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Cover Feature

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Review

Review: Direct Analysis of Metal Constituents in Complex Samples by Mass Spectrometry

Lili Song,[a] Wu Zhang,[b] Luyao Zhong,[a] Chun Wan,[a] Hui Li,[a] Xinglei Zhang,[a,*] and Jiaquan Xu [a,*]

[a]Jiangxi Key Laboratory for Mass Spectrometry and Instrumentation, East China University of Technology, Nanchang 330013, P. R. China.

[b]Nanchang Ecological Environment Monitoring Center of Jiangxi Province, Nanchang 330038, P. R. China

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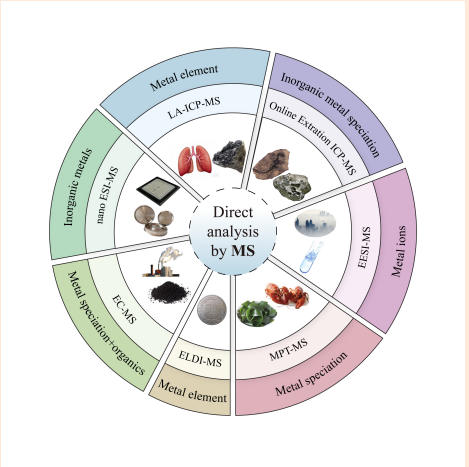
ABSTRACT: The information of metal constituents in complex samples is crucial for understanding the physicochemical properties, and formation mechanisms of samples. Moreover, direct analysis of metal constituents in such samples without sample pretreatment not only enhances analytical efficiency but also facilitates the elucidation of physical and chemical relationships among the constituents, which has attracted wide spread attention. Mass spectrometry possesses remarkable advantages in both qualitative and quantitative analyses of metal constituents. This review systematically summarizes recent advances in mass spectrometry-based methods for the direct analysis of metal constituents over the past decade. Unlike existing reviews, this work offers an overview of both hard ionization and soft ionization mass spectrometry techniques applied to the direct analysis of metallic elements. In this review, we present the fundamental principles of mass spectrometry relevant to this application, highlight representative applications across diverse fields such as environmental science, geology, and materials science, and critically discuss the advantages and limitations of each approach. Finally, we outline future research directions for advancing mass spectrometry in the direct analysis of metal constituents. This review provides valuable insights for the development of high-performance analytical methods for metal constituent analysis.



INTRODUCTION

The analysis of metal constituents in complex samples is of critical importance across various fields. For instance, in environmental science, the analysis of heavy metals such as lead and mercury in soil or water samples allows for a deeper understanding of contamination sources and a robust assessment of ecological risks.[1, 2] In biology, analyzing the distribution of metals in animal and plant tissues supports the investigation of metal bioaccumulation and bioavailability, thereby enhancing ecological and toxicological risk assessments.[3, 4] In geology, analyzing metal compositions in rocks, ores, and minerals plays a key role in geological exploration and resource management.[5, 6] Furthermore, studying the metal content of geological formations provides insights into Earth's internal processes and its historical geological evolution.[7] In materials science, quantification of metal constituents in alloys and composites is essential for quality control and enhancing material performance.[8]

To date, numerous of methods have been developed for the analysis of metals in complex samples, including spectrometry (*e.g.*, X-ray fluorescence spectrometry, atomic emission spectroscopy)[9, 10], energy spectrometry (*e.g.*, X-ray photoelectron spectrometry, auger electron spectroscopy)[11, 12] and mass spectrometry (*e.g.*, inductively coupled plasma mass spectrometry, electrospray ionization mass spectroscopy).[13, 14] Among them, mass spectrometry (MS) demonstrated remarkable advantages in both qualitative and quantitative analyses of metal constituents.[15-18] In a typically MS analytical procedure, metal constituents were extracted from the complex sample using chemical reagents to prepare analyte solutions, which were subsequently analyzed by mass spectrometry. Especially, for metal speciation analysis,

multiple step extractions were always necessary, such as Tessier and Community Bureau of Reference (BCR) methods.[19, 20] The extracted compounds were then analyzed by chromatography methods (*e.g.*, High-performance Liquid Chromatography, gas chromatography, Capillary electrophoresis chromatography, etc.) to identify the speciation by retention time, followed by coupling with inductively coupled plasma-mass spectrometry (ICP-MS) for quantitative analysis[21-23] and electrospray ionization MS for structural analysis.[24] These methods offered high accuracy and precision, and have been widely adopted as national standard methods. However, complex sample pretreatment not only prolonged analysis time, but may also lead to the loss of some information, such as the physical and chemical relationships among the constituents. For example, in BCR method,[25] acetic acid (HAc), $NH_2OH,{\cdot}HCl$, H_2O_2 and NH_4Ac were used sequentially to extract metal constituents with different speciation from soil, respectively. Each extraction step took more than 16 hours. In the Tessier method,[19] NaAc solution (pH=8.2), NaAc/HAc (pH=5.0), $Na_2S_2O_4$ + Na-citrate + $NH_2OH{\cdot}HCl$ in Hac, HNO_3 + H_2O_2 (pH=2), HF-$HClO_4$ were used to extract exchangeable, bound to carbonates, bound to Fe-Mn oxides, bound to organic matter, and residual fraction or speciation, respectively. The whole procedure would take more than 40 hours. Moreover, this offline sample pretreatment will destroy the sample structure and leads to the loss of spatial distribution information of the metal constituents. Therefore, direct analysis of metal constituents in complex samples was essential, characterized by: (1) do not require any offline pretreatment or only require minimal sample preparation; (2) metal components are desorbed online or ionized *in-situ* from the sample for MS analysis.

Nowadays, significant efforts have been dedicated to the development of MS methods for the direct analysis of metal constituents. The general strategy was coupling online extraction with mass spectrometry. On the other hand, with the development of ambient ionization mass spectrometry, it has emerged as another ideal option for directly analyzing metal constituents in complex samples. In this review, we provide an overview of both hard ionization and soft ionization mass spectrometry techniques applied to the direct analysis of metallic elements. Hard ionization MS offers high sensitivity and is primarily used for quantitative analysis of metal elements, while soft ionization mass spectrometry, on the other hand, is well suited for analyzing the molecular structures of metal constituents. Given the diverse demands for analyzing metal constituents in complex samples, this review introduced the principles, instrumentation, typical applications, characteristics and future direction of mass spectrometry-based techniques. A literature survey of the last about 10 years was included. Only articles published in English and Chinese have been considered. Databases of Elsevier, Springer, Wiley, and China National Knowledge Infrastructure were used. The keywords of "direct analysis", "mass spectrometry", "metal", "online extraction", "ICP-MS" "ambient ionization" were used. Topics of direct analysis of metals without complex sample pretreatment via mass spectrometry were included. The authors apologize for any works not included in this review article.

DIRECT ANALYSIS OF METAL CONSTITUENTS BY ICP-MS

ICP-MS is widely recognized as a highly effective analytical technique for analysis of metals due to its broad linear dynamic range, capability for isotopic analysis, exceptionally low limits of detection (LOD) (often in the ng/L range for many elements), and the ability to perform simultaneous multi-element analysis. Moreover, the ICP ion source exhibit remarkable versatility in interfacing with various sample introduction systems, *e.g.,* wet, dry aerosols, and vapors. Therefore, in addition to conventional pneumatic nebulization, which is the standard sample introduction method, online extraction and laser ablation (LA) can also be coupled with ICP. The implementation of the specialized sample introduction system can significantly enhance the performance and analytical capabilities of ICP-MS, including improved limits of detection (LOD), shorten the analysis time, reduced the sample consumption, and minimized the sample pretreatment.

Spatial analysis of metal constituents in samples by laser ablation-ICP-MS (LA-ICP-MS)

Principle. LA-ICP-MS is a well-established method for the direct determination of metal elements in the micro-area of samples.[26, 27] LA is the initial step in LA-ICP-MS analysis and is essential for the direct analysis of samples without prior pretreatment. LA utilizes a laser beam with high energy density focused on the sample surface. A large amount of energy is released instaneously, causing the material in a tiny area (at the micrometer to nanometer scale) on the sample surface to absorb energy. This energy absorption leads to the evaporation, gasification, and even plasma formation of the sample, creating gaseous or aerosol substances. These gaseous or aerosol particles are online transported to the ICP for ionization. During the ionization process, the metal constituents are converted into metal ions, which are subsequently analyzed by MS to obtain qualitative and quantitative information.

Application. With unique advantages of high sensitivity, high spatial resolution, low sample consumption, *in-situ* analysis, and simultaneous multi-element analysis, LA-ICP-MS has been widely applied in numerous fields, including geology, metallurgy, environmental science, biology, chemistry, materials science and archeology, *etc.*[28] A large number of reviews and books have been published to summarize the principle, instrument, and applications.[3,4,28-32] Herein, several representative recent applications of LA-ICP-MS were presented, encompassing both

typical inorganic samples (*e.g.*, lunar soil) and organic samples (*e.g.*, biological tissue).

The main application of LA-ICP-MS is to analyze the metal constituent in inorganic samples, such as whole-rock and soil samples,[33, 34] silicate and carbonate minerals,[35-37] metal oxides and metal sulfides,[38] individual melt inclusion and fluid inclusion.[39, 40] The characteristics of paleoclimate changes could be inversed through the characteristics of trace element changes recorded in the growth textures of stalagmites or corals.[41] The changes of trace elements in mineral rocks could be used to trace the evolution characteristics of magma and fluids, *etc.*[42] U-Th-Pb or Lu-Hf determinations of various minerals (apatite, zircon, titanite or allanite) was performed for fission track dating.[43, 44] Accurately characterizing the distribution and concentration of elements in solid wastes was essential for sustainable reuse, effectively monitoring and reducing the release of harmful pollutants into the environment.[45] Recently, a significant achievement of LA-ICP-MS was its successful application in the analysis of lunar soil, unveiling unprecedented insights into extraterrestrial geochemistry. Imaging and isotope ratio analysis of lunar soil samples via LA-ICP-MS were beneficial for researching the dynamic aspects of lunar fire-fountain eruptions, thermo-chemical evolution, and the discovery of new mineral substences.[46-48] Tian *et al.*[47] presented a petrological and geochemical study of the basalt clasts from the PKT Procellarum Potassium, Rare-Earth Elements and Phosphorus Terrane (PKT) returned by the Chang'e-5. These two-billion-year-old basalts represent the youngest lunar samples reported to date. The trace-element abundances of pyroxene and plagioclase in basalt fragments were determined by LA-ICP-MS, and Sr-Nd isotopic were measured *in-situ* by LA-multiple collector (MC)-ICP-MS. The results suggested that the KREEP component may not be essential for young mare volcanism. Absolving the need to invoke heat-producing elements in their source implies a more sustained cooling history of the lunar interior to generate the Moon's youngest melts.

In addition to direct analysis of the metal constituents in inorganic samples, LA-ICP-MS has also been employed to obtain the spatial information of metal constituents in organic samples, such as biological tissues.[3,49] The spatial resolution typically ranged from 10 to 100 μm, and could even reach as low as 1 μm. It contributed to addressing fundamental questions in biomedical research and facilitates bioaccumulation and bioavailability studies for ecological and toxicological risk assessments in humans, animals, and plants.[3] For example, Sara Escudero-Cernuda *et al.*[50] used LA-ICP-MS with a time-of-flight (TOF) mass analyzer (LA-ICP-TOF-MS) enabling multi-element detection in each recorded pixel to assess the elemental composition of metastatic, non-metastatic, and healthy breast tissues. It may have utility to be considered for detecting cancer areas and tumor segmentation. Quantitative analysis of Cu, Fe, Zn, Ba, and Sr showed a significant increase of these elements in cancer samples. In addition to tissue slices, LA-ICP-MS could also be employed for the imaging of tissues with various morphologies. Fernandes *et al.*[51] developed a precise and accurate LA-ICP-MS method for determining element concentrations in a single hair strand along cross-sections to investigate the element uptakes. LA-ICP-MS line transactions revealed that Mn, Cu, Zn, Sr, Ag, and Hg were more elevated in the cuticle, which indicated inhomogeneous distribution of elements across the cuticle and cortex.

Furthermore, in addition to analysis of solid samples, LA-ICP-MS can also be employed for analysis of liquid samples, such as juice and blood. In general, prior to conducting LA-ICP-MS testing, the liquid samples required to transform into solid samples, including three main strategy: (1) depositing the liquid onto a substrate and making it to dry; (2) mixing it with high-molecular-weight organic compounds to form a polymer film; (3) immersing a substrate in the liquid to facilitate analytes adsorption, followed by drying.[52-55] For example, Winfried Nischkauer *et al.*[55] developed a method for direct quantitative detection of the lead in whole blood. A small droplet (approximately 5 μL) of blood was deposited on a polymeric slide with micro-grooves array on its surface. The blood was then evenly distributed across the grooves using a rubber spatula, allowing small volumes of blood to be retained within each groove. Iron was introduced in the blood sample as an internal standard for quantification analysis. After the sample was dried the polymeric slide was analyzed by LA-ICP-MS. The micro-grooves array enables high-throughput parallel testing. The detection limit for lead in whole blood was determined to be 10 μg/L, with a single analysis completed within 3 seconds. This procedure of converting liquid samples into solid-state samples is straightforward; however, one major risk lies in compromising the natural homogeneity inherent in the dried sample, which can lead to inaccuracies in quantitative analysis. Thus, a strategy by mixing liquid sample with high-molecular-weight organic compounds to form a polymer film was proposed. For example, Dos Santos *et al.*[54] developed a method for quantitative detection of Ca, Cd, Cr, Cu, Fe, Mg, Pb, and Zn in orange juice. Juice was first mixed with polyvinyl alcohol (PVA) solution. After homogenization, the mixtures were transferred to an aluminum holder placed on a glass support and subsequently dried in an oven to obtain a solid plain film. A calibration strategy was used by adding element standard solutions into the sample to address the matrix interferences. Except Ca, Mg, and Zn, accuracy values between 60-120% were obtained for most metal constituents.

Summary. LA-ICP-MS is a powerful method for direct analysis of metal constituents in samples with the advantages of high sensitivity (ppt level), high spatial resolution (submicron), high analytical speed (several seconds per point), low sample consumption (microgramme level), simultaneous multi-element analysis (dozens of metals), and suitable for both solid samples

(*e.g.* geological samples, biological samples) and liquid samples (*e.g.* environmental samples, biological samples). However, the primary challenge associated with LA-ICP-MS was quantitative analysis due to matrix interferences. To address this issue, different calibration strategies were proposed, including internal standardization, external calibration, standard addition, on-line standard addition, isotope dilution, matrix matched standards, and novel methods such as film coating and printing were required. On the other hand, LA-ICP-MS can only determine the total concentration of metal constituents and is unable to provide speciation information, particularly structural details of organometallic compounds.

Speciation analysis of metal constituents by ICP-MS combination of online extraction

Principle. In addition to LA-ICP-MS, online extraction coupled ICP-MS is another method that can directly analyze the metal constituents from samples without sample pretreatment. Moreover, this strategy can obtain the speciation information of metals. Different speciation of metal constituents can be selectively and sequentially extracted via chemical reaction or solvent extraction. For example, the water-soluble metal speciation can be extracted with water, while ion-exchangeable metal can be extracted with $(NH_4)_2CO_3$. The extracted metal constituents are transmitted online to the ICP where they are ionized to generate metal ions. Subsequently, the metal ions are subjected to further analysis using MS. Quantitative detection can be achieved using either the internal standard method or the external standard method, based on the signal area obtained from the extracted ion chromatogram. This technology integrates the advantages of online extraction for sample preparation and the high sensitivity detection of ICP-MS, enabling direct speciation analysis of metal constituents in samples with remarkable efficiency and accuracy.

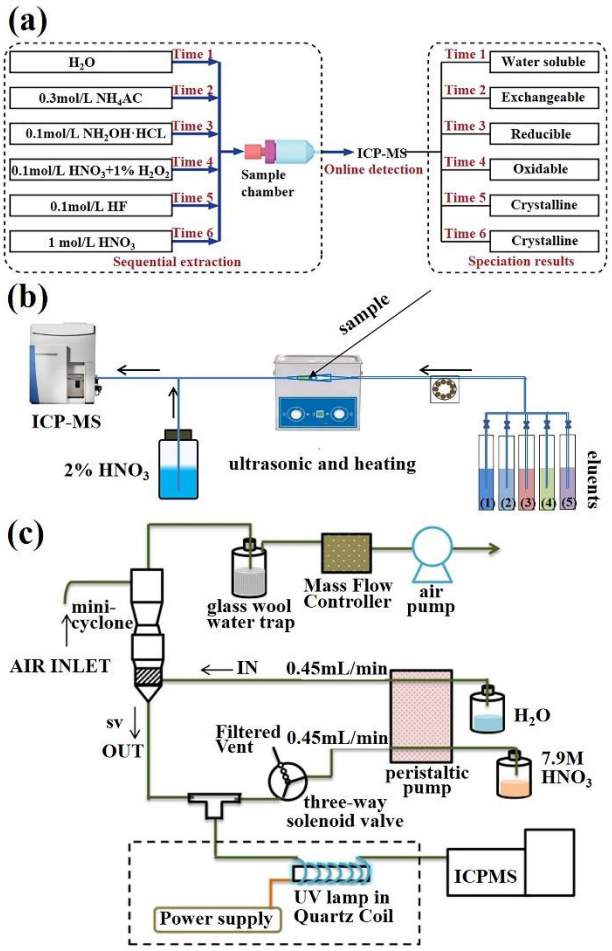


Fig. 1 Schematic of sequential online detection of inorganic metals with different speciation employing ICP-MS. (a) REEs species in raw ore samples (reprinted from[57]), (b) As species adsorbed onto ferrihydrite (reprinted from[59]), (c) continuous measurement of ambient aerosol (reprinted from[61]).

Application. In general, a solid sample was introduced into the online extraction device and subsequently subjected to chemical reagent extraction to isolate the metal constituents for subsequent online ICP-MS analysis. For example, Li *et al.*[56] developed an online extraction coupled ICP-MS method for the direct analysis of uranium in ore. They used a mixture of 5% nitric acid and 5% hydrogen peroxide to continuously extract uranium from uranium ores, and then transferred it online to ICP-MS for analysis. The results demonstrated that the total uranium content in the sample could be determined within 15 min with a recovery rate of approximate 90%, whereas the national standard method requires at least 2 h. On this basis, Xu et al.[57] developed a method combination of online sequential extraction and ICP-MS analysis to obtain the speciation information of rare earth metals (REEs) in rare earth ore samples (Fig. 1a). Six kinds of solution (H_2O, 0.3 mol/L NH_4Ac, 0.1 mol/L $NH_2OH{\cdot}HCl$, 0.1 mol/L HNO_3 + 1% H_2O_2, 0.1 mol/L HF; 1 mol/L HNO_3) were sequentially employed to extract corresponding REEs speciation of water-soluble, exchangeable, reducible, oxidable and crystalline, respectively. The solution containing the corresponding REEs fractions was mixed online with 4% HNO_3 and subsequently transferred for ICP-MS detection. Quantitative information of five speciation of 15 REEs were obtained in a single run with the advantages of low sample consumption (1.0 mg), high sensitivity (LOD of 3.6-10.6 pg), and high recovery (≥ 95%). This speciation information was helpful to determine the mining technology. Compared with the BCR method, this method could greatly shorten the analysis time (1 h vs. 80 h). Furthermore, due to the low sample consumption (1 mg), Li *et al.*[58] used this method to get the distribution of REEs in a fossil of dinosaur bone, which was useful for studying the formation mechanism of fossil. They collected milligram sample form micro-area of the fossil, followed by online sequential extraction and ICP-MS analysis. The speciation and concentration of the REEs from different location were obtained efficiently, demonstrated the formation mechanism of the fossil. A single run

required only 30-50 min. In addition to geology, this sequential extraction coupled ICP-MS method could also use for environmental analysis, which was useful for revealing the toxicity, mobility, bioavailability, and transformation of metal. For example, Wu *et al.*[59] used this online sequential extraction coupled ICP-MS for analysis of the metal speciation in environmental. Solutions including H_2O, NH_4NO_3, $NH_4H_2PO_4$, and $(NH_4)_2C_2O_4$ were used to sequentially dissolve five speciation of As (water-soluble, nonspecifically adsorbed, specifically adsorbed and iron oxide bonded) from the surface of ferrihydrite. Ultrasonication and heating were applied to improve the extraction efficiency (Fig. 1b). The total analysis time required for the approach was less than 2 h. It showed a detection limit of 0.008 μg/kg for As(III) and 0.013 μg/kg for As(V). The results showed that the fraction of As bonded to iron oxide was the dominant speciation (>80%). The specifically adsorbed and residual As accounted for a substantial amount (10%). Asante *et al.*[60] employed the method to screen four model dust source samples (soil, coal, mine overburden, and road dust). The solvents of deionised water, NH_4NO_3 (0.05 mol/L), CH_3COOH (0.11 mol/L), and $NH_2OH{\cdot}HCl$ (0.04 mol/L, pH=2) were used for extraction of metals of water soluble, exchangeable, acid soluble and reducible species. A fully optimized run took approximately 80 min. Characteristic fractograms were obtained, which demonstrated the difference in mobility of various elements (Na, Mg, Al, K, Ca, V, Cr, Mn, Co, Ni, Cu, Zn, Rb, Sr, Cd, Ba, and Pb) in the chosen sample matrices.

In addition to the solid sample, liquid sample and aerosol sample could also be analyzed by the online extraction coupled ICP-MS method. Prior to analysis, the liquid sample and aerosol sample were deposited on a substrate (*e.g.*, filter paper, SPE membrane). Then the substrate was placed in the online extraction device for analysis. For example, in the atmospheric analysis, the air was collected using a mini-cyclone through an inverted funnel sample inlet extending from the exterior wall of the building (Fig. 1c).[61] The cyclone air exit was followed by a glass wool-flask water trap, a mass flow controller and an air pump aspirating air at 30 standard liters per minute. Particles (diameter ≥ 12 μm) were collected in a polytetrafluoroethylene (PTFE) sample collection cup, which equipped with two PTFE tubes to function as ultrapure water (0.45 mL/min) inlet and exit. Ultrapure water continuously flowed through the collection cup forming aerosol slurry with the particles, followed by mixing with 7.9 M HNO_3 via a three-way solenoid valve. The flow rates of HNO_3 to the tee and ultrapure water input to the cyclone varied in the range 0.37-0.45 mL/min to match the liquid aspiration rate into the ICP-MS. Subsequently, the mixed stream optionally proceeded through a quartz photo reactor for digestion assistance before being aspirated by an ICP-MS. The analysis of the macrosample collected yielded sufficient concentrations for the elements Be, Na, Al, K, Ca, Ti, V, Cr, Mn, Co, Ni, Cu, Zn, Ga, Rb, Zr, Nb, Mo, Ag, Cd, Cs, Ta, W, Tl, Pb, and U with concentrations at least 20-fold higher than blank variations. However, due to a high blank value for Fe, it did not meet the aforementioned criteria. Relative standard deviations of the data for all 26 elements ranged from 3% to 11% (n=3).

Summary. Combination of online extraction with ICP-MS is a simple and efficient strategy for direct analysis of metal constituents. This strategy enables the simultaneous determination of both speciation information and total content of metal constituents by adjusting the extraction solutions. It has the potential to automation and programmable analysis, and is suitable for a wide range of samples across diverse fields such as environmental, geological, and biological research. Due to its completeness and selectivity in extraction, this method effectively mitigates matrix interference, thereby enabling reliable quantitative performance, particularly for particulate samples of small size (nanometer to micrometer scale). However, it should be noted that larger sample sizes (millimeter scale or above) may lead to reduced extraction efficiency for metal constituents located in the internal regions of the sample during sequential extraction, potentially compromising the quantitative accuracy of speciation analysis. Besides, this method could not obtain the structural information of organometallic compounds.

DIRECT ANALYSIS OF METAL CONSTITUENTS BY SOFT IONIZATION MS

In natural environments, heavy metals exist in diverse chemical speciation, each demonstrating marked variations in properties.[62-64] For example, organic lead is 10 to 100 times more toxic than inorganic lead. What's more, fat-soluble and water-soluble Pb are easily assimilated by the body. Whereas, the toxicity of inorganic arsenic is significantly higher than that of organic arsenic. Therefore, the speciation analysis of metals, particularly the acquisition of structural information, is essential for investigating their toxicity and biological effects. Furthermore, simultaneous analysis of the coexisted organic constituent not only enables a comprehensive evaluation of the characterization of the sample, but also facilitates the investigation of the interaction between the organic constituents and the metal constituent. For example, simultaneous analysis of the metal constituents and organic constituents in PM2.5 is useful for assessing its toxicity, tracing its sources, and studying its formation mechanisms.[65] However, the simultaneous detection of inorganic metals and organics posed a significant challenge. The general analytical strategy for analysis of metal compounds and organic compounds involves coupling ICP-MS with electrospray ionization mass spectrometry (ESI-MS).[66, 67] In this strategy, the metal compounds separated by HPLC were divided into two fractions: one was analyzed by ICP-MS, and the other was analyzed by ESI-MS. ICP-MS was employed to obtain the total amount of metal constituents, while ESI-MS was used to analyze the structure of organometallic

compounds. However, this method required relatively expensive equipment leading to high operational costs. Moreover, this strategy also requires complex sample preparation, resulting in prolonged analysis time and loss of spatial distribution information. Therefore, many soft ionization mass spectrometry methods have been developed to facilitate the simultaneous detection of metal constituents and organic constituents.

Spray based ambient ionization mass spectrometry (AIMS)

Principle. AIMS represents an innovative MS technique that enables the direct analysis of samples in their native state. It streamlines the operation process for MS analysis, enhancing speed, sensitivity, and portability. One of the categories of AIMS is spray-based AIMS, which employs charged droplets to directly extract and ionize the analytes in sample. Extractive electrospray ionization mass spectrometry (EESI-MS) and desorption electrospray ionization mass spectrometry (DESI-MS) are two representative spray-based AIMS techniques that are suitable for the direct analysis of liquid, aerosol, and solid samples. During the direct analysis of metal compounds in complex samples, charged droplets containing organic ligands generated from ESI were employed to extract or desorb metal compounds from the samples into the droplets by forming metallo-organic complexes. These metallo-organic complexes subsequently underwent solvent evaporation and coulomb fission, generating ions for mass spectrometric analysis.

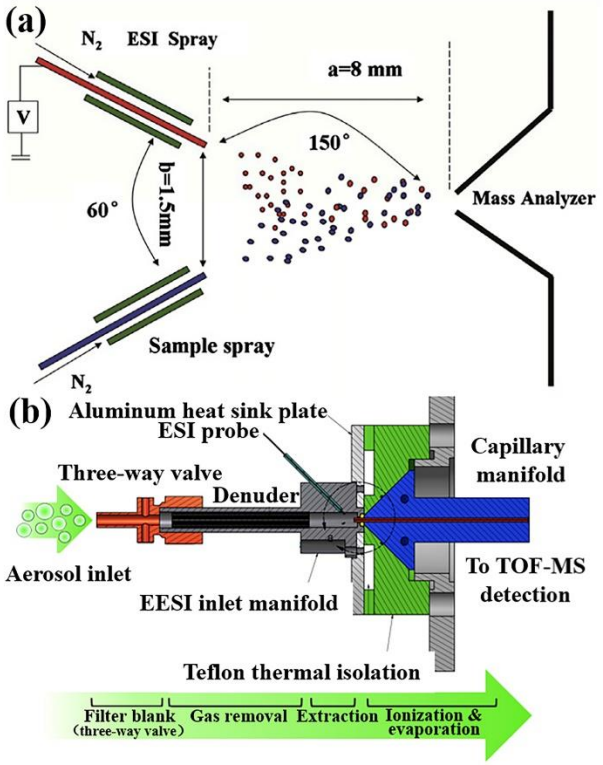


Fig. 2 Schematic of the EESI-MS for detection of trace metals (a) liquid samples (reprinted from[74]), (b) aerosol samples (reprinted from[76]).

Application. EESI-MS was always used for direct analysis of metal constituents in liquid samples, which comprising two sprayers: a neutral sample sprayer and a charged reagent sprayer (Fig. 2a).[68-70] In a typical analytical procedure, the liquid samples containing metal constituents is introduced into the neutral sample sprayer to form microdroplets, which subsequently undergo collisions with the charged droplets contained organic ligand generated by the charged reagent sprayer. During the collisions between sample droplets/aerosol and charged droplets, online complexation reactions between metal ions and organic ligands, droplet-droplet extraction and ionization would occur to form organic-metal ions for MS analysis.[71] Due to droplet-droplet extraction, this method can overcome matrix interference by selectively extracting analytes from the matrix, enabling direct analysis of complex samples without sample pretreatment. For example, Liu *et al.*[72] successfully determined the uranium isotopic ratio ($^{235}U/^{238}U$) in natural water samples using EESI-MS. Without prior separation or pre-concentration, the water sample was directly introduced into the EESI source, employing CH_3OH/H_2O as the charged solvent. Uranyl nitrate forms of $[UO_2(NO_3)_3]^-$ complex ions were observed. The single analytical procedure took only 5 min. Due to the high complexation constant between Ac^- and UO_2^{2+}, acetic acid (HAc) was used as an organic ligand introduced in the charged solvent. During the EESI-MS, Ac^- can react with the uranyl species to form ionic uranyl acetate clusters $(UO_2(Ac)_2)_nAc^-$ (n=1-5), which are readily detected by mass spectrometry during EESI-MS analysis. This enables the rapid identification of uranyl species in various natural water samples, including river water, lake water, and well water.[73] The average time for each sample analysis was about 10 s. The LOD was calculated to be 10^{-3} ng/L, and the dynamic response range was 10^{-1}-10^3 ng/L, 5 orders of magnitude, for uranium in water samples. This method provided a reasonable relative standard deviation (RSD) of 6.9-8.1% (n=8). Note that the metal ions were always detected in the form of metallo-organic complex in EESI-MS instead of free metal ion. Thus, universal ligands are commonly employed, enabling simultaneous detection of multiple metal ions. For example, ethylene diamine tetraaceticacid (EDTA) solution was always used in the ESI channel to produce primary ions. Liu *et al.*[74] employed EESI-MS for the rapid and sensitive detection of trace Pb^{2+} levels in liquid samples using EDTA as organic ligand (Fig. 2a). The method's quantitative performance was evaluated for the direct analysis of Pb in various aqueous matrices, including mineral water, lake water, tap water, energy drinks, soft drinks, beer, orange juice, and tea. Each analysis was completed within 2 minutes, yielding low relative standard deviations (4.6-7.6%), low limits of detection (10-13 g/mL), and acceptable recovery rates ranging from 91.5% to 129%. These findings demonstrated that EESI-MS could be used for quantitative measurement of metal ion

in complex matrixes.

Furthermore, EESI-MS has been improved for the direct analysis of aerosol samples. Portable EESI-TOF-MS was developed for the real-time detection and monitoring of soluble metals in aerosol particles *in-situ*.[75, 76] Fig. 2b shows a schematic of the main components of the EESI.[74] It consists of the following main components: a three-way valve (orange), a denuder (black), an ESI probe, and a polytetrafluoroethylene (PTFE) manifold (green). The spray probe and assembly were coupled to the TOF-MS via the PTFE manifold, which thermally isolated the sample flow from the heated capillary manifold (blue). Aerosol particles were continuously sampled through a three-way valve and denuder into the EESI source and intersect with a charged spray of ethylenediaminetetraacetic acid disodium salt (EDTA-2Na in (H_2O:CH_3OH=1:1)) generated by the ESI probe. As particles collided with the primary electrospray droplets, water soluble metal compounds would be extracted into the spray forming stable metal complexes with EDTA-2Na which were then ionized for TOF-MS analysis. Direct sampling and sampling through a Teflon filter (pore size of 1 μm) were alternated via the three-way valve. The difference between the direct and filter blank measurements was the background-corrected particle-phase signal. The denuder improved instrument detection limits by reducing the gas-phase background and at the same time provided a laminar stable sample flow. Low weight and size of the EESI-TO-FMS allowed its portability, making it an ideal tool for *in-situ* analytical applications. Results for water-soluble metal compounds were obtained. Representative metal ions of Pb^{2+}, Cd^{2+}, Zn^{2+}, Ce^{3+}, Ba^{2+}, Ni^{2+}, Fe^{2+}, Fe^{3+}, Cu^{2+}, Cr^{3+}, Mo^{2+}, Co^{2+}, Mg^{2+}, Nd^{3+}, Li^{+}, Ti^{4+}, Ca^{2+}, Cs^{+}, Ag^{+}, Tm^{3+}, Er^{3+}, La^{3+}, Yb^{3+}, Eu^{3+}, Pr^{3+}, Gd^{3+}, Lu^{3+}, Dy^{3+}, Tb^{3+}, Ho^{3+} and Ru^{3+} were examined. Results showed very good linearity (R^2 up to 0.999) within the examined concentration range, limit of detection (LOD) lower than the ICP-MS, and fast response times (1 s). Proof-of-concept field measurements were conducted on atmospheric aerosols in the urban environment of New Delhi, India and positive results were obtained.

In addition to liquid and aerosol samples, solid samples can also be directly analyzed using AIMS, with DESI-MS being the most representative approach. DESI-MS involves a three-step process wherein primary charged droplets are generated by electrospray, followed by spraying of droplets on the sample surface to create a liquid film and extract the analytes; the continued impact of subsequent electrospray droplets on the liquid film leads to the ejection of secondary charged droplets that are captured by the mass spectrometer for analysis. In the direct analysis of metal compounds by DESI-MS, an organic ligand (*e.g.*, EDTA-2Na) was mixed into the solvent to generate primary charged droplets, which were subsequently sprayed onto the sample surface. Chelation reaction between the metal and the organic ligand occurred on the surface, and the resulting organometallic complexes were incorporated into secondary droplets that desorbed from the sample surface for subsequent ionization. This method can direct analysis of metal compounds in various samples. For example, Schulz *et al.*[77] reported a DESI-MS for direct analysis of heavy metals in consumer goods. Heavy metals Pb, Cd, and Ni in the form of oxide were detected in eight out of nine authentic samples ranging from jewelry to tableware and toys. The reproducibilitys of the method were determined to be 7% to 24% for Fe, Ni, Cd, Pb. The LOD was 25 pmol/mm^3 for Cd, 44 pmol/mm^3 for Pb, and 279 pmol/mm^3 for Ni. Moreover, the method can also be used for spatially resolved analysis with a resolution of about 200 μm. However, DESI-MS has limitations in the analysis of metal constituents in soft and porous solid materials.

Summary. Spray-based AIMS is a powerful technique for the direct analysis of metal speciation in complex samples without sample pretreatment, and is applicable to various sample types, including liquids, aerosols, and solids. The detection sensitivity of spray-based AIMS for metal ions is closely related to the organic ligand, with higher association constants generally exhibiting a positive correlation with sensitivity for a given metal ion. Furthermore, the positive ion detection mode typically offers higher sensitivity compared to the negative ion detection mode. Thus, by adjusting the organic ligands, spray-based AIMS can effectively overcome interference from major metal constituents and enable selective detection of trace metal constituents in complex samples. On the other hand, various organometallic ions may be detected for a given metal ion, resulting in more complex spectra. Besides, another limitation of this method is that it cannot directly analyze elemental metal. A potential solution to address this limitation involves coupling online extraction with EESI-MS, which also enables effective analysis of metal constituents in soft and porous solid materials..

Plasma-based AIMS

Principle. Plasma-based AIMS is another category of AIMS, such as microwave plasma torch mass spectrometry (MPT-MS)[78-80], desorption atmospheric pressure chemical ionization mass spectrometry (DAPCI-MS)[81], dielectric barrier discharge ionization mass spectrometry (DBDI-MS)[81]. In contrast to spray-based AIMS, which typically requires the use of organic ligands, plasma-based AIMS enables direct ionization of metal constituents without the addition of external ligand during the ionization process. Among the plasma-based AIMS, MPT-MS is a representative technique that has been widely used for direct analysis of metal constituents in complex samples. MPT utilizes microwave energy to generate a plasma torch for direct ionization of analytes.[78, 79] The plasma can direct applied on the sample surface to desorb and ionize the metal constituents and organic constituents.[80] For liquid and aerosol samples, the sample can direct injected into the MPT central tube or introduced into the plasma torch.[82] Since the plasma produced by MPT was in direct

contact with the atmosphere, there were several reagent ions in MPT plasma, such as NO_3, NO_2, O, H_2O, OH, *etc.*[83, 84] Thus, the MPT mass spectrometry method exhibited novel complex cations or anions (*e.g.* $[M(NO_3)_x]^-$, $[M(NO_3)_x(H_2O)_y(OH)_z]^+$) formation for most transition metal elements, which made the detection of transition metal elements easier and more sensitive.[85] For example, uranyl species in water were detected as uranyl nitrate or uranyl acetate using EESI-MS, depending on the type of ligands (*e.g.* nitric acid, acetic acid) used. However, only signal of uranyl nitrate was observed in MPT-MS analysis no matter which type of the ligand (formic acid, acetic acid, methanol, ethanol, and acetone) was added into the uranyl aqueous solution.

Application. Many studies have shown that the MPT coupled with a linear ion trap mass spectrometer could be a potent analytical tool in the direct and sensitive detection of many kinds of metal elements in water samples.[86-90] However, for conventional pneumatic atomization devices, high moisture content in the aerosol resulted in the MPT-MS technique being unable to effectively detect metal elements. Thus, before the aqueous solution flowed into the plasma through the central tube of the MPT, a sampling system was assembled for desolvation, containing a pneumatic nebulizer, spray chamber, Nafion tube, and a drying device of about concentrated sulfuric acid (Fig. 3a). By adopting adesolvation unit, the amount of water entering the microwave plasma was reduced, which improved the utilization efficiency of the microwave power and enabled better ionization of the elements in the aerosol by the plasma. A variety of metal ions (U, Bi, Cu, Zr, Zn, Mo, Ti, Cd, Fe, Co, and Ni) in liquid samples (*e.g.*, environmental water, mine water, lake water, drinking water, milk, urine) were detected using this method with high sensitivity and a short analysis time for a single sample (less than 1 min).[85, 87, 90, 91] For current real-world samples under testing, the average levels for iron, cobalt, and nickel reached allowable concentrations of national standards, which indicating this method was practically effective and usable.

Furthermore, in the MPT-MS, the negative ion mode usually exhibited lower background and a simpler spectral peak structure than the positive ion mode. Therefore, compared with the positive composite ions of the transition metals, the negative ionic ones were more suitable for the quantitative monitoring. Under the negative working mode, the LODs of MPT-MS were determined to be in the range of 0.03-10.20 μg/L for U, Bi, Cu, Zr, Zn, Mo, Ti, Cd, Fe, Co, and Ni with acceptable recovery rates ranging from 79.0% to 123.8%. The analysis time for a single sample was 30 seconds to 6 minutes.[82, 85-87, 90, 91] The proposed method was also applied to the direct analysis of inert metals (*e.g.*, Pd)[92] and REEs (La, Ce, Eu, Pr, Nd, Sm, and Y)[84] solutions at sub-trace level. LOD of the method employing LTQ-MS/MS was estimated at the level of 0.5 μg/L for Pd and 0.04-0.574 μg/L for the REEs with the square correlation coefficient R^2 larger than 0.99.

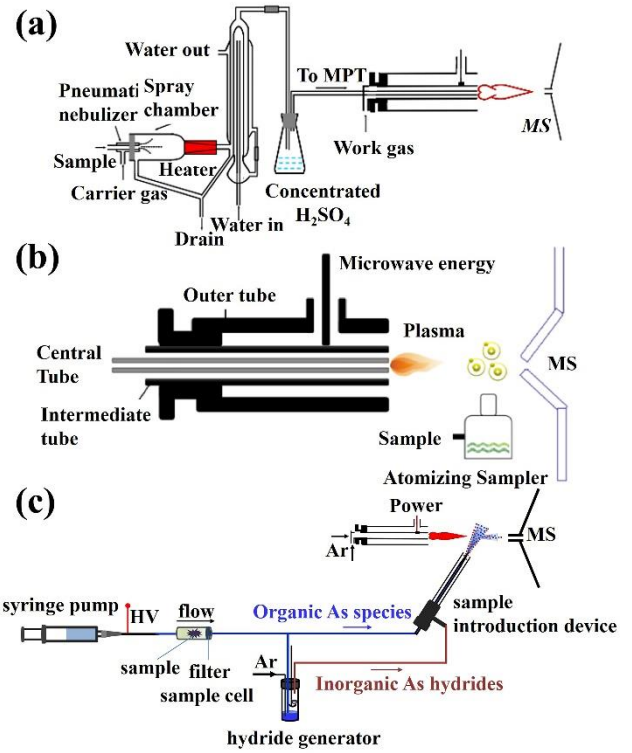


Fig. 3 Schematic diagram of typical MPT-MS method for detection of metals. (a) hectowatt-MPT-MS (reprinted from[91]), (b) NI-PIMS (reprinted from[93]), (c) EESI-HG-MPT-MS (reprinted from[94]).

An analytical technique of nebulization-assisted injection plasma ionization mass spectrometry (NI-PIMS)[93] based on the MPT-MS technique was developed, which enables the simultaneous detection of heavy metals and organic compounds in water systems with high sensitivity (Fig. 3b). A novel nebulization injector was employed to generate particles with a size of around 5 μm by high-frequency oscillations. These particles then entered the plasma and were efficiently ionized by the active substances like high-energy electrons and metastable Ar. By manipulating microwave plasma power and carrier gas flow rate, the microwave plasma coupled with the ultrasonic atomization injector facilitated the ionization of both organic and metal constituents. The method showed a semi-quantitative ability to detect organic substances, *e.g.*, ciprofloxacin, enrofloxacin, and clenbuterol with LODs of 0.99, 0.92, and 0.46 μg/L, respectively. The coefficients of determination (R^2) ranged from 0.9921 to 0.9997. The instrument could identify metal elements of Cd, Ba, and Pb with LODs of 0.58, 0.48, and 0.35 μg/L. The R^2 values ranged from 0.9904 to 0.9970. Moreover, the method was successfully applied to quantitatively analyze real surface water samples collected from urban and rural areas in China. The analytical results were available in less than 0.5 min, with consumption of a few microliters of sample. Compared to traditional methods, NI-PIMS exhibited higher efficiency, sensitivity, no or lower sample preparation, and less sample consumption.

Combination of microwave plasma torch (MPT) and extraction electrospray ionization mass spectrometry (EESI-MS), an online speciation analysis method named extraction electrospray ionization-hydride generation-microwave plasma torch mass spectrometry (EESI-HG-MPT-MS) was developed, which allowed molecular characterization of both inorganic and organic As species at trace levels from original bio-matrices without tedious sample pretreatment.[94] As shown in Fig. 3c, the device mainly consisted of a sample cell, a hydride generator, a sample introduction device, a microwave plasma torch and a mass spectrometer. Biological samples were simply placed in the sample cell. With the continuous infusing of charged extraction reagent, various As with different speciation were efficiently extracted and divided into two ways. One way of the effluent was directly drawn into the homemade sample introduction device and formed a stable electrospray plume at the tip, through which organic As were ionized for detection by mass spectrometry. The other part of effluent was transported to the hydride generator, in which inorganic As species were converted into volatile hydrides and transported through the sample introduction device to the MS inlet area via a carrier gas of Ar. The hydrides were ionized and determined by the mass spectrometer with the ignition of the MPT. With a single run of a short overall time (12 min), the method effectively conducted the molecular characterization of trace inorganic As (As(III), As(V)) and organic As (MMA, DMA, AsB, and AsC) in different biological tissues, such as crayfish, laver, and kelp. The LOD of As(III), As(V), MMA, DMA, AsB and AsC were 0.01, 0.02,0.08, 0.08, 0.05 and 0.02 μg/kg. And a recovery of 94-111% with an RSD less than 10% was gained. The method had potential applications in studying the chemical or biological behaviors of As in various environments. This method can also be used for the direct analysis of Sb in soil, demonstrating a comparable detection limit (0.05 μg/L) to ICP-MS, with recovery rates ranging from 90% to 100%.[95]

The MPT can also be directly applied to the sample surface for desorption and ionization of metal constituents. Wu et al.[80] employed MPT-MS to directly analyze metals in a series of solid samples, including metals, metal oxides, soil, stibnite, and traditional Chinese medicines (TCMs). Various metal elements, such as Ag, As, Sb, Te, Bi, Cu, and Pb, were successfully detected. The detection limits were 1.4 mg/g for As and 0.35 mg/g for Sb in soil. [80] In TCMs, the detection limit for As was 1.1 μg/g, with a recovery rate of 112.0% and a relative standard deviation (RSD) of 7%.[81] Moreover, Wu *et al.*[81] compared the detection results of As in TCM using MPT-MS, DAPCI-MS and DBDI-MS. They found that, unlike DAPCI-MS, which only allowed ionization of organic components in TCM, both MPT and DBDI additionally achieved *in-situ* desorption and ionization of As from TCM. This enhanced capability can be attributed to the combination of thermal effect and momentum effect.

Another advantage of MPT is that the ionization energy can be precisely controlled and adjusted. Pan et al.[96] developed a wide-energy programmable microwave plasma ionization mass spectrometry (WPMPI-MS) system with multiple energy scanning modes. This technology can achieve high coverage of substances with various characteristics by digitally regulating the microwave energy. In addition, ionization energy can be rapidly scanned using programmable waveforms, enabling the simultaneous detection of biomolecules, heavy metals, non-polar molecules, etc., in seconds. This WPMPI-MS system performed well in the analysis of real samples, including direct analysis of nine toxicological standards in one drop of serum and concurrent detection of perfluoroalkyl and polyfluoroalkyl pubstances, and heavy metal contamination in spiked soil samples.

Summary. Plasma-based AIMS techniques combined the advantages of hydrothermal effect, efficient desorption and adjustable energy, enabling programmed ionization of analytes (*e.g.*, metal ions, metabolites, *etc.*) with different ionization energies. This technology enables the analysis of a significantly broader range of compounds compared to other ambient ionization methods. Moreover, this programmable energy scanning mode leads to more flexibility and functionality during analysis. For example, MPT-MS may have the function of a tandem mass spectrometry via adjusting the microwave energy to dissociate the analyte ions into fragment ions. The limitation of this plasma-based AIMS lies in the absence of a standardized analytical protocol, which restricts its application and scalability.

Speciation analysis of metal constituents in samples by online extraction coupled soft ionization mass spectrometry

Principle. For comprehensive analysis of the organic and inorganic metal constituents in a complex sample, a strategy combining soft ionization mass spectrometry with online extraction was proposed, which also enables simultaneous analysis of organic compounds. This strategy contained two essential steps including sequential extraction and online efficient ionization. In sequential extraction, a series methods including solvent extraction[97-99], chemical reaction[100] and electrochemical reaction[101] were used to extract the analytes from samples. The "like dissolves like" strategy is used to extract organic and metal constituent with different polarities in samples. For example, water was used to extract water-soluble organic (*e.g.*, methylamine) or metal (*e.g.*, $Cu(NO_3)_2$) constituent in samples, while methanol was used to extract fat-soluble organic (*e.g.*, polyaromatic hydrocarbon) or metal (*e.g.*, $Pb(CH_3)_3Cl$) constituent in samples. Complexation reactions were used to extract insoluble metal constituent (such as metal oxides and metal carbonates) from samples by converting them into soluble metal-organic complexes. This strategy avoided the use of strong acid solutions in traditional extraction methods. Electrochemical oxidation was used to extract metal elements from samples by gently converting into soluble metal ions. This

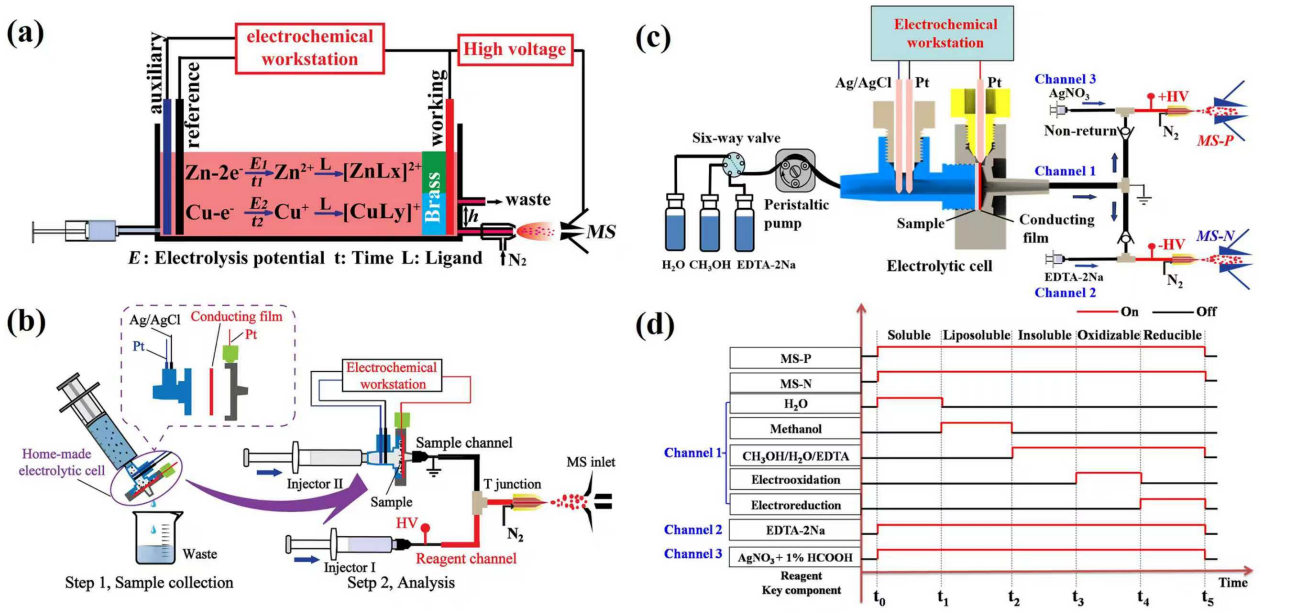


Fig. 4 Schematic illustration of the device and procedure of EC-MS. (a) device for alloy samples (reprinted from[101]), (b) device for SPM in water. (reprinted from[105]), (c) device for PM2.5 (reprinted from[106]), (d) procedure for analysis of PM2.5 (reprinted from[106]).

strategy also eliminated the need for strong acid solutions traditionally used in the extraction of metal elements. The extracted constituents were then transmitted online to the ionization source for ionization. Electrospray ionization or atmospheric pressure chemical ionization could be used to ionize polar or weakly polar organic compounds, including organometallic compounds, which had been extracted. Inorganic metals usually need to be converted into metal-organic complexes before they could be ionized by an electrospray ionization source.

Application. This method could be used for direct analysis of metal constituents in solid, liquid and aerosol samples.[100, 102, 103] For example, Xu *et al.*[104] developed an electrochemical mass spectrometry (EC-MS) to directly characterize alloys at the molecular levels without tedious sample pretreatment. As schematically shown in Fig. 4a, charged electrolytic solution (*e.g.*, H_2O/CH_3CN, 1:1, v/v) was injected at 2.0 μL/min by a syringe pump to flow through a 50 μL flowing electrolytic cell, inside which the organic chemical species on the alloy surface took the precedence over the alloy to be extracted into the solution. Subsequently, the elemental components were successively converted into the corresponding metal ions by tuning the electrolysis potentials. Note that the electrolysis potential was floated on the ESI voltage (±3.0 kV), such that the ESI high voltage brought no interference to the electrolysis. Once the metal ions were formed, they reacted immediately with the organic ligands in electrolyte solvent to form metal-organic complexes, which were carried by the solvent flow towards the outlet of the electrolytic cell to produce ambient ions for mass analysis using a LTQ-Orbitrap-MS instrument. The elemental composition of an alloy cast post and the biochemical substances coated thereon were successfully analyzed using this method. Moreover, it was reported that organic ligand is closely associated with the MS sensitivity of metal-organic complexes. The stability constant of the complex is a key parameter that exhibits a positive correlation with sensitivity. Therefore, general ligand such as EDTA-2Na is commonly employed for the simultaneous analysis of multiple metals, whereas specific ligand is typically utilized for selective detection of target metals. In addition, positively charged metal-organic complex ions generally exhibit higher sensitivity compared to the negatively charged metal-organic complex ions; for instance, $[phenanthroline+Cu]^{2+}$ demonstrates higher sensitivity than $[EDTA+Cu-4H]^{2-}$.

In addition to solid, liquid and aerosol could also be analyzed by this strategy. For example, Song *et al.*[105] developed an electrochemical mass spectrometry for sequential analysis of metal speciation on suspended particulate matter (SPM) in water. Fig. 4b displayed the experimental protocol for sequential analysis of metal speciation in SPM. An electrolytic cell was designed for particulates sampling and analyzing which was shown in Fig. 4b and marked in purple solid line ellipse. It had both filtration and electrolysis functions. The EC-MS device used in this experiment mainly included three parts: sample channel, reagent channel and electrospray ion source. Sample channel and reagent channel were connected to the electrospray ionization (ESI) using a "T" junction. The particulates were gathered on the conductive film of the electrolytic cell, which would be equipped into sample channel.

Then, the sequential speciation analysis was carried out as follows: Metals of water-soluble speciation, organic speciation, and insoluble speciation were dissociated via extraction with H_2O, CH_3OH, and EDTA-2Na used as extraction solvent, respectively. For elemental speciation, +0.8 V voltage was applied on the conductive membrane to transform the elements into metal ions using EDTA-2Na as electrolyte. The produced inorganic metal ions in the "T" junction to form EDTA-metal chelates, and organic metals mixed with charged CH_3OH. The mixtures were then transferred on-line to the ESI-MS for detection. By using this method, Mn, Cu, Zn, Pb, Ni, and Fe compounds in four speciation forms—water-soluble, fat-soluble, insoluble, and elemental were successfully detected in the SPM.

To further improve the coverage of the sequential ionization method, Song *et al.*[106] developed an electrochemical mass spectrometry by using two mass spectrometers for simultaneous analysis of positive ions and negative ions (Fig. 4c). Similarly, H_2O, CH_3OH, EDTA-2Na, electrochemical oxidation, and electrochemical reduction were sequentially utilized to extract the chemical constituents from complex samples (Fig. 4d). The extracted constituents were split into two equal parts, followed by simultaneous detection of the extracted chemical species in PM2.5 by the two MS instruments in positive and negative modes. After a single analytical procedure (about 6 h), dozens of metals (*e.g.*, Pb, Cr, and Cu), organic compounds (*e.g.*, amines, polycyclic aromatic hydrocarbons, and aliphatic acids), and negative ions (*e.g.*, NO_3^-, NO_2^-, and Cl^-) were comprehensively detected in the water-soluble, liposoluble, insoluble, oxidizable, and reducible fractions of PM2.5 samples. In contrast to conventional methods, which only provided elemental information through ICP-MS or SEM-EDS, anion information via ion chromatography, and organic compound information by means of ESI-MS or FTIR, this method enabled acquisition of qualitative and quantitative information about metal, organic, and anion species from a single sample in a single run without sample pretreatment. More importantly, the extractive ion spectrogram profiles of these species provided insight into their mutual chemical relationships and spatial distribution within PM2.5. This chemical fingerprint of PM2.5 was valuable for assessing its toxicity, tracing its sources, and studying its formation mechanisms.

Summary. The combination of online extraction with soft ionization mass spectrometry enables sequential analysis of organic constituents with varying polarities and different speciation of metal constituents. This strategy takes advantages of broad analyte coverage and high analytical speed, particularly in establishing the relationship between organic and metallic constituents. However, this method is not suitable for analyzing organic or metallic constituents encapsulated within samples that require high-concentration acid for dissolution or extraction, such as SiO_2 or crystalline minerals, which required the use of HF to dismantle the sample structure. A potential solution is to develop an online acid removal technique prior to soft ionization.

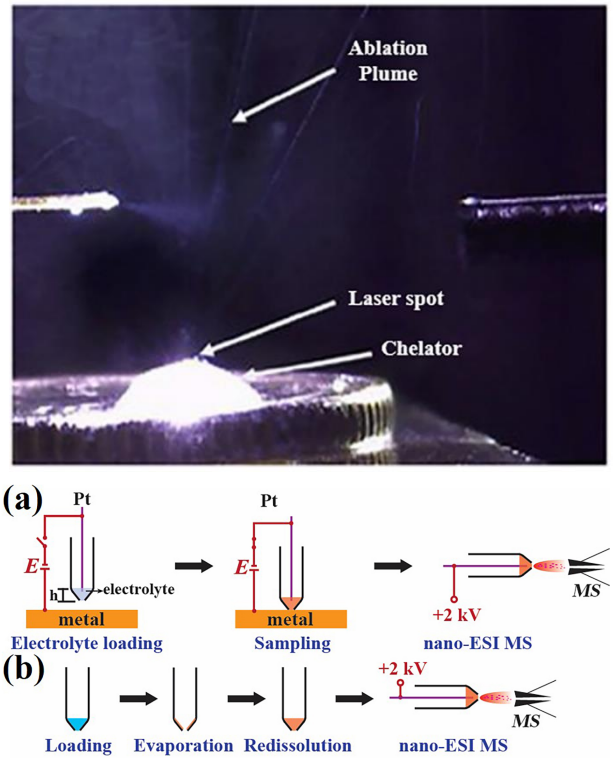


Fig. 5 Schematic illustration of ELDI (a) (reprinted from[107]), μECP-MS (b) (reprinted from[108]) and ER-nano-ESI MS (c) (reprinted from[109]) for detection of metals in solid samples.

Micro-area analysis of metal constituents in samples

Principle. Micro-area analysis of organic and metal constituents has great significance for obtaining the distribution information and investigating the relationship between the organic and metal constituents. Similar to LA-ICP-MS, a general strategy for micro-area analysis of organic and metal constituents contained two essential steps, including spatial sampling and soft ionization. The primary sampling methods employed were laser desorption and solvent extraction. The primary soft ionization techniques were ESI and nanoelectrospray ionization (nano-ESI). For example, in laser desorption electrospray ionization mass spectrometry (LD-ESI-MS), a laser is employed to directly desorb organic and metallic components from the sample, generating an aerosol. The ESI source produces charged microdroplets, which subsequently interact with the desorbed aerosol to ionize the analytes. To achieve high detection sensitivity for metal constituents, organic ligands are commonly employed to react with the metal species to form stable metal-organic complexes. These ligands can be introduced either onto the sample surface or into the electrospray ionization (ESI) source. In liquid extraction surface analysis mass spectrometry (LESA-MS), a micropipette preloaded with solution containing organic ligand was employed to sample organic and

metallic constituents from the micro-area of the sample. After sampling, the micropipette can be employed as a nano-ESI to ionize the sampled organic and metal constituents for MS analysis. In addition to the two-step strategy involving separate sampling and ionization, an alternative approach integrates both sampling and ionization into a single step. The typical methods are laser ionization mass spectrometry (LI-MS) and secondary ion mass spectrometry (SIMS). Laser irradiation (1064 nm) or ion beam were applied on the samples to desorb and ionize the organic and metal constituents from samples for MS analysis.

Application. Micro area analysis of alloys has great significance for material science. Shiea *et al.*[107] developed an electrospray laser desorption ionization mass spectrometry (ELDI-MS) for direct analysis of metals. Metals from samples were desorbed by laser irradiation (Fig. 5a). Before the pulsed laser beam was used to irradiate the sample, chelating solution (EDTA) was placed on solid sample surface. Metals from samples were desorbed by laser irradiation and reacted with EDTA *in-situ* to form M-EDTA complexes. The complexes would move upward and enter the ESI plume, in which they were subsequently post-ionized for MS detection. The present method was employed to direct analysis of the alloy samples. The metal constituents in the aluminum (Al) plate, copper (Cu) foil, nickel (Ni) plate, lead (Pb) plate, and stainless steel 301, 304, 305, and 403 plates were characterized in seconds without sample pretreatment, resulting in minimal damage to the samples. Signals of $[Al+EDTA-4H]^-$, $[Cu+EDTA-4H]^{2-}$, $[Ni+EDTA-4H]^{2-}$, and $[Pb+EDTA-4H]^{2-}$ ions were successfully obtained from the respective metal foils and plates, while $[Fe+EDTA-4H]^-$ was detected on stainless steel plates and foils. This method was applied to rapidly distinguish authentic coins from fakes. However, this method was difficult to obtain the speciation information of metal constituents.

In addition to laser sampling, Xu *et al.*[108] developed a micro-electrochemical probe mass spectrometry (μECP-MS) for chemical profiling of bulk alloys based on the solvent sampling strategy. This method combined micro-electrochemical sampling with nano-ESI MS for trace analysis. Before the micro-sampling, a nanoliter volume of electrolyte (*e.g.*, EDTA in CH_3CN/H_2O) was sucked into the μECP. Then, the μECP was quickly moved forward to the alloy surface by micro manipulator. After the μECP was gently touched with the alloy and a liquid junction formed between the μECP and the alloy, the organic compound or soluble metal compound will be extracted into the μECP. For elemental metal, electrolysis sampling was conducted by applying an appropriate voltage between the μECP (used as the cathode) and the alloy (used as the anode) (Fig. 5b). The elemental metal would be transformed into metal ions and react with the ligands *in-situ* (*e.g.*, EDTA) to form a metal-organic complex. After electrolysis/extraction for a short time (*e.g.*, 20 s), the electrolyte was enriched with the organics and metal ions, which were subsequently analyzed by mass spectrometry using the μECP as a nano-ESI emitter. Note that, in addition to 2D analysis, this method could also be used for depth profiling of metal materials. The etching depth could be controlled by adjusting the duration of electrochemical etching. The lateral resolution of alloy chemical profiling was ≤10 μm, and the depth resolution was ≤0.5 nm. The limit of detection for Rhodamine B, Zn, and Cu depositions were 4.47, 9.58, and 24.25 ag per μm^2, respectively. By using this method, the organic and metallic contaminant of semiconductor chip or circuit were detected. Subsequently, Xu *et al.*[109] developed an ER-nanoESI-MS method for micro-area analysis of ore (Fig. 5c). This ER-nanoESI-MS method consisted of three essential steps, including "Evaporation" (abbreviated to "E"), "Redissolution" (abbreviated to "R") and nanoESI-MS detection. Because the metal component in the ore was difficult to extract through conventional methods such as "Like dissolves like" solvent extraction, chelating reactions, or electrochemical reactions, concentrated strong acids (*e.g.*, HNO_3, HCl) were commonly employed to extract the analytes. However, the strong acids with high concentration would damage the instrument and weaken the MS signal in nanoESI-MS, whereas the use of ER-nanoESI-MS can effectively resolve this issue via evaporation of the acids. In a typical analytical procedure, 1 nL HNO_3 (1 mol/L) was first loaded in the micropipette (10 μm tip) by a microinjector. Then, the micropipette was accurately moved to the mineral sample surface by a micromanipulator with the assistance of a microscope. After the micropipette was connected with the mineral sample, HNO_3 was reacted with the mineral to extract the component from the mineral. After extraction, the micropipette was moved away from the mineral, followed by placed on a heating plate at 100 °C with the tip towards the heating plate. The distance between the micropipette tip and the heating plate was 1 cm. The boiling point of HNO_3 was 83 °C, whereas that of metal nitrates salts was considerably above 100 °C. Therefore, during evaporation, the residual HNO_3 could be effectively removed, leaving the metal nitrates deposited on the inner wall of the nano-ESI emitter tip. Then, a fresh new solvent 10 ppm phenanthroline (CH_3OH/H_2O, v/v=1:1) was loaded in the micropipette to dissolve the residual analyte. After that, the micropipette was used as a nano-ESI emitter to ionize the analytes for MS analysis. Moreover, the concentration of the extracted mineral component in the micropipette could be calculated by the corresponding intensity and standard curve, which could provide the proportion or semi-quantitative results of the co-existing metals mineral component. Obvious signals of $[Ni+2(phenanthroline)]^{2+}$ (m/z 209.0364), $[Zn+2(phenanthroline)]^{2+}$ (m/z 212.0335), $[Fe+3(phenanthroline)]^{2+}$ (m/z 298.0704), $[Ni+3(phenanthroline)]^{2+}$ (m/z 299.0725), $[Zn+3(phenanthroline)]^{2+}$ (m/z 302.0676) were observed in gabbro mineral, which agreed with the constitute of gabbro mineral as previous reports.

As a representative technique that integrates sampling and ionization into a single step, time-of-flight secondary ion mass

Table 1. The summarization of the MS method for direct analysis of metal constituents in complex samples

Method	Sample	Analytes	Advantages	Limitations	Ionization mechanism	Analysis time	LOD	Ref.
LA-ICP-MS	Solid sample (breast tissue, human hair, mineral, lunar soil, etc.)	Metal elements and isotopic analysis	*In-situ* imaging of metal element distribution in solid samples	Calibration strategies were required to address matrix interferences.	Plasma	Quick response	11-83 ng/g for Cu, Fe, Zn, Sr, Ba	[50, 51]
	Liquid sample (orange juices, whole blood)		Quick response			2 min	---	[54, 55]
Online extraction coupled with ICP-MS	Aerosol	Total amount of metal	Analysis in real time	Impossible to distinguish the speciation of metals		---	---	[61]
	Solid sample (REEs Ore, dinosaur bone, Ferrihydrite, soil, coal, mine overburden, and road dust)	Inorganic metal speciation	Speciation analysis of inorganic metal components	Impossible to distinguish organic metals		30-50 min	3.6-10.6 pg for 15 REEs	[57, 58]
						Less than 2 h	0.008 μg/kg for As(III) and 0.013 μg/kg for As(V)	[59]
						80 min	---	[60]
EESI-MS	Liquid sample (mineral water, lake water, tap water, energy drinks, soft drinks, beer, orange juice, and tea)	Water soluble metals	No pretreatment of the sample	Detection of only water soluble metals	Electricity	2 min	10^{-13} g/mL for Pb^{2+}	[74]
	Aerosol sample	Water soluble metals	Analysis in real time	Detection of only water soluble metals		Response time of 1 s	ng/$m^3$for 32 metals	[75, 76]
DESI-MS	Solid samples (jewelry, tableware and toys)	Metal oxide	No pretreatment of the sample	Detection of only metal oxide	Electricity	0.4 min	25 pmol/mm^3 for Cd，44 pmol/mm^3 for Pb，279 pmol/mm^3 for Ni	[77]
MPT-MS	Liquid sample (drinking water, milk, urine)	Water soluble metals	Desolvation online	Detection of only water soluble metals	Plasma	Less than 1 min	0.03-28 μg/L for 19 metals	[80, 84-87, 90-92]
NI-PIMS	Liquid sample (Water)	Water-soluble metals and organics	Detection of metals and organics Simultaneous	Detection of only water soluble metals	Plasma	Less than 0.5 min	0.46-0.99 μg/L for 3 organics, 0.35-0.58 μg/L for 3 metals	[93]
EESI-HG-MPT-MS	Solid sample (crayfish, laver, and kelp)	Organic and inorganic metal speciation	Speciation analysis of inorganic and organic metal components	Two ionization sources were needed	Electricity/Plasma	12 min	0.01-0.08μg/kg for As(III), As(V), MMA, DMA, AsB and AsC	[94]
ELDI-MS	Solid sample (metal foils and plates)	Elemental metals	Quick response	Detection of only elemental	Electricity	Within seconds	---	[107]

				metals				
EC-MS	Aerosol sample	Organic and inorganic metal speciation, organics, spatial distribution in aerosol sample	Speciation analysis of inorganic and organic metal components with their mutual chemical relationships and spatial distribution	Difficult to analysis samples containing high Silicon dioxide.	Electricity	6 h	47.1 pg for Mn^{2+}, 99.1 pg for Ni^{2+}	100, 106
	Liquid sample (water, suspented particles) Solid sample (alloys, drinking water pipe scales, soil)	Organic and inorganic metal speciation	Speciation analysis of inorganic and organic metal components				0.65 pg for Pb^{2+}, 0.16 pg for $Pb(CH_3)_3Cl$	105
							0.1 μg/L for Cu and Zn	101-103
μECP-MS	Solid sample (alloy)	Elemental metals	Micro-area analysis	Hard operation	Electricity	About 20 min	1.59 and 4.03μg/L for Zn^{2+} and Cu^{2+}	108
ER-nanoESI-MS	Solid sample (mineral)	Total amount of metals	Micro-area analysis	Hard operation	Electricity	About 20 min	0.2 μg/L of Cu^{2+}	109
TOF-SIMS	Solid sample (metal anodes)	Metal salts	Micro-area analysis	Instrument is expensive	Ion beam	Within seconds	---	110

spectrometry (TOF-SIMS) is a powerful analytical method for obtaining nanoscale three-dimensional chemical information from solid samples, such as semiconductor materials, metal anodes and alloys. Owing to its exceptional sensitivity to all elements, it could detect ionized elements and molecular fragments at the ppb level simultaneously. Ma *et al.*[110] employed TOF-SIMS to obtain all composition, both inorganic and organic components, from solid electrolyte interface (SEI) at the lithium metal anode after electrochemical cycles. To prevent the sample from exposure to air, a special transfer vessel was used to directly transfer it from the glove box to the TOF-SIMS vacuum chamber. A Bi^{3+} beam was used as the primary beam to detect the samples, and an Ar^{+} beam was used for sputter etching to obtain the desired depth profile. The analysis area was 100 × 100 μm^2, while the sputtering area was 400 × 400 μm^2. It was found that SEI was composed of organics (*e.g.* CH_3OCH_2OH, $C_6O_4H_{11}$, and $C_2F_6S_2O_4N$) and lithium salts (*e.g.* Li_3SO_2, Li_2N_2O, and LiF). In addition, the distribution of lithium salt analyzed by TOF-SIMS could be used to judge the change degree of SEI. The work provided significant guidance for accurately characterizing the SEI layer and constructing a more realistic interface layer model.

Summary. Laser and ion beam sampling methods can achieve high spatial resolution, with ion beams enabling nanometer-scale resolution. However, these techniques face challenges in obtaining the speciation information of metals. In contrast, the solution extraction strategy can selectively extract metals of different speciation by modulating the extraction conditions, thereby enabling sequential speciation analysis using nano-ESI MS. However, the spatial resolution of the solution extraction strategy is lower than that of laser and ion beam sampling.

CONCLUSIONS AND FUTURE PROSPECT

Conclusions. In this review, we briefly summarized the principles and applications of MS-based techniques for direct analysis of metal constituents in different types of real samples. These techniques took the advantage of high analytical speed, high coverage, simplicity, and enable online analysis of samples. In brief, ICP-MS-based methods offer high sensitivity, whereas soft ionization MS-based methods provide broad coverage and enable structural analysis. The specific advantages and limitations of each method are summarized in the corresponding section and Table 1. For example, LA-ICP-MS enabled the direct analysis of metal constituents on the surface of solid samples by laser sampling. However, the substantial complication associated with LA-ICP-MS was the requirement of solid standards with similar composition for quantitative analysis. Online sequential extractions coupled with ICP-MS realized the speciation analysis of the metal constituents in the solid samples addressing many of the challenges encountered in offline ICP-MS methods. Since ICP-MS could not give the structural information of the analytes, the ability to determine valence state of the metals and the structure

of organic metals was problematic. Soft ionization-MS was developed to analyze metals in different types of samples. Compared to ICP-MS, soft ionization-MS enables simultaneous detection of metal constituents (including metal salts, metal oxides, organometallic compounds, and metallic elements) as well as organic constituents. However, the sensitivity of soft ionization-MS methods is generally lower than that of ICP-MS, which is strongly influenced by the choice and properties of the organic ligand. Moreover, the soft ionization-MS mass still lacks of standardized protocols in the current, resulted in limitation in quantitative accuracy and stable.

Future prospects. The future research directions in this field are outlined as follows:

(i) Construction of standard operating procedure. Most of the techniques introduced herein remain at the research stage. Thus, optimize and standardize the operating procedure are therefore essential for accuracy and precise analysis.

(ii) Development of instruments and equipment. The development of miniaturized and portable instruments is highly significant for field analysis. The integration of mass spectrometry with other analytical instruments (*e.g*., microscopes) enables the acquisition of more comprehensive information. Furthermore, the advancement of intelligent operating systems and data analysis systems represents an important future direction.

(iii) Expansion of the application. Given the advantages of direct analysis of metal constituents by mass spectrometry, greater efforts should be devoted to expanding its applications in field analysis, such as public safety screening and environmental pollution monitoring.

AUTHOR INFORMATION

Jiaquan Xu, born in 1986, obtained his B.S. and M.S. degrees in Chemistry from Sichuan University in 2009 and 2012, respectively, and his Ph.D. from Wuhan University in 2016. He is a professor of Analytical Chemistry at East China University of Technology. His major research interests are theoretical research, instrument development, and application development of sequential ionization mass spectrometry for complex samples. He is a recipient of the National Natural Science Foundation of China's Outstanding Youth Fund, a member of the Medical Mass Spectrometry Branches, Environmental Branches, and Materials Branches of the China Association for Instrumental Analysis, and a young editorial board member of Chinese Chemical Letters. Jia-Quan Xu is author or co-author of over 40 articles published in peer-reviewed scientific journals, such as *Angew. Chem.*, *Anal. Chem.*, *Sci. China Chem.*, and *Environ. Sci. Technol.* He has received one Gold Award from the Science and Technology Award of the China Association for Instrumental Analysis (BCEIA) and one Second Prize from the Natural Science Award of the Chinese Nuclear Society as the first author.

Xing-Lei Zhang received his BSc in 2007 from East China University of Technology, and PhD in 2023 from East China University of Technology. His major research interests are basic theories, instrument development and application research in direct mass spectrometry analysis of complex matrix samples. Xing-Lei Zhang is author or co-author of over 30 articles published in scientific journals.

Corresponding Authors

*J. Q. Xu

Email address: jiaquan_xu@foxmail.com

*X. L. Zhang

Email address: leizi8586@126.com

Notes

The authors declare no competing financial interest.

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