AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

A Review on Effect of Impurities in Pharmaceutical Substances

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ABSTRACT

Unwanted materials that coexist with active pharmaceutical ingredients (APIs), surface during formulation, or become apparent after the formulation and API have run out are known as pharmaceutical impurities. The therapeutic properties of generic drugs may be affected, even in minute quantities, by the creation of these chemical pollutants. The pharmaceutical business is currently facing significant issues with impurity control. Researchers from the International Conference on Harmonization (ICH) have worked to manage pollutants. This review describes various impurity types, sources, and degrading transcription factors using specific examples.

Keywords: Impurities, Formulation, efficacy, degradation.

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Received 10 December 2023, Accepted 28 December 2023

Please cite this article as: Dongare GD *et al*., A Review on Effect of Impurities in Pharmaceutical Substances . American Journal of PharmTech Research 2024.

INTRODUCTION

Any substance that coexists with the drug in question, such as the nitrogen source or that is created as a result of any adverse effects, is referred to as an impurity.

Three different types of impurity exist.

1. Substances that are closely linked to the outcome and are produced chemically or through a biosynthetic process.
2. Impurities developed as a result of the drug's spontaneous disintegration during following extreme climate exposure or during storage.
3. The precursors that could end up as contaminants in the finished product. Selective procedures should be employed to identify and quantify any pollutants found in excess of 0.1%. The impurity's suggested structures could be produced, offering the conclusive proof for those structures which spectroscopic techniques had previously verified—for those structures. Therefore, understanding the composition of these impurities inside the material's bulk is crucial[1]

In order to change the parameters of the reaction and reduce the impurity concentration to a level that can be controlled.

Impurities can be extracted, located, and quantified using a variety of procedures to create a pure product that is safer and less hazardous for use in pharmaceutical therapy.

Pharmaceuticals may contain unwanted substances known as impurities that develop during manufacturing or as API matures. Utilization and security of natural products contaminants, even in minute quantities, may have an impact. Impurities that provide APIs are therefore growing in popularity. Impurity profiles have gained importance in the drug development process in recent times. The Food and Drug Administration (FDA) and the International Conference on Harmonization are two regulatory entities that recommend reporting contaminants that occur in excess of or within acceptable limits (ICH). [2]

The United States Pharmacopeia (USP) and the British Pharmacopeia have both indicated permissible limits of pollutants present in API and formulation (BP). In order to foresee the degradation products and routes that can help determine the drug substance's intrinsic stability and in the creation of stability indicating assay methods, the regulatory authorities have also produced recommendations for stress testing drug substances and injectable (SIAM). Both regulatory agencies and pharmaceutical companies now have a substantially greater need for the fluorine reference standard.

Classification of Impurities [3, 4]

Drug substance impurities may occasionally be referred to as common or ICH impurities.

Common terminology

The regulatory authorities and ICH use the words below to describe impurities. Intermediate compounds produced either during the synthesis of the intended material or as a result of the synthesis process. Penultimate intermediate It could be the final compound in the synthesis chain before the desired chemical is produced. By-products - the product of the reaction that is not one of the necessary intermediates.

Transformation products

They pertain to both theoretical and speculative byproducts of reactions. Interaction products These items were created either purposefully or accidentally as a result of chemical interactions. Related products- These have biological activity and are chemically related to pharmacological substances.

Degradation Products

They develop as a result of the decomposition of an adjuvant or other relevant material under the influence of outside elements like heat, light, and moisture. Impurities are divided into three categories by the ICH: organic impurities, inorganic impurities, and residual solvents.

Organic chemistry impurities Starting materials, byproducts, synthesis intermediates, degradation products, and leachable from contact materials are only a few possible sources for contamination.

Inorganic chemistry impurities Inorganic impurities, which are commonly known and recognized as reagents, ligands, inorganic salts, heavy metals, catalysts, filter aids, and charcoal, among other things, may be produced during the production process.

Residual solvents Remaining solvents are the leftover solvents from the production process. The amount of residual solvents and inorganic pollutants from the aforementioned three groups is limited.

Official compendia terminology-ICH Terminology

According to the ICH recommendations, each contaminant must be identified from both a chemical and a safety standpoint. Impurities are classified and identified, reports are generated, impurities are listed specifications, and the chemistry viewpoints have a quick conversation on analytical methods. It is composed of

Sources of Impurities [5]

1. Synthesis related impurities.
2. Impurities are related to dosage form
3. Impurities create an aging.

4. Not pure on aging

Mutual interaction:

The interaction of the substances used in formulation results in the production of impurities through mutual interaction.

The majority of the time, vitamins in various dosage forms is particularly susceptible to instability with ageing. i.e., the breakdown of vitamins like cyanocobalamins, folic acid, and thiamine does not result in the production of harmful contaminants but rather causes a significant loss in potency. More importantly, Thiamine degrades to a dangerous level over the duration of a vitamin-B complex injection's one-year shelf life because nicotinamide is included in formulations that contain four vitamins - nicotinamide, pyridoxine, riboflavin, and thiamine. A similar mutual interaction was seen in both the traditionally produced vehicle using din-sodium edentate and benzyl alcohol as well as the bespoke formulation in a basic distilled water vehicle. The bulk of vitamins are quite labile, especially in liquid dosage forms, and as they age, they become unstable. Thiamine degrades to a dangerous level within a year of its expiration date in multivitamin formulations that also contain the four vitamins nicotinamide, pyridoxine, riboflavin, and thiamine as a result of interactions with the other three vitamins. [6]

Hydrolysis

A process that results in precipitation and uses water as the reactant. Esters and amides are well-known examples of these reactions in medicinal substances. Numerous medications contain functional groups based on the moiety or are derivatives of carboxylic acids. For instance, compound, Esters, amides, lactones, lactams, imides, and carbamates are examples of molecules that are susceptible to acid base hydrolysis. These include atropine, chloramphenicol, 12 barbiturates, chlordiazepoxide, oxazepam, and lincomycin. [7]

Oxidation

Medications that are vulnerable to oxidation include hydrocortisone, methotrexate, adinazolam, catecholamine, conjugated-dienes (Vitamin-A), heterocyclic aromatic rings, nitroso and nitrite derivatives. In the pharmaceutical sector, the most common form of oxidative degradation is auto oxidation by a free radical chain mechanism. For instance, research on the ascorbic acid auto-oxidation demonstrates that the cupric ion has the ability to quickly oxidise ascorbic acid to dehydroascorbic acid and potassium cyanide. The chain cleaves as a result of the formation of copper complexes. Studies on substituted 5-amino-ethyl-1, 3-benzenediol sulphate (AEB) stability indicate that copper can effectively catalyze AEB breakdown down to 10 ppb levels in the

presence of oxygen, which causes product discoloration. When it comes to AEB, metals perform best in the order Cu, Fe, and Ca. 2+ 3+ 2+ degradation. [8]

Photolysis:

Examples of photolytic cleavage on ageing include medications and other products that are prone to degradation when exposed to UV radiation. Throughout the production process as a solid or solution, during packaging, or during storage, medications such ergometrine, nifedipine, nitropruside, riboflavin, and phenothiazine's are vulnerable to 20–22 photo oxidation. The free radical intermediate created by this oxidation will destroy the goods. For instance, photolysis is initiated and an ethylene 23 di-amine analogue of ciprofloxacin is created when ciprofloxacin eye drops 0.3% is exposed to UV light. [9]

Decarboxylation:

Some carboxylic acids show carbon dioxide leakage from the carboxyl group when heated, including p-amino salicylic acid. For instance, the calcium carbonate and cellulose acetate phthalate (CAP) sub-coating on the rufloxacin tablet caused the CAP to hydrolyze, releasing acetic acid. Acetic acid then reacted with the calcium carbonate to produce carbon dioxide, a byproduct that blew the cap off the bottle once the cap was loosened. [10]

Packaging material:

Additionally, packing components like containers and closures produce impurities. The majority of medications' reactive species for contaminants include; Hydrolysis of the active component by water. Aldehydes and derivatives of carboxylic acids are small electrophiles. Some medications are oxidised by peroxides. Metals - accelerate drug oxidation and the process leading to drug breakdown. Glass, rubber stoppers, and plastic materials are all extractable or leachable, with oxides such NO, 2 SiOCaO, and MgO being the main elements taken or leached from glass. Styrene derived A few examples of synthetic materials made from polystyrene are polypropylene, diethylhexylpthalate (DEHP) plasticizer in PVC, dioctyltin isooctyl mercaptoacetate stabiliser for PVC, and zinc stearate stabilizer in PVC. [11]

Analytical methodology:

Impurity profiling (characterization and isolation) is a critical step in the creation of novel drugs. Regulatory organizations like the US FDA and the EU require estimation of impurities beyond 0.1% level. For the evaluation and analytical validation of impurities, ICH provided guideline documents. As a result, numerous analytical techniques have developed to track contaminants found in new medicinal ingredients and new drug products.

Numerous variables, such as the drug substance's synthetic pathway, reaction circumstances, the caliber of the starting material, reagents, solvents, purification procedures, and storage of the finished product, all affect the type and quantity of these impurities. Numerous spectroscopic and micro chemical techniques have been developed that require minuscule amounts of material and easily allow the structural elucidation of the impurity because the structure of the impurities is occasionally unknown. For the detection and monitoring of contaminants in drug substances and drug products, versatile analytical approaches are also available. The ability to distinguish between chemicals of interest is the main criterion for analytical methods. Combining separation (isolation), detection, and quantification (spectroscopy) are often utilized techniques. [12]

The separation technique uses capillary electrophoresis, gas chromatography, thin layer chromatography, and high-performance liquid chromatography (CE).

The most popular and affordable approach for impurity monitoring is HPLC. TLC is effective for separating a variety of chemicals. The technique of capillary electrophoresis is helpful. When very few samples in large volumes are available and high resolution is needed. Ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry are examples of spectroscopic techniques (MS). One-shot ultraviolet spectroscopy.

While the availability of diode array detectors delivers far more information at various wavelengths to assure higher selectivity, wavelength only provides minimal analytical selectivity. Specific information on some functional groups that might enable quantization and selection is provided by infrared spectroscopy. [13]

Nuclear magnetic resonance spectroscopy is a highly helpful technique for characterizing the target product and any related contaminants because it provides reasonably precise structural information on molecules. Based on the patterns of mass ion fragmentation, mass spectrometry, which only needs very little amounts of sample, provides good structural information. Thus, characterization and analysis of pharmaceutical compounds and impurities can be accomplished with great success using UV, IR, NMR, and MS techniques. [14]

At various stages of the development process, new drugs must be produced and require meaningful and trustworthy analytical data. a) Choosing a sample set for the development of an analytical method b) Chromatographic conditions and phases are screened, usually utilizing the linear solvent-strength gradient elution model. c) Method optimization to adjust parameters for robustness and ruggedness.

Strategies for method of developed

The impurities we can be identified already by following 5 methods: [15]

1. Separation method of impunity
2. Isolation method of impunity
3. Characterization method of impunity
4. Reference standard method of impunity
5. Spectroscopic method of impunity

Spectroscopic methods

The UV, IR, MS, NMR and Raman spectroscopic methods these are routinely we can used for characterizing impurities in substance. [16]

Separation methods

The Capillary electrophoresis (CE), Chiral Separations, Gas Chromatography (GC), Supercritical Fluid Chromatography (SFC), TLC, HPTLC, HPLC are regularly we can used for separation of the impurities and degradation products. [17]

Isolation methods

It is often necessary to Isolating contaminants is frequently necessary. However, since instrumental methods directly characterize the impurities, isolation of impurities is avoided when using them. Generally, contaminants are isolated before being characterized using chromatographic and non-chromatographic techniques. The use of an analytical-scale column as a flow-through reactor and, at the same time, as a medium for reactant and product separation is referred to as a "chromatographic reactor" (s). The solution-phase hydrolysis kinetics of the Aprepitant (EmendTM) prodrug, fosaprepitant dimeglumine, was examined utilizing an HPLC, chromatographic reactor method. Ofloratidine, another impurity discovered in loratidine, as well as celecoxib and amikacin, are some other instances.

The following is a list of techniques that can be used to isolate contaminants.

• Solid-phases 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). [18]

Characterization methods highly sophisticated instrumentation, such can MS attached to a GC or HPLC, are inevitable tools in those identification of minor components (drugs, impurities, degradation products, metabolites) in various matrices. For characterization of impurities, different techniques are used; which are as follows;

NMR Spectroscopy

NMR is a potent analytical tool for structural elucidation since it can reveal details about the unique bonding structure and stereochemistry of compounds of medicinal relevance. A common mixture of real materials containing both monomers and dimmers was used to validate the NMR-based diffusion coefficient determination's capacity to discriminate between monomeric and dimeric compounds.

Unfortunately, compared to other analytical methods, NMR has historically been utilized as a less sensitive method. In contrast to MS, which takes less than 1 mg of sample, conventional NMR requirements are on the order of 10 mg. [19]

Mass Spectroscopy

Over the past few decades, it has had an ever-greater impact on the process of developing pharmaceuticals. New opportunities for monitoring, characterising, and quantifying drug-related substances in active pharmaceutical ingredients and pharmaceutical formulations have been made possible by improvements in the design and effectiveness of the interfaces that directly connect separation techniques with mass spectrometers. [20]

If a single method is unable to provide the required selectivity, orthogonal coupling of chromatographic techniques such as HPLC-TLC and HPLC-CE, or coupling of chromatographic separations with information-rich spectroscopic methods such as HPLC-MS or HPLC-NMR may need to be considered. Hopefully, however, these techniques will only be used as development tools rather than tools for routine QC use. [21]

Hyphenated Methods:

• LC-MS-MS

• HPLC-DAD-MS

• HPLC-DAD-NMR-MS

• GC-MS

• LC-MS

Two different soft ionization methods, atmospheric pressure ionization with electrospray source (API-ESI) and chemical ionization of d-allethrine, are examples of reverse-phase LC-MS analysis in gradient elution. 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 such other techniques are largely to blame for the popularity of LC-MS-MS systems for complex mixture analysis of thermally labile and biologically relevant molecules, viz. mosapride.

Now that NMR has been included, a commercial device can offer HPLC-DAD-NMR-MS capabilities. [22]

Numerous different chromatographic and spectroscopic configurations are discovered to be absolutely acceptable for initial evaluation of the contaminants in GC-MS of methamphetamine and in LC-MS of risperidone and cetirizine tablets. Determining which of the numerous potential impurities are actually formed in the production process and which occur under a certain set of storage conditions is a common goal for analysis of both process and product degradation-related impurities. [23]

Remedies:

Controlling contaminants in active medicinal components requires a number of key aspects (API). If drug molecules are stuck during crystallization, chemicals from mother liquor cause drug breakdown. In order to avoid entrapment, the API maker should take care to generate finer crystals. To get rid of undesirable chemicals, including leftover solvents, proper cleaning is required. [24]

Packing

Light sensitive pharmaceuticals have been packed is in proper way to Avoid the exposure of light. The choice of production technique should be based on stability studies. Aseptic filtration has been utilized in place of the autoclave procedure to make high-quality diclofenac sodium injections.

Pharmacopoeias should generally be more exact and limit-specific, and regulatory agencies like the FDA and ICH should be stringent in this regard. [25]

Table 1: Current marketed formulation which contains impurity.[26]

Sr. No.	Drug	Impurity	Method
1	Atopine sulphate	Tetraenes	Ultra Violet Spectroscopy
2	Amphotericin B	Apo atopine	Ultra Violet Spectroscopy
3	Cloxacilin	N,N, dimethylaniline	Gas Chromatography
4	Doxirubicine hydrochloride	Acetone &Ethanol	Gas Chromatography
5	Dextrose	5-hydroxy methyl fulfural	Ultra Violet Spectroscopy
6	Ethambytal Hydrochloride	2 amino butanol	Thin layer Chromatography

7	Flurescene sodium	Dimethyl formamide	Gas Chromatography
8	Farmyctin Sulphate	Neamine	Thin layer Chromatography
9	Marcptopurine	Hypoxinthine	Ultra Violet Spectroscopy

Critical Factors Affects the Quality of Bulk Drugs [27,28]

Crystallization:

The quality and stability of the synthesized molecule are determined by the crystals that form during the crystallization process. Larger-sized crystals can be formed by trapping solvent traces, which could lead to drug breakdown. Therefore, when separating their goods, makers of bulk medications should be careful to create finer crystals.

Washing the wet cake:

Unwanted chemicals and leftover solvents can be completely eliminated from samples by washing them in the wet cake condition or by washing the samples in the wet cake condition.

Drying:

For the manufacture of bulk pharmaceuticals, a vacuum dryer or a fluid-bed dryer is preferred over a tray dryer due to the reduction of drying time and uniform drying, which is also beneficial for thermolabile compounds.

Appropriate packaging:

To prevent deterioration during storage, the bulk medications should be packaged according their nature.

CONCLUSION

A viewpoint on contaminants in drug substance and drug product is offered by this review. Pharmaceutical impurity profiles are becoming increasingly significant, and the public and the media are paying more and more attention to drug safety. This page offers useful information on the many types of impurities and their classification, different separation and characterization procedures, analytical techniques for the determination, qualification of impurities, and important considerations to take into account while preparing the bulk.

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