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Review Article

ANALYTICAL METHODS FOR ESTIMATION OF METALS

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ABSTRACT

Modern analytical methods today have been proven to be very useful for accurate determination of metals. It is required to determine optimum concentration of some essential metals as deficiency or excess may cause abnormalities in body. Also there is strict legal requirement to monitor and control levels of metals in food, environment and medicines. Estimation of concentration of metals in body tissues is also essential. Various methods described are atomic spectroscopy, voltammetry, X-ray fluorescence and ICP-MS along with principle and instrument. These methods are very sensitive and very low detection limits of upto pictogram levels have been achieved. High toxicity of metals to living organisms depends on their species. In some cases the elemental state of these heavy metals is critical however in other cases their various organometallic species are more hazardous. Hence speciation analysis of metals is necessary which are done using voltammetric methods and by ICP-MS.

Keywords: Metals, Speciation, Atomic absorption spectroscopy, X-ray fluorescence, Stripping Voltammetry, ICP-MS.

INTRODUCTION

Some metals are essential to be present in body for healthy functioning of body as they play critical roles in the structures of proteins and the activities of enzymes. For example, chromium aids in glucose metabolism and helps regulate blood sugar by potentiating insulin and serving as a component of glucose tolerance factor. Manganese is key component of enzyme systems, including oxygen-handling enzymes; it supports brain function and is required for blood sugar regulation. These metals have to be present in optimum concentration in body. Deficiency or excess amounts of specific metal in body can cause inappropriate functioning or toxicity.

Many metals are reported to be toxic in low levels. For example, lead causes adverse effects on psychological and behavioral activities in living beings. It also causes kidney dysfunction, osteomalacia and obstructive lung diseases[1,2]. Cadmium is carcinogenic with serious health hazards. Mercury is highly toxic element and it tends to bioaccumulate in the living organisms and food chain[3]. Chromium, in its hexavalent form, is also carcinogenic[4]. So metal contamination in food, water and pharmaceutical products pose serious risk

to human beings. Monitoring of metals in process intermediates and final products is an important activity in food and pharmaceutical industry. Metals act as catalysts for decomposition of pharmaceutical products. Also monitoring of metals in environment is essential to prevent health hazards. Sources of metal impurities include those that are deliberately added to the process (e.g., catalysts), those that are carried through a process (e.g., undetected contaminants from starting materials or reagents), those coming from the process (e.g., leaching from pipes and other equipment), and those that occur naturally (e.g., from naturally derived plant or mineral sources)[5]. The pharmacopeial forum of USP has proposed two chapters- 1) Elemental Impurities-Limits and 2) Elemental Impurities-Procedures to replace the general test chapter-Heavy Metals[6,7]. The first chapter is proposed to set limits on amount of elemental impurities in pharmaceuticals. In this chapter elemental impurities are classified as shown in Table 1.

Class 1 impurities: Class 1 elemental impurities (Table 2), because of their unacceptable toxicities or deleterious environmental effects, should not be present in a drug substance, excipient, or drug product. However, if their presence is unavoidable, their levels should be restricted as shown in Table 2, unless otherwise stated in the individual monograph.

Class 2 impurities: Class 2 elemental impurities (Table 3) should be limited in drug substances, excipients, and drug products because of inherent toxicities.

The determination of elemental impurities in pharmaceuticals, excipients or drug products has been performed as recommended by pharmacopoeias, generally based on limit tests. In general, the analysis procedure is based on sample dissolution, or wet-acid digestion or dry ashing and ignition followed by precipitation of metals as sulphides using thioacetamide at pH 3.5. The presence of metals is detected by visual comparison with a standard solution of lead. The main disadvantage of this method is the lack of specificity and sensitivity. Because the method rely on a subjective visual examination and comparison of the sample solutions to a lead standard solution, they require large amounts of sample to obtain parts per million (µg/g). Moreover, this method is prone to interference by other concomitant elements that also react with thioacetamide and precipitate. Also the ashing step causes loss of volatile elements[8]. Because of the limitations of compendial method, there was a need for the development of more reliable and accurate method to estimate metals in pharmaceutical products. Most commonly techniques are atomic spectroscopy, voltammetry and X-ray methods. The pharmacopeial forum of USP has suggested use of techniques, viz., inductively coupled plasma-atomic emission spectroscopy (ICP-AES) and inductively coupled plasma-mass spectrometry (ICP-MS) for element determination.

Speciation is an important factor that is to be considered when metals are determined[9]. The potential of some metals to be harmful or beneficial is dependent on their speciation. Speciation analysis is defined as the determination of the concentrations of the different physicochemical forms of the element which make up its total concentration in the sample. Metals can exist in a range of physicochemical forms in environmental samples, including hydrated metal ions, inorganic and organic complexes, and adsorbed on organic and inorganic colloidal particles. Toxicity of metals may depend on the physicochemical form in which it is present. For example, chromium in its trivalent form is essential in low level concentration in metabolic

operations while its hexavalent form is highly toxic and carcinogenic. Arsenic is present in wide variety compounds of widely differing toxicity. Inorganic compounds such as arsenite and arsenate are known to be highly toxic, while organics are generally considered to be non-toxic.

Sample preparation is very important area in pharmaceutical and biological analysis[10]. When the analyte is present in trace amount special care has to be taken for sample preparation. The grades of reagents that are to be used for sample preparation should be of highest purity to avoid risk of contamination. When the amount of element to be detected is below or close to the limit of detection of the technique being used, a preconcentration step is needed. Preconcentration methods that are generally used include chromatography, solvent extraction, decomposition using a reagent and/or heat.

ATOMIC ABSORPTION SPECTROSCOPY[11,12,13]

Atomic Absorption spectroscopy is based on absorption of radiation by atoms. The passage of polychromatic ultraviolet or visible radiation through a medium that consist of monoatomic particles, such as gaseous mercury or sodium, results in the absorption of few well-defined frequencies. Absorption results in excitation which occurs only by an electronic process in which one or more electrons of the atom are raised to a higher energy level. For example, sodium vapour exhibits two closely spaced, sharp absorption peaks in the yellow region of the visible spectrum (589 & 589.6 nm) as a result of the excitation of the 3s electron to two 3p states that differ only slightly in energy.

Instrumentation

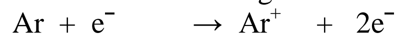
The main components of an atomic absorption spectrometer are a radiation source, an atomisation cell and a method of wavelength selection and detection (fig.1). The radiation source generates the characteristic narrow-line emission of a selected metal .The atomisation cell is the site where the sample is introduced. The atomisation cell causes the metal containing sample to be dissociated, such that metal atom are liberated from a hot environment.

Radiation Sources

Hollow-Cathode Lamps (HCL)

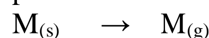
HCL (fig. 2) is the most common source for atomic absorption measurement. The lamp consists of a tungsten anode and a cylindrical cathode sealed in a glass tube filled with an inert gas usually argon or neon at a pressure of 1 to 5 torr. The cathode is constructed of the metal whose spectrum is desired or serves to support a layer of that metal.

In order to initiate the lamp a voltage (100-400v) is applied across the electrodes, corresponding to a current of 2-30 mA. The passage of the current causes ionisation of the fill gas.



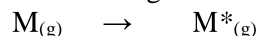
$$Ar + e^- \rightarrow Ar^+ + 2e^-$$

The positive fill gas ions are then attracted to the cathode and upon impact the energy of the incoming fill-gas ions is sufficient cause metal atoms to be liberated in a process which is known as 'sputtering'.



$$M_{(s)} \rightarrow M_{(g)}$$

Upon liberation, the metal atoms further collide with the fill-gas ions and electrons thus causing excitation of the metal.



$$M_{(g)} \rightarrow M^*_{(g)}$$

The excited metal atoms return to the ground state and emit characteristic wavelengths of the metal itself. Multielement cathode lamps can also used which permit determination of more than a single element.

Atomisation cells

Most common atomisation cell used is flame cell. For greater sensitivity a graphite furnace is required.

Flame Atomization Cell

In flame atomic absorption spectroscopy (FAAS), a liquid sample is aspirated into a flame via a nebulizer. In the nebulizer, the sample is converted to a mist, and the droplets of the mist are easily burned in the flame, which serves as the sample cell. The flame provides a source of neutral atoms or molecules to absorb energy, and acts to desolvate and atomize the sample. Table 4 shows temperature of some flames used in FAAS. The most commonly used flame is an air/acetylene flame, which burns within at temperature 2400°C, while the nitrous oxide-acetylene flame which burns at 2800°C is used for refractory compounds (that is, compounds that are highly resistant to thermal decomposition such as the oxides of boron, tungsten, uranium, zirconoium). Both are located in a slot burner which is positioned in the lightpath of hollow cathode lamp. A nebuliser/expansion chamber arrangement (fig. 3) is used for introduction of aqueous sample into the flame.

Most commonly used nebulizer used is pneumatic nebulizer. It consists of a concentric glass tube through which a capillary tube is fitted (fig. 4). The sample is drawn up through the capillary by the action of the carrier gas (argon, at a pressure of 70-350kPa) escaping through the exit orifice that exists between the outside of the capillary tube and the inside of the capillary tube and the outside of the glass concentric tube. The size of toroid created by the two tubes is of the order of 10-35µm in diameter. The action of the escaping argon gas and liquid sample is sufficient to produce a coarse aerosol (the Venturi effect). The typical uptake rate of this nebulizer is between 0.5 and 4 ml per minute. As a consequence of Venturi effect it is not necessary to use a peristaltic pump.

The expansion chamber converts the coarse aerosol into finer aerosol. FAAS is relatively inexpensive and simple to operate.

Limitations of flame atomic absorption spectroscopy:

1) The sample introduction system is inefficient and requires large volumes of aqueous sample.

2) The residence time, i.e. the length of time that the atom is present in the flame is limited due to the high burning velocity of the gases, thus leading to rather high detection limits.

3) An inability to analyze solid samples directly, solid require dissolution prior to analysis.

Graphite Furnace (Electrothermal atomizer)

In this device, atomization occurs in a cylindrical graphite tube that is open at both ends and that has a central hole for introduction of samples by means of a micropipette. The tube is about 5cm long and has an internal diameter of about 3-8mm. Heating of the graphite tube is achieved by the passage of an electric current through the unit via water cooled contacts at each end of the tube. Various stages of heating are required to dry the sample matrix and finally to atomize the analyte (fig. 5). An additional heating cycle may be introduced for cleaning i.e. removal of any residual material. The drying stage is necessary to remove any residual solvent from the sample. This is achieved by maintaining the heat of the graphite tube above the boiling point of the solvent, e.g. water at 110°C for 30s. The second step concerns the destruction of the sample matrix in a process called ashing; this involves heating the tube between 350°C and 1200°C for 45s. Finally, the temperature of the graphite tube is raised to between 2000°C and 3000°C for 2-3s, allowing atomization of the analyte of interest. During this final atomization step, the absorption of the radiation source by the atomic vapor is measured.

An internal flow of an inert gas (N_2 or Ar) is maintained during the drying and ashing stages to remove any extraneous material. Figure 6 illustrates L'vov platform, which is often used in graphite furnaces. The platform is also made of graphite and is located beneath the sample entrance port. When the tube temperature is increased rapidly, however, atomization is delayed because the sample is no longer directly on the furnace wall. As a result atomization occurs in an environment in which the temperature is not changing so rapidly, which improves the reproducibility of analytical signals.

X-RAY FLUORECENCE SPECTROSOPY[14,15,16]

X-ray fluorescence methods have been of great use for non-destructive analysis of sample.
When a primary X-ray excitation source from an X-ray tube or a radioactive source strikes a sample, the X-ray can either be absorbed by the atom or scattered through the material. The process in which an X-ray is absorbed by the atom by transferring all of its energy to an innermost electron is called the photoelectric effect. During this process, if the primary X-ray had sufficient energy, electrons are ejected from the inner shells, creating vacancies. These vacancies present an unstable condition for the atom. As the atom returns to its stable condition, electrons from the outer shells are transferred to the inner shells and in the process give off a characteristic X-ray whose energy is the difference between the two binding energies of the corresponding shells. Because each element has a unique set of energy levels, each element produces X-rays at a unique set of energies, allowing one to non- destructively measure the elemental composition of a sample. The process of emissions of characteristic x-rays is called X-ray Fluorescence or XRF. Analysis using x-ray fluorescence is called X-ray Fluorescence Spectroscopy. In most cases the innermost K and L shells are involved in XRF detection.

Instrumentation

Two primary types of X-ray spectrophotometers used are wavelength-dispersive X-ray fluorescence(WDXRF) and energy-dispersive X-ray fluorescence(EDXRF).

1) Wavelength-dispersive X-ray fluorescence spectrometers

In Wavelength-dispersive spectroscopy photons emitted by the sample are separated or dispersed by diffraction before hitting the detector (fig. 7). This is accomplished by placing an analyzing crystal between the sample and the detector. There are two types of WDXRF spectrometers: simultaneous and sequential. In simultaneous WDXRF spectrometers, multiple detectors placed at different angles are used to analyze multiple elements simultaneously. In sequential WDXRF spectrometers, the crystal is turned while elements are analyzed sequentially. WDXRF spectrometers have better resolution than energy dispersive x-ray fluorescence spectrometers. WDXRF spectrometers typical have a lower efficiency than EDXRF spectrometers because energy is lost when X-ray beam is dispersed into its component wavelengths. Hence the spectrometers require high power X-ray tube.

2) Energy-Dispersive X-ray fluorescence spectrometers

In an energy dispersive X-ray fluorescence spectrometer (EDXRF Spectrometer), the fluorescent photons from the irradiated sample are detected without being separated first (fig. 8). The semiconductor detectors such are used which directly measures the different energies of the emitted X-Rays from the sample. One advantage of EDXRF Spectrometer is the simplicity and lack of moving parts in the excitation and

detection components of the spectrometer. Furthermore, the absence of collimators and crystal diffractor, as well as the closeness of the detector to the sample, result in 100-fold or more increase in energy reaching the detector. These advantages permit use of low power X-ray tubes.

3) Total Reflection X-Ray Fluoroscence Spectroscopy

In contrast to conventional XRF equipment, where the angle of incidence of the exciting radiation is about 45°, the angle of incidence for TXRF is below the critical angle of the sample (typically 0.05°), such that the radiation is totally reflected from the highly polished sample support. In this case the primary beam has virtually no interaction with the sample support, thus leading to a drastic reduction in scattered radiation and a substantial improvement in the peak-to-background ratio. The sample is placed on the sample carrier as a thin film made from solutions or at least as fine suspensions produced by evaporating the solvent. The fluorescence radiation, which is doubled in intensity because of excitation of the sample by both the incident and the reflected beam, is detected perpendicular to the carrier. A schematic view of the total reflection X-ray optics is shown in fig. 9.

The main advantages of the TXRF set-up are the following:

1) Due to the total reflection of the incident photons, only a very small part of the primary beam penetrates into the sample carrier. This leads to a reduced spectral background contribution, which originates from scattering on the substrate.

2) The incident beam is totally reflected from the sample carrier and the sample is excited by both the incident and the reflected beam, resulting in doubled fluorescence intensity.

3) The extreme grazing incidence geometry allows the detector to be placed very close to the sample surface. This results in a large solid angle for the detection of the fluorescence radiation.

XRF methods are used for non-destructive analysis of samples. It is convenient and fast method. Elements in concentration of ppm can be measured by WDXRF and EDXRF methods. Because of its higher sensitivity elements in concentration of ppb can be measured by TXRF.

VOLTAMMETRY[17,18,19]

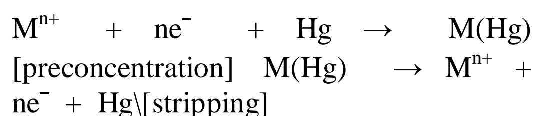
In an electrolysis cell the current produced is a measure of the amount of chemical change occurring at the electrodes. There are a variety of electro-analytical techniques which are designed to measure cell current (i) as function of electrode potential (E). These techniques all belong to the branch of electro-analytical techniques family known as voltammetry. Voltammetry exhibits a wide dynamic range, from sub-ppb to ppm or higher. For the higher concentrations (ppm or high ppb), direct measurement by differential pulse voltammetry or square-wave voltammetry is possible; for lower concentrations, these voltammetric techniques are combined with a preconcentration step. These latter techniques are referred to as stripping techniques.

Stripping voltammetry

Stripping voltammetric method can be used for yielding low detection limits. The sensitivity of voltammetric method is enhanced by use of preconcentration, or accumulation, step in which the element is accumulated at electrode. Anodic stripping voltammetry (fig. 10) is the most widely used for estimation of metals.

In this case, the metals are preconcentrated by electro-deposition onto a small-volume mercury electrode (thin mercury film or a hanging mercury drop). The deposition is done at a potential usually 0.3–0.5 V more negative than peak potential for the metal ion to be

determined. The metal ions are reduced at the mercury electrode and concentrated as amalgam. The solution is stirred during preconcentration in order to achieve convection transport. The deposition period may vary from a few seconds to about 20 min depending on the sensitivity required. After preconcentration, the potential is scanned anodically using linear or pulse ramps. During this scan, amalgamated metals are reoxidized and stripped out of the electrode. As a result, current flows through the cell. This current is directly proportional to the concentration of the metal in the solution.



$M^{n+} + ne^{-} + Hg \rightarrow M(Hg)$ [preconcentration] $M(Hg) \rightarrow M^{n+} + ne^{-} + Hg$\[stripping]

Advantages of Stripping voltammetric method:

1. It is a sensitive method (elements can be measured at ppm concentration)
2. Simultaneous determination of several elements is possible.
3. It is capable to distinguish between oxidation states of atomic ions.
4. It is useful for speciation studies.

PLASMA EMISSION SPECTROSCOPY[11,20,21]

It is a type of atomic emission spectroscopy which is based on the principle that atoms emit light when excited. In PES, the exciting media is plasma. The term 'plasma' means a very hot/high temperature ionised gas. The temperature range of plasma is 7000-10000K, which causes breakdown of all types of molecular bonds. Free atoms or ions (electrically charged atoms) are produced, which emit their characteristic spectra.

Plasma sources

Plasma can be thought of as the co-existence of the positive ions, electrons and neutral species of an inert gas (argon or helium) in a confined space. Types of plasma used for plasma emission spectroscopy are inductively coupled plasma (ICP) and direct current plasma (DCP).

Inductively coupled plasma

An ICP is formed within the confines of three concentric glass tubes or plasma torch (fig. 11). Each tube has an entry point, with those of intermediate (plasma) and external (coolant) tubes being arranged tangentially to that of inner tube, where the latter consists of a capillary tube through tube which the aerosol is introduced from the nebulisation/spray chamber. Located around the glass tube is a coil of copper tubing through which water is recirculated. The power input to the ICP is achieved through this load or induction coil, and is typically in the range 0.5-1.5kW. The inputted power induces an oscillating magnetic field, whose lines of force is axially oriented inside the plasma torch and follows elliptical paths outside the induction coil (load coil). At this point in time, no plasma exists. In order to initiate the plasma, the carrier gas flow is first switched off and a spark is then provided momentarily from Tesla coil, which is attached to the outside of the plasma torch by means of a copper wire. Instantaneously, the spark, which is a source of 'seed' electrons, causes ionization of the argon carrier gas. This process is self-sustaining, so that argon, argon ions and electron now co-exist within the confines of plasma torch, and can be seen protruding from the top in the shape of a bright white luminous bullet. This characteristic bullet shape is formed by the escaping high-velocity argon gas causing the entrainment of air back towards the plasma torch itself. In order to

introduce the sample aerosol into the confines of the hot plasma gas (7000-10000K) the carrier gas is introduced, this punches a hole in the centre of the plasma, thus creating the characteristic doughnut or toroidal shape of the ICP.

Sample Introduction

Nebulizer

The most common method of liquid sample introduction in plasma emission spectroscopy involves the use of a nebulizer. The basic function of nebulizer is to convert an aqueous sample into an aerosol by the action of a carrier gas. In order to produce an aerosol of sufficient particle size (ideally <10μm) it is necessary to introduce the generated aerosol into a spray chamber. The spray chamber will further reduce the original aerosol particle size towards the ideal size by providing a surface for collisions and/or condensation. The nebulization of aqueous sample is affected by their viscosity and surface tension, both of which have an influence on the carrier gas and uptake rate. It is possible to overcome these problems by using a peristaltic pump to transport the aqueous sample to the nebulizer. The various type nebulizers that are commonly used are described below.

Pneumatic concentric nebulizer

This is the most common type of nebulizer used. It has already been described in atomic absorption spectroscopy.

Cross flow nebulizer

In cross flow nebulizer (fig. 12) two capillary needles are positioned at 90° to each other with their tips not quite touching. The carrier gas flows through one capillary tube while the liquid sample is pumped through the other capillary. At the exit point, the force of the escaping carrier gas is sufficient to shatter the sample into a coarse aerosol.

Ultrasonic Nebulizer

In an ultrasonic nebulizer (fig. 13), the sample is delivered on to a vibrating piezoelectric crystal (at a frequency of 200 to 10 MHz). The action of the vibrating crystal is sufficient to transform the liquid sample into an aerosol which is then transported by the argon carrier gas through a heated tube and then a condenser. This has the effect of removing the solvent. In this situation, the aerosol is desolvated and reaches the plasma source as a fine dry aerosol. The major advantage of the ultrasonic nebuliser is its increased transport efficiency when compared to the pneumatic nebulizer.

If introduced into the plasma source directly, the coarse aerosols generated by the nebulizer would either extinguish or induced cooling of the plasma. This in turn would lead to severe matrix interferences unless a spray chamber is added to the system. Hence, spray chambers and desolvation system is used. This system removes the excess amount of solvent and further reduces the aerosol towards an ideal particle size. It has been determined that the ideal size for desolvation and ionisation / excitation in the plasma source is about 10μm.

Electro Thermal Vaporization

The principle of electrothermal vaporization (ETV) is that the sample should be vaporized and not atomized. In ETV (fig. 14) the sample is pipetted on to graphite or modified graphite surface. The passage of current through the graphite causes heating which is recorded as a temperature. The temperature a graphite surface can be controlled to preferentially allow destruction and removal of sample matrix. After ashing, the current is rapidly increased to allow vaporization of the analyte directly into the plasma source.

Laser Ablation [22]

The Laser is used to mobilize the solid sample. In this situation, a laser is directed on to the surface of a sample enclosed in silica windowed-cell (fig. 15). The mobilized sample is transported away from the site of ejection by the argon carrier gas directly to the plasma source.

Advantages of Plasma Emission Spectroscopy

1) A good emission spectra result for most elements under a single set of excitation conditions, consequently spectra for dozens of elements can be recorded simultaneously. This property is of particular importance for the multielement analysis of very small samples.

2) Another advantage of the more energetic plasma sources is that they permit the determination of low concentrations of elements that tend to form refractory compounds.

ADVANCED TECHNIQUE–INDUCTIVELY COUPLED PLASMA MASS SPECTROMETRY [23,24,25,26,27]

Principle of operation

Inductively coupled plasma mass spectrometry (ICP-MS) (fig. 16) which is composed of plasma, as the high temperature (8000 K) ionization source, quadrupole mass spectrometer (MS) analyzer, as the sensitive rapid scanning detector and a distinctive interface has emerged as a new and powerful technique for element and isotope analysis.

It is the most suitable technique for the analysis of trace elements in bulk drugs and pharmaceuticals. Also it is being applied for biopharmaceutical analysis of drugs.

The ion source used in this technique is the inductively coupled plasma. It is the same source that is used for plasma emission spectroscopy. In PES, the torch is positioned vertically so that emission is observed at right angles the spectrometer. In MS, the torch is positioned horizontally so that ions can be extracted from the ICP directly into the spectrometer. As a consequence of this horizontal positioning of the ICP torch in relation to the mass spectrometer, all species that entered the plasma are transferred into the machine. In addition, all of the sample introduction devices used for PES can be similarly used for ICP-MS.

The major instrumental development which was require in order to fully establish ICP-MS as a major analytical technique was the efficient coupling of an ICP, which operates at atmospheric pressure, with a mass spectrometer which operates under high vacuum. The development of a suitable interface has the key to the establishment of this technique. The interface allows the coupling of the ICP source with the mass spectrometer maintaining a high degree of sensitivity. The interface (fig. 17) consists of a water cooled outer sampling cone which is positioned in close proximity to the plasma source. The sampling cone is made of nickel because of its high thermal conductivity, relatively resistance to corrosion and robust nature. The pressure differential created by the sampling cone is such that ions from the plasma and the plasma gas itself are drawn into the region of lower pressure through the small orifice (1mm) of the cone. The region behind the sampling cone is maintained at a moderate pressure of about 250Pa by a rotary vacuum pump. As the gas flow through the sampling cone is large a second cone is placed enough behind it to allow the central portion of the expanding jet of plasma gas and ions to pass through the skimmer cone. The later is also made of nickel and as an orifice diameter of about 0.75mm. The pressure behind the skimmer cone is maintained at about 0.01Pa. The extracted ions are then focused by a series

of electrostatic lenses into the mass spectrometer.
A quadrupole consists of four cylindrical or hyperbolic rods of the same length and diameter. Quadrupoles used in ICP-MS are typically 8-12 cm in length and about 1cm in diameter. By placing a direct current (dc) field on one pair of rods and an rf field on the other opposite pair, ions of a selected mass are allowed to pass through the rods to the detector, while the others are ejected from the quadrupole.
ICP-MS offer several benefits when compared to other techniques used for estimation of metals. It is a highly sensitive method for most of the element. Both major as well as trace components can be detected simultaneously. ICP-MS can easily handle both simple and complex sample matrices. ICP-MS offers extremely low detection limits ranging from part per billion (ppb) to trillion (ppt). Individual isotopes can be measured using ICP-MS. Despite of the advantages of ICP sources compared to other ionization sources, the analytical precision in these systems is limited by the inherent instability of the ion signal by the ICP source and the sample introduction devices. Instabilities may arise from either a change in energy transfer from the plasma to the sample, or variation efficiency of the nebulisation and transportation of sample. This limitation can be overcome by use of internal standard or by use of isotope ratio analysis.

CONCLUSION

The requirements for analysis of pharmaceutical products for purity are becoming increasingly demanding. The analytical methods discussed above have been shown to be effective in detecting and measuring a number of elements in samples at extremely low concentration levels. An important part of the use of these methods is to understand and to recognise their capabilities and limitations to estimate their suitability for the analytical task. With further improvements in the available techniques still lower measurements can be achieved.

Table 1: Elemental Impurity Classes

Class	Assessment
Class1	Elements should be essentially absent Known for strongly suspected human toxicants Environmental hazards
Class 2	Elements should be limited Elements deliberately added to an article

Table 2: Class 1 Elemental impurities

Element	Component Limit (µg/g)	Oral Daily Dose PDE* (µg/day)	Parenteral Component Limit (µg/g)	Parenteral Daily Dose PDE (µg/day)
Arsenic	1.5	15	0.15	1.5
Cadmium	0.5	5	0.05	0.5
Lead	1	10	0.1	1
Mercury	1.5	15	0.15	1.5

*Permitted daily exposure

Table 3: Class 2 Elemental Impurities

Element	Component Limit (µg/g)	Oral Daily Dose PDE* (µg/day)	Parenteral Component Limit (µg/g)	Parenteral Daily Dose PDE (µg/day)
Chromium	25	250	2.5	25
Copper	250	2500	25	250
Manganese	250	2500	25	250
Molybdenum	25	250	2.5	25
Nickel	25	250	2.5	25
Palladium	10	100	1.0	10
Platinum	10	100	1.0	10
Vanadium	25	250	2.5	25
Osmium Rhodium Ruthenium Iridium	10 (combination not to exceed)	100 (combination not to exceed)	1.0 (combination not to exceed)	10 (combination not to exceed)

*Permitted daily exposure

Table 4: Commonly used premixed flames

Fuel	Oxidant	Temperature (°C)
Acetylene	Air	2400
Acetylene	Nitrous oxide	2800
Acetylene	Oxygen	3140
Hydrogen	Air	2045
Hydrogen	Nitrous oxide	2690
Hydrogen	Oxygen	2660
Propane	Air	1925

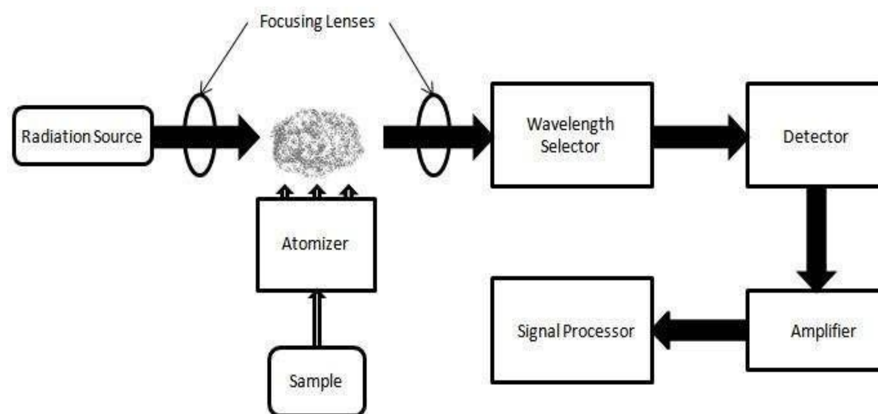


Fig. 1: Block diagram of atomic absorption spectrometer

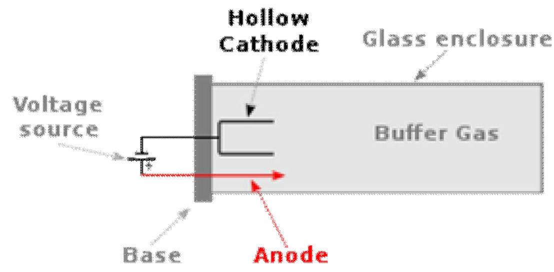


Fig. 2: Hollow cathode lamp

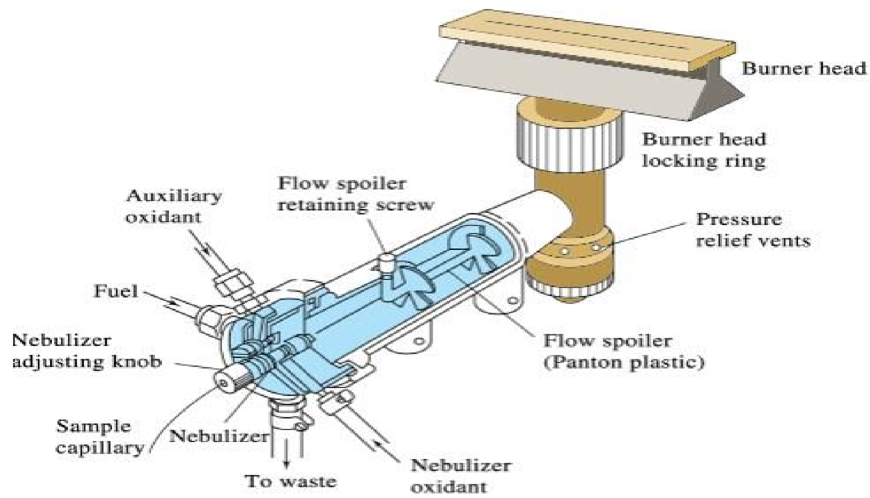


Fig. 3: Nebulizer/expansion arrangement with flame burner head

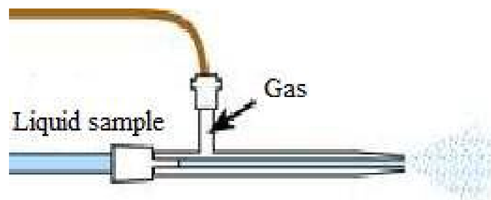


Fig. 4: Pneumatic concentric nebulizer

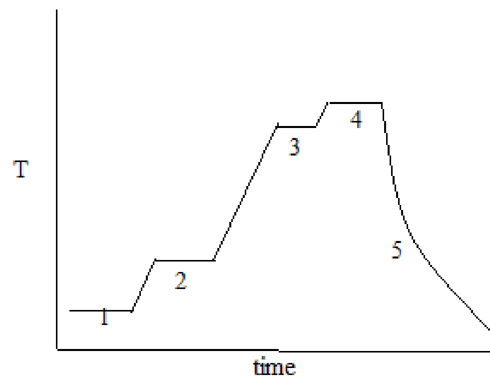


Fig. 5:Temperature-time profile for a graphite furnace: (1) drying; (2) thermal pre-treatment (ashing); (3) atomization; (4) cleaning; (5) cooling

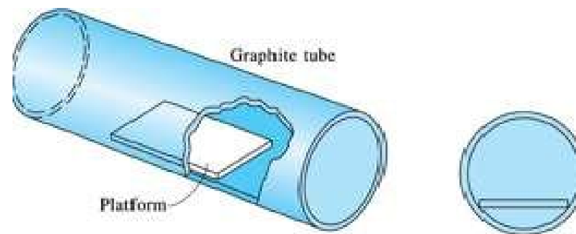


Fig. 6: Graphite tube with L'Vov platform

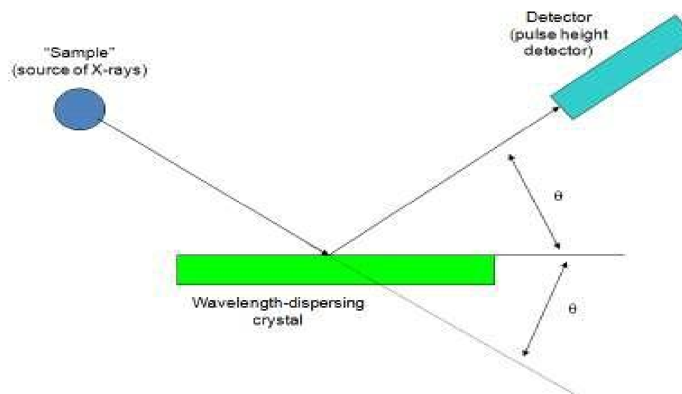


Fig.7: Experimental set-up of Wavelength-dispersive X-ray fluorescence spectrometer

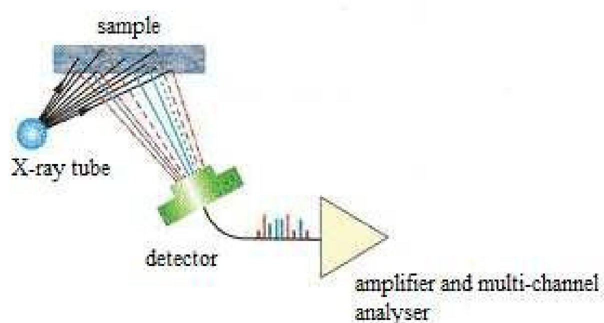


Fig. 8: Experimental set-up of Energy-dispersive X-ray fluorescence spectrometer

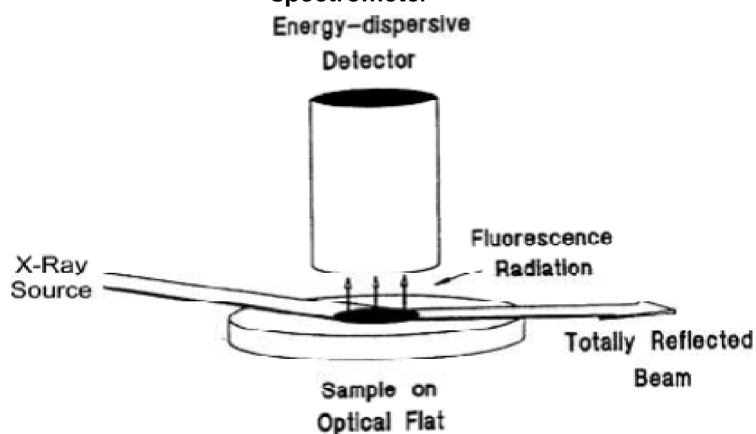


Fig. 9: Experimental set-up of Total Reflectance X-Ray Fluoroscence Spectroscopy

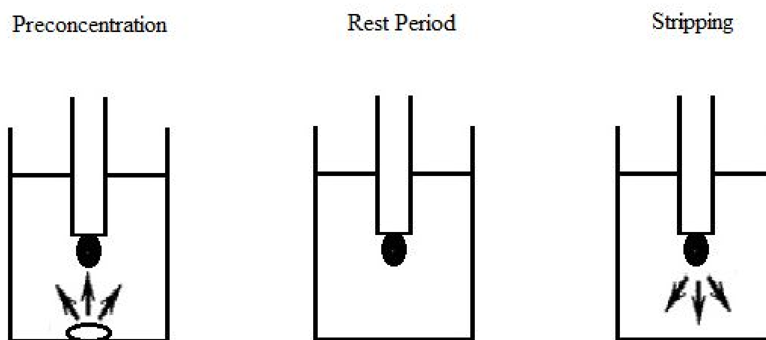


Fig. 10: Principle of anodic stripping

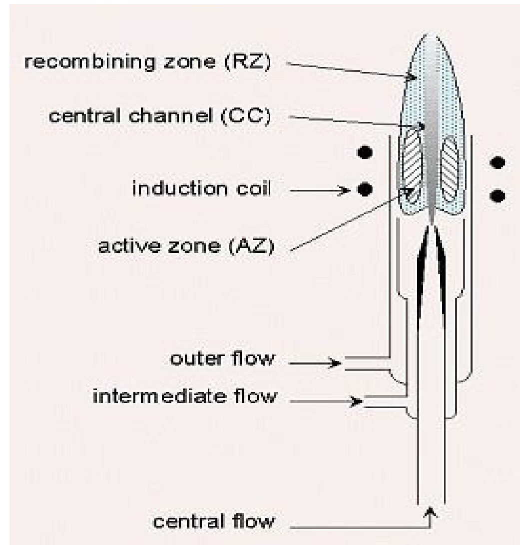


Fig. 11: Inductively coupled plasma

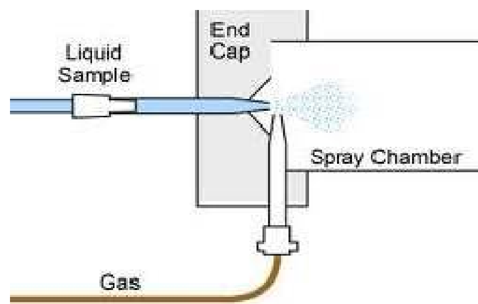


Fig. 12: Cross flow nebulizer

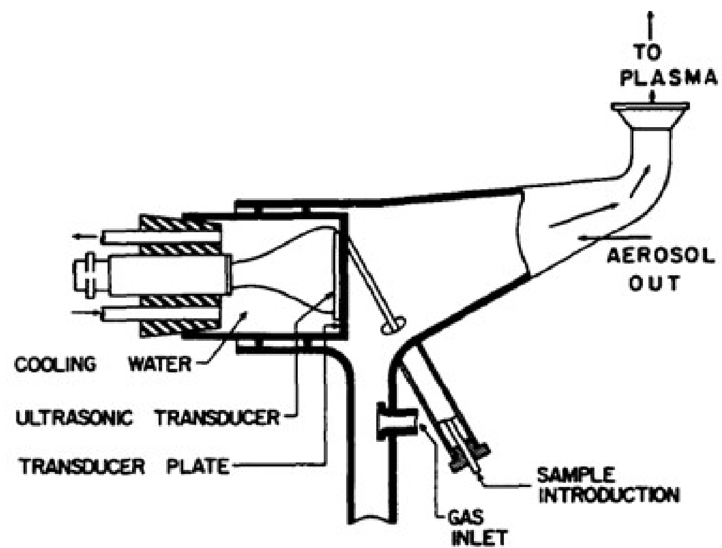


Fig. 13: Schematic diagram of ultrasonic nebulizer

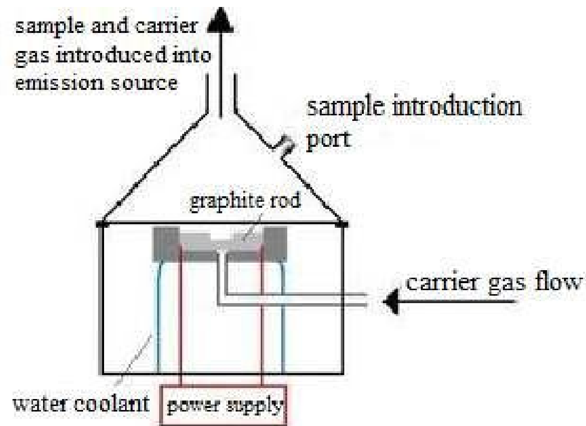


Fig. 14: Electrothermal vaporization

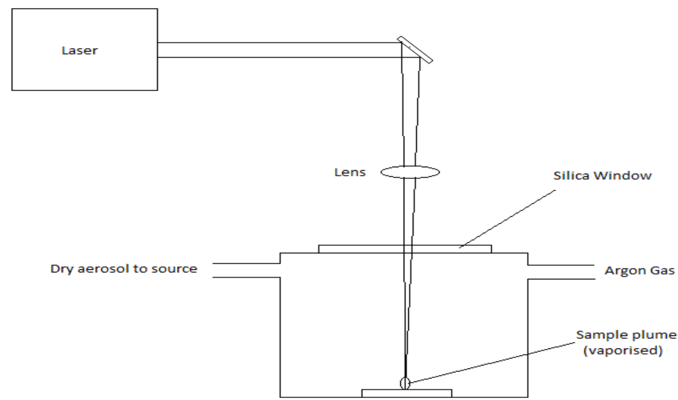


Fig. 15: Laser Ablation

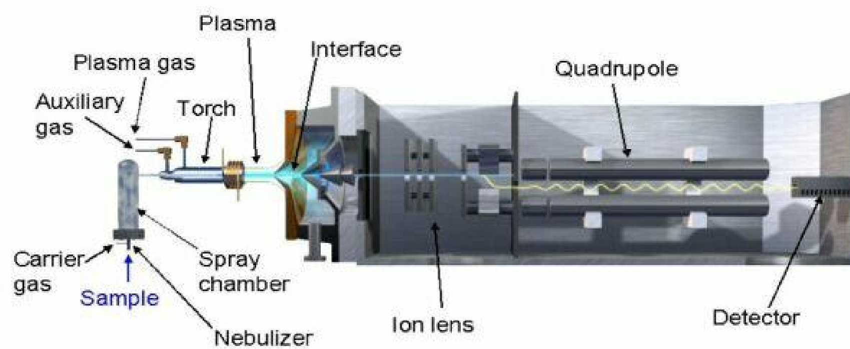


Fig.16: Inductively coupled plasma-mass spectrometer

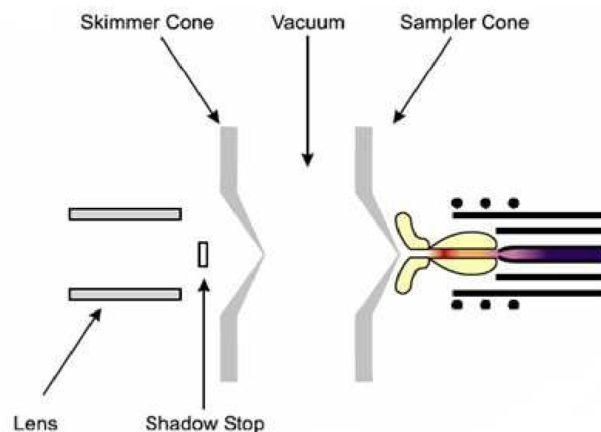


Fig. 17: ICP-MS Interface

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