Review Article

FOURIER TRANSFORM ION CYCLOTRON RESONANCE-MASS SPECTROMETER: A "PROMISING TOOL" IN IMPURITY PROFILING

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ABSTRACT

Impurity is an unspecified component which is not the synthesized moiety marked as the active element or an excipient in the product. Analytical methods are monitored at two stages. First is during the investigation phase of drug development, second during shelf life. Major sources of impurity are organic, inorganic, residual solvent. Impurities may not have a therapeutic effect but may be potentially harmful. Therefore they need to be controlled. It is essential to study potential sources of impurities for its identification and Quantification. A scientific approach for impurity investigation gives a total understanding of a drug substance impurity profile to dominate toxic impurities. Variety of analytical techniques &/or their combination are important tools for identification and quantification of impurities of chemical & biological origin. Modern analytical methods include High-performance liquid chromatography (HPLC), Thin-layer Chromatography (TLC), Liquid chromatography-mass spectroscopy (LC-MS), Fourier Transform Ion Cyclotron Resonance-Mass spectrometer (FTICR-MS), Gas chromatography-Mass spectrometer (GC-MS) etc. The FTICR-MS can outstandingly be applied for biological impurities where it utilizes bimolecular ionization techniques and Orbitrap mass analyzer. FTICR-MS is having advantageous over other methods includes ultra-high resolving power with sub-parts-per million mass accuracy, reduces the time for analysis and precise mass to charge ratio. It makes FTICR-MS an attractive method for impurity profiling of pharmaceuticals.

Key Words: Impurity profiling of drug; Regulatory guidelines; Analytical technique; FTICR-MS.

INTRODUCTION

As per the International conference on harmonization (ICH) guidelines impurity is, "Any component of the new drug substance or new drug product which is not the chemical entity defined as the new drug substance or an excipient in the drug product".

Mainly 3 purpose of impurity study:

1. It gives evidence on HOW quality changes with time
2. It increases the safety & efficacy regarding the drug product
3. It also minimizes the adverse effect of drug material.

1. STANDARD REGULATORY GUIDELINE [1-4]

The United States food and drug administration (US-FDA) has endorsed the guidelines prepared by International Conference on Harmonization (ICH). Various regulators like Europian Union (EU), Japan & United States with joined efforts developed ICH guidelines for impurities and help to ensure data requirement consistently that should be submitted to various regulatory agencies.

Table 1: The various regulatory guidelines regarding impurities (1-7)

	GUIDELINE NO.	CONTENT
ICH	Q1A Q3A(R1) Q3B(R2) Q3C(R4)	Stability testing of substances and products Impurity study in new drugs Impurity study in new products Guideline for residual solvents
US-FDA		Impurity in New Drug Applications (NDA's) Impurity in Abbreviated New Drug Applications (ANDA's)

2. CLASSIFICATION OF IMPURITY

As per ICH guidelines, impurities are classified as follows:

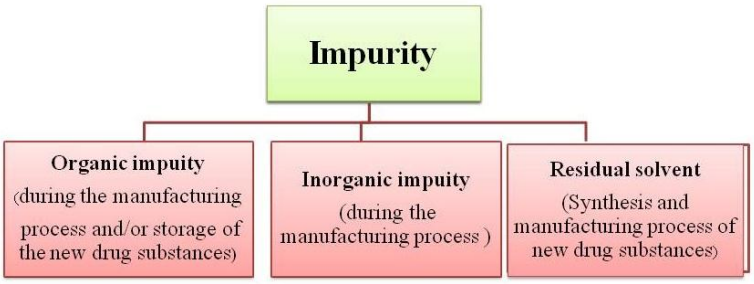


Fig. 1: Classification of impurities

Nowadays metallic impurities and microbiological impurities are also having high importance in final drug product and parental drug formulation respectively.

Organic Impurity

These impurities occur during the production process and/or storage of the new drug substance. They can be known or unknown, volatile or non-volatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands, and catalysts

Inorganic impurities

It can result from the production process. They are normally known and identified and include:

- Reagents, ligands, and catalysts
- Heavy metals or other residual metals
- Inorganic Salts
- Other materials (e.g., filter aids, charcoal)

Residual Solvents

The Liquids of organic and inorganic origin majorly employed as media drug synthesis of new drug substances or regarded as a residual solvent. Different official pharmacopeial or ICH Q3(C) prescribed the limits of acceptance for residual solvents in new drug substances. Depending on the ability of residual solvents to harm human health, they are classified into three classes as shown in table:

Table 2: Classification of residual solvents

Sr. No.	Solvent	Risk Assessment	Example
1	Class I	Solvents to be avoided	Benzene(2ppm), Carbon tetrachloride (4ppm), Methylene chloride (600ppm), Methanol (3000ppm), Pyridine (200ppm), Toluene(890ppm)
2	Class II	Solvent to be limited	N,N-dimethyl formamide(880ppm), Acetonitrile (410ppm)
3	Class III	Solvent with low toxic potential	Acetic acid, ethanol, acetone has permitted daily exposure of ≤ 50 mg/day

3. SOURCES OF IMPURITIES

Impurity can enter in the drug products or drug substances through different sources such as raw material used in the manufacturing of product, manufacturing process, storage condition, and transportation process. Physical contamination and the storage condition are the major reasons for the impurity formation. The variety of impurity present in the chemicals or pharmaceutical materials depends upon the following factors:

A) Raw materials used in Manufacture.
B) Method or process employed in manufacture.
C) Reagents/solvents/Reaction vessels.
D) Atmospheric contaminants
E) Particulate contamination
F) Cross-contamination
G) Microbial contamination
H) Packing errors
I) Due to the impact of heat, light, oxidants on drug Product
J) Change in pH
K) Presence of trace metals which may catalyse and accelerate the reaction

Limits for impurities

According to Q3B (R2) guidelines issued by ICH, it is not necessary that impurities should be below 0.1% level except potential impurities are toxic or unusually potent. Following is the acceptance criteria for the daily dose qualification:

Table 3: Drug substance impurities thresholds

Maximum daily dose [a]	**Reporting threshold** [b,c]
≤ 1 gm	>1 gm
0.1%	0.05%
Maximum daily dose [a]	**Identification threshold** [b,c]
< 1 mg	1.0% or 5 ug Total Daily Intake, whichever is lower
1 mg- 10 mg	0.5% or 20 ug TDI, whichever is lower
>10mg-2gm	0.2% or 2 mg TDI, whichever is lower
>2 gm	0.10%
Maximum daily dose [a]	**Qualification threshold** [b,c]
<10 mg	1.0% or 50 ug TDI, whichever is lower
10 mg- 100mg	0.5% or 200 ug TDI, whichever is lower
>100 mg-2 gm	0.2% or 3 mg TDI, whichever is lower
>2 gm	0.15%

4. ANALYTICAL METHOD FOR IMPURITY TESTING

Suitable analytical techniques are used to examine the impurity profiling of pharmaceutical compound. The impurities could be identified & quantified by performing various analytical techniques, individually or in combination.

The Identification and quantification of impurities are performed by several individuals or a combination of analytical techniques

It involved

1. High-Performance Liquid Chromatography (HPLC)
2. Thin Layer Chromatography (TLC)
3. UV-Visible Spectrophotometer
4. Nuclear Magnetic Resonance (NMR)
5. Capillary electrophoresis (CE)
6. Mass spectrometry (MS)
7. Supercritical fluid chromatography (SFC)
8. Gas chromatography
9. Fourier transform Infra red spectrometry (FTIR)
10. Liquid Chromatography (LC)
11. Liquid chromatography-mass spectroscopy (LC-MS)
12. High-Performance Liquid Chromatography- Nuclear Magnetic Resonance (HPLC-NMR)
13. Fourier Transform Ion Cyclotron Resonance-Mass spectrometer (FTICR-MS)
14. Gas chromatography-Mass spectrometer (GC-MS)
15. Liquid-liquid extraction
16. Capillary electrophoresis-mass spectrometry (CE-MS)

High-Performance Liquid Chromatography

The chromatographic and spectroscopic techniques are used for impurity profiling in pharmaceuticals. But due to higher detector sensitivity and number of choices of Stationary and Mobile Phases HPLC is most widely used technique in impurity profiling than other methods such as UV, TLC, LC, and HPTLC etc.

Thin-Layer Chromatography

TLC is mainly used for separation purpose. It having advantageous over other methods includes ease of use, cost-effectiveness, good sensitivity, the speed of separation, as well as its capacity to analyze multiple samples concurrently. TLC performs a vital function in the early stage of drug development when knowledge about the impurities and degradants in drug substance and drug product is limited.

UV spectrometry

UV spectrometry helps to recognize impurity in drug materials based on the maximum absorption of the sample to be analyzed. It becomes a valuable and handy analytical method for routine analysis because of its high selectivity.

Nuclear Magnetic Resonance

This technique provides data regarding molecular structure and stereochemistry of compound. It can also be used for multi component mixtures analysis. It is an important technique for the characterization and quantification of impurities and degradants present at the minimum quantity due to its non-destructive, non-invasive nature.

Capillary Electrophoresis

CE is a technique mainly used for separation and quantification of charged impurities. In instrumentation it consists of a high voltage power supply (0 to 30 kV), two buffer reservoirs, fused silica (SiO2) capillary, an on-column detector, and two electrodes. It achieves high separation efficiencies compared to other chromatographic techniques.

Mass Spectrometry

It is mainly used for determination of molecular mass and elemental form of the desired compound as well as also in monitoring, characterizing and quantification of drug-related substances in API. If an individual method does not provide significant selectivity, the coupling of this technique with GC, HPLC, and LC lead to rich information.

Supercritical fluid chromatography

In SFC, supercritical carbon dioxide is used as a mobile phase for detection of impurity. It gives HPLC-level sensitivity with lessened organic solvent usage. Its major advantage is an analysis of chiral or enantiomeric impurities present in drug substances at a very low level or low concentration.

Gas chromatography

GC is mainly used for analysis of volatile organic impurities includes such as residual solvents with a combination of flame ionization detector (FID). As per ICH Q3C guideline, headspace GC is worldwide used for residual solvent analysis in Quality control laboratories**.**

Fourier Transform Infrared spectrometry

It is very helpful for recognizing and verifying the structural composition of an impurity or degradant. FTIR provides a complex fingerprint that is specific to a particular compound. The functional groups of organic molecules are determined by FTIR techniques.

Liquid Chromatography

Impurities inside the drug material are normally present at very low quantities, so the complete analysis is entirely possible upon isolation of the impurities. Preparative LC is used for separation of impurities in enough amounts to carry out the structural investigation, regularly utilizing techniques such as FTIR, NMR**,** LC/MS, or GC/MS**.**

Liquid chromatography-mass spectroscopy

LC/MS is a potent scientific tool that is routinely applied in pharmaceutical development to test and recognize product impurities present at concentrations greater than 0.1 %. MS-based hyphenated techniques generally give extra robustness and ruggedness than related to other systems such as UV individual, because of their high specificity and sensitivity. It having advantageous over other methods include mass accuracy and higher resolution, giving them very useful for genotoxic impurity analysis. It has the potential to give nearly clear structural information about the unknown analyte.

Gas chromatography-Mass spectrometer

In GC-MS, GC separates semi-volatile and volatile components whereas MS gives detailed structural information. Several residual solvents are examined by GC such as ethanol, hexane, benzene, carbon tetrachloride etc. It was the first hyphenated technique introduced for determination of organic volatile impurities, and residual solvents in a sample and used till today. Due to the vaporization and thermal stability of analyte few kinds of literature exist on the characterization of impurities by GC-MS.
Drugs, its corresponding impurities and method used for identification are given below in Table 4.

Table 4: Drugs, its corresponding impurities and method used for identification

Drug Name	Impurity	Analytical method	Reference
Amphotericin B	Tetraenes	UV Spectroscopy	5, 44, 46
Atropine sulphate	Apo tropine	UV Spectroscopy	5, 44, 46
Mercaptopurine	Hypoxanthine	UV Spectroscopy	5, 45, 46
Cloxacillin	N,N-dimethyl aniline	GC	5, 46
Doxorubicin	Acetone and ethanol	GC	5, 46, 47
Methamphetamine	Ephedrine, methylephedrine, N-formylmethamphetamine, N-formylphedrine, N-acetylephedrine.	GC	5, 46
Fluroscene sodium	Dimethyl Formamide	GC	5, 47
Framycetin Sulphate	Neamine	TLC	5, 48
Ethambutol hydrochloride	2-amino butanol	TLC	5, 46, 48
Cimetidine	2,5-bis[(N'-cyano-N''-methyl) guinidinoethylthiomethyl]-4-methylimidazole and 1,8- bis[(N' cyano- N''- methyl) guinidino]-3,6-dithiaoctane	HPLC	46
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	46
Morphine sulphate	5-(hydroxymethyl)-2- furfural, 10-hydroxymorphine, 10-Oxomorphine	HPLC	46
Lincomycin	Lincomycin B	Capillary electrophoresis	5, 49
Meclophenoxate	N,N-dimethyl ethanolamine	Capillary electrophoresis	5

5. FTICR-MS FOR IMPURITY PROFILE STUDY

DESCRIPTION

Hybrid quadrupole-FTICR-MS or Fourier transforms mass spectrometry (FTMS). It has a leak valve and pulse valve for ion-molecule reactions in gas phase, Electrospray & nanospray sources and Electron Capture Dissociation (ECD). A tunable UV-visible laser is joined to the FTICR.

PRINCIPLE OF OPERATION

FTICR-MS is based on the circular movement of charged particles in a high magnetic field i.e. cyclotron movement. Circular motion keeps a blend of ions in a fixed space. Specific ion mass is absorbed in the specific resonance frequency (RF) and its separation depends on the mass-to-charge (m/z) ratio of the ions. The periodical movement of ion ratio is recorded which turned to a frequency spectrum with a Fourier transform, and then calibration of spectra which is converted to a mass spectrum. The significant advantage of this technique is ultrahigh resolution mass spectrometer with high mass accuracy (2 ppm) & its ability to resolve interferences. These performances make the technique higher value for multiple residue analyses.

INSTRUMENTATION

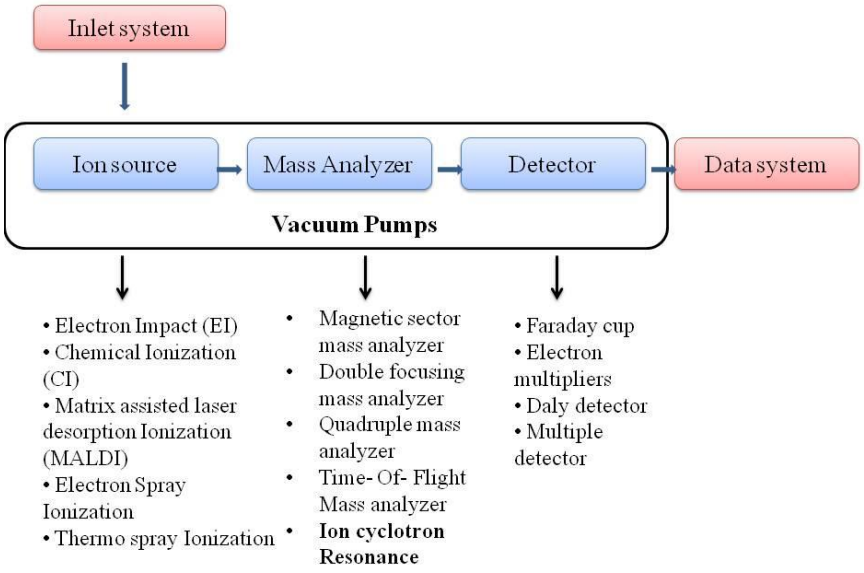


Fig. 3: Instrumentation of FTICR-MS

All FTICR-MS technique has common five main components.
a. Ionization source
b. Superconducting magnet
c. Analyzer cell
d. Detector
e. Sophisticated data system

a. Ionization source-

The sample is introduced in the ion trap also known as Ion Cyclotron Resonance (ICR).
A sample can be solid or liquid.
Ionization techniques involve- Matrix assisted laser desorption ionization (MALDI),
Electro spray ionization (ESI),
Chemical ionization (CI),
Atmospheric Pressure Photo ionization (APPI).
Once the sample goes in ICR, a magnetic field applied to sample.

b. Analyzer cell (ICR cell)-

ICR cell is an essential part of the FTICR-MS instrument. In which ions are collected, mass analyzed and detected.

When the sample in the magnetic field, ions rotate circularly this is perpendicular to the direction of the field**.** The angular frequency of this motion is called the cyclotron frequency.

The resonance condition is reached when cyclotron frequency (ωc) equals the frequency of the radiofrequency source and at resonance; measurable radiofrequency energy passes from the RF circuit to the ion beam.

Formula

$$\omega c = (\vartheta)/r = zeB/m$$

Where v= velocity
r= radius
z= charge
B= magnetic field
m= mass

Once, the ion in the magnetic field and rotating circularly then electrical field applied to increase the velocity and radius to maximize cyclotron frequency.

After reach to cyclotron frequency, electrical field shut off. Ions are decelerating it shows the frequency of each ion.

Record the decelerating ion that's velocity depends on their mass and charge are shown in this equation,

$$\omega c = (\vartheta)/r = zeB/m$$

For performance improvement, an increase in the magnetic field strength (B) and its homogeneity are very important

c. Detector-

The detector converts the angular frequency to the time domain and further, it is converted to the mass domain.

d. Data

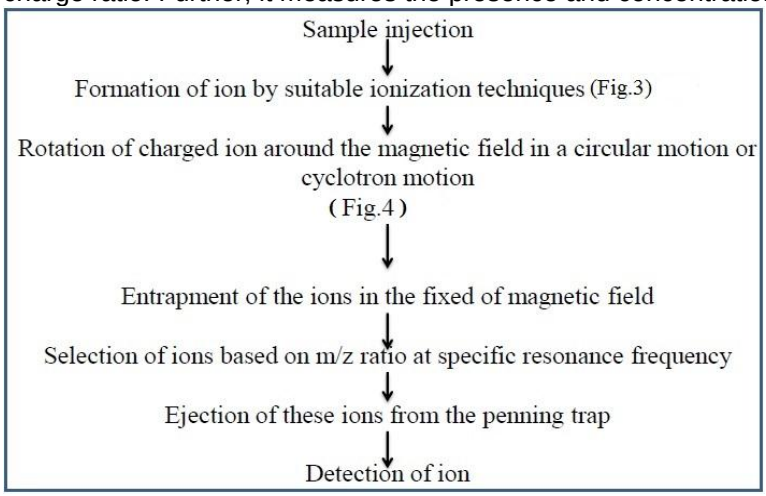
The data gives a graph of relative abundance vs. m/z ratio.

Data including their

- High Resolution Mass Spectrometry (HRMS),
- Fragmentation patterns,
- Mass spectrometry spectra.

WORKING-

1. FTICR-MS is identical to other mass spectrometers. They ionize a sample and ion separation is carried out by their mass-to-charge ratio. Further, it measures the presence and concentration of those ions.



Scheme 1: Work flow of FITCR-MS

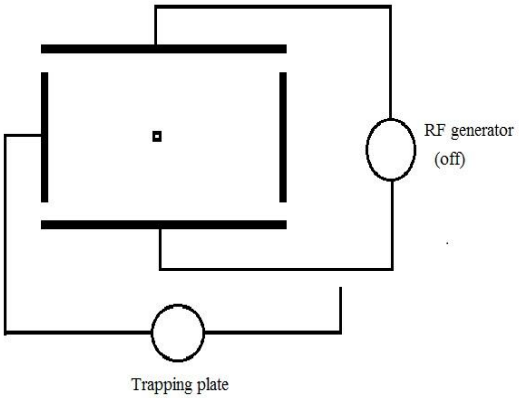


Fig. 3: Trapping plates keeps the ions in the centre of the cell

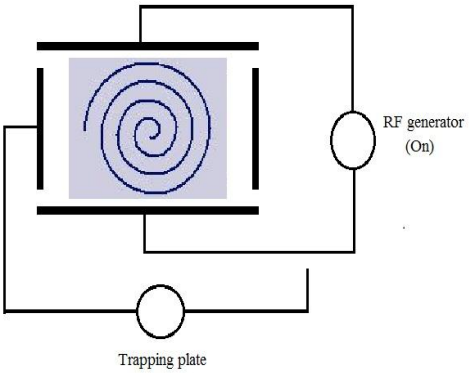


Fig. 4: The Resonance Frequency (RF) moves the ions into the higher orbit

ADVANTAGES

1) High accuracy and ultrahigh resolution with sub-parts-per-million mass accuracy and reduces the time for analysis.
2) Two molecules that differ by only 0.1amu give well-separated signals using broadband detection.
3) We can change the ionization technique in accordance with the nature of the sample.
4) It having flexibility in selecting the ionization source or fragmentation system.

DISADVANTAGES

1) It had relatively slows acquisition rates

APPLICATION

1. FTICR-MS in LC-MS and CE-MS used for metabolomics study.
2. In LC-FTICR-MS, fused core column is used for analysis of lipid in human and mouse plasma.
3. LC-ESI-FTMS is used for identification of isobariclyso phosphatidylcholines in lipid extract of gilthead sea bream with high resolution for phospholipid.
4. FTICR-MS is mainly used for metabolomics study such as organic, fatty and amino acids, sugar alcohols, sugars, amines, vitamines and hormones, as well as in terpenoids, phenolics, alkaloids and flavonoids study and also in lipidomics study.
5. Profiling of Serum Peptides and Proteins & Salivary Peptides and Proteins MALDI-FTICR-MS are mainly used. Also, it is utilized for Qualitative analysis and structure elucidation of tiny molecules like DNA, proteins.
6. APPI-FTICR-MS applied in the discovery of about 30000 Chemical Components into the Shale Oils.

7. FTICR-MS is used during fuel purification process for accurate mass measurement of elemental composition and also in metal-organic complexes identification and determination from natural waters.
8. In petroleum field, for determination of the molecular structures of petroleum samples, collision induced dissociation (CID)-FTICR-MS technique is most commonly used.
9. FTICR-MS used for examination of the naphthenic acid content of unrefined oils to avoid the corrosion of instruments.
10. ESI-FTICR-MS is mainly used in rock fuel and coal tar examination. It is used for investigation and analysis of oxygen composites in shenmu coal tar and longkou rock fuel.
11. MALDI-Time of flight (TOF)-MS technique is used for analysis of endogenous monoclonal immunoglobulins from serum and urine samples.
12. ESI and APPI sources coupled with A12T FTICR MS majorly used for the study of Athabasca oil from sands process water.

CONCLUSION

From the above data, it is concluded that FTICR-MS is a potential analytical technique in the investigation of complex sample systems such as metabolomics, lipidomics crude oil, and a variety of precious biological sample. The techniques provided a result with high mass accuracy and ultra-high resolution within the predefined time frame.

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