Review Article

Impurity Profile in Bulk Drugs and Pharmaceutical Preparation

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ABSTRACT
In the pharmaceutical sciences, an impurity is an any other organic material, besides the drug substance, or ingredients, which arise out of synthesis or redundant chemicals that remains with API's. The impurity may be raised either during formulation, or upon aging of active content of formulation. The presence of such superfluous impurity influence the efficacy and safety of the pharmaceutical products. Presence of such substances affects the ADMET properties of drug(s) in human body. Hyphenated instrumentation, are inevitable tools in the identification of inconsequential components like drugs, impurities, degradation products, and metabolites in various matrices.

Keywords: Impurity profiling, HPLC, Hyphenated Methods, ICH guidelines.

INTRODUCTION[1-55]

Impurities in pharmaceuticals are the surplus chemicals that stay behind with the active pharmaceutical ingredients or develop during formulation or upon aging of both active content and formulated active ingredients to medicines. The efficacy and safety of pharmaceutical product is affected by presence of unwanted traces of impurities. Impurity profiling is deals with detection, identification/structure elucidation and quantitative determination of organic and inorganic impurities as well as residual solvents in bulk drugs and pharmaceutical formulations.

Biological safety of impurity is established by qualification of impurities present. International Conference on Harmonization has published guidelines for impurities in new drug substances, products and residual solvents. Current practice of isolation and identification of impurities raised during process and degradation products using Chromatographic and Spectroscopic techniques is in progress. Analysis has gone beyond traditional chromatographic techniques, such as HPLC and GC, in order to resolve potential impurities through efforts that embrace diverse chemical environments. This concept is known as 'orthogonality'. One such employable orthogonal technique is Supercritical Fluid Chromatography (SFC). SFC is considered a normal phase technique because it utilizes the relatively nonpolar, liquid carbon dioxide as the bulk of the mobile phase and due to higher diffusivity of the mobile phase yields greater efficiency. ICH Q3A and Q3B cover drug substance and drug products respectively.

Impurities in Active Pharmaceutical Ingredient[9-55]

Identified and unidentified impurity present in a typical batch is revealed in impurity profile. The impurity profile is dependent upon the process or origin of the API.

Classification of impurities is as follows (as per ICH):

1. Organic impurities
2. Inorganic impurities
3. Residual solvents

Others-Enantiomeric impurities: In optically active drug there could be an isomer with enantiomeric impurities. Many drugs are chiral and are often supplied as mixtures of enantiomers rather than single enantiomers.

Critical Factors Affects The Quality Of Bulk Drugs

1. Crystallization
2. Washing the wet cake
3. Drying
4. Appropriate packaging

The formulation related impurities can be classified as follows[9-55]

1) Method related
2) Environmental related

The prime ecological factors that can diminish stability include the following

i) Exposures to adverse temperatures
ii) Light-especially UV light
iii) Humidity

3) Dosage form related
   i. Mutual interaction amongst ingredients
   ii. Functional group- related typical degradation
   iii. Ester hydrolysis
   iv. Hydrolysis
   v. Oxidative degradation
   vi. Photolytic cleavage
   vii. Decarboxylation.

Qualification of Impurities

Qualification involves acquisition of data for each kind of impurity present in formulation or API with respect to the biological safety within specified limits.

1) When it is identified that the factor which is responsible for it if differing significantly from the original assumptions, it may be better to re-measure the actual amount of the impurity there and re-evaluate against the qualification threshold (see Table1).[56]
2) For verification, when a threshold is exceeded, a reported result has to be evaluated against the thresholds as below: when the threshold is described in %, then reported result should be rounded to the same decimal place as the threshold should be compared directly to the threshold and if the threshold is described in TDI, the reported result should be in converted to TDI, rounded to the same decimal place as the threshold and compared to the threshold. For example the amount of impurity at 0.12% level corresponds to a TDI of 0.96 mg (absolute amount) which is then rounded up to 1.0 mg; so the qualification threshold articulated in TDI (1.0 mg) is not exceeded. [56]

Table 1: Thresholds specifications[56]

Max. daily dose	Reporting Threshold	Identification Threshold	Qualification Threshold
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake(whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

Table 2: Paradigm 1

Raw Result (%)	Reported Result(%) Reporting threshold=0.05%	Calculated Total Daily Intae (TDI) (mg) of the impuity (rouded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 0.15% exceeded?)
0.044	Not reported	0.2	None	None
0.0963	0.10	0.5	None	None
0.12	0.121	0.6	Yes	None
0.1649	0.161	0.8	Yes	Yes

The table is only expounding and is not anticipated to provide as template how consequences on impurities should be offered in an appliance file. Generally raw data are not offered.

Paradigm 1: 0.5 g maximum daily dose
Reporting threshold = 0.05%
Detection threshold = 0.10%
Prerequisite threshold = 0.15%

paradigm 2: 0.8 g Maximum Daily Dose
Reporting threshold = 0.05%
detection threshold = 0.10%
prerequisite threshold = 1.0 mg TDI

Table 3: Paradigm 2[56]

"Raw"Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 1.0 mg TDI exceeded?)
0.066	0.07	0.6	None	None
0.124	0.12	1.0	Yes	None
0.143	0.14	1.1	Yes	Yes

Isolation with Characterization

It is recurrently obligatory to isolate and characterize impurities in order to monitor them accurately, because approximate estimations of impurities are generally made against the material of interest and can be incorrect. These estimations are based on the assumption that impurities are structurally related to the material of interest and thus have the same detector response. It is important to test this assumption because impurities frequently have different structures with significantly different detector responses.

Number of methods can be used for isolation and characterization of impurities. But the application of any method depends on the nature of impurity (i.e.) its structure, physicochemical properties and availability. The following methods are commonly used for the isolation, they are

1. Extraction
2. Column Chromatography
3. Preparative Separations

Extraction

1. Liquid-Solid extraction
2. Liquid-Liquid extraction

Liquid-Solid Extraction

For this, a solvent is selected in such a way that impurity of interest must be dissolved 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. Then volatilize the organic solvent at low temperatures in order to concentrate the impurity. Commonly using various organic solvents are enlisted in Table No. 4 with boiling point and dielectric constant.

Table 4: List of solvents for Liquid-Solid extraction

Solvents	Boiling Point	Dielectric constant
n-Hexane	190	1.9
Cyclohexane	81	2.0
Carbon tetrachloride	77	2.2
Toluene	110	2.4
Ethyl ether	35	4.3
Chloroform	61	4.8
Methylene chloride	40	8.9
Ethanol	78	24.6
Methanol	65	32.7
Dimethyl formamide	153	36.7
Acetonitrile	82	37.5
Water	100	80
Formamide	210	111

Soxhlet Extraction

It is a trendy method for extracting compounds of interest from solids eg. Natural products are isolated by reputed extraction with the suitable solvent. The advantage of this method is that it permits exploitation of a small volume of solvent to produce a fairly concentrated extract. The material is placed in the Soxhlet extractor for extraction and is heated adequately to ensure volatilization of solvent vapors, which are condensed in the top of the material to be extracted. The process is repeated by draining the percolated solvent back inside extraction vessel.

Steam Distillation

Used for extracting volatile components from natural materials and other matrixes.

Supercritical fluid extraction (SFE)

SFE gives 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 within minimum time. The critical parameters like pressure, temperature and density of a few compounds used for SFE are given in Table 5. But carbon dioxide is most frequently used for SFE because of its accessibility, ease of exploit and temperament.

Table 5: List of solvents for SFE

Solvent	Pressure(ATM)	Temperature	Density(g/ml)
n-Pentane	33.3	196.6	0.232
Carbondioxide	72.9		9.448
Ammonia	111.3	132.3	0.24

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 constraint 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. Hence the choice of solvents must be made with that consideration in mind.

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

Kd = Ca / Cb

Kd is the distribution co-efficient or partition coefficient.

Column Chromatography

This method is used for the separation of pharmaceutical compounds in preparative chemistry. The separation of quantities ranging from µg to kg, which depends on the size of the columns. 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 chromatography. Ion exchange resins to chemically modified polydextran gels used primarily for the analysis of biological samples. For liquid-liquid partition chromatography columns, inert carrier such as celite or kieselguhr is impregnated with an aqueous buffer or another polar solvent such as dimethyl formamide or dimethyl sulfoxide and elution is carried out with non-polar solvents.

Thin Layer Chromatography

It is a valuable technique for isolation and purification of compounds. All the approaches of chromatography including adsorption, partition, ion exchange and gel filtration can be utilized. In addition choosing a sorbent and an eluent for performing TLC it is necessary to select a suitable method for applying a sample to the plate. Silica gel plates with or without fluorescent indicator are frequently used for most application. Detection is frequently performed by UV eg. 366nm or Iodine vapors can help to detect most of the organic substance. To elute the material from the plates, the simplest method is scraping the sorbent containing the material of interest and it is extracted with a suitable solvent, followed by filtration or centrifugation. The solvent is removed to collect the desired substance. If aluminium plates are used means cut the sample and eluted.

Gas Chromatography

It is very useful for isolation and characterization of volatile components or those components that can be made volatile by derivatization technique and the detector used should be non destructive. Now GC is more apt to be used in combination with mass spectrometry (GC/MS) for characterization of impurities.

Analytical Methodology

As the structures of impurities are sometimes unknown, several spectroscopic and microchemical techniques have been developed which require minute quantities of material and readily enable the structural elucidation of the impurity. It is necessary for monitoring impurities in pharmaceutical by very selective analytical methodology. A good method should be able to reliably determine the impurity of interest at a 0.1% level means the methods must be developed to detect at least at 0.05% level to provide assurance for quantitation at the desired level.

Strategy for Method Development

Method development strategy should have the following details.

1. Physico chemical data
   Ionization constant
   Solubility
   Water absorption

Distribution co-efficient
Optical rotation
Crystal form

Impurities can be analyzed by the following instruments:

1. Ultra Violet Spectroscopy
2. IR Spectroscopy
3. NMR Spectroscopy
4. Mass Spectrometry
5. Gas Chromatography
6. HPLC [57-69]

Characterization of impurities

Depending on availability use the authentic sample. As per FDA impurity should not be more than 0.1%. Initial characterization involves application of Hyphenated techniques.

Characterization methods

Highly sophisticated instrumentation, such as mass spectroscopy attached to a Gas Chromatography or High Performance Liquid Chromatography, are foreseeable paraphernalia in the recognition of minor components in assorted matrices. For characterization techniques exploited are as follows:

(1) N.M.R.

The ability of NMR (Nuclear Magnetic Resonance) 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. The ability of NMR- based diffusion coefficient determination to distinguish between monomeric and dimeric substances was validated using a standard mixture of authentic materials containing both monomers and dimers. Unfortunately, NMR has traditionally been used as a less sensitive method compared to other analytical techniques. Conventional sample requirements for NMR are on the order of 10 mg, as compared with MS, which requires less than 1 mg.

(2) M.S.

Mass spectroscopy 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 formulations.

Hyphenated Methods:

1. LC-MS-MS
2. HPLC-DAD-MS
3. HPLC-DAD-NMR-MS
4. GC-MS
5. LC-MS

An illustration of reverse-phase LC-MS analysis in gradient elution with two distinct soft ionization techniques is the Atmospheric Pressure Ionization with Electrospray Source (API-ESI) and the chemical ionization of d-allethrine. The popularity of LC-MSMS systems for complex mixture analysis of thermally labile and biologically relevant molecules, viz mosapride, is largely attributed to the “soft” nature of Atmospheric Pressure Chemical Ionization (APCI), and Atmospheric Pressure Ionization (APPI). HPLCDAD-MS (HPLC coupled with a Diode Array UV Detector and a Mass Spectrometer), and such other techniques are almost routinely used. NMR has now been added to this combination to provide HPLCDAD-NMR-MS capabilities in instruments.

General method for drug impurity profiling

Well sophisticated instrumentation, like mass spectrometers attached to a Gas Chromatography or HPLC, are used for detection of minor components like drugs, impurities, degradation products, metabolites in diverse matrix. NMR spectroscopy reveals structural details for that preparative HPLC has been exploited for isolation of larger number of components. Spectrophotometrically active

components can be identified by UV-HPLC technique.

Purposeful Degradation Studies

This method applied for identification of impurities of a new drug or a chemical. Drugs being stored get affected by factors like temperature, humidity, pH, light, enclosing system, and reaction among components i.e. ingredients and excipients and as such assembly is made for studying these factors, what we call it impurity profile library.

Applications

It has extensive applications in design and monitoring of quality, stability, and safety of drug. Pharmaceutical drug may have origin either natural, synthetic or r-DNA technology product. It constituent almost all categories of drugs.

Following are the few examples of impurities which are reported in the API'S.

Table 6: Various impurities reported in API's[86]

Drug	Impurity	Method
Amphotericin B	Tetraenes	UV Spectroscopy
Atropine sulphate	Apo atropine	UV Spectroscopy
Cloxacillin	N,N- dimethyl aniline	GC
Dextrose	5-hydroxy methyl furfural	UV Spectroscopy
Doxorubicin	Acetone and ethanol	GC
Ethambutol hydrochloride	2-amino butanol	TLC
Mercaptopurine	Hypoxanthine	UV Spectroscopy
Cimetidine	2,5-bis[(N'-cyano-N''-methyl) guinidinoethylthiomethyl]-4-methylimidazole and 1,8- bis[(N' cyano- N''- methyl) guinidino]-3,6-dithiaoctane	HPLC
Celecoxib	[5-(4-methylphenyl)-3- trifluromethyl-1H-pyrazole], 4- [5-(2'-methylphenyl)-3- (trifluoromethyl)-1H-pyrazol-1-yl] benzenesulphonamide, and 4-[4-(4'-methylphenyl)-3-(trifluromethyl)-1H-pyrazole- 1-yl]-banzenesulfonamide	HPLC, LC, LC-MS-MS
Methamphetamine	1,2-dimethyl-3- phenylaziridine, ephedrine, methylephedrine, N- formylmethamphetamine, N-acetylmethamphetamine, N formylphedrine, N-acetylephedrine,N,O-diacetylephedrine, methametamine dimmer	GC
Morphine sulphate	5-(hydroxymethyl)-2- furfural, 10-hydroxymorphine, 10-Oxomorphine	HPLC

CONCLUSION

Impurity profile of pharmaceuticals is receiving an increasing importance and drug safety receives more and more attention from the public and from the media. 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. Nowadays, it is mandatory requirement in various pharmacopoeias to know the impurities present in API's.

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