

RECENT APPROACHES FOR IMPURITY PROFILING: A REVIEW

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Abstract: Now days it becomes major challenge to find out impurities and remove them which is present in our preparations. So, Impurity profile has become necessary according to various regulatory authorities i.e. International Conference on Harmonization (ICH) as well as the United States Food and Drug administration (FDA) are contributing on the identification of impurities in Active Pharmaceutical Ingredients (APIs) and maintaining their purity for better results. Impurity profiling is the common name of a group of analytical activities such as description, quantitation & characterization of the identified and unidentified impurities present in new drug substances. So generally it includes stages of detection of various impurities, identification of different impurities and quantitative determination of organic, inorganic impurities, as well as residual solvents in bulk drugs and pharmaceutical formulations. Since this is the best way to characterize the Quality, Purity, Stability and stability of bulk drugs and pharmaceutical formulations and this becomes the core activity in modern drug analysis.

Keywords: Impurity profiling; Classification; Sources of impurities; Analytical method development and validation for impurity profile; Current marketed formulation which contain impurity.

INTRODUCTION:

Impurity can be defined as the substance coexisting with the original drug i.e. intermediates as well as starting material or that is formed, due to any side reactions. The impurity may be developed either during product formulation developments. The bulk manufacturing, processing industry forms base of all pharmaceutical industries as it is the source of active pharmaceutical ingredients (APIs) of specific quality. The quality as well as purity must be maintained for pharmaceutical product that enters in the market. Now days the major challenge is occurring to produce quality that involves safety as well as purity of substances products in pharmaceutical industry and it depends upon the on many factors such as raw materials, manufacturing method and the type of processes of APIs. In pharmaceuticals, Impurities are nothing but unwanted chemicals that remain with the APIs. The presence of these unwanted chemicals even in small amounts may influence the quality, efficacy and safety of the pharmaceutical products. It is necessary to find out impurities present in API's as per various regulatory requirements.

The various regulatory guidelines regarding impurities are given as follows:

1. US-FDA gives guidelines in "NDAs and ANDAs -Impurities in New Drug Substances".
2. Australian regulatory guideline for medicines, Therapeutic Governance Authority (TGA), Australia.
3. ICH guidelines i.e. stability testing of new drug substances and products- Q1A, Impurities in New Drug Substances- Q3A, Impurities in New Drug Products- Q3B and Impurities: Guidelines for residual solvents- Q3C etc.

IMPURITY PROFILING:

It gives an account of impurities present in it. Impurity profile of a substance under examinations gives different types of impurities present in it. It also estimates the actual amount of different kinds of impurities present in pharmaceutical products As per ICH Guidelines.

CLASSIFICATION:

The ICH guideline classifies impurities in three sections- organic, inorganic and residual solvents given in below,

(1) Organic impurities:

To detect organic impurities present in the drug substance, the laboratory studies are conducted, which include test results of materials during production and manufacturing in development process. The impurity profile of the drug which will use for marketing should be compared with those used in development.

(2) Inorganic impurities:

Like organic impurities, Inorganic impurities are also detected from the manufacturing processes which are used in bulk drugs formulation. They are normally known and identified like heavy metal impurities, residual solvent impurities, filter aids, charcoal etc.

(3) Residual Solvents:

Residual solvents are inorganic or organic liquids used as vehicles for the preparation of suspensions or solutions in the manufacturing of new drug products. The control of residual solvents used in the manufacturing process for the drug substance is necessary.^[3]

SOURCES OF IMPURITIES IN DRUG PRODUCTS:

The various types of impurities that comes from following sources which is present in pharmaceutical products:

1. Synthesis-related impurities:

An impurity in a drug substance mainly comes from raw materials, solvents, intermediates. These impurities arise during synthesis of pharmaceutical products. During synthesis the Solvents used may contain many types of impurities; furthermore they can react with many chemicals to produce other impurities during synthesis of substances. These impurities are hard to detect and monitor.

2. Formulation-related impurities:

These impurities are classified into followings ways:

a. Method Related:

Method related impurities are formed during diclofenac sodium ampoule production in parenteral dosage form. The impurity is - indoline-2-one. So, by using autoclave it is sterilized.

b. Environmental related:

In liquid formulation, Vitamin products expose to UV light i.e. Exposures to adverse temperatures. Some products like Ergometrine injection when kept 42 hrs. In direct sunlight shows complete degradation. Like this in Humidity, hygroscopic products are involved.

c. Dosage form related:

As compare to other dosage forms, microbiological contamination and degradation is easily occurs into liquid dosage forms. For this water content, mutual interaction of ingredient and the primary container are responsible one.

3. Degradation related impurities:

These impurities are produced from API degradation during interactions on storage e.g. Nicotinamide present in a formulation containing 4 vitamins namely riboflavin, pyridoxine, nicotinamide and thiamine etc. causes degradation of thiamine. For that stability studies and kinetic studies are conducted to detect, analyse them.^[9] The stability studies are performed under different conditions of temperature, humidity and light.^[10]

ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR IMPURITY PROFILE:

The impurities can be identified, minimized by various methods like reference standard method, spectroscopic method, separation method, characterization method and isolation method.^[14-22]

1. Reference Standard Method:

It is the benchmarks for assessment of drug safety for patient consumption. These methods provide clarity to the overall life cycle as well as qualification in the development and control of new drugs. A reference standard includes evaluation of process and product performance. These standards are required for starting materials, APIs, excipients, impurities, degradation products and process intermediates in pharmaceutical dosage forms.

2. Spectroscopic Method:

The UV, IR, MS, NMR and Raman spectroscopic methods are used for analysing various types of impurities.

a) UV-Spectrophotometry:

UV-Spectroscopy is a technique mainly used to determine purity and concentration of substance. According to Beer-Lambert law, the absorbance of a solution is directly proportional to the concentration of the substance in the solution and the path length. Therefore for a fixed wavelength and path length the UV-Spectroscopy can be used to determine the concentration as well as purity of the absorber in a solution. ^[5]

b) Infrared Spectroscopy:

Infrared spectroscopy is the type of absorption spectroscopy that deals with the infrared region of the electromagnetic spectrum. It is used to identify compounds and investigate sample compositions by using infrared spectrophotometer instrument. The IR electromagnetic spectrum is usually divided into three regions i.e. near, mid and far- infrared used to study the fundamental vibrations and associated rotational-vibrational structure present in samples. ^[6]

3. Separation Method:

Capillary Electrophoresis (CE), Gas Chromatography (GC), Supercritical Fluid Chromatography (SFC), Thin Layer Chromatography (TLC), High Performance Thin Layer Chromatography (HPTLC), High Performance Liquid Chromatography (HPLC) has mainly used for impurity separation as well as degradation products.

a) Gas Chromatography:

Gas chromatography (GC) is mainly used to identifying a compound, separation, test the purity and analyse compounds in analytical chemistry with obtaining pure compounds. In that chromatography the substance can be vaporized without decomposition in to the mixture of compounds. ^[23]

b) Thin Layer Chromatography (TLC):

Thin layer chromatography is performed on a sheet of various types of materials like plastic foil, aluminium foil as well as on glass materials. This is coated with silica gel or aluminium oxide in a thin layer. That layer of adsorbent is called the stationary phase. A solvent mixture i.e. mobile phase is drawn up the plate via capillary action after the sample has been applied on the plate. At different rates, concentrations and compositions the separation is achieved. Thin layer chromatography mainly applicable to identify, determine the components that are present in plants, monitoring of organic reaction, detection of pesticides or insecticides in food and water as well as unknown compounds analysis.

c) High Performance Liquid Chromatography (HPLC):

HPLC mainly used for separation of compounds. It is based onto the adsorption and partition principle of chromatography. In this the normal phase and reverse phases are used with various types of suitable detectors like refractive index detector, PDA detector, fluorescence detectors, electrochemical detectors, electrical conductivity detectors, light scattering detectors, evaporative light scattering detectors, Corona Charged Aerosol Detector (CAD), Nano Quantity Aerosol Detector (NQAD), etc. HPLC provide an accurate, precise and robust method for quantitative analysis for pharmaceutical products as well as impurities analysis because it has speed, high resolution, sensitivity, reproducibility automation. HPLC mainly used for qualitative, quantitative analysis of degradation products like Stability indicating method for simultaneous determine the compounds present in diprosalic lotion like salicylic acid, betamethasone dipropionate and their other related compounds by using HPLC instrumental method. ^[36-42]

4. Characterization Method:

In this method LC-MS or GC-MS are used mainly in the identification of metabolites, drugs, impurities as well as degradation products as a minor component. Furthermore the NMR and MS are used to characterize them after identification of these minor components.

a) Liquid Chromatography -Mass Spectrometry (LC-MS):

Liquid Chromatography -Mass Spectrometry is a powerful analytical tool used to test and identify product impurities in pharmaceutical development process. The detection limit of a few hundred PPM is difficult to achieve with identification of all the impurities present at concentrations greater than 0.1%. MS based methods is high specificity and sensitivity to provide additional robustness and ruggedness as compared to UV techniques. Highly precise, sensitive Q-TOF mass spectrometers provide higher resolution as well as mass accuracy that enable the identification of unknown trace impurities. And it is mainly used for genotoxic impurity analysis.

b) Gas Chromatography-Mass Spectroscopy (GC-MS):

Gas chromatography-mass spectrometry is powerful tool in test sample to identify trace elements, different unknown substances with drug detections present in it. The GC-MS has also applicable into forensic substance identifications because it identifies the actual presence of a particular substance in a given sample. ^[7]

5. Isolation Method:

Chromatographic and non-chromatographic techniques are used for isolation of impurities because isolation of impurities becomes prior one. The analytical scale columns involved flow through reactor for separation of medium for the reactant & product under term chromatographic reactor. For example, ofloratidine impurity was found in loratidine. Other examples like Amikacin & Celecoxib also included in this one.

CURRENT MARKETED FORMULATION WHICH CONTAIN IMPURITY:

Indian pharmacopoeia specifies qualitative, quantitative tests for monitoring known impurities present in certain drugs. A few examples of impurities present in drug and identified by using particular method have given in following table. ^[8]

Table No.1: Drug names and their impurities with methods of detection.

Sr. No.	DRUG NAME	IMPURITY PRESENT	METHOD USED
1	Amphotericin B	Tetraenes	UV-Spectroscopy
2	Atropine Sulphate	Apo atropine	UV-Spectroscopy
3	Flurescene sodium	Dimethyl formaamide	Gas Chromatography
4	Cloxacilin	N,N, dimethylaniline	Gas Chromatography

CONCLUSION:

An Active Pharmaceutical Ingredient should pass not only the test such as C-GMP, QC, QA tests but also should qualify for the specified threshold of a new impurity which is necessary today. Monitoring of impurities is mandatory for acquiring and evaluating data that establishes biological safety, which reveals the need and scope for impurity profiling of drugs in various substances. To identify, isolate, monitor and quantify the impurities, various instrumental analytical techniques have been used depending upon their impurity types. The monitoring impurity has become very difficult. ICH, FDA has given various guidelines regarding it. Hence, there is need to have achieve standards with regard to impurities.

ACKNOWLEDGEMENTS:

The authors would like to acknowledge Principal Dr. R.V. Shete, Rajgad Dnyanpeeth's College of Pharmacy, Bhor for providing laboratory facilities and encouragement.

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