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BESIC REVIEW OF IMPURITY PROFILE

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ABSTRACT

Impurity profiling helps in detection, identification and quantification of various types of impurities as well as residual solvents in bulk drugs and in pharmaceutical formulations. It is a best way to characterize quality and stability of bulk drugs and pharmaceutical formulations. ICH instructs workable guidelines to drug developers and regional agencies on how to evaluate and control impurities in drug substances and drug products. Impurity profiling is the process of acquiring and evaluating data that establishes biological safety of an individual impurity. Identification of impurities is done by variety of Chromatographic and Spectroscopic techniques, either alone or in combination with other techniques. There are different methods for detecting and characterizing impurities with TLC, HPLC, HPTLC, AAS *etc*. As per International Conference on Harmonization guidelines, the Impurity may be defined as any component of new drug product that is not the drug substance or an excipient in drug product.

Keywords: Impurity Profiling, Guidelines, ICH, Organic Impurities, Inorganic Impurities Residual Solvents.

INTRODUCTION

Identification and quantification of impurities is a crucial task in pharmaceutical process development for quality and safety [1]. Related components are the impurities in pharmaceuticals which are unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during stability testing, or develop during formulation or upon aging of both API and formulated APIs to medicines. The presence of these unwanted chemicals even in small amounts may influence the efficacy and safety of the pharmaceutical products. Various analytical methodologies were employed for the determination of related components in pharmaceuticals. There is a great need for development of new analytical methods for quality evaluation of new emerging drugs [2].
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. Impurity can be of three types: Impurities closely related to the product and coming from the chemical or from the biosynthetic route itself, Impurities formed due to spontaneous decomposition of the drug during the storage or on exposure to extreme conditions, or the precursors which may be present in the final product as impurities. 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.

Identification of impurities is done by variety of Chromatographic and Spectroscopic techniques, either alone or in combination with other techniques. There are different methods for detecting and characterizing impurities with TLC, HPLC, HPTLC, AAS *etc* [3]. Conventional Liquid Chromatography, particularly, HPLC has been exploited widely in field of impurity profiling; the wide range of detectors, and stationary phases along with its sensitivity and cost effective separation have attributed to its varied applications. Among the various Planar Chromatographic Methods; TLC is the most commonly used separation technique, for isolation of impurities; due to its ease of operation and low cost compared to HPLC. An advancement of thin layer chromatography HPTLC, is a well-known technique for the impurity isolation [4].

SOURCES OF IMPURITIES

The type and amount of impurity present in the chemicals or pharmaceutical substances depends upon

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following factors [5]

A. Raw materials used in Manufacture.
B. Method or process employed in manufacture.
C. Reagents/solvents/Reaction vessels
D. Atmospheric contaminants
E. Particulate contamination
F. Cross contamination
G. Microbial contamination
H. Packing errors
I. Due to impact of heat, light, oxidants on drug Product
J. Change in PH.
K. Presence of trace metals which may catalyse and accelerate the reaction.

CLASSIFICATIONS OF IMPURITIES

Impurities have been named differently or classified as per the ICH guidelines as follows [6-7]

A] Common names

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

B] United State Pharmacopeia

The United States Pharmacopoeia (USP) classifies impurities in various sections:

1. Impurities in Official Articles
2. Ordinary Impurities
3. Organic Volatile Impurities

C] ICH Terminology

According to ICH guidelines, impurities in the drug substance produced by chemical synthesis can broadly be classified into following three categories

1. Organic Impurities (Process and Drug related)
2. Inorganic Impurities
3. Residual Solvents

Organic Impurities

The actual and potential impurities most likely to arise during the synthesis, purification, and storage of the drug substance should be summarized ,based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the drug substance [8,9].

The laboratory studies conducted to detect impurities in the drug substance, which include test results of materials manufactured during the development process and batches from the commercial processes. The impurity profile of the drug lots, intended for marketing should be compared with those used in development [10].

The spectroscopic studies (NMR, IR, MS etc.) conducted to characterize the structure of actual impurities present in the drug substance above an apparent level of 0.1% (e.g., calculated using the response factor of the drug substance) should be described. All recurring impurities above an apparent level of 0.1% in batches manufactured by the proposed commercial process should be identified of these studies.

Inorganic Impurities

Inorganic impurities are normally detected and quantified using Pharmacopeial or other appropriate standards. Carryover of catalysts to the drug substance should be evaluated during development.

Residual Solvents

The control of residues of solvents used in the manufacturing process for the drug substance should be discussed. Acceptance criteria should be based on Pharmacopeial standards, or ICH guidelines or known safety data, depends on the dose, duration of treatment, and route of administration [11,12].

As per ICH guidelines, organic and inorganic solvents used in manufacturing of drug substances classified into four types [13]

Class-I (to be avoided): Class-I solvents and their permissible concentration limits given in Table-4. Because of their unacceptable toxicity they are not used, if their use is unavoidable, it should be restricted.

Class-II: (should be limited): usage should be limited because of their inherent toxicity. Class- II solvents with their daily permissible exposure are listed in Table-5.

Class-III: They have less toxic potential and possess lower risk when compared to class I or II and permitted daily exposure (PDE) of 50 mg or more. Some solvents are: acetic acid, anisole, butyl acetate, butanol, methyl acetate, isopropyl acetate, pentene, dimethyl sulfoxide, ethyl acetate, ethanol, formic acid, isobutyl ketone, 1-pentanol, heptane, methyl ethyl ketone, 2-propanol, methyl isobutyl ketone.

Class-IV: Adequate toxicological data is not available. Class- IV solvents are 1, 1-dimethoxy propane, 1,1-diethoxy propane, 2,2-dimethoxy propane, isooctane, methyl isopropyl ketone, isopropyl ether ,petroleum ether, methyl tetra hydro furan, trichloro acetic acid.

ACCEPTANCE CRITERIA FOR IMPURITIES

For newly synthesized drug substances, the specification should include acceptance criteria for impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product.

A rationale for the inclusion or exclusion of impurities in the specification should include a discussion of the impurity profiles observed in batches under consideration, together with a consideration of the impurity profile of material manufactured by the proposed commercial process. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation or detection limit of the analytical methods should commensurate with the level at which the impurities need to be controlled. Appropriate qualitative analytical descriptive label included in the specification of unidentified impurities. A general acceptance criterion of not more than 0.1 % for any unspecified impurity should be included.

Acceptance criteria should be set, based on data generated on actual batches of the drug substance, allowing sufficient latitude to deal with normal manufacturing and analytical variation, and the stability characteristics of the drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels could indicate that the manufacturing process of the drug substance is not adequately controlled and validated.

The acceptance criteria should include limits for organic impurities; each specified identified impurity, each specified unidentified impurity at or above 0.1%, and any unspecified impurity, with a limit of not more than 0.1%, total impurities, residual solvents and inorganic impurities.

General Scheme for Drug Impurity Profiling

The procedure of impurity profiling, begins with the detection of the impurities using the thin-layer chromatogram, high-performance liquid chromatogram or gas chromatogram. Procurement of standard impurity samples from the synthetic organic chemists which include, last intermediate of the synthesis, products of predictable side reaction, degradation products if any etc

In the case of unsuccessful identification with standard samples the most reasonable way to determine the structure of impurity starts with the investigation of the UV spectra, easily obtainable with the aid of the diode-array detector in the case of HPLC and the quantification with the help of densitometer. In exceptional cases, with full knowledge of the synthesis of drug martial, the structure of the impurity can be generated on the basis of NMR spectral data.

If the information obtained from the UV spectrum is not sufficient, the next step in the procedure of impurity profiling is to take the mass spectrum of the impurity. The major disadvantage of this method is the volatility and thermal stability. problems of the impurities. The use of derivatization reactions widely used in GC/MS analysis is problematic because the side-products of the derivatization reaction can be confused with the impurities.

The next step in the impurity profiling is the synthesis of the material (*impurity standard*) with the proposed structure. The retention and spectral matching of the synthesized material with the impurity in question is carried out as outlined above.

The possibilities of spectroscopic techniques in drug impurity profiling without chromatographic separation are also worth mentioning. Spectra obtained by using high-resolution, highly sensitive NMR spectrometers and mass spectrometers with APCI /ESI facilities are suitable to provide a fingerprint picture regarding the purity of the sample.

GUIDELINES FOR IMPURITY PROFILE

It is now getting important critical attention from regulatory authorities. The different pharmacopoeias, such as the British Pharmacopoeia (BP), the United States Pharmacopoeia (USP) and the Indian Pharmacopoeia (IP) are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations. Also, the International Conference on Harmonization (ICH) has published certain guidelines on impurities in drug substances, products and residual solvents. There is a significant demand for the impurity reference standards and the API reference standards for both regulatory authorities and pharmaceutical companies. According to ICH guidelines on impurities in new drug 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. Limits for impurities in drug substances are shown in table1 while limits for impurities in degraded products of drugs are shown in table 2 [14].

Specifications should be set for identified and unidentified impurities expected to be present in the drug substances and drug products over the period of intended use and under recommended storage conditions. These impurities are known as specified impurities and they should be individually listed in the specifications. Stability studies, chemical development studies and routine batch analyses can be used to establish impurities likely to occur in the commercial new drug substances and new drug products. A general specification limit of not more than 0.1% for any unspecified impurity should also be included. A rationale for why impurities were included or excluded from the specifications for the drug substance and drug products should be provided. Limits for impurities should be set no higher than the level which can be justified by safety data and unless safety data indicate otherwise, no lower than the level achievable by the manufacturing process and the analytical capability.

APPLICATIONS OF IMPURITY PROFILING

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 etc.

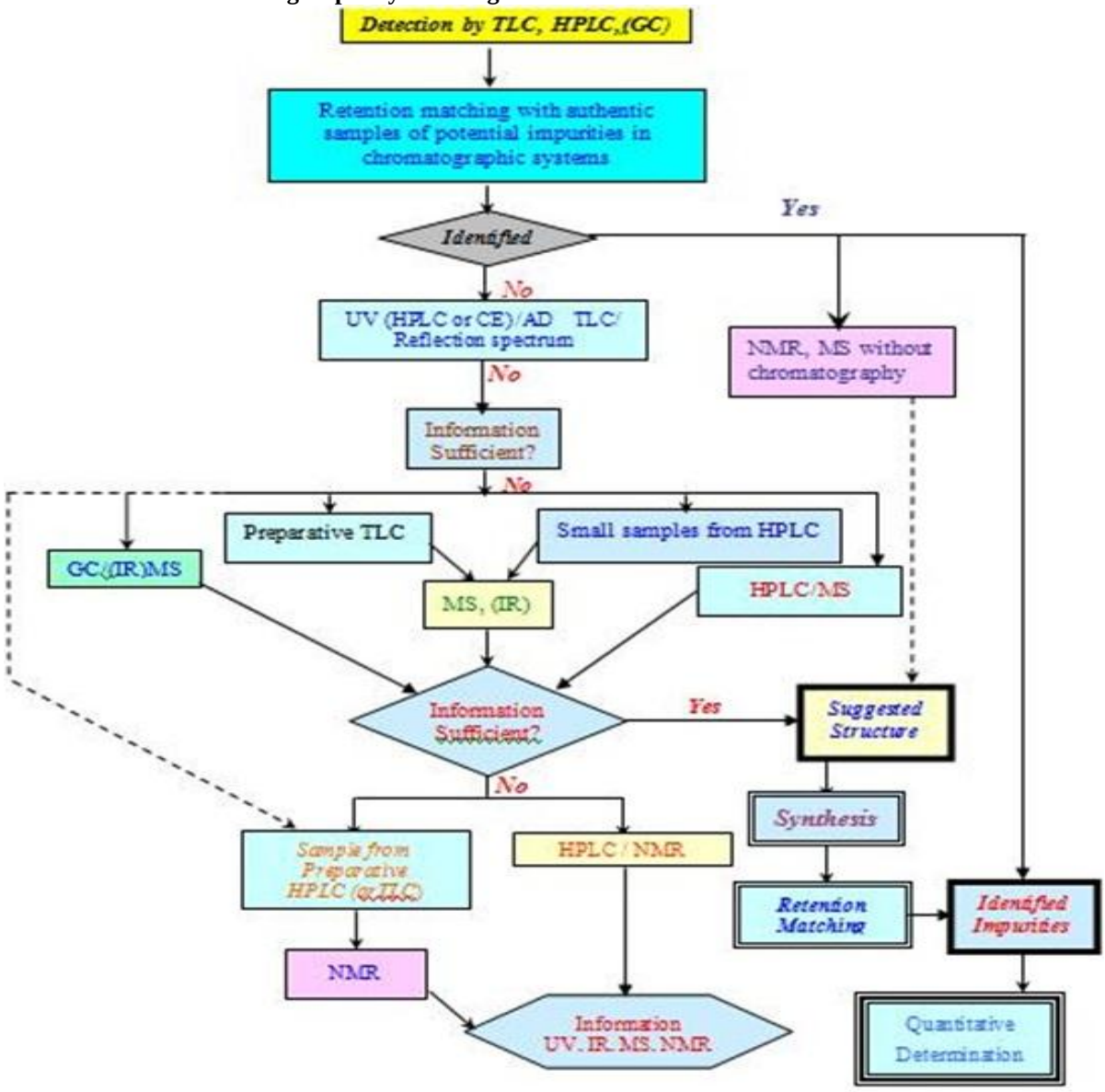
Table 1. Limits for impurities in drug substance

Drug Substance Impurity	Limits
Each identified specified impurity	Not more than 0.5 per cent
Each unidentified impurity	Not more than 0.3 per cent
Total impurities	Not more than 1.0 per cent

Table 2. Limits for impurities in degradated products of drugs

Degradation Product Impurity	Limits
Each identified degraded product	Not more than 1.0 per cent
Each unidentified degraded product	Not more than 0.5 per cent
Total degraded products	Not more than 2.0 per cent

Figure 1. General Scheme for Drug Impurity Profiling



CONCLUSION

Impurity profiling of a substance under investigation gives maximum possible account of impurities present in it. The establishment of guidelines for impurity levels in drug substances and products provides the quality criteria for manufacturers. The key aspect is that the impurity profiling of a new chemical entity must be shown to be qualified. With a qualification threshold of 0.1%, or lower for high dose compounds, the pharmaceutical analyst must give careful thought to their analytical technology. 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. The importance of qualifying impurity profiles are relevant to the development scientists to ensure consideration is given to the impurities present in the batches being used in safety studies starting from limit tests for impurities, this field of impurity identification and quantitation has progressed. With newer techniques like UV spectroscopy with diode array detection, HPLC, GCIR, NMR, CE-MECC. This review article is an attempt to understand the concept of impurity profile and various aspects and techniques related to it.

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