Active Pharmaceutical Ingredients (APIs) and Their Impurity Profiling in Pharmaceutical Analysis

Rajeshwari V. Dugdhe[1], Kanchan J. Jagtap[2], Avinash B. Darekar[3]
[1]*Student K.V.N.Naik Institute of Pharmaceutical Research & Education, Nashik, Maharashtra. India.*
[2]*Department Pharmaceutical Chemistry K.V.N.Naik Institute of Pharmaceutical Research and Education, Nashik, Maharashtra. India.*
[3]*Department of Pharmaceutics, K.V.N.Naik Institute of Pharmaceutical Research and Education, Nashik, Maharashtra. India.*

Abstract—**Impurity The term impurity is not liked by pharmaceutical and industry personnel, as quality is a priority for them. Here we discuss various impurities that may be present in API preparations. This review article describes various terminologies, regulatory guidelines, and basic techniques, e.g. HPLC, LC-MS, TLC, aimed to help the newcomer understand and identify impurities and quantify them quantitatively with the added advantage of profiling as well. This paper stresses mainly the identification and control of various impurities, namely organic, inorganic, and genotoxic. For all materials, the ultimate goal is quality. Impurities can affect quality; therefore, knowing the type of impurities will help them in formulating quality products. USFDA, ICH, and other regulatory bodies have increased their attention on the identification of impurities in pharmaceutical active ingredients and the purity requirements that must be met.The process of collecting and evaluating data to determine the biological safety of an individual impurity, and thus its qualification level, provides the need and necessity of profiling in the study of medicines. Profiling of impurities involves the detection, identification, quantitation, and characterization of these undesirable chemical substances to meet regulatory requirements and ensure patients' safety. The quality, purity, and safety of APIs need to be guaranteed in pharmaceutical analysis, since impurities may result from synthesis routes, starting materials, deterioration, or storage environments. Generally speaking, the comprehensive evaluation of impurities is indispensable in the generation of safe, effective, high-quality pharmaceutical products.**

Index Terms—**Active Medicinal Component (AMC), Impurity analysis, Drug analysis, Natural contaminants, Chemical contaminants, Residual solvents LC-MS, Spectrophotometric techniques, Chromatographic methods.**

I. INTRODUCTION

The leading pharmaceutical industry is the foundation for all other pharmaceutical companies as it provides specialized, high-quality APIs in medicines [8]. During the last decades, there has been great interest in the quality of medicines introduced to the market. Production of high-quality goods is the main challenge facing the pharmaceutical and bulk medicine sectors[1]. In every industry, strict quality controls are required to ensure that production maintains its quality and integrity. Many factors can affect the purity of a pharmaceutical ingredient, including the raw material used, the manufacturing process, the type of crystallization, and the purification process.

Over time, medicines were also prepared from animals, microbes, and chemical synthesis, which also enhanced the effectiveness of the medication by removing its unwanted components[2]. A medicine mainly contains two entities: an active ingredient and an inactive ingredient. The active ingredient is a chemical compound responsible for enabling the medicine to treat the sickness, while the inactive ingredient is composed of excipients, binders, colors, and flavors. Even in small concentrations, impurities have the potential to compromise the safety and efficacy of drug substances and drug products, which are closely linked to their quality[3].

Purification analysis has grown to be a very labor-intensive process that includes method development, impurity synthesis, separation, and the use of several

analytical techniques to determine the unambiguous identification of the impurity of interest[4]. As a result, there is a constant need to develop new techniques for evaluating the quality of newly developed medications. A high-resolution chromatography technology that can accurately and consistently separate and identify all of the active chemicals' known and unknown impurities is necessary for impurity profiling[5]. To identify contaminants in raw material, intermediate, and end product samples, a variety of techniques must be developed. These techniques ought to be stability-indicating and thoroughly validated using parameters specified in the pharmacopoeias and guidelines of the International Council for Harmonization (ICH)[6].

Identification of impurities

It is among the actions of Impurity. profiling, whose objective is to recognize the chemical structures of contaminants found in the medication compounds or noted in the stability research beyond a specific limit. Understanding of the chemical composition of Impurity and its development the mechanism is crucial for evaluating its toxicological Consequences thereby enhancing the artificial chemical methodologies to lessen or remove the Contaminant. Recognition of medication impurities can be analyzed using different spectroscopic methods. Methods like Ultraviolet (UV) and Infrared (IR) Mass spectrometry (MS) and Nuclear Magnetic Resonance (NMR) resonance (NMR) whereas its measurement can be executed through chromatographic methods like High high-performance liquid chromatography (HPLC), Gas chromatography (GC), Supercritical fluid chromatography (SFC) and Thin-layer chromatography (TLC/HPTLC). ICH recommendations show that all the contaminants found in the medication substance must be identification threshold.

Detection method for impurities

It is highly important to confirm the sample for assessments, when it is accessible. If the

Assessments indicate that specific levels of impurities is more than 0.1% and must then be assessed according to the FDA guideline. Hyphenated approaches for illustration mass spectrometry, vapor chromatography or liquid chromatography, or the figures of other

The chromatographic-spectroscopic relationship is ideally suited for initial characterization regarding the contaminants.

II. CHEMICAL MANAGEMENT AND SAFETY REQUIREMENTS

When handled correctly, chemicals can be used safely in laboratories, businesses, and pharmaceutical companies[2].

General safety guidelines:

- Before using any chemical, read the safety data sheet (SDS).
- Wear the right personal protective equipment, such as a lab coat, gloves, safety glasses, and a mask or respirator if needed.
- For dangerous, corrosive, or volatile substances, use a fume hood.
- Avoid touching chemicals on the skin and inhaling their vapours.
- Make sure each container is clearly labeled.
- Store chemicals, flammable materials, acids, oxidizing agents, and other substances properly in the correct areas.
- Do not eat or drink in areas where chemicals are used.

Safe handling practices:

- Use only the amount needed.
- Keep containers closed when they are not being used.
- Use non-sparking tools when working with flammable materials.
- Carefully mix substances to prevent unwanted reactions.
- Dispose of waste following the rules for hazardous materials.

Be Ready for Emergencies:

Know the locations of:

- Eye wash stations
- Safety showers
- Fire extinguishers
- First aid kits
- Report any incidents immediately
- Follow the emergency procedures if there is a spill, fire, or exposure.

Goals:

The main purpose is to prevent pollution, explosions, fires, and damage, ensuring a safe work environment.[3]

III. PHARMACEUTICAL IMPURITIES

What is Meant by Impurities?The various official pharmacopoeias, groups, bodies, and ICH define impurities as follows. The following is the definition of impurity that appears in United States Pharmacopoeia (USP) general chapter <1086> Impurities in drug substance and drug product. Any component of a drug substance that is not the chemical entity defined as the drug substance is considered an impurity, as is any component of a drug product that is not an ingredient in the formulation[4].

General chapter 5.10 of the European Pharmacopoeia (EP) defines an impurity as any part of a drug intended for medicinal use that is not the chemical entity that is specified as the substance[5]. Impurity is defined as follows by the International Council for Harmonization (ICH). Any element of the drug substance that is not the chemical entity classified as a drug substance is referred to as an impurity[6].

Active Pharmaceutical Ingredients (API)

Definition and Role

- APIs are biologically active substances that provide the desired pharmacological effects of a dosage form
- Properties such as therapeutic efficacy, dosage, stability, and efficacy depend on the properties of the API[7]

API Source

- Chemical synthesis
- Fermentation
- Products derived from biotechnology
- Natural compounds/extracts[8]

API Quality Requirements

- APIs must meet certain quality attributes, such as:
  - Identity
  - Cleanliness
  - Power
  - Polymorphic form
  - Stability
  - Residual solvent level
- Regulatory authorities require that APIs comply with the requirements of various pharmacopeias such as USP, EP, and IP, as well as guidelines provided by ICH[9]

Impurities in API

Definition

Impurities are defined as unwanted chemicals in active pharmaceutical ingredients. They can occur naturally or be introduced during synthesis, processing or storage[1].

Types of Impurities (ICH Classification)

1. Organic Impurities

These impurities can originate from raw materials, intermediates, by-products, degradation products, or reagents used during synthesis[2].

2. Inorganic Impurities

These include[3]:

- Metal residue
- Catalyst remaining
- Reagents and inorganic salts
- Filter medium

3. Residual Solvents

Residual solvents remain after manufacturing or purification processes. ICH Q3C classifies them as follows[10]:

- Class 1: Highly toxic (avoid)
- Class 2: Restricted use
- Class 3: Low potential for toxicity

ICH Limits for Impurities

The International Conference on Harmonization (ICH) Guidelines regarding impurities in New Drug Products states that a new drug product cannot be evaluated based on impurity detection below 100% (or if there are not enough data available to prove that the impurities will not cause harm) unless the level of potential impurity is expected to have a very high pharmacologic efficacy or produce a substantial toxic effect[11].

The maximum daily dosage evaluation, which includes any chemicals that may affect the drug chemically or through toxicity, will be determined by:

- For $\leq$ 2 g/day - 0.1% or 1 mg per day of drug product (whichever is less)
- For > 2 g/day - 0.05%

All impurities listed in the New Active Substance Specifications will include limits for:

- Organic Impurities (each individual structurally identified and each unknown structurally unidentified at $\geq$ 0.1%)
- Residual Solvents (less than 2000 ppm)

- Inorganic Impurities

Pharmaceutical Analysis Impurity Profiling

Definition

The thorough examination of impurities in an API or pharmaceutical product, including identification, quantification, and structural clarification, is known as impurity profiling[4].

Significance of Impurity Profiling

• Ensures efficacy and security
• Assists in the analysis of toxicology
• Supports stability research
• Ensures compliance with legal obligations
• It enables the possibility of quality control and process enhancement[5]

Separation of Contaminants

• Technique for separating liquids
• Column chromatography (CC)
• Techniques for solid phase extraction
• Thin film chromatography [TFC]
• High-efficiency liquid chromatography [HELC]

Study on Induced Decline

• performed to detect possible degradation products:
• Acidic hydrolysis
• Fundamental hydrolysis
• Oxidative damage
• Stress caused by heat
• Stress caused by photolysis

Impurity Type	Impurity Source
Process-related drug substance (Organic)	Starting material, Intermediate, By-product, Impurity in starting material
Process-related drug product (Organic or inorganic)	Reagents, catalysts, etc
Degradation drug substance or drug product (Organic)	Degradation products
Degradation drug product	Excipient interaction

Table 1: Description of impurity types and their sources

Sources of Impurities

This review has shown that impurities can come from many different sources[6]:

1. Impurities associated with crystallization
2. Impurities associated with stereochemistry
3. Residual solvents
4. Synthetic intermediates and by-products
5. Formulation-associated impurities
6. Storage-associated impurities
7. Method-related impurities
8. Impurities resulting from mutual interaction of ingredients
9. Typical degradation of functional groups

Crystallization-Related Impurities

Crystallization can have a profound effect on the solid-state properties of this system, requiring the pharmaceutical industry to take a strong interest in polymorphism and solvatomorphism according to the rules set by regulatory authorities[7]. The term polymorphism is used to indicate crystal systems in which substances can exist in different crystal packing arrangements, all of which have the same elementary structure.

Stereochemistry-Related Impurities

It is of paramount significance to search for stereochemistry associated compounds; this is, the ones compounds which have comparable chemical shape however specific spatial orientation, those compounds can be taken into consideration as impurities in the API's[8]. Chiral molecules are regularly referred to as enantiomers. The single enantiomeric form of

chiral drug is now considered as an advanced chemical entity that could offer a better pharmacological profile and an elevated healing index with a greater beneficial unfavourable response profile.

However, the pharmacokinetic profile of levofloxacin (S-isomeric shape) and ofloxacin (R-isomeric form) are comparable, suggesting the shortage of benefits of single isomer on this regard[9]. The prominent unmarried isomer capsules, which might be being marketed, consist of levofloxacin (S-ofloxacin), lavalbuterol (R-albuterol), and esomeprazole (S-omeprazole)[10].

Residual Solvents

Residual solvents are organic chemicals that can evaporate and are used during the making of medicines or are created during the production process[11]. Some of these solvents are harmful and

should not be used when making large amounts of drugs. Based on how dangerous they can be to people's health, these solvents are grouped into three classes[12].

Class I solvents, like benzene (with a limit of 2 ppm), carbon tetrachloride (4 ppm), methylene chloride (600 ppm), methanol (3000 ppm), pyridine (200 ppm), and toluene (890 ppm), should be avoided[13]. Class II solvents include N, dimethylformamide (880 ppm) and acetonitrile (410 ppm). According to ICH guidelines, solvents like acetic acid, acetone, and dichloromethane are used to check the purity of acetone, dichloromethane, and toluene. This method helps find out the main impurities in each solvent[14].

Synthetic Intermediates and By-products

Impurities in pharmaceutical compounds or a new chemical entity (NCE) can arise from raw materials, intermediates and/or by-products during the synthesis process[15]. For example Impurity profiling of Ecstasy tablets with GC-MS and MDMA samples generates intermediate impurities via the reductive amination pathway.

Formulation-Related Impurities

Many impurities in a substance can come from excipients, which are other ingredients used to make the substance[16]. During the process of making a medicine, it is exposed to a number of conditions that can cause it to break down or react in undesirable ways. If the excipient used varies between batches, it can also affect the quality of the final product, making it unreliable.

Liquid forms such as solutions and suspensions are particularly susceptible to degradation due to reactions such as hydrolysis or solvolysis. A typical example is fluocinonide topical solution USP, 0.05%, which was recalled in the United States because it was defective or contained impurities that made it less effective[9]. Liquid medications are also more likely to be affected by both degradation and microbial growth.

Important factors that influence this are the amount of water, pH level, how well different ions work together, how the substances interact with each other and environmental conditions. Microbial growth can occur when bacteria, fungi or yeast multiply in hot and humid environments, making the product unsafe for human use. This can happen during storage or while the product is being used, either because the preservatives used were not sufficient or because the containers are semi-permeable and allow microorganisms to enter[2].

Mutual Interaction Amongst Ingredients

Most nutrients are very labile and on getting old they invent a hassle of instability in extraordinary dosage forms, specifically in liquid dosage bureaucracy[17]. Degradation of nutrients does not give toxic impurities; however, efficiency of lively components drops below Pharmacopoeial specs. Because of mutual interplay, the presence of nicotinamide in a method containing 4 vitamins (nicotinamide, pyridoxine, riboflavin, and thiamine) can cause the degradation of thiamine to a sub-fashionable stage inside a twelve months shelf existence of nutrition B-complicated injections[18].

The marketed samples of nutrition B-complicated injections have been found to have a pH variety of 2.8-4.0. A customized formulation with simple distilled-water and a typical formulated automobile along with disodium edetate and benzyl alcohol have been investigated, and similar mutual interactions inflicting degradation have been found[19].

Developments and Trends in Impurity Profiling

- Quality by Design (QbD) Approaches: Help pinpoint which process variables are critical in determining the formation of impurities[6]
- Forced Degradation Studies: Used to develop stability-indicating methods and to identify degradation pathways[18]
- Computer-Aided Structure Prediction: Software technologies speed up the process of identifying unknown contaminants
- Analytical Green Chemistry: Give emphasis to energy-efficient analytical techniques and eco-friendly solvents
- Analytical Method Development: New drug development requires meaningful and reliable analytical data to be produced at various stages of the development[7]

Analytical Method Development Components

1. Sample set selection for analytical method development
2. Screening of Chromatographic conditions and Phases, typically using the linearsolvent-strength model of gradient elution
3. Optimization of the method to fine-tune parameters related to ruggedness and robustness[8]

The impurities can be identified predominantly by following methods:

- Reference standard method
- Spectroscopic method
- Separation method
- Isolation method
- Characterization method

Reference Standard Method

The main objective is to provide clarity in the general life cycle, qualification and management of reference standards used in the development and control of new medicines[20]. Reference standards serve as a basis for evaluating both process and product performance and are standards for evaluating drug safety for patient consumption. These standards are required not only for active ingredients in dosage form, but also for impurities, degradation products, starting materials, process intermediates and excipients[21].

Spectroscopic Methods

The UV, IR, MS, NMR and Raman spectroscopic methods are routinely being used for characterizing impurities[9].

Separation Methods

The Capillary electrophoresis (CE), Chiral Separations, Gas Chromatography (GC), Supercritical Fluid Chromatography (SFC), TLC, HPTLC, HPLC are regularly being used for separation of impurities and degradation products[22].

Isolation Methods

It is often needed to separate impurities. But if we use special instruments, we don't need to isolate the impurities because the instruments can directly identify them[23]. Usually, either chromatographic or non-chromatographic methods are used to separate impurities before they are studied.

Methods that can be used to separate impurities:

- 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)

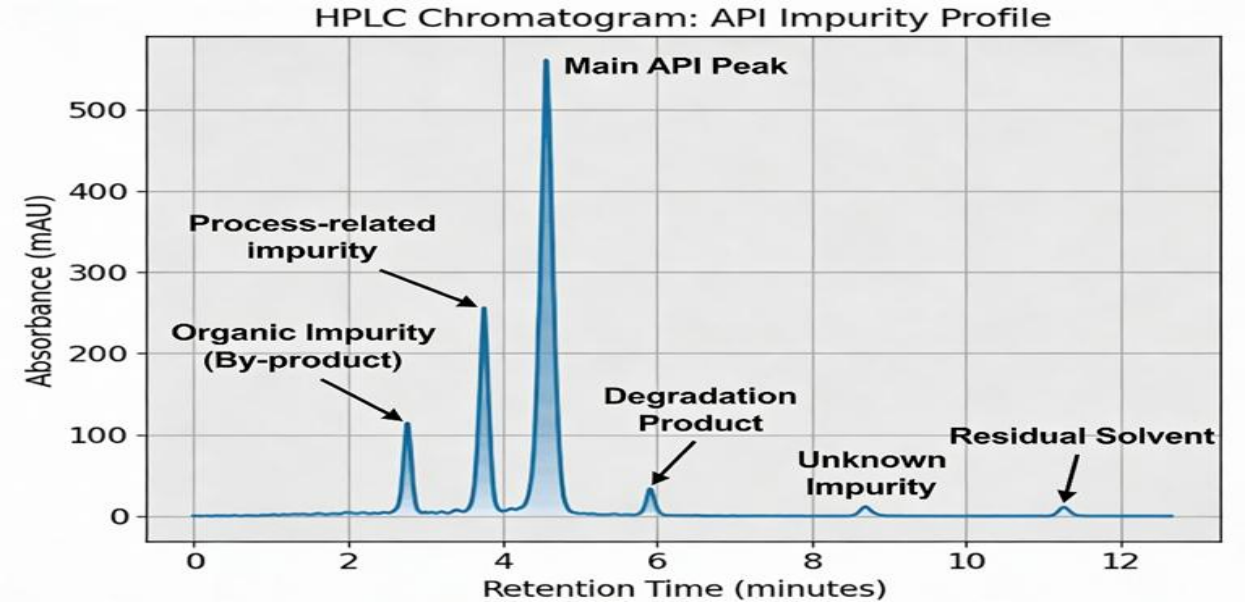

Fig 1. HPLC Chromatogram: API Impurity Profile

Characterization Methods

Highly sophisticated instrumentation, such as MS attached to a GC or HPLC, are inevitable tools in the identification of minor components (drugs, impurities, degradation products, metabolites) in various matrices[8]. For characterization of impurities, different techniques are used.

1. NMR

The ability of NMR to offer facts regarding the particular bonding shape and stereochemistry of molecules of pharmaceutical interest has made it a powerful analytical device for structural elucidation[20]. The potential of NMR-based diffusion coefficient determination to distinguish between monomeric and dimeric materials turned into established the use of a general mixture of real materials containing both monomers and dimers. Unfortunately, NMR has historically been used as a much less touchy method in comparison to different analytical strategies. Conventional pattern requirements for NMR are at the order of 10 mg, as compared with MS, which calls for less than 1 mg[24].

2. MS

It has an increasingly more great impact at the pharmaceutical development manner over the past several many years[6]. Advances within the design and performance of the interfaces, that immediately join separation techniques with Mass Spectrometers have afforded new possibilities for monitoring, characterizing, and quantification of drug-associated materials in active pharmaceutical ingredients and pharmaceutical formulations[11].

If single method fails to provide the necessary selectivity, orthogonal coupling of chromatographic techniques inclusive of HPLC-TLC and HPLC-CE, or coupling of chromatographic separations with statistics rich spectroscopic methods which include HPLC-MS or HPLC-NMR may want to be pondered[9].

Hyphenated Methods:

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

The popularity of LC-MS-MS systems for complex mixture analysis of thermally labile and biologically relevant molecules, such as mosapride, is largely attributed to the "soft" nature of atmospheric pressure chemical ionization (APCI) and atmospheric pressure chemical ionization (APPI)[7].

HPLC-DAD-MS (HPLC coupled with a diode array UV detector and a mass spectrometer, and such other techniques are almost routinely used. NMR has now been added to this combination to provide HPLC-DAD-NMR-MS capabilities in a commercial instrument[8].

Applications

Numerous packages have been sought within the regions of drug designing and in tracking excellent, balance, and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced by way of recombinant methods[12]. The packages encompass alkaloids, amines, amino acids, analgesics, antibacterials, anticonvulsants, antidepressant, tranquilizers, antineoplastic marketers, nearby anesthetics, macromolecules, steroids, miscellaneous.

Contaminant Control Rules

Key Guidelines Include

- ICH Q3A(R2): New drug compound impurities[5]
- ICH Q3B(R2): Impurities in New Pharmaceutical Products[6]
- ICH Q3C: Residual solvents[10]
- ICH Q2(R1): Validation of methods
- USP, IP, and EP pharmacopeial standards

Guidelines Define

- Levels of threshold
- Reporting restrictions
- Qualification processes
- Requirements for analytical methods

IV. CONCLUSION

The impurity profile of the test substance provides the most complete description of impurities present[13]. Manufacturer's quality standards are determined by the amount of impurities in medicines. It is very important to be able to show that the impurity profile of the new compound is qualified[14].

High doses of drugs require careful analysis if the qualification threshold is 0.1% or less, so pharmaceutical analysts should consider the analysis with utmost care[15]. Some very selective steps may be required, such as the hyphenated method during the development stage. It is something that a developmentalist should recognize as important[16].

Impurity profiling profiles ensure that kits used in security research are free of relevant foreign substances. For this purpose, APIs need to be of high purity to ensure therapeutic efficacy and patient

safety[17]. Impurity profiling is, therefore, an integral component of pharmaceutical analysis, governed by detailed regulatory frameworks and supported by advanced technologies of analysis[18]. Understanding impurity origins, classification, and control strategies is vital for robust drug development and quality assurance[19].

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