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Journal of Chromatography A, 856 (1999) 243–258

JOURNAL OF CHROMATOGRAPHY A

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Review

Liquid chromatography–inductively coupled plasma mass spectrometry

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Abstract

The technique of coupling liquid chromatography to inductively coupled plasma mass spectrometry (ICP-MS) is reviewed. A brief introduction to the ICP-MS instrument is given as well as methods to couple the two analytical instruments together. The various types of LC that have been used with ICP-MS detection are discussed and advantages over traditional methods of detection are highlighted, such as the improvements in sensitivity and selectivity. Several applications that have been described in the literature are reviewed. An outlook for the future of LC–ICP-MS, particularly with regard to elemental speciation is given.

Keywords: Reviews; Inductively coupled plasma mass spectrometry; Interfaces, LC–MS; Trace analysis

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1. Introduction

The presence of trace elements in the environment may pose threats to organisms and humans, even at very low levels. It is now recognized that the increasing need for trace elemental analysis also requires very sensitive analytical techniques for quantification and qualitative identification. The chemical form or the oxidation state of organometallic compounds, inorganic molecules and biomolecules in the environment may be essential if their toxicological impact is to be assessed. For this

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0021-9673/99/$ – see front matter
PII: S0021-9673(99)00580-4

reason, the traditionally reported total element concentrations in a sample are no longer sufficient for risk determination. Methods to separate and identify the various species present are now becoming a necessity for any elemental analysis. Techniques to achieve such separations of chemical species are known as *elemental speciation* methodologies.

Inductively coupled plasma mass spectrometry (ICP-MS) has fast become the technique of choice for the determination of elements in a wide range of samples at concentrations in the ng l^{-1} to μg l^{-1} range. The versatility and reliability of the technique in terms of element specificity and sensitivity make it ideally suitable for use as a chromatographic detector. ICP-MS has been coupled to all forms of chromatographic techniques for speciation analyses, including gas chromatography, liquid chromatography (LC), supercritical fluid chromatography and capillary electrophoresis [1–8]. The detection technique has several inherent advantages over other possible methods of detection including a wide linear dynamic range, low limits of detection, high speed of analysis, multielement capability, simple spectra and the ability to perform isotopic analysis [1].

Many elements have received attention in the literature since the first instance of coupling of LC to ICP-MS. These include As, Cd, Cr, Au, Pb, I, Fe, Hg, Se, Te, Sb, Sn, V, Pt [9]. A suitable chromatographic method must first be developed to separate the species of interest followed by transportation of the chromatographic eluent from the column to the ICP-MS system.

2. Inductively coupled plasma mass spectrometry

An inductively coupled plasma is a well characterized, high-temperature source, suitable for the atomization and ionization of elemental species [10–12]. The plasma is formed within a quartz torch, which consists of three concentric quartz tubes, through which argon gas flows. The outer gas flow is known as the ''plasma'', ''coolant'' or ''support'' gas flow and is introduced into the torch tangentially, which enables it to form a vortex flow. It is this gas flow which sustains the ICP. The central gas flow is known as the ''auxiliary'' gas flow and is used to keep the plasma away from the edge of the quartz torch. The inner gas flow, known as the ''nebulizer'' gas flow, transports the analyte to the plasma. Radiofrequency (RF) power of 27.12 or 40.68 MHz is coupled to the torch using a ''load coil'' so that oscillating electric and magnetic fields are formed at the top of the torch. The plasma is formed when a spark is used to seed electrons, which are subsequently accelerated by the magnetic and electric field vectors so that their energy is sufficient to cause ionization of the argon gas. The further collisions that ensue cause further ionization and the plasma becomes self-sustaining. A portion of this plasma's energy is then transferred to excite and ionize the analyte.

The conventional means of introducing sample into the ICP is as a liquid. Typical sample introduction systems consist of a nebulizer (pneumatic or ultrasonic), which forms a fine aerosol, followed by a spray chamber, which separates the large droplets from the small droplets coming from the nebulizer. The aerosol is then transported to the plasma by the nebulizer gas flow where it rapidly undergoes desolvation, vaporization, atomization and ionization.

The ICP produces singly charged ions for MS very efficiently. In order to transport the ions to the mass spectrometer, a multiple stage differentially pumped interface is used. The ions are extracted from the atmospheric plasma into the low-pressure mass spectrometer through a cooled nickel or platinum sampling cone. The orifice of this cone is approximately 1 mm diameter. Expansion of the gas then occurs in the low-pressure region behind the cone before a fraction of the ions pass through another cone, known as the skimmer cone, and the majority of the argon is pumped away. The ions are focused into a more direct path to the mass analyzer using a series of ion ''lenses'' which are simply a series of electrodes, held at variable voltages. The ions are then separated in the mass analyzer according to their mass-to-charge ratio. The most commonly used mass analyzer is a quadrupole although the need for mass analyzers to achieve higher resolution has been identified and commercial instrumentation is now becoming available. Mass analyzers, such as double focusing sector mass analyzers may be used to reduce isobaric interferences (for example $^{40}Ar^{35}Cl^{+}$ interfering with $^{75}As^{+}$). Fig. 1 is a schematic

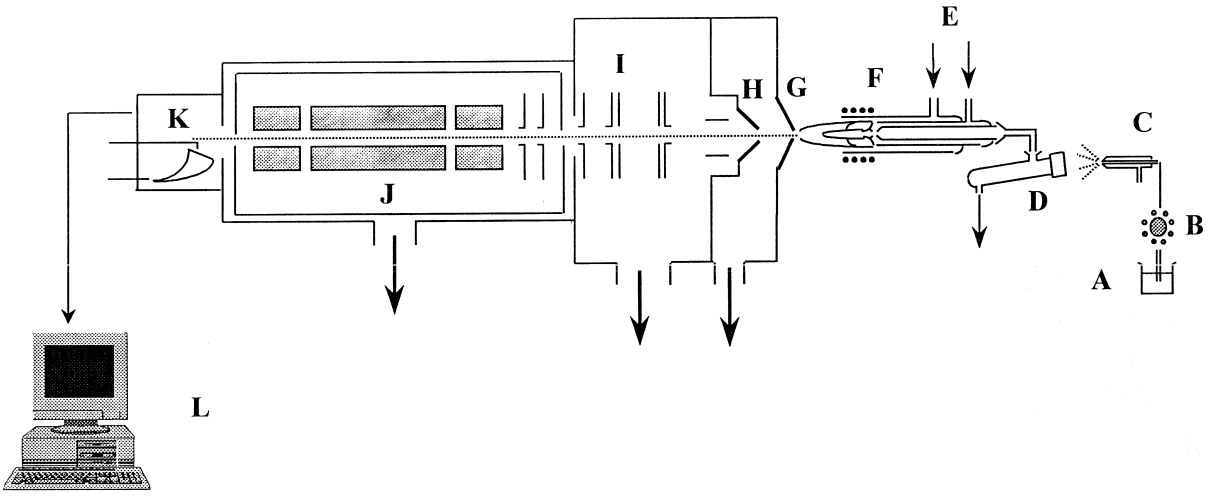

Fig. 1. Schematic diagram of an inductively coupled plasma mass spectrometer. (A) Liquid sample, (B) pump, (C) nebulizer, (D) spray chamber, (E) argon gas torch inlets, (F) torch, (G) sampler cone, (H) skimmer cone, (I) ion lenses, (J) quadrupole mass analyzer, (K) electron multiplier detector, (L) data collection.

diagram of a quadrupole ICP-MS instrument with pneumatic sample introduction system.

3. Interfacing liquid chromatography with inductively coupled plasma mass spectrometry

Traditional detectors for LC, such as UV–Vis absorbance and refractive index detectors, lack the sensitivity that is required for the necessary quantitative determination of elements in environmental and biological samples. ICP-MS overcomes this problem and has been shown to offer improvements in sensitivity of approximately three orders of magnitude, depending on the element being studied. In addition, ICP-MS is an element selective detector. The mass spectrometer may be set to monitor the isotopic signal of an element, or several elements, with respect to time and so the resulting chromatograms show peaks which must contain the isotope of interest. This is a distinct advantage when compared to detectors such as UV–Vis absorbance, which produce chromatograms that highlight all species, which absorb at the specified wavelength. This is a particular problem when analyzing real samples with complex matrices as the presence of many absorbing species complicate the interpretation of the chromatogram.

The liquid flow-rates commonly used with ICP-MS are of the order of 0.1 to 1 ml min^{-1} and various nebulizers may be used for accommodating these flows. For flow-rates of the order of 1 ml min^{-1}, cross flow nebulizers or concentric nebulizers are commonly used. Liquid chromatography is the easiest of the chromatographic separation techniques to couple with ICP-MS, principally because the flow-rates used with LC are of the order of 0.1 to 1.0 ml min^{-1} and the ICP sample introduction system are comparable. In addition, as the LC mobile phase elutes from the column it is at atmospheric pressure, which is ideally suitable for the sample introduction systems of ICP-MS instruments.

Liquid chromatography with ICP-MS detection is principally used for speciation analyses and the literature reflects the versatility of the technique. In addition, LC–ICP-MS may be used for sample preparation and preconcentration purposes. Many samples, such as seawater, contain high dissolved solids, producing matrix loading; therefore the determination of trace elements may be problematic. The presence of high dissolved solids (salts) often results in constriction of the sampler and skimmer cone orifices of the mass spectrometer owing to prolonged build-up of solids. This ultimately affects the sensitivity and precision of the analysis as well as the long term stability of the instrument [13]. A

water–sample matrix may also contain significant amounts of Na, Cl, Ca and S, particularly for seawater samples, which result in polyatomic ion interferences. The analysis of such water samples, therefore, requires matrix separation prior to sample analysis. Methods based upon liquid chromatography may be used to achieve matrix elimination. An example is shown in the work of Ketterer [14] who used on-line cation-exchange LC for the removal of cationic constituents of water samples prior to the determination of rhenium by ICP-MS. At a particular pH, matrix components (such as the alkali and alkaline earth metals) are not retained strongly on the cation-exchange LC column and thus are separated from the elements of interest.

Further, many elements in environmental samples are present at very low concentration levels, below the limits of detection of ICP-MS instruments. A method to concentrate the analytes of interest from a large volume of sample solution is therefore desirable and is known as ''preconcentration''. Preconcentration may be achieved by one or a combination of a number of methods which may be separated into four major categories: ion-exchange, chelating ion-exchange, co-precipitation and solvent extraction [15]. For the two former methods, LC columns are used. After the sample matrix solution has been run through the column, the mobile phase conditions are altered so that the loaded species have more affinity for the mobile phase than the column. The sample then elutes off the column, ideally as a low volume sample plug, and passes into the ICP-MS detector.

The coupling of LC to ICP-MS is achieved by connecting the outlet of the column to the liquid sample inlet of the nebulizer using a length of inert polymeric or stainless steel tubing. The length of the tubing should be kept as short as physically possible so that the dead volume of the transfer line and resultant peak broadening are minimized. The liquid flow-rate to the nebulizer is determined by whether a regular bore (4.6 mm I.D.), minibore (2.0 mm I.D.), microbore (1.0 mm I.D.) or a capillary (around 300 μm) LC column is used. These narrow bore columns offer several advantages over regular bore columns including low dispersion characteristics and reduced mobile phase consumption. The flow-rate of the mobile phase to the nebulizer determines the type of nebulizer that should be used.

As mentioned previously, cross flow and concentric pneumatic nebulizers may be used when regular bore LC columns are coupled to ICP-MS. These nebulizers, however, often do not perform efficiently when the lower liquid flow-rates associated with narrow bore columns are used. For this reason, ''low flow'' nebulizers have been developed which operate at optimum flow-rates in the region of 0.01 to 0.1 ml min^{-1}. These nebulizers include the microconcentric nebulizer [16], which has been used with capillary LC at liquid flow-rates of 10 μl min^{-1} [16] and the direct injection nebulizer (DIN) [17–20]. The latter nebulizer directly injects the entire sample into the ICP and a spray chamber is not required (Fig. 2). In this way the sample transport efficiency approaches 100%, a considerable improvement over the 1 to 2% efficiency with most nebulizer–spray chamber combinations.

The hydraulic high-pressure nebulizer has been shown to give improvements in detection limits when compared to conventional pneumatic nebulizers for chromatographic detection by ICP-MS [21,22]. A liquid chromatographic pump is used to achieve a pressure of 9 MPa as the chromatographic eluent passes though a Pt–Ir nozzle. The resultant aerosol is then transported to a single pass spray chamber with impact bead and desolvated using a Peltier element cooling device.

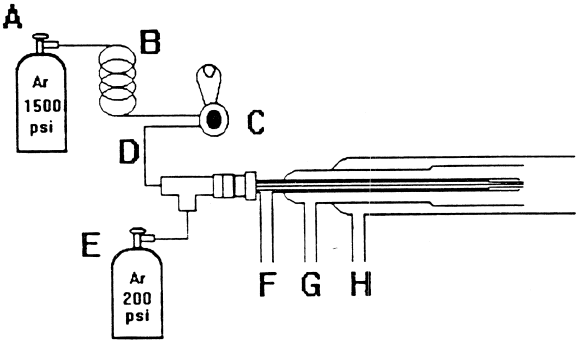

Fig. 2. Schematic diagram of a direct injection nebulizer, sample introduction system and gas displacement pump. (A) Argon supply for gas displacement pump, (B) PTFE-lined stainless steel tubing, (C) high-pressure metal free flow injection valve, (D) 50 μm I.D. fused-silica sample transfer line, (E) nebulizer argon supply (200 p.s.i.; 1 p.s.i=6894.76 Pa), (F) make-up injector gas, (G) auxiliary gas, (H) plasma gas. Taken from Ref. [16] with permission of The American Chemical Society.

Thermospray nebulization is another technique that has found practical application as an interface between LC and ICP-MS [23–25]. This method of nebulization improves sample transport efficiency to the plasma owing to its ability to produce smaller droplets. A liquid sample is pumped through a uniformly, electrically heated capillary at flow-rates of up to 2 ml min^{-1}. The high temperature decreases the surface tension of the liquid so that it exits the capillary as a velocity vapor jet, which is partially desolvated.

For elements that form volatile metal hydrides (e.g., As, Sn, Se, Bi, Hg, Sb) sample introduction by hydride generation may be used [26–28]. The eluent exiting from the column is converted to a hydride using sodium tetrahydroborate in a continuous manifold system and then transported to the plasma as a gas. In this way the sample transport efficiency is improved significantly resulting in low detection limits. It should be noted that the detection response for hydride generation is species selective: some species give very high signal intensity whereas many species cannot be detected.

B'Hymer et al. [29] compared an oscillating capillary nebulizer (OCN), a concentric nebulizer and a high efficiency nebulizer (HEN) as part of a minibore chromatographic interface. Single pass, double pass and cyclonic spray chambers were evaluated for each nebulizer and detection limits were measured. It was found that the HEN–cyclone spray chamber combination gave better detection limits whereas the OCN, with any spray chamber combination, gave the worst. Seven different spray chambers were also evaluated in a separate study and again, the cyclonic spray chamber was found to have a superior sample transport efficiency [30].

Faltner and Wilken [31] used ultrasonic nebulization when interfacing high-performance liquid chromatography (HPLC) with ICP-MS for the determination of platinum compounds. The resultant aerosol was driven by the nebulizer gas stream through a heating path followed by a cooling path or desolvation. The detection limits were in the pg range for the two species.

For many types of chromatographic separations, the mobile phases are prepared with a proportion of organic solvent, such as methanol or acetonitrile. When such solvents are aspirated into the plasma, combustion of the organic compounds occurs and carbon is formed. This carbon often deposits in the injector tube of the torch or around the orifices of the sampler and skimmer cones. If chromatographic runs are prolonged, the carbon may build-up to such a degree so that the injector and cone orifices become blocked and the sensitivity of the instrument is lowered. The addition of oxygen to the nebulizer gas flow (around 10%, v/v) is one of the best ways to minimize this problem. The oxygen reacts with the carbon compounds in the plasma to form carbon dioxide and so carbon deposits may be virtually eliminated. In addition, the use of a water cooled spray chamber (0–5°C) and increased RF powers (up to 1.7 kW) help to stabilize the plasma when organic mobile phases are required for separations. The type of organic modifier used for a separation is therefore determined by its effect on the ICP. Boorn and Browner [32] discussed the effects of organic solvents in the ICP in detail. The lack of carbon deposition on the torch injector in 1 h was used as a yardstick to gauge the maximum liquid flow-rate and tolerance of the plasma for the solvent. A membrane desolvation device at the interface between the two instruments may be used to remove the organic solvent and up to 100% organic solvent removal is possible [33].

Larsen [34] has discussed the effect of organic solvents on the analytical signal in speciation studies. He states that the spray chamber and nebulizer of the sample introduction system can often be a source of error, especially when a gradient elution is used. Further, if the organic solvent is trapped or adheres to the walls of the spray chamber, a gradually changing signal enhancement effect will be observed for elements such as As, Se and other elements with high first ionization energies. The changing signal for an element such as arsenic is caused by the gradual change in concentration of organic solvent adhered inside the spray chamber [34]. The methanol is gradually washed out until the signal reaches a stable value, which takes approximately 35 min.

Similarly, the use of mobile phases with high salt contents should be avoided with ICP-MS detection as mass spectra become more complex and salt deposits build up around the cones over time, thus degrading sensitivity [3]. As a basic rule, the amount of dissolved solids in a mobile phase should be kept

to below 2% and, if this is not possible, nitric acid should be run between chromatographic runs to dissolve any salt deposits from the sample introduction system. The use of narrow bore chromatography is a means to reduce the amount of undesirable organic and salt buffers into the ICP and the number of applications using such techniques is rapidly increasing. The prolonged use of organic modifiers is known to reduce the lifetime of RF generators, therefore any means to reduce the damage that they may induce is obviously beneficial to the cost-effective analytical laboratory.

One more requirement when performing LC with ICP-MS is the ability to perform transient signal analysis. Current commercial manufacturers of ICP-MS instrumentation are now realizing that many users of these instruments couple chromatographic methods with the mass spectrometer. Instruments therefore require software that is suitable for transient signal acquisition as well as data processing software to enable integration of the chromatographic peak area for quantitative analysis. Integration software is not always available when purchasing a new instrument and separate integration programs often have to be purchased, an additional expense.

4. Liquid chromatographic techniques

The relative polarity, solubility and molecular mass of the species of interest determine the type of liquid chromatography used for a specific application. The various modes of liquid chromatography include reversed-phase, reversed-phase ion-pair, micellar, ion-exchange, size-exclusion and chiral LC. Each of the separation modes will be described in the following sections and accompanying tables are given which demonstrate the applicability of the techniques for the separation of a wide variety of compounds. A complete review of the literature has recently been published [3].

4.1. Partition chromatography

One of the most commonly used modes of LC is partition chromatography. The terms normal-phase and reversed-phase are used to describe the mobile and stationary phase polarities. When partition chromatography was developed, separations were achieved using highly polar alumina or silica stationary phases with non-polar mobile phases such as hexane. This initial method of achieving separations has been termed ‘‘normal-phase’’ LC. It was realized that similar separations could be achieved using a polar mobile phase and a relatively non-polar stationary phase, the only difference being that the elution order of the peaks changed. This method of achieving separations was termed ‘‘reversed-phase’’ LC. Obviously, the use of a non-polar mobile phase is more attractive in terms of plasma stability, waste disposal and safety so the use of reversed-phase LC is now the most popular mode of partition chromatography when ICP-MS is used as a detector.

Commonly used reversed-phase stationary phases are prepared from siloxanes where the substituent group of the siloxane is a hydrophobic hydrocarbon containing 18, eight or one carbon atom(s). These columns are normally named by the number of carbon atoms of the substituent group, e.g., $C_{18,}$ C_8 or C_1 or by the full name of the substituent group, e.g., octadecylsilane (ODS). Separation of the analytes is achieved owing to differences in their hydrophobicities. The analytes interact with the stationary phase and mobile phase to different degrees and the selectivity of the separation is controlled by adjusting the type and quantity of the modifier in the mobile phase. Methanol and acetonitrile are the most common modifiers employed, although other organic solvents may be used to control the selectivity where appropriate. Binary, tertiary or quaternary combinations of the solvents may be used to achieve the desired selectivity.

Reversed phase chromatography has been used for separating species of a wide variety of elements. Table 1 is a selection of some of the species that have been separated and quantified using this technique. The table is ordered according to the elements analyzed and the specific applications are given.

4.2. Reversed phase ion-pair chromatography

Reversed phase ion-pair chromatography (hereafter referred to as ion-pair chromatography) is a variation of reversed-phase chromatography. The technique may be used to separate both non-ionic and ionic compounds in a single run using the same

Table 1
Specific applications of reversed-phase LC with ICP-MS detection

Element(s) analyzed	Species analyzed	Sample type	Chromatography	Detector	Notes	Ref.
Cr	Cr(III) and Cr(VI)	Azo dyes (acid blue 158 and acid blue 193)	Baxter ODS 250×4.6 mm, 5 μm particle diameter Isocratic mobile phase: methanol–water (80:20, v/v) at 1 ml min^{-1}	VG PlasmaQuad II. Concentric nebulizer, double pass spray chamber 1500 W, 0.7 l min^{-1} Ar and 0.07 l min^{-1} O_2 neb. gas	m/z 53 used (abundance 9.55%) to avoid ArC^+ interference Unbound and bound Cr species determined	[64]
Cr	Cr(III) and Cr(VI)	Galvanic waste waters	LiChrospher 60 RP-select B 125×4.6 mm, 5 μm particle diameter Isocratic mobile phase: acetonitrile–water (67:33, v/v) at 0.5 ml min^{-1}	VG PlasmaQuad II+ Turbo. Hydraulic high-pressure nebulizer with desolvation unit. 1500 W, 0.85 l min^{-1} Ar and 0.08 l min^{-1} O_2 neb. gas	Different complexes with ammonium pyrrolidinedithioate formed and preconcentrated using solid-phase extraction. Detection limits at μg l^{-1} level	[65]
Se	Selenocystine Selenocystamine Selenomethionine Selenoethionine		Nucleosil 120 Å, C_{18}, 250×4.6 mm, 5 μm particle diameter. Pre-column, 30×4.6 mm I.D. Mobile phase: 30 m*M* ammonium formate, methanol–water (5:95, v/v) at 1.20 ml min^{-1}	Finnigan MAT ELEMENT double focusing ICP-MS. Hydraulic high-pressure nebulizer at 1.06 l min^{-1} neb. gas flow. 1350 W, low resolution mode	Detection limits below 0.02 ng ml^{-1} with this nebulizer system	[66]
I	Iodide ion and five iodo amino acids (monoiodotyrosine, diiodotyrosine, 3,3′,5- and 3,3′,5′-triiodothyronine and thyroxine)	Bovine thyroglobulin enzymatic digest	Shiseido C_{18} SG120 (35×4.6 mm I.D.). 5 μm diameter particles Mobile phase: 10% or 50% methanol at 1 ml min^{-1}. 25°C	Seiko SPQ-6100 ICP-MS. Meinhard concentric nebulizer and double pass spray chamber. Nebulizer gas 0.7 l min^{-1} with 0.057 O_2 fraction. 1300 W forward power	Absolute detection limits range 35–130 pg as iodine. RSD of peak area measurements less than 6% for each species	[67]
Co, Fe and Zn	Cobalt protoporphyrin, hemin, zinc protoporphyrin	Whole blood of a lead poisoned patient	Hypersil SAS C_1 250×4.6 mm I.D., 5 μm particle size Mobile phase: 68% methanol at pH 4.5	VG Elemental PQ II with double pass spray chamber (cooled to −15°C) Nitrogen added to nebulizer gas to prevent carbon deposition	Detection limits for the species in the microgram range for hemin and nanogram range for cobalt and zinc	[68]
Pt	Organoplatinum compounds (cisplatin and carboplatin)	Organoplatinum drug (JM-216)	Alltech Hypersil Phenyl 5 μm bonded silica column 250×4.6 mm with 10 mm guard column	Fisons PQ II+. Heated cyclone spray chamber used. 1.5 kW forward power	Desolvation by a cryogenic condenser and Nafion membrane used so that 100% organic mobile phase could be introduced to plasma. Absolute limit of detection was 120 pg of Pt	[33]
Te	$HTeO_4^-$ and TeO_3^{2-}	Waste water samples	Nucleosil 120-5 C_{18} column, 250×4 mm Mobile phase: 4% propanol in water, 0.1 ppm Rh at 2 ml min^{-1}	Perkin-Elmer Sciex ELAN 5000. Organic spray chamber at 1°C Neb gas 1.1 l min^{-1} argon with 0.05 l min^{-1} oxygen addition	All Te compounds converted into $HTeO_4^-$ and TeO_3^{2-}. Waste water fed to HPLC column and the Te compounds were retained	[69]

Table 2
Specific applications of reversed-phase ion-pair LC with ICP-MS detection

Element(s) analyzed	Species analyzed	Sample type	Chromatography	Detector	Notes	Ref.
As	15 different arsenic compounds	Urine after digestion of fish	Intersil ODS-2 reversed-phase, 250×4.6 mm. Mobile phase, 10 m*M* 1-butane sulfonic acid, 4 m*M* tetramethylammonium hydroxide, 4 m*M* malonic acid in water–methanol (99.95:0.05, v/v), pH 3. Flow-rate 0.75 ml min^{-1}	PMS100 Yokogawa ICP-MS. 1.3 kW with concentric nebulizer	Ghost peaks observed when chloride ion was present	[70]
As	Arsenite, arsenate, monomethylarsonic acid, dimethylarsinic acid and arsenobetaine	Dogfish muscle reference material	Various reversed-phase columns evaluated. Mobile phase: 5% methanol, pH 7, 0.005 *M* TBAH used as the ion-pairing reagents. 1 ml min^{-1} flow-rate used	Perkin-Elmer Sciex ELAN 250. Extended length torch used 1.4 kW RF power, 0.9 l min^{-1} nebulizer gas flow-rate	Anion pairing compared to anion-exchange chromatography. Anion-exchange was found to be more tolerant because of higher buffering capacity of the mobile phase	[71]
As	Arsenite, arsenate, monomethylarsonic acid, dimethylarsinic acid, arsenobetaine and arsenocholine	Spring waters and bottled mineral waters	Hamilton PRP1 resin based, reversed-phase column, 250×4.6 mm. Mobile phase: 0.5 m*M* tetrabutylammonium phosphate, pH buffered with 4 m*M* Na_2HPO_4 and adjusted to pH 9 with ammonia	VG Elemental PlasmaQuad II+ with concentric nebulizer and double pass spray chamber. Acquisition of data in both scanning and peak jump modes.	Detection limits in the range 1.0–3.0 μg l^{-1}. Good mass balance obtained with a hydride generation method for total As	[72]
As	Arsenite, arsenate, monomethylarsonic acid, dimethylarsinic acid, arsenobetaine, arsenocholine	Urine, after digestion of sea-food samples	Phenomenex μBondclone reversed-phase C_{18} column, 300×3.9 mm or Waters Bondpack C_{18} 300 mm×3.9 mm column. Various ion pairing reagent and mobile phase compositions evaluated	VG PlasmaQuad II+ with Meinhard nebulizer and cooled spray chamber (4°C)	Mixed ion-pairing reagents used (10 m*M* hexanesulfonate and 1 m*M* tetraethylammonium hydroxide. Complete separation in 12 min of all species. 70% of total arsenobetaine ingested was excreted into urine	[73]
As	As species in animal feed additives	Environmental and biological reference materials	Reversed-phase micro HPLC used. Isco Spherisorb 3 μm C_{18} material, 150×1 mm I.D. Mobile phase: 0.1% trifluoroacetic acid and 5–10% methanol in water. Tetrabutyl ammonium hydroxide (1–5 m*M*) ion-pairing reagent. Flow-rate 15–40 μl min^{-1}	VG PlasmaQuad II STE	Reversed phase chromatography minimized co-elution of species. Low flow-rates minimized waste. Limits of detection in sub pg range.	[74]
Pb	Inorganic lead, triethyllead chloride, triphenyllead chloride, tetraethyllead	Lead in reference fuel and water	Nucleosil C_{18} 5 μm (250×4.6 mm I.D.). Mobile phase: 8 m*M* PIC-B5 at pH 3. Gradient elution 40–90% methanol in water over 10 min, held at 90% methanol for 20 min. Flow-rate 1 ml min^{-1}.	VG PlasmaQuad. Forward power 1.40 kW. Nebulizer gas flow 0.68 l min^{-1} Concentric nebulizer with double pass spray chamber cooled to −10°C.	Detection limits in range 0.37–3.9 ng for the various species	[75]
Pb	Inorganic lead, trimethyllead and triethyllead		5 μm Hypersil ODS column, gradient elution of 10:90 to 30:70 methanol–buffer eluent Buffer prepared from 0.1 *M* sodium acetate, 0.1 *M* acetic acid and 4 m*M* sodium pentanesulfonate	Single pass 40 ml spray chamber and concentric nebulizer used to minimize dead volume. Isotope dilution measurements made.	Long term stability of Et_3PbCl questioned. Data acquisition made complicated by lack of suitable software	[76]
Hg	Inorganic mercury and methylmercury		Four different ODS columns evaluated. Various mobile phases evaluated all containing 10 m*M* tetrabutylammonium bromide	Perkin-Elmer Sciex Elan 5000A with a cooled double pass spray chamber and a cross flow nebulizer	The method was unsuccessful as Hg was absorbed by the ODS column, leading to a slow bleed of mercury. Use of non-stainless steel components and glass lined columns reduced these problems	[77]

Hg	Inorganic mercury, methylmercury and ethylmercury	Open ocean sea water reference material and tap water	Spherisorb ODS-2 (150×4.6 mm I.D.) column. Mobile phase: 0.5% (m/v) L-cysteine, pH 5 at flow-rate of 1.6 ml min^{-1}	Perkin-Elmer ELAN 5000. Samples introduced using in situ vapor generation	Cold vapor generation with LC–ICP-MS found to be better than conventional pneumatic nebulizer in terms of sensitivity	[78]
P and S	Anionic phosphorus and sulfur compounds	Inorganic phosphates and nucleotides	Various reversed-phase columns and ion pairing reagents used Various mobile phases also used	Perkin-Elmer Sciex ELAN 250. Forward power 1.25 kW. Laboratory-constructed torch used. Continuous flow ultrasonic nebulizer with aerosol desolvation	Detection limits in range of 0.4–4 ng for P and ~7 ng for S. The analyte sensitivity decreased as the concentration of the organic modifier increased	[79]
Se and As	13 selenium and arsenic species	Canned tuna fish and human urine	Phenomenex reversed-phase C_{18} (250×4.6 mm) with guard column 10 m*M* sulfonate and 0.1% methanol mobile phase, pH 3.5 at 1.0 ml min^{-1}	VG Elemental PQ2+ Turbo with Meinhard concentric nebulizer and cooled spray chamber (4°C)	*m/z* 75, 77 and 78 enabled simultaneous monitoring of arsenic, selenium and potential interfering species	[80]
Se	Selenoamino acids	Selenium enriched yeast	Zorbax SB-C_8 (150×4.6 mm) and guard column (12.5×4.6 mm). Mobile phase: methanol–water (98:2), 0.1% (v/v) trifluoroacetic acid	Perkin-Elmer SCIEX ELAN ICP-MS with cross flow nebulizer and double pass spray chamber	Presence of selenocystine, selenomethionine and methylselenocysteine confirmed	[81]
Se	Selenate, selenite, trimethylselenonium	Urine	Hamilton PRP-1 5 μm, 150×4.6 mm I.D. Mobile phase flow-rate 1.7 ml min^{-1}, 3% methanol, 5 m*M* tetrabutylammonium phosphate, pH 7.6	Perkin-Elmer ELAN 5000 ICP-MS with ultrasonic nebulizer. Desolvation tube temperature 110°C and condenser temperature 20°C	Detection limits in the range 22–74 pg selenium for various species	[82]
Se	Selenocystine, selenomethionine and trimethylselenonium ion	Enriched yeast, human serum and urine	Hamilton PRP1, 150×4.1 mm. Mobile phase: water–methanol (98:2) and 0.1 m*M* $C_5H_{11}SO_3^-$, pH 4.5	Perkin-Elmer SCIEX ELAN 5000 with cross flow nebulizer and Ryton double pass spray chamber.	Choice of column and solvents was found to be critical. Good reproducibility and detection limits (less than 1 μg l^{-1} for each species)	[83]
Sn	Tributyltin, triphenyltin	Waters	Kromasil-100 C_{18} column. Mobile phase: 82% (v/v) methanol, 2.5% acetic acid, 0.3% tetraethylamine and 10 mg l^{-1} oxalic acid	Perkin-Elmer ELAN 5000A with double-skinned, silvered glass spray chamber at −15°C. 1250 W forward power. Nebulizer gas flow 0.95 l min^{-1}	Preconcentration first performed on a Sep-Pak C_{18} minicolumn to obtain a detection limit of 2 ng l^{-1} for TBTCl	[84]
Sn	Trimethyl-, triphenyl- and tributyltin chlorides	Fish tissue	Silica and polymer stationary phase C_{18} columns compared Sodium pentane sulfonate ion pairing reagent	VG PQ I with 1% argon addition to the nebulizer gas flow. A cooled (−20°C) double pass spray chamber was used	Inorganic tin was held more strongly on the silica based column Extraction and recoveries were reasonable	[85]
V	V(IV) and V(V)	Water samples	Reversed phase C_8 with 3 m*M* EDTA, 0.5 m*M* tetrabutylammonium phosphate and 12% (v/v) methanol solution (pH 6.5)	Perkin-Elmer SCIEX ELAN 5000 with 1050 W RF power and 0.88 l min^{-1} nebulizer gas flow. Ultrasonic nebulizer used	Limits of detection were 0.025 and 0.041 ng ml^{-1} for V (IV) and V (V), respectively	[86]

stationary phases employed in reversed-phase chromatography (e.g., C_{18}). To achieve such separations of highly polar, multiply charged and strongly basic compounds, an ion-paring reagent is added to the traditional reversed-phase mobile phase. The ion-pairing reagent is a compound with a polar head group (such as ammonium or sulfate) and a non-polar tail (such as phenyl or pentyl). Commonly used ion-pairing reagents are tetraalkylammonium salts, triethyl alkyl ammonium salts or anions such as alkylsulfonates. This ion pairing reagent binds to the ionic analytes to form an ion-pair, which is then retained by the reversed-phase column. Again, selectivity of the column for the analytes may be adjusted by changing the mobile phase composition.

The concentration of ion-pairing reagent added to the mobile phase should typically be in the range of 0.001 to 0.005 *M*. Increasing the concentration of the ion-pairing reagent causes an increase in the capacity factor values. When selecting an appropriate ion-pairing reagent, several factors should be considered. The most important is the charge compatibility of the analyte to be separated with the counter-ion of the ion-pairing reagent. The counter-ion should be soluble in the mobile phase (care should be taken to ensure solubility when a gradient elution is used) and it should be univalent, aprotic and non-destructive to the chromatographic column.

Table 2 shows a selection of some of the species that have been separated and quantified using reversed-phase ion-pairing LC. The table is ordered according to the elements analyzed and the specific applications are also given.

4.3. Micellar chromatography

Micellar liquid chromatography is a variation of ion-pair reversed-phase chromatography where the counter-ion, present in the mobile phase, is a relatively high concentration of surfactant. The counter-ion for micellar LC must possess a long chain hydrocarbon tail. When the concentration of the counter-ion exceeds the ''critical micelle concentration'', the ions start to aggregate and form spheres with a hydrophobic center (all the hydrophobic tails point inwards) and a hydrophillic head. The hydrophilic part of the molecule is therefore in contact with the water molecules in the mobile phase. Uncharged species are attracted to the hydrophobic center and will partition between the counter-ion spheres, the mobile phase and the stationary phase, whereas charged species will partition between the stationary and mobile phase and will elute at a different rate through the column. A mixture of ionic and non-ionic compounds may be separated in this manner.

Suyani et al. [35] used the technique to separate a variety of alkyltin compounds. Trimethyltin chloride, triethyltin chloride, triethyltin bromide and tripropyltin chloride were separated on a C_{18} stationary phase using a mobile phase of 0.1 *M* sodium dodecyl sulfate (SDS). A gradient elution was initially used and detection limits were in the picogram (as tin) range. It was found that SDS concentrations should not exceed 0.1 *M* to prevent clogging of the torch and sampling cone orifice.

In a further study, the same group performed arsenic speciation of four biologically and environmentally significant arsenic species with micellar LC. The micellar mobile phase consisted of 0.05 *M* cetyltrimethylammonium bromide, 10% propanol and 0.02 *M* borate buffer, which showed good compatibility with ICP-MS. No O_2 addition to the nebulizer gas was necessary with this mobile phase. Urine samples were analyzed successfully, illustrating the potential of the technique for ''dirty samples''.

4.4. Ion-exchange chromatography

Ion exchange is a process in which the charged solute ion of an analyte flowing through a column competes with an ion in the mobile phase for sites of opposite charge on a stationary phase (functional groups). Before injection of the analyte onto the column, the mobile phase ions are paired with the functional group ions and electrical neutrality is maintained in the stationary phase. When an analyte mixture is injected onto the column, the newly introduced ions compete with the mobile phase ions at the functional group site. Separations occur when analyte ions of a particular species interact more favorably with the functional group sites and are retained longer than others. The more time an analyte spends in the stationary phase, the slower it moves through the column. Obviously such a sepa-

ration is pH dependent as the separation is based on charge interactions. The diffusion of the analytes through the column is dependent on the size and porosity of the resin beads and the viscosity of the eluent.

Packing materials in ion-exchange columns are beads commonly formed from the emulsion copolymerization crosslinking of styrene and divinylbenzene. Ionic functional groups are bonded to this rigid structure. A strong cation-exchange resin typically contains the sulfonic acid group $-SO_3H$; a weak cation-exchange resin contains the carboxylic acid group. Quaternary or primary amine groups are commonly used in anion-exchange columns.

By far the most studied element using this technique is arsenic and numerous papers have been published, describing the separation of a great number of arsenic species [36–56]. When determining the presence of arsenic in urine by ion-exchange LC–ICP-MS there are often problems from $^{40}Ar^{35}Cl^+$ (m/z 75) interfering with $^{75}As^+$. The chlorine is found in the urine owing to the presence of salts. By separating chloride from the arsenic compounds, anion-exchange chromatography may be successfully used for the sample preparation of urine samples prior to determination of arsenic by ICP-MS [34,57].

Table 3 shows the great versatility of the technique and highlights a few applications of ion-exchange chromatography for the determination of number of elements in various sample matrices. The table is not a comprehensive review of the literature, but serves to illustrate the wide applicability of ion-exchange to current analytical problems. Applications of both cation-exchange and anion-exchange are given, listed according to the elements analyzed.

Chelating ion-exchange chromatography is used for the preconcentration of samples of high ionic strength, where simple ion-exchange columns may undergo significant capacity reduction. This results in poor retention for the metals of interest and poor separation from the matrix constituents. Chelating ion-exchange is an alternative to simple ion-exchange and is dependent on the conditional stability constants between a complexing ligand and the metal of interest. The separation mechanism is significantly more selective than simple ion-exchange. In addition, the greater selectivity of the chelating ion-exchange resin means that capacity factors for divalent and trivalent ions may be far greater than those of monovalent ions. For example, separations of transition metals from alkali metals may be obtained using this technique. These separations are generally controlled by pH. The use of chelating ion-exchange as a preconcentration method in the analysis of water samples has recently been reviewed [15]. The two most commonly used chelating resins contain iminodiacetate or 8-hydroxyquinoline functional groups.

4.5. Size-exclusion chromatography

Size-exclusion chromatography is used for the separation of compounds of high molecular mass, such as proteins and polymers. The separation is achieved by differences in the physical size of the analytes. The particles in the stationary phase have a uniform network of pores into which some compounds of certain molecular size may diffuse. Molecules that are larger than the pore size are excluded and are unretained by the column. Conversely, molecules that are smaller than the pore size are retained for a longer period of time. The retention is based on the physical impedance of the analytes through the column, not by chemical interactions, so the mobile phase does not play a critical role in the separation of the species. If the chromatographic system is calibrated according to molecular mass, it is possible to approximate the molecular mass of unknown species being separated. In size-exclusion chromatography, the solvent molecules are normally the smallest molecules being eluted through the column and so the solvent peak is the last peak on the chromatogram. In other LC modes, the solvent peak elutes first and is the first peak on the chromatogram.

There have been several applications using size-exclusion chromatography coupled to ICP-MS. Many of these applications concern the analysis of large biomolecules. Table 4 highlights some of the studies that have been performed in this area. The table is ordered according to the elements analyzed.

4.6. Chiral liquid chromatography

The last decade has seen efforts to improve

Table 3
Specific applications of ion-exchange LC with ICP-MS detection

Element(s) analyzed	Species analyzed	Sample type	Chromatography	Detector	Notes	Ref.
As	As (III), As (V), dimethylarsinic acid, monomethylarsonic acid	Soil and sediment samples	Anion-exchange. Hamilton PRP-X100 anion-exchange column (250×4.6 mm). Mobile phase: $(NH_4)_2HPO_4$ 10–100 m*M*, 3% MeOH. Gradient elution at 1.0 ml min^{-1} flow-rate	VG PlasmaQuad II+. 1350 W RF power, nebulizer gas 0.80 l min^{-1}, glass concentric nebulizer and borosilicate glass double pass spray chamber (5°C)	Recoveries of up to 80% of the total arsenic content were obtained. The detection limits were in the range 1–2 mg kg^{-1} for all species. Arsenate was found in the soil and arsenite in the sediment	[45]
As	As (III), As(V), methylarsonic acid, dimethylarsinic acid, arsenobetaine	Urine	Anion-exchange. Dionex IonPac AS14 4 mm. Mobile phase: 2 m*M* tetramethylammonium hydroxide, 10 m*M* ammonium carbonate, flow-rate 1.5 ml min^{-1}	Perkin-Elmer ELAN 5000, with Meinhard concentric nebulizer and cyclone spray chamber	To avoid matrix effects, the urine samples were diluted 1:5 with water and filtered	[41]
As	As (III), As(V), dimethylarsinate, monomethylarsonate, arsenocholine and arsenobetaine	Mung bean seedlings, used as a bioindicator for arsenic contamination	Anion-exchange. Waters IC-PAK (75×4.6 mm). Mobile phase: 80% NaH_2PO_4, 20% Na_2HPO_4, pH 6 at 0.5 ml min^{-1}	VG PQII+, nebulizer flow-rate of 0.9 ml	Most of the arsenic is accumulated in the roots. A reduction of As(V) to As(III) occurs in the roots	[43]
As	Several cationic arsenic species	Seafood samples	Cation-exchange. Chrompack Ionosphere-C (100×3 mm I.D.) 100 m*M* NH_4HCO_3 adjusted to pH 10.3 with NH_4OH. Flow-rate 1 ml min^{-1}	Perkin-Elmer SCIEX ELAN 5000 with cross flow nebulizer and double pass spray chamber (20°C). Nebulizer gas flow 0.98 l min^{-1}. RF power 1300 W	An unknown arsenic species was found in all samples. The intake of inorganic arsenic via ingestion of the seafood samples did not represent a toxicological problem to humans	[36]
Br	Bromate	Drinking waters	Anion-exchange. Dionex AG 10. Mobile phase: 100 m*M* NaOH. Preconcentration also performed using this column	VG PQII. Ultrasonic nebulizer	Detection limits of 50 ppt for bromate obtained with ultrasonic nebulizer	[87]
Cr	Cr(III) and Cr(VI)	Aquatic samples	Anion-exchange. IC-Pak Cation-exchange Guard-Pak CM/D (150×3.9 mm)	VG PQII with a concentric nebulizer, Scott type spray chamber (4°C) RF power 1350 W. Neb gas flow 0.80 l min^{-1}	Separate fraction divided into species retained on cation column, anion column and those that elute in void volume	[88]
Cr	Cr(III) and Cr(VI)		Anion-exchange. IonPac-AG5 (50×4 mm). Mobile phase of HNO_3 at flow-rate of 1.2 ml min^{-1}	VG PQII+. With hydraulic high-pressure nebulization and desolvation system	Discontinuous elution in two steps by injection of 0.3 *M* HNO_3 for Cr(VI) and 1.0 *M* HNO_3 for Cr(III)	[89]
Cs, Ba, lanthanides (La to Gd) and actinides (U to Cm)		Fission products in spent nuclear fuels.	Cation-exchange. Various cation-exchange columns with isocratic elution of acidic mobile phases	Perkin-Elmer SCIEX Elan 5000 modified with glove-box installation. Cross flow nebulizer and double pass spray chamber. Platinum sampler and skimmer cones	Performance characteristics of the modified system evaluated in terms of stability, plasma conditions, sensitivity, detection limits, and interferences	[90]
Lanthanides	Spallation nuclides	Irradiated tantalum target	Cation-exchange. Dionex IonPac CS5A. Various mobile phases used with gradient elution at 1 ml min^{-1}	Finnigan MAT ELEMENT double focusing sector field. RF power 1280 W, Meinhard nebulizer and double pass spray chamber	Nucleide abundances of each lanthanide were in good agreement with theoretical values	[91]
Se	Selenomethionine, selenocystine, selenite, selenate	White clover plant sample	Anion-exchange. Merck Polyspher IC AN-2 (120×4.6 mm). Mobile phase: 6 m*M* salicylate, 3% methanol, pH 8.5 with Tris. Cation-exchange. Ionosphere-C (100×3 mm) Mobile phase: 2 m*M* pyridinium in 3% methanol at pH 2.9 with formic acid	Perkin-Elmer SCIEX Elan 5000. Cross flow nebulizer and double pass spray chamber. ^{82}Se isotope monitored	Selenate and a compound of unknown identity were present in the plant samples	[92]

Table 4
Specific applications of size-exclusion LC with ICP-MS detection

Element(s) analyzed	Species analyzed	Sample type	Chromatography	Detector	Notes	Ref.
Cd	Metallothionein-like protein	Pig kidney	Pharmacia-LK B Superose-12 column with guard column. Mobile phase flow-rate 0.75 ml min^{-1}, 0.12 *M* Tris–HCl, pH 7.5	VG Elemental PQ	Simulated gastric digestion of pig kidney performed. Majority of soluble cadmium associated with a metallothionein like protein	[93]
Cu	Protein bound Cu	Serum	Pharmacia G25 Sephadex. Eluted with deionized water	VG Elemental PlasmaQuad. 1370 W, 0.70 l min^{-1} Scott-type water cooled	SEC used to separate Cu from interfering sodium and phosphate ions. ^{63}Cu:^{65}Cu ratio measured	[94]
Cd, Co and Fe	Metalloprotein species		Pharmacia-LK B Superose-12 column with guard column. Flow-rate 0.5–1.5 ml min^{-1}. Mobile phase 0.12 *M* Tris–HCl, pH 7.5	VG Elemental PlasmaQuad. Forward RF power 1350 W, Nebulizer gas 0.75 l min^{-1}	Number of theoretical plates, peak tailing, rise time and wash-out time all measured	[95]
Cd, Cu, Pb and Zn	Phytochelatin complexes	Plant cell cultures	Knauer Eurogel GFC (300×7.5 mm) with anion-exchange scavenger column. 10 m*M* ammonium acetate, pH 7 mobile phase	VG Elemental PQ2+ with v-groove nebulizer and water cooled spray chamber	Both in vitro and in vivo experiments performed. Cu binds most strongly to phytochelatins	[96]
Pb	Lead binding protein fractions	Blood	TSK G 3000 SW column (300×7 mm). Mobile phase: 0.1 *M* Tris–HCl, pH 7.2 Flow-rate 0.5 ml min^{-1}	Perkin-Elmer SCIEX ELAN 250 with Scott type spray chamber and cross-flow nebulizer (1.0 l min^{-1})	Lead detected in various molecular mass fractions Detection limit was 0.15 μg l^{-1}	[97]
Pb	Biomolecular complexes	Wine	Pharmacia Superdex-75 HR 10/30 column 30 m*M* Tris–HCl, pH 7.2 mobile phase	Perkin-Elmer SCIEX ELAN 6000 with Ryton spray chamber and cross flow nebulizer	Dominant species, which accounted for 40–95% of lead was the dimer of a pectic polysaccharide, rhamnogalacturonan II. Other species were not identified	[98]

separations of chiral compounds. A chiral compound possesses a central carbon atom and four different constituent groups around the central atom. Owing to the fact that the orientation of the groups around the central atom may vary, several isomers (enantiomers) of the compound may exist. Separations of the enantiomers may be achieved by adding chiral additives to the mobile phase, or by using chiral stationary phases. The latter has received the most attention. Chiral stationary phases are commonly silica gel supports with the chiral agents immobilized on the surface. Several chiral stationary phases, are available and have been the subject of a review [58]. These include cyclodextrin phases, macrocyclic antibiotic phases, $\pi-\pi$ interaction phases, protein phases, cellulosic and amylosic phases and chiral crown ether phases. Chiral separations using such columns arise owing to the formation of transient diastereomeric complexes between the enantiomers and the chiral ligand of the stationary phase. Derivatization is not always necessary, depending on the specific analyte, type of column and method of detection used [58].

Mendez et al. [59] performed the speciation of D,L-selenomethionine enantiomers on a β-cyclodextrin column with on-line hydride generation ICP-MS. Pre-column derivatization was required to develop the separation using UV fluorimetric detection. In complex samples such as selenium enriched yeast, the presence of other interfering amino acids reacted with the derivatization reagents and made the determination of selenomethionine difficult. Chromatograms of the yeast samples with ICP-MS detection showed irregular baselines, making identification of the species difficult.

In a recent study, several selenoamino acids were separated on a chiral crown ether column [60]. Both UV and ICP-MS detection were compared simultaneously and it was found that ICP-MS offered improvements in sensitivity and selectivity. For the analysis of commercially available selenium supplements, it was found that the principle species in the samples were D- and L-selenomethionine along with two enantiomers of an unidentified selenoamino acid.

5. Conclusions and future directions

The use of ICP-MS as a detector for liquid chromatography is now very well established and the extensive number of publications and presentations at plasma spectroscopy conferences are testament to this. Well established LC separation modes, such as reversed-phase, ion-pair, ion-exchange, micellar and size-exclusion chromatography with ICP-MS detection, are continuing to be used to solve analytical problems. The need for toxicological information for environmental, biological and clinical samples is gaining momentum. Regulatory agencies such as the United States Environmental Protection Agency, the US Food and Drug Administration and the United Kingdom Ministry of Agriculture Fisheries and Food now realize that stating the total amount of an element in a sample is no longer sufficient and the speciation information regarding a particular element is extremely important. Methods that are now being developed will be used in forming new regulations.

The problem of species interconversion during a chromatographic run may often be identified when suitable standards are available. When they are not, alternative plasma sources may provide additional information for species identification. The use of alternative plasma techniques, such as helium reduced pressure, low power plasmas and the RF glow discharge are now being investigated as detectors for liquid chromatography. These instruments yield more molecular fragment information than the well described argon ICP, and so may be used to obtain a wealth of speciation information. Although the number of papers in this area is currently small, conference proceedings reflect the growing interest.

Sample preparation is now recognized as being an area that requires much research when speciation information is required. Methods to extract molecular species, with conditions mild enough to maintain the molecular integrity of the species are required. Microwave assisted extraction [61], solid-phase microextraction [62] and accelerated solvent extraction [63] are all being investigated for this purpose.

A few papers have recently been published where microbore and minibore LC columns were used. These columns may be more amenable for ICP-MS detection as the amount of buffer salt and organic modifier constituents in the mobile phase is reduced considerably, therefore plasma stability is not compromised. Future studies will see the increasing use of such narrow bore columns.

Finally, instrument manufacturers are now realiz-

ing that many users of ICP-MS employ the spectrometer as a chromatographic detector. This has introduced demands on the instrument software capabilities. New instruments are now being marketed with chromatographic software, capable of integrating peak-facilities that have long been available to the analyst using conventional modes of LC detection.

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