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ICP-MS and ICP-OES – A Review

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ABSTRACT

The most important aspect of pharmaceuticals is its safety and efficacy which determines the fundamental aspect of its drug therapy. Therefore controlling the levels of impurities in drugs is important. There are many different types of impurities that are present in pharmaceuticals, in this study the focus is on inorganic impurities and the analytical techniques used for its detection mainly ICP-MS, ICP-OES. These new methods address the limitations of the current methods like 'heavy metal tests', extending the list of analytes, reducing maximum permitted exposure limits and taking account of the route of exposure. In this study, we found that ICP-MS is an effective tool in impurity profiling of Single, Multi and speciation analysis of different element's present in bulk drugs and formulations. In recent scenario, many of the pharmaceutical industries are adopting these hyphenated techniques.

Keywords: *Impurity profiling, ICP-MS, ICP-OES.*

1. INTRODUCTION

An impurity as defined by the ICH (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines is "any component of the medicinal product which is not the chemical entity defined as the active substance or an excipient in the product[1]".

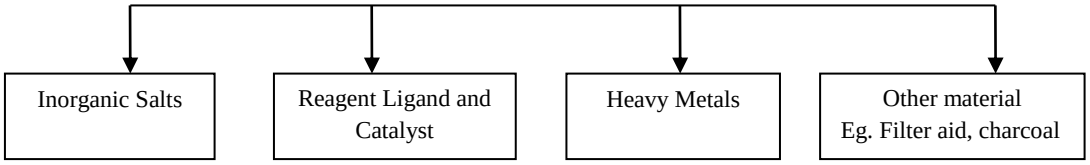
Identification of an impurity plays a significant role in the pharmaceutical formulation as safety and efficacy of the compound is a concern. Quantification of an impurity in a given compound is a key parameter as safety and efficacy of given compound is a concern. The determination of impurities is a critical issue as in pharmaceutical industry. There is various method is available for determination of impurities but this article is stressed on Inductively coupled plasma mass spectroscopy (ICP-MS) and Inductively coupled plasma atomic emission spectroscopy (ICP-OES).

Table 1: Regulatory Guidelines on the impurity

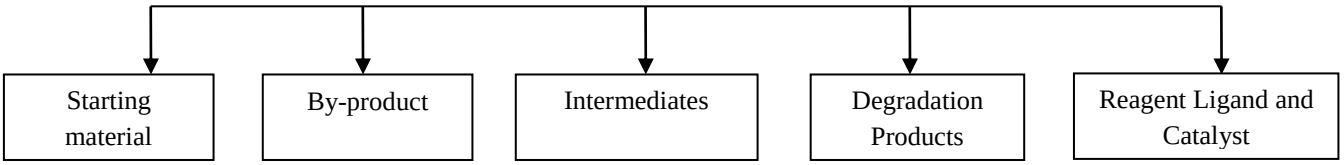
Sr. no	GUIDELINE	TITLE
1	ICH Q3A	Impurities in New Drug Substances
2	ICH Q3B	Impurities in New Drug Products
3	ICH Q3C	Impurities: Guidelines for residual solvents
4	ICH Q3D	Guidelines for elemental analysis

2. SOURCES OF IMPURITIES

A) Inorganic impurities



B) Inorganic impurities



Methods for determination and quantification of impurities

- Reference standard method
- Spectroscopy
- Chromatographic method
- Isolation method
- Characterization method

An analytical technique for elemental analysis

There are various techniques are available for elemental analysis but in this review inductively coupled plasma mass spectroscopy (Icp-Ms) and inductively coupled plasma atomic emission spectroscopy (ICP AES) These two methods are studied in detail.

3. INDUCTIVELY COUPLED PLASMA MASS SPECTROMETRY

An inductively coupled plasma (ICP) is a type of plasma source in which the energy is supplied by electric currents which are produced by electromagnetic induction, that is, by time-varying magnetic fields1. There are two types of ICP geometries: planar and cylindrical. In a planar geometry, the electrode is a coil of the flat metal wound like a spiral. In cylindrical geometry, it is like a helical spring. Inductively Coupled Plasma Mass Spectrometry was commercially introduced in 1983 and has gained general acceptance in many types of laboratories. Inductively Coupled Plasma Mass Spectrometry is an analytical technique used for elemental determinations[2].

Mass spectrometer coupled with inductively coupled plasma ionization (ICP-MS) is one of the most sensitive analytical techniques for fast multi-element determination of heavy metals in trace and ultra-trace concentrations in different sample matrices. Recently, it has emerged as a powerful technique and at present, it is the most suitable technique for the analysis of trace elements in bulk drugs and pharmaceuticals. It provides a major service to the pharmaceutical industry in the analysis of heavy metals in drugs[2]**.**

3.1 Principle

This technology applies the principle of generation of high-temperature plasma source at 10000-degree Celsius, through which the pretreated sample is passed. The elements in the sample at such high temperature are ionized and directed further into the MS. The MS then sorts the ion according to their mass to charge ratio followed by directing them to an electron multiplier tube detector this detector then identifies and quantifies

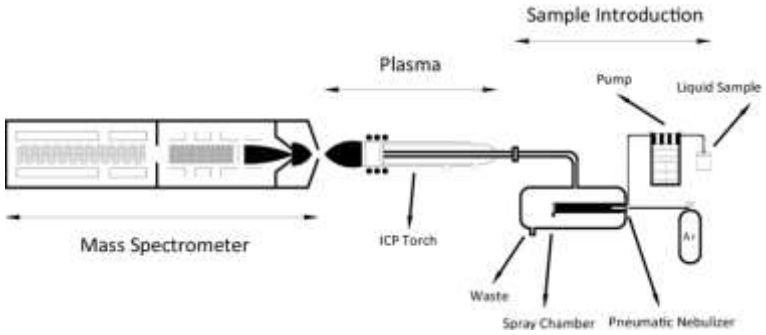


Fig. 1: Diagrammatic representation of ICP MS

Source: (A. Kashani, J. Mostaghimi, aerosol characterization of concentric pneumatic nebulizer used in inductively coupled plasma—mass spectrometry (ICP-MS, Atomization, and Sprays, 20(5): xxx–xxx, 2010), 2)

3.2 Components of ICP MS

1) **Inductively coupled plasma**
   - This is plasma that contains more no of ions
   - It makes compound electrically conductive
2) **Mass spectrometry**
   For coupling to mass spectrometry, the ions from the plasma are extracted through a series of cones into a mass spectrometer, usually a quadrupole. The ions are separated on the basis of their mass-to-charge ratio and a detector receives an ion signal proportional tithe concentration
3) **ICP-MS Interface**
   Placed between ICP and MS**.** It is having the main role in the formation of vacuum... the MS system required vacuum for ionization hence interferences is important in vacuum creation.

4) Plasma Torch

Inductively coupled plasma (ICP) for spectrometry is sustained in a torch that consists of three concentric tubes, usually made of quartz. The end of this torch is placed inside an induction coil supplied with a radiofrequency electric current. A flow of argon gas (usually 14 to 18 liters per minute) is introduced between the two outermost tubes[2]

5) Detector

The most common type of ion detector found in an ICP-MS system is the channeltron electron multiplier. This cone or horn-shaped tube has a high voltage applied to it opposite in charge to that of the ions being detected. Ions leaving the quadruple are attracted to the interior cone surface. When they strike the surface additional secondary electrons are emitted which move farther into the tube emitting additional secondary electrons[2]

3.3 Advantages

- The extremely low detection limit
- Possibility to detect isotope composition of the element
- Ability to quantify elements in any source like blood, serum, urine.

4. INDUCTIVELY COUPLED PLASMA-ATOMIC EMISSION SPECTROMETRY (ICP-AES)

In these in instrument contain hot plasma and also contains a mixture of electrically conducting cations and electrons which is gaseous in nature. A gaseous mixture of cation and electrons maintain the conductance

4.1 Principle

Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) is the measurement of the light emitted by the elements in a sample introduced into an ICP source.

The ICP is argon-based, radio frequency plasma & input Rf frequency is either 27 or 40 MHz at powers from 1 to 2 kW. The temperature in the central analytes channel ranges from about 6000 to 8000° K. At these temperatures most elements are largely atomized and ionized, these emit characteristic radiation.[4]

4.2 Instrumentation

These instruments consist of various parts which have a significant role in working on the instrument.

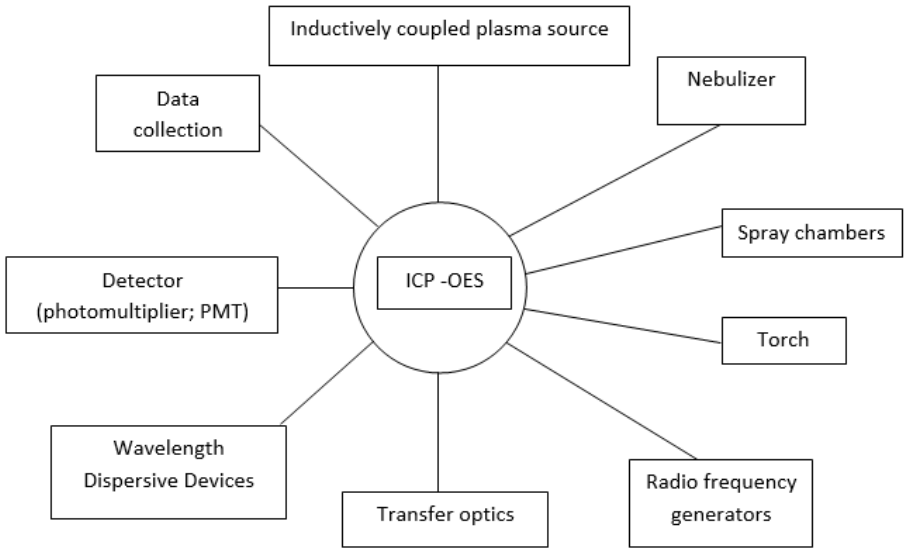


Fig. 2: Various parts of ICP –OES

4.3 Various parts of ICP-OES

In inductively coupled plasma-optical emission spectrometry, the sample is usually transported into the instrument as a stream of the liquid sample. Inside the instrument, the liquid is converted into an aerosol through a process known as nebulization. The sample aerosol is then transported to the plasma where it is desolvated, vaporized, atomized, and excited and/or ionized by the plasma. The excited atoms and ions emit their characteristic radiation which is collected by a device that sorts the radiation by wavelength. The radiation is detected and turned into electronic signals that are converted into concentration information for the analyst.[4]

Nebulizer:

The test sample is treated with 2-3 percent of HNO3 this prevents adsorption of metals on instrument tubing and bottle before the introduction of the test sample into the plasma. Nebuliser breaks liquid test sample into gaseous aerosols. Then it is transferred to the plasma.

Forces which break the liquid

- Pneumatic forces
- Ultrasonic mechanical forces

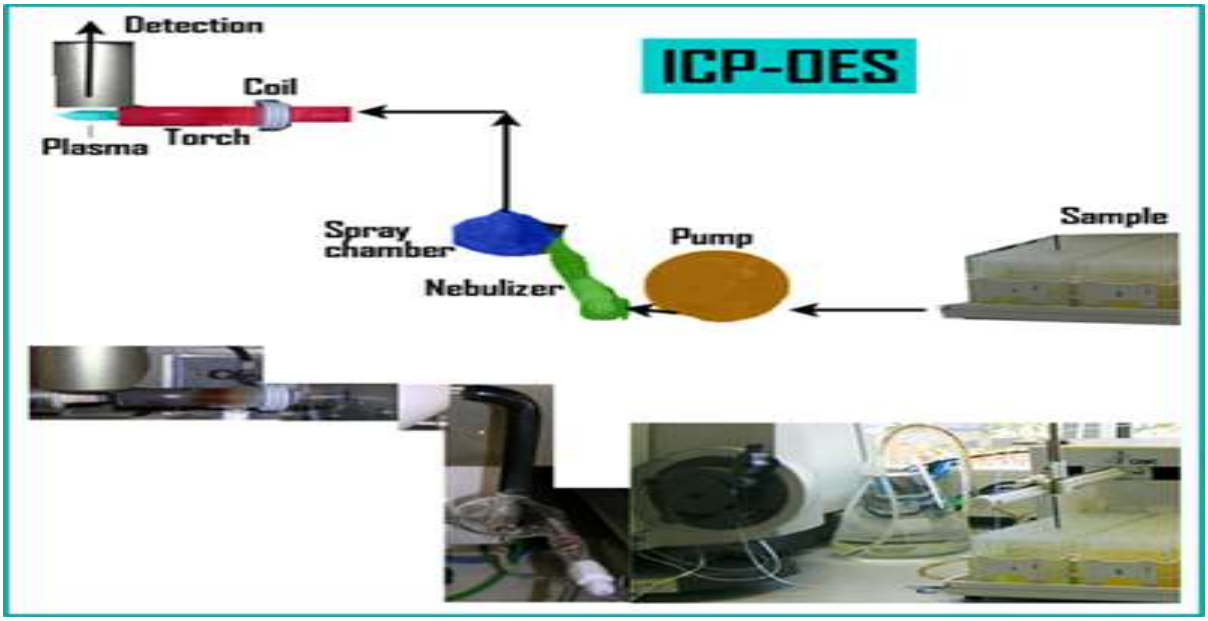


Fig. 3: Diagrammatic representation of ICP-OES

(Source: https://www.ru.nl/science/gi/facilities-activities/elemental-analysis/icp-oes/)

Pumps:
A peristaltic pump is generally preferred. It is used for pumping the test sample.

Spray Chambers:
Once the sample aerosol is created by nebulizer, it is transported to the torch & injected into the plasma. A spray chamber is placed between nebulizer and torch. The primary function is to remove large particles from the aerosol. A secondary purpose is to smooth out pulses that occur during nebulization while smaller particles travel by the Airflow and enter the torch. Evaporation, atomization, and excitations/ionizations occur in the plasma at temperatures reaching 10000 K[3]

Torch:
The torches contain three concentric tubes for argon flow and aerosol injection. The spacing between the two outer tubes is kept narrow so that the gas introduced between them emerges at high velocity. This outside chamber is also designed to make the gas spiral tangentially around the chamber as it proceeds upward. One of the functions of this gas is to keep the quartz walls of the torch cool and thus this gas flow was originally called the coolant flow or plasma flow but is now called the "outer" gas flow. For argon ICPs, the outer gas flow is usually about 7 - 15 liters per minute. The chamber between the outer flow and the inner flow sends gas directly under the plasma toroid. This flow keeps the plasma discharge away from the intermediate and injector tubes and makes sample aerosol introduction into the plasma easier. In normal operation of the torch, this flow formerly called the auxiliary flow but now the intermediate gas flow is about 1.0 L/min. The intermediate flow is usually introduced to reduce carbon formation on the tip of the injector tube when organic samples are being analyzed[4].

Radio frequency generators:
It is part of the instrument which provides the power for the generation of plasma discharge. It generates 700 to 1500 watts of power then it is transferred to the plasma gas. It has two types as given below:

- Crystal controlled generators
- Free running generators.

Wavelength dispersive devices:
Physical dispersion consists of following devices:

- Diffraction grating,
- Prisms, filters,
- Interferometers,
- Echelle grating

Multi-element analysis is possible with conventional polychromatic where each slit aligned to allow a specific wavelength of radiation to pass to a detector

Detectors:
Photomultiplier tube is most widely used detector in ICP –OES. But there are various detectors are also used which are listed below:

- Photomultiplier tube
- Array detectors
- Photodiode array
- Charge-injection device (CID)
- Charge-coupled device (CCD)

4.4 Applications

i. Agricultural and Foods[6]:

This is an important sector in which ICP-OES is applied. The test sample includes agriculture soil fertilizers, plant materials, feedstuff, foods, animal tissues, and body fluids.
Analysis of infant formula for Ca, Cu, Fe, Mg, Mn, etc[6].

ii. **Biological and Clinical[6]:**

To find out Cr, Ni, Au in urine[6].
Determination of Aluminium in human blood[6]
To find out se in liver[6]

iii. Geological[6]:

The technique is also used for applications such as determining origins of rock formations and for marine geochemistry.

- Determination of U in ore grade material[6].
- Analysis of river sediments for several metals[6].
- Analysis of carbonate drill cores for major, minor and trace elements[6].
- Determination of rare earth elements in rock formations[6].
- Analysis of plankton for several elements[6]

iv. Metals[6]:

Determination of toxic, trace and major constituents in coal and slags[6].
Analysis of low alloy steels for As, B, Bi, Ce, La, P, Sn, and Ta; high-precision determination of Si in steels[6];
Determination of contaminants in high-purity Al[6].
Analysis of superconducting materials for trace contaminants[6].

5. CONCLUSION

Impurity is compound other than excipients and API which affect the safety and efficacy of the formulation. To determine safety and efficacy of drug the determination and quantification of the impurity are required. There are several guidelines as per ICH guidelines. There are several methods for determination and quantification of impurity. For elemental analysis, ICP MS and ICP OES Are two widely used method. ICP-MS and ICP-OES can trace and ultra-trace level in pharmaceuticals.

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