

Inductively Coupled Plasma-Tandem Mass Spectrometry (ICP-MS/MS) and Its Applications

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Abstract

During the last about 10 years, the inductively coupled plasma tandem quadrupole mass spectrometry (ICP-MS/MS) technique with reaction cell is being utilized for the analyses of several trace elements/isotopes at very low concentration levels in a variety of matrices including geological, environmental, biological, medical, nuclear, agriculture, food, material and metallurgical sciences. Both solution nebulization, as well as direct analysis of samples by laser ablation (LA-ICP-MS/MS), are utilized for sample introduction. In fact, ICP-MS/MS technique with collision reaction cells eliminated the need for laborious chemical separations using methods such as ion-exchange or solvent extraction procedures to eliminate/minimize spectral and matrix interference effects as these interferences are removed using online chemical reactions within the instrument itself (chemical resolution). In addition, the technique is hyphenated with chromatographic techniques such as GC and HPLC for a variety of applications. The detection limits for several elements in the periodic table lie in the pg/ml-fg/ml range, and the technique compares favourably with the expensive, complex, and superior high resolution-ICP-MS (HR-ICP-MS), both in terms of the detection limits as well as the ability to remove the most complex interferences. Thus, the ICP MS/MS made the determinations of elemental as well as isotopic concentrations very simple and easy even in complex materials with several novel quantification approaches. This article provides an overview of these new developments during the last decade along with several applications in all areas of science and technology.

Key words: ICP-MS/MS, LA-ICP-MS/MS, GC-ICP-MS/MS, collision reaction cell, reaction gas, speciation.

Introduction

From the time the first publication¹ on inductively coupled plasma mass spectrometry (ICP-MS) by Houk et al. in 1980 and the first commercial instruments released in 1983, the ICP-MS technology has become more efficient and more powerful over the years with a lot of significant instrumental developments leading to the development of powerful instruments such as ICP-time-of-flight-MS (ICP-TOF-MS), high resolution-ICP-MS (HR-ICP-MS) and multi collector-ICP-MS (MC-ICP-MS) incorporating a variety of technologies for the interference removal such as cool plasma, collision/reaction cell technology (CCT), dynamic reaction cell (DRC) technology, collision reaction interface (CRI), kinetic energy discrimination (KED), tandem mass spectrometry (ICP-MS/MS)/triple quadrupole ICP-MS, and multi-quadrupole ICP-MS with each technique having its strengths and limitations^{2,3}. Several companies have developed quadrupole-based ICP-MS instruments equipped with extra quadrupole-, hexapole- or octopole- containing cells that can be pressurized with a gas (e.g., H₂, O₂, NH₃) or a combination of these gases to remove interferences with reasonable success. But despite these developments in ICP-MS technology, the removal of spectroscopic interferences has been a continuous problem in several cases all these years. Though most of the interferences can be removed by utilising HR-ICP-MS instrumentation, its higher cost and the instrument complexity prohibit its abundant usage. In addition, there is also a limitation (maximum ~10,000R) on the resolution of commercial HR-ICP-MS instruments. But the recently developed ICP tandem mass spectrometry or ICP-MS/MS brought a remarkable change in the ways to manage and effectively eliminate even the most complex interferences in ICP-MS studies. Zhu et al.⁴ recently reviewed the trends, advances, and a few applications of ICP-MS/MS, based on the studies published mainly from January 2018 to July 2021. But this article aims to provide a comprehensive overview of the ICP-MS/MS from its development to its current status, emphasizing its growing applications in different areas during the last decade.

Instrumentation

ICP-tandem mass spectrometer or ICP-MS/MS is a new type and the latest generation ICP-MS instrument. The main difference between ICP-MS/MS and the traditional ICP-MS system is the introduction of an additional quadrupole (Q1) before a collision reaction cell (CRC). Sample introduction and all other related aspects remain more or less the same. When a particular m/z is fixed in Q1, only that m/z is allowed to enter into the CRC, as a result, more

efficient interference correction even for the most complex matrices is possible in the CRC before the analyte is finally detected by the analyzer quadrupole (Q2) (Fig. 1a). For example, for the determination of iron (^{56}Fe) in a rock matrix when 56 mass is chosen, all other masses will be rejected by Q1, and ions having only m/z 56 will be allowed to enter the CRC. As a result, $^{56}\text{Fe}^+$ and $^{40}\text{Ar}^{16}\text{O}^+$ only will enter the CRC. In CRC, the ion, $^{40}\text{Ar}^{16}\text{O}^+$ reacts with gas like H_2 and breaks, and as a result, only ^{56}Fe will only be allowed to pass through the analyser quadrupole (Q2) and detected without any interference by the *on-mass* mode⁵. In another example, Ti^+ is made to react with a mixture of hydrogen and oxygen and converted to TiO^+ and determined by the *mass-shift* mode which eliminates all interferences on Ti^+ ions. One firm uses an octopole-based reaction system (ORS³) for CRC and this instrument is named as triple quad ICP-MS. When the *mass-shift* mode is selected, Q1 filters only the selected m/z ratio which will enter into the CRC filled with reaction gas. Under selected optimum conditions analyte ions will react efficiently with gas molecules while the interfering ions will not react at all. This allows the analyte ion to be converted into a reaction-product ion with a different m/z ratio than the original ion which had interference problems. The new m/z formed after the reaction in the CRC is then selected in Q2 and detected. When the *on-mass* mode is selected, the same m/z is fixed on both quadrupoles and spectral interferences are removed by making the interfering ion to react efficiently with the reaction gas. As a result, interfering polyatomic species will be converted into new species with a m/z ratio different than the one of the analytes and will not get detected by the second quadrupole. The choice between these two different modes depends on the reaction efficiency. Recently Fu et al.⁶ proposed N_2O as a universal reaction gas to overcome spectral interferences since N_2 has a lower O atom affinity (1.6 eV) than the O atom (5.2 eV), and also N_2O was a more effective O atom transfer gas than O_2 . In addition, when N_2O was selected as the reaction gas, high sensitivities and low limits of detection (LODs) were obtained by mass shift methods for several analytes. In an attempt to understand the need for an internal standard in ICP-MS/MS studies, Bolea-Fernandez et al.⁷ made a study both *on-mass* as well as a *mass-shift* mode on 17 elements covering a wide range of masses (24–205 amu) and ionization energies (3.89–9.39 eV), and concluded that the internal standard must also be detected in the same way as analyte masses for obtaining the best results.

Performance characteristics and other advancements

Balcaen et al.⁸ provided the details of the development of ICP-MS/MS and its performance characteristics with examples of a few applications. Sample introduction by all possible methods: i) sample solution nebulisation, ii) laser ablation sampling (LA-ICP-MS/MS), iii) sample introduction through GC (GC-ICP-MS/MS), and iv) sample introduction through LC/HPLC (LC/HPLC-ICP-MS/MS) are possible for a variety of applications (Fig. 1b-e). The major advantage is that the existing single quadrupole ICP-MS solution nebulisation methods and most of the collision and reaction methods used can be simply transferred to ICP-MS/MS applications without significant modifications. The combination of separating techniques such as GC or LC or HPLC when coupled with ICP-MS/MS, becomes an important analytical tool for diverse applications. In fact, GC-ICP-MS has proven to be very useful for classical organometallics analysis (i.e., Sn, Pb, Hg, and As) in environmental-, biological- and industrial-related samples⁹. The analysis is relatively easy as the interferences are removed only using online chemical reactions. The two-quadrupole arrangement helps to drastically reduce the chemical noise levels, leading to much better detection limits that fall in the sub-ng/g-pg/g range for most elements in the periodic table. Fig. 2: presents a comparison of limits of detection for various elements/isotopes between ICP-MS/MS and HR-ICP-MS. It can be seen that for the majority of the elements, the detection limits of ICP-MS/MS are approaching those obtainable by HR-ICP-MS. Additionally, a number of elements can be determined simultaneously under the same set of instrument settings without compromising the accuracy and precision of the results.

Applications

Despite the fact that ICP-MS/MS technique is only a decade old, it has become very popular because of its versatility, capability to resolve even the most complex interferences, and offer lower detection limits and accuracy of determination¹⁰. Following are some of the application studies reported during the past decade in a wide range of scientific fields.

i) Geological

Geological, geochemical, and mineral exploration studies require the determination of major, minor, trace, and ultra-trace elements in different types of geological materials¹¹. Isotope geochemical and geochronological studies require the accurate and precise determination of

isotopic concentrations and isotopic ratios of different elements¹². Zimmermann et al.¹³ optimised a new and total digestion protocol (50 mg aliquots, microwave digestion, 5 mL HNO₃, 2 mL HCl, 1 mL HBF₄) for the analysis of 48 elements in different sediment reference materials by ICP-MS/MS. Zhi-fei et al.¹⁴ used oxygen reaction mode with ICP-MS/MS to eliminate Zr and Mo ion interference on Cd, for its determination in soil samples. Attapulgitte clay is a water-rich magnesium aluminosilicate mineral with a layered chain structure. The different geneses of the deposit results in a different composition of trace elements in attapulgitte clay. Li and Li-15 determined several trace elements in attapulgitte clay samples by ICP-MS/MS by NH₃/He as reaction gases¹⁵. Whitty-Léveillé et al.¹⁶ made a comparative study of sample dissolution and instrumental analytical techniques for the determination of rare earth elements (REE) in mineral matrices and some related reference materials. The combination of the high digestion temperatures (1050°C) and using LiBO₂ as a flux was found to be the most effective strategy for the sample digestion compared to open-vessel acid and microwave digestions, and the REE data provided by ICP-MS/MS was in excellent agreement with the certified values compared to those obtained by conventional single quadrupole ICP-MS and microwave plasma atomic emission spectrometry (MP-AES). This was mainly because of the perfect elimination of the spectral interferences by tandem ICP-MS, which is not possible by conventional single quadrupole instruments. MP-AES is already an inferior technique compared to ICP-MS, especially for the determination of REE in geological materials¹⁷. Zhu et al.¹⁸ determined REE concentrations in natural waters by ICP-MS/MS directly without any separation or preconcentration. Oxygen as the reaction gas was used for eliminating spectral interferences. REE data in SLR-4, the natural river water reference material (NRC-CNRC), obtained by ICP-MS/MS are presented in comparison with other well-established analytical techniques such as conventional single quadrupole ICP-MS, HR-ICP-MS, isotope dilution-HR-ICP-MS, along with certified or compiled values (Table 1). The precisions and accuracies achieved for different REE at different concentrations are sufficient to identify the natural variations or anomalies of Ce, Eu, and Gd in the REE distribution patterns in natural waters.

Yang et al.¹⁹ measured ng/g contents of Rh and Pd in Cu-rich minerals by LA-ICP-MS/MS, using a mixture of ammonia (NH₃)/He (10%/90%) reaction gas, respectively, to attenuate CuAr⁺ interfering species on ¹⁰³Rh and ¹⁰⁵Pd. According to the authors, when compared with that of a single quadrupole ICP-MS, the most accurate and precise measurements of Rh at less than 10 ng/g and Pd at ~ 100 ng/g in Cu-rich minerals were achieved by LA-ICP-MS/MS

at an optimized NH_3/He reaction gas flow rate. LA-ICP-MS/MS was used for *in-situ* dating of K-rich minerals, e.g., micas and K-feldspar, by the Rb–Sr isotopic system. Online chemical separation of Rb and Sr is possible by the reaction of Sr with O_2 in the reaction cell leading to the formation of SrO^+ and Rb doesn't react. Use of O_2 reactions provide stable analytical conditions sufficient for precise and accurate determination of Rb/Sr and Sr/Sr isotopic ratios using 80-micron laser ablation spots. It was also found that by using N_2O or SF_6 as a reaction gas for *mass-shifting* of ^{87}Sr to avoid interference on ^{87}Rb , sensitivity improved by ~ 10 and ~ 8 times, respectively, compared to the use of O_2 ²⁰. Re-Os dating of molybdenite by LA-ICP-MS/MS was reported recently by Hogmalm et al.²¹. A major advantage of *in-situ* LA-ICP-MS/MS dating is the direct analysis of molybdenite in thin-sections and epoxy mounts, which allows analysis of sub-millimeter grains in a microtextural context. The Rb/Sr isotopic system, one of the most established geochronological methods and is a useful tool for constraining the timing of magmatic and metamorphic events through geological history. It is based on the radioactive β^- decay of ^{87}Rb to ^{87}Sr , with a half-life of 48.8 billion years²². The precision of this technique is largely dependent on the laser system and ICP–MS/MS conditions used. Traditionally, $^{87}\text{Rb}/^{86}\text{Sr}$ and $^{87}\text{Sr}/^{86}\text{Sr}$ isotopic ratios were measured by thermal ionization mass spectrometry (TIMS) or more recently by MC-ICP-MS²³. However, these approaches require isotopic spiking and time-consuming chemical separations of Rb and Sr from the sample matrix. LA-ICP-MS/MS was used to date the Cu–Au mineralization event in the Arabian Shield, Saudi Arabia using the *in-situ* Rb–Sr dating technique. These studies indicated that the development of the Umm Farwah shear zone occurred at 651 ± 20 Ma, followed by the emplacement of Mount Ablah pegmatite dated at 625 ± 19 Ma. Subsequent greisenisation of local igneous rocks took place between 613 Ma and 589 Ma, followed by a younger reactivation event(s) dated between 580 Ma and 530 Ma during which period the Cu–Au mineralisation was believed to form in the Mount Ablah region²⁴. Another interesting study is the dating of apatite mineral, which is an accessory mineral in various igneous, metamorphic and clastic sedimentary rocks, by the U–Pb method. However, ^{204}Pb is difficult to measure using ICP-MS instruments because of the isobaric interference of ^{204}Hg on ^{204}Pb . Even HR-ICP-MS cannot resolve the overlap of ^{204}Hg on ^{204}Pb , as this requires a resolution of 500,000 as commercial HR-ICP-MS can go maximum up to 10,000R. In such situations, one needs to utilize alternative approaches such as the use of ICP-MS/MS as it can allow the online chemical separation by using NH_3 which reacts efficiently ($> 98\%$) with Hg while isotopes of Pb are not affected. Gilbert and Glorie²⁵ proved that the Hg interference on ^{204}Pb can be efficiently removed using NH_3 as the reaction gas for

LA-ICP-MS/MS analysis, and used the $^{206}\text{Pb}/^{204}\text{Pb}$ and $^{207}\text{Pb}/^{204}\text{Pb}$ ratios for accurate common Pb corrections. Simpson et al.²⁶ used LA-ICP-MS/MS for the direct *in-situ* geochronological studies of garnet, apatite, and xenotime minerals with several advantages such as very rapid and no chemical separations required. Despite all these advantages, there are still problems with this technique for the successful application of the LA-ICP-MS/MS for isotopic ratio determinations. For example, the Rb-Sr dating studies are currently poorly quantified and unconstrained ‘elemental fractionation phenomena’ and ‘matrix effects’, as well as the general lack of suitable chemically/mineralogically well-characterized reference materials (i.e., mineral-specific standards) that are homogeneous at the micro-scale level.

ii) *Marine sciences*

Precise data of trace elements/isotopes in ocean waters, sediments, and biological species in marine environments are required for understanding various marine geochemical aspects such as the sources and processes that define the distribution of different elements/isotopes in marine environments and biogeochemical cycling. Sulphur isotopic concentrations both in marine waters as well as in sediments are useful for tracing seawater intrusion in coastal systems in addition to several other applications such as providing insights into the early earth sulphur cycle, paleo-redox conditions of the ocean-atmosphere system, and ancient microbial/abiotic processes. Determination of sulphur isotopes in complex natural liquid or solid samples by conventional gas source isotope ratio mass spectrometry (GS-IRMS) is complicated, time-consuming, and relatively expensive. Leyden et al.²⁷ utilised ICP-MS/MS for the accurate and precise determination of sulphur isotope abundances (i.e., $^{34}\text{S}/^{32}\text{S}$ ratios, expressed as $\delta^{34}\text{S}$) in coastal waters proving that this method can meet the growing applications of sulphur isotopes. Interaction of seawater with oceanic lavas at low temperatures (10’s of °C) away from mid-ocean ridges plays a significant role in the major element composition of seawater. The secondary minerals that form during these processes are important for understanding this process properly. Laureijs et al.²⁸ dated celadonite from altered upper oceanic crust using LA-ICP-MS/MS using CH_3F as a collision reaction gas. Based on these studies, the authors concluded that the environmental conditions within the first ~20 My after-crust formation will control the intensity of alteration and chemical exchanges between seawater and basalt. Jackson et al.²⁹ determined the concentrations of Mn, Fe, Ni, Cu, Zn, Cd and Pb in seawater using offline extraction, and ICP-MS/MS.

iii) Nuclear

Plutonium (Pu) isotopes, especially ^{239}Pu and ^{240}Pu with half-lives of 24,110 years and 6561 years, respectively, are among the most important and dangerous transuranic nuclides in the environment due to their high radiotoxicity and long retention time in the environment. Pu is released to the environment mainly through atmospheric nuclear weapons testing, nuclear accidents, and nuclear fuel reprocessing plants. Xing et al.³⁰ used three different digestion methods (acid leaching with 8 M HNO_3 , aqua regia, and lithium metaborate fusion) for the accurate determination of Pu in soils by ICP-MS/MS using NH_3/He as cell gas. Determination of low-level plutonium in high uranium samples is challenging because of the abundance sensitivity (tailing of ^{238}U to $m/z = 239$ and 240), isobaric and polyatomic ions interferences (e.g., $^{238}\text{U}^1\text{H}^+$). Hou et al.³¹ combined ICP-MS/MS with a dynamic collision/reaction cell and eliminated the interference of uranium hydrides ($^{238}\text{U}^1\text{H}^+$ and $^{238}\text{U}^1\text{H}^{2+}$) using CO_2 as reaction gas by converting hydrides to oxides of uranium ions ($\text{UO}^+/\text{UO}_2^+$) but still keeping the intensity of the Pu^+ signal. The tailing interference of $^{238}\text{U}^+$ (abundance sensitivity) was eliminated significantly by suppressing the $^{238}\text{U}^+$ signal. This method enabled accurate determination of $<10^{-15}$ g/g level plutonium isotopes in environmental samples even in a uranium debris sample with a U/Pu atomic ratio of up to 10^{12} . The presence of fission products including numerous isotopes of lanthanides released from nuclear power plants and nuclear weapons testing can impact the environment. ICP-MS/MS was used as a tool to evaluate variations in isotopic ratios of selected lanthanides as tracers for the assessment of nuclear anthropogenic contamination in the environment³².

Both ^{135}Cs and ^{137}Cs , enter the environment due to anthropogenic nuclear activities. Zheng et al.³³ used ICP-MS/MS and N_2O as collision gas to significantly reduce the isobaric interferences ($^{135}\text{Ba}^+$ and $^{137}\text{Ba}^+$) and polyatomic interferences ($^{95,97}\text{Mo}^{40}\text{Ar}^+$, $^{119}\text{Sn}^{16}\text{O}^+$, and $^{121}\text{Sb}^{16}\text{O}^+$) to determine ^{135}Cs and $^{135}\text{Cs}/^{137}\text{Cs}$ isotope ratio at global fallout source environmental samples. Analysis of concrete is of significant importance for nuclear decommissioning as some concrete structures are exposed to high neutron fluxes, resulting in activation products. For example, neutron activation of stable ^{40}Ca (96.94% abundance) will lead to the production of ^{41}Ca [half-life; $(9.94 \pm 0.15) \times 10^4$ years]³⁴. Measurement of ^{41}Ca by conventional ICP-MS is prevented by multiple interferences, some of which cannot be removed by offline chemical separations. ICP-MS/MS technique with NH_3 , H_2 , and He as

collision gases proved to be most effective in accurately detecting and determining ^{41}Ca in concrete samples. More details are provided by Russell et al.³⁵.

iv) *Petroleum industry*

Petroleum products can be analyzed using ICP-MS/MS by direct injection of petroleum products after solvent dilution. For the determination of heavy elements ($Z > 70$) in organic matrices, the ICP-MS/MS was less sensitive than the HR-ICP-MS. For light elements ($Z < 40$), the sensitivity was similar or better using ICP-MS/MS (Figure 2). For elements such as Si, S, Ca, Fe, which have severe interference problems, but by using He, O₂ or H₂ as reaction gases, ICP-MS/MS gave similar or better detection limits (LOD) than the HR-ICP-MS in medium resolution³⁶. Though silicon plays a crucial role in many fields such as food, semiconductor, steel, and oil industries, monitoring its concentration in the petroleum industry during the refining process is important due to its poisoning effect and decreasing its activity on hydrogenation catalysts which will have a great economic impact. Silica can be determined by a number of techniques like inductively coupled optical emission spectrometry (ICP-OES) and ICP-MS, but the situation becomes more complex when speciation analysis is required as gasoline samples may contain around 200 different hydrocarbon compounds. Sánchez et al.³⁷ used GC-ICP-MS/MS for the analysis of different petroleum derivatives. Hydrogen was used as a reaction gas in the octopole reaction cell (ORC) to eliminate the interference of $^{12}\text{C}^{16}\text{O}^+$ and $^{14}\text{N}^{14}\text{N}^+$ on $^{28}\text{Si}^+$. Cyclic siloxanes (D3-D6) were confirmed as the main silicon compounds present in coker naphtha samples. Such silicon speciation studies in real coker naphthas will allow the development of trapping systems to remove these compounds before hydrotreating catalysts. GC-ICP-MS/MS was also used to determine the sulphur-containing petroleum derivatives³⁸. Chlorinated compounds (HCl or organic chlorides) in crude oils can create problems during refinery operations. Cl is a known challenging element to be determined by quadrupole ICP-MS. Nelson et al.³⁹ developed a method for the accurate determination of chloride in crude oils by direct dilution using ICP-MS/MS. Complex interferences including sulphur-based interferences were effectively eliminated using H₂ cell gas and mass-shift mode. Amais et al.⁴⁰ determined P, S, and Si in biodiesel, diesel, and lubricating oil by ICP-MS/MS using oxygen gas as a reaction gas for eliminating interferences. Phosphorus, S, and Si are challenging elements to be determined by quadrupole-based ICP-MS due to severe polyatomic interference.

Environmental

The platinum-group elements (PGE: Pt, Ir, Os, Pd, Rh, and Ru) consist of six elements; those are among the least abundant in the continental crust and have similar physical and chemical properties. Recent studies are showing that the concentrations of Pt, Pd, and Rh are constantly increasing in the environment because of the use of these elements in autocatalytic converters in all automobile vehicles for the reduction of harmful carbon monoxide, nitrogen dioxide, and unburnt hydrocarbon emissions. Their emissions, distribution, migration in different environmental compartments, and their bioavailability are posing one of the biggest human health risks^{41,42}. Measurement of PGE and Re in environmental samples, such as soils and water is extremely difficult because of their low-level concentrations. In addition, severe isobaric and polyatomic interferences make their determination by conventional ICP-MS difficult. Mitra et al.⁴³ determined PGE and Re in road dust samples using ICP-MS/MS after sample decomposition by high-pressure asher (HPA) at a pressure of 130 bars and a temperature of 220°C, and also adopting a cation exchange procedure for the separation of PGE and Re from the sample matrix, and for complete removal of potentially interfering species arising from Cd, Hg, Zr, Hf, Mo, and W, and with isotope dilution (ID) as a calibration strategy. Table 2 presents the PGE and Re data obtained in a road dust reference sample and a base metal sulphide bearing komatiite sample in comparison with certified values and the values obtained by a nickel sulphide fire-assay ICP-MS procedure⁴⁴.

Determination of elemental as well as isotopic concentrations of uranium and thorium is important in monitoring the quality of drinking water, and other environmental issues such as nuclear emergency responses⁴⁵. Ni et al.⁴⁶ determined Th (²³⁰Th, ²³²Th) and U (²³⁴U, ²³⁵U, ²³⁸U) isotopes in small volume (20 mL) of water matrices using ICP-MS/MS. Detection limits going down to pg/ml – fg/ml levels for these elements. Amaral et al.⁴⁷ described a novel strategy to determine As, Cr, Hg, and V in drinking water by ICP-MS/MS with the detection limits in pg/ml at the 99.7% confidence level. Small volume digests of Antarctic atmospheric particulates (PM₁₀) and of soils, from Australia and South America as potential source areas for atmospheric particulates reaching East Antarctica, were analyzed by ICP-MS/MS. For the introduction of low-volume samples, a setup consisting of a syringe-driven pump that allows it to work at low and stable sample introduction flow rates was utilized. The method requires 240 µL of the sample only, introduced at a sample uptake rate of 20 µL/min,

and allows the straightforward measurement of the $^{87}\text{Sr}/^{86}\text{Sr}$ isotope ratio without prior Rb/Sr separation⁴⁸.

Monitoring pesticide residues in food products is important especially from the point of the health of infants and children, as the quantity of food they ingest per kilogram of body weight is relatively high. Nelson et al.⁴⁹ used the GC-ICP-MS/MS method with oxygen as a reaction gas for the selective, sensitive detection and determination of specific hetero-atoms of phosphorus, sulphur, and chlorine-containing pesticides in various food matrices. Zhang et al.⁵⁰ used GC-ICP-MS/MS with a *mass-shift* mode for the indirect determination of polybrominated diphenyl ethers in fish tissue using bromine oxide ion. The highest sensitivity was found using N_2O as the reaction gas when compared to other gases such as O_2 and H_2 , and He. Klencsár et al.⁵¹ determined the total contents of drug-related Cl and Br in human blood plasma using HPLC-ICP-MS/MS. Hydrogen was used as a reaction gas for monitoring the $^{35}\text{ClH}^{2+}$ reaction product at a mass-to-charge ratio of 37. Br could be measured by "*on mass*" mode at a mass-to-charge of 79. HPLC was used for the separation of the drug-related entities from the substantial amount of inorganic Cl. It is well known that molybdenum oxides affect Cd determination by conventional ICP-MS. By using ICP-MS/MS, Amais et al.⁵² eliminated Mo oxide-based interferences and determined both Cd and Mo using an octopole reaction system (ORS³) pressurized with oxygen gas in milk powder after microwave-assisted digestion using diluted HNO_3 and H_2O_2 .

vi) Biological and medical

Element constitution and distribution in body tissues and fluids have increasingly become key pieces of information in life sciences and medicine, and trace elements may be successfully used as disease biomarkers. Titanium is an inert and biocompatible metal, and its elastic modulus is similar to that of the natural human bone, making it an ideal metal for human implants, such as dental implants and other artificial implants, along with various surgical reconstruction techniques. It is also a highly corrosion-resistant metal because of the thin and stable protective oxide layer spontaneously formed on its surface⁵³. However, very minor degradation of all types of metal implants in the human body is observed and the worn metal particles and/or ions get released into body fluids such as serum and urine. Fu et al.⁵⁴ used ICP-MS/MS to determine ultra-trace concentrations of Ti in human blood serum using a mixture of H_2 and O_2 as a reaction gas in the CCT for converting Ti^+ to TiO^+ and determined in the *mass-shift* mode by eliminating all spectral interferences. These authors also

successfully cross-checked the results by HR-ICP-MS. Virgilio et al.⁵⁵ evaluated ICP-MS/MS protocols using oxygen in the octopole reaction system for the accurate and precise determination of As, Cd, Cr, Ni, Pb, and V in phytotherapy medicines. Two plant-certified reference materials (apple leaves and tomato leaves) were used to check the accuracy. Use of both *on-mass* and *mass-shift* modes for different analytes demonstrated as efficient strategies to correct for spectral overlaps and provided accurate determinations. Despite significant breakthroughs in the understanding, prevention, and treatment of cancer, the disease continues to affect millions of people worldwide. A potential solution to this challenge may lie in nanomedicine, including the use of various nanomaterials for the diagnosis and treatment of cancer⁵⁶. In this context, superparamagnetic iron oxide nanoparticles (SPIONs) are widely tested as tools for drug delivery, magnetic hyperthermia, magnetic resonance imaging, and catching tumor cells⁵⁷. Complete physicochemical characterization of properties of SPIONs is extremely important for safe biomedical applications in vivo. Single particle-ICP-MS/MS (SP-ICP-MS/MS) studies allowed fast and straightforward monitoring of the changes in the structure of SPIONs upon interaction with serum proteins thereby helping to shortlist the investigational nanomaterials before in-depth preclinical testing⁵⁸. Gd has been used in a chelated form as a contrast agent in magnetic resonance imaging (MRI) measurements^{59,60}, though new research finds direct evidence of gadolinium deposition in biological tissues which can be harmful to patients and is a major concern. However, no data are available in human beings or animals to show adverse clinical effects due to the gadolinium deposition in the brain^{61,62}. Clases et al.⁶³ presented a novel analytical method based on LA-ICP-MS/MS to detect the retention of Gd from contrast agents for MRI in brain and skin tissue samples of patients. Gadolinium was monitored in *mass-shift* mode and this resulted in an improved detection limit. Radium (Ra) is a naturally occurring metal found in uranium and thorium ores in trace quantities. It can cause harmful health effects to humans by getting incorporated into biochemical processes because of its radioactivity and chemical reactivity. Chronic exposure to higher levels of radium over a long period of time may result in an increased incidence of anemia. If radium is swallowed through water or with food, most of it will promptly leave the body in the feces. Xiao et al.⁶⁴ developed a method for monitoring ²²⁶Ra in urine using ICP-MS/MS.

vii) Agriculture

The mineral fertilizers are used in agriculture for the proper growth of the crops and to increase the yield during agricultural practices. These mineral fertilizers contain macronutrients (Ca, Mg, N, P, and S), micronutrients (such as Fe and Si), REE, and, in some cases, toxic elements (As, Cd, Hg, and Pb) in their composition. In order to understand the environmental effects and legislations established for controlling agricultural products, it is necessary to analyze mineral fertilizers and agricultural gypsum for toxic elements. Machado et al.⁶⁵ evaluated the application of ICP-MS/MS for the determination of As in agricultural inputs with high REE contents. The use of MS/MS in *mass-shift* mode was effective to remove doubly charged interferences from REE on As. When operating in single quadrupole mode, recoveries ranged from 59 to 151%; while values obtained by MS/MS mode varied from 81 to 105% when 0.30 mL/min O₂ was introduced into the ORS reaction cell, demonstrating the usefulness of MS/MS mode. Wang et al.⁶⁶ developed a method to determine the content of 30 trace elements in rice from different production areas in China using the ICP-MS/MS method. Different gases such as H₂, O₂, He, and NH₃/He, both *on-mass* and *mass-shift* modes were used under optimized conditions. China is a vast country with diverse climatic and geographical conditions, and the crops have different biological characteristics and physical and chemical indices. Principal component analysis of the multielement content of rice samples was used to provide a method basis for rice origin traceability. Molybdenum is an important micronutrient for the plant's growth and the ideal concentration range for this micronutrient in plants is 0.2–2.0 µg/g. However, there are some species in which Mo concentrations as low as 0.02 µg/g, which are enough to maintain vital functions, Mo contents higher than 1000 µg/g can be potentially toxic and hence monitoring of Mo becomes important. Barros et al.⁶⁷ determined Mo concentrations in plant materials such as tomato, apple and spinach leaves, and wheat and rice flour, with excellent selectivity, sensitivity, and accuracy by ICP-MS/MS with an octopole reaction system and pressurized oxygen gas and the *mass-shift* mode to remove K-based interferences after microwave digestion using H₂O₂.

viii) Food safety

Different government agencies and the World Health Organization (WHO), are putting efforts to standardize food testing practices around the world. Both the world's population and food production are growing at a significant rate and currently, there is a greater need to

be more careful to prevent food contamination. For example, though the intake of fluorine at low concentrations is considered essential, it can become toxic through elevated intake of water or food, which can result in fluorosis and in renal, gastrointestinal, and immunological disorders. Guo et al.⁶⁸ developed a method for the determination of total fluorine in foods by ICP-MS/MS using NH_3 as reaction gas with a *mass-shift* strategy. Nelson et al.⁴⁹ used GC-ICP-MS/MS with oxygen as a reaction gas for the selective, sensitive detection, and determination of specific hetero-atoms of phosphorus, sulphur, and chlorine-containing pesticides in various food matrices. Although seafood has several advantages for human nutrition, it can accumulate high levels of potentially toxic elements (such as arsenic and mercury) in its tissues, which may represent a risk to human health. Schmidt et al.⁶⁹ utilized LC-ICP-MS/MS for the As speciation analysis [AsB, As (III), DMA, MMA, and As (V)] in several types of seafood such as shark, shrimp, squid, oyster, and scallop. Since its development, ICP-MS/MS has been used to analyze several types of food materials including fruit wines, fruit juices, medicinal plants, and bone tissue samples from lambs, piglets, and calves⁷⁰⁻⁷³.

ix) *Material science*

Molybdenum's strength and stability at higher temperatures make it attractive to several high technology applications such as petroleum refining, and optoelectronic devices. Some applications require ultrapure molybdenum, and ICP-MS/MS was utilized for the determination of 28 ultra-trace impurities in molybdenum metal by using H_2 , NH_3/He as reaction gases by both *on-mass* and *mass-shift* mode⁷⁴. Fu et al.⁷⁵ used ICP-MS/MS for the determination of metallic impurities in $(\text{Mg}(\text{TFSI})_2)$ electrolytes for rechargeable magnesium batteries using N_2O as a reaction gas. No significant difference was observed between the ICP-MS/MS and HR-ICP-MS results at a 95% confidence level. Soft magnetic ferrite, the most important magnetic material, possesses many excellent magnetic properties and is used in various fields such as electronics, and mobile communications. The impurity elements in soft magnetic ferrite significantly affect the magnetic performance of the materials and hence there is a need to monitor its purity. Fu et al.⁷¹ developed a method for the accurate determination of harmful, and doping elements in soft magnetic ferrite powders using ICP-MS/MS. Thus, this analytical technique with several applications in material scientific studies in recent times proved to be very versatile.

x) Speciation analysis

The quantitative determination or qualitative assessment of different chemical species requires the development of sufficiently sensitive, and selective methods. Speciation analysis is a key aspect of modern analytical chemistry, as the toxicity, environmental mobility, and bioavailability of different elements are known to depend strongly on an element's chemical species. Thus, speciation analysis offers deeper insight into molecular mechanisms and pathways of disease by determining the speciation of an element, particularly in the environment and health-related studies. For example, organomercury compounds, such as methylmercury (CH_3Hg^+), are more toxic than inorganic forms of mercury (Hg^{2+}). Chromium (Cr^{3+}) is considered a micronutrient whereas Cr^{6+} is classified as carcinogenic⁷⁶. In general, a separation method like HPLC when coupled to an element-specific technique like ICP-MS is best utilized for speciation analysis. ICP-MS/MS was used for the ultra-sensitive speciation analysis of tellurium by coupling to manganese and iron-assisted photochemical vapor generation (PVG)¹⁷. Te^{4+} was selectively determined by direct PVG and validated for speciation analysis of Te in water samples of different origins such as freshwater, well water, seawater, and contaminated water⁷⁷. In another interesting example is the determination of different arsenic species by LC-ICP-MS/MS in seafood. Seafood is one of the major sources of dietary exposure to As. As species arsenobetaine (AsB) tends to be the major species in fish, mollusk, and crustacean products. The As speciation analysis showed that in addition to AsB, AsC, dimethylarsenate (DMA), monomethylarsenate (MMA), and the inorganic As species arsenate and arsenite, a total of 15 unknown As peaks were present across the various seafood products, highlighting the diverse amount of As species that people are getting exposed to via this diet⁷⁸. A few more examples of speciation can be found in other sections of this article such as environmental applications and food safety.

xi) Current application trends

The literature on the ICP-MS/MS during the last 10 years reveals that solution nebulization is the most popular method of sample introduction, followed by laser ablation, GC, and LC/HPLC in that order. On the other hand, when looking at the number of applications points of view, geological, biological, medical, environmental, and food safety in that order, are the most reported during the last decade. But the technique seems to be popular even in other areas such as marine, nuclear, petroleum, agricultural, material sciences, and speciation

analysis (Fig.3). Table 3 presents a few more striking and exciting applications of ICP-MS/MS in recent literature.

Conclusion and future

The ICP-MS/MS instrumentation has taken the conventional ICP-MS technology to the next level through its capability of interference-free elemental/isotopic determination of the majority of the elements in the periodic table including the challenging elements such as P, S, Si, Cl, As, Se, and Br, by resolving even very difficult interferences and providing accurate data at ng/g-pg/g levels required in a variety of science and technology applications with matching performance with that of expensive HR-ICP-MS in many cases and even excelling in some cases. ICP-MS/MS offers high sensitivity taking the detection limits for several elements to pg/ml or better, with excellent accuracy and precision. Due to the outstanding capability of eliminating all kinds of spectral interferences, ICP-MS/MS is able to find wide applications in multiple research areas such as geological, environmental, biological, medical, nuclear, and agricultural sciences. Another important aspect is this instrument is less expensive compared to HR-ICP-MS, relatively easy and less complex to handle, and has less recurring maintenance expenditure. GC-ICP-MS/MS and HPLC-ICP-MS/MS have been established as the best instrumental choices for speciation analysis, and also for the extremely sensitive and robust analysis of highly interfered elements present in numerous potential targets in complex sample matrices such as pesticides and petroleum-related products. ICP-MS/MS technology enabled the determination of femtogram-level plutonium isotopes in environmental samples. The lower purchase cost of the ICP-MS/MS makes this a useful instrument, a valuable addition for laboratories aiming to expand their analytical capabilities. Future developments may focus on some of the drawbacks of the current systems particularly related to isotope ratio determinations such as ‘elemental fractionation phenomena’ and matrix effects, as well as the general lack of suitable chemically/mineralogically well-characterized reference materials that are homogeneous at the micro-scale level.

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Figures:

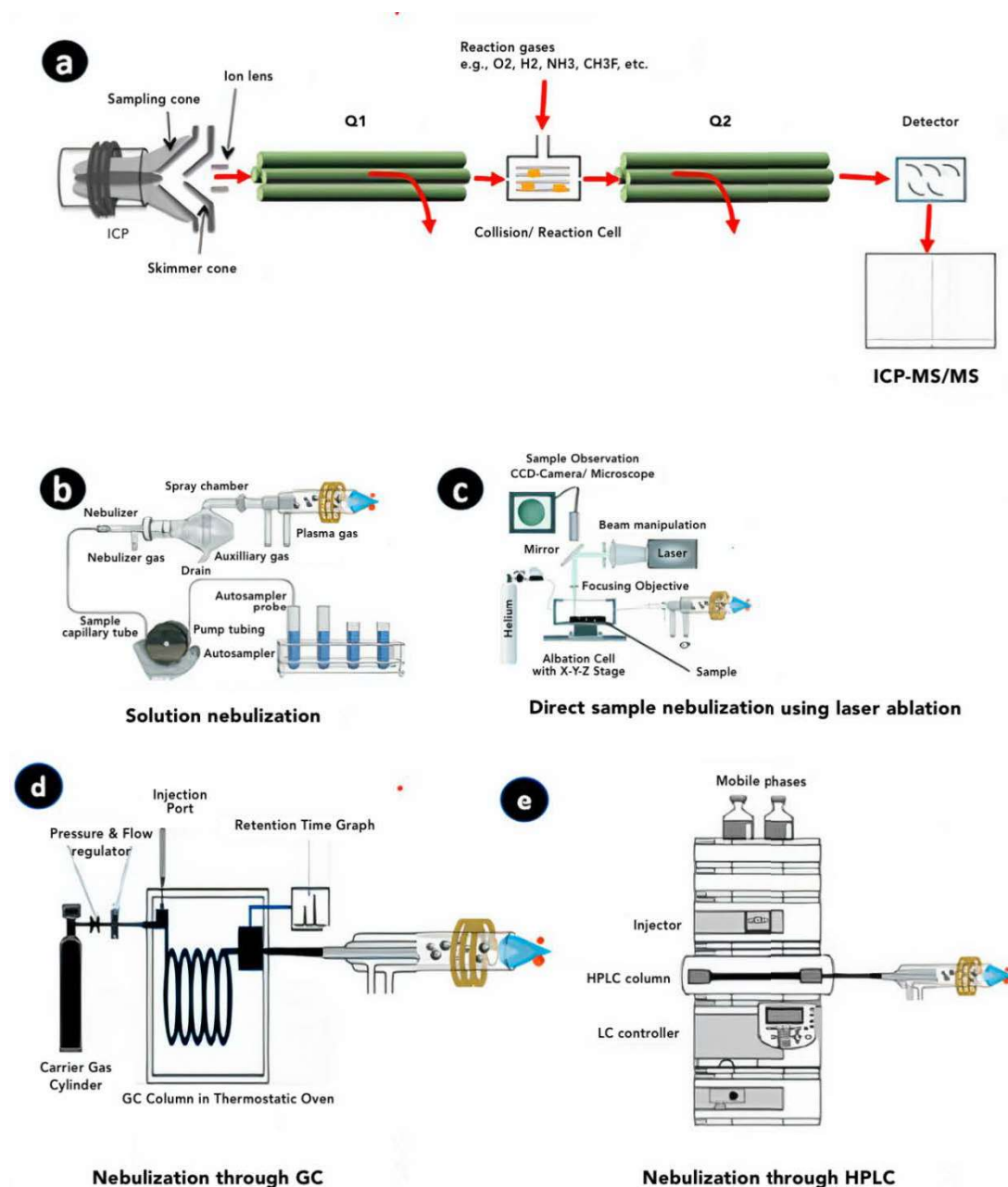


Fig. 1: Schematic diagram of a) a typical ICP-MS/MS instrument, b) with sample introduction by solution nebulization set-up, c) direct sample nebulization by laser ablation, d) sample introduction through GC, and e) sample introduction through LC/HPLC (Author's design).

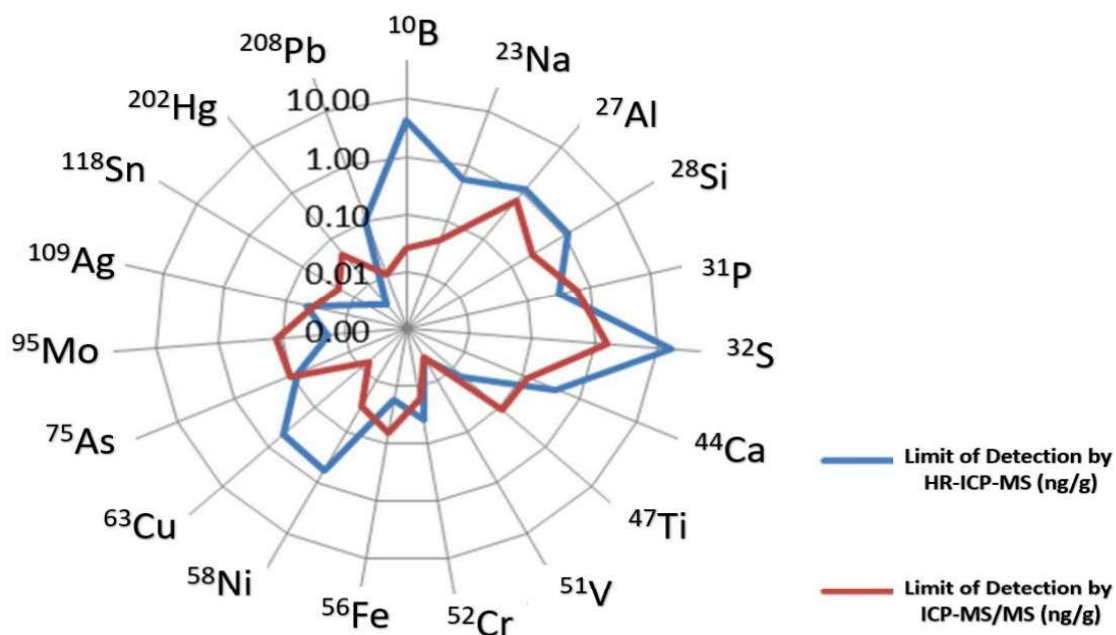


Fig. 2: Comparison of limit of detection for various elements/isotopes between ICP-MS/MS and HR-ICP-MS³⁶.

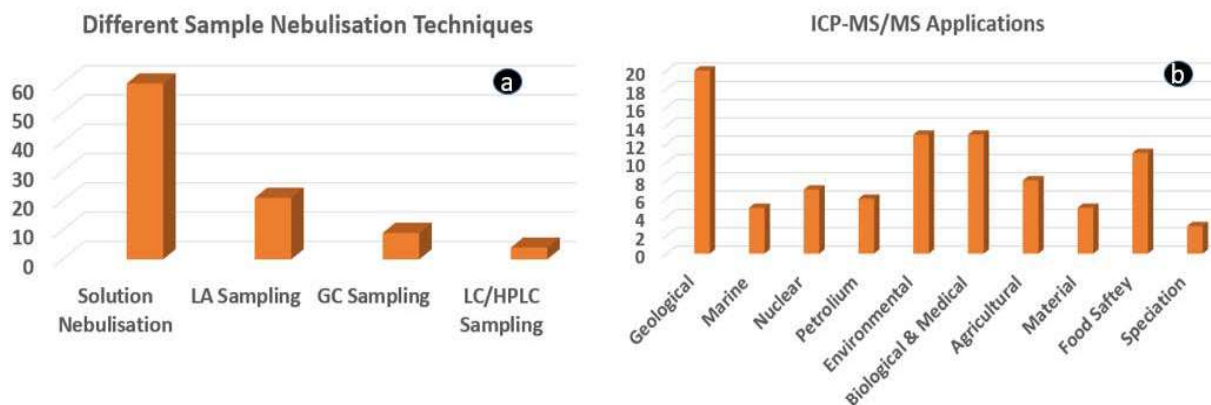


Fig. 3: Trends in the application of different modes of sample nebulization methods (a), and various areas of applications (b) of ICP-MS/MS in the literature during the last decade.

Tables:**Table 1:** The analytical results of REE in water reference material, SLRS-4 obtained by different well-established analytical techniques in comparison with those obtained by ICP-MS/MS

REE	Concentration (ng/mL)				
	ICP-MS/MS ¹⁸	ICP-MS ⁹²	HR-ICP-MS ⁹³	ID-HR-ICP-MS ⁹	Compiled value ⁹⁵
La	294.5 ± 3.2	302.2 ± 7.3	279±12	290.3±6.4	287±8
Ce	357.5 ± 3.2	378.4 ± 8.2	369±15	364.1±3.5	360±12
Pr	70.9 ± 0.4	73.6 ± 1.5	75.4±8.0	70.6±2.3	69.3±1.8
Nd	274.2 ± 3.2	277.4 ± 5.7	261±9	270.3±2.8	269±14
Sm	58.5 ± 1.9	59.3 ± 1.4	54.3±5.0	57.2±0.3	57.4±2.8
Eu	8.06 ± 0.41	8.09 ± 0.61	8.4±0.8	8.00±0.7	8.0±0.6
Gd	33.86 ± 1.46	35.13 ± 1.01	38.3±6.0	33.80±0.36	34.2±2.0
Tb	4.27 ± 0.20	4.50 ± 0.23	4.1±0.5	4.30±0.12	4.3±0.4
Dy	22.82 ± 0.75	23.91 ± 0.66	21.7±3.0	23.60±0.16	24.2±1.6
Ho	4.39 ± 0.19	4.86 ± 0.11	4.2±0.5	4.60±0.18	4.7±0.3
Er	13.21 ± 0.46	13.53 ± 0.70	11.4±3.0	13.10±0.06	13.4±0.6
Tm	1.75 ± 0.11	1.91 ± 0.04	1.8±0.2	1.80±0.02	1.7±0.2
Yb	11.73 ± 0.36	12.03 ± 0.51	10.6±2.0	12.30±0.07	12.0±0.4
Lu	1.76 ± 0.09	1.86 ± 0.11	1.7±0.4	1.95±0.02	1.9±0.1

Table 2: Concentrations of PGE and Re (ng/g) in road dust reference samples obtained by ICP-MS/MS in comparison with those obtained by NiS fire-assay-ICP-MS and certified values

CRM/ Element	BCR 723			OKUM	
	ICP-MS/MS ⁴³	NiS FA-ICP-MS ⁴¹	Certified value	ICP-MS/MS ⁴³	Consensus value
Ru	0.67±0.25	-	0.85± 0.29	3.75±0.17	4.66±0.56
Rh	10.39± 0.80	14.4 ± 1.5	12.80±1.2	1.54±0.03	1.74±0.63
Pd	6.00±0.23	9.2 ± 1.6	6.0±1.8	11.59±0.32	11.50±1.0
Re	6.49±0.52	-	6.65±0.09	0.52±0.0	0.50±0.04

Os	0.42±0.16	-	0.46±0.10	0.57±0.04	0.85±0.12
Ir	0.36±0.1	-	0.53±0.58	0.64±0.02	1.00±0.13
Pt	81.56±3.53	83.3 ± 4.9	81.3±3.3	10.32±0.48	11.79±1.46

BCR 723 is a road dust certified reference material; OKUM is a base metal sulphide bearing komatiite

Determined values are average of 4 (ICP-MS/MS) and 6 (NiS FA-ICP-MS) determinations.

Mixed acid dissolution in HPA-S, matrix removal by cation-exchange column followed by ICP-MS/MS determination⁴³.

Table 3: Some important applications of ICP-MS/MS from the recent literature.

Matrix	Elements determined	Sample digestion	Remarks	Reference
Fruit juices	Al, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Cd, Hg, and Pb	After dilution, acidified with HNO ₃ , Li, Sc, Ge, Y, In, Tb, and Bi were used for online corrections of matrix effects and signal drift	ORS ³ was used with the mixed reaction gases O ₂ /H ₂ and NH ₃ /He/H ₂ for eliminating the spectral interferences	71
Atmospheric particulate matter (PM)	67 elements including important aerosol source markers such as P, S & Si.	Microwave digestion with HNO ₃ , HCl & HF	O ₂ reaction mode for analysis of Ca, P, S, and Si, and no-gas or KED mode by He collision on SQ mode for the rest of the 63 elements.	96
Drug-related chlorine and	Br and Cl	After collection, the samples were stored	H ₂ reaction gas was used in the	51

bromine contents in human blood plasma		at -20°C until analysis. The suspension was centrifuged the volume of the supernatant was reduced by solvent evaporation under N ₂ flow.	collision/reaction cell during HPLC-ICP-MS/MS method	
Medicinal plants	As, Cd, Cr, Ni, Pb, and V	Microwave-assisted digestion using HNO ₃ and H ₂ O ₂	MS/MS mode, the use of O ₂ as reaction gas combined with and <i>on-mass</i> mode were used	55
Smolina samples obtained from the durum wheat	57 elements including phosphorus and sulfur	Not available	Recoveries of the elements were found in the range of 92-108% for the digested CRM	97
Metalloids in complex food	B, Si, As, Se and Sb	Not available	ORS ³ system, O ₂ reaction gas, <i>on-mass</i> and mass shift mode was utilized	98
NIST salmon reference materials	Sr and S isotope ratios		O ₂ as reaction gas and mass shift were utilized.	99

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