Clinical Images and Case Reports

Received 5 May 2024 | Revised 7 May 2024 | Accepted 28 May 2024 | Published Online 7 Jun 2024

Published By: Vision Publisher

CICR 02 (6), 22-42

ISSN 2942-0776

Original Article

Inductively Coupled Plasma Mass Spectrometry (ICP-MS) Instrumentation, Analysis, Strengths, Limitations, Biomedical and Pharmaceutical Applications

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Abstract:- An argon gas plasma is delivered to an aerosol created by pumping a pre-prepared liquid containing the analyte through a nebulizer in the simplest type of ICP-MS. Plasma with temperatures ranging from around 5500 to 6500 K is hot enough to atomize and ionise nearly every element, even the ones with the strongest ionisation potentials. A mass spectrometer can be used to segregate the analyte ions into their mass to charge (m/z) ratio and detect them after guiding the ions into it using electrostatic ion optic components. For the most part, ionisation is very efficient, therefore the number of identified ions for a given element should be considered a good indicator of its concentration in the sample. Launched in 1983, the technique has progressed from a single-detector, quadrupole mass spectrometer-equipped instrument to modern time-of-flight (TOF) mass spectrometers that can measure the full mass spectrum simultaneously, as well as single-and double-focusing magnetic sector instruments that can measure isotope ratios with high precision thanks to single- or multicollector detection systems. Though advancements in pharmaceutical, biomedical, and life sciences are crucial, medical science as a whole is important for everyone. Additional research is being conducted in these areas to ascertain, with remarkable precision, the concentrations and amounts of organic molecules and inorganic elements to be utilised in pharmaceuticals, including nucleotides, peptides and proteins containing sulphur and phosphorus, and so on. An innovative and potent method for elemental and isotope analysis, inductively coupled plasma-mass spectrometry (ICP-MS) has been available since 1980. It allows for the simultaneous examination of the vast majority of the elements listed in the periodic table, as well as an extraordinarily broad spectrum of elements. It can also be used for mass-to-charge ratio measurements of isotope ratios and for qualitative, quantitative, and semiquantitative analysis. When it comes to biological and pharmaceutical inorganic impurity quantification, ICP-MS has lately become the gold standard.

Keywords: ICP-MS, Instrumentation, Analysis, Strengths, Limitations, Pharmaceutical Applications

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Introduction:

When it comes to medication treatment, the pharmaceutical industry has two primary concerns: safety and efficacy. In order to establish the safety standards and dose forms for bulk drug scanning, it is necessary to study the effects of elemental impurities in pharmaceuticals using toxicological and pharmacological profiles. This is critical since elemental contaminants and incorrect medication dosage forms might induce undesirable pharmacological and toxicological effects. Therefore, in order to guarantee quality and safety and to manage elemental impurities, it is necessary to characterise all products meant for human consumption as thoroughly as possible. As a result, pharmaceutical analysis is a crucial step in guaranteeing the security of medications [1]. One versatile chemical analysis tool that may be adapted to suit the needs of many different sectors is inductively coupled plasma mass spectrometry, or ICP-MS.

- **Natural resource exploration**
- **Petrochemicals**
- **Environmental (including soil analysis)**
- **Food and beverage (including wine and drinking water analysis and pesticide screening)**
- **Regulatory**
- **Medical**
- **Pharmaceutical**
- **Materials and metallurgy**
- **Nuclear**
- **Nanotechnology**

Laser ablation (LA) in conjunction with inductively coupled plasma mass spectrometry (ICP-MS) has replaced acid digestion as the standard procedure for pre-preparation of solid materials, allowing for spatially resolution analysis and elemental mapping. Moreover, ICP-MS has been integrated with separation techniques to enable the measurement of molecules, specifically biomolecules. By combining ICP-MS with separation techniques like liquid chromatography (LC), gas chromatography (GC), capillary electrophoresis (CE), or gel electrophoresis (GE), we have successfully circumvented the issue of ionisation destroying all molecular information from the sample.2,3 Isolating all species containing the target element and sending them one by one to the ICP-MS apparatus for detection is possible using the separation process. The different parts of an ICP-MS system are shown in Figure 1, which is a schematic illustration. The nebulizer uses a peristaltic pump or self-aspiration to transfer liquid samples into a fine-particle aerosol. The sample's purity, volume, and viscosity are some of the variables that determine which nebulizer type is most suited for analysis.

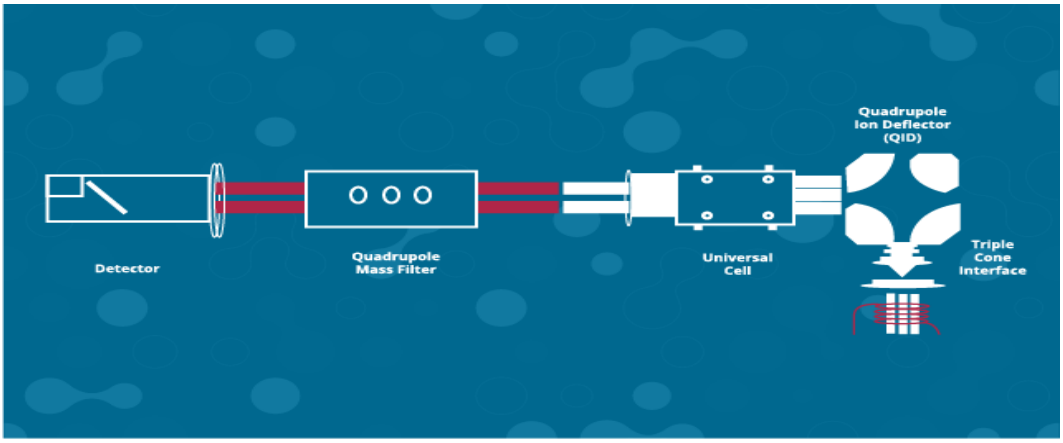


Figure 1: Illustration depicting the primary elements of an ICP-MS system that are elaborated upon in the accompanying text. Attribution: Networks in Technology.

The nebulizer's tiny droplets are introduced to the plasma after passing through a spray chamber. Again, there are a variety of options, but the basic idea is the same: let a lot of tiny droplets into the plasma while blocking the bigger ones that could mess with the analysis. A radio frequency (RF) coil is used to hold one end of the ICP torch, which consists of concentric quartz tubes, and send argon gas through them to produce argon plasma that reaches temperatures of 5500-6500 K. Plasma is created when argon gas and energy from an RF generator combine in the coil. The droplets change from liquid to gas as they dive into the hot plasma. Eventually, they will release an electron to create a single positively charged ion as their energy absorption increases. An engineering problem arises at the interface region where the mass spectrometer receives the ions created by the plasma. At first, the area around the torch gets hot, reaching over 6,000K, but the opposite side of the interface stays at ambient temperature. Second, in order to create plasma, the torch must have been backfilled with Ar gas, and the mass spectrometer must be operated in a highly vacuumed environment. Ions are focused into the collision cell or the mass spectrometer by means of two or more cone structures, or lenses; however, the exact mechanisms by which this is accomplished vary from manufacturer to manufacturer. Photons and neutral atoms will accompany ions as they leave the plasma. It is crucial to eliminate photons from the path of ions since they can cause misleading ion counts. Different manufacturers may take somewhat different approaches to this problem, but a typical method involves using a lens element to focus in on the ions and direct them into the quadrupole mass spectrometer.
A "universal" or "reaction/collision" cell, sandwiched between the mass spectrometer and the ion optic elements, is a common feature of contemporary equipment designed to mitigate the issue of mass interferences. This happens when two ions, one of which is an elemental ion (56Fe+) and the other a molecular ion (40Ar16O+), which could be produced by the sample matrix interacting with the Ar gas in the plasma, appear to have the same m/z value of 56 amu. The mass spectrometer's resolving capacity alone won't be enough to distinguish many of these interferences. The subsequent measurement will be impacted by a high background and a decreased detection limit caused by the 40Ar16O+ or other interfering ions unless this mass interference is removed.

When operating in collision mode, the cell is partially filled with inert gas, causing the elemental and molecular ions to collide with the gas atoms and impart some of their kinetic energy to the ions. Due to its bigger size, 40Ar16O+ is more likely to experience such collisions, resulting in a significantly higher loss of kinetic energy by the time it reaches the end of the cell. Just 56Fe+ will proceed into the quadrupole mass spectrometer after passing via a kinetic energy band pass filter, which efficiently separates the two ion types due to their kinetic energy differences. On the other hand, the energy filter will have also reduced the 56Fe+ intensity, albeit only by a modest amount. However, there will be a negative impact on the detection limit. A gaseous species that is reactive is introduced into a reaction cell in place of the atoms of an inert gas. The idea is that the neutral species formed by the reaction between the interfering species and the added gas will be immune to the effects of the ion optics' and the quadrupole's electrostatic fields. We will make sure to filter it out. Since the analyte ion is unaffected, this method of removing mass interferences is more effective than the collision cell. It must be carefully avoided, however, that no "new" mass interferences be created in the course of this operation.

Though there are alternatives based on time-of-flight and magnetic sectors, the most prevalent type of mass spectrometer in ICP-MS devices is the quadrupole. With the RF voltage and DC offset voltage configured to permit only ions of a single specified m/z value to oscillate across the space between the four poles that comprise the spectrometer, quadrupole mass spectrometers may measure one mass at a time. The rods will eliminate ions of different masses by colliding with them. In order to detect within the necessary m/z range in an analysis, the RF and DC voltages can be serially scanned. While both types of mass spectrometers rely on a scanning magnetic field to direct ions in a specific m/z range towards detectors, the configuration of the former determines how it operates. It is crucial that this area is under high vacuum since mass spectrometers might have long paths that ions must travel through to achieve mass separation. Avoiding collisions between gas molecules and analyte ions could prevent charge exchange reactions, which would reduce sensitivity and increase undesirable mass interferences.

Evaluate ICP-MS Data

As isotope ratio measurements or isotope dilution analysis, data in ICP-MS is typically analysed quantitatively or semi-quantitatively.

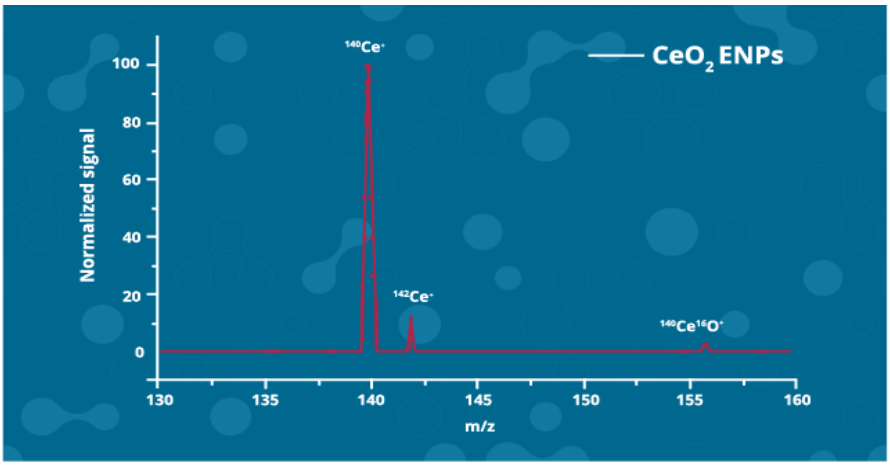


Figure 2: Example of an ICP-MS mass spectra.

This information will be useful for planning comprehensive quantitative analyses with suitable standards and for adjusting instrument operation protocols in case of possible mass interference issues. To begin quantitative analysis, a calibration curve is constructed to transform the number of analytes detected into a concentration. In order to construct this curve, the unknown sample is tested using the same instruments as a set of reference standards with a confirmed concentration of the analyte. It is sufficient to configure the quadrupole RF and DC voltage settings or the magnetic sector magnetic fields for the m/z values of interest in order to conduct these kinds of investigations. Scanning the entire mass range is unnecessary. Lastly, isotope dilution is a way to get the most precise quantitative results. A known amount of 57Fe, a stable isotope with a natural abundance of 0.29% and the same chemical and physical properties as 56Fe, could be added to a sample if the analyte is 56Fe+, for instance. So, it's like having your own personal standard. Since we know how much 57Fe was added, we can determine the concentration of 56Fe by measuring the isotope ratio 57Fe/56Fe. This method's strength is that it eliminates instrumental influences by doing analysis, standardisation, and quantification in a single experiment and arriving at the conclusion by a ratio.

What ICP-MS Does Well and What It Can't

Among ICP-MS's many virtues is its wide dynamic range, which allows it to efficiently analyse a wide variety of compounds at concentrations as low as a few nanograms per millilitre. One of its strengths is their high sample throughput, which is perfect for their industrial uses. Typically, the necessary results can be obtained with relatively small sample volumes and relatively easy preparation methods. In addition to measuring isotope ratios with great accuracy, the approach can differentiate between stable and radioactive isotopes. As we've already established, hyphenated procedures that employ a separation technique to determine analyte species are ideal for employing ICP-MS as a selective detector. One drawback is the expensive equipment, which necessitates highly skilled workers [2]. Also, mass interferences can be an issue, but as we've shown, there are a number of strategies to lessen or even remove their impact.

Issues that often arise with ICP-MS

In most cases, issues with the nebulizer or the cone ion optics components are the root of the most prevalent ICP-MS problems. Repeated measurements of the same sample may reveal inconsistent ion count rates and precision if these components are contaminated or broken. The peristaltic pump could be at fault as well, causing comparable problems. Memory or carryover effects can occur due to the technique's sensitivity; these occur when an analyte's detection limits are artificially raised by the residual presence of the element in the instrument, which occurs when samples or calibration standards with high concentrations of the element were previously analysed. Mass interferences are a constant problem, but there are techniques to lessen their impact. Isobaric mass interferences (two elemental ions with the same isotopic mass, for example 58Ni and 58Fe) or interferences at m/z caused by doubly charged ions (z = 2; for example 56Fe++ and 28Si+) are significantly more difficult for collision and reaction cells in single quadrupole systems to eliminate than molecular and elemental ion mass interferences. In most cases, triple quadrupole systems are necessary for the separation of such interferences. Lastly, to avoid accidental sample or standard contamination, all lab

components, including chemicals, water, and glassware, must be extremely pure and spotless.

The MC-ICP-MS and LA-ICP-MS methods for enhancing analytical capabilities

Multicollector (MC) ICP-MS systems and laser ablation (LA) of solid samples are two examples of recent developments that increase the capabilities of ICP-MS. The former eliminates the need for spatial information removal and digestion in liquid, while the latter simplifies the process of introducing samples into the ICP-MS system. Magnetic sector instruments often have MC-ICP-MS systems installed, which allow for the multicollector array to concentrate the mass-separated ions' dispersion. This makes instrumental effects time invariant and enables steady-state sample analysis with simultaneous measurement of all isotopes. When very exact isotope ratios are needed, as in geochronology and cosmochemistry, they are most useful.

When a thorough understanding of the analyte's distribution throughout the sample or in certain regions is necessary, LA-ICP-MS is a popular tool for directly determining elements in solid samples with little sample preparation. It allows for imaging ICP-MS. In an ablation chamber or cell that has been purged with Ar, the surface of the sample is exposed to a high-energy laser beam, such as deep ultraviolet light with a wavelength of 213 nm. As a first estimate of the method's spatial resolution, the beam diameter can be changed from less than 5 µm to 300 µm. The sample-interacting laser produces an aerosol, which is then transported to the ICP in Ar to be ionised and examined [3]. You can use the beam in spot mode to examine particular sample features, or you can raster it across the sample to see how the trace elements are distributed. Because there are more matrix effects, it is more difficult to quantify because various materials will have different interactions with the laser beam. Matrix matching standards are thus preferable for optimal quantification results.

ICP-MS vs ICP-QQQ

There are still cases where the target detection limits are not reachable using reaction and collision cells in ICP-MS, even if these cells have helped to reduce mass interferences. Mass interferences caused by mixtures of analyte and sample matrix will be insurmountable when using reaction or collision cells alone. Section 5 brought up the issue of doubly charged ions and isobaric interferences are two examples. Trace elements 75As and 78Se, which are important in the food industry due to their toxicity (As) and nutritional relevance (Se, which is necessary for formation of selenoproteins), are interfered with by the doubly charged ions of rare earth elements Nd, Sm, and Gd. The "triple quad" method involves inserting an extra quadrupole into the reaction cell. As a result, prior to entering the reaction cell, all ions are significantly reduced in size by mass filtering to within 1 amu. As an example, the cell will only admit ions having a m/z value of 75, such as arsenate and its mass interferences. This paves the way for the design of highly tailored chemical reactions. Since the initial quadrupole would have already rejected 91Zr ions, the use of O2 in the reaction cell to generate 75As16O+ (a process known as mass shifting) allows for detection at m/z = 91 without interference [4].

What Sets ICP-MS Apart from ICP-OES

Inductively coupled plasma optical emission spectroscopy (ICP-OES) and inductively coupled plasma mass spectrometry (ICP-MS) are comparable in that they both use nebulizers to draw liquid samples into an argon plasma, which is then sprayed with the resulting aerosol. Instead of measuring the m/z of ionised atoms, optical emission spectroscopy detects the wavelength of the characteristic energy emitted from atoms when their electrons fall from a highly excited state back to the ground state. From a practical standpoint, ICP-OES is the way to go [5, 6]. In most cases, reagent grade chemicals are adequate for analysis, the equipment is less costly than ICP-MS, and it does not necessitate the same degree of staff experience to run. Another perk is that it works well with solutions that would be problematic for ICP-MS instruments due to their high concentrations of dissolved solids. But unlike ICP-MS, the detection limits here won't be very low.

From combating fraud to identifying food toxins and making accurate medical diagnoses, mass spectrometry (MS) is an indispensable tool. But, ionisation is required prior to MS analysis of any material. Depending on the sample type, target analyte, and intended workflow, there are various methods to achieve sample ionisation. Among these methods are those that involve gas, desorption, spray, and thermal ionisation, plasma, and liquid metal ions. Gas phase methods include electron ionisation (EI), chemical ionisation (CI), direct analysis in real time (DART), and inductively coupled plasma (ICP). Desorption methods include matrix assisted laser desorption ionisation (MALDI), fast atom

bombardment (FAB), and LMIS. Electrospray ionisation (ESI) and desorption electrospray ionisation (DESI) are examples of spray methods. Here we take a look at a few popular ionisation methods and the kinds of samples that work best with them.

Methods involving gas phase ions

Below, you can find descriptions of many of the most used ionisation procedures. You can get more information in Siuzdak's review.

Atomic ionisation

Dempster initially created EI in 19182, and it is a relatively severe technique for ionising and fragmenting molecules. For electron interaction (EI), the analyte molecules need to be in the vapour phase so that the energetic electrons generated in a vacuum by a heated filament (like an incandescent light bulb) can interact with them effectively [6-10]. On average, the ion source produces electrons with a kinetic energy of 70 eV. Figures 3, 4 show that even if the molecule just absorbs 10–12 eV of this energy, it will be in a state where it has a lot more energy than its ionisation potential, and one electron will be ejected. A positively charged ionised state is the result for the molecule. The possibility remains, though, that it has residual energy to release. It does this in part by breaking chemical bonds, which results in a more stable ion. Deducing information about the molecular compound's structure through these fragmentation processes can be achieved using understanding of organic and physical chemistry.

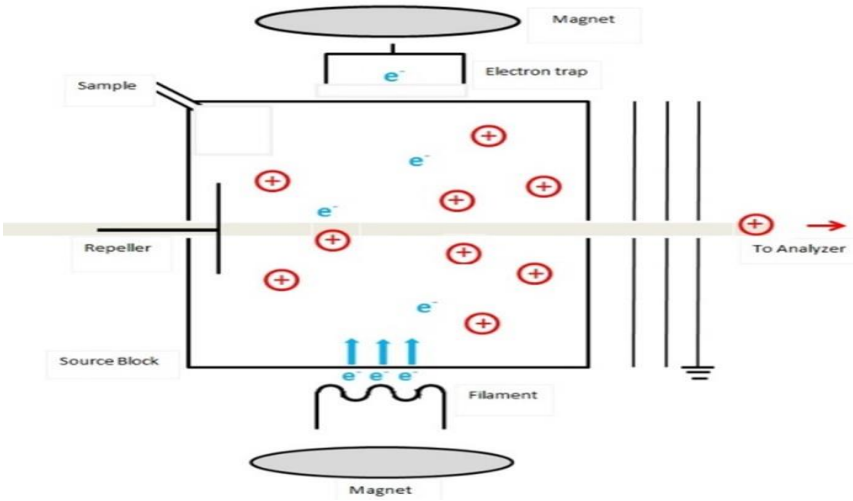


Figure 3: Illustration of an ion source for electron ionisation. Original work by Thilini Ukwaththage; this copy is licenced under the CC Attribution-ShareAlike 4.0 International Creative Commons Licence.

When working with substances that are both highly volatile and relatively light in molecular weight, EI is the method of choice. Volatilization occurs when a solid sample is heated in the ionisation chamber, or when they are delivered to the ionisation source as effluent from a gas chromatography (GC) system.

Ci - Chemical Ionisation

Analyte molecules are not extensively fragmented by CI, a gentle ionisation approach, in contrast to EI. So much fragmentation occurs in the case of certain chemical species (such as alcohols, ethers, amines, and amino acids) when subjected to EI that the resultant mass spectra for the intact molecule do not show any peaks. Perhaps CI is the best way to ionise these kinds of compounds. A gas, usually methane, ammonia, or isobutane, is injected into an EI ionisation chamber in CI at a concentration greater than the analyte's [11, 12]. Different molecular ions will be formed when the excess carrier gas reacts with the molecular ions that are produced when the electrons interact with the carrier gas. Analyte molecular ions will be formed when these ions undergo a series of reactions with analyte molecules.

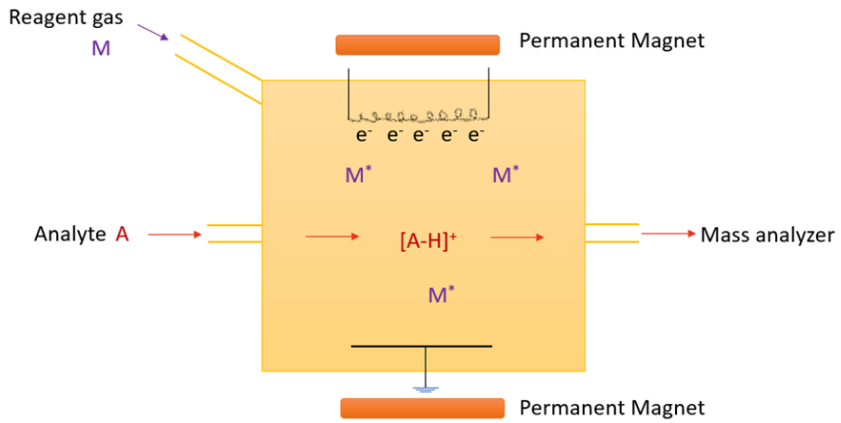


Figure 4: Mass spectrometry's chemical ionisation schematic. Using the Creative Commons Attribution-Share Alike 4.0 International licence, this image was reproduced with the permission of OviniW.

The mass spectra that emerge from using this low-energy ionisation technique are frequently easier to understand because there are fewer peaks. There is also a protonated analyte [13–16] molecular ion peak that is usually visible, which makes molecular mass determination easier. The amount of structural information about the analyte molecule that can be determined is limited, nevertheless, due to the lack of fragmentation.

Actual, real-time analysis (DART)

In 2003, development began on the DART source, and by 2005, it had reached full commercialization.5 One of its strongest points is that it doesn't need any sample preparation in order to examine materials of varying shapes and sizes. Figure 5 shows the DART source in action, which begins by generating ions, electrons, and excited-state species from helium or nitrogen plasma. The gas is passed from the plasma chamber to another chamber that removes ions. A third part of the source can be used to heat the gas if needed, which helps with desorption of some compounds [17, 18]. A grid electrode, which has multiple uses and improves the signal, directs the gas from the source to a sample in the liquid, solid, or vapour phase that is placed in front of the mass spectrometer's input. Ionisation of the analyte molecule occurs as a result of the interaction of excited state species. There are a lot of components that go into the intricate processes by which this happens.

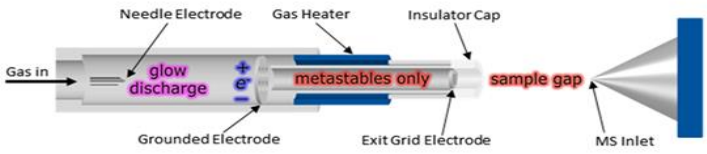


Figure 5: Visual representation of a DART supply. With permission from the Creative Commons Attribution-Share Alike 4.0 International licence, this work was re-created by Rbcody.

The adaptability and capability to analyse in ambient atmosphere of the DART source have led to its extensive use [19–21]. Common applications include food analysis, forensics, and drug testing.

Plasma that is inductively connected (ICP)

Samples in liquid form (such as acid digestions of solids) are the most common candidates for ICP analysis. An argon gas plasma is delivered to an aerosol formed by pumping a pre-prepared liquid containing the analyte through a

nebulizer in the most basic version of ICP. The liquid droplets transform into gaseous form as they enter the plasma at a high temperature (~ 5500-6500 K). As they continue to absorb energy, they will finally separate into one positively charged ion by releasing an electron (Figure 6).

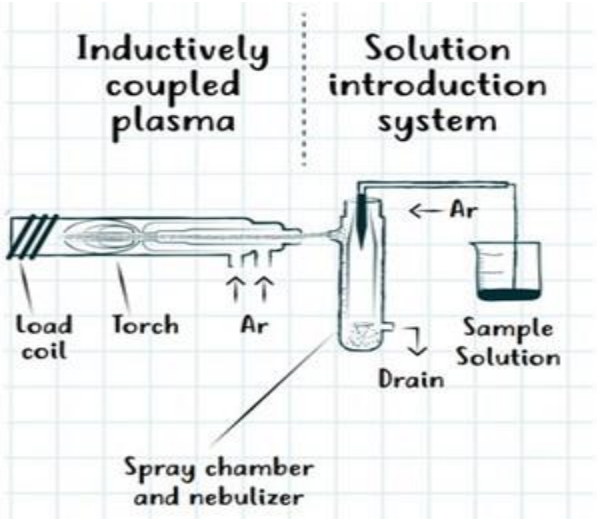


Figure 6: Schematic diagram of an ICP source.

Even the elements with the highest ionisation potentials can be ionised by ICP. Ionisation and subsequent mass spectrometric detection can be achieved by utilising the effluents of other separation techniques, such as liquid chromatography (LC), gas chromatography (GC), capillary electrophoresis (CE), and gel electrophoresis (GE). If you want to learn more about ICP-MS, you can do so by clicking here.

Methods for desorption involving ions

A technique called matrix aided laser desorption ionisation

One of the most prominent "soft" ionisation methods utilised in MS nowadays is the MALDI technique, which has been around since its inception in 1985. Proteins, peptides, oligonucleotides, polymers, and lipids are only a few examples of the big or unstable compounds that benefit greatly from its examination. The method uses an extra "matrix" that is added to the material that will be analysed (Figure 7). To be valid, the matrix must have these characteristics:

Must be able to co-crystallize with the analyte to form a solid solution

- Be able to transfer or accept protons from the analyte
- Be chemically inert
- Stable under vacuum and soluble in solvents

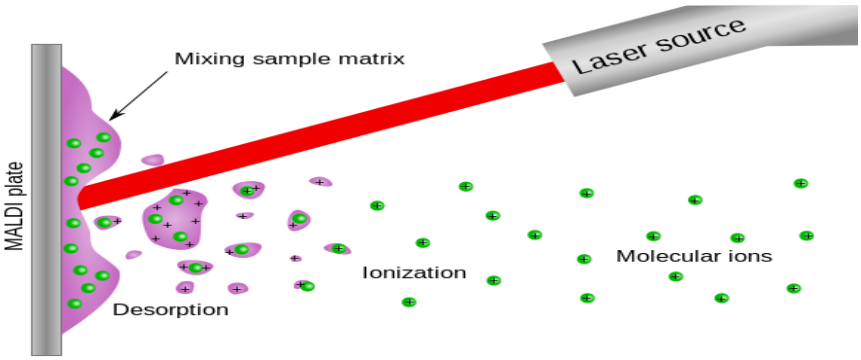


Figure 7: An MALDI source schematic. Mikayé is the rightful owner of this work, which is why it is available under the AGPL. version 3.0, version 2.5, version 2.0, and version 1.0 licences.

One example of a matrix is 2,5-dihydroxybenzoic acid. Other examples include sinapinic acid, picolinic acid, α-cyano-4-hydroxycinnamic acid, and many more.11 Depending on the target molecule, a specific matrix will be used. After applying the matrix, the sample is subjected to laser irradiation [22-26]. This not only ionises the analyte molecules to create positively or negatively charged ions, but it also transfers energy to the matrix, vaporises them with minimal fragmentation or decomposition, and so forth.

Atom bombardment with speed (FAB)

FAB is another method of soft ionisation that involves focusing a beam of accelerated atoms—usually inert gases like argon or xenon—onto the sample that needs to be examined. Ionising the atoms allows them to be focused using electrostatic lenses and accelerated by high electric fields, which is the first step in creating the "fast" beam [27-30]. Charge exchange processes will neutralise the inert gas ions by sending this ion beam into a collision cell that also contains the same inert gas.

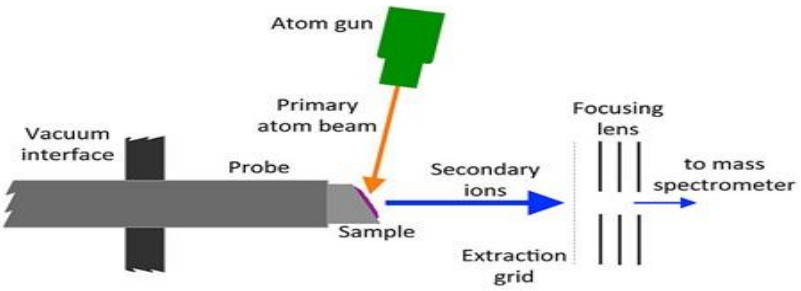


Figure 8: A schematic depicting the ionisation of FABs. Creative Commons Attribution-Share Alike 4.0 International licence; original work by Kkmurray.

A matrix, usually glycerol, is utilised, much like MALDI. For FAB, this is to lessen the possibility of atom beam damage to the sample, avoid analyte molecule agglomeration [31, 32], and, similar to MALDI, to enhance ejected analyte molecule ionisation. The ionisation process, like MALDI, uses protonation to create positive ions and deprotonation to create negative ions.

Emissions from thermal ionisation

When doing secondary ion MS investigations, the Cs+ primary ion source is by far the most frequent thermal ionisation source used. It is a basic source that uses thermal energy to ionise Cs atoms. The source of Cs is in the reservoir, and the ioniser is a porous tungsten frit kept at a high temperature (> 1000 °C). To create a vapour of Cs atoms, the pellet of Cs carbonate (or chromate, another option) [33, 34] is heated in the reservoir until it sublimes. These atoms can be retrieved and focused using electrostatic ion optics elements once they reach the heated frit, where they are ionised as positive ions. Due to the inherent hazard of handling this material during source changes, old systems that used liquid Cs as the source material are no longer routinely used in practice.

Ionisation sources for plasma

The production of gaseous ion beams for MS, especially of oxygen species O- and O2+, is another typical application of duoplasmatrons. A cathode filament in the duoplasmatron releases electrons that are bled with pure oxygen until the pressure reaches approximately 10 to the power of 5 torr. As the gas molecules mix with the electrons and other gas in the chamber, it becomes ionised and forms a plasma (Figure 8). A initial beam of oxygen ions is produced after the plasma is propelled through a sequence of two or more highly charged grids. This sort of source usually employs a Wien filter to isolate O- and O2+ ions since, otherwise, there will be a wide variety of oxygen ion species present.

Initial Impact of the Sample

It is greatly dependent on the aerosol transport efficiency and the size distribution of the aerosol droplets that the sample aerosol is delivered to the plasma in the sample introduction mechanism. Thus, the observed analyte signal will be impacted by changes in aerosol characteristics caused by changes in physical and chemical properties [35, 36]. Fluidity, surface tension, ionic strength, acidity, and vapour pressure of the sample are crucial factors.18 Assuming the plasma is not overwhelmed, alterations that improve sample transport to the plasma—for example, decreasing the

sample's viscosity or increasing the vapour pressure—will result in an amplified signal. Suppressing signals occurs when ionisation drops due to a cooling impact caused by adding too much solvent to the plasma. This is typically only an issue with organic solvents with a high vapour pressure, which aren't tested often in clinical labs. Signal suppression due to improper dilution can occur in laboratories when working with extremely viscous samples, such as joint fluids.

There are two distinct methods that can cause high-ionic-strength samples to undergo noticeable matrix effects in the sample introduction system.62 Aerosol transport efficiency to the plasma drops as ionic strength rises [37, 38], but high ionic strength also enhances coulomb fission of aerosol droplets in the spray chamber. In contrast to the signal reduction caused by the previously indicated decline in volatility, the smaller droplets produced by Coulomb fission are more efficiently delivered to the ICP.

The design of the sample introduction system, including the type of nebulizer and spray chamber, as well as the temperature of the chamber, influence these effects. Consequently, it is not uncommon for the impact of a specific sample matrix to be unexpected. Actually, ICP-MS matrix effects are most strongly felt in the plasma and interface/ion optics area, which is downstream from the sample introduction system.

Impacts of Plasma

The ionisation of analytes in plasma can be influenced by a variety of factors that are unique to each sample. The instrument signal is reduced when there are high concentrations of sodium and potassium, which are easily ionised, in the sample because they cause the analyte's thermal ionisation equilibrium to move towards the neutral atom. However, for analyte ionisation, carbon in the sample matrix actually works in the opposite way, increasing it (at least for elements with a large ionisation potential) [39, 40]. Carbon ion (C+) and analyte charge transfer processes in plasma are considered to represent the mechanism at work here. Arsenic, selenium, mercury, and tellurium are among the many elements that have been found to exhibit this effect; their ionisation potentials are considerable, although they are still lower than carbon's. Depending on the instrument and carbon source, the amount of signal augmentation caused by carbon can range from negligible to five times stronger for arsenic and selenium. To improve analytical sensitivity, laboratories frequently employ this phenomenon. In order to facilitate speciation procedures, it is common practice to add organic solvents like isopropanol or methanol to sample diluent solutions or mobile phases.

Effects of Space Charges

The space-charge effect, which happens in the interface and ion optics of the instrument, is the primary cause of matrix effect in ICP-MS. Ions in the ion beam that have positive charges repel each other electrostatically, leading to space-charge. Even though the plasma gas that is drawn out of the sample cone is basically neutral, the net positive charge occurs because electrons diffuse away from the ion beam due to the dramatic drop in pressure.68 Because positively charged ions are repulsive to one another, the ion beam widens and less ions are transmitted to the detector. Light analytes are more strongly impacted than heavier ones because their kinetic energy (inertia) is lower [41, 42]. Also, when comparing an equimolar quantity of heavy and low mass matrix elements, the suppression from the former is greater. Because of the close relationship between mass and space-charge, it is crucial to choose an internal standard that is about the same mass as the analyte.

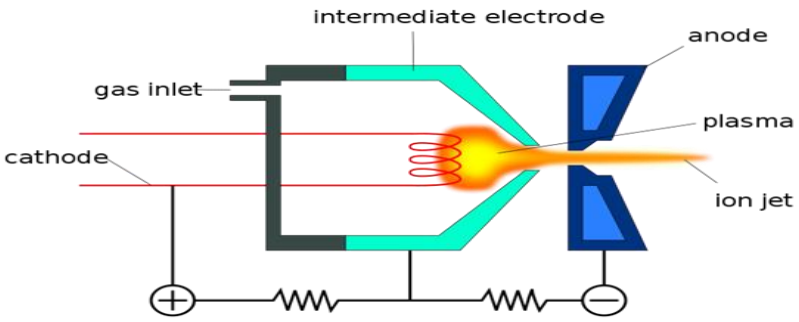


Figure 9: A duoplasmatron schematic. This work is based on an original by Evan Mason and is licenced under the Creative Commons Attribution-Share Alike 4.0 International.

Sources of liquid metal ions (LMIS)

Produced by LMIS ion beams are known for their utmost brightness and smallest spot sizes. Their ability to achieve spot sizes as small as 5 nm, which is comparable to the spatial resolution of a scanning ion mass spectrometer, makes them ideal for use in MS imaging, which demands high spatial resolution. A metal with a low melting point is necessary for these sources [43–45], with Ga being the most popular choice. For an electron microscope, the source resembles a tungsten filament, but it actually contains a second reservoir of Ga. As the filament is heated, Ga will flow down its surface and eventually reach the tip, where it will be field ionised from a tiny point source due to the combination of the short tip radius and the large electric field produced by the applied extraction voltages.

Sources of ions - spray techniques

The process of electrospray ionisation

Another soft ionisation method that works well for macromolecule and large molecule analysis is electrospray ionisation (ESI). A few kilovolts of electricity is used to hold a capillary while the sample is put into it. The result is a fine mist made up of identically polarised charged droplets. A drying gas or high temperatures are used to minimise the size of the solvent as the charged droplets travel through the source, increasing the surface charge density [46-47]. The electric field intensity inside the droplet reaches a critical point when surface ions are able to eject into the gaseous phase (Figure 10).

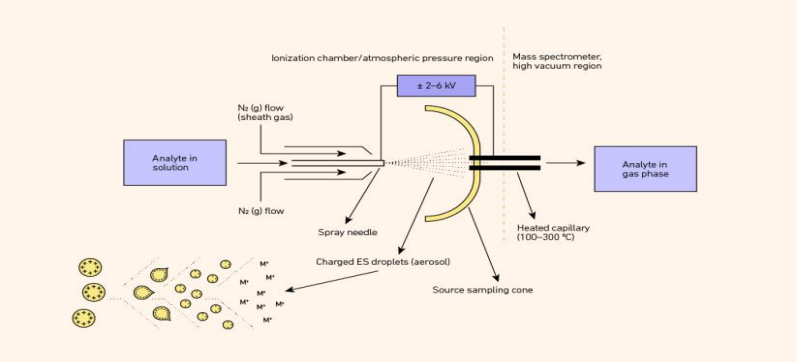


Figure 10: Schematic of ESI source and depiction of ionization mechanism.

Method of desorption electrospray ionization

The name "DESI" gives away the fact that it's quite similar to "ESI," but instead of charged droplets created in the ESI source, DESI uses them as a source and directs them to a sample maintained at ambient pressure, much like DART. It is possible to route the sample's reflected or "splashed" droplets, which include desorbed and ionised analytes, into a mass spectrometer (Figure 9). There may be intricate ionisation mechanisms.

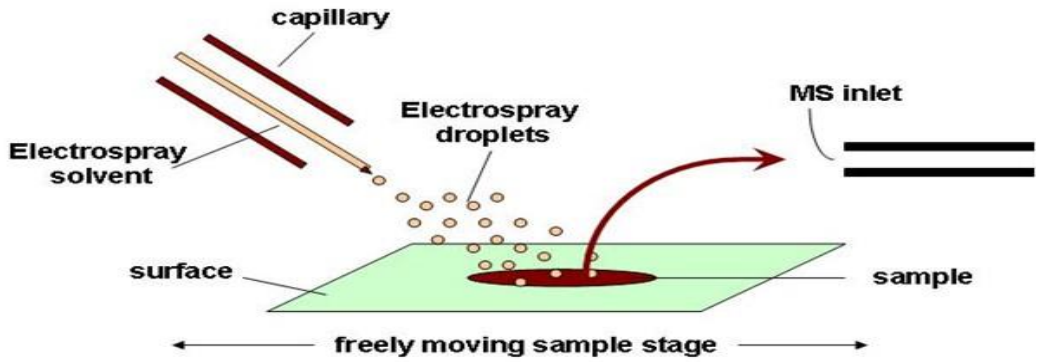


Figure 11: The DESI ion source schematic. Using the Creative Commons Attribution-Share Alike 3.0 Unported licence, this work was reprinted with permission from Anzhela016.

The following links will take you to pages on mass analyzers and ion detectors, where you may learn more about the further stages of the MS process. GC-MS opens up a world of new possibilities in a number of fields thanks to its improved sample identification, better sensitivity, expanded range of analyzable samples, and lightning-fast findings.

Medical Uses in Pharmacy

Screening assays for many congenital metabolic illnesses employ GC-MS. It can identify chemicals in patients' urine at low concentrations who have inherited metabolic diseases. It is also able to identify lotions, ointments, and creams that include oils. Research, production, and quality control all make use of GC-MS in the pharmaceutical business [48–51]. Impurities in active medicinal components can be detected using this method. Pharmacological biotechnology and medicinal chemistry both make use of GC-MS for chemical production and characterisation.

Investigative Purposes

Analyses of fire debris can be conducted using GC-MS in accordance with ASTM standards [52, 53]. Both forensic toxicology and anti-doping laboratories rely on GC-MS for the detection of performance-enhancing substances like anabolic steroids in biological material. Agilent, a maker of life science instruments, provides GC-MS systems—both single and triple quadrupole—that are ideal for toxicology, food testing, and forensics because of their sensitivity and low detection limits.

Monitoring the Environment

One of the main uses of GC-MS is the monitoring of contaminants in the environment. It finds extensive application in the detection of phenols, chlorophenols, herbicides, sulphur, pesticides, dioxins, and dibenzofurans in water, soil, and air.

Evaluation of Flavours and Foods

Food and drink containing aromatic chemicals including terpenes, alcohols, esters, aldehydes, and fatty acids can be simply analysed with GC-MS. The method can also be applied to identify food contamination or rotting. By utilising GC-MS, a diverse array of oils, including spearmint, olive, and lavender oils, as well as essential oils, scents, allergens, menthol, and syrups, can be analysed.

Environmental, food, forensic, and industrial applications are just a few of the many that can benefit from the precise data and deeper insights provided by Perkin Elmer's GC-MS systems, which are used in healthcare and laboratory solutions [54, 55]. The GC-MS systems offered by the business provide both high-throughput processing and sensitivity, making them ideal for the study of a wide range of volatile and semi-volatile substances.

Analyses of Living Things

Pharmacological substances such as alcohols, barbiturates, narcotics, anticonvulsants, antihistamines, sedative hypnotics, and anti-epileptic medications can be identified through the bioanalysis of bodily fluids using GC-MS. Additionally, it can be employed to identify metabolites and contaminants in serum as well as to profile fatty acids in microorganisms [56]. Food, environmental, forensic, and therapeutic applications can all benefit from Thermo Fischer Scientific's GC-MS equipment and software, which together simplify GC-MS workflows and data.

Chemical Weapons

For the purpose of analysing and detecting chemical warfare chemicals, explosive detection systems installed in public spaces employ the GC-MS technology.

Investigating Geochemistry

The structurally significant mass spectral peaks, extended range of analyzable low volatility materials, improved molecular ions, and rich isotope ratio information make GC-MS a potent tool for geochemical applications. Both the Viking programme on Mars and the Venus atmosphere have made use of GC-MS for analysis. Furthermore, the Rosetta mission has analysed the components in comet 67P/Churyumov-Gerasimenko using a chiral GC-MS technique.

Practical Uses in Industry

Inorganic gas and aromatic solvent analysis, as well as cosmetic impurity and allergy detection, are GC-MS's strong suits. Synthetic fibres, polyethylene, polyvinyl, and cellulose acetate are all made using it.

Since automated GC-MS systems provide fast and repeatable results in various applications, it can be concluded that

they are a good choice.

Common Types of Mass Analyzer?

In a mass spectrometer, the mass analyzer is the central component. This section sorts the ionised masses according to their m/z ratio, which measures their mass-to-charge ratio. Orbitrap, ion trap, magnetic sector, time-of-flight (ToF), and tandem mass spectrometry (MS) are some of the types of mass analyzers available. Various mass analyzers are discussed in this article along with their pros and cons.

Thermo-flight mass spectrometers

A type of mass spectrometer that is often used is the tofu (ToF) instrument. Ions can be separated by their m/z ratio using the time it takes for them to go through a flight tube of specified length to reach a detector; this is the fundamental principle underpinning time-of-flight mass spectrometers. When it comes to ions, the smaller the m/z, the faster they will move and the first to reach the detector, and the largest the m/z, the slower they will travel and the last to arrive. These mass spectrometers often employ a pulsed ion source due to the ToF concept. This is why they are often connected to MALDI sources, which use pulsed laser desorption ionisation, since lasers are also commonly used for this purpose.

One major benefit of time-of-flight systems is that they can simultaneously gather a vast array of m/z values, which may then be stored and retrieved for use in further analyses. Additionally, as shown in Figure 12, they exhibit excellent mass resolution, especially when reflectrons are included into the flight tube to account for variations in the kinetic energies of the analyte ions.

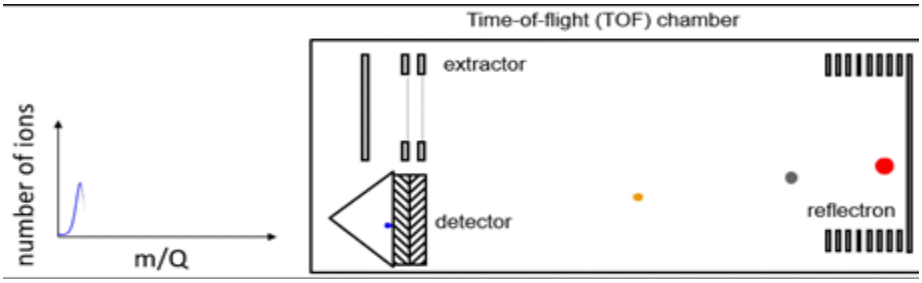


Figure 12: Schematic of a ToF system. Animated version available here. Credit: Abigail Koss, TOFWERK.

Analysis of mass using quadrupoles

Two sets of metal rods, spaced equally apart and biassed at opposite potentials, make form a quadrupole mass analyzer. These two potentials have a constant direct current (DC) and a variable alternating radio frequency (RF) component. A potential that is directly proportional to the m/z value will divert the trajectory of any ion that enters the quadrupole. Only one particular m/z value will resonance with the field at certain RF values, making it to the end of the quadrupole and being identified. Quadrupole collisions cause ion loss of charge and subsequent invisibility for ions with different m/z values. Figure 13 shows an animation that explains the main idea.

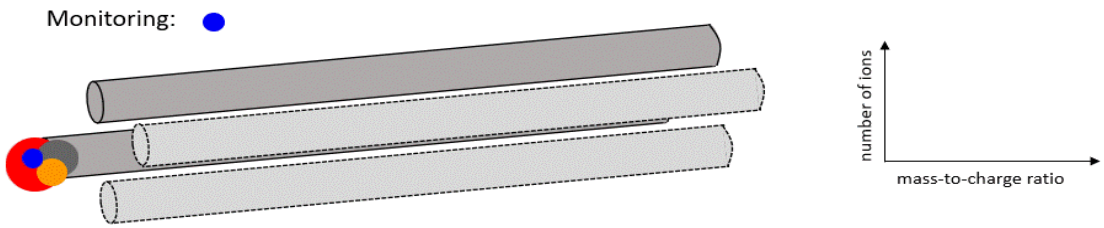


Figure 13: Animation showing how a quadrupole mass analyzer works. Credit: Abigail Koss, TOFWERK.
Operating and maintaining a quadrupole MS system is less of a hassle because their separating principle is simple. The quadrupole is not only effective, but also cheap, small, and sturdy. This leads to its widespread use as an analytical tool for a variety of purposes. Moreover, quadrupole MS is functionally superior to other MS types that necessitate high vacuum levels, even at lower pressure levels (10-2 to 10-3 Pa). A gas chromatography (GC) or liquid chromatography (LC) unit can be interfaced with them, and the mass separation performance is unaffected by the

interface-induced drop in vacuum level, making them ideal for use with chromatographic procedures. The sensitivity and scan speed of quadrupole systems are excellent, and they can detect masses up to 2,000 m/z. Also, it's capable of fast polarity flipping, which lets you watch many ions with varied polarity at once. On the other hand, when used alone, without further separation or MS procedures, it has fairly poor mass resolution.

Separators for magnetic sectors

Like a glass prism divides light into its many wavelengths and colours, magnetic fields can scatter ions along paths determined by their mass-to-charge ratios; this principle is the basis of magnetic sector mass analyzers (Figure 14).

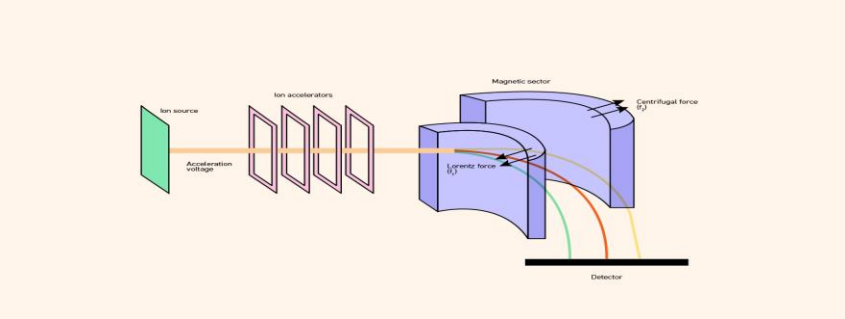


Figure 14: The magnetic sector mass spectrometer, graphically depicted. Attribution: Networks in Technology.

One of these modifications, called the "double focusing" version, uses an electrostatic sector to account for ion kinetic energy differences (Figure 4). Instead of cycling the field, some systems use a multicollector detection system that can measure an unlimited number of masses serially by employing a static magnetic field (Figure 15).

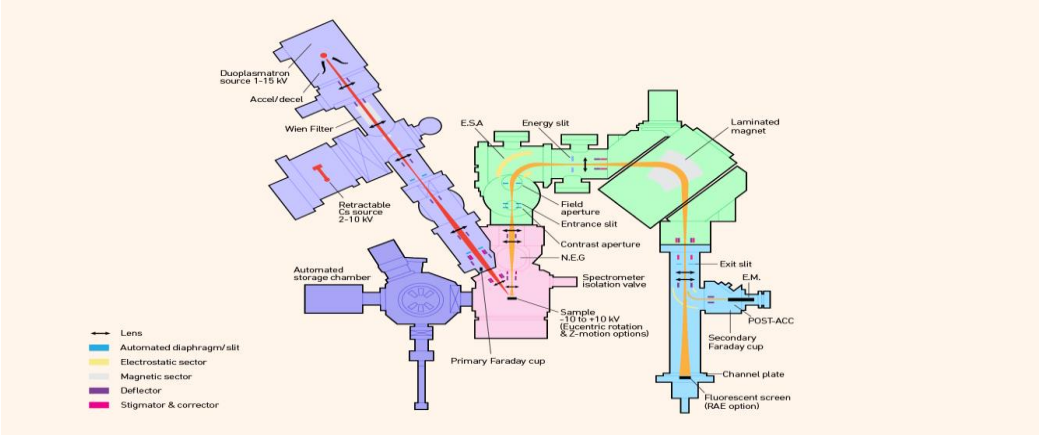


Figure 15: Oxygen plasma and cesium ionisation sources are shown in this schematic of a double-focusing magnetic sector mass spectrometer..

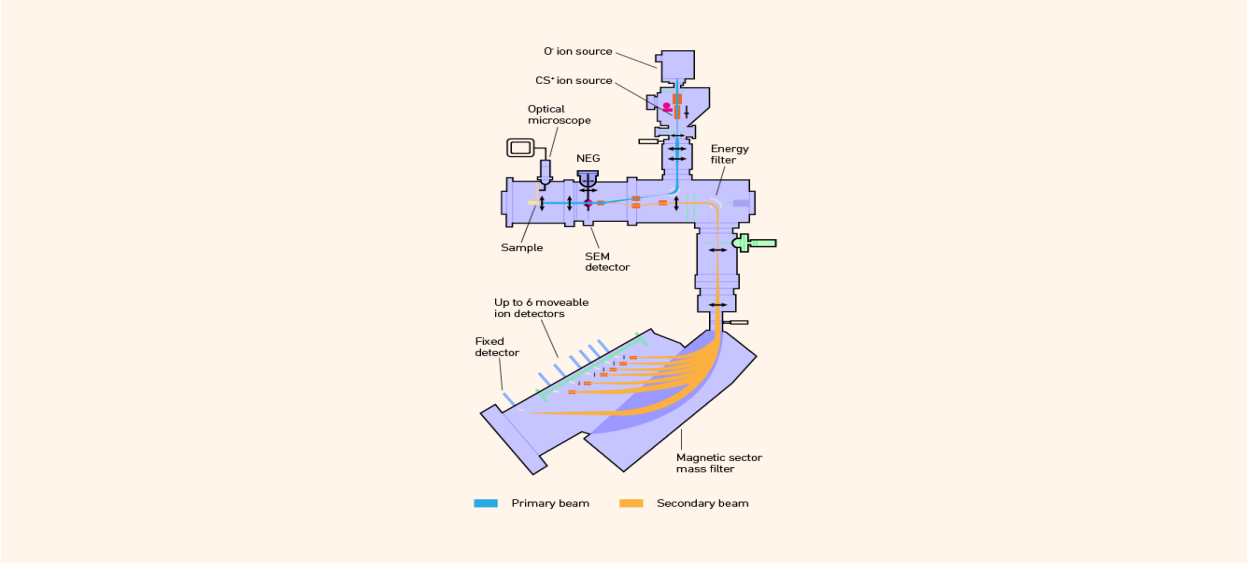


Figure 16: Nanoscale secondary ion mass spectrometer (NanoSIMS) schematic: a two-stage focusing magnetic section mass spectrometer with a static magnetic field and several collectors.1 Point: Networks in Technology. Although these systems are costly and necessitate operators with specialised knowledge, their exceptional sensitivity and mass resolution make them well worth the investment. These mass spectrometers aren't ideal for linking with separation techniques like LC because they need to be kept under ultrahigh vacuum.

Evaluators of ion trap mass

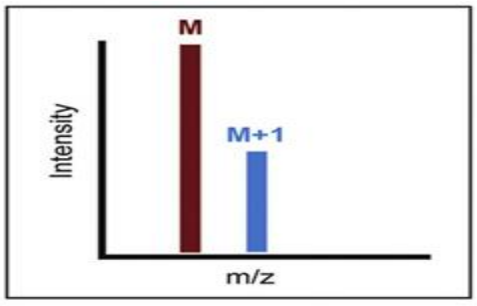
While the quadrupole and ion trap MS share certain common concepts, there are also important distinctions. The standard configuration for an ion trap is an electrode in the shape of a ring with two electrodes on either end. At the entry, you'll find an ionisation unit, and at the exit, you'll find a detector. You might think of the ring electrode as being similar to the two ends of a quadrupole. In contrast to the quadrupole system, where electrode voltage is present, ions in an ion trap often flow horizontally. Before applying a low RF voltage to the ring electrode, the end-cap electrodes are grounded during analysis. All of the ions are momentarily contained inside the electrode when they are delivered into the trap in pulse mode [57-60]. Within the trap, ions of different masses are now undergoing steady oscillations. Gradually increasing the RF voltage allows for the detection of individual ions. A hole in the end-cap electrode is used to discharge ions whose oscillations become unstable as the voltage increases, for a given m/z ratio. Ion trap systems separate and detect ions by discharging ions with unstable oscillations into the detector, in contrast to quadrupole systems that allow oscillating ions to pass through.

Ion traps are advantageous due to their small size, low cost, high sensitivity, and high mass resolution.

Mass analyzers on orbit

A lot of other mass analyzers' technologies have been included into the Orbitrap. It has a core electrode that acts as a spindle and two outside electrodes in the shape of cups that face each other; these electrodes are electrically disconnected. An electric field with a radial component significantly pulls ions [61, 62] to the central electrode when a voltage is placed between the outer and central electrodes; this field is linear along the axis. A groove carved into one of the outside electrodes allows for the tangential injection or pulsed delivery of ions into the volume spanning the central and outer electrodes.

Elevating the inner electrode's voltage gradually raises the electric field. The ions are guided into the desired orbit inside the trap by being squeezed towards the inner electrode. When it happens, the electric field stays put and doesn't change. Ions injected into the system will have a common axial frequency but vary in their rotational frequencies. Ions with a given mass-to-charge ratio form rings that move in an oscillatory or orbital pattern around the inner spindle (Figure 6). The ion's path is bent towards the central electrode due to a radial electric field and an opposing centrifugal force caused by tangential velocity when a voltage is put between the two electrodes [63, 64]. The ions stay in the trap in an almost circular orbit for a specific range of parameters. Their m/z ratio is proportional to their rotational frequency.



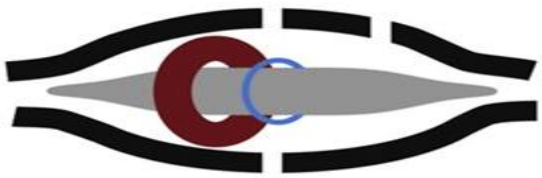


Figure 16: Diagram depicting the orbital ion trajectories in an Orbitrap and an example of the mass spectrum that is produced. Original work: [2]; reprinted with permission from Creative Commons, Attribution 4.0 International.

Ions are drawn to the broadest area of the trap by the axial electric field generated by the unique conical shape of the electrodes. Next, current is detected using the outer electrodes. The digital picture, which is now in the time domain, is first translated into a mass spectrum by Fourier-transforming it into the frequency domain. It is unique among the methods discussed here in that it employs an image current instead of a detecting device to identify ions [63-65]. The Orbitrap's compact design, together with its exceptional mass resolution and accuracy, are its primary selling points.

Combined mass spectrometry

Tandem mass spectrometry, in its broadest definition, is a hybrid approach that uses more than one kind of mass spectrometer to improve selectivity and/or mass resolving capacity. These methods are often mentioned in the literature as MS/MS techniques. Additional separation technologies, such GC or LC, are commonly incorporated into these systems.

In most cases—

Step one in using an ion source is to pass an ion via the first mass analyzer (MS).

2. Subsequent reaction cells may expose these filtered ions to further reactions.

Third, a second mass analyzer examines the charged byproducts that come out of this cell.

The setup of the MS/MS system and the type of reaction carried out between analysis stages have a significant impact on the data type and quality. Multiple tandem MS variations are reviewed by Glish and Burinsky.3 Following the links to articles on ionisation sources and ion detectors will take you to more information about the other important steps in the MS process.

Pharmaceutical and Biomedical Uses

Implementation of ICP-MS for use in biological research

The area has made great strides thanks to the integration of organic and inorganic MS and other methodological advancements used in the life sciences. When it comes to inorganic MS and the biological sciences, ICP-MS has become an essential tool for researchers in the field of biomedicine. This section will delve into a few of the biomedical uses of ICP-MS.

Genomic DNA analysis by means of ICP-MS

Styrene oxide is one of many nucleobases that can be chemically modified to produce cancer cell growth and DNA alterations. Several approaches rely on standard reference materials to identify cancer and DNA adducts; they include mass spectrometry, P labelling, and immunoassays; however, these have not been produced in thirty years, so they are not easily accessible. The issue is that it is not possible to identify unknown modifications. Using internal standards, regardless of their structure, can lead to issues like selectivity, sensitivity, and the softening of qualitative and quantitative techniques. Using bis(4-nitropenyl)phosphate (BNNP) as an internal standard, ICP-MS quantitatively engages phosphorus signals in modified nucleotides, for instance [66, 67]. As a result, ICP-MS can detect, identify, and select for elements independently.

Proteins analysed by ICP-MS

For biological analyses and metal concentration measurement in proteins, ICP-MS has seen heavy application in proteomics in recent years [36]. Quantitative bromine detection in rat and human plasma metabolism by ICP-MS was also found in these investigations [36]. Metals are essential cofactors in many biological systems, but notably in proteins. Metals like manganese, iron, copper, molybdenum, and zinc, as well as non-metals like selenium and iodine, would be in short supply without proteins. Illnesses and catalytic cytotoxic processes result from a lack of these metals and non-metals. Proteomics, which studies proteins for their metal content, must deal with the difficult problem of determining which metals are present and in what amounts. This calls for an analytical method that is more specific, sensitive, and powerful. Researchers studying neurodegenerative illnesses have utilised ICP-MS to quantitatively identify phosphorus, iron, zinc, and copper within brain proteins.

Examination of trace elements in relation to human health

Everyone is aware that certain elements are necessary for human health while others are harmful. The quantity consumed, the element's mobility, its storage and interaction in metabolites, its oxidation number, the metal-ligand ratio, and the complexity of its interactions with other elements determine the benefits and hazards of each element. When it comes to studying elemental speciation, ICP-MS is now among the most powerful methods available. Iron and its isotope ratio have been quantified in human blood and livers, and copper and its isotope ratio 63Cu/65Cu have been precisely measured in HepG2 cell and liver cell lines using ICP-MS [39]. Compared to blood and muscles, the iron content and isotopic composition of the liver are significantly higher.

CONCLUSION

When it comes to clinically relevant trace element determination in biological fluids, ICP-MS is the analytical method of choice due to its extreme sensitivity. The clinical laboratory finds ICP-MS appealing due to its many features. Among these are the following: fast sample throughput, easy sample preparation, high sensitivity, wide elemental coverage, and wide linear dynamic range. Scientists and doctors using mass spectrometry should be aware that, despite its great specificity, there is a chance of interference and analytical variables that could impact the reliability of the data. When choosing a method for a clinical application, laboratories must consider all relevant aspects, including initial capital investment (equipment cost and laboratory set-up) and ongoing operating costs (argon supply).

The capabilities of ICP-MS make it an ideal tool for the sensitive analysis of trace element concentrations; the technique offers ultra-trace elemental detection, low detection limits, increased elemental mass selectivity, and information about the isotope ratio. An essential tool for trace element analysis in the biomedical and pharmaceutical domains, it accurately determines the amounts of inorganic and organic elements present in a wide variety of drugs, including nucleotides, sulfur-containing proteins, and phosphorus-containing compounds.

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