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RECENT TRENDS IN IMPURITY PROFILING METHODS USING ANALYTICAL TECHNIQUES

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ABSTRACT

Any component of the new drug substance that is not the chemical entity defined as the new drug substance or excipient in the drug product. Now a days, Impurity profile has become mandatory according to various regulatory authorities. This review describes the recent trends in analytical perspectives of Impurity Profiling. In this review article mainly focuses an various method available to identify & characterize impurities in pharmaceutical dosage form. The highlights the different types of impurities & various method for isolation, separation & characterization of impurities. There are different methods for detecting & characterization impurities with TLC,HPLC,HPTLC,AAS. etc.

KEYWORDS: Impurity profiling, Isolation, Identification.

INTRODUCTION

The impurity profile is a description of identified and characterize impurities in pharmaceutical dosage forms. The impurity may be developed either during formulation or in the final product upon ageing or contact with packaging of the various impurities that can be found in drug product.

Impurity profiling is a general term including structure elucidation/identifification as well as determination of the impurities of a chemical substance. The significance of this process in pharmaceutical research and development has been emphasized multiple times[1-3] with TLC/HPTLC and other planar chromatographic techniques always being mentioned as a widely used and extremely valuable analytical tool in this field. The importance of drug

impurity profiling is that it affords data which can directly contribute to the safety of drug therapy by minimizing the impurity-related adverse effects of drug materials and the preparations made thereof. In recent years the importance of assay methods for characterising the quality of bulk drug materials has decreased considerably.[4-6] At the same time the importance of impurity profiling is continuously increasing.

Impurity profiling is of most importance in all phases of synthetic drug research and production from the gram scale preparation of new compounds for pharmacological screening up to the scaling up procedure and finally the production of bulk drug.

The latter aspect should be emphasised, since even minor changes in the production technology, source of starting materials, conditions of purification and storage can greatly influence the impurity profile. Its importance in the research and production of pharmaceutical formulations is also immense. The pharmaceutical technologist should have a clear picture of the impurity profile of the bulk-drug material used for the development of formulations in order to be able to differentiate between synthesis-related impurities and degradation products. In this way, it is possible to develop a stability-indicating analytical method necessary in the course of the development of a drug formulation.

IMPORTANCE

Differentiate between synthesis related impurities & degradation products.

1. For pharmacological screening up to the scaling up procedure & finally the production of bulk drugs.
2. All phases of synthetic drug research & production from the gram scale preparation of new compounds.

CLASSIFICATION OF IMPURITIES

Impurities can be classified are as follows;

A. Organic Impurities
B. Inorganic Impurities
C. Residual Solvent

A. Organic Impurities

In this impurities can arise during the manufacturing process or storage of the new drug substance. They can be identified, volatile or non-volatile & include;

- Starting Materials
- By Products
- Intermediates
- Degradation products
- Reagents. ligand & catalyst

B. Inorganic Impurities

They can result from the manufacturing process. They normally known & identified & include;

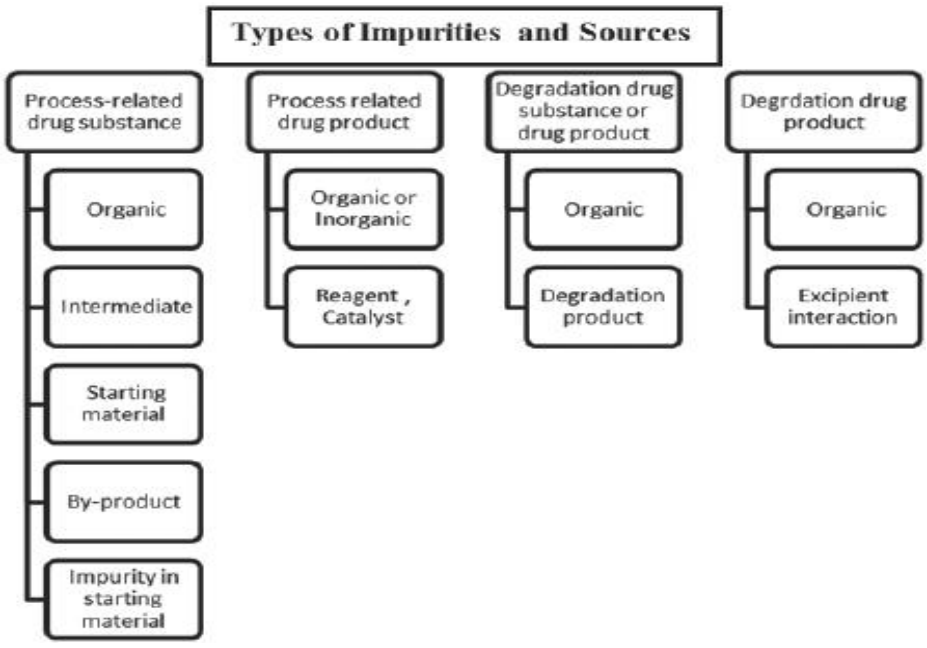
- Reagents. ligand & catalyst
- Heavy metals or other residual metals
-Inorganic salts
-Other material (e.g filter aids, charcoal)

C. Residual Solvents

Residual solvents is defined as Organic volatile chemicals that are used or produced in the manufacturing of drug substance.

SOURCES OF IMPURITIES

Impurities may also arise from physical contamination & improper storage conditions.



ICH Guidelines for Impurities

1. Q1A Stability testing of new drug substances & products.
2. Q3A Impurities in drug substance.
3. Q3B Impurities in drug products.
4. Q3C Impurities in residual substance.
5. Q6A Acceptance criteria for new drug substance

ANALYTICAL METHODS USED FOR IMPURITY PROFILING

Impurity profiling is the common name of a group of analytical activities, the aim of which is the detection.

A. Spectroscopic Methods

a) - Ultraviolet
b) - Infrared
c) - Nuclear Magnetic Resonance
d) - Mass Spectrometry

B. Separation Methods

a) -TLC
b) -GC
c) -HPLC
d) -CF
e) -SFC

C. Hyphenated Methods

a) -GC-MS
b) -LC-MS
c) -LC-NMR

A) Spectroscopic Methods

a) Ultraviolet

UV is a form of electromagnetic radiations. It is study of absorption of UV radiations which ranges from 200-400nm. This Absorption is characteristic & depends on the nature of electron present.

Terms used in UV spectroscopy

Chromophore: The nucleus or any covalently bonded group responsible for the absorption of light radiation.

Auxochrome: It is also known as colour enhancing group. These are coordinately saturated or unsaturated group which themselves do not absorb radiations, but when present along which a Chromophore enhances the absorbing properties of Chromophore.

b) Infrared

Infrared radiation does not have enough energy to introduce electronic transitions as seen with UV. Infrared spectrum determine the functional group & it is important record which gives sufficient information about structure.

c) Nuclear Magnetic Resonance

It is a physical phenomenon in which in a strong constant magnetic field are pertubed by a weak oscillating magnetic field.

It is a technique that exploits the magnetic properties of nuclei.

d) MS

In this technique molecules are bombarded which a beam of energetic electrons.

The molecules are ionized & broken up into many fragments, some of which are the ions. It is most accurate method for determining the molecular mass of compound & its elemental composition.

B) Separation Method

a) Thin Layer Chromatographic

TLC plays an essential role in the early stage of drug development when knowledge about the impurities & degradants in drug substance & drug product is limited. TLC is widely use method in pharmaceutical analysis both in its classical semi quantitative form. A simple TLC used for monitoring fermentation process.

b) Gas Chromatography

The father of GC is Nobel Prize Winner John Porter Martin, who also developed the first liquid Gas Chromatography (1950). It is very useful for isolation & characterisation of volatile & semi-volatile organic compound in complex mixtures.

GC consist of GSC (Gas Solid Chromatography) & GLC (Gas Liquid Chromatography).

c) High Performance Liquid Chromatography

In many cases use of traditional RP-HPLC condition & UV detection mostly employed for separation. RP-HPLC has nonpolar stationary phase & polar mobile phase.

d) Capillary Electrophoresis

It is separation technique based on the differential transportation velocities of charged species in electric field through conductive medium. Primary candidates for Capillary Electrophoresis separation are ions.

e) Supercritical Fluid Chromatography

It is used an analytical scale. It is combination of HPLC & GC. It is important for the chiral separation & analysis of high-molecular. It can be used with universal flame ionization detector. Principle is based on super critical fluid. It is a material that can be either liquid or gas used in state above critical temperature or critical pressure where gases & liquid can coexist.

C) Hyphenated Methods

a) GC-MS

It is advanced analytical instrumental technique that combine physical separation capabilities of GC with the mass analysis capabilities of mass spectrophotometer.

b) LC-MS

It is combination of liquid chromatography & mass spectrometry. It is combines physical separation capabilities of LC with the mass analysis capabilities of mass spectrometry. LC-MS is a powerful technique used for many application which has very high sensitivity & specificity. LC-MS are removing detector from the column of LC & fitting the column to interface of MS.

c) LC-NMR

It is innovative technique that connects NMR with HPLC.

For. e.g LC-NMR has been applied for the analysis of medicinal metabolites.

LC-NMR is successful for impurities identification in vestipitant.

Among all hyphenated technique the most exploited technique for impurity profiling of drugs are GC-MS, LC-MS, LC-MS-MS & LC-NMR.

CONCLUSION

In conclusion, impurity profiling helps in conforming guidelines by regulatory authorities regarding impurity level in a drug. Impurity profiling is beneficial in deciding safety parameters for drugs. In these review highlights the importance of impurity profiling & use of recent technique for the same purpose. This article provides the descriptive information about the impurity type & its classification various technique of isolation & characterization analytical technique for the determination, qualification of impurities & critical factors to be considered while preparation of the bulk drugs. Isolation & Characterization of impurities is required for evaluating data that establishes biological safety.

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