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REVIEW ARTICLE **OPEN ACCESS**

Role of Impurity Profiling in Analytical Chemistry

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ABSTRACT
An impurity is characterized as any substance present alongside the original pharmaceutical compound, including starting materials, intermediates, or byproducts resulting from side reactions. As per the guidelines established by the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), an impurity is delineated as 'any constituent of the novel drug substance that deviates from the chemical entity defined as the novel drug substance'. The identification of impurities is achieved through a myriad of chromatographic and spectroscopic methodologies, either individually or in conjunction with other analytical techniques. Various methods are employed for the detection and characterization of impurities, such as thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), and high-performance thin-layer chromatography (HPTLC), among others. Among the multitude of techniques utilized for impurity profiling of pharmaceuticals, LC-MS-MS (liquid chromatography-tandem mass spectrometry), LC-NMR (liquid chromatography-nuclear magnetic resonance), LC-NMR-MS (liquid chromatography-nuclear magnetic resonance-mass spectrometry), GC-MS (gas chromatography-mass spectrometry), and LC-MS (liquid chromatography-mass spectrometry) stand out as the most commonly exploited methodologies.
Keywords: *Impurity, profiling, pharmaceutical product, spectroscopy, chromatography*

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INTRODUCTION

Impurity is designated as the material which accompanies along with initial drug as an intermediate, also as a primary material that is created because of changes in reaction or reactant conditions [1]. Impurity profiling involves the systematic analysis and depiction of impurities contained in a chemical matter or drug substance. Within current times, demand for the impurity profiling of drug products have been multiplied. Appearance of impurities in minute quantities within a pharmaceutical product is inevitable. So the levels must be managed and observed to prevent any decrease in therapeutic response related to the active pharmaceutical ingredient (API) [2]. In some cases, impurities can have mutagenic, teratogenic or carcinogenic effects. Impurities are considered unsafe as they can cause genetic mutations, chromosomal breaks and even be carcinogenic, interacting with DNA. Fluctuations in quality, safety and efficacy of drug substance can affect biological condition of human. Therefore, monitoring and controlling impurities in pharmaceutical products plays a crucial role. API impurity profiling involves the separation, detection and characterization related to impurity for getting an authentic element which is less harmful and increased efficacy in pharmacological treatment. If the impurities range exceeding0.1%, they are detected and calibrated by various methods. The multifaceted aspects of impurity analysis is explored to elucidate it's significance in safeguarding public health, meeting regulatory requirements and also enhancing product development [3]. To ensure that patients won't receive any dangerous or carcinogenic compounds, contaminants found in the API must be located. Pharmaceutical medication development requires structural characterization of contaminants and degradation products in bulk medicinal compounds [4]. Impurities can be managed by comprehending how they form, accumulate and purge during the manufacturing process and by putting in place the necessary controls where they do so [5].

Impurity profiling significance:

To assure more precise efficacy of pharmaceutical substances, screening of impurities which are existing in the medicinal product must be done throughout the process of manufacturing. In toxicological research, synthesized impurity is employed, and it also serves as the benchmark for impurity determination. Impurities present in drug products can lead to variations in the dissolution and solubility parameters. Thus, impurity profiling is important to assure the quality, efficacy and safety of drugs [6]. In chemical

development different process is done such as research and development where the impurity profiling plays an important role. Comprehending the development of contaminants during the manufacturing process is crucial for managing and adjusting reaction conditions to minimize impurity formation to a manageable extent [7]. For each batch, specifications and techniques that are based on quantitative parameters and are used to estimate detected or undetermined contaminants should be supplied. Impurities thought to be identified using a code. The total amount of contaminants, which is the sum of all impurities above the reporting threshold, need to be reported [8].

Classification of Impurities:

Impurities are categorized as:

- Organic impurities (process and drug related)
- Inorganic impurities
- Residual solvents

Organic Impurities:

In major drugs, these kinds of contaminants are less dangerous and, at least in small quantities, do not significantly disrupt biological processes. It may occur when the novel medication material is being manufactured or stored. These organic contaminants may be volatile or non -volatile recognized or unknown and also include

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

Starting materials

These are the most typical contaminants that are present in all APIs unless great care is taken at each stage of the synthesis.

Degradation products

Common contaminants in medications are also created throughout the production process of bulk pharmaceuticals as the finished product degrades.

Reagents ligands and catalysts

Although these kinds of compounds are less frequently detected in APIs, they can occasionally cause issues and be categorized as contaminants [9]

Intermediates

$6KOH+3I2$ → **$5KI+KIO_3+3H_20$**

Potassium Hydroxide → potassium iodide

KIO3+ 3C → **KI +3 CO**

Potassium iodide

INORGANIC IMPURITIES

Pharmacopoeia or other applicable principles are often used for the identification and characterization of inorganic contaminants. During the course of development, carryover of catalysts to the drug substance should be assessed. The process of production might lead to these sorts of contaminants. These are often recognized and known to be as follows:

a) Reagents, ligands and catalysts:

$CaCl_{2+}Na_2Co_3$ → **$CaCO_3+2NaCl$**

Calcium Chloride +sodium carbonate → calcium carbonate +sodium chloride

Excess Na2CO3 and CaCl2 are removed from the calcium carbonate precipitate by washing. The precipitate may remain an impurity if not thoroughly cleaned.

b) Heavy metals:

The water utilized in the procedures and, in the case of stainless steel reactors, the reactors themselves—where hydrogenation and acidification occur—are the primary sources of heavy metals. This may be avoided with the use of demineralized water and glass-lined reactors.

c) Other ingredients such as charcoal and filter aids:

Charcoal activated fibers and black particles must be avoided in the bulk drug manufacturing process using filters and filter aids such as centrifuge bags [10].

Residual Solvents:

Solvents are either natural or synthetic liquids that are employed as a carrier to produce suspensions or solutions during the manufacture of a novel medication.

Classification of residual solvents

Class 1

Solvents to be avoided

It is not advisable to employ them in the production of active and inactive ingredients or pharmaceutical products because of their established carcinogenicity and environmental hazards.

Benzene(2ppm), carbon tetrachloride(4ppm), methylene chloride(600ppm), methanol(3000ppm), toluene(890ppm). Table1 shows the list of class 1 residual solvents.

Class 2

Solvents to be limited

Although they may not be as harmful as class 1 solvents, they should nonetheless be restricted as PDEs because of their intrinsic toxicity.

N, N-dimethyl formamide (880ppm), acetonitrile (410ppm). Table 2 shows the list of class 2 residual solvents.

Class 3

Solvents have PDEs of 50 mg or greater per day, making them less hazardous to humans. Such as acetic acid, ethanol, acetone. Table 3 shows the list of class 3 residual solvents.

Sources of impurities:

From the data, it is noted that contaminants can be formed by various sources, such as:

- Crystallization related impurities
- Stereochemistry related impurities
- Residual solvents
- Synthetic intermediates and by-products
- Formulation related impurities
- Impurities arising during storage

Crystallization related impurities

The structure that a particular molecule adopts during crystallization can have a significant impact on the characteristics of that system in its solid form. polymorphism is the existence of a material in more than one crystalline form [13].

Stereochemistry-related impurities

It is necessary to carefully examine substances related to stereochemistry, especially those that have similar chemical structures but different spatial orientations, as these substances might be interpreted as contaminants in active pharmaceutical ingredients (APIs). It is widely recognized that a chiral drug's single enantiomeric form is an improved chemical entity. Interestingly, even though the pharmacokinetic characteristics of ofloxacin (the R-isomeric form) and levofloxacin (the S-isomeric form) are similar, suggesting that there aren't any clear benefits to use a single isomer in this situation, several single-isomer medications have become well-known in the marketplace. These include the R-isomer of albuterol, lavalbuterol, and the S-isomer of omeprazole, levofloxacin (the S-isomer of ofloxacin) [12].

Residual Solvents

A specialized gas chromatography (GC) technique was formulated for assessing the quality of acetone, dichloromethane, methanol, and toluene. The technique enables precise quantification of primary impurities present in each organic solvent. Furthermore, the devised approach facilitates the concurrent assessment of ethanol, isopropanol, chloroform, benzene, acetone, dichloromethane, methanol, and toluene, utilizing propionitrile as an internal reference standard. By employing this methodology, a comprehensive understanding of the composition and quality of these solvents can be achieved, ensuring their suitability for various applications across diverse industries, synthetic intermediates and by-products [13]. Impurities within drug products or novel chemical entities (NCEs) may stem from multiple sources along the synthetic pathway, including starting products, intermediates, and/or by-products. Notably, during the synthesis process, impurity formation can occur at various stages, such as in the transformation of raw materials, the progression through intermediates, or the generation of by-products [14].

Formulation-related impurities

Numerous contaminants found within a pharmaceutical substance can trace their sources back to the excipients employed in its formulation. Furthermore, the drug substance undergoes a myriad of parameters during the formulation method, which may provoke other unfavorable conditions. Should the impurity stem from an excipient, variations from batch to batch could result in a substandard product, rendering it unsuitable for reliable use. Solutions and suspensions, by their nature, are inherently susceptible to degradation, often attributed to processes like hydrolysis or solvolysis. Factors such as water content, pH levels of the solution or suspension, compatibility of anions and cations, mutual interactions

among raw materials, and the quality of the starting material play pivotal roles in ensuring product stability and efficacy.

Impurities arising during storage

Drug items can get contaminated in a variety of ways during transportation or storage. To anticipate, assess, and guarantee the safety of pharmaceutical products, stability studies are crucial [15]. Impurity associated with the method Upon autoclaving a parenteral dosage form of diclofenac sodium for final sterilization, a known contaminant known as 1-(2,6-dichlorophenyl) indolin-2-one appears. Diclofenac sodium undergoes an intramolecular cyclic reaction that is catalysed by the autoclave technique at 123 + 2 degrees Celsius. This reaction produces sodium hydroxide and an indolinone derivative. Both the formulation's starting pH and the interactions between its constituent parts affect how quickly this impurity degrades 16]. Typical Degradation Related to Functional Groups A variety of reactions, such as oxidative degradation, ester hydrolysis, hydrolysis, photolytic cleavage, and decarboxylation, are included in functional group-related degradation pathways. Many medications are impacted by oxidative degradation, including hydrocortisone and methotrexate, which are more prone to it. Drugs like aspirin and benzocaine are examples of ester hydrolysis, which emphasizes how ester-containing substances are vulnerable to this breakdown mechanism. For medications of the ester type, hydrolysis is a normal occurrence that mostly impacts liquid dose forms and medications like benzylpenicillin. Decarboxylation is the process by which carboxylic acids lose carbon dioxide when exposed to heat or photoreaction. Examples of these chemicals are rufloxacin and p-aminosalicylic acid [17].

Advancement of analytical methods

At different phases in the development of new drugs, useful and trustworthy analytical data must be generated.

a) Sample selection is required for the creation of an analytical technique;

b) Chromatographic parameters and phases are screened; this is usually done using the gradient elution linear- solvent -strength concept;

c) The method is optimized to fine-tune parameters relevant to toughness and sturdiness.

Analytical Method:

The impurities can be identified predominantly by following methods as shown in fig 1:

- Reference standard method
- Isolation method
- Characterization method [18]
- Separation method
- Spectroscopic method

Reference standard method

In addition to the active ingredients in dosage forms, the primary goal is to provide understanding on all stages of life, eligibility, and management of reference criteria used in the production and monitoring of new medicinal products. This includes initial ingredients, additives, waste products, impurities, and process intermediates [19]. The creation and management of novel pharmaceutical products are subject to these regulations. Spectroscopic Approaches Impurity characterization frequently involves the use of spectroscopic techniques such as UV, IR, MS, NMR, and Raman spectroscopy. Separation methods Impurities and degradation products are often separated using capillary electrophoresis (CE), chiral separations, gas chromatography (GC), supercritical fluid chromatography (SFC), TLC, HPTLC, and HPLC [20].

Isolation method

Isolating contaminants is typically required. However, since the impurities are directly characterized when instrumental techniques are employed, impurity isolation is avoided. Prior to characterizing impurities, chromatographic and non-chromatographic procedures are often employed to isolate them. The employment of an analytical scale column as a flow reactor and a medium for reactant and product separation is referred to as a "chromatographic reactor" The solution phase hydrolysis kinetics of the prepitant (EmendTM) Prodrug, fosaprepitant dimeglumine, were examined using an HPLC, chromatographic reactor technique.

- Solid-phase extraction methods
- Liquid-liquid extraction methods
- Accelerated solvent extraction methods
- Supercritical fluid extraction
- Column chromatography
- Flash chromatography
- TLC

- GC
- HPLC
- HPTLC
- Capillary electrophoresis (CE)
- Supercritical fluid chromatography (SFC) [21].

Characterization technique: The attributes of impurity A sufficient amount of impurity must first be isolated using appropriate separation techniques, after which the discovered impurity is further described using a variety of spectroscopic techniques. According to the International Council for Harmonization (ICH) standard, an impurity should be properly identified and characterized when its level exceeds 0.1%. Figure 2 lists the numerous methods for impurity profiling by using characterization of technique.

Separation Techniques:

Accelerated solvent extraction:

Accelerated solvent extraction is a special technique used in pharmaceutical fields to extract chemically active constituents from solid matrix pores. It is particularly useful for extracting natural chemical constituents from herbal plant materials and impurity profiling of drug substances. High temperatures and pressure are used to improve the extraction process, enhancing kinetics and reducing viscosity of the sample medium. This process also eases the solvent's entry into the sample medium pore [24].

Supercritical fluid extraction (SFC):

An ingredient that exceeds its critical pressure and temperature is termed to as a supercritical fluid (SCF). It provides an extra edge over other techniques sinceit possesses both fluid and gas-like properties. It has mass transmission similar to that of a gas and solvating power similar to that of a fluid. In addition to being useful for extracting natural components from plant materials, the supercritical fluid is still active in impurity profiling [22].

Thin-layer chromatography (TLC):

Testing the purity and identity of compounds can be done with high reliability using thin-layer chromatography (TLC). It uses less solvent and requires smaller sample sizes, taking less time to produce, making visualization and separation processes easier. It is also less expensive. To identify contamination, TLC can test a larger range of polarity. Not involving laborious isolation and mass spectrometry (MS) determination, unknown contaminants can be identified using the liquid chromatography-mass spectrometry (LC-MS) technology. Drug calibration is done in the pharmaceutical industry using TLC and other planar chromatography methods [23].

Gas Chromatography (GC):

For quantification, gas chromatography is an essential technique. It can offer the required selectivity, resolution, and quantitation simplicity. The main restriction of the sample it needs to be volatile or derivatized in order to become volatile. For organic volatile contaminants, this method is quite helpful. GC separated the medicines from their contaminants. Table 4 shows the impurities quantification by gas chromatography.

High-Performance Liquid-Chromatography (HPLC):

Most effective separation technique for identifying and separating contaminants is high-performance liquid chromatography (HPLC). The identification of drug components was based on retention time and a direct comparison with established data. To isolate and identify contaminants using HPLC, a column, an optimized system, and an appropriate mobile phase system are needed. HPLC is done in the preparative mode using specialized equipment. HPLC is the most studied analytical technique for impurity separation [25].

Capillary Electrophoresis (CE):

When high resolution is needed and relatively little sample is available, CE is a useful approach. Relatively lower repeatability is the main source of complexity. The process of using capillary electrophoresis to separate contaminants from drugs [26]. Table 5 shows the quantification of impurities by capillary electrophoresis.

Nuclear Magnetic Resonance (NMR):

NMR is a very useful analytical tool for structural elucidation because of its capacity to provide details about the precise stereochemistry and bonding structure of compounds of medicinal relevance. A typical combination of real materials comprising both monomers and dimers was used to validate the NMR-based diffusion coefficient determination method's capacity to discriminate between monomeric and dimeric substances. Regretfully, NMR has a reputation for being a less sensitive approach than other analytical methods. Compared to MS, which takes less than 1 mg of material, conventional NMR requires samples of around 10 mg [27].

Mass spectroscopy (MS):

Over the past few decades, it has had an ever-more-significant influence on the pharmaceutical development process. Improvements in the functionality and design of the interfaces that directly link mass spectrometers and separation techniques have opened up new possibilities for the identification, evaluation, and estimation of drug-related substances in medicinal products and drug formulations. Opposite connection of chromatographic techniques, such as HPLC-TLC and HPLC-CE, or linking of chromatographic separations with rich in information 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, however, these attachments will only be considered as development tools rather than tools for routine QC use [28].

UV-Visible Spectroscopy:

There is limited usage in using UV-VIS spectroscopy as a technique to identify and clarify the structure of contaminants in medications without chromatographic separation. Only contaminants that selectively absorb in the ultraviolet range above 200 nm can benefit from this technique. One method for identifying pure pharmacological molecules is UV-Visible. Chromophores-containing compounds absorb certain UV or visible light wavelengths, which are directly correlated with the sample's concentration. Impurity identification using UV-visible spectroscopy [24]. Table 6 shows the quantification of impurities by UV visible spectroscopy.

Hyphenated Methods:

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

The chemical ionization of d-allethrine and pressurized air electrification with electrospray source (API-ESI) are two different soft ionization procedures used in gradient elution for reverse-phase LC-MS analysis. Because of the "soft" nature of atmospheric pressure chemical ionization (APCI), atmospheric pressure ionization (APPI), HPLC-DAD-MS (HPLC coupled with a diode array UV detector and a mass spectrometer), and other techniques that are almost always used, LC-MS-MS systems are popular for complex mixture analysis of thermally labile and biologically relevant molecules, like mosapride. Now, NMR has been used in this combination to provide a commercial equipment the ability to do HPLC-DAD-NMR-MS. Several more chromatographic and spectroscopic configurations are discovered in the GC-MS of methamphetamine and the LC-MS of risperidone and cetrizine tablets [29]. Table 7 shows the list of various impurities reported in API's[30] [31] and table 8 shows the impurities reported in pharmacopoeia [32].

Impurities of carvedilol, an antihypertensive drug:

The substance carbazolyl-(4)-oxypropanolamine and its pharmaceutical formulations are recommended for the prevention of heart and circulatory illnesses, such as angina pectoris and hypertension [33]. Carvedilol is a multi-action medication that alters how different body components react to certain nerve signals. Consequently, by lessening the strain of the heart, b-clockers lower the heart's requirement for blood and oxygen. Another well-known vasodilator effect of carvingilol is a-adrenoreceptor blockade. Carvedilol has several different effects that contribute to its antihypertensive and congestive heart failure management properties. The quality and safety of pharmaceutical products can be significantly impacted by the presence of contaminants in an active pharmaceutical ingredient (API) [34]. Studying the impurity profile of the API that will be employed in the production of the medicinal product is therefore essential. Numerous analytical techniques have been documented for the quantification of carvedilol in pharmaceutical formulations and biological fluids. The significance of carvedilol impurities has also been discussed. Using mass, infrared (IR), and nuclear magnetic resonance (NMR) techniques, impurities related to the process were identified, synthesized, and characterized in bulk carvedilol [33].

Source of nitrosamine impurity:

Nitrosamine are the groups containing carcinogenic contaminants obtained by reactions of secondary amide carbamates amines derivatives of urea with nitrite and other Nitrogenous substances. The impurity of nitrosamine is found out during manufacturing and packaging of Drug. The major procedure of identification of nitrosamine impurities are HS-GC-MS, LC-MS/MS.

The drug from which nitrosamine contaminants are derived:

- Sartan medicine
- Rifampicin drug
- Ranitidine
- Metformin-Containing medicine

- Champix medicine

Methods for detection of Nitrosamine impurities:

The FDA has released the following methods for the determination of NDMA impurities in drugs. GC/MS Headspace Chromatography Mass Spectrometry Approach.

Liquid Chromatography - Tandem Mass Spectrometry (LC - MS / MS) Method for the Determination of NDMA in Ranitidine Drug Substance and Solid Dosage Drug Product [35].

Analytical methods:

Methods of nitrosamine testing in sartan include the use of chromatographic techniques (reversed phase liquid chromatography - RP - LC or gas chromatography - (GC) combined with mass spectrometry (MS), spectrophotometry (UV) or nitrogen chemiluminescence (NCD). USP proposes four analytical methods that manufacturers can use to identify potential nitrosamine in their products:

• The first method recommends high-performance liquid chromatography-high resolution mass spectrometry (HPLC-HRMS) for measuring NDMA, NDEA
NDIPA, NEIPA, NMBA and NDBA.

• The second recommends gas chromatography mass spectrometry (GC-MS) for NDMA, NDEA, NDIPA, NEIPA.

• Third party recommends HPLC-Tandem Mass Spectrometry for NDMA, NDEA, NDIPA, NEIPA, NEIPA, NEIPA, and NMBA.

• Fourthly recommends GC-Tandem Mass Spectrometry for NDMA, NDEA, NDIPA, NMBA and NDMA [36].

Applications of impurity profiling:

Drug design and quality, stability, and safety monitoring of pharmaceutical compounds that are synthesized, extracted from natural products, or created using recombinant techniques are just a few of the areas where impurity profiling has been used [37]. Alkaloids, amino acids, amines, analgesics, antibacterials, anticonvulsants, antidepressants, tranquillizers, anti-neoplastic medicines, local anesthetics, macromolecules, steroids, and other miscellaneous substances are among the applications [38]. In drug development, impurity detection, measurement, and control in APIs and medicinal products are essential. Free radicals from byproducts, intermediates, or breakdown products are frequently found in organic contaminants. Transition metals, reagents, and ligands are examples of inorganic impurities. The only method for directly identifying and non-invasively quantifying paramagnetic impurities is electron paramagnetic resonance (EPR) spectroscopy.

Drugs: For pharmaceutical medicines to be safe and effective, purity must be guaranteed. Impurities that could lower a drug's potency or have unfavourable effects can be found and measured with the use of impurity profiling.

Drug Safety: In pharmaceutical industry Identification and quantification of impurities in pharmaceuticals ensure compliance with regulatory standards (e.g., ICH guidelines).

Stability Studies: Monitoring impurity levels over time to assess the stability and shelf-life of drugs.

Process Optimization: Identifying sources of impurities helps in optimizing manufacturing processes to minimize impurity formation.

Chemical Manufacturing: By identifying undesired by-products or impurities, impurity profiling protects the quality and safety of the final products in industries including specialty chemicals, agrochemicals, and fine chemicals [39].

Food and Beverages: To guarantee adherence to legal requirements and the safety of consumers, impurity profiling is used to identify pollutants, additives, or processing residues in food and beverages.

- Some food products may contain organic impurities. 18-22 A current focus in food chemistry devoted to the safeguard of human health concerns synthetic dyes, which are widely added to a large number of meals and are largely preferred to natural colours, mostly because of their superior stability along the manufacturing industrial process. 18 The use of artificial colours in food has a long history. During the 18th and 19th centuries, "unnatural" colours and vegetable extracts were utilised in food and beverages. Sweets, for example, were tinted with lead chromate, mercuric sulphide, lead oxide, and copper arsenite. Legislation and newly developed chemically synthesised colours reduced the need for these metallic compounds. Synthetic dyes were much brighter, cheaper, more consistent, and more stable (in their reactions).
- Many beverages contain sodium benzoate and ascorbic acid, which is the next stage in the vitamin C procedure. When benzoate salts impurity profiling is performed on the mass spectrum, Vitamin C comes into touch with high amounts of the impurity. The main disadvantage of using light and/or heat is that there is a high probability of a chemical reaction occurring due to the volatility and thermal stability. Impurities in benzene might be problematic. How will this process's output be used? Benzene

derivatization processes, commonly utilised in GC/MS analysis, can induce adverse effects such as sodium benzoate confusion with impurities (mications per kilo).

- Ascorbic acid is an approved food additive (antioxidant) that can be added to beverages. It is also found naturally in fruits and fruit juices. Ascorbic acid combines with metals (copper and iron) in water to make hydroxyl radicals, which then react with benzoic acid to produce low quantities of benzene. Benzene levels are likely to be higher in beverages where benzoic and ascorbic acid are purposefully included to assure microbiological safety [40].

Environmental Monitoring: To help evaluate the environmental impact and regulatory compliance, environmental science uses impurity profiling to identify pollutants and contaminants in air, water, and soil. In environmental monitoring, the term "impunity profiling" refers to the methodical examination of trends in which environmental crime perpetrators escape punishment or suffer less severe penalties. The following are some important applications:

Finding Hotspots: Impunity profiling assists in locating areas or industries where environmental regulations are often broken but not adequately enforced. Authorities can now allocate resources for enforcement and monitoring in a more priority manner.

Targeting interventions: Authorities can create targeted interventions by knowing who commits environmental crimes and why they frequently go unpunished. This could entail strengthening monitoring systems, developing legislative frameworks, or stiffening punishments for particular kinds of infractions.

Policy development: To improve environmental governance, policy makers can benefit from the insights gained via impunity profiling. For instance, it can draw attention to gaps in the law that need to be fixed or to the necessity of improved cooperation between the enforcement agencies.

Public Awareness and Advocacy: Educating the public about the scope and consequences of environmental crimes can be accomplished by highlighting impunity. This has the potential to galvanize advocacy efforts in order to put more pressure on corporations and governments to prosecute violators more severely.

Enhancing Data Collection: Comprehensive data on environmental infractions and enforcement results are necessary for effective impunity profiling. Monitoring efforts can be strengthened by enhancing the accuracy and reliability of impunity profiles through improved data gathering procedures and systems. Enhancing Data Collection: Comprehensive data on environmental infractions and enforcement results are necessary for effective impunity profiling. Monitoring efforts can be strengthened by enhancing the accuracy and reliability of impunity profiles through improved data gathering procedures and systems.

Overall, impunity profiling in environmental monitoring is crucial for enhancing accountability, deterring future violations, and promoting sustainable development practices globally.

Forensic Analysis: Impurity profiling of materials such as explosives or drugs can be used in forensic science to determine the source, method of manufacture, or connection of the material to illicit activity.

Material Science: By locating and measuring leftover monomers, catalysts, or other impurities, impurity profiling guarantees product quality during the development of materials and polymers. Impunity profiling, as it relates to material science, involves understanding how materials behave under extreme conditions without the risk of degradation or failure. Here are some applications:

High-Temperature Materials: Impunity profiling helps in studying materials that can withstand extreme heat without degradation. This is crucial for applications in aerospace (e.g., turbine blades), power generation (e.g., gas turbines), and metallurgical processes.

Corrosion Resistance: Materials used in corrosive environments (e.g., marine environments, chemical processing plants) need to maintain their structural integrity over time. Impunity profiling helps identify materials that resist corrosion effectively.

Structural Integrity under Pressure: For applications such as deep-sea exploration or high-pressure industrial processes, materials need to maintain their mechanical properties without deformation or failure. Impunity profiling aids in selecting materials capable of withstanding such conditions.

Radiation Resistance: In fields like nuclear energy and space exploration, materials must endure high levels of radiation without becoming brittle or losing functionality. Impunity profiling assists in evaluating materials for these environments.

Wear and Abrasion Resistance: Materials used in manufacturing and construction equipment need to withstand wear and abrasion over prolonged use.

Biocompatible Materials: In medical and biomedical applications, materials must be biocompatible to avoid adverse reactions within the human body.

Electronics & Semiconductor Industry: Since even minute impurities can have an impact on an electronic device's performance, impurity profiling is essential to semiconductor manufacturing in order to guarantee the purity of the materials used to fabricate chips. Impurity profiling is crucial in the electronics and semiconductor industry for several reasons:

Quality Control: Impurity profiling helps ensure the purity of materials used in electronic components. Even trace amounts of impurities can significantly affect the performance and reliability of semiconductors and electronic devices. By identifying and quantifying these impurities, manufacturers can maintain high-quality standards.
Process Optimization: Understanding impurity profiles can aid in optimizing manufacturing processes. It allows engineers to pinpoint sources of contamination or inefficiencies in production lines, thereby improving yield and reducing costs.
Reliability and Longevity: Impurities can degrade the reliability and longevity of electronic devices. By characterizing and controlling impurity levels, manufacturers can enhance the durability and operational lifespan of their products.
Performance Enhancement: In semiconductor devices, impurities can alter electrical properties such as conductivity and bandgap. By controlling impurity levels, manufacturers can fine-tune these properties to achieve desired performance characteristics in devices like transistors and diodes.
Compliance and Standards: Many electronic products must comply with stringent regulatory standards regarding the presence of certain impurities (e.g., ROHS compliance). Impurity profiling ensures that products meet these regulatory requirements.
Research and Development: Impurity profiling is crucial in R&D for developing new materials and technologies. Researchers need to understand the impurity profiles.
Quality Control: To guarantee the uniformity, dependability, and safety of products, quality control measures such as impurity profiling are applied in a variety of industries. All things considered, impurity profiling is essential to upholding strict quality, safety, and effectiveness criteria in a variety of scientific and industrial domains.
Security Evaluation: Drugs may contain impurities that are toxic or harmful to human health. By distinguishing and evaluating these pollutants, drug organizations can survey the potential dangers related with their items and go to proper lengths to alleviate them.
Process Improvement: Impurity profiling can tell you a lot about how well manufacturing processes work. By checking pollutions at different phases of creation, producers can advance their cycles to limit debasement arrangement and further develop yield.
Solidness Studies: Impurity profiling is necessary for drug degradation monitoring during stability studies. Impurity profiles can change, indicating degradation pathways and assisting in determining the best storage conditions and shelf life.
Administrative Consistence: Administrative specialists, for example, the FDA and EMA require far reaching contamination profiles as a component of the medication endorsement process. Satisfying administrative guidelines guarantees that medications are protected and compelling for use.
Consistency from batch to batch: Observing debasement profiles across various clusters of a medication guarantees consistency in quality and execution. This is especially crucial for medications with narrow therapeutic indices, where even minute variations in impurity concentrations can have an effect on safety or efficacy.
Examination of Clump Disappointments: Impurity profiling can assist in determining the root cause of a drug product batch that fails to meet quality standards. This could involve figuring out if impurity levels are too high or if they are too low to be considered acceptable.
Relative Investigations: For comparative studies between various drug formulations or generic versions, impurity profiling can be utilized. It helps in surveying likeness or contrasts in contamination profiles that might influence bioavailability, adequacy, or wellbeing [41].

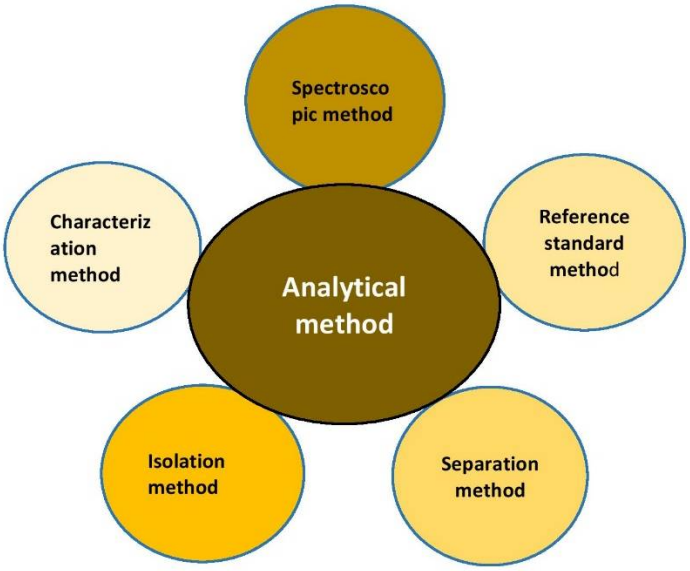

FIG 1: Analytical method for identification of impurities profiling

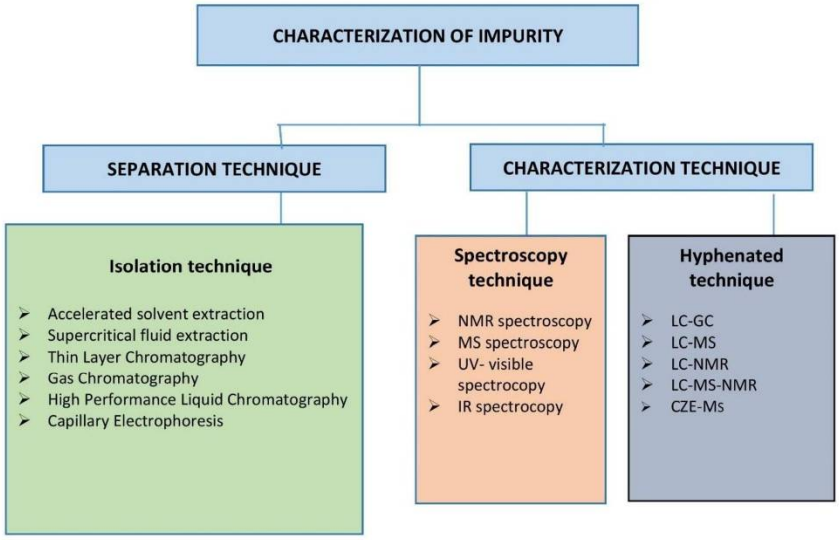

Figure 2: Characterization of impurity

TABLE 1: Class 1 of residual solvents

SOLVENT	CONCENTRATION LIMIT (ppm)	CONCERN
benzene	2	carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-dichloromethane	5	toxic
1,1-dichloroethane	8	toxic
1,1,1-trichloroethane	1500	Environmental hazard

Table 2: Class 2 of residual solvents

SOLVENT	PDE(mg/day)	CONCENTRATION LIMIT(PPM)
acetonitrile	**4.1**	**410**
chloroform	**0.6**	**60**
cyclohexane	**38.8**	**3880**
formamide	**2.2**	**220**
methanol	**30**	**3000**

Table-3: Class 3 of residual solvents

acetone	methylisobutylketone	Ethyl ether
Acetic acid heptane	Dimethyl sulphoxide	Ethyl formate
Anisole	ethanol	Formic acid
Methyl acetate	Ethyl acetate	3-methyl 3-butanol
Butyl acetate	t-buthyl methyl ester	Iso butyl acetate
2-butanol	methylethylketone	3-pentanol

TABLE 4: Quantification of impurities by Gas Chromatography

Drug	Mobile phase/solvent	Impurity	References
Cloxacillin	Cyclohexane	N,N-Dimethyl aniline	3
Doxorubicin hydrochloride	Dioxane	Acetone and ethanol	2
Fluoroscence sodium	Methanol	Dimethyl formamide	2
Methamphetamine	n-hexane and phosphate buffer	1,2-dimethyl-3-phenylaziridine ,ephedrine ,methyl ephedrine ,N -formyl methamphetamine ,N-acetyl methamphetamine, N-formylphedrine,N-acetyl ephedrine ,N,Odiacetylephedrine, methametamine dimmer	138

Table 5: Quantification of impurities by Capillary electrophoresis

Drug	Impurity
Alcuronium	Diallylcaracurine(DAC),monomeric allyl-wieland-gumlich-aldehyde(WAG)
Ceftazidimepentahydrate	Antiisomer of ceftazidime,7-epimer of ceftazidime,3-methylidene compound
Cephotaxime	6 impurities
Cephadrine	Cephalexine
Fluvoxamine maleate	An addition product (adduct)and fluvoxketone(ketone)
Gentamicin sulphate	Germaine,paromamine,2-deoxystreptamine
Lincomycin	Limcomycin-B
Meclophenoxate	N-N,Dimethyl ethanolamine
Minocycline	4-epiminocycline,6-deoxy-6-demethyltetracycline,7-didemethylminocycline,7-monodemethylminocycline,9-minocycline

Table 6: Quantification of impurities by UV Visible Spectroscopy

Drug	Mobile phase/solvent	Impurity
Amphotericin -B	Dimethyl sulphoxide and methanol	Tetraenes
Atropine sulphate	Methanol	Apo atropine
Dextrose	Water	5 hydroxymethyl furfural
Mercaptopurine	Dimethyl sulphoxide and 0.1M HCL	Hypoxanthine
Norgestrel	Ethanol	3,17α-diethinyl-13-ethyl-3,5-gonadiene-17-ol

Table -7: Various impurities reported in APIs

Drug	Impurity	Analytical method
Atropine sulphate	Apo atropine	Ultra violet spectroscopy
Cloxacillin	N,N dimethyl aniline	Gas chromatography
Dextrose	5 hydroxy methyl furfural	UV spectroscopy
Diclofenac sodium	1-(2,6-dichlorophenyl)indolin-2-one	Liquid Chromatography
Ethambutol hydrochloride	2- Amino butanol	Thin layer chromatography
Framycetin sulphate	Neamycin	Ultra violet spectroscopy
Methamphetamine	1,2-dimethyl-3-phenylaziridine, ephedrine, methyl ephedrine, N formyl methamphetamine, N acetyl methamphetamine, N formylphedrine, N acetyl ephedrine, N, Odiacetylephedrine, methametamine dimmer	Gas chromatography
Mercaptopurine	Hypoxanthine	UV spectroscopy
Doxorubicin	Acetone and ethanol	Gas chromatography
Fluoroscene sodium	Dimethyl formamide	Gas chromatography
Amphotericin B	Tetraenes	UV spectroscopy
Celecoxib	[5-(4-methylphenyl)-3-trifluromethyl-1H-pyrazole], 4-[5-(2'-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulphonamide, and 4-[4-(4'-methylphenyl)-3-(trifluromethyl)-1H-pyrazole-1-yl]-benzenesulfonamide	HPLC ,LC,LC-MS-MS
Repaglinide	4-carboxymethyl-2-ethoxy benzoic acid, 4cyclohexylaminocarbamoyl-methyl-2-ethoxy-benzoic acid, 1-cyclohexyl-3-[3-methyl-1-2-(piperidin-1-yl-phenyl)-butyl]-urea, 1,3 dicyclohexyl urea	HPLC
Morphine sulphonate	5-(hydroxymethyl)-2-furfural, 10 hydroxymorphine, 10-oxomorphine	HPLC
Morphine	6-monoacetylmorphine	HPLC
Norgestrel	3,17α-diethinyl-13-ethyl-3,5-gonadiene-17-ol	TLC, HPLC and UV spectroscopy
Ethynodiol diacetate	17 α-ethinyl-estr-4-ene-3β,17-diol-3-acetate-17-(3'-acetoxy-2'-butenoate), 17 α-ethinyl-estr-4-ene-3β,17-diol-3-acetate-17-(3-oxo-butanoate)	HPLC

Table 8: Reported impurities in pharmacopoeia

Drug	Reported impurities	Category	Pharmacopoeia
Acetyl salicylic acid	6	NSAID	EP2005
Acyclovir	8	Antiviral	EP2005
Aceclofenac	9	NSAID	EP2005
Betamethasone	10	Anti-inflammatory	EP2005
Bacitracin	11	Antibiotic	EP2005
Carbamazepine	6	Anticonvulsant	EP2005
Cephixime	6	Antibiotic	EP2005
Diltiazem HCL	6	Antianginal	EP2005
Digoxin	2	Anti-arrythmic	EP2005
Disulfiram	2	Antialcoholic agent	EP2005
Econazole	3	Antifungal	EP2005
Etoposide	14	Anti-cancer	EP2005
Furosemide	5	Diuretic	EP2005
Flutamide	6	Anti-androgen	EP2005
Fluoxetine HCL	3	Antidepressant	EP2005

CONCLUSION

This review offers a perspective on impurity profiling in drug substance and drug product. This article includes essential information regarding the types of impurities, their sources and classification, various isolation and characterization as well as several analytical techniques for determination identification

qualification of impurities. The detection of various form of impurities is critical during the development of an analytical method for any pharmaceutical product it gives critical information about the drug's quality safety and efficacy. Different regulatory bodies and the ICH have already set criteria in their guidelines, but they are insufficient to ensure product quality 100% of the time, and thus they need to be amended for further improvement for better quality pharmaceutical products. During analytical technique validation, many forms of contaminants must be appropriately assessed for detection quantification limitations. Thus, the data of analytical technique development and validation will help a lot in impurity profiling and makes the impurity profiling process easier because impurity profiling is required to establish the quality, safety, and efficacy of any pharmaceutical product.

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