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Advancements in Analysis: Inductively Coupled Plasma- Mass Spectrometry

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ABSTRACT

The present review provides an overview on recent development and capabilities of inductively coupled plasma mass spectrometry (ICP-MS) technique which allows the determination of elements and isotopes from the biological tissues and related materials with the spatial resolution which typically ranges from 10 to 100 μm. The outstanding properties such as high sensitivity (ranging, ppt–ppq), relative salt tolerance, compound-independent element response and highest quantitation accuracy leads to an unchallenged performance of ICP MS in its efficiency in detection, identification and quantification of trace elements. The elements that are detected are mostly ‘‘trace’’ and can be analyzed from both body tissues and body fluids. The accurate determination of elemental distribution in neurodegenerative diseases like Alzheimer’s disease, Parkinson’s disease, etc., helps in the better understanding of the particular diseases. ICP-MS can be applied also in environmental and bioanalytical fields when coupled/combined with different separation techniques for the quantitative determinations.

Keywords: ICP-MS, Quantitation, Sensitivity, Bioanalytical.

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INTRODUCTION

Inductively coupled plasma mass spectrometry (ICP-MS)

ICP-MS is a type of mass spectrometry which is capable of detecting metals and several non-metals at concentrations as low as one part in 10^{15} (part per quadrillion, ppq) on non-interfered low-background isotopes. This is achieved by ionizing the sample with inductively coupled plasma and then using a mass spectrometer to separate and quantify those ions. A number of different ICP-MS designs are commercially available today, each with its own strengths and limitations. They all share similar components such as the nebulizer, spray chamber, plasma torch, interface and detector but can differ significantly in the design of the mass spectrometer and in particular the mass separation device[1]. The schematic representation of ICP-MS is shown in Figure 1.

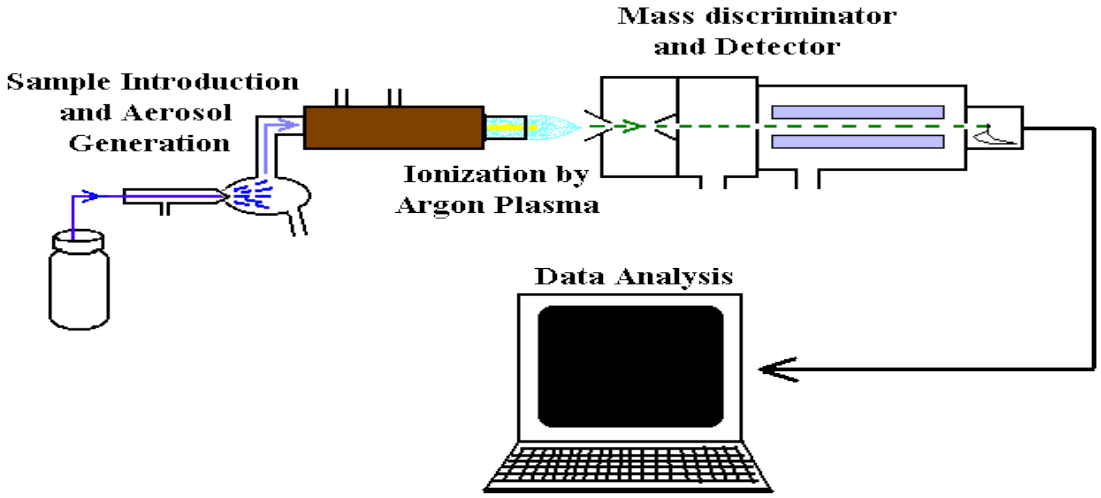

Figure 1: Schematic representation of ICP-MS main processes

Principle of ICP-MS

The principle involved in ICP-MS is the sample material is introduced into high-energy argon plasma that consists of electrons and positively charged argon ions. In the plasma, the material is split into individual atoms. These atoms will lose electrons and become (singly) charged positive ions. Most elements ionize very efficiently (> 90%) in the hot plasma[1].

Principle of operation

Here is an overview of the principles of operation of ICP-MS shows the basic instrumental components that make up an ICP-MS system. ICP technology was built upon the same principles used in atomic emission spectrometry. Samples are decomposed to neutral elements in high temperature argon plasma and analyzed based on their mass to charge ratios. The sample, which is in a liquid form, is pumped at 1 ml/min (usually with a peristaltic pump) into a nebulizer, where it is converted into a fine aerosol with argon gas at about 1 L/min. The fine droplets of the aerosol,

which represent only 1 - 2% of the sample, are separated from larger droplets using a spray chamber. The fine aerosol then emerges from the exit tube of the spray chamber and is transported into the plasma torch via a sample injector[2]. The plasma torch plays a very different role in ICP-MS. In this technique, the plasma is produced by the interaction of an intense magnetic field on a tangential flow of gas (normally argon), at about 15 L/min flowing through a concentric quartz tube (torch). The plasma torch is positioned horizontally, and is used to generate positively charged ions rather than photons. In fact, every attempt is made to stop the photons reaching the detector because they have the potential to increase signal noise[2]. Once the ions are produced in the plasma, they are directed into the mass spectrometer via the interface region, which is maintained at a vacuum of 1 - 2 torr with a mechanical roughing pump. This interface region consists of two metallic cones (usually made of nickel)[3], called the sampler and a skimmer cone. Each cone features a small (0.6 - 1.2 mm) orifice to allow the ions to the ion optics, where they are guided into the mass separation device. In few cases a capacitive coupling occurs between the rf coil and the plasma, which produces a potential difference of a few hundred volts. If this wasn't eliminated, an electrical discharge (called a secondary discharge or pinch effect) would appear between the plasma and the sampler cone[3]. This discharge increases the formation of interfering species and also dramatically affects the kinetic energy of the ions entering the mass spectrometer, making optimization of the ion optics very erratic and unpredictable. For this reason, the secondary charge must be eliminated by using some kind of rf coil grounding mechanism. The ions that are extracted from the interface region are directed into the main vacuum chamber by a series of electrostatic lenses called ion optics. A turbo molecular pump in it maintains the operating vacuum in this region at about 10^{-2} torr. The ion beam which contains the analyte and matrix ions exits the ion optics and passes into the heart of the mass spectrometer, where a second turbo molecular pump in it maintains an operating vacuum of approximately 10^{-6} torr[4]. Depending on the design of the mass spectrometer the ions arrive at the detector in the sequentially or simultaneous process where the ions are sampled at the same time. In the final process, an ion detector converts the ions into an electrical signal. The most common design used today is a discrete dynode detector, which contains a series of metal dynodes along the length of the detector. In this design, when the ions emerge from the mass filter, they impinge on the first dynode and are converted into electrons. As the electrons are attracted to the next dynode, electron multiplication takes place, resulting in a very high stream of electrons emerging from the final dynode. This electronic signal is then processed by the data handling system in the conventional way and converted into analyte concentration using ICP-MS calibration standards[4].

Instrumentation& Working

Inductively Coupled Plasma

The plasma that is ionized by inductively heating the gas with an electromagnetic coil, and contains a sufficient concentration of ions and electrons to make the gas electrically conductive is called *Inductively coupled plasma*. It is a powerful tool for the determination of metals in a variety of different sample matrices. With this technique, samples are injected into a radiofrequency (RF)-induced argon plasma using one of a variety of sample introduction techniques. The plasma used in this analysis must be electrically neutral, with each positive charge on an ion, balanced by a free electron. In these plasmas the positive ions are almost all singly charged and there are few negative ions, so there are nearly equal amounts of ions and electrons in each unit volume of plasma. Inductively coupled plasma (ICP) for spectrometry is sustained in a torch that consists of three concentric tubes, usually made of quartz. Although the inner tube (injector) can be sapphire if hydrofluoric acid is being used. The end of this torch is placed inside an induction coil supplied with a radio-frequency electric current. A flow of argon gas (usually 13 to 18 liters per minute) is introduced between the two outermost tubes of the torch and an electric spark is applied for a short time to introduce free electrons into the gas stream. These electrons interact with the radio-frequency magnetic field of the induction coil and are accelerated. The acceleration is first done in one direction and then extends to the other directions as the field changes at high frequencies (usually 27.12 million cycles per second). The accelerated electrons collide with argon atoms; sometimes the collision may cause the argon atom to part with one of its electrons. The released electron is in turn accelerated by the rapidly changing magnetic field. The process continues until the rate of release of new electrons in collisions is balanced by the rate of recombination of electrons with argon ions (atoms that have lost an electron). This produces a 'fireball' that consists mostly of argon atoms with a rather small fraction of free electrons and argon ions. The temperature of the plasma at this stage is very high (10,000 K)[5]. The plasma also produces ultraviolet light, so it should not be viewed directly. The ICP can be retained in the quartz torch because the flow of gas between the two outer most tubes keeps the plasma away from the walls of the torch. A second flow of argon (around 1 liter per minute) is usually introduced between the central tube and the intermediate tube to keep the plasma away from the end of the central tube. A third flow (again usually around 1 liter per minute) of gas is introduced into the central tube of the torch. This gas flow passes through the centre of the plasma, where it forms a channel that is cooler than the surrounding plasma but still much hotter than a chemical flame. Samples to be analyzed are introduced into this central channel, usually as a mist of liquid formed by passing the

liquid sample into a nebulizer[6]. To maximize plasma temperature (and hence ionization efficiency) and stability, the sample should be introduced through the central tube as little (solvent load) as possible in the form of liquid, with consistent droplet size. A nebulizer can be used for liquid samples, followed by a spray chamber to remove larger droplets, or a desolvating nebulizer can be used to evaporate most of the solvent before it reaches the torch. Solid samples can also be introduced using laser ablation. The sample enters the central channel of the ICP, evaporates, molecules break apart, and then the constituent atoms ionize. The plasma temperature is selected to maximizeionization efficiency for elements with high first ionization energy, while minimizing second ionization (double charging) for elements that have a low second ionization energy[6].

Mass Spectrometry

It is an analytical chemistry technique that helps to identify the amount and type of chemicals present in a sample by measuring the mass-to-charge ratio and abundance of gas-phase ions. 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 to the concentration. The concentration of a sample can be determined through calibration with certified reference material such as single or multi-element reference standards. ICP-MS also lends itself to quantitative determinations through isotope dilution, a single point method. Other mass analyzers coupled to ICP systems include double focusing magnetic-electro static sector systems with both single and multiple collector, as well as time of flight systems (both axial and orthogonal accelerators have been used)[7].

Sample preparation & introduction

Sample preparation process in ICP-MS is relatively simple and quick for clinical methods when compared to other techniques. The main component is an internal standard which can also be used as diluent which primarily consists of deionized water with nitric or hydrochloric acid, and Indium and/or Gallium. Depending on the sample type, usually 5 ml of the internal standard is added to a test tube along with 10–500 micro liters of sample. This mixture is then vortexed for several seconds or until mixed well and then loaded onto the auto sampler tray. Sample digestion has to be done for the viscous samples and samples that have particulate matter. Sample can be either in the form of solid, liquid or slurry[1].

Sample introduction in ICPMS can be achieved through various means like:

- Laser ablation method – Used for solid samples
- Nebulizer method – Used for liquid samples

- Gaseous samples can be introduced directly

The most common method is the use of a nebulizer which converts liquids into an aerosol, which is further treated to form only in to smallest droplets, commonly by means of a double pass or cyclonic spray chamber as shown in Figure 2. The aerosol can be swept into the plasma to create the ions. Nebulizer aspirates the sample with high velocity argon, to form a fine mist. The aerosol then passes into a spray chamber where larger droplets are removed via a drain. Other methods of sample introduction can also be utilized like Electro thermal vaporization (ETV) and in torch vaporization (ITV) hot surfaces (graphite or metal, generally) are used to vaporize samples for introduction[1].

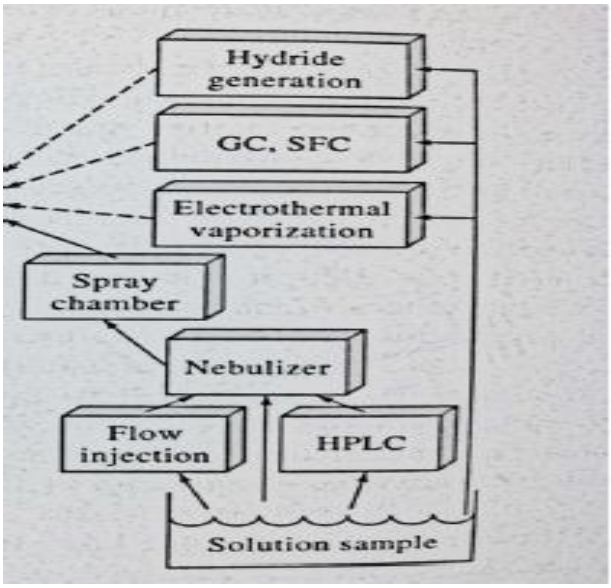

Figure 2: Potential sample entry pathways

Components of Icp

ICP-MS combines a high-temperature Inductively Coupled Plasma source with a mass spectrometer. The ICP source converts the atoms of the elements in the sample to ions. These ions are then separated and detected by the mass spectrometer.

Nebulizers

The systematic rotation of the nebulizer should be carried out to identify the orientation of the gas outlet of the nebulizer with respect to the sample outlet providing maximum sensitivity[8]. Direct injection nebulizers provide quantitative sample introduction in the plasma with lower detection limits. However, they are more expensive than conventional sample introduction systems and those based on micro nebulizers[9]. Furthermore, they are not as easy to install and operate, are prone to blockage or melting, and the resulting signal is noisier because the droplet size distribution is broader (as no pre-evaporation occurs). A demountable and hence lower cost, direct-

injection, high efficiency nebulizer (DIHEN) was described, where the solution capillary is adjustable so that a better optimization may be carried out[10]. Although it is operated at similar aerosol carrier gas flow rates, rf power, and sample uptake rate than regular direct injection nebulizers, its optimum position is 5 mm, instead of 2mm, below the torch intermediate tube, which decreases the likelihood of it melting[10]. Furthermore, the aerosol produced has a narrower droplet size distribution and lower mean droplet velocities, which resulted in enhanced sensitivity for 16 analytes spanning the mass range. However, this translated into significantly improved detection limit for only two analytes (As, Se), whereas similar (for the majority of analytes) or even degraded (Mg, Mn, Cu) detection limits were reported. On the other hand, although the oxide levels were similar, the relative oxide ion intensities were reduced, because of the longer residence time resulting from the lower droplet velocities. A hydraulic high-pressure nebulizer (HHPN), combined with a desolvation system involving heating (160 °C) and cooling (0 °C) stages, was used as the sample introduction system for ICP-TOFMS, to allow high sample throughput multi elemental analysis of digests of biological materials by flow injection[11] . Filtering the sample prior to its injection and degassing the carrier (using an ultrasonic bath) were required to stabilize the nebulizing pressure. The particles in the micrometer range could partially or totally clog the HHPN nozzle, whereas bubbles in the carrier liquid induce pressure drops. The detection limits obtained with this sample introduction system were improved compared to those obtained on a similar ICP-TOF MS instrument by flow injection hydride generation, which furthermore does not allow the determination of nonhydride- forming elements. As expected, detection limits were degraded compared to those obtained by continuous nebulization with a conventional sample introduction system (i.e., with concentric nebulizer and spray chamber) because of the loss of sensitivity incurred by using the FI mode, which however provided freedom from memory effects[11].

Spray Chambers

Improved performance of spray chambers can be obtained by using a PFA cyclonic spray chamber in tandem with a PEEK Scott-type spray chamber as to avoid non spectroscopic interferences. This arrangement indeed results in signal enhancement of 2.5-3 times, lighter elements being enhanced less than heavier ones. The slightly dried aerosol exiting in the two spray chambers is also translated in better signal precision by a factor of ~3. The arrangement was also more matrix tolerant than the cyclonic spray chamber alone, where a 50% suppression of analyte signal could be observed in riverine water. The use of numerical computer simulations became a valuable tool for the design of spray chambers. These simulations indeed offer a less costly and time-consuming

means of optimizing the design of spray chambers than their empirical development, through trial and error, which does not guarantee a top performance[12].

Vapor Generation

To perform the gas-phase separation of analyte from troublesome matrix (such as a saline matrix), preconcentrate it, and allow its direct introduction into the ICP. This was demonstrated for the total ultra trace determination of Cr in seawater using isotope dilution with gas chromatography(GC) and detection by sector field ICPMS[13].

Laser ablation (LA)

LA is frequently used for direct solid analysis by ICPMS. It pointed out that the very high photon intensities with femtosecond pulse duration of Femtosecond lasers makes them predominantly non thermal, which may eliminate fractionation and matrix dependence since there is less sample heating, no laser-plasma interaction, and smaller aerosol particle sizes result. This was demonstrated to be true for the analysis of NIST glasses, two monazites, and the CNRS-CRPG zircon standard 91500. The results demonstrated that analysis by **Femtosecond LA-ICPMS** was independent of the matrix for these sample types and of the integration time slice[14, 15].

Isotope Dilution (ID)

Isotope dilution is an alternative calibration strategy, which was demonstrated to provide accurate results for various powdered sample types when matrix-matched standards were not available. The powdered sample was simply suspended in a solution of isotopic spike, allowed to dry, and then pressed into a pellet for LA-ID-ICPMS analysis.

Argon Plasma/Sample Ionization

Once the sample passes through the nebulizer and is partially de solvated, the aerosol moves into the torch body and is mixed with more argon gas. A coupling coil is used to transmit radio frequency to the heated argon gas, producing an argon plasma "flame" located at the torch. The hot plasma removes any remaining solvent and causes sample atomization followed by ionization. In addition to being ionized, sample atoms are excited in the hot plasma, a phenomenon which is used in ICP-atomic emission spectroscopy. Shown to the right is an ICP torch. The aerosol moves into the bottom of the torch body. The green ports on the right side of the body are where more argon is introduced to the flow. At the top are two high quality quartz tubes and an inner alumina injector tube as shown in the Figure 3.

Figure 3: Photo of argon plasma in operation

ICP-MS Interface

During atomization/ionization occurs at atmospheric pressure, the interface between the ICP and MS components becomes crucial in creating a vacuum environment for the MS system. Ions flow through a small orifice (approximately 1 mm in diameter), and into a pumped vacuum system. Here a supersonic jet forms and the sample ions are passed into the MS system at high speeds, expanding in the vacuum system. The entire mass spectrometer must be kept in a vacuum so that the ions are free to move without collisions with air molecules. Since the ICP is maintained at atmospheric pressure, a pumping system is needed to continuously pull a vacuum inside the spectrometer. In order to most efficiently reduce the pressure, several pumps are typically used to gradually reduce pressure to 10^{-5}mbar (milli bar) before the ion stream reaches the quadruple. If only one pump were used, its size would be excessive to reduce the pressure immediately upon entering the mass spectrometer.

Plasma torch

The plasma used in an ICP-MS is made by partially ionizing argon gas. The energy required for this reaction is obtained by pulsing an electrical current in wires that surround the argon gas. After the sample is injected, the plasma's extreme temperature causes the sample to separate into individual atoms (atomization). Next the plasma ionizes these atoms, so that they can be detected by the mass spectrometer.

Working of Icp Ms

ICP

Argon gas flows inside the concentric channels of the ICP torch. The RF load coil is connected to a radiofrequency (RF) generator. As power is supplied to the load coil from the generator, oscillating electric and magnetic fields are established at the end of the torch. The sample is typically introduced into the ICP plasma as an aerosol, either by aspirating a liquid or dissolved solid sample into a nebulizer or using a laser to directly convert solid samples into an aerosol. Once the sample aerosol is introduced into the ICP torch, it is completely desolvated and the elements in the aerosol are converted first into gaseous atoms and then ionized towards the end of the plasma. These ions next enter into the Mass Spectrometer for further process.

MS

In the first stage of the mass spectrometer ions are removed from the plasma by a pumped extraction system. An ion beam is produced and focused further into the actual unit. There are several different types of mass analyzers which can be employed to separate isotopes based on their mass to charge ratio. Quadrupole analyzers are compact and easy to use but offer lower resolution when dealing with ions of the same mass to charge ratio (m/z). Double focusing sector analyzers offer better four metal rods aligned in a parallel diamond pattern. A combined DC and AC electrical potential is applied to the rods with opposite rods having a net negative or positive potential and the ions enter into the path between all the rods. When the DC and AC voltages are set to certain values, only one particular ion is able to continue on a path between the rods and the others are forced out of this path. This ion will have a specific m/z ratio. Many combinations of voltages are chosen which allows an array of different m/z ratio ions to be detected. Three mass fragments enter into the quadrupole vacuum chamber. The voltage of the rods is set so that only the required mass fragment passes completely through the quadrupole rod array and into the detector. The fragments which are unstable at this voltage combination, their path eventually brings them into contact with the rods so that they never reach the detector. Quadrupole rods require periodic maintenance and cleaning due to the build up of ions which are removed during the mass discrimination process. These ions form a film which eventually builds up and dulls the metallic surface. To remove this film the vacuum chamber must be repressurized and disassembled. This process can be time consuming and very delicate but is essential to keep a mass spectrometer performing well. Once the ions enter the mass spectrometer, they are separated by their mass-to-charge ratio. The most commonly used type of mass spectrometer is the quadrupole mass filter. In this type, 4 rods (approximately 1 cm in diameter and 15-20 cm long) are arranged as shown in Figure4. In a quadrupole mass filter, alternating AC and DC voltages are applied to opposite pairs of the rods. These voltages are then rapidly switched along with an RF-field. The

result is an electrostatic filter is established that only allows ions of a single mass-to-charge ratio (m/e) pass through the rods to the detector at a given instant in time. So, the quadrupole mass filter is really a sequential filter, with the settings being change for each specific m/e at a time which is shown in Figure 5. However, the voltages on the rods can be switched at a very rapid rate. The result is that the quadrupole mass filter can separate up to 2400 amu/s (atomic mass units per second).

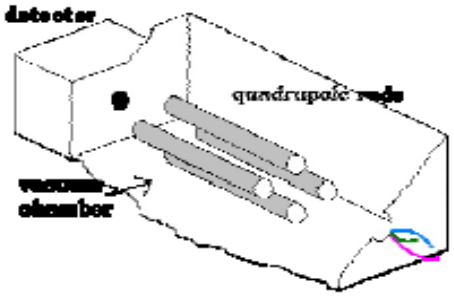

Figure 4: Animation of quadrapole mass filter separating ions

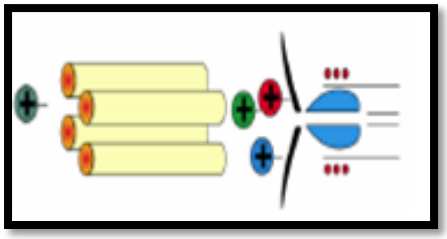

Figure 5: Schematic diagram of quadrupole mass filter

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 quadrupole 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. As the process continues more electrons are formed, resulting in as many as 108 electrons at the other end of the tube after one ion strikes at the entrance of the cone.

A few things to remember about the ICP-MS detector

It is a consumable item. As ions hit the surface of the detector and are converted to electrons, the active film coating will be consumed. Depending on usage, a typical discrete dynode detector will last 6-18 months in a quadrupole ICP-MS.

It should be protected from high signal count rates. Most manufacturers' design the detector circuitry to protect it from potentially fatal ion count rates. However, the users can further this by diluting samples with known high concentration values or choosing a less abundant isotope for their analysis.

They are expensive. So Care should be taken to protect it.

They are light sensitive. Most detectors are as sensitive to photons as they are to ions. Care should be taken to store spare detectors in the dark and never expose a detector to the light while the high voltage power supply to it is on.

Detection Limits:

One of the great advantages to ICP-MS is extremely low detection limits for a wide variety of elements. Some elements can be measured down to parts per quadrillion range while most can be detected at parts per trillion levels. The table below shows some common detection limits by element.

Table:1 elements detection limit

Element	Detection limit(ppt)
U, Cs, Bi	Less than 10
Ag, Be,Cd,Rb,Sn,Sb,Au	10-50
Ba, Pb, Se, Sr ,Co, W, Mo, Mg	50-100
Cr,Cu,Mn	100-200
Zn,As,Ti	400-500
Li,P	1-3ppb
Ca	Less than 20ppb

Maintenance of Instrument

There are many aspects of maintenance that need to be encompassed by daily, weekly and annual procedures. The frequency of maintenance is typically determined by the sample volume and cumulative run time that the instrument is subjected to. One of the most frequent forms of routine maintenance is replacing sample and waste tubing on the peristaltic pump, as these tubes can get worn fairly quickly resulting in holes and clogs in the sample line, resulting in skewed results. Other parts that need regular cleaning and/or replacing are sample tips, nebulizer tips, sample cones, skimmer cones, injector tubes, torches and lenses. It may also be necessary to change the oil in the interface roughing pump as well as the vacuum backing pump, depending on the workload put on the instrument.

Elemental Analysis

The ICP-MS allows determination of elements with atomic mass ranges 7 to 250. This encompasses Li to U. Some masses are prohibited such as 40 due to the abundance of argon in the

sample. Other blocked regions may include mass 80 (due to the argon dimer), and mass 56 (due to ArO), the latter of which greatly hinders Fe analysis unless the instrumentation is fitted with a reaction chamber. A typical ICP-MS will be able to detect in the region of Nano grams per liter to 10 or 100 milligrams per liter or around 8 orders of magnitude of concentration units.

Applications

1. One of the largest volume uses for ICP-MS is in the medical and forensic field, specifically, toxicology.
2. In recent years, industrial and biological monitoring has presented another major need for metal analysis via ICP-MS.
3. Regardless of the sample type, blood, water, etc., it is important that it be free of clots or other particulate matter.
4. ICP-MS is also used widely in the geochemistry for radiometric dating, in which it is used to analyze relative abundance of different isotopes, in particular Uranium and Lead.
5. In the field of flow cytometry, a new technique uses ICP-MS to replace the traditional fluorochromes.

CONCLUSION

From this review we can conclude that this technique is superior to other techniques with respect to accuracy, speed, precision, detection limits, dynamic range and many other parameters and thus giving a results by using minute amount of sample up to level of one part in quadrillion.

The technique has the wide applications in the fields of drug development and in other bio-analytical applications like immuno assays, proteomics and also in many life and earth sciences

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