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A Review on Pharmaceutical Impurities and its Importance in Pharmacy.

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ABSTRACT

In the field of pharmaceutical chemistry, impurities are considered as unwanted chemicals that present in the therapeutically active pharmaceutical compounds. They are unusually potent and expected to produce toxicity; hence it may be shows unexpected pharmacological actions which are harmful to human health. The control of impurities is currently a critical issue to the pharmaceutical industry. The most possible source of impurities is the synthesis that involves various steps, *i.e.* from starting materials to finished products through the intermediate steps. Impurities in drug substances and drug products are key regulatory issues in the office of generic drugs and have significant impact on the approvability of drugs hence International Conference on Harmonization (ICH) and Food and Drug Administration (FDA) guidelines introduce the identification and qualification procedures for them, by using various analytical techniques like TLC, LC, GC, MS, NMR, IR, UV, GC-MS, LC-MS, LC-NMR *etc*,.

Keywords: Impurities, importance.

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INTRODUCTION

The impurity profile of a drug can be defined as "A description, characterization and quantification of the identified and unidentified impurities present in a new drug substance" [(1)]. In the present era, there is a tremendous upsurge for the impurity profiling of pharmaceutical products. Presence of impurities in trace quantity in drug substance or drug product is inevitable. Therefore, their level should be controlled and monitored. They can diminish or decrease the pharmacological efficacy of the active pharmaceutical ingredient (API). Sometimes, the effect produced by the impurities can be mutagenic, teratogenic or carcinogenic [(2)]. Some impurities may act as genotoxic impurities, which are considered unsafe at any level because they produce genetic mutations, chromosomal breaks, chromosomal rearrangements and act as carcinogenic which interact with DNA [(3)]. Hence, this can jeopardize the human health by affecting quality, safety and efficacy (QSE) of the pharmaceutical products. Therefore, it is very crucial to monitor and control the impurities in API/pharmaceutical products. Hence, API impurity profiling (Isolation, identification and characterization) is required. Their limits and threshold values should comply with the limits set given by ICH and FDA [(2)]. According to the ICH guidelines on impurities in new drug products and new drug substances, identification of impurities below the level 0.1% is not necessary unless their potency and genotoxicity should be qualified. If data which is related to qualification of the given specification level of an impurity is not available then studies were required to get such data. According to the ICH guidelines the maximum daily dose qualification threshold is ≤2g/day 0.1% or 1mg/day intake and ≥2g/day 0.05 % [(4)]. As impurity profile received a critical attention from regulatory authorities, different pharmacopoeias such as British pharmacopoeia (BP), United States of pharmacopoeia (USP), Indian pharmacopoeia (IP), European pharmacopoeia (EP) are incorporating limits to the allowable levels of impurities in new drug products or formulations [(5)]**.**

Sources of Impurities:

Impurities in API may be formed from starting materials or raw materials which was then carried out by the final products through several intermediate steps. During this process that formed by-products or intermediates may be carried into the final stages of process there they may be act as a source for the formation of other impurities. Some other sources of impurities are listed below

- Raw materials used at initial stages of synthesis.
- Reagents or solvents that are used for the reaction process. *e.g,*. Catalysts.
- From the different side reactions during synthetic process.
- By-products produced intermediately during the synthesis.

- From the contaminants of packing materials.
- From therapeutically active ingredients.
- From the improper storage of drug substances.
- Impurities formed due to unfavourable conditions maintained during the process which leads some types of unwanted reactions like thermolytic, photolytic, hydrolytic degradation reaction in drugs substances.
- Impurities formed due to incompatibility of excipients, steps followed, type of equipment used and environmental conditions maintained during process [6].

CLASSIFICATION OF IMPURITIES [7, 8, 9]:

Pharmaceutical formulations or pharmaceutical chemicals used in the production of APIs involved a major broad classification of impurities *i.e.*

Synthesis related impurities

1. Organic impurities
2. Inorganic impurities
3. Residual solvents

Formulation related impurities

Synthesis related impurities

These are the type of impurities in pharmaceutical compounds or new chemical entities arise mainly during synthetic process from starting materials, solvents or reagents, intermediates. Hence, the impurities during synthetic process categorized as

Organic impurities: - These types of impurities mainly arise during synthetic process or storage conditions of drug substance. This impurity further classified as starting materials, by-products, degradation products and chiral impurities.

Starting materials – Impurities in the form of unreacted raw materials or intermediates will be found in every drug substance if proper care not taken during the process which involved a multistep synthesis. Also products frequently exposed to solvent for washing had a chance to formation of impurities due to incomplete removal of solvent.

Degradation products – During production of bulk drugs due to maintaining of unfavourable conditions leads to degradation of end products which results in the formation of impurities. A degradation product also arises from type of synthetic process, storage conditions, formulation of dosage form and aging.

By-products – In synthetic organic chemistry, getting a single final product with 100% yield is highly difficult because synthetic reaction involve a variety of side reactions, isomerization, over reactions, dimerization, rearrangement reaction, cyclization and crystallization or unwanted reactions between raw materials (due to incompatibility) or reagents or catalysts which produces the by-products [10].

Enantiomeric impurities – In all cases compound in the form of racemic mixture which has equal amounts of right and left handed enantiomers are not useful. Hence, single Enantiomeric form of a chiral compound is preferred as an improved chemical compound that may shows a better pharmacological profile and increased therapeutic index, with a more favorable adverse reaction profile [11].

Inorganic impurities: - Inorganic impurities derived from the manufacturing processes used for bulk drugs. They are normally known and identified.

Reagents, ligands and catalysts: - The chances of having these types of impurities are rare however; these could create a problem unless the manufacturers take proper care during production.

Heavy metals: - The main sources of heavy metals are depending on the types of reactors used (*e.g.* stainless steel reactors), where acid hydrolysis or acidification reaction takes place. By using of demineralized water and glass-lined reactors these impurities of heavy metals can be easily avoidable [12].

Residual solvents: - Residual solvents are potentially undesirable substances. They either change the properties of some compounds or may be harmful to human health. They will also affect physicochemical properties of the bulk drug compounds such as crystallites of bulk drug, which may affect the odour, dissolution properties and colour changes in final products. According to the ICH guidelines, the solvents used in the manufacturing of drug substances classified into four types [13, 14].

Class I solvents: These solvents are not employed in the manufacture of drug substances, excipients and formulations because of their deleterious effects or their unacceptable toxicity. If use of these types of solvents is unavoidable, then their usage should be restricted. Class I and their permissible concentration limits given in below table 1.

Table 1:

Residual solvent	Concentration limit(ppm)
Benzene	2 (carcinogenic)
Carbon tetrachloride	4 (toxic)
1,1 Dichloro ethene	8 (toxic)

1,1 Dichloro ethene	5 (toxic)
1,1,1 Trichloro ethane	1500 (environmental hazard)

Class II solvents: Class II solvents usage should be limited in pharmaceutical products because of their inherent toxicity. Below given table shows the class II solvents with their daily permissible exposure.

Table 2:

Solvents	Permissible daily exposure (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cycloehexane	38.8	3880
1,2 Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,1 Dimethoxyethane	1.0	100
N,N-Dimethyl acetamide	10.9	1090
N,N Dimethyl formamide	8.8	880
1,2-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxy ethanol	0.5	50
Methyl butyl ketone	0.5	50
Methyl cyclo hexane	11.8	1180
N-Methyl pyrrolidone	48.4	4840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfulane	1.6	160
Tetraline	1.0	100
Toluene	8.9	890
1,1,2-Trichloro ethane	0.8	80
Xylenes	21.7	2170

Class III solvents: These classes of solvents are less toxic and shows lower risk to human health than class I or class II solvents [15]. Long term toxicity or carcinogenic activity still not reported, which is obtained from the available data for the solvents under this class. Some of the solvents are Acetic acid, anisole, butanol, 2-butanol, isopropyl acetate, methyl acetate, butyl acetate, ter-butyl methyl ether, formic acid, heptane, cumene, tetrahydro furane, ethylacetate, dimethyl sulfoxide, 1-pentanol, ethanol, isobutyl ketone, propanol, methyl isobutyl ketone, propyl acetate.

Class IV solvents: Adequate toxicological data is not available for the class IV solvents. Hence, the manufacturer should justify the residual levels whenever they use this class of solvents in pharmaceutical products. *e.g.* 1, 1-diethoxy propane, 1, 1-dimethoxy propane, 2, 2-dimethoxy propane, methyl isopropyl ketone, petroleum ether, isooctane, isopropyl ether, methyl tetrahydro furan, Trichloro acetic acid.

Formulation related impurities: -

APIs are formulated with excipients into tablets, semi-solids, solutions, capsules, aerosols and Novel Drug Delivery Systems. During the formulation, excipients are added to API to render the product elegant. They can be sometimes heterogeneous mixtures. In such a case, compatibility problems will arises between API and excipients which may leads to formation of products with the affected therapeutic efficacy. Any undesirable reaction produced due to the impurities which is associated with excipients can provide a source for many potential reactions. The source of these potential reactions may be because of excess amount of water, which is present in API or use of hygroscopic materials.

Dosage form related impurities: - In liquid dosage form precipitation of main ingredient can occur due to various environmental factors like pH or leaching [(10)].

Method related impurities: - Formation of impurities depends on initial pH of the preparation and the condition of sterilization [(16)] *etc.,*

Environmental related impurities:-

Temperature: The classes of compounds which are thermo liable in nature, when subjected to extreme temperature leads to loss of potency.

E.g. During formulation of vitamins and antibiotics, extreme care should be exercised to prevent them from degradation.

Light/UV light: Photolytic reaction is one of the important factor by which the formulation degrades. Exposure of light is known to be deleterious on a number of pharmaceutical substances. For example, sunlight having about 8000 foot-candles can destruct nearly 34% of vitamin–B in 24hrs [(17)].

Humidity: Humidity is one of the important key factors in case of hygroscopic compounds. It is detrimental to both bulk powder and formulated solid dosage form [(5)].

IMPURITIES ON AGING:

Mutual interaction amongst ingredients: - Most often, vitamins are highly prone to instability on aging in different dosage forms. i.e., degradation of vitamins such as folic acid, thiamine and cyanocobalamines does not yield toxic impurities but lose their potency [(18)].

Hydrolysis: - A reaction which involved water used as a reactant causing precipitation. Examples of such reactions in pharmaceutical compounds are esters and amides. Many drugs are derivatives of carboxylic acids or contain functional groups based on the moiety which are prone to hydrolysis.

Oxidation: - Hydrocortisone, methotrexate, adinazolam, catecholamine, conjugated-dienes (vit A) heterocyclic aromatic rings, nitroso and nitrite derivatives are prone to oxidation. In pharmaceuticals, the most common form of oxidative decomposition is auto oxidation through a free radical chain process.

Photolysis: - Photolytic cleavage on aging includes examples of pharmaceutical drugs or pharmaceutical products that are prone to degradation on exposure to UV-light. During manufacturing process solid or solution, packaging or on storage, drug like nitropruside, ergometrine, nifedipine, phenothiazine and riboflavin are liable to photo oxidation [19-21].

Decarboxylation: - Some of the carboxylic acids such as *p*-amino salicylic acid will shows loss of carbon dioxide from carboxyl group when heat is applied. For example, photo reaction of enteric coated rufloxacin tablet with cellulose acetate phosphate (CAP) and sub-coating with calcium carbonate cause hydrolysis of CAP liberating acetic acid, which on reacting with calcium carbonate produced carbon dioxide, a by-product that blew off the cap from the bottle after cap was loosened [22].

Packaging material: - Formation of impurities also results from packaging materials *i.e.*, containers and closures [23]. For most drugs the reactive species for impurities consists of Water - hydrolysis of active pharmaceutical ingredient. Small electrophiles - Aldehydes and carboxylic acid derivatives. Metals- catalyse oxidation of drugs and their degradation pathway. Extractable or leachable- emerge from glass, rubber stoppers and plastic materials, in which oxides like NO_2, SiO_2, MgO are major components leached or extracted from glass.

ANALYTICAL METHOD DEVELOPMENT

Reliable and meaningful analytical data is needed to manufacture a new drug in various stages of development [24-26].

1. For the analytical method development sample set selection is required.
2. Screening of chromatographic conditions and phase, typically using the linear solvent strength model of gradient elution.
3. Optimization of the method to fine-time parameters related to ruggedness and robustness.

Assuring the safety of a new pharmaceutical product or drug substance demands that the new drug substance should meet the established standards for purity and safety as a chemical entity or when

admixed with animal feeds for toxicity studies or when formulated with or without pharmaceutical excipients for human use. Furthermore, it should exhibit excellent stability throughout its shelf life. These requirements mandate that the analytical method (s) employed for this purpose should be sufficiently sensitive to measure low levels of impurities. This has resulted in development of analytical techniques that are appropriate for measurement of trace/ultra-trace levels, i.e., sub-microgram quantities of a variety of chemical entities [24].

The role of reference standards

Reference standards serve as the basis of evaluation of both process and product performance and are the benchmarks for assessment of drug safety for patient consumption. These standards are needed not only for the active ingredients in dosage forms but also for impurities, degradation products, starting materials, process intermediates and excipients.

Analytical techniques:

- Spectroscopic methods
- Chromatography methods or Separation methods

Spectroscopic methods

The following spectroscopic measurement techniques have been used for characterizing impurities; most of these are very useful as detectors for chromatographic methods:

1. Ultraviolet (UV).
2. Infrared (IR).
3. Raman spectroscopy.
4. Mass spectrometry (MS).
5. Nuclear magnetic resonance (NMR).

Separation methods

The following methods can be used for separation of impurities and degradation products:

1. Capillary electrophoresis (CE).
2. Chiral separations.
3. Gas chromatography (GC).
4. High-pressure liquid chromatography (HPLC).
5. Supercritical fluid chromatography (SFC).
6. High performance thin-layer chromatography (HPTLC).

REGULATORY PERSPECTIVE

The International Conference on Harmonization (ICH) addresses the questions relating to impurities as follows:

1. Q1A(R) Stability testing of new drug substances and products.
2. Q3A(R) Impurities in drug substances.
3. Q3B Impurities in drug products.
4. Q3C Impurities in residual solvents.
5. Q6A Specifications: test procedures and acceptance criteria for new drug substances and new drug products.

Regulatory Requirements Ethical, economic, and competitive reasons, as well as those of safety and efficacy, support the need to monitor impurities in drug products. However, monitoring impurities and controlling of those impurities mean different things to different people or to the same people at different times, even those in the pharmaceutical sciences and industry. A number of requirements have an effect on monitoring impurities. For example, a country's pharmacopeia or the one accepted by that country often provides the primary guidance about how impurities are to be monitored and controlled. In a majority of countries these pharmacopoeias are run under the auspices of the government. If a product is considered a Pharmacopeial product, it must meet the all requirements. The United States Food and Drug Administration (USFDA) have endorsed the guidance which was prepared under the auspices of the ICH. The guidance, developed with the joint efforts of regulators and industry representatives from the European Union, the United States and Japan, has helped to ensure that the different regions have consistent requirements for the data that should be submitted to the various regulatory agencies. The guidelines not only aid the sponsors of New Drug Applications (NDA) or Abbreviated New Drug Applications (ANDA) with the type of information that should be submitted with their applications, but also assist the Food and Drug Administration reviewers and field investigators in their consistent interpretation and implementation of regulations [24,27-29].

Remedies:

1. Critical factors for controlling impurities in API:

a) During crystallization, the manufacturer of API should take care to produce finer crystals to prevent entrapment of minute amounts of chemicals from mother liquor, which causes the degradation of drug.

b) Washing the wet cake or powder should be thorough to remove unwanted chemicals including residual solvents.

2. Packaging- Light sensitive pharmaceuticals have to pack in light protective packaging.

3. Production method selection is depending upon the stability studies. For Diclofenac sodium injections, the aseptic filtration process has been recently recommended as the alternative to the autoclave method that produces 16 impurities.

4. Pharmacopoeias should take measures to incorporate impurity limits for drug products made of raw materials. ICH should lay stringent regulations to incorporate limits for the impurities present in both drug substance and drug products. Diclofenac sodium is an example where an impurity limit is not mentioned in the case of injections.

CONCLUSION

This review provides a perspective on impurities in drug substance and drug product. Impurity profile of pharmaceuticals is receiving an increasing importance and drug safety receives more attention from the public. Also provides the valuable information about the impurities, their types and classification, various analytical techniques for the determination, qualification of impurities and critical factors to be considered while preparation of the bulk drugs. Now a day, it is mandatory requirement in various pharmacopoeias to know the impurities present in API's. Isolation and characterization of impurities is required for acquiring and evaluating data that establishes biological safety which reveals the need and scope of impurity profiling of drugs in pharmaceutical research.

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