical Analysis 15.7 (2019): 669-680.

13.Venkatesan, P.; Valliappa, K. Impurity profiling: Theory and practice. JPSR., 2014, 6(7), 254-259.

14.Shah, Shreya R., et al. "RECENT APPROCHES OF" IMPURITY PROFILING" IN PHARMACEUTICAL ANALYSIS: A REVIEW." International Journal of pharmaceutical sciences and research 3.10 (2012):3603.