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Review Paper

# Innovative Techniques for Impurity Profiling of Pharmaceutical Raw Materials

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## ABSTRACT

Impurities in pharmaceutical substances refer to any unintended chemicals or materials that are present alongside the active pharmaceutical ingredient (API) during synthesis, formulation, or storage. These impurities may arise as by-products during manufacturing or develop over time due to degradation of the drug substance. In contemporary pharmaceutical analysis, impurity profiling has become a critical area of focus, encompassing the identification, structural characterization, and quantitative estimation of impurities. The growing concern in this field is primarily due to the potential toxic effects and safety risks associated with unknown or harmful impurities. Therefore, it is essential to employ selective and sensitive analytical methods to detect and control these substances, ensuring the safety and efficacy of drug products. This review highlights the latest analytical approaches used for impurity detection and quantification in drug substances and formulations, with particular emphasis on advanced hyphenated chromatographic techniques that enhance separation and characterization. Additionally, the role of regulatory frameworks, especially ICH guidelines, in managing and controlling pharmaceutical impurities is also discussed

## INTRODUCTION

Impurity profiling of drug material is define according to ICH Guidelines “A description of the identified and unidentified impurities, present in a new drug substance"(ICH Guidelines 2002). Impurity profiling is considered to as one of the major analytical activities and the object 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(S. Gorog et al., 2000). Impurity can be categorized in three types in the drug materials:

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(1) Impurities comes from the chemicals or from the biosynthetic routes itself and closely related to the drug products.
(2) During the storage or on exposure to an extreme condition impurities are formed due to spontaneous decomposition of the drug.
(3) In the final product the precursor present may be considered as impurities. In excess of 0.1% presence of impurities should be identified and quantified by selective methods.

The Quantitative determination of impurities may be used as method for quality control and validation of drug substances. Various regulatory authorities such as US FDA (United States Food and Drug Administration), CGMP (Current Good Manufacturing Practice), TGA (Thermo Gravimetric Analysis), and MCA (Ministry of Corporate Affairs) emphasize on the impurity profiling of drugs. Two aspects can be addressed impurities present in new drug substances:

**(1) Chemical aspects:** These include classification, identification and brief discussion of analytical procedure of impurities, report generation, list of impurities in specifications.

**(2) Safety aspects:** These include specific guidance for quantifying impurities, significantly present at lower levels, in drug substance used in clinical studies(S. Ahuja et al., 1998).

## SOURCES OF IMPURITIES

The major source of impurities is in drug products and pharmaceutical chemicals.

1) **In drug products:** it include
   - Type of raw material used
   - Process of manufacturing
   - Due to product instability
   - Foreign matter present in atmosphere.
2) **In pharmaceutical chemicals:** Various qualitative and quantitative tests are specified by Indian Pharmacopoeia for limiting known impurities in certain drugs. Few such drugs and corresponding impurities are shown in Table 1(I.P, 1996) The basic scheme for impurity profiling of drugs are shown in figure 1.

**Table 1:- (Drugs and corresponding impurity**

| Drug | Impurity | Method |
|---|---|---|
| AmphotericinB | Tetraenes | Ultra violet spectroscopy |
| Atropine sulphate | Apo atropine | Ultra violet spectroscopy |
| Cloxacillin | N,N dimethyl aniline | Gas chromatography |
| Dextrose | 5- hydroxy methyl fulfural | Ultra violet spectroscopy |
| Ethambutol hydrochloride | 2- amino butanol | Thin layer chromatoraghy |
| Fluorescene sodium | Dimethyl formamide | Gas chromatography |
| Mercaptopurine | Hypoxanthine | Ultra violet spectroscopy |

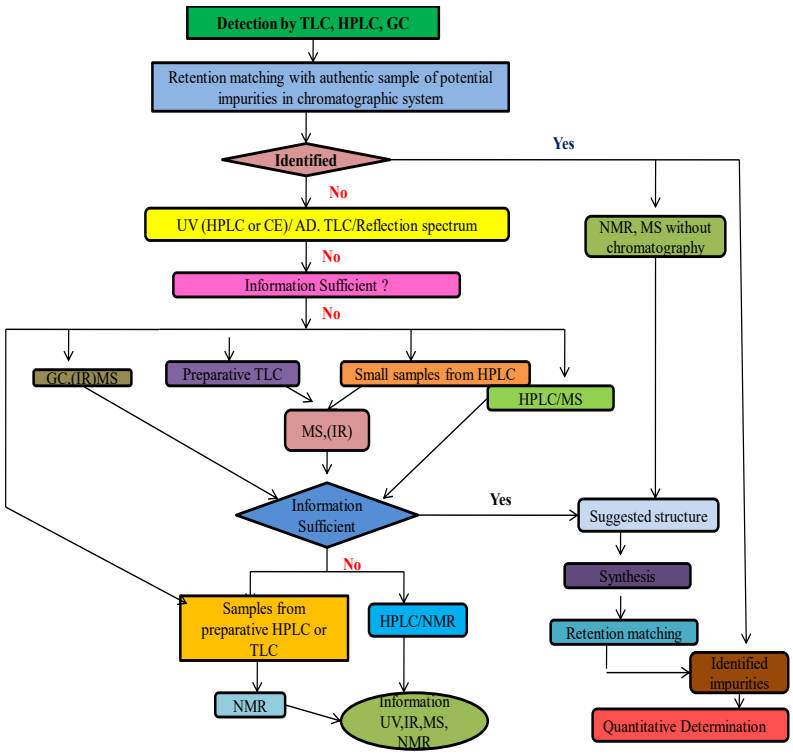



**Figure 1: Schematic representation of scheme for impurity profiling of drugs**

## Classification of Impurities

This guideline is correspondent to the ICH Q3A(R) guideline "Impurities in New Drug Substances", which should be considered for basic principles. The ICH Q3C guideline "Residual Solvents" should also be considered, if appropriate(K. M. Alsante, P. Boutres et al., 2004).

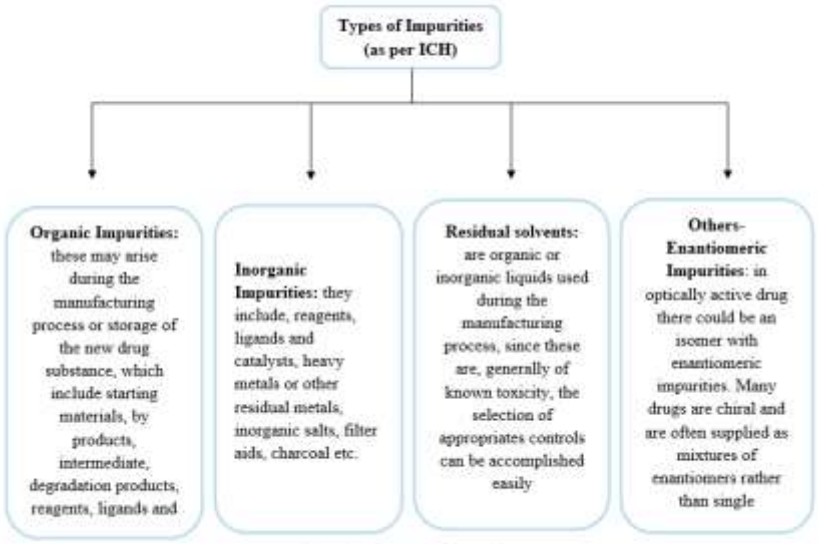



**Figure 2: Types of Impurities**

**The formulation related impurities can be classified as follows:**

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.

**I.C.H. Guidelines for Impurity Profiling**

In New Drug Substances and drug products are dealt with new approaches to quantification and qualification. Regulatory requirements for the identification, quantification and control of impurities in drug substances and their formulated products are now being increasingly explicitly defined, particularly through the I.C.H. (International Conference of Harmonization). The implications of recent are important both from their regulatory impact and the impact upon analytical technology.This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered.Biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation and semi-synthetic products derived there from, herbal products, and crude products of animal or plant origin are not covered under it.

**In new drug substance impurities are addressed from two perspectives according to I.C.H. Guidelines**

**(1) Chemical aspects:** These include classification, identification and brief discussion of analytical procedure of impurities, report generation, list of impurities in specifications.

**(2) Safety aspects:** These include specific guidance for quantifying impurities, significantly present at lower levels, in drug substance used in clinical studies(ICH Guidelines).

**Impurity Qualification**

Qualification is defined as the process of collecting and assessing data that demonstrates the biological of a given individual impurity at level specified. A draft for Guidance for Industry on "ANDAs: Impurities in Drug Substances" has been given by U.S. Department of Health and Human Services, Food and Drug Administration Centre for Drug Evaluation and Research (CDER) in January 2005. The current thinking on this topic of Food and Drug Administration's (FDA's) has been shown after finalization of this draft guidance. This does not establish or confer any rights for or on any person and does not operate to bind FDA or the public(U.S. Department, 2005)

**New impurities**

The qualitative degradation profile of a new drug product may change during the course of drug development studies which results in new degradation products that exceed the identification and/or qualification threshold. During this event, several new degradation products should be identified and/or qualified. These various changes call for attention of the need for qualification of the level of the impurity unless it is below the threshold values as noted(S. Ahuja et al., 1998).

**Methods for isolation of impurities:**

In order to monitor the impurities accurately, it is usually mandatory to segregate and identifies the impurities because approximate evaluation of impurities aregenerally made against the material of interest and can be incorrect. These evaluations are established on the premises that impurities have the same detector response due to structurally related to the material of

interest. It is significant to test this premises because impurities frequently have different detector responses with different structures. Various 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.

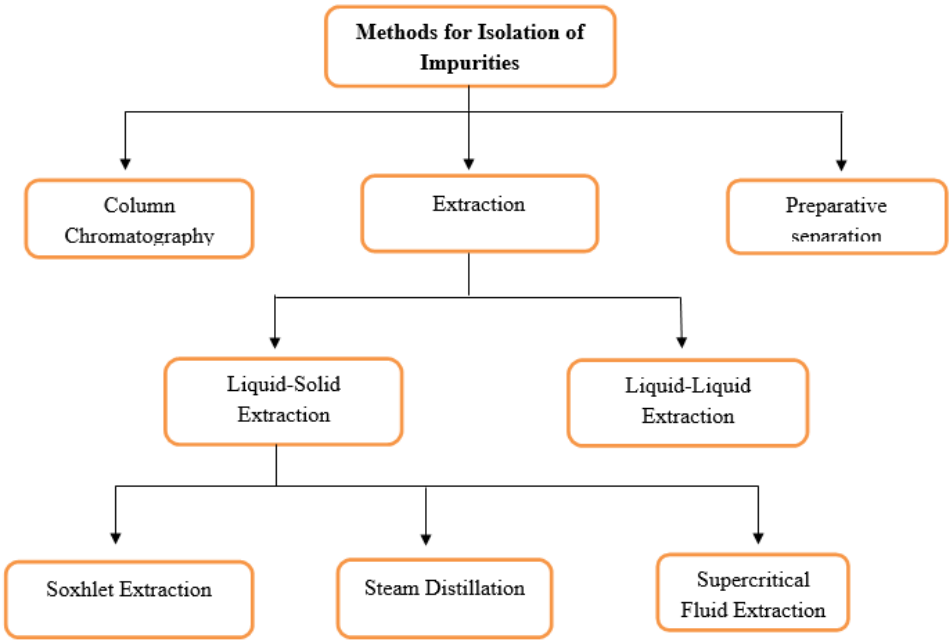



**Figure 3: Methods for Isolation of Impurities**

**Liquid-Solid Extraction**

In this, a solvent (hydrophilic or hydrophobic, acidic, neutral or basic) is added to a solid in such a way that impurity of concern must be dissolved but not the solid matrix. Insoluble impurity material can be separated by gravity or vacuum filtration, and soluble material is 'extracted' into the solvent. If mixture contains more than one impurity, an organic solvent is used for extraction due to its unique properties. To concentrate the impurity, the organic solvent is then volatilized at low temperature. Various commonly using organic solvents are enlisted in Table 2 with boiling point and dielectric constant.

**TAB**

**LE 2:- List of organic solvents with boiling point and dielectric constant**

| Solvents | Boiling point (°C) | 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 |

**Soxhlet Extraction**

A **Soxhlet extractor** is a piece of laboratory apparatus. It was originally designed for the extraction of a lipid from a solid material. For example, natural products are extracted with suitable solvent. Typically, a Soxhlet extraction is

used when the desired compound has a limited solubility in a solvent, and the impurity is insoluble in that solvent. This method has advantage that it allows for unmonitored and unmanaged operation while efficiently recycling a small amount of solvent to dissolve a larger amount of material.

For extraction, the material is placed in the Soxhlet extractor and is heated sufficiently to ensure volatilization of solvent vapours, 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**

Steam distillation is a special type of distillation (a separation process) for temperature sensitive materials like natural aromatic compounds and for extracting volatile components from natural materials and other matrixes.

**Supercritical fluid extraction (SFE)**

SFE provideslower viscosity, high solute diffusivity, and excellent solvating properties can alsobe obtained with supercritical fluids. They provide attractive means of isolating impurities and other compounds of interest within minimum time. Various critical parameters like pressure, temperature and density of a few compounds used for SFE are given in Table 3. But carbon dioxide is most frequently used for SFE because of its accessibility, ease of exploit and temperament.

**Table 3:-Various critical parameters used for Supercritical fluid extraction**

| Solvents | Pressure (ATM) | Temperature (°C) | 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 (LLE)**

LLE also known as solvent extraction and partitioning, is a method to separate compounds or metal complexes, based on their relative solubilities in two different immiscible liquids, usually water (polar) and an organic solvent (non-polar). The essential constraint is that the two liquids must be immiscible or only slightly miscible; this allows them to form dispersion, with one liquid dispersed as droplets in the other.

This procedure is very effective for mixtures in which liquid having material of interest is easy to volatilize, thus allowing concentration of the material. Hence with this consideration in mind, the choice of solvent is made. In this liquid – liquid extraction process, solute is dispersed between two immiscible solvents. The principle of this type of extraction is based on distribution or partition co-efficient which defines the ratio of concentration of the solutes in two solvents a and b as given below:

$K_d = C_a / C_b$

$K_d$ is the distribution co-efficient or partition coefficient.

**Column Chromatography**

This method is used for the separation of pharmaceutical compounds in preparative chemistry. Depending on the size of columns, the separation of quantities ranging from µg to kg. UV spectrophotometryis generally performed for detection of the eluent, either periodically by monitoring the collected fractions from a given sample or continuously by using a flow cell. Silica gel and alumina is commonly used in classic adsorption chromatography. For the analysis of biological samples ion exchange resins to chemically modified polydextran gels are widely used. 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 nonpolar solvents (S. Lakshmana et al., 2010)

**Characterization of impurities:**

It is important that for estimation authentic sample should be used, when it is available. If through the estimations a given impurity content is found to be greater than 0.1% then it must be characterized as per the FDA requirements. Various hyphenated methodsare perfectly suitable for initial characterization of the impurities such as gas chromatography, mass spectroscopy, or liquid chromatography, mass spectrometry or the number of other chromatographic-spectroscopic configuration.

**Methods for characterization of impurities**

Highly sophisticated instrumentation, such as MS attached to HPLC (High Performance Liquid Chromatography) or GC (Gas Chromatography), are inevitable tools in the identification of minor components (drugs, impurities, degradation products, metabolites) in various matrices. For characterization of impurities, different techniques are used; which are as follows;

**(1) Nuclear Magnetic Resonance (NMR)**

NMR is a powerful analytical instrument for structural elucidation due to its ability of providing information regarding the specific bonding and stereochemistry of molecules of pharmaceutical interest. The capability of NMR- based diffusion coefficient determination to differentiate between monomeric and dimeric substances was ratified using a standard mixture of authentic materials containing both monomers and dimers. Unfortunately, compared to other analytical techniquesNMR has traditionally been used as a less sensitive method. For example, conventional sample requirements for NMR are of 10 mg, as compared with MS, which requires less than 1 mg.

**(2) Mass Spectroscopy (MS)**

Over the past several decades MS has an increasingly significant impact on the pharmaceutical development process. Various separation techniques such as Mass Spectrometers have afforded new opportunities from advancement in the design and efficiency of the interfaces for monitoring, characterizing, and quantification of drugrelated substances in active pharmaceutical ingredients and pharmaceutical formulations. If the necessary selectivity is fails from single method, then orthogonal coupling of chromatographic techniques is used such as HPLC-CE (High Performance Liquid chromatography coupled with Capillary Electrophoresis) and HPLC-TLC, or coupling of chromatographic techniques with information rich spectroscopic methods such as HPLC-MS or HPLC-NMR, but fortunately only as a development tool rather than a tool for routine QC (Quality control) use.

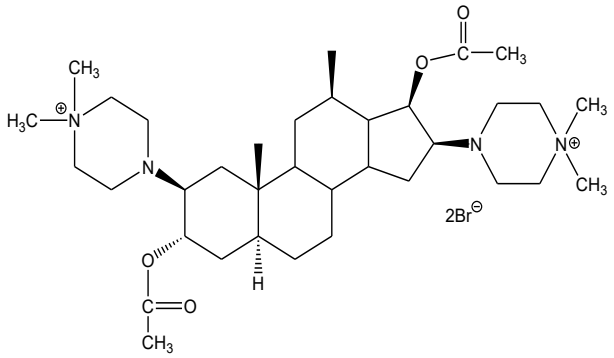
**Hyphenated Techniques**

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

**High Performance Liquid Chromatography-Ultraviolet Spectroscopy (HPLC-UV) Studies**

Ultraviolet spectroscopy among the spectroscopic techniques is the less informative and used in combination with separation methods in drug impurity profiling. The major reason for this is that (unlike with other spectroscopic methods) it provides information on the chromophoric moiety and its close neighbourhood only. However, UV spectra are obtainable almost automatically during

the HPLC run by the use of diode-array detectors and due to this reason in some cases UV spectra drawn very useful information before the application of more developed spectroscopic techniques. A characteristic (S. Gorog et al., 2003)example is the identification of an impurity in pipecuronium bromide. As seen in Figure (1), the drug material having fully saturated structure is spectrophotometrically practically inactive where as the impurity with it'sexamine structure has a well-defined absorption maximum at 236 nm. In several casesthe drug material and its impurities even with minor differences between the spectracan be of diagnostic value. In a recent paper by (L. Zhou, B. Mao, R. Reamer and T. Novak et al., 2007), where a general strategy and several case studies are described for the structure elucidation of impurities in various drugs, the evaluation of diode-array UV spectra played an important role.



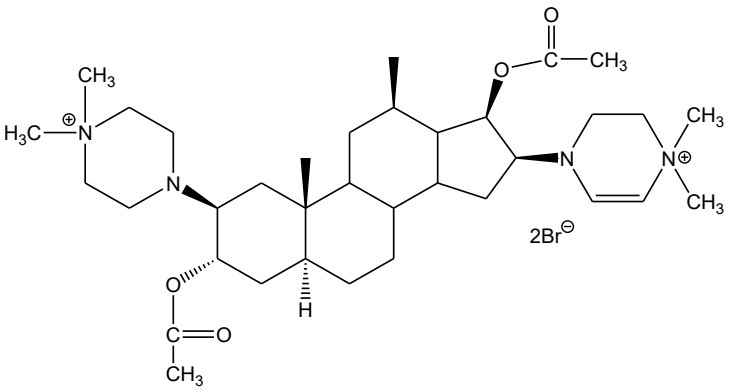




**Figure 4: Structure of pipecuronium and its impurity**

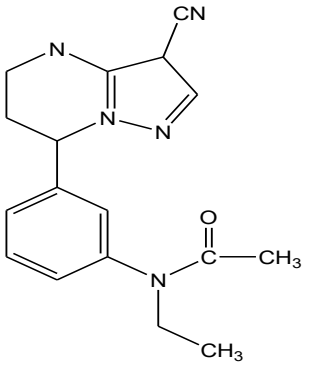
**High Performance Liquid Chromatography-Mass Spectroscopy (HPLC-MS) Studies**

The HPLC-MS is the preferred method in the majority of laboratories where online separation/spectroscopy facilities are available for impurity profiling. The standard soft ionisation techniques of HPLC-MS is generally used for obtaining the molecular mass of the impurities and it is enough for the structure of the impurity to set up at least a working hypothesis, especially if the mass spectrometer allows exact molecular mass to be determined. The chances to describe the valid structure are greatly increased when tandem mass spectrometer is available (HPLCMS/ MS) and hence fragmentation of the impurity can also be used for the structure elucidation. Some further characteristic examples of the many studies in the literature are as follows:(Ch. Bharathi and K. J. Prabahar et al., 2007).

1) The provisional structure elucidation by HPLC-MS/MS followed by preparative HPLC separation of the impurities using crude

drug material as the starting material and IR as well as NMR studies of the isolated impurities in **zaleplon.**

2) HPLC-DAD-MS (HPLC coupled with a Diode Array UV Detector and a Mass Spectrometer), and such other hyphenated techniques are almost regularly used. NMR has now been added to this combination to provide HPLC-DAD- NMR-MS capabilities in instruments.

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**Gas Chromatography-Mass Spectroscopy (GC-MS) Studies**

Classically, the use of GC-MS foregoes that of HPLC-MS. However, limited volatility and thermal stability of most of the drugs, the possibility of formation of trace level artefacts even in the case of relatively stable and volatile drugs are few limitations of GC-MS. Due to this reason, the importance of GC-MS is greatly decreasing in drug impurity profiling after introducing of HPLC-MS which soon became most widely used technique in impurity profiling. At the same time, GC-MS has some advantages as well such aswide ionisation capabilities and high-resolution separations with highly selective and sensitive detection. For this reasonGC-MS is still an important tool in the impurity profiling of certain drugs and a useful complementary method for others. GC and GC-MS play potent role in the identification and quantification of traces of volatile genotoxic impurities in drugs.

**Thin Layer Chromatography-Mass Spectroscopy (TLC-MS) Studies**

There were successful experiments to on-line coupling of TLC with MS. For reviews see (I. D. Wilson et al., 1999; J. K. Rozylo et al., 2001). Although,in the identification of impurities in drugs on-line TLC-MS has never played important role. The work of (A. Crecelius, M. R. Clench et al., 2003) merits mentioning. Separated spots on the plate could be subjected to direct matrix-assisted-laser-desorptionionisation time-of-flight mass spectrometry (TLC-MALDI-TOF- MS) without the obligation to remove the spots from the plate. To transfer the analyte from inside the silica gel to the surface only wetting the spot with methanol was necessary and thus enhancing the MALDI-TOF-MS signal. This technique was successfully applied to the identification and quantification of impurities in an experimental drug material (A. Crecelius, M. R. Clench et al., 2000).

**(LC-MS)Studies:**

In gradient elution reverse-phase LC-MS analysis with two distinct soft ionization techniques is the Atmospheric Pressure Ionization with Electrospray Source (API-ESI) and the chemical ionization of d-allethrine. LC-MS systems are widely used for analysis of complex mixtureof 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).

**Analytical challenges to current methods and potential new methods**

For the majority of compounds the threshold for identification and qualification of organic impurities is set at 0.1%. It is important to observe that the implication is that a Limit of Quantification (LOQ) ofapproximately 0.05% will

be required. For a compound having 98% purity, the 2% impurities could be composed of between 10 and 20 components at a level of analysis of 0.05%. It may become essential in future to increaseselectivity through the use of gradient separation, both in HPLC and TLC, or through the use of alternativetechnologies.(P. Sattanathan et al., 2006)However, gradient HPLC is the more usual technique, If the necessary selectivity is fails from single method, then orthogonal coupling of chromatographic techniques is used such as HPLC-CE (High Performance Liquid chromatography coupled with Capillary Electrophoresis) and HPLC-TLC, or coupling of chromatographic techniques with information rich spectroscopic methods such as HPLC-MS or HPLC-NMR, but fortunately only as a development tool rather than a tool for routine QC (Quality control) use. For impurity measurement the use of spectroscopic techniques may be further increased significantly. NMR has shown results for process related impurity and forstereo isomers, but still does not quite show the sensitivity required. The use of nearinfrared spectroscopy is rapidly increasing for detecting impurities, although more trials of true validation for low levels of impurities are required (S. Ahuja 'Chromatography' et al., 1992).Capillary Electrophoresis (CE) is one single method that is showing great promise in pharmaceutical analysis. With its great variety of separation modes and much increased efficiency it may provide sufficient peak capacity, and indeed CE is finding increasing favour for pharmaceutical analysis. CE also adds speed to selectivity, and many of the concerns over the robustness and transferability of CE separations have been dispelled recently through a number of collaborative studies. Additionally, while enantiomers are outside the scope of the current ICH guidelines, there is no doubt that, their level(s) must be controlled when they are potential impurities.CE-MECC can provide the necessary detectability to control enantiomers to the 0.1% level.(S. Ahuja 'HPLC' et al., 1992).

**Applications:**

In design and monitoring of quality, stability, and safety of drugs, spectroscopic techniques have various applications. Pharmaceutical drug may have origin either natural, synthetic or r-DNA technology product. It constituent almost all categories of drugs. Following Table 4 are the few examples of impurities which are reported in the API'S.

**TABLE 4:- (Impurities are reported in the API'S)**

| 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- | HPLC |

| | | |
|---|---|---|
| | methylimidazole and 1,8- bis[(N' cyano- N''- methyl) guinidino]-3,6-dithiaoctane | |
| **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, Nacetylmethamphetamine, N formylphedrine, N-acetylephedrine,N,Odiacetylephedrine, methametamine dimmer | GC |
| **Morphine sulphate** | 5-(hydroxymethyl)-2- furfural, 10-hydroxymorphine, 10-Oxomorphine | HPLC |

## CONCLUSION

Impurity profiling is a vital aspect of pharmaceutical analysis, ensuring the safety, quality, and efficacy of drug products. The presence of impurities can impact drug stability and therapeutic performance, making their identification and control essential. Advanced analytical and hyphenated techniques have significantly improved the detection and quantification of impurities at trace levels. Regulatory frameworks, such as those by the International Council for Harmonisation, provide standardized guidelines for impurity assessment and risk management. Ongoing advancements in analytical technologies will further enhance impurity profiling, supporting the development of safer, high-quality pharmaceutical products and ensuring better patient outcomes.

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