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Drug Impurity profiling an emerging task to Pharmaceutical Industries now days - A Review

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ABSTRACT

The impurities in pharmaceuticals are unwanted chemicals that remain with the active pharmaceutical ingredients (APIs). Impurities plays a major role in pharmaceuticals therefore profiling of impurity is very important. The pharmaceutical impurities are the unwanted chemicals that remain or are generated during the manufacturing process. These impurities are classified into three main categories such as organic, inorganic and residual solvents. Organic impurities include intermediate, starting material, degradation products, reagents, ligands, catalyst and by products. Whereas inorganic impurities are heavy metals, residual solvent, inorganic salt, filter, aids, charcoal and reagents. Impurity profiling helps in detection, identification and quantification of various types of impurities. It is a best way to characterize quality and stability of bulk drugs and pharmaceutical formulations. Due to rapid development of the analytical methodology it is imperative to review problems related to impurities present in the drug substances and drug products with their solutions. Various regulatory authorities like ICH, USFDA TGA, WHO, ANVISA, Canadian Drug and Health Agency are emphasizing on drug substance and drug product purity requirements and on identification of impurities in active pharmaceutical ingredients as presence of impurities even in small amounts may influence the efficacy and safety of the pharmaceutical products. Thus enlightening the need of impurity profiling of drug substances in pharmaceutical research this review focuses on various classification for identification as well as quantification of impurities present in the pharmaceuticals. The analytical techniques used for impurity profiling of drugs are LC-MS-MS, LC-NMR, LC NMR- MS, GC-MS, and LC-MS, DSC, TGA, ICP-MS, IC, HPLC and GC.

Keywords: Impurity, Impurity profiling, hyphenated techniques, LC-Mass, GC-Mass.

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INTRODUCTION

Impurity is any component of the new drug substance that is not the chemical molecule defined as the new drug substance. Impurities in pharmaceuticals are the unwanted chemicals that remain in active pharmaceutical ingredients (APIs), or develop during formulation, or upon aging of both API and formulated APIs to medicines. It is important to give higher consideration to these impurities. In general, most of these impurities are small molecules. For most drugs, the reactive species consist of water (which causes hydrolyze some drugs or effect the dosage form performance), small electrophiles (aldehyde and carboxylic acid derivatives), peroxides (which cause oxidase some drugs), and metals (which may catalyze oxidation and other drug degradation pathways). Additionally, some impurities can cause toxicological problems. The presence of these unwanted chemicals, even in small amounts, may influence the efficacy and safety of the pharmaceutical drug products. In order to ensure that accurate amount of the drug substance is being administered to the patient, drug substance purity must be assessed independently from these unwanted materials.

Impurity profiling is the common name of a group of analytical activities, the aim of which is the detection, identification/structure elucidation and quantitative determination of organic and inorganic impurities as well as residual solvents in bulk drugs and pharmaceutical formulations. The different pharmacopoeias, such as the British Pharmacopoeia (BP) Indian Pharmacopoeia (IP) and the United States Pharmacopoeia (USP) are incorporating limits to allowable levels of impurities present in the API's or formulations. Thus the details classification of impurities profile are as follows.

Classification of Impurities:

USP Classification:

According to united state pharmacopoeia impurities are classified as,

- Impurities in official articles
- Ordinary impurities
- Organic volatile impurities

ICH Classification:

➢ **Organic impurities**

Organic impurities may arise during the manufacturing process and/or storage of the drug substance. These type of impurities may be identified or unidentified, volatile or non-volatile, and

these include the starting material, intermediates, degradation products, by-products and reagents, ligands and catalyst used at different stages of synthesis of API and drug products. These are described as follows:-

Starting materials or intermediates:

These are the most common impurities found in API unless a proper care is taken in every step involved throughout the multi-step synthesis. Although the end products are always washed with solvents, there are always chances of having the residual unreacted starting materials unless the manufacturers are very careful about the impurities.

By-Products:

In synthetic organic chemistry, getting a single end product with 100% yield is very rare; there is always a chance of having by-products. By-products from the side reactions are among the most common process impurities in drugs. By-products can be formed through a variety of side reactions, such as incomplete reaction, overreaction, isomerization, dimerization, and rearrangement, unwanted reactions between starting materials or intermediates with chemical reagents or catalysts.

Degradation Products:

Impurities can also be formed by degradation of the end product during manufacturing of bulk drugs. However, degradation products resulting from storage or formulation to different dosage forms or aging are also common impurities in the medicines.

Reagents, ligands and catalysts:

These chemicals are less commonly found in API's; however, in some cases they may pose a problem as impurities. It has also been found that the presence of certain chemicals such as triethylamine has a degradative effect on the product.

Impurities originated from reaction solvents:

Some solvents which are the part of the reaction act as a source of impurities. E.g. Methylene chloride, which is often used as the solvent of friedel-craft acylation of benzene or phenyl derivatives. Impurities in the solvents can also be source of impurities. E.g. 2-hydroxytetra - hydrofuran is an impurity in tetrahydrofuran, which is often used as the solvent of Grignard reagents.

- **Inorganic impurities**

Inorganic impurities may also be derived from the manufacturing processes used for bulk drugs. They are normally known and identified, and include the following,

Reagents, ligands, and catalysts:

The chances of having these impurities are rare: however, in some processes, these could create a problem unless the manufacturers take proper care during production.

Heavy metals:

The main sources of heavy metals are the water used in the processes and the reactors (if stainless steel reactors are used), where acidification or acid hydrolysis takes place. These impurities of heavy metals can easily be avoided using demineralized water and glass-lined reactors.

Other materials: (e.g., filter aids, charcoal etc.)

The filters or filtering aids such as centrifuge bags are routinely used in the bulk drugs manufacturing plants and in many cases, activated carbon is also used. The regular monitoring of fibers and black particles in the bulk drugs is essential to avoid these contaminations.

- **Residual solvents**

Organic Volatile Impurities relates to residual solvents that may be found in the drug substance. 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.

Depending on the possible risk to humans, residual solvents are divided into 3 classes,

Class 1: Human carcinogens.

Class 2: Non genotoxic.

Class 3: Lower risk to human health.

Table 1: Other Impurities:

Class of residual solvents	Description	Examples	Conc. Limit (ppm)
Class I	Unacceptable toxicity hence avoid use manufacturing of drug product. (Human carcinogens)	Benzene (Carcinogenic)	2
		Carbon tetrachloride (Toxic)	4
		1,1,1-trichloroethane (Environmental hazard)	1500
Class II	The use of these solvents are limited in drug product because inherent toxicity. (Non-genotoxic)	Chloroform	60
		Acetonitrile	410
		Methanol	3000
Class III	These are less toxic and possess lower risk to human health than class I and II. Lower	Acetic acid, ethanol, dimethyl sulfoxide.	5000

	risk to human health		
Class IV	Adequate toxicological data is not available.	Methyl isopropyl ketone, isopropyl ether.	Base on PDE

Enantiometric Impurities:

Naturally occurring biosynthetic products having high level of enantioseletivity of their biosynthesis. In synthetic chiral drugs, if pure enantiomer is therapeutically active, then other enantiomer is considered as impurity. Theses impurities comes due to incomplete enantioseletivity of the synthesis or incomplete resolution of the enantiomer of the racemic mixture.

Polymorphic Impurities:

Usually, the most stable form of drug is used as active ingredient in formulation. The metastable polymorphic form may generated either due to temperature, moisture or mechanical treatment during processing of storage of the drugs product. The polymorphic impurities present in final drug product can adversely alter the stability and efficacy of it.

Genotoxic Impurities:

These are mutagenic and could damage DNA

Classification of Genotoxic impurities

Table 2:

Classification	Qualification Strategy
Class I	Known Genotoxic and carcinogenic (Compound Specific Limit)
Class II	Genotoxic but with unknown carcinogenic potential (Limit to staged TTC)
Class III	Altering structure, unrelated to API and of unknown genotoxic potential. (Further evaluation limit as appropriate)
Class IV	Altering structure, related to API. (Treat similarly as API)
Class V	Neither altering structure nor indication of genotoxic potential. (Treat as routine impurity)

Note: TTC: Threshold of Toxicological Concern.

- **Dosage form related Impurities:**

Mutual interaction amongst Ingredients:

Most vitamins are very labile and on aging they had a problem of instability in different dosage forms, especially in liquid dosage forms. Degradation of vitamins such as folic acid, pantothenic acid, Cyanocobalamine, and thiamine do not give toxic impurities; however, potency of active ingredients decreases below pharmacopeia limits.

Functional group related typical Degradation:

Ester hydrolysis

Examples included the following: Aspirin, benzocaine, cefotaxime, cocaine echothiophate, ethyl paraben, cefpodoxime proxetil.

Hydrolysis - Hydrolysis is a common phenomenon for the ester type of drugs, especially in liquid dosage forms. Examples include benzylpenicillin.

Oxidative degradation

Hydrocortisone, methotrexate, adinazolam, hydroxyl group directly bonded to an aromatic ring (e.g., phenol derivatives such as catecholamines and morphine), conjugated dienes.

Photolytic cleavage

Pharmaceutical products are exposed to light while being manufactured as a solid or solution, packaged, held in pharmacy shops or hospitals pending use, or held by the consumer pending use.

Decarboxylation

Some dissolved carboxylic acids, such as p-aminosalicylic acid, lose carbon dioxide from the carboxyl group when heated.

- **Common Terms of Impurities:**

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

1.Intermediate:

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

2. Penultimate intermediate:

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

3. By-products:

The compound produced in the reaction other than the required intermediates.

4. Transformation products:

They are related to theorized and nontheorized products that can occur in a reaction.

5. Interaction products:

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

6. Related products:

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

7. 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.

➢ REGULATORY GUIDELINES FOR IMPURITY PROFILE :

Ethical, economic and competitive reasons as well as those of safety and efficacy support the need to monitor impurities in drug products. It is now getting important critical attention from regulatory authorities. The United States Food and Drug Administration (USFDA) have endorsed the guidance prepared under the guidance of the International Conference of harmonization (ICH). The ICH guideline for impurities in pharmaceuticals was developed with joint efforts of regulators and industry representatives from the European Union (EU), Japan and United States and it has helped to ensure that different regions have consistent requirements for the data that should be submitted to various regulatory agencies. The guidelines not only aid the sponsors of New Drug Applications (NDA) or Abbreviated New Drug Application (ANDA) with the type of information that should be submitted with their applications, but also assist the FDA reviewers and field investigators in their consistent interpretation and implementation of regulations. 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

Limits for impurities in drug substances as per ICH are shown in below table while limits for impurities in degradated products of drugs are shown in table.

➢ QUALIFICATION OF IMPURITIES:

Qualification is the process of collecting and evaluating data that establishes the biological safety of any impurity or a given impurity profile at the level (s) being considered. An impurity is considered qualified when it meets one or more of the following conditions:

- When the observed level and proposed acceptance criterion for the impurity do not exceed the level observed in an FDA approved drug product.
- When the impurity is a significant metabolite of the drug substance.

- When the observed level and the proposed acceptance criterion for the impurity are adequately justified by the scientific literature.
- When the observed level and proposed acceptance criterion for the impurity do not exceed the level that has been adequately evaluated in comparative in vitro genotoxicity studies.

Recommended qualification thresholds based on the maximum daily dose as described in following table for drug substance and for drug product, which are provided in ICH Q3A1 and ICH Q3B2.

Table 3: Drug substance impurities thresholds:

Maximum daily dose [a]	**Reporting limit [b,c]**	**Identification limit [b, c]**	**Qualification limit [b, c]**
≤ 2g/day	0.05%	0.10% or 1.0 mg/day (intake whichever is less)	0.15% or 1.0 mg/day (intake whichever is less)
≥ 2g/day	0.03%	0.05%	0.05%

a- The amount of drug substance administered per day.

b- Higher reporting threshold should be scientifically justified.

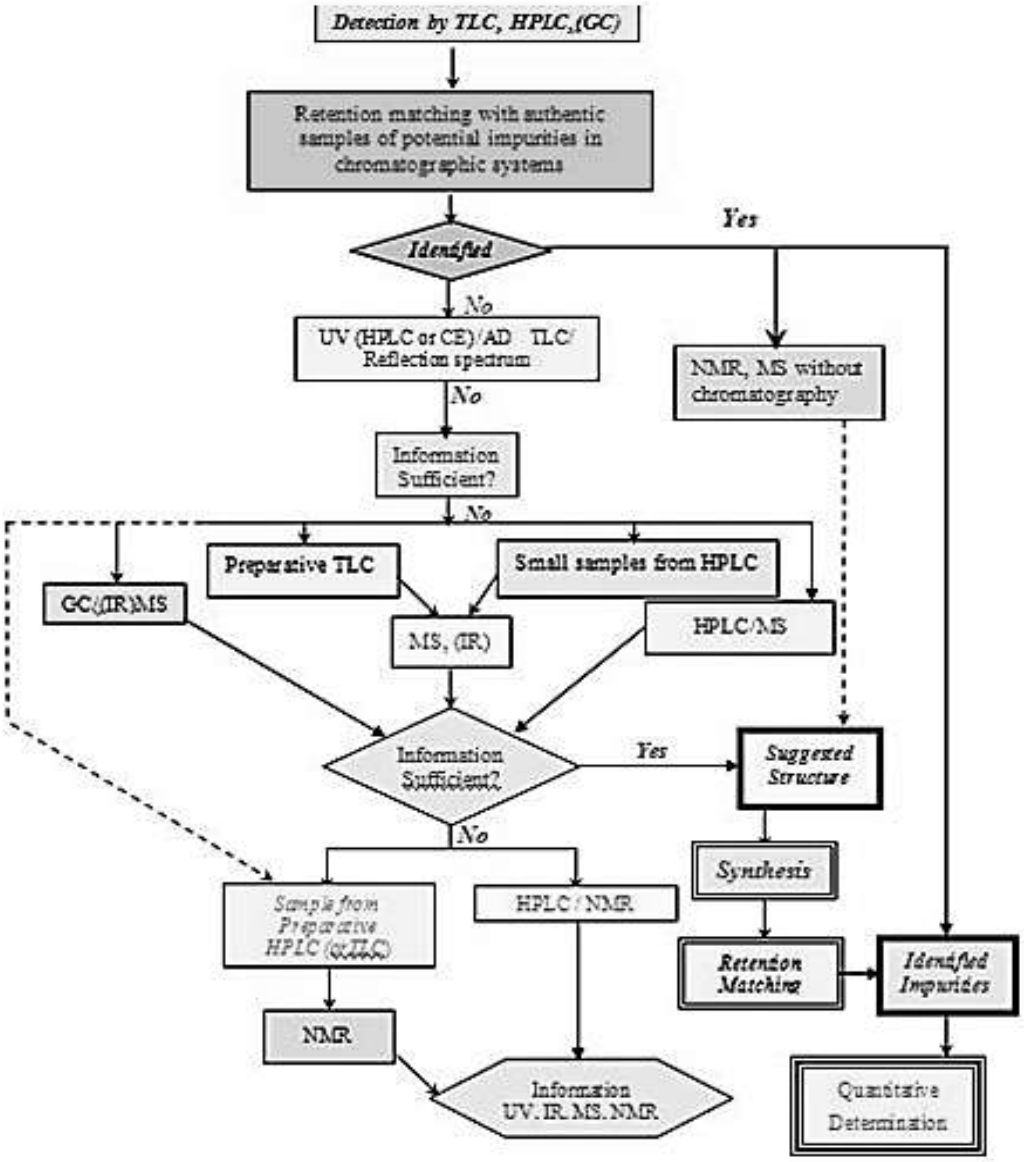
c- Lower threshold can be appropriate if the impurities are unusually toxic.

Table 4: Thresholds for degradation products in drug products:

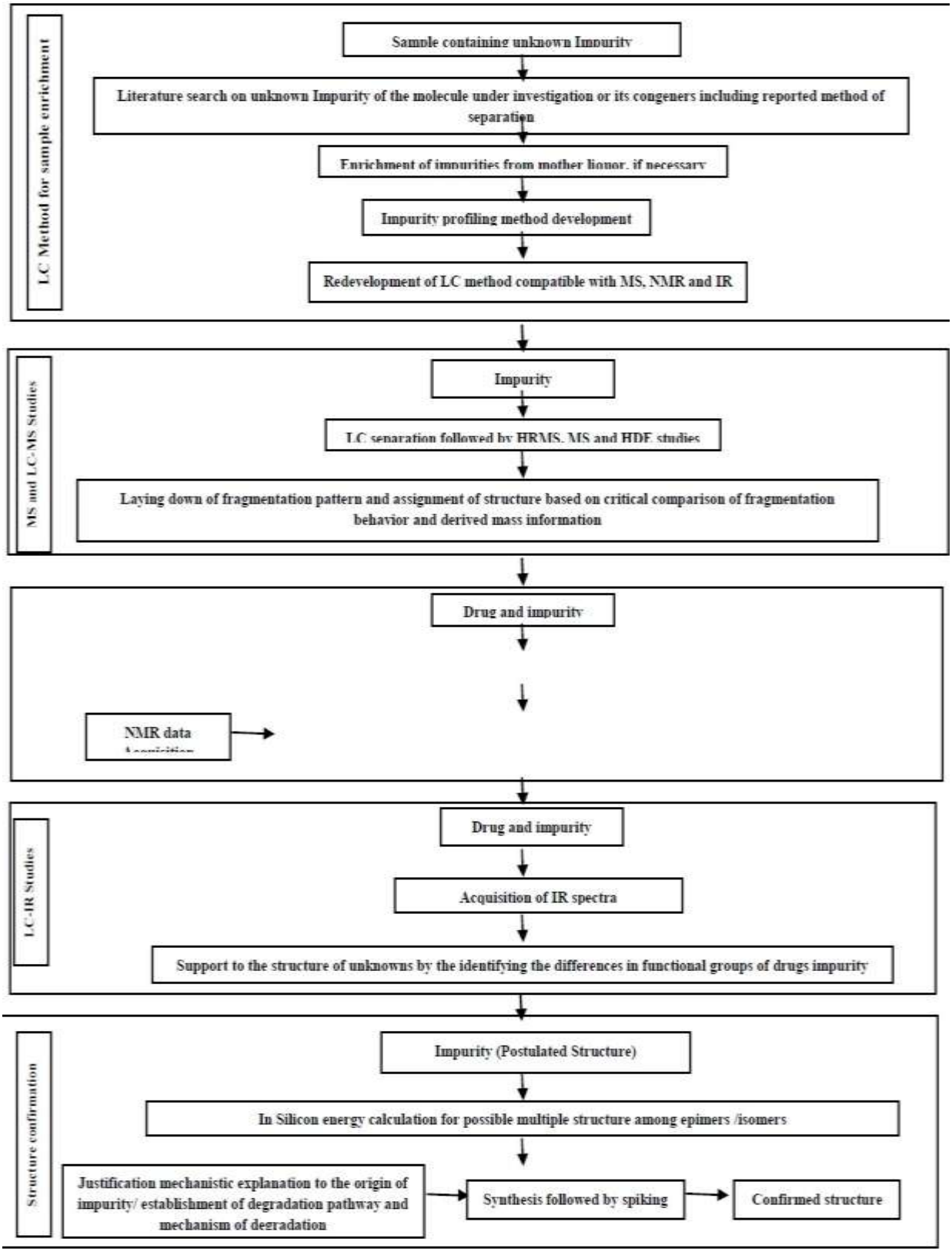
Maximum daily dose [a]	**Reporting threshold [b,c]**
≤1 g	0.1%
>1 g	0.05%
Maximum daily dose [a]	**Identification threshold [b,c]**
<1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg–10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg–2 g	0.2% or 2 mg TDI, whichever is lower
>2 g	0.10%
Maximum daily dose [a]	**Qualification threshold [b,c]**
<10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg–100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg–2 g	0. 2% or 3 mg TDI, whichever is lower
>2 g	0.15%

1. The amount of drug substance administered per day.
2. Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.
3. Higher thresholds should be scientifically justified

➢GENRAL SCHEME FOR DRUG IMPURITY PROFILING:



Conventional approach for the characterization of impurities



Comprehensive strategy for unequivocal structural characterization of Impurities/DPs using modern hyphenated techniques

Methods involved in impurity profiling:

- Identification Methods: Reference standard method, Spectroscopic methods (UV, IR, NMR, MS)
- Separation Methods: Chromatographic methods (GC, TLC, HPTLC, HPLC) Capillary electrophoresis.
- Isolation Method: Liquid-Liquid extraction method, supercritical fluid extraction method, accelerated solvent extraction method, solid-phase extraction method.
- Characterization method: NMR, MS, Hyphenated methods (GC-MS, LC-MS-MS, HPLC-DAD-MS, HPLC-DAD-NMR-MS).
- Validation process: It is the challenge to developed method and determine the limits of allowed variability for the conditions need to run the method. The parameters of validation includes specificity, accuracy, linearity, range, precision, robustness, LOD, LOQ.

Identification Methods:

Reference standard method:

The key objective of this is to provide clarity to the overall life cycle qualification and governance of reference standard used in development and control of new drug. 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 standard are needed, not only for the active ingredients in dosage forms but also for impurities, degradation products, starting materials, process intermediates, and excipient.

Spectroscopic methods: UV, IR, NMR, MS

Ultraviolet (UV):

UV at a single wavelength provides minimal selectivity of analysis; however with the availability of diode array detectors (DAD), it is now possible to get sufficient simultaneous information at various wavelengths to ensure greater selectivity.

Infrared Spectrophotometry:

Infrared spectro-photometry provides specific information on some functional groups that may allow quantification and selectivity. However, low level delectability is frequently a problem that may require more involved approaches to circumvent the problem.

Nuclear Magnetic Resonance Spectroscopy:

Nuclear magnetic resonance spectroscopy provides fairly structural information on a molecule and is a very useful method for characterization of impurities; however, it has limited use as a quantitative method because of cost and time considerations.

Mass Spectrometry:

Mass spectrometry provides excellent structural information, and, based on the resolution of the instrument; it may provide an effective tool for differentiating with small differences in molecular weight. However, it has limited use as a quantitative technique because of cost and time considerations.

Separation Methods: Chromatographic methods (GC, TLC, HPTLC, HPLC) Capillary electrophoresis.

GC:

Gas chromatography is a very useful technique for quantification. It can provide the desired resolution, selectivity, and ease of quantification. However, the primary limitation is that the sample must be volatile or has to be made volatile by derivatization. This technique is very useful for organic volatile impurities.

TLC:

A broad range of compounds can be resolved using TLC by utilizing a variety of different plates and mobile phases. The primary difficulties related to this method are limited resolution, detection, and ease of quantification. The greatest advantages are the ease of use and low cost.

HPLC:

This is a useful technique with applications that have been significantly extended for the pharmaceutical chemist by the use of a variety of detectors such as fluorescence, electrometric, MS, etc.

Capillary electrophoresis: It is a useful technique when very low quantities of samples are available and high resolution is required. The primary difficulty is assuring reproducibility of the injected samples.

Isolation of impurities:

It is necessary to isolate impurities from drug substance in order to monitor them accurately, because approximate estimations of impurities are generally made against the material of interest and can be incorrect. Various methods can be used for isolation of impurities. But the use of any method depends on the nature of impurity i.e. its structure, physicochemical properties and

availability. Following are the commonly used methods for the isolation of impurities from drug substances.

Extraction

Liquid-Solid extraction:

To simplest form, a solvent is selected that would dissolve the impurity of interest but not the solid matrix. If compound contains more than one impurity means, in that case desirable to use an organic solvent for extraction because of its unique properties.

Soxhlet Extraction:

It is a popular method for extracting compounds of interest from solids. The main advantage of this method is that it allows utilization of a small volume of solvent to produce a fairly concentrated extract. The material to be extracted is placed in the Soxhlet extractor, the extraction vessel is heated adequately to ensure volatilization of solvent vapors, which are condensed and the top of the material to be extracted. The condensed solvent percolates through the material and drains back into the extraction vessel to repeat the process.

Steam Distillation:

It is another method that can be used for extracting volatile components from natural materials and other matrixes of interest.

Supercritical fluid extraction (SFE):

Supercritical fluid extraction provides idealized means of extracting materials, since high solute diffusivity, lower viscosity and excellent solvating properties can be obtained with supercritical fluids, they provide excellent means of isolating impurities and other compounds of interest in a short period of time.

Liquid-Liquid extraction

This simply entails extraction of one liquid with another generally one of those liquid is aqueous and other is organic. The primary requirement is that these liquids to be immiscible. This procedure is very useful when the liquid into which the material of interest is being extracted is easy to volatilize, thus permitting concentration of the material.

In this type of extraction process, a solute is distributed between two immiscible solvents. The extraction is controlled by distribution or partition co-efficient (Kd) which defines the ratio of concentration of the solute in two solvents a and b

$$Kd = Ca / Cb$$

Column chromatography

This technique is commonly used for the separation of pharmaceutical compounds in preparative chemistry. The separation of quantities ranging from micrograms to kilograms, which depends on the size of the column. Detection of the eluent is generally performed by UV spectrophotometry, either continuously by using a flow cell or periodically by monitoring the collected fractions from a given sample that alerts the emergence of UV active components. Commonly silica gel or alumina is used in classic adsorption

Characterization method: NMR, MS, Hyphenated methods.

Hyphenated methods

Limitations of conventional methods of impurity profiling are as follows,

1. The process is time consuming and sometimes become complicated if several impurities have to be characterized in a single sample.
2. If the impurity formed are present in trace amount and cannot be find out, the process become more tedious.
3. If unstable impurity is formed, or if there is possibility of secondary reaction during processing, isolation becomes difficult.

Due to these limitation, hyphenated techniques are used for the identification and characterization especially if impurity formed are in trace level. Mostly the used hyphenated instruments have LC, GC or CE on the front end connected to MS, NMR or IR on the detection side. These are GC-MS, LC-MS, CE-MS, LC-NMR, LC-IR, HPLC-DAD-MS, and HPLC-DAD-NMR-MS.

GC-MS:

It was the first hyphenated technique introduced for determination of organic volatile impurities, and residual solvents in a sample and used till today. GC is able to separate the volatile and semi volatile impurities but it unable to identify them whereas MS can identify the impurities by giving its structural information at molecular level but it unable to separate them. Therefor the combination of these two techniques is took place shortly after the development of GC.

LC-MS:

This is the most popular hyphenated technique for characterization of impurities, as it has potential to give nearly clear structural information about unknown analyte. Although it was introduced much after GC-MS, several advancements and ranges of this instrument is available commercially. These are: LC-MS (Single Quad), LC-MS-MS (Triple Quad), LC-TOF, LC-MS-TOF (Q-TOF, Triple TOFTM), LC-MS-3DTRAP (MSn), LC-MS-2DTRAP (Q-TrapTM), LC-Hybrid Trap TOF Systems (LCMS-IT-TOF®), LCOrbitrapTM, LC-FTICR (Fourier Transform Ion Cyclotron

Resonance). These are either used alone or in combination to get desired information useful for structural characterization of impurities.

CE-MS:

CE (Capillary electrophoresis) and CEC (capillary electro-chromatography) is important techniques for separation and identification of impurities and DPs. CEC is a hybrid technique that involves both high efficiency of CE and stationary and mobile phase selectivity of LC.

SFC-MS:

Small number of reports are available on the use of SFC-MS for characterization of impurities for pharmaceutical substances and products. The technique has its advantage of saving LC solvents but its bench-top instrument was not available commercially for analysis; recently it has been introduced in to the market.

LC-NMR:

In 1978 for the first time, the coupling of LC effluent to NMR was reported. To improve the instrument sensitivity and resolution, modern LC-NMR instruments are accompanied with multiple technological advancements, like microprobes, strong field magnets (above 500 MHz), and cryoprobe technology. SPE units are embedded in between LC and NMR to overcome the requirement of high volumes of expensive deuterated solvents in mobile phase. The LC effluent contains low sample concentrations, due to which 13C detection is usually not possible. Also insufficient quantity of analyte did not allow acquisition of heteronuclear HSQC and HMBC spectra. Specific NMR pulse sequences are used to obtain clean spectra free from corresponding residual non-deuterated solvents. Usually supportive information are gathered from LC-NMR for structural confirmation for the components separated on LC column. Several reports are available on the use of LC-NMR for structural characterization of impurities and DPs.

CE-NMR

If analytes are present in relatively small amounts, hyphenated CE-NMR provides similar advantages as LC-NMR with respect to separation, chemical identification, and structural information. Both continuous and stopped flow modes, similar to LC-NMR are used in CE-NMR. The typical problem associated with CE-NMR is the shorter residence time of sample in NMR due to small sample volume output from CE that affects the detection sensitivity.

LC-FTIR:

Conventional FT-IR system requires 1–5 mg of sample hence recording becomes difficult when analytes are present or generated in trace quantities or cannot be isolated. LC-IR provides benefits

in such cases and has been recently commercialized. Some limitations exist while recording IR spectrum of impurities or DPs at levels of 0.1% in LC-IR, these include,

- On-line enrichment of analyte is essential.
- Interference of mobile phase components.
- It is difficult to apply chemometrics especially in case of gradient elution, since the background absorption is strongly influenced by the slight variation in mobile phase composition.
- Complete removal/ elimination of the solvents are difficult.
- Analytes should have low volatility than the mobile phase.
- Differential nature i.e. amorphous or crystalline; of analyte post deposition and also post solvent elimination.

Interface constitutes most critical component in LC-IR due to above cited reasons. It is available in two types- (i) flow cell (on-line) (ii) solvent elimination (semi on-line). On-line LC-IR have limited use and are restricted to major constituents only due to its poor detection limits, while semi on-line has comparatively better sensitivity and gives improved spectral data.

CONCLUSION:

A pharmaceutical ingredient should pass not only the test such as CGMP, QC, QA tests, water activity but also should qualify for the specified threshold of a new impurity. Impurity profiling is very important during the synthesis of drug substances and manufacture of dosage forms, as it can provide data regarding the toxicity, safety, various limits of detection, and limits of quantitation, of several organic and inorganic impurities, usually accompany with bulk drugs and finished products. 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 days, it is mandatory requirement in various pharmacopoeias to know the impurities present in API's. Impurity profiling of a substance under investigation gives maximum possible account of impurities present in it. The key aspect is that the impurity profiling of a new chemical entity must be shown to be qualified. With a Qualification threshold or lower for high dose compounds. To isolate and quantify the impurities, various instrumental analytical techniques have been used routinely. Hyphenated techniques which are used now a days for impurity profiling. Chromatographic techniques GC, LC etc. are used for separation and spectroscopic

techniques such as NMR, MS, IR used for identification purpose. Combination of these techniques gives better analysis of the impurities.

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