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A Review on Impurities Profiling in Pharmaceutical Analysis

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ABSTRACT

In the pharmaceutical industry an impurity is considered, defined the any other organic material besides the drug substance or pharmaceutical ingredients. The impurity may be formed during the formulation or upon aging of two APIs in medicines. The highly sophisticated instrumentation, such as mass spectra meters attached to the gas chromatography or HPLC in various matrices. GC is the most useful technique for identification of residual solvent. The advent of hyphenated technique has revolution any impurity profiling, by not only separation but structural identification of impurities as well among all techniques. The most exploited techniques for impurities profiling of drug are LC-MS-MS, LC-NMR, LC-NMR-MS, GC-MS AND LC-MS.

Keywords Impurity, Chromatography, Hyphenated technique, Regulatory bodies

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INTRODUCTION

Impurity is defined as any substance coexisting with the original drug, such as starting material or intermediates or that is formed, due to any side reactions. Impurities present in excess of 0.1% should be identified and quantified by selective methods. The suggested structures of the impurities can be synthesized and will provide the final evidence for their structures, previously determined by spectroscopic methods. Therefore, it is essential to know the structure of these impurities in the bulk drug in order to alter the reaction condition and to reduce the quantity of impurity to an acceptable level [1]. Impurity profile is description of the identified and unidentified impurities present in a typical batch of API produced by a specific controlled production process 8-10. It is one of the most important fields of activity in contemporary industrial pharmaceutical analysis. The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances, products and residual solvents [3]

Common Terms of Impurities [12]

Following terms are used by various regulatory bodies and ICH to describe the impurities:

1. Intermediate
2. Penultimate intermediate
3. By-products
4. Transformation products
5. Interaction products
6. Related products
7. Degradation products

Intermediate: The compounds produced during synthesis of the desired material or as a part of the route of synthesis.

Penultimate Intermediate: It is the last compound in the synthesis chain prior to the production of the final desired compound.

By-products: The compound produced in the reaction other than the required intermediates. They can occur through a variety of side reactions, such as overreaction, incomplete reaction, demonization and rearrangement, unwanted reactions between starting materials or intermediates with chemical reagents or catalysts.

Transformation Products: They are related to theorize and none theorized products that can occur in are action. They are similar to by-products except that more is known about these reaction products.

Interaction Products: These products formed either intentionally or unintentionally interaction between various chemicals involved.

Related Products: These are chemically similar to drug substance and may even possess biological activity.

Degradation Products: They are formed by the decomposition of active ingredient or other material of interest by the effect of external factors like heat, light and moisture.

Formulation related impurities (impurities in drug products) [4, 6]

Number of impurities in a drug product can arise out of inert ingredients used to formulate a drug substance. In the process of formulation, a drug substance is subjected to a variety of conditions that can lead to its degradation or other deleterious reaction. Solutions and suspensions are potentially prone to degradation due to hydrolysis. The water used in the formulation cannot only contribute its own impurities; it can also provide a ripe situation for hydrolysis and catalysis. Similar reactions are possible in other solvents that may be used. The formulation related impurities can be classified as follows:

Method related

Environmental related

The primary environmental factors that can reduce stability include the following:

I. Exposures to adverse temperatures

II. Light-especially UV light

III Humidity

IV Dosage form related

Factors Affecting on Formulation Related Impurities [1, 5, 6]

a. Environment related

I. Exposed to adverse temperature: Substance which are labile to heat or in tropical temperature lead to degradation of active constitute and formation of impurity occurs. E.g. Vitamins are heat sensitive and its degradation lead to loss in potency.

II. Exposed to light: Photosensitive material when exposed to light / UV light undergo degradation which forms impurity.

III. Humidity: It can be detrimental to bulk powder and formulation containing solid dosage form.

b. Formation of impurities on ageing: Mutual interaction: Interaction between ingredients involved in formulation leads to mutual interaction which causes impurity formation.

C. Functional Group Related Impurities

- **Ester hydrolysis:** Drugs like aspirin, benzocaine, cefoxime, cocaine, ethyl paraben undergo ester hydrolysis.
- **Hydrolysis:** Commonly drugs like benzyl penicillin, barbital, and chloramphenicol undergo hydrolysis.
- **Oxidative degradation:** Drugs like hydrocortisone, methotrexate, heterocyclic aromatic ring, nitroso / nitrile derivative.
- **Photolytic cleavage:** Product exposed to light while manufacturing or storage in hospital pending use or by consumer pending use.
- **Decarboxylation:** Some dissolved carboxylic acid such as p-amino salicylic acid loose CO2 when heated.

Analytical method development [3, 4]

New drug development requires meaningful and reliable analytical data to be produced at various stages of the development:-

a) Sample set selection for analytical method development
b) Screening of Chromatographic conditions and Phases, typically using the linear solvent-strength model of gradient elution
c) Optimization of the method to fine-tune parameters related to ruggedness and robustness.

USP S/N= 2 x height x scale to UV/peak to peak noise

Method for determining or establishing exposure limit:

Residual solvent class

CLASS A: solvent to be avoided, Known human carcinogen

CLASS B: solvent to be limited, neurotoxin, teratogenicity

CLASS C: Low toxic potential

Limit of class [3, 4]

Option 1: Calculated assuming 10 gm orally

Concentration (ppm) = (1000ug/mg) x PDE)/dose

Option 2: By adding the amount of residual solvent

According to ICH guidelines on impurities in new dry products, identification of impurities below 0.1% level is not considered to be necessary, unless potential impurities are expected to be unusually potent or toxic. According to ICH, the maximum daily dose qualification threshold to be considered is as follows as shown in table no.2-5;< 2g/day 0.1 % or 1 mg per day intake (whichever is lower) >2g/day 0.05%

The various regulatory guidelines regarding impurities are as follows:

1. ICH guidelines “stability testing of new drug substances and products"- Q1A
2. ICH guidelines “Impurities in New Drug Substances”- Q3A
3. ICH guidelines “Impurities in New Drug Products”- Q3B
4. ICH guidelines “Impurities: Guidelines for residual solvents”- Q3C
5. US-FDA guidelines “NDAs -Impurities in New Drug Substances”
6. US-FDA guidelines “ANDAs – Impurities in New Drug Substances”
7. Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia.

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Characterization methods [8, 12]

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.

NMR

The ability of NMR to provide information regarding the specific bonding structure and stereochemistry of molecules of pharmaceutical interest has made it a powerful analytical instrument for structural elucidation.

MS

It has an increasingly significant impact on the pharmaceutical development process over the past several decades. Advances in the design and efficiency of the interfaces, that directly connect separation techniques with Mass Spectrometers have afforded new opportunities for monitoring, characterizing, and quantification of drug related substances in active pharmaceutical ingredients and pharmaceutical formulation.

Hyphenated Methods [13-14]

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

- LC-MS

A common goal for investigation of both process and product degradation-related impurities is to determine which of the many potential impurities are, in fact, produced in the manufacturing process and which occur under a given set of storage conditions.

Applications

Numerous applications have been sought in the areas of drug designing and in monitoring quality, stability, and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced by recombinant methods. The applications include alkaloids, amines, amino acids, analgesics, antibacterial, anticonvulsants, antidepressant, tranquilizers, antineoplastic agents, local anesthetics, macromolecules, steroids, miscellaneous.

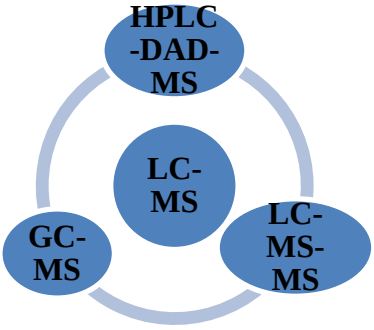

Figure 1: Hyphenated techniques

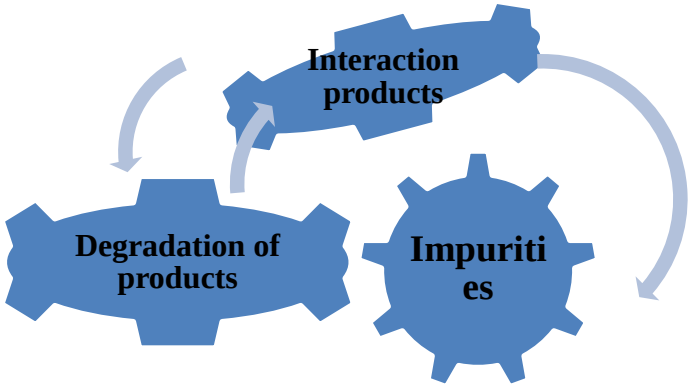

Figure 2: Common terms of impurities

Table 1: Description of impurity types and their sources

Sr. no.	Impurity type	Impurity source
1	Degradation drug product	Organic
2	Process-related drug product	Inorganic or organic
3	Process-related drug substance	Organic, By products etc.
4	Degradation drug substance or drug product	Organic, Degradation products etc.

Table 2: Various impurities reported in API's

Sr. no.	Method/Technique	Drugs	Impurities
1	HPLC	Morphine	6-monoacetylmorphine
2	UV spectroscopy	AmphotericinB	Tetraenes
3	GC	Cloxacillin	N,N dimethyl aniline
4	UV spectroscopy	Dextrose	5 hydroxyl methyl furfural
5	TLC	Ethambutol	2 amino butanol
6	TLC	Framycetin sulphate	Neamine
7	UV spectroscopy	Atropine sulphate	Apo atropine
8	GC	Fluorescene sodium	Dimethyl formamide

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 and more attention from literature. This article provides the valuable information about the impurities types and its classification, various techniques of isolation and characterization, 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 APIs and finished drug products. Thus impurity profiling can act as a Quality Control tool. It can provide crucial data regarding the toxicity, safety, various limits of detection and limits of quantization of several organic and inorganic impurities, usually accompany with APIs and finished products. There is strong requirement to have unique specifications/standards with regard to impurities.

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