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Review

Inductively coupled plasma mass spectrometric detection for chromatography and capillary electrophoresis

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Abstract

Inductively coupled plasma mass spectrometry (ICP-MS) is now a well established detection technique for liquid chromatography, gas chromatography, supercritical fluid chromatography and capillary electrophoresis. A review of the literature with particular regard to ICP-MS as a chromatographic and capillary electrophoretic detector is presented. The various modes of chromatography and capillary electrophoresis are discussed and practical descriptions for hyphenating the techniques with the ICP mass spectrometer are given. Sample introduction systems and data acquisition methods are reviewed along with the numerous applications of ICP-MS as a chromatographic detector. In addition, alternative plasma sources, such as the atmospheric and reduced pressure helium microwave-induced plasmas for chromatographic detection are described.

Keywords: Reviews; Inductively coupled plasma mass spectrometry; Detection, LC; Detection, GC; Detection, electrophoresis; Detection, SFC

Contents

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1. Introduction

Inductively coupled plasma mass spectrometry is now recognised as a useful and powerful technique for the detection of trace elements in chromatographic eluents. The analysis of both metals and non-metals in a wide variety of samples may be achieved using this sensitive and selective method of detection. The use of inductively coupled plasma (ICP) MS as a chromatographic detector was first described in the late 1980s and, since that time, the versatility of the detector has been realised for many chromatographic applications.

Compared to other methods of detection, ICP-MS offers unique advantages, including element specificity, a wide linear dynamic range, low detection limits and the ability to perform isotope dilution analysis. The use of chromatography hyphenated with ICP-MS has been reviewed by Byrdy and Caruso [1,2] Heitkemper et al. [3] and Bloxham et al. [4] for the analysis of environmental samples. Other reviews have mentioned the use of ICP-MS for various chromatographic applications [5–13] including metal ion analysis [10], gas chromatography [7], ion chromatography [12], human nutrition and toxicology [9] and selenium in environmental matrices [11].

Many papers describing ICP-MS as a chromatographic detection method have been specifically aimed towards speciation analyses. The determination of the chemical form of an element in a sample is particularly advantageous to the analyst, especially where risk assessment is required. Direct aspiration of a liquid sample into the ICP-MS immediately atomises and ionises the elements present so that information regarding the chemical form cannot be obtained. By separating the various species using a chromatographic method and analysing these species by ICP-MS, toxic and innocuous forms of an element may be separated. The fate and mobility of certain compounds in biological and environmental systems may also be monitored, for instance for tracing the metabolism of drugs in the human body or the breakdown of organometallic compounds in aqueous systems. Reviews concerning elemental speciation are also available [14–24].

The use of various chromatographic separation methods is reviewed in this work for both multielement and elemental speciation analyses. The different chromatographic techniques reported in the literature are discussed individually and the use of capillary electrophoresis, with directly coupled ICP-MS, as a separation technique is also described. This review is intended to provide instruction and insight regarding the potential for coupling chromatography with ICP-MS. The use of other spectrometric tech-

niques such as ICP atomic emission (AES) and atomic absorption spectrometry (AAS) as chromatographic detectors are not discussed.

2. Liquid chromatography

2.1. Interfacing liquid chromatography with ICP-MS

Liquid flow-rates used in most liquid chromatography techniques are of the order of 1 ml min^{-1} which are comparable to conventional liquid flow-rates for direct aspiration of solutions into the ICP. Conventional pneumatic nebulisation with cross-flow and concentric nebulisers may, therefore, be used along with single or double-pass spray chambers. To provide a connection between the LC column outlet and the ICP-MS sample introduction system, a transfer line must be constructed. This is commonly a relatively simple task and a length of polyether ether ketone (PEEK) or PTFE inert tubing may be used. The length and inner diameter of the transfer line must be kept to a practical minimum, commonly 20–50 cm, to ensure that peak broadening is not observed.

Use of a conventional sample introduction system with pneumatic nebulisation and spray chamber are inefficient and only 1–3% of the sample entering the nebuliser is actually transported to the plasma. It is apparent that if this sample transport efficiency is increased, the sensitivity of the technique should improve and lower detection limits should be possible. Nebulisers with higher transport efficiencies have been described for LC–ICP-MS. An increase in the amount of solvent reaching the plasma results in higher reflected powers and this causes plasma instability, possibly detrimental to the RF generator. This problem may be solved by desolvating the sample aerosol before it reaches the plasma and is commonly achieved using a cooled spray chamber which serves to condense the solvent. Membrane dryers and Peltier condensers have also been utilised for this purpose [25] and are able to desolvate approximately 89% of the liquid sample when coupled to the front of the nebuliser/spray chamber arrangement [25].

Many variations of the conventional pneumatic nebuliser/spray chamber sample introduction system have been described in the literature for improved sensitivity with LC–ICP-MS. The use of hydraulic high pressure nebulisation (HHPN) has been shown to increase sensitivity for many elements when compared to conventional pneumatic nebulisation [26].

Thermospray has also been applied as an LC–ICP-MS interface [27,28] and involves forcing the chromatographic eluent through an electrically heated capillary at flow-rates of about 2 ml min^{-1}. Heating serves to desolvate the droplets before aspiration into the plasma.

An oscillating capillary nebuliser has also been shown to improve detection limits when compared to a concentric glass nebuliser [29]. The nebuliser is essentially two fused-silica capillary tubes, mounted concentrically. The nebuliser gas flows through the outer tube while the liquid sample flows through the inner tube. This nebuliser may be operated at flows as low as 1 μl min^{-1} and may be interfaced with macrobore, microbore and capillary LC columns [29].

An ultrasonic nebuliser (USN) may also improve sample transport, and efficiencies are generally in the region of 10–30%. Commercial USNs have in-built desolvation systems which remove most of the solvent. The nebuliser shows excellent improvements in sensitivity.

The direct injection nebuliser was developed by Shum et al. [30–32] specifically for LC–ICP-MS interfacing. The nebuliser is positioned inside the ICP torch and the tip is situated a few mm from the base of the plasma. Theoretically, 100% transport efficiency may be obtained and, as the nebuliser operates at very low liquid flow-rates (30–120 μl min^{-1}), plasma instability is not significant. Detection limits should theoretically be improved thirty fold at a flow-rate of 100 μl min^{-1} but, as there is no desolvation, local plasma cooling occurs and detection limits are only improved by a factor of 2.5 [33].

The effect of different spray chambers on sample transport efficiency should also be considered when optimising sample transport efficiency. Several different spray chambers have been examined by Rivas et al. [34]. Seven different single pass, double-pass and cyclone-type spray chambers were compared

when connected to a concentric nebuliser and it was found that a transport efficiency of 7.5% could be obtained with the cyclone-type spray chamber.

2.2. Reversed-phase chromatography

2.2.1. Introduction

Reversed-phase (RP) chromatography is one of the most commonly used LC techniques. It achieves the desired separation of analytes using columns where the stationary phase surface is less polar than the mobile phase.

The retention mechanism in RP-HPLC arises due to the relative hydrophobicity of the analyte. The separation selectivity is a result of interactions of the solute with the stationary and mobile phases. Adjustment of the selectivity may be achieved by altering the type and quantity of the organic modifier (solvent) in the mobile phase. Common organic modifiers include methanol and acetonitrile although other organic solvents have been selected to control retention and selectivity. These solvents may be used in binary, tertiary or quaternary combinations with water. Marked differences in separation selectivity may be observed by changing the organic solvent. However, the use of a particular organic modifier is determined according to plasma stability and instrument performance upon solvent aspiration.

The most common stationary phases used in reversed-phase chromatography are prepared from silica-based compositions, usually siloxanes, where the R group of the siloxane may be a C_{18}, C_8 or C_1 hydrophobic hydrocarbon. The C_8 and C_{18} stationary phases are normally used for the separation of relatively low molecular mass analytes and the C_1 phase may be used for the separation of larger molecules.

When performing reversed-phase separations, care should be taken to avoid pH values of greater than 7.5 as hydrolysis of the siloxane stationary phase will occur, resulting in gradual degradation of the packing material. Buffer solutions may be used to control the pH of the mobile phase when coupled to ICP-MS. Phosphate or acetate salts are common, although care must be taken to maintain a minimum level of these compounds in the mobile phase to prevent clogging of the sampler cone.

2.2.2. Environmental and general applications

Reversed-phase chromatography coupled with ICP-MS has been employed extensively for the analysis of environmental and general analytical samples.

Dauchy et al. [35] used RPLC–ICP-MS for the speciation of butyltin compounds which are used extensively in polyvinylchloride production, fungicides, bactericides, insecticides and other general applications. A 0.1% (m/v) tropolone in a methanol–water–acetic acid solution (80:14:6) was used as the mobile phase after optimization studies were performed using different solvent volume combinations. Monobutyltin (MBT), dibutyltin (DBT) and tributyltin (TBT) compounds were separated using isocratic elution with absolute detection limits of 0.24 ng, 0.24 ng and 0.15 ng (as tin), respectively. Triethyltin was added as an internal standard to improve reproducibility and analysis time, which did not exceed 11 min.

The speciation of inorganic lead (Pb^{2+}), trimethyllead (TML) chloride, triethyllead (TEL) chloride and triphenyllead (TPhL) chloride was achieved using RPLC–ICP-MS by Al-Rashdan et al. [36]. Optimum chromatographic separations were achieved using ICP-AES detection with an acetate buffer and a step gradient of 10–70% methanol. Upon coupling to the ICP-MS, however, an isocratic elution was employed, owing to plasma instability as the organic component of the mobile phase changed. An isocratic separation with a 30% methanol mobile phase was found to give the best compromise between plasma stability and chromatographic resolution (Fig. 1). A C_{18} column was used and pH effects were studied. Detection limits using ICP-MS as a detector were improved by three orders of magnitude when compared to ICP-AES detection. Isocratic RP-HPLC showed superior detection capabilities when compared to ion-pair and cation-exchange chromatography.

In the work of Bushee [37], ICP-MS was used in the reversed-phase separation of mercury compounds. The method was subsequently applied to the determination of methylmercury in an NBS SRM-50 Albacore tuna sample with good agreement between experimentally obtained and certified values. Liquid chromatography and flow injection techniques were found to be favourable in comparison to direct ICP-

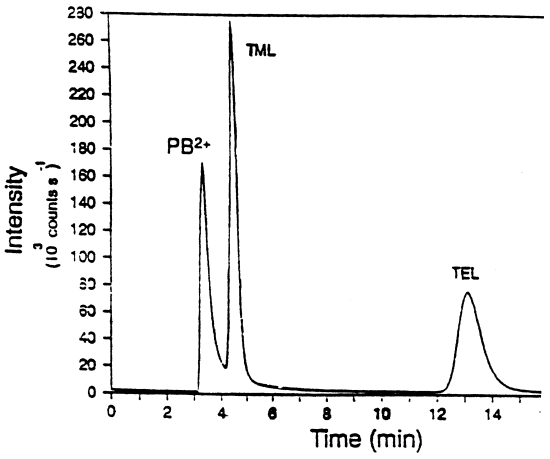

Fig. 1. LC–ICP-MS chromatogram of a standard mixture of organolead and inorganic lead compounds (Pb^{2+}, trimethyllead and triethyllead) using reversed-phase HPLC. Mobile phase, 0.1 *M* ammonium acetate and 0.1 *M* acetic acid at pH 4.6, 30% methanol. Flow-rate, 1 ml min^{-1}. Reprinted from Al-Rashdan et al. [36] by permission of Preston Publications, a division of Preston Industries.

MS because of a 'large persistent, mercury memory problem in conventional ICP-MS'.

Mercury speciation has received a great deal of attention in recent years due to environmental and toxicological effects which are dependent upon the particular form of the metal in the sample. Huang and Jiang [38] used RP-HPLC coupled to ICP-MS with ultrasonic nebulisation for the determination of methylmercury, ethylmercury and inorganic mercury. Absolute detection limits were in the range 70–160 pg of Hg which were ten times better than results achieved using conventional pneumatic nebulisation and were comparable to values obtained using cold vapour generation. The concentration of methyl mercury in NRC Dorm-1 Dogfish muscle reference sample and inorganic mercury in a waste water reference solution were determined and results were comparable to certified values with precisions less than 8% R.S.D. for all determinations.

Ebdon et al. [39] described the analysis of geoporphyrins by RPLC–ICP-MS. Geoporphyrins occur in oils, oil shales and sediments as Ni^{2+} and vanadyl (VO^{2+}) complexes and are used in oil exploration and as oil maturity indicators. Julia Creek and Serpiano nickel porphyrins were analyzed using both LC–ICP-MS and HPLC–UV–Vis. The two methods of detection showed good quantitative agreement of analytical data of the nickel porphyrin fractions. The authors state that '' . . . the system was limited for routine use by the need for high oxygen concentrations in the plasma gas''. Limits of detection were not reported therefore no indication is given regarding the best method of detection. However, the authors realised the potential for multielement, multiisotopic detection for future studies.

Tellurium speciation has been described by Klinkenberg et al. [40] using reversed-phase LC–ICP-MS for the analysis of tellurium in samples from a wastewater treatment plant. A method was developed for the separation of TeO_3^{2-} and $HTeO_4^-$ and, although at least 11 different organic Te compounds were detected, no attempt was made to identify them. This is essentially a problem with ICP detection since all structural information is lost by plasma sample decomposition.

2.2.3. Clinical applications

RPLC–ICP-MS has been used for clinical analyses by a number of workers, particularly with regard to speciation studies.

Takatera and Watanabe [41] used this technique for the speciation of iodide ion, I^-, and five iodo amino acids (monoiodotyrosine (MIT), diiodotyrosine (DIT), 3,3,5-triiodothyromine (T_3), 3,3,5′-triiodothyromine (rT_3), and thyroxine (T_4)) which are all found in thyroid hormones. The speciation of these compounds in clinical samples such as blood plasma and urine may assist in the identification of thyroid diseases. The RPLC–ICP-MS system was able to detect all of the I-containing compounds with no interferences. Detection limits were in the range 35–130 pg for the six compounds using a 50% methanol eluent. Detection limits were better for species eluted at a shorter retention time since the peak shapes were sharper. The detection limits calculated were an order of magnitude lower than for methods where UV absorbance detection was used.

Owen et al. [42] used RPLC–ICP-MS to separate Zn-containing species in an in vitro gastrointestinal digest of chicken meat that had been isocratically labeled with Zn both intrinsically and extrinsically. Single ion monitoring was used for two separate isotopes, ^{66}Zn and ^{68}Zn. Aqueous Zn eluted from C_8

and C_{18} columns connected in series, with separate peaks observed for the chicken meat (Zn associated with 3 fractions) and enzyme blanks (zinc associated with a single fraction). Data handling using time-resolved acquisition was found to be cumbersome and it was not possible to evaluate directly the net peak area. The authors recognised the need for further work to standardise the chromatographic runs with the use of a post-column internal standard. The effect of gradient elution on plasma stability was also a further problem to be addressed. Detection limits were not reported in this study.

ICP-MS was used for the detection of biologically significant metalloporphyrins separated by RP-HPLC by Kumar et al. [43]. Cobalt protoporphyrin (CoPP), iron protoporphyrin (hemin) and zinc protoporphyrin (ZnPP) were separated using a C1 column (due to the relatively large molecular mass of the compounds) and a mobile phase optimised with 68% methanol at pH 4.5 (Fig. 2). Detection limits were 0.1 ng, 5.8 μg and 4.6 ng for CoPP, hemin and ZnPP, respectively. R.S.D. values for each porphyrin were within 5%. The technique was then used to quantify zinc protoporphyrin from the blood of a lead-poisoned patient. The authors indicated that the method could be applicable to detection of metalloporphyrins in urine and other body fluid extracts.

The analysis of thimerosal (sodium ethylmercurithiosalicylate), a mercury-containing antimicrobial agent, in biological products has been described by a number of authors [29,37,44]. Bushee [37] described the speciation of several organomercury species and the subsequent identification and quantification of thimerosol using RPLC–ICP-MS. It was found that all the mercury was in the thimerosol form. The detection limits for four organomercury compounds were stated to be in the range 7–20 ng ml^{-1} Hg. A C_{18} column with 3% acetonitrile mobile phase was utilised for the separation at pH 6.8 for the methylmercury and pH 4.3 for the

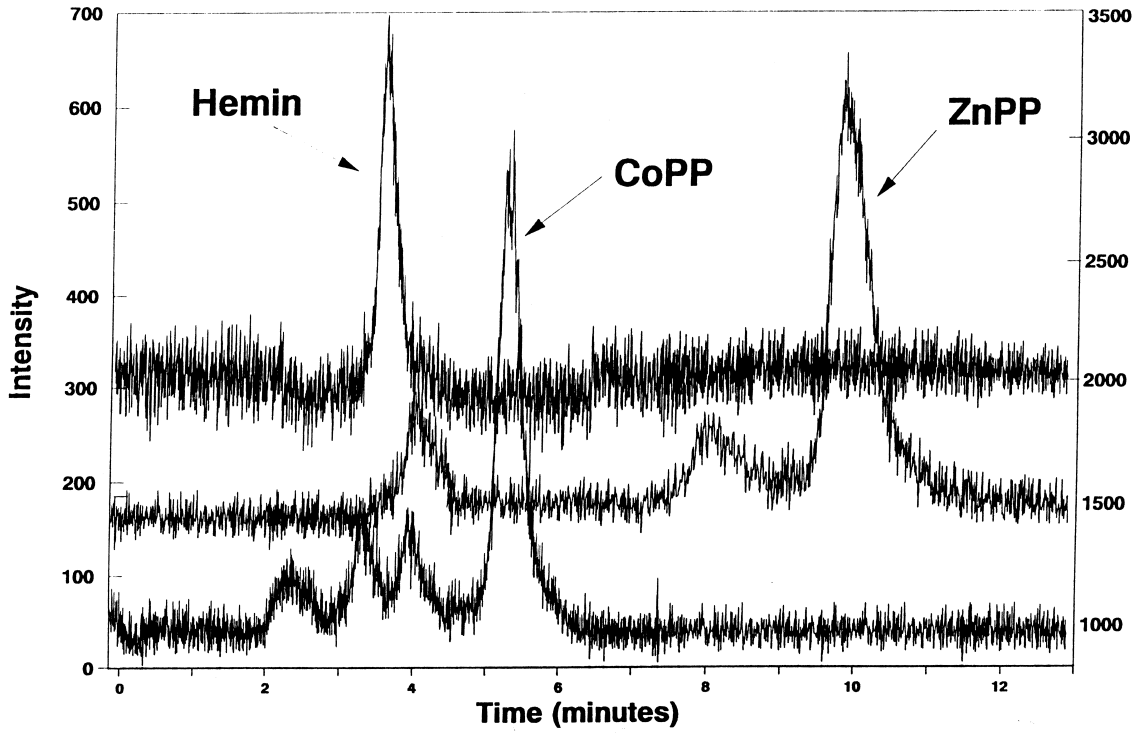

Fig. 2. Multielement chromatogram of metalloporphyrins. The intensity scale on the left corresponds to CoPP and ZnPP; the intensity scale on the right corresponds to hemin. Reprinted from Kumar et al. [43] by permission of Preston Publications, a division of Preston Industries.

thimerosol studies. In a further study, Bushee et al. [44] also determined thimerosol in injectable biological products (influenza virus vaccine and tetanus toxoid) and thimerosol decomposition products [methyl mercury chloride, dimethylmercury and mercury(III) chloride]. The group employed the same C_{18} column and mobile phase as used in the previous study [37] and flow injection was used to measure total mercury levels to confirm that all mercury species were determined by liquid chromatography. Evidence of long-term degradation of thimerosol was demonstrated.

The speciation of platinum compounds in chemotherapy drugs using RPLC–ICP-MS has been demonstrated by Cairns et al. [25]. A novel desolvation interface comprising a membrane drier and Peltier condenser situated between the chromatographic module and the ICP mass spectrometer was described. The desolvation device enabled 100% organic solvents such as methanol and acetonitrile to be used, as well as solvent gradients, with minimal baseline drifts. A new generation drug, JM-216, was shown to completely metabolise in the human body into a number of compounds. The drug was separated from its metabolites using a C_{18} column with a solvent gradient of 95:5 to 30:70 water–acetonitrile in 25 min at a flow-rate of 1 ml min^{-1}. Peak broadening was attributed to the increased dead volume of the desolvation system. Detection limits were 0.6 ng ml^{-1}, representing an actual mass of 120 pg of Pt.

A number of selenide species have been separated by RPLC–ICP-MS using an oscillating capillary nebuliser [29]. Five organoselenium compounds, phenyl-2-aminoethylselenide (PAESe), 4-hydroxyphenyl-2-aminoethylselenide (HO-PAESe), 4-fluorophenyl-2-aminoethylselenide (F-PAESe), phenyl-2-acetamidoethylselenide, *N*-acetylPAESe and (RS)α-methylphenyl-2-aminoethylselenide (RS)-MePAESe were separated using a C_{18} column. Each selenide was shown to have a different response factor. The mobile phase was optimised for organic modifier concentration, pH, ionic buffer concentration and the elution gradient. The absolute limits of detection of the selenide compounds were reported to be in the range 30–400 pg Se and were dependent on the solvent flow-rate.

The various applications of RPLC are listed alphabetically in Table 1 according to sample type. The chromatographic parameters, instruments used for detection and elements analyzed are summarised.

2.3. Ion-pair liquid chromatography

2.3.1. Introduction

A variation of reversed-phase chromatography, known as ion-pair (or paired ion) chromatography (IPC) is one of the most widely employed chromatographic techniques to be interfaced with ICP-MS.

Ion-pair chromatography may be used for the separation and determination of ionic and non-ionic species. The technique may be carried out in either normal-phase or reversed-phase modes, however only the latter mode has been used with ICP-MS detection. The stationary phase in reversed-phase IPC is a standard silanised silica packing such as that used in conventional reversed-phase chromatography, e.g. C_8 or C_{18}. The mobile phase is comprised of an aqueous buffer such as a phosphate or acetate salt, an organic modifier (commonly methanol or acetonitrile) and an ion-pairing reagent. The counter ion of the ion-pairing reagent combines with the analyte in question to form an ion-pair which is then retained by the reversed-phase column. Elution and separation of the analytes is then achieved using the aqueous solution with organic modifier. Commonly used ion-pairing reagents are long chain alkyl anions (such as tetraalkylammonium salts or triethyl C_5–C_8 alkyl ammonium salts) or cations (such as C_5–C_{10} alkylsulphonates). The concentration of ion-pairing reagent used typically varies from 0.001 to 0.005 *M*. In general, increasing the concentration of the counterion in the mobile phase causes an undesirable increase in capacity factor (k') values for reversed-phase IPC. The principle consideration when selecting a counterion for a particular separation is the charge compatibility. The counterion of the ion-pairing reagent should ideally be soluble in the mobile phase, univalent, aprotic and should be non-destructive to the chromatographic system as a whole. In addition, pH changes may affect the hydrophobic interactions governing the separation resulting in significant changes in the chromatogram. It is therefore important to buffer the aqueous phase with respect to both pH and concentration of the counterion to avoid peak tailing or multiple peaks. In

Table 1
Liquid chromatography applications

Sample	Chromatography	Detector	Elements	Limits of detection	Ref.
Blood	Reversed-phase Hypersil SAS C_1 column 68% methanol pH 4.5	VG Plasma Quad PQS 1500 W FP Column connected to cross-flow nebuliser	Co, Fe and Zn	0.1, 5.8 and 4.6 ng, respectively (as porphyrin)	[43]
Blood	TSK G 3000 SEC column with 0.1 *M* Tris HCl buffer	Perkin-Elmer SCIEX ELAN 250 1300 W FP <5 W RP Cross-flow nebuliser, Scott-type spray chamber and Sciex 'long torch'	Pb	0.15 ng ml^{-1}	[111]
Bovine thyroglobulin	Reversed-phase Shiseido C_{18} SG120 10% or 50% methanol–0.1 *M* $(NH_4)_2HPO_4$	1300 W FP <5 W RP for 10% methanol eluent 1700 W FP <5 W RP for 50% methanol eluent Meinhard nebuliser and STDP spray chamber, water-cooled	Iodine (speciation)	35–130 pg as iodine	[41]
Chemotherapy drugs	Reversed-phase In-house PEEK column packed with Hypersil Phenyl 5 μm silica Mobile Phase acetonitrile–water (25:75)	Fisons Plasma Quad 2+ 1500 W FP Membrane drier and Peltier driven condenser used as desolvation device Meinhard Nebuliser and cyclone spray chamber	Pt (speciation)	0.6 ng l^{-1} (120 pg of Pt)	[25]
Chicken tissue	PEP RPC HR reversed-phase column. Mobile phase: 5% methanol:95% 0.01 *M* orthophosphoric acid	VG PlasmaQuad 2 1300 W FP 10 W RP. Concentric glass Meinhard nebuliser. Water-cooled Scott-type spray chamber	As	Limit of quantification 25 ng g^{-1} in solid sample	[78]
Coal fly ash	Wescan Anion/R IC column. 2% propanol eluent and 50 m*M* carbonate buffer used at pH 7.5	VG Plasma Quad 2 with concentric nebuliser and double-pass Scott spray chamber at 5°C 1350 W FP <2W RP	As (speciation), V and Ni	Not reported	[74]
Coastal seawater (CASS-2), lobster hepatopancreas tissue LUTS-1, harbour sediment PACS-1	Whatman cation-exchange column 1400 W FP Thermostatted nebuliser spray chamber used for organic solvent introduction	Perkin-Elmer SCIEX ICP-MS 1200 W FP Glass concentric nebuliser and thermostatted spray chamber	Cr, Ni, Cu, Zn, Mo, Cd, Pb, V, Sr, Hg, Sn	5–12 ng for Sn speciation	[95]
Contact lens solution	Reversed-phase Waters PicoTag C_{18} 0.06 *M* ammonium acetate, 3% acetonitrile and 0.005% (v/v) 2-mercaptoethanol pH 6	VG PlasmaQuad 1.3 kW FP Turbomolecular pumps used instead of original diffusion pumps. Additional ventilation for temperature stability	Hg (speciation)	40 ng ml^{-1} (as thimerosal)	[37]
Cooked cod	Polysphere IC AN-2 column and guard column Mobile phase: 5 m*M* salicylate adjusted to pH 8.5 with TRIS	VG PlasmaQuad 2 Turbo Plus 1350 FP <1 W RP	Se (speciation)	0.008 mg kg^{-1} in dry solid	[81]
Dogfish muscle	C_{18} reversed-phase column with mobile phase 3% (v/v) methanol, 1.5% acetonitrile, 0.1% 2-mercaptoethanol containing 0.06 mol l^{-1} ammonium acetate	Elan 5000 ICP-MS 1200 W FP Ultrasonic nebuliser used with condenser temp. 0°C and desolvation tube temperature 100°C	Hg (speciation)	70–160 pg of Hg	[38]

Table 1. Continued

Sample	Chromatography	Detector	Elements	Limits of detection	Ref.
Dogfish muscle DORM-1	Benson strong anion-exchange column resin. Mobile phase: 1 m*M* K_2SO_4 for 3 min then 50 m*M* K_2SO_4 at pH 10.5	VG Plasma Quad 2 with high solids nebuliser 1500 W FP <10 W RP	As (speciation)	Not reported	[76]
Dogfish muscle DORM-1	Anion-pairing HPLC, anion-exchange HPLC and cation-pairing HPLC techniques all used. Various columns, ion pair reagents, buffers and organic modifiers used	Perkin-Elmer SCIEX ELAN 250 Shorter ICP torch used and an *x*, *y*, *z* translational stage	As (speciation)	50–300 pg of As	[46]
Dogfish muscle DORM-1	Ion-pair chromatography Pierce C_{18} column Mobile phase: 10 m*M* sodium dodecyl sulphate solution, 5% methanol and 2.5% glacial acetic acid	Perkin-Elmer SCIEX ELAN 250 1400 W FP Column directly interfaced with Teflon tubing to nebuliser	As (speciation)	0.3 ng of As	[45]
Drinking water	Dionex AG10 column and 100 m*M* eluent	Fisons PlasmaQuad 2	Br (as bromate)	0.1–0.2 ng ml^{-1}	[90]
Fish and sediment extracts	Hamilton PRP X100 anion-exchange column. Mobile phase: 10 m*M* ammonium dihydrogenphosphate and 10 m*M* diammonium monohydrogenphosphate at pH 6.5–7.5	VG Plasma Quad 2+ 1400 W FP Fassel torch, Meinhard nebuliser and Scott-type spray chamber	As (speciation)	10–30 pg As	[75]
Fly ash (SRM 1633a)	Ion-pair reversed-phase separations. Isocratic separation on Waters PicoTag C_{18} column Mobile phase 0.4 *M* HIBA, 0.02 *M* octanesulphonic acid at pH 3.8	VG Plasma Quad 1300 W FP	Lanthanides	0.4–5.0 ng ml^{-1}	[65]
Fuel (SRM 2715)	Ion-pair chromatography. Nucleosil C_{18} column. Gradient elution from 40 to 90% methanol over 10 min then isocratic elution for 20 min. Sodium pentane sulphonate mobile ion-pair reagent used. pH optimised for separation	VG Plasma Quad 1400 W FP <20 W RP SIM used at m/z 208	Pb (speciation)	0.14–3.9 ng of Pb	[56]
Harbour water sample	Ion-pair separation Perkin-Elmer C_8 column. Mobile phase 5 m*M* sodium 1-pentanesulphonate, 5% acetic acid and 50% methanol	Perkin-Elmer SCIEX ELAN 5000 1150 FP. Ultrasonic nebuliser used with condenser temp. −10°C and desolvation temp. 80°C	Sn (speciation)	2.8–16 pg Sn	[59]
Human blood	Bio-Sil TSK 250 size-exclusion column with isocratic mobile phase of 25 m*M* Tris buffer at pH 7.7	Perkin-Elmer SCIEX ELAN 250 ICP-MS 1300 W FP <5 W RP Meinhard Nebuliser and Scott-type spray chamber	Au	35 pg Au	[112]
Human serum	Ion pair chromatography Hamilton PRP1 column. Mobile phase: methanol–water (98:2) and 10^{-4} *M* $C_5H_{11}SO_3^-$ pH 4.5	Perkin-Elmer SCIEX ELAN 5000 Cross-flow nebuliser and Ryton double-pass spray chamber 1100 FP. ^{82}Se monitored	Se (organoselenium compounds)	<1 ng ml^{-1} for each species	[54]

(Continued on p. 94)

Table 1. Continued

Sample	Chromatography	Detector	Elements	Limits of detection	Ref.
Metalloprotein	Asahipak GFA-30F size-exclusion guard and analytical column Mobile phase 0.2 *M* $(NH_4)_2SO_4$, 0.05 *M* Tris-HCl and 1 m*M* EDTA	Seiko ICP-MS	Hg, Zn, Cd	Not reported	[102,108–110]
Metalloproteins in biological samples	Spherogel SW 2000 size-exclusion column and guard column Mobile phase 0.06 *M* Tris-HCl, 0.05% NaN_3	VG PlasmaQuad PQ1 1250 W FP Concentric Meinhard nebuliser and cooled double-pass spray chamber Ames torch	Cd, Zn, Ga, Y and Cu	8.75, 46, 18, 0.21 and 378 pg for Cd, Zn, Ga, Y and Cu, respectively	[104]
Methamphetamine	SAM3-125 anion-exchange column and guard column. Mobile phase: 4.4 m*M* sodium carbonate and 1.2 m*M* sodium bicarbonate	Yokogama Model PMS 100 ICP-MS 1500 W FP	Na, Pd, Ba, I and Br	4–60 ng ml^{-1}	[91]
Metalloporphyrins in coal extracts	Ion-pair chromatography. C_{18} reversed-phase column with 15% 1 m*M* tetrabutylammonium dihydrogenphosphate in methanol mobile phase	VG Plasma Quad 2 1750 FP. 25 W RP Ebdon v-groove nebuliser and cooled double-pass spray chamber. Oxygen with nebuliser gas flow	Ga	64 pg s^{-1}	[64]
Natural waters	Ion pair separation Hamilton PRP1 resin based, reversed-phase column. Mobile phase: 0.5 m*M* tetrabutylammonium phosphate (ion-pair reagent), 4 m*M* $Na_2HPO_4 \cdot 2H_2O$, adjusted to pH 9 with dilute ammonia. Methanol added to increase signal sensitivity	VG Elemental Plasma Quad Turbo 2+ 1350 W FP 1 W RP Meinhard concentric glass nebuliser and water-cooled Scott double-pass spray chamber	As (speciation)	1.0–3.0 ng ml^{-1}	[51]
Nuclear fuels	Various cation-exchange columns used for different elemental separations, along with various mobile phases. Isocratic elution in all cases	Perkin-Elmer Elan 5000 ICP-MS Modified glove box used for handling of hazardous substances	Cs, Ba, lanthanides, actinides	0.002–0.100 ng ml^{-1}	[98]
Pig kidney	Superose-12 size-exclusion column Mobile phase 0.12 *M* Tris–HCl at pH 7.5	VG PlasmaQuad	Cd (speciation)	Not reported	[107]
Proteins in human serum	SynChropak GPC 300 size-exclusion column with mobile phase 0.1 *M* Tris-HCl at pH 6.9	Perkin-Elmer Elan 250 with modified short torch 1400 W FP	Na, Cu, Fe, Zn, Pb, Ba and Cd	0.5–3 pg of metal	[32]
Sea water	Dionex MetPac CC-1 column Various eluent compositions investigated. pH 5.5	Perkin-Elmer ELAN 5000 ICP-MS 1050 W FP	Rare earths, Co, Cu, Mn, Ni, Zn, Pb and U	1–50 pg ml^{-1}	[100]
Sea water and human urine	Dowex 1-X8 resin column. Mobile phase: dilute nitric acid eluent (sea water) and acetate eluent (serum)	VG PlasmaQuad 1350 FP <5 W RP. Meinhard-type nebuliser and cooled double-pass spray chamber	As and Se	Not reported	[79]
Seafood samples	Cation-exchange column Ionosphere-C Mobile phase 20 m*M* pyridinium ion adjusted to pH 2.65 with HCO_2H ION 120 anion-exchange column with 100 m*M* NH_4HCO_3 adjusted to pH 10.3 with NH_4OH	Perkin-Elmer Sciex ELAN 5000 ICP-MS MS with cross-flow nebuliser and double-pass spray chamber. 1300 W FP	As	10–50 ng g^{-1} (dry mass)	[94]

Table 1. Continued

Sample	Chromatography	Detector	Elements	Limits of detection	Ref.
Sediment reference material PACS-1	Ion-pair separation Perkin-Elmer C_8 column. Mobile phase 5 m*M* sodium 1-pentanesulphonate, 5% acetic acid and 50% methanol	Perkin-Elmer SCIEX ELAN 5000 1150 FP. Ultrasonic nebuliser used with condenser temp. −10°C and desolvation temp. 80°C	Sn (speciation)	2.8–16 pg Sn	[59]
Soils, percolate water, sewage and human serum	Dowex 1-X8 anion-exchange resin column Mobile phase 0.0014 mol l^{-1} HNO_3	VG PlasmaQuad 2 1350 W FP <5 W RP Meinhard concentric nebuliser and water-cooled double-pass spray chamber	Cl and S	Not reported	[89]
Thimerosal	C_{18} reversed-phase column with mobile phase 3% (v/v) methanol, 1.5% acetonitrile, 0.1% 2-mercaptoethanol containing 0.06 mol l^{-1} ammonium acetate	Perkin-Elmer Elan 5000 ICP-MS 1200 W FP Ultrasonic nebuliser used with condenser temp. 0°C and desolvation tube temperature 100°C	Hg (speciation)	70–160 pg of Hg	[38]
Tuna	Reversed-phase Waters PicoTag C_{18} 0.06 *M* ammonium acetate, 3% acetonitrile and 0.005% (v/v) 2-mercaptoethanol pH 6.8	VG PlasmaQuad 1.3 kW FP Turbomolecular pumps used instead of original diffusion pumps. Additional ventilation for temperature stability	Hg (speciation)	40 ng ml^{-1} (as thimerosal)	[37]
Uranium materials	IonPac CS10 column and guard column used Linear 18 min gradient from 0.04 to 0.265 *M* HIBA used to separate lanthanides 2 *M* HNO_3, 1 *M* HCl and 0.4 *M* HIBA gradient used for actinide separation	Fisons PlasmaQuad 2+ Glove box used for handling and measuring toxic radioactive samples 1350 W FP	Lanthanides and actinides	Not reported	[99]
Urine	Ion-pair chromatography. Hamilton PRP-1 column 3% methanol, 5 m*M* tetrabutylammonium phosphate mobile phase at pH 7.6	Perkin-Elmer ELAN 5000 ICP-MS Cetac U-5000 ultrasonic nebuliser	Se	22–74 pg Se	[52]
Urine	Ion pair chromatography Hamilton PRP1 column. Mobile phase: methanol–water (98:2) and 10^{-4} *M* $C_5H_{11}SO_3^-$ pH 4.5	Perkin-Elmer SCIEX ELAN 5000 Cross-flow nebuliser and Ryton double-pass spray chamber 1100 W FP. ^{82}Se monitored	Se (organoselenium compounds)	<1 ng ml^{-1} for each species	[54]
Urine	Micellar LC separation Alltech RP metal free column and guard column. 0.05 *M* Cetyltrimethyl-ammonium bromide (CTAB) and 10% propanol mobile phase. pH 10	VG Plasma Quad PQ2+. C-1 type concentric nebuliser and double-pass spray chamber cooled to 5°C	As (speciation)	90–300 pg for various species	[68]
Urine	Anion-exchange on a weak anion-exchange column Adsorbosphere-NH_2 column. Mobile phase: 30% ethanol, 15 m*M* $NH_4H_2PO_4$ and 1.5 m*M* CH_3COONH_4 at a pH of 5.75	VG Elemental Plasma Quad. 1500 W FP and <10 W RP. Concentric nebuliser and Scott double-pass spray chamber with cooling jacket	As (speciation)	36–96 pg	[70]

(Continued on p. 96)

Table 1. Continued

Sample	Chromatography	Detector	Elements	Limits of detection	Ref.
Urine	Anion-exchange. Wescan Anion/R IC column and guard column Mobile phase of 5 m*M* phthalic acid at pH 2.7	VG Elemental Plasma Quad. 1350 W FP <5 W RP Concentric nebuliser and cooled double-pass spray chamber	As (speciation)	3.4–7.0 ng ml^{-1} for various species	[71]
Urine (human)	Ion-pair chromatography Cetac C_{18} reversed-phase packing material Various ion-pairing reagents investigated and converted to ammonium salts to avoid clogging of DIN	Perkin-Elmer SCIEX Elan 250 1400 W FP Modified SCIEX short torch and DIN used	Hg and Pb (speciation)	0.2 pg Pb and 7 pg Hg	[31]
Urine (human)	Anion-exchange: ION 120 column with 0.10 *M* NH_4HCO_3 at pH 10.3 with NH_4OH Cation-exchange: Ionosphere-C column with 0.1 *M* pyridinium ion at pH 2.65 with HCOOH	1350 W FP cross-flow nebuliser with sapphire bits. Spray chamber maintained at 20°C	As (speciation)	3–6 ng ml^{-1} for cations and 7–10 ng ml^{-1} for anions	[73]
Urine, freeze dried	Dionex CS5 mixed mode column and Dionex AS11 anion-exchange column Mobile phase: 6 m*M* 2,6-pyridinedicarboxylic acid and 8.6 m*M* LiOH at pH 6.8	VG PlasmaQuad 2 1350 WFP 1 W RP Concentric nebuliser and double-pass spray chamber	Cr (speciation)	3 pg for each species	[82]
Urine, freeze dried		VG PlasmaQuad	Cr, V, Ni	0.042 and 0.017 for Cr (III) at *m*/*z* 52 and 53, respectively 0.055 and 0.022 ng for Cr (VI) 0.031 ng for Ni	[96]
Urine, wine, club soda	Wescan Anion/R IC column Carbonate buffer mobile phase	VG Plasma Quad ICP-MS. 1350 W FP <5 W RP Type C-1 concentric nebuliser and double-pass spray chamber cooled to 5°C	As (speciation)	3–10 ng ml^{-1} for various species	[72]
Vaccines and toxoids	Reversed-phase Waters PicoTag C_{18} column Mobile phase 0.06 *M* ammonium acetate, 3% acetonitrile and 0.005% (v/v) 2-mercaptoethanol pH 5.3	VG PlasmaQuad Spray chamber cooled to 8°C. 60 cm of FEP tubing used to connect column to nebuliser	Hg	Not reported	[44]
Waste water	C_{18} reversed-phase column with mobile phase 3% (v/v) methanol, 1.5% acetonitrile, 0.1% 2-mercaptoethanol containing 0.06 mol l^{-1} ammonium acetate	Perkin-Elmer Elan 5000 ICP-MS 1200 W FP Ultrasonic nebuliser used with condenser temp. 0°C and desolvation tube temperature 100°C	Hg (speciation)	70–160 pg of Hg	[38]
Waste water treatment stream	Nucleosil 120-5 C_{18} column. 4% propanol in water, 10^{-2} *M* H_3PO_4, 0.1 ppm Rh	Perkin-Elmer Sciex ELAN 500 Meinhard-type nebuliser and DSM organic spray chamber	Te (speciation)	Not reported	[40]
Water	Ion-pair chromatography. Nucleosil C_{18} column. Gradient elution from 40 to 90% methanol over 10 min then isocratic elution for 20 min. Sodium pentane	VG Plasma Quad 1400 W FP <20 W RP SIM used at *m*/*z* 208	Pb (speciation)	0.14–3.9 ng of Pb	[56]

Table 1. Continued

Sample	Chromatography	Detector	Elements	Limits of detection	Ref.
	sulphonate mobile ion-pair reagent used. pH optimised for separation				
Water samples	Vydac 201TP C_{18} column. Mobile phase: 2% methanol, 1 m*M* tetrabutylammonium phosphate, 2 m*M* ammonium acetate at pH 5.99	Perkin-Elmer ELAN 5000 1100 FP Cross-flow pneumatic nebuliser and Scott-type spray chamber with cooling system	As (speciation)	11–51 pg ml^{-1}	[50]
Yeast	Ion pair chromatography Hamilton PRP1 column. Mobile phase: methanol–water (98:2) and 10^{-4} *M* $C_5H_{11}SO_3^-$. pH 4.5	Perkin-Elmer SCIEX ELAN 5000 Cross-flow nebuliser and Ryton double-pass spray chamber 1100 FP. ^{82}Se monitored	Se (organoselenium compounds)	<1 ng ml^{-1} for each species	[54]

reversed-phase IPC, maximum k' values are obtained at intermediate pH. At lower pH values a smaller number of ion pairs are formed in the stationary phase and sample compounds elute more quickly, thus improving peak shapes. Selectivity of a separation may be effectively controlled by varying the pH of the mobile phase.

Solvent strengths may be varied by changing the mobile phase polarity, i.e. by varying the relative concentrations of a binary organic modifier. The selectivities of the solutes for an ion-pair chromatographic technique depend on the mobile phase composition and on the organic solvent selected. Generally, as the amount of water in the mobile phase is decreased, the solvent becomes stronger and k' values decrease.

2.3.2. Environmental, clinical and general applications

IPC coupled to ICP-MS has been used by Beauchemin et al. [45,46] for the identification and quantification of arsenic species in a dogfish muscle reference material, DORM-1. A C_{18} column and a mobile phase of 10 m*M* sodium dodecylsulphate solution ion pair reagent, 5% methanol and 2.5% glacial acetic acid was used at pH 2.5 in both studies. It was found that the aspiration of organic solvents into the plasma required a slightly higher RF power to maintain the sensitivity normally acquired using aqueous arsenic solutions. The species identified were monomethylarsenic (MMA), dimethylarsinic acid (DMA), arsenobetaine (AB), arsenocholine (AC), As (III) and As (V). AB was found to be the principal As species in DORM-1 (84% of total). The detection limit reported for AB in the earlier paper [45] using LC–ICP-MS was 300 pg of As which was found to be 25 times better than that determined using ICP-AES detection.

Early studies investigating the feasibility of employing ICP-MS as a detector for HPLC were performed by Thompson and Houk [47]. IPC was successfully used to separate six As and Se species with detection limits approaching 0.1 ng of the element. The ion-pair reagents used were sodium pentanesulphonate (PIC-B5) and tetrabutylammonium phosphate (PIC-A) and methanol was employed as the organic modifier. A C_{18} type column was used. In addition, the same authors analyzed a 15 element mixture using the same IPC system and multiple ion monitoring with similar (0.1 ng) detection limits.

Shibata and Morita [48] reported a preliminary separation of arsenobetaine and cacodylate arsenic compounds using IPC–ICP-MS. An Internal ODS-2 RP column was used for the separation with tetraalkylammonium ion (TRA) as the ion-pairing reagent and a malonic acid buffer.

Arsenic is a monoisotopic element (molecular mass 75) which is known to suffer from an isobaric interference during ICP-MS analyses owing to the presence of $ArCl^+$ if chlorine is introduced to the plasma as a concomitant species. This is particularly apparent for samples such as sea water, serum and urine and the problem has been addressed by Story et al. [49] when analysing ultra trace As concentrations. These workers used hydride generation to reduce this interference (Fig. 3). The element was acidified and then reacted with sodium borohydride to form a

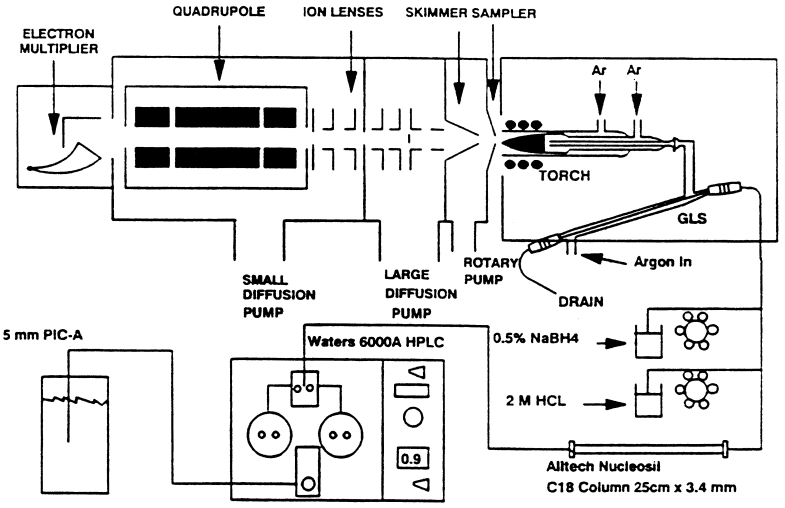

Fig. 3. Schematic diagram of a LC–ICP-MS interface with hydride generation system. Reprinted from Story et al. [49] by permission of Preston Publications, a division of Preston Industries.

volatile hydride which, in turn, was transported to the plasma more efficiently. The authors made use of a polypropylene tube as a gas liquid separator for selective transportation of the hydrides and hydrogen and removal of the argon chloride. PIC-A was used as the ion pairing agent for the reversed-phase chromatographic separation of three As species in an estuarine certified reference sample. Total As concentrations measured using the hydride generation technique fell within the certified precision values whereas values obtained using conventional pneumatic nebulisation did not. The authors concluded that the gas liquid separator eliminated the chloride interference to the point that samples did not require matrix matching.

In a similar study ionic compounds, containing arsenic, in several natural water samples were separated using IPC–HPLC [50]. The compounds separated were As(III), As(VI), dimethylarsonic acid (DMAA) and monomethylarsonic acid (MMAA). The ion-pairing reagent used was PIC-A (1 m*M*) with 2% methanol as the organic modifier and 2 m*M* ammonium acetate at pH 5.99. A post-column hydride generation system was again utilised and optimised using flow-injection analysis. Superior detection limits were obtained when compared to LC–ICP-MS with conventional nebulisation (11–51 ng l^{-1}). The total amount of arsenic present in the four species agreed with the certified values for the reference water samples analyzed.

Thomas and Sniatecki [51] also performed an analysis of trace amounts of arsenic species in natural waters using hydride generation IPC–ICP-MS. Six arsenic species were determined with detection limits in the range 1.0–3.0 $\mu g\, l^{-1}$ and total arsenic was determined using hydride generation by atomic fluorescence detection. It was found that the predominant species present in bottled mineral water samples was always As(V) with very low levels of As(III). The authors described how the system required ‘‘ . . . further work using special chromatographic software . . . to improve the quantitative measurement at a natural level.’’

Three recent papers [52–54] have used IPC–ICP-MS for the speciation of Se in environmental and clinical samples. Yang and Jiang [52] determined selenite, selenate and trimethylselenonium using a 3% methanol, 5 m*M* PIC-A mobile phase at pH 7.6 with ultrasonic nebulisation of the eluent into the ICP. Absolute detection limits for the three species were in the range 22–74 pg Se which corresponds to relative values of 0.11–0.37 ng ml^{-1}. In the analysis of urine, selenite was found to be the principle selenium species although trimethylselenonium was detected in a number of samples. The formation of several unidentified chromatographic peaks was at-

tributed to the presence of selenoamino acids. Total selenium values calculated agreed well with certified concentrations. Detection limits in the urine samples were slightly higher (0.17, 0.76 and 0.53 ng ml^{-1} for $TMSe^{+}$, Se(IV) and Se(VI), respectively) and this was attributed to an increase in background noise caused by the injection of the highly ionic urine sample.

The study by Muñoz Olivas et al. [54] has addressed the speciation of organic selenium species, in particular the separation and identification of two selenoamino acids: selenomethionine (SeMet) and selenocystine (SeCys), and the trimethylselenonium ion ($TMeSe^{+}$) (Fig. 4). The technique used was based on that presented by Jiang and Houk [55] for sulphur amino acid separation. The counter ion used was anionic (PIC-B5 was the ion-pairing reagent) so that cationic species such as $TMSe^{+}$ were retained on-column, and a methanol–water mixture was used as the mobile phase (pH 4.5). The concentration of mobile phase and ion-pairing reagent, along with the ionic strength and pH were optimised to give the best plasma stability and chromatographic separation. The method was evaluated by measuring the concentration of the various Se species in an enriched yeast sample. The total selenium concentrations (the sum of the concentrations of the various species) agreed well with the total selenium value measured using direct sample introduction into the ICP-MS system. Detection limits were calculated to be 0.20, 0.60 and 0.20 $\mu g\,l^{-1}$ (as Se) for SeCys, SeMet and TMSe, respectively. A certified serum standard and human urine sample were also analyzed using the same technique. A single peak was identified for the serum sample and was attributed to be SeCys, however the authors explained that, due to the poor retention of SeCys on column, other species may have been co-eluting and, therefore, further studies were required. As shown by previous workers [52] the chromatograms for the urine samples showed increased noise levels. Again, the main peak was attributed to SeCys. The main limitation of the system was the inability to separate both inorganic and organic species together.

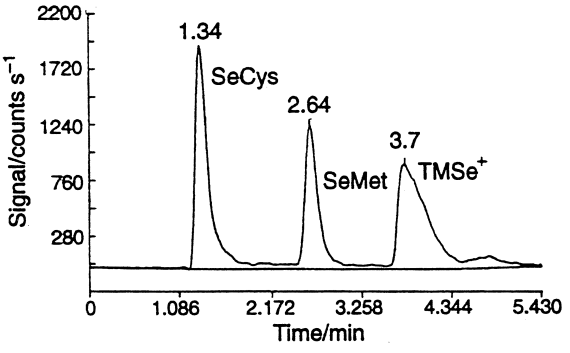

Fig. 4. Chromatogram obtained for separation of SeCys, SeMet, and $TMSe^{+}$ (100 $\mu g\,l^{-1}$ as Se) under optimum experimental conditions. Reprinted from Munoz Olivas et al. [54] by permission of The Royal Society of Chemistry.

The ability to separate a number of lead compounds by IPC–ICP-MS has received attention in recent years [31,36,56,57]. Al-Rashdan et al. [36] described the separation of inorganic lead (Pb^{2+}) and several trialkyllead species [trimethyllead (TML) chloride, triethyllead (TEL) chloride and triphenyllead (TPL) chloride]. Reversed-phase, ion-pairing and ion-exchange LC modes were compared as well as both ICP-MS and ICP-AES as detection methods. For ion-pairing studies, a C_{18} column with a methanol mobile phase was used. The ion-pairing reagent was sodium pentane sulfonate. In the reversed-phase studies, a C_{18} column was again used with an acetate buffer containing varying percentages of methanol. Cation-exchange LC was used with an acetate buffer containing methanol. For all three modes, organic modifier concentration and pH was optimised. As expected, LC with ICP-MS detection gave detection limits improved by three orders of magnitude when compared to ICP-AES. Isocratic RP-HPLC was the method of choice and was able to yield a separation of Pb^{2+} from TML whereas attempts to perform this separation using IPC were unsuccessful. Strong cation-exchange also did not give an adequate separation. A separation of the two peaks was observed using RP-HPLC but resolution was poor. An obvious answer to improve the resolution would be to use a gradient elution; however, an unstable plasma and high reflected power were obtained so only isocratic elution was feasible.

In a further study [56] the same group used IPC with a C_{18} column, methanol–water mobile phase and PIC-B5 for the separation of inorganic lead (Pb^{2+}), TEL, TPLL and tetraethyllead (TTEL). Detection limits were 0.37, 0.14, 0.17 and 3.9 ng of Pb for the four compounds, respectively. Method

evaluation was performed by calculating the TEL concentration in Standard Reference Material Lead in Fuel and inorganic lead in a water Quality Control sample from the US Environmental Protection Agency. The results obtained experimentally compared well with reference values. It was found that a post-column derivatisation method could probably be used to further increase sensitivity of the method for studies on the environmental fate of alkyllead species in the environment.

Brown et al. [57] described the development of a coupled LC isotope dilution ICP-MS method for lead speciation. Pb^{2+}, TML and TEL were separated using IPC on a C_{18} column using a mobile phase gradient of 10:90 to 30:70 methanol–buffer eluent with 0.1 mol^{-1} sodium acetate, 0.1 mol^{-1} acetic acid and 4 $mmol^{-1}$ PIC-B5 as the ion-pairing reagent. Following on from the work of Al-Rashdan [36] the principal aim of this work was to optimise the separation of Pb^{2+} from TML. The gradient elution employed affected the chromatographic baseline but, with respect to the TML and Pb^{2+} separation, the fluctuations were deemed irrelevant. An artificial rainwater sample was analyzed to assess the method accuracy with encouraging results. A lack of suitable 'customised' software for LC–isotope dilution-ICP-MS was identified as an unresolved problem, however the authors manipulated their data using a graphics package off-line.

Shum et al. [30] investigated lead and mercury speciation using ion-pair microbore column LC–ICP-MS with direct injection nebulisation. Inorganic lead, two trialkyl lead species, inorganic mercury and three organomercury species were separated using an acetonitrile–water (20:80, v/v) mobile phase with 5 m*M* ammonium pentanesulphonate ion-pairing reagent at pH 3.4. Detection limits for all the lead compounds were 0.2 pg of Pb. The detection limits were 7, 18, and 16 pg of Hg for inorganic mercury, $MeHg^{+}$ and $EtHg^{+}$, respectively. Peak areas were used in these calculations. The separation method was evaluated by measuring Pb and Hg species in human urine (NIST SRM 2670 freeze dried urine). Inorganic Pb^{2+} was retained permanently on the column (as the column was not completely end-capped) and was removed by flushing the column with EDTA. Only inorganic lead was found in the urine sample at a concentration of 10.3 $\mu g\,l^{-1}$ Pb which compared well to the certified value (10 $\mu g\,l^{-1}$). Spiked urine samples were used to evaluate the feasibility of the remaining lead compounds using this method. Similarly, no organomercury species were identified in the urine sample and the experimentally measured inorganic mercury concentration (28 $\mu g\,l^{-1}$) compared well with the certified concentration (28 $\mu g\,l^{-1}$). Again a spiked urine sample was analyzed to determine method performance for the organomercury samples. In this instance, the sensitivities for $MeHg^{+}$ and $EtHg^{+}$ were reduced by a factor of two in the urine matrix due to an easily ionisable element interference from Na which is present at a concentration of 1000 $mg\,l^{-1}$. Sensitivity for Hg^{2+} was not affected as the Na^{+} was retained by the anionic pairing reagent and so eluted after Hg^{2+}. Conversely, the tail of the Na^{+} chromatographic peak interfered with the inorganic species.

Suyani et al. [58] compared ICP-MS and ICP-AES as detection methods for organotin speciation and, in addition, evaluated the separation using both cation-exchange and ion-pair HPLC. Detection limits obtained using ICP-MS were, not surprisingly, three orders of magnitude lower than those measured using ICP-AES for trimethyltin chloride (TMT-Cl), tributyltin chloride (TBT-Cl) and triphenyltin acetate (TPhT-Ac). The linear dynamic ranges were three orders of magnitude for cation-exchange and two orders of magnitude for ion-pair HPLC, with the exception being TPhT-Ac due to poor resolution. When the two chromatographic modes were compared it was observed that ion-exchange chromatography provided better resolution but the separation time was longer. Conversely, ion-pair chromatography gave a shorter analysis time but poorer resolution.

Yang et al. [59] also studied the speciation of tin compounds using IPC–ICP-MS. Inorganic tin, trimethyltin (TMT), triethyltin (TET), tripropyltin (TPT), tributyltin (TBT) and triphenyltin (TPhT) were separated in less than 6 min using a C_8 column and a 50% methanol mobile phase with 5% acetic acid and 5 m*M* PIC-B5 added. Calculated detection limits were in the range 2.8–16 pg Sn for the various species. Various tin species in harbour sediment reference sample PACS-1 (prepared using a tropolone–benzene extraction) and in a harbour water sample were analyzed. TBT was the principal

species in the sediment sample with Sn(IV) and an unidentified species also present. The concentration of Sn as TBT obtained experimentally agreed with the certified value. TPhT and TBT were identified in the harbour water sample and recoveries approached 100% for TPT, TPhT and TBT.

Kumar et al. [60] described the effect of inorganic tin chloride on the separation of trimethyl-, tributyl- and triphenyltin chlorides using IPC–ICP-MS. Two columns, a PRP-1 and a silica-based column were investigated. For the latter, inorganic tin was held on-column and did not affect the separation unless the concentration exceeded 1 $\mu g\,g^{-1}$ inorganic tin chloride. There was less retention of inorganic tin on the PRP-1 column. A good separation between inorganic and organotin compounds was achieved at pH 6 using the PRP-1 column. Detection limits were 1.6 pg, 1.5 pg and 2.3 pg as Sn for TMT, TBT and TPhT, respectively.

The same group also used supercritical fluid extraction (SFE) to extract TBT and TPhT from biological samples in about 15 min [61]. IPC was subsequently used to separate the compounds in the extracts. Extraction temperature, pressure and modifier were optimised. The amount of sample used was reduced to 0.14 g using SFE as compared to 2.5–5.0 g. Low recoveries, however, were obtained, indicating the need for procedural modifications. Further work by Vela et al. [62] described the optimisation of cartridge size, modifier type and restrictor temperature for SFE before analysis of the same organotin compounds by IPC–ICP-MS. This analysis indicated that the extracted species varied with the type of modifier employed. Lower extraction efficiencies were obtained with 'real samples' indicating that modifications to the extraction procedure were required for further work.

Limited work has been performed in the area of chromium speciation using IPC–ICP-MS which is surprising as the element is widely distributed in the environment owing to its use in industrial applications. Jakubowski et al. [26] used IPC–ICP-MS with hydraulic high pressure nebulisation for the separation of Cr(III) and Cr(VI). A 5 μm Eurospher 100-C_{18} column was used with a mobile phase of 25% methanol, ammonium acetate and tetrabutylammonium acetate as the ion-pairing reagent. Carbon interferences, caused by the use of organic solvents, were reduced upon oxygen addition to the nebuliser gas flow and by the use of desolvation. Detection limits were 0.6 and 1.8 $ng\,ml^{-1}$ Cr for the two species, respectively, which were better than those obtained using ICP-AES detection and when nebulisers such as the DIN and USN were used.

Jiang and Houk [55] investigated the separation of anionic compounds of phosphorus and sulphur using ion-pair chromatography with ICP-MS detection. For the separation of inorganic phosphates a PRP-1 divinylbenzene co-polymer column was used with 0.005 *M* triethylammonium nitrate as the ion-pairing reagent. MeOH (2%) was used as the organic modifier at pH 6. Orthophosphate $(PO_4)^{3-}$, pyrophosphate $(P_2O_7)^{4-}$ and tripolyphosphate $(P_3O_{10})^{5-}$ were successfully separated with detection limits of 0.4, 0.6 and 1 ng P, respectively. These detection limits were superior by a factor of 200–2000 compared to the best LC–ICP-AES results reported in the literature for the same compounds. For the analysis of adenosine phosphates, the same column was used but with 0.01 *M* triethylammonium bromide as the ion-pairing reagent. The nucleotides AMP, ADP, ATP and cyclic 2,3-AMP were separated successfully although resolution was not ideal for the separation of ADP and ATP. Detection limits ranged from 0.8–4.0 ng P which, again are superior to detection limits reported using ICP-AES. This chromatographic system was also employed for the separation of sulphur containing amino acids, this time with 1% acetonitrile as an organic modifier at pH 7.5. Cysteine and methionine were successfully separated with estimated detection limits of 150 $ng\,ml^{-1}$ sulphur. Finally, inorganic sulphates were separated using a silica-based C_{18} column with 0.005 *M* PIC-A and 5% methanol at pH 7.1. It was found that sulphate and sulphite could not be separated under any conditions and the authors suggested that this could be due to sulphite converting to sulphate during the chromatographic process.

Heumann et al. [63] used isotope dilution mass spectrometry as an element specific detector for the determination of iodide and iodate in mineral water using an IPC system and a species specific spiking method. A known quantity of a ^{129}I enriched iodide and iodate spike was mixed with the sample before injection into the chromatograph. Detection limits were stated to be in the $pg\,ml^{-1}$ range although

detection limits for the specific analytes were not reported.

IPC–ICP-MS has been used by Pretorius et al. [64] for the determination of gallium porphyrins in coal extracts. As certified reference materials with accurate metalloporphyrin concentrations are not available, the technique was compared to HPLC with UV–Vis detection. Compounds were separated on a Novapak C18 column using 1 m*M* PIC-A as an ion-pair reagent and 15% methanol. The technique was applied successfully to the analysis of gallium porphyrin distributions in three coal extracts. The estimated detection limit was 64 $pg\,s^{-1}$, although peaks were rather broad.

A study carried out by Braverman [65] involved the use of IPC–ICP-MS for the separation of 14 rare earth elements. An isocratic separation on a C_{18} column was performed with a mobile phase of 0.14 *M* 2-hydroxy-2-methylpropanoic acid (HIBA) and 0.02 *M* octanesulphonic acid at pH 3.8. Detection limits were in the range 0.4–5.0 $ng\,ml^{-1}$ for the elements. The technique was used for the analysis of NIST Fly Ash. All elements except for Er, Tm, Yb and Lu exhibited good recovery. The author suggested the use of isotope dilution or an improved clean up separation stage in the analysis to improve upon this.

Zhao et al. [66] used IPC–ICP-MS with platinum specific detection to determine cisplatin (an anti-tumour drug) and its possible metabolites in the human body. The reaction products of cisplatin with various proteins and cisplatin hydrolysis products were separated using a ODS C_{18} column and 1-heptanesulphonate negatively charged ion-pairing agent. In order to retain the thiol containing Pt complexes, the pH was adjusted to 2.6. The authors concluded that, compared to conventional detection techniques, the use of ICP-MS as a detector is more efficient in terms of selectivity and sensitivity with respect to Pt species. Using heptanesulphonate, all Pt complexes were resolved and the method was applied to the determination of cisplatin and its metabolites in urine and blood samples.

The various applications of IPC listed alphabetically in Table 1 according to sample type. The chromatographic parameters, instruments used for detection and elements analyzed are summarised.

2.4. Micellar liquid chromatography

2.4.1. Introduction

Another variation on reversed-phase and ion-pair chromatography is micellar liquid chromatography (MLC) where the counter ion is a relatively high concentration of a surfactant (detergent). The counter ion in MLC possesses a long-chain hydrocarbon 'tail'. Formation of micelles occurs in aqueous solutions when the concentration of these counter ions exceeds what is known as the 'critical micelle concentration'. Around 40–100 ions aggregate, forming spherical particles with the hydrophobic tail directed towards the centre and the hydrophillic head directed towards the outside so they are in contact with water molecules. In this way a 'second phase' is created and uncharged species may be solubilised as micelles. If a sample containing compounds of varying polarity is introduced into such a system, the compounds will partition between the aqueous and hydrophobic phases and, thus, a separation may be achieved. Using such a system, both ionic and non-ionic compounds may be separated.

2.4.2. Applications

Suyani et al. [67] used micellar liquid chromatography for the speciation of alkyltin compounds [TMT-Cl, triethyltin-chloride (TET-Cl) and tripropyltin-chloride (TPT-Cl)] using a micellar mobile phase of 0.1 *M* sodium dodecylsulphate (SDS) and a C_{18} Spherisorb column. The detection limits obtained were 27, 51 and 111 pg (Sn), respectively. For the separation of monoethyltin chloride (MET-Cl), dimethyltin chloride (DMT-Cl) and TMT-Cl the concentration of the mobile phase was increased to 0.02 *M* SDS. In this instance the detection limits were 46, 26 and 126 pg (Sn), respectively. SDS is a negatively charged surfactant. The use of a positively charged or nonionic micelle mobile phase results in the elution of compounds in the void volume or irreversible absorption onto the stationary phase due to low electrostatic interactions. The authors suggested that the concentration of the surfactant should not exceed 0.1 *M* in order to avoid clogging of the torch and sampling cone orifice in the ICP-MS.

Ding et al. [68] employed micellar LC for arsenic speciation using ICP-MS detection. Dimethylarsenic

acid (DMA), monomethylarsonic acid (MMA), As(III) and As(V) were separated using a mobile phase of 0.05 *M* cetrimide (cetyltrimethylammonium bromide) as the micelle forming agent, 10% propanol and 0.02 *M* borate buffer (Fig. 5). Cetrimide was used as it exhibited favourable electrostatic interactions between the solutes and micelles. Again, the k' values decreased with increased micelle forming agent, which favoured the chromatography, but care was taken not to introduce excessive amounts of salt that would result in sample cone clogging. The detection limits for the four compounds ranged from 90–300 pg (As) and R.S.Ds. were all below 5%. The dynamic range was linear to three orders of magnitude for each of the species. Urine samples (so-called 'dirty samples') were easily analyzed with little back pressure increase and the total arsenic concentration (0.52 ± 0.02 ppm) agreed favorably with the certified value (0.48 ± 0.10 ppm).

The various applications of micellar liquid chromatography are listed alphabetically in Table 1 according to sample type. The chromatographic parameters, instruments used for detection and elements analyzed are summarised.

2.5. Ion-exchange chromatography

2.5.1. Introduction

Processes involving ion-exchange chromatography (IEC) are based upon the utilisation of exchange equilibria between charged solute ions and oppositely charged ions on the surface of a stationary phase. Solute ions and ions of equivalent charge in the mobile phase compete for the counter ion on the stationary phase and the extent of this competition determines the relative retention of the ions. A commonly used strong cation-exchange resin contains the sulphonic acid group $-SO_3H$ and a typically weak cation-exchange resin contains the carboxylic acid group $-COOH$. Anion-exchangers commonly use quaternary or primary amine groups.

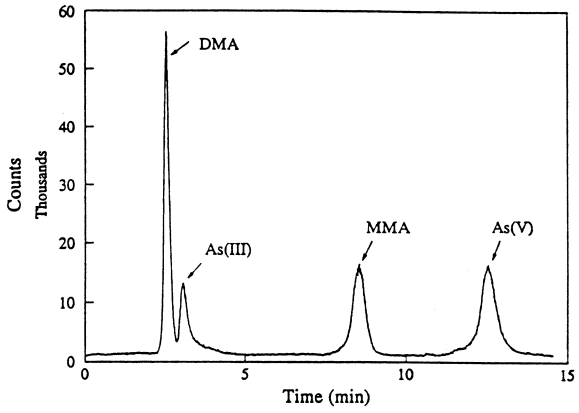

Fig. 5. Chromatogram of mixture of four arsenic standards using micellar liquid chromatography. Reprinted from Ding et al. [68] by permission of Elsevier Science.

Ion-exchange packing materials are traditionally formed from the emulsion copolymerisation of styrene and divinylbenzene, the latter polymer is used to provide cross linking and thus increase the rigidity of the beads. Ionic functional groups are chemically bonded to this backbone. Pellicular silica-based packing materials may also be used which are then coated with a synthetic ion-exchange resin but these tend to have comparatively less sample capacity.

Ion-exchange chromatography may be used to separate ionic species at a particular pH. Ion-exchange packings may also be used to separate charged species from uncharged species. Factors, other than simple coulombic interactions, may influence retention in IEC. For instance, when organic ions are injected into an IEC, hydrophobic interactions between the nonionic carbon backbone of the stationary phase and the sample cause organic ions to be retained in a manner characteristic of reversed-phase chromatography. The sample may then diffuse to the charged region of the support where an ionic interaction may occur.

The retention of a sample by a column and the resultant column efficiency is principally dependent on the rate of diffusion of the analyte through the column. The diffusion rate is dependent upon both the size and porosity of the resin beads and the viscosity of the eluent. The mean free path of an analyte through a column is increased when the resin particle diameter is reduced and also if the stationary phase resin is more porous. The combination of these diffusion mechanisms is the rate determining step in IEC.

The resolution of an ion-exchange separation may

be adjusted by optimising the ionic strength, pH, buffer concentration, organic modifier concentration, temperature and liquid flow-rate. Resolution may be improved by increasing the counter ion concentration (and thus the ionic strength) of the mobile phase so that there is more competition between the sample and counterions for the exchangeable ionic centres. The selectivity of the separation may be greatly influenced by small variations in the pH of the mobile phase. A pH change will affect the ionisation of the sample and the equilibria between the analyte buffer and stationary phase. Both ionic strength and pH gradients may be used to optimise a separation.

An increase in the column temperature may result in increased column efficiency and large changes in separation selectivity due to improved solute diffusion and mass transfer. Column efficiency may also be achieved using low flow-rates. The pH of the mobile phase for ion-exchange chromatography is most effectively controlled by the use of a buffer. The type and concentration of the buffer are of importance since the ionic strength, which determines the relative retention, affects the competition between the analyte and mobile phase ions. An organic modifier at a concentration of less than 10% may also influence the selectivity of the separation by affecting the mechanism controlling the hydrophobic interaction of the solutes with the matrix. Owing to the number of papers published in the area of IEC, anion-exchange and cation-exchange chromatography will be discussed separately. The various applications of ion-exchange liquid chromatography are listed alphabetically in Table 1 according to sample type. The chromatographic parameters, instruments used for detection and elements analyzed are summarised.

2.5.2. Applications of anion-exchange chromatography

Anion-exchange chromatography has been used extensively for arsenic speciation studies. Arsenic exists in many forms which vary in toxicity according to the following order arsenite (most toxic)> arsenate>monomethylarsonic acid (MMA>dimethylarsinic acid (DMA)>arsenobetaine (least toxic). Branch et al. [69] described preliminary results for the speciation of these five arsenic species using a column packed with Benson 7–10 μm anion-exchange resin with a 50 m*M* K_2SO_4 mobile phase at pH 10.5. The sulphate concentration was not detrimental to the cones and the plasma was found to be stable for up to 4 h.

A number of workers have investigated the speciation of As in urine using this technique [70–73]. Heitkemper et al. [70] separated As(III), As(V), DMA and MMA using a weak custom made anion-exchange column with Adsorbosphere-NH_2 packing. A guard column dry packed with a pellicular amino packing was used along with a presaturation column. Initial studies using ICP-AES as a detector used a buffered mobile phase of 30% methanol, 50 m*M* ammonium dihydrogen phosphate and 5 m*M* ammonium acetate was used with good results. However, when ICP-MS was used as the detector, clogging of the sampling cone and rapid erosion occurred due to the high buffer concentration. A mobile phase of 30% methanol, 15 m*M* ammonium dihydrogen phosphate and 2 m*M* ammonium carbonate at pH 5.75 was finally used. In order to achieve a satisfactory separation of MMA and As(V), a flow-rate change was programmed. Absolute detection limits ranged from 20 to 91 pg As in aqueous media. The method was subsequently applied for the analysis of urine. Standard additions were used to determine the four species in two freeze dried urine standards. Detection limits in the real samples were found to be slightly higher (36–96 pg). The R.S.Ds. for each species was found to be less than 10%. Chloride interference ($^{40}Ar^{35}Cl$) resulted in an interfering peak which complicated the determination of As (III).

In a subsequent paper [71], the same research group discussed overcoming the ArCl interference which was detrimental in the former study. A Wescan anion-exchange column was used with a mobile phase of aqueous phthalic acid. The authors explained that the concentration of sodium chloride in urine is about 0.15 *M* and that normal levels of As are in the region of 100 ppb. Thus, chloride concentrations are five orders of magnitude higher than any As species and the potential $AsCl^+$ interference may be substantial. The anion-exchange column was used to chromatographically separate Cl^- from arsenic. A high dilution of the urine samples was used so that column overloading did not occur. Drawbacks to this procedure include an increase in

detection limits (3.4–7 ppb) due to the dilution factor and an incomplete separation between DMA and MMA.

The next study by this group [72] extended the chloride removal technique for the separation of four As species (As(III), As(V), DMA and MMA) (Fig. 6). A Wescan Anion IC column was again employed with a 2% propanol, 50 m*M* carbonate mobile phase at pH 7.5. Urine samples and spiked beverage samples were analyzed. The authors investigated the potential of using a He–Ar mixed gas plasma to reduce detection limits. This alternative ionisation source improved detection limits but also intensified the $ArCl^+$ interfering signal. Chromatographic methods were again used to eliminate the argon chloride interference. It was found that arsenite oxidised to arsenate in urine samples at high concentrations, but this problem was overcome by diluting one part urine with four parts water. The ClO^+ ion was monitored and it was found that the chloride eluted 100 s after the last analyte peak. Cation-exchange chromatography was also used in this study to separate four arsenic cationic species: arsenobetaine (AB), trimethylarsine oxide (TMAO), arsenocholine (AsC) and tetramethylarsonium ion (TMAs). An ionosphere column was used in this instance with a pyridinium ion (0.1 *M*) mobile phase. Detection

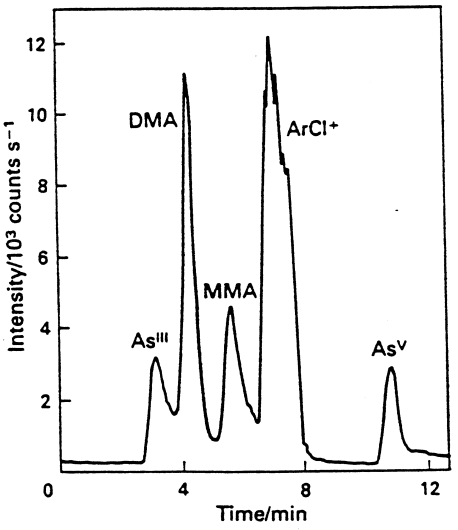

Fig. 6. Separation of four As species and chloride by ion chromatography with ICP-MS detection. Reprinted from Sheppard et al. [72].

limits for the anions in the urine sample were 7–10 ng ml^{-1} and 3–6 ng ml^{-1} for the cations with the recovery of all arsenic species in urine approaching 100%.

Wang et al. [74] reported the conversion of As(III) to As (V), especially at low pH, during the speciation of arsenic in coal fly ash. The authors suggested that oxidation may be attributed to harsh sample preparation techniques or by co-existing high oxidation state elements in the solution extraction procedures. Oxidation was not attributed to the presence of atmospheric oxygen from air entrainment.

Demesmay et al. [75] used anion-exchange chromatography, again for speciation of six arsenic species. Three anionic species (DMA, MMA and As (V)), nonionic As (III), a cationic species (AC) and a zwitterion (AB) were separated using a 2% acetonitrile mobile phase and a Hamilton PRP X100 anion-exchange column at pH 6.5. Detection limits ranged from 10 to 30 pg As and both R.S.Ds. and linearity were good. The method was extended for the analysis of As species in a fish extract. No significant interference effects were noted for the presence of chloride in the fish sample and this was attributed to the organic solvent having a masking effect.

Six different fish samples were analyzed for As species by Branch et al. [76]. Five species were separated [AB, DMA, As(III), MMA and As(V)] using a Benson strong anion-exchange resin. The predominant arsenic compound was found to be AB which is non-toxic. Arsenic levels were in the range 1.0 mg kg^{-1} dry mass in mackerel to 187 mg kg^{-1} dry mass in plaice. Nitrogen addition was used to remove $ArCl^+$ interference at m/z 75.

Chen et al. [77] studied metabolites of dimethylarsinic acid in the urine of rats exposed to DMA in drinking water. Anion-exchange chromatography was used to monitor the increased concentrations of arsenite, DMA, trimethylarsine oxide and an unidentified compound in the urine. Results showed that DMA was demethylated to inorganic As which is achieved by the action of intestinal bacteria.

Analysis of the growth promoter 4-hydroxy-3-nitrophenylarsonic acid (roxarsone) has been investigated by Dean et al. [78]. Tissue, sampled from chickens with a roxarsone supplemented diet was digested using a trypsin enzymolysis technique. Anion-exchange chromatography was used to per-

form bulk matrix separation and three anion-exchange columns were used in series. The anionic roxarsone was retained whereas, at the particular pH, non-ionic and cationic species had no affinity for the columns. The roxarsone concentration was then determined by reversed-phase HPLC with a 5% methanol mobile phase and 0.01 *M* orthophosphoric acid. The limit of quantification was 25 ng of roxarsone per gram of muscle tissue. The authors found that no roxarsone was detected in muscle tissue from chickens fed with the growth promoter following a seven day withdrawal period.

Goossens et al. [79] described an anion-exchange separation method for the determination of As and Se with ICP-MS detection. A Dowex-IX8 anion-exchange column was used to separate As and Se in nitrate form from Cl^-. The As and Se species were eluted with 0.03 mol l^{-1} HNO_3 whereas Cl^- was retained. In this way the $ArCl^+$ interference was eliminated. The method was applied to the determination of As and Se in sea-water, human serum and human urine samples. For the latter sample, dilute acetic acid was used instead of nitric acid as the eluent. As and Se results compared well with certified values whereas, for the human serum sample, experimental concentrations did not fall within the certified range.

Shum and Houk [32] described the use of a direct injection nebuliser (DIN) for use with packed micro-columns for anion-exchange chromatography coupled to ICP-MS. A 5 μm anion-exchange resin with a mobile phase of 5 m*M* NH_4HCO_3 and 5 m*M* $(NH_4)_2CO_3$ was used for the separation of SeO_3^{2-} [Se(IV)] and SeO_4^{2-} [Se(VI)]. Calculated detection limits were 14 and 15 pg of Se for Se(IV) and Se(VI), respectively. The isotopes ^{74}Se and ^{78}Se were monitored during the chromatographic separation. The detection limits were an order of magnitude better than those obtained using a traditional pneumatic nebuliser. Isotope ratios were calculated using the area under the chromatographic peak for each isotope. The R.S.Ds. obtained improved when the amount of sample injected was increased.

The application of anion-exchange chromatography for the speciation of Se has been well documented in the literature. Cai et al. [80] performed on-line preconcentration of Se(IV) and Se(VI) in aqueous matrices followed by IPC or anion-exchange chromatography and ICP-MS detection. It was found that detection limits and background levels were superior for the anion-exchange chromatography compared to IPC. A preconcentration column was coupled on-line with the anion-exchange system and used in the analysis of spiked water matrices. Detection limits obtained using the preconcentration method were in the range 0.16–0.42 and 0.08–0.19 ng ml^{-1} of Se for selenite and selenate, respectively. These detection limits were improved by two orders of magnitude when compared to those obtained without the preconcentration step.

Crews et al. [81] investigated the speciation of Se in in vitro gastrointestinal extracts of cooked cod using anion-exchange HPLC–ICP-MS. Four Se standards were measured, selenomethionine, selenocystine, sodium selenite and sodium selenate, along with a gastrointestinal extract. A Polysphere IC AN-2 column was used with a 5 m*M* salicylate mobile phase at pH 8.5. The ^{82}Se isotope was used throughout the study. 12% of total Se measured in the cooked cod was found to be in the form of selenite. The remaining Se did not correspond to any of the Se standards measured but was believed to be an organoselenium compound.

Chromium speciation has been the subject of several recent chromatographic studies where ICP-MS was used as a detector. Chromium(III) is an essential metal that must be incorporated into the diet to aid in the metabolism of insulin and other biological systems. Conversely, chromium(VI) is highly toxic in the human body and has the ability to traverse biological membranes. Exposure to Cr(VI) may result in dermal reaction. The speciation of chromium, is, therefore, essential to gauge if toxic or nontoxic forms of the metal are prevalent in a sample.

Zoorob et al. [82] used a direct injection nebuliser and anion-exchange LC–ICP-MS for chromium speciation (Fig. 7). A Dionex ASII microbore column was used with a mobile phase of 6 m*M* 2,6-pyridine dicarboxylic acid (PDCA) and 8.6 m*M* lithium hydroxide at pH 6.8. Chromium(III) was pre-complexed with PDCA by warming for 2 h at 65°C until the colour changed from pink to purple indicating formation of $Cr(PDCA)_2$. Chromium(VI) did not require complexing. Detection limits were calculated to be 3 pg Cr. The technique was success-

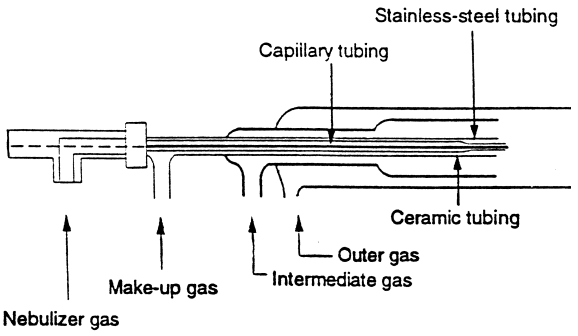

Fig. 7. Schematic diagram of a direct injection nebulizer. Reprinted from Zoorob et al. [82] with permission of the Royal Society of Chemistry.

fully used for the analysis of chromium species in a freeze dried urine certified reference material.

In another study, Byrdy et al. [83] also performed chromium speciation by anion-exchange HPLC using ICP-AES detection for preliminary studies and ICP-MS for final work. Again Cr(III) and Cr(VI) were separated, this time using an EDTA chelation procedure to stabilise Cr(III), an ammonium sulphate-ammonium hydroxide mobile phase and an IonPac AS7 mixed mode column and guard column. A high SO^+ polyatomic interference was observed, therefore the more abundant m/z 53 isotope was monitored instead of the m/z 52 isotope. This served to reduce the mobile phase background, however it should be noted that m/z 52 may be monitored to avoid possible chloride interference at m/z 53. The absolute detection limits were 40 pg for Cr(III) and 100 pg for Cr(VI) in aqueous standards, based on peak height calculations. The linear dynamic range extended to approximately three orders of magnitude for both species. A certified water sample reference material was analyzed for the presence of Cr(III) and the species was detected at the 20 $\mu g\,l^{-1}$ level. The use of gradient elution to reduce the duration of chromatographic runs was identified as a region for future studies.

Inoue et al. [84] also used EDTA chelation to stabilize Cr(III) prior to separation by anion-exchange chromatography and detection by ICP-MS at m/z 52 and 53. No $ArCl^+$ and ClO^+ interferences were observed and detection limits were $8.1\cdot10^{-5}$ and $8.8\cdot10^{-5}$ $\mu g\,ml^{-1}$ of Cr for Cr(III) and Cr(VI), respectively, with a linear dynamic range of four orders of magnitude.

Pantsar-Kallio and Manninen [85] optimised a unique coupled cation- and anion-exchange chromatographic system for Cr speciation. The need for Cr(III) species conversion by oxidation was eliminated by the use of dilute nitric acid eluents. Detection limits using the system were 0.3 $\mu g\,l^{-1}$ for Cr(III) and 0.8 $\mu g\,l^{-1}$ for Cr(VI) in lake water samples.

Roehl and Alforque [86] developed a method for the determination of hexavalent chromium in aqueous samples by isocratic anion-exchange-HPLC. A Dionex AS4A anion-exchange column was used with a 6 m*M* $(NH_4)_2SO_4$ mobile phase at pH 9. Detection limits and linear dynamic ranges compared well to an existing method of detection comprising a post-column reactor and colorimetric diphenylcarbohydrazide complex. Arar et al. [87] also determined the isotopic composition of hexavalent chromium in wastewater sludge incinerator emission.

Ding et al. [88] used anion-exchange chromatography–ICP-MS to determine different forms of chromium in chromium picolinate products which are used as dietary supplements and appear to assist in weight loss. A Dionex AS7 anion-exchange column was used to separate Cr(III)–EDTA chelate and Cr(VI) in the supplements. Only 1% total chromium recoveries were obtained and this was attributed to retention of the chromium species on-column. The use of RP-HPLC proved to be more effective and complete chromium recoveries were obtained, based on the amounts stated on the manufacturer's product labels.

Tomlinson and Caruso [28] also performed the speciation of Cr(III) and (VI) using a Dionex AS-11 anion-exchange microbore column and 6 m*M* 2,6-PDCA–8.6 m*M* lithium hydroxide mobile phase. A thermospray source was used as the interface between LC and ICP-MS. Absolute limits of detection were at the pg level for both species using this instrument assembly.

Goossens and Dams [89] developed a method to separate chlorine and sulphur interferents from V, Cr, Cu, Zn, As and Se in various samples using a Dionex-1 anion-exchange column and dilute nitric acid eluent. The analytes were collected in the eluent whereas Cl^-, ClO_4^-, SO_4^{2-} and SO_3^{2-} interferents

were retained on the column in the NO_3^- form. This procedure illustrates a method for the simultaneous separation of cations and anions from S and Cl.

The determination of bromate in drinking water by anion-exchange LC–ICP-MS was described by Creed et al. [90]. Bromate is a carcinogenic agent and is found in drinking water owing to the oxidation of bromide by ozone. A Dionex AG10 column and 100 m*M* NaOH mobile phase was found to be suitable for the determination of bromate in a 1000 ppm chloride matrix. In addition, sulphate and nitrate, which are the principle anions found in drinking water, did not interfere with ICP-MS detection. Excellent recoveries were obtained in the presence of high concentrations of chloride, nitrate and sulphate with R.S.Ds. of less than 6%. Preconcentration of samples was attempted and yielded detection limits in the 0.1–0.2 $\mu g\,l^{-1}$ range. With an ultrasonic nebuliser the detection limit was 50 $ng\,l^{-1}$ for bromate but the precision of samples was degraded due to an adjacent peak interference.

A species specific spiking method has been demonstrated by Heumann et al. [63] for the determination of iodide and iodate in mineral water using anion-exchange ion chromatography. An exact known quantity of an ^{129}I enriched iodide and iodate spike was mixed with the sample before separation. Iodate concentrations were determined in the range of 0.5–20 $ng\,ml^{-1}$ and for iodide in the range 0.1–5 $ng\,ml^{-1}$. For the analysis of two mineral water samples, the sum of the two inorganic iodine species was comparable to the total iodine concentrations. In a third sample, a third peak was identified and attributed to an organo-iodine species.

A number of inorganic impurities was identified in the analysis of methamphetamine by anion-exchange–ICP-MS [91]. A SAM3-125 anion-exchange column was used with a 4.4 m*M* sodium carbonate and 1.2 m*M* sodium bicarbonate mobile phase. The 21 elements (including metals and non-metals) were identified and separated. The authors identified the potential of this technique for the discrimination of various methamphetamines by inorganic elements in forensic studies.

Jiang et al. [92] separated metal oxide ions of titanium, molybdenum and uranium from singly charged metal species. Diatomic oxide ions, MO^+ cause overlap interferences in ICP-MS at m/z 16–18 units above M^+ and are particularly problematic for elements such as tungsten and the rare earth elements which have a high tendency to form these species in plasmas. The authors used an anion-exchange column to retain interfering molybdenum, titanium and uranium complexes while copper, zinc and cadmium were eluted rapidly. The complexes were readily washed from the column. This technique may potentially be used to separate various other interfering elements such as Sn, W, Hf or Zr.

Anion-exchange chromatography with ICP-MS detection has been used for the determination of gold drug metabolites and related metals in human blood [93]. Gold-based drugs are often used in the treatment of rheumatoid arthritis but metabolism of the drugs in the human body and their action upon the disease is not completely understood. A weak anion-exchange column was used with a mobile phase linear gradient starting with 20 m*M* aqueous Tris buffer at pH 6.5. Human blood serum was analyzed for Au, Zn and Cu. Three Zn species, two Au species and at least four Cu containing species were identified. The chromatographic retention times were not consistent from patient to patient, and, therefore identification of the species was difficult.

2.5.3. Applications of cation-exchange chromatography

Arsenic speciation was perfomed in a rigorous study by Larsen et al. [94] for the analysis of several seafood sample extracts. Several arsenicals were detected with an Ionosphere cation-exchange column using the trimethylselenonium ion as an internal chromatographic standard and a mobile phase of 20 m*M* pyridinium ion, adjusted to pH 2.65 with acetic acid. The cationic compounds AsC, TMA, trimethylarsine oxide, two unknown cationic substances and inorganic As were detected and quantified at low levels. The concentration of each species (as arsenic) relative to total arsenic was 19–98% (arsenobetaine), 0–0.6% (arsenocholine and trimethylarsonium ion) in the seafood samples. The first unknown cationic species was present at 3.1–18% in shell fish and lobster and the second was present at 0.2–6.4% in all the samples. The concentration of arsenite and arsenate was 0–1.4%, dimethylarsinate constituted 8.2–29% whereas 0.3% monomethylarsonate was detected in oyster tissue. It

was concluded that the concentration of toxic arsenic species in the samples was low, and, therefore, tolerable in the human diet according to levels set by the World Health Organisation.

Suyani et al. [58] employed ICP-MS as a detector for the speciation of organotin compounds by both cation-exchange and IPC. TMT-Cl, TBT-Cl and TPhT-Cl were separated using a Spherisorb ODS-2 C_{18} column for IPC and an Adsorbosphere SCX column for cation-exchange LC studies. It was found that ion-exchange chromatography gave a linear dynamic range of over three orders of magnitude while IPC was two orders of magnitude due to poor resolution.

In the work of McLaren et al. [95] butyltin species in the certified reference harbour sediment, PACS-1 were separated by cation-exchange. TBT and DBT species were speciated with a Whatman SCX column and a step gradient elution of 0.3 *M* ammonium acetate in 60:40 methanol:water in which the pH was altered from 6 to 3 after 1 min elution. The limits of detection reported for TBT and DBT in sediment samples were 5 ng g^{-1} and 12 ng g^{-1}, respectively.

Tomlinson, Wang and Caruso [96] used an Alltech Adsorbosphere cation-exchange column for the speciation of vanadium (IV) and (V) with ICP-MS detection. Single ion monitoring at m/z 51 was used and the mobile phase consisted of 7 m*M* 2,6-pyridine carboxylic acid and 9.6 m*M* lithium hydroxide at pH 4.0. Absolute detection limits were 0.024 ng and 0.114 ng for vanadium(V) and (IV), respectively. Other metals, nickel(II), chromium(III) and chromium(VI) were separated using the same column but with a slight modification to the mobile phase. Detection limits for chromium(III) at m/z 52 and 53, respectively, were 0.042 and 0.017 ng whereas for chromium(VI) the detection limits were 0.055 and 0.022 ng for the same masses. The limit of detection for nickel was 0.031 ng.

Trace amounts of rare earth elements that exist as impurities in other materials have also been analyzed using cation-exchange HPLC [97]. Ion chromatography was used to separate 14 rare earth elements and to eliminate interferences from polyatomic ions upon direct introduction of the eluent into the HPLC system (Fig. 8). The detection limits of the elements were in the range 1–5 pg ml^{-1} in solution and ng g^{-1} in the solid. The linear range extended to six orders of magnitude from 10 pg ml^{-1} to 10 μg ml^{-1}. R.S.Ds. were also favourable (±1% for Lu).

Fission products and actinides in spent nuclear fuels have also been analyzed using cation-exchange LC [98]. Chromatography was essential in order to separate fission Cs from Ba for the analysis of the lanthanides and to eliminate isobaric interferences in the separation of the actinides. Separation of fission

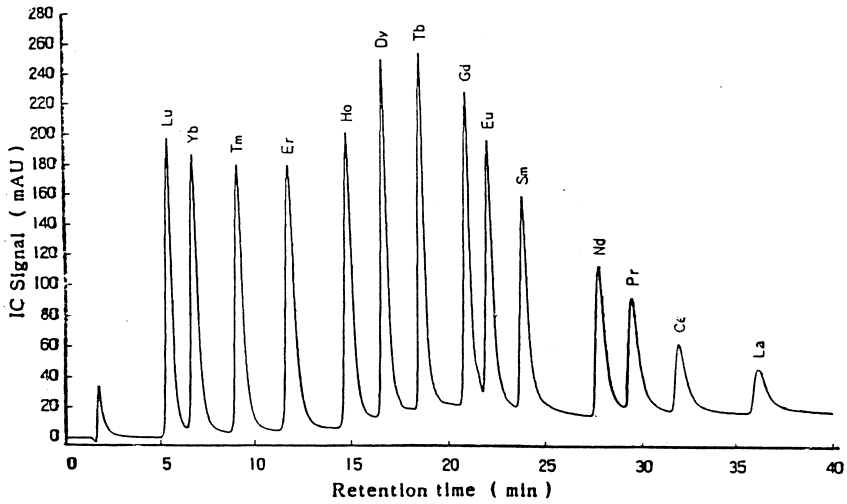

Fig. 8. Chromatograms of rare earth elements using ion chromatography, each 5 μg ml^{-1}. Reprinted from Kawabata et al. [97] by permission of the American Chemical Society.

Cs and Ba was achieved using a Dionex CS3 column with 1 *M* nitric acid as an eluent in about 10 min. The sample, which contained fission Cs of a different isotopic composition to natural Cs, was an acidified leachate from spent nuclear fuel. The separation of the lanthanides was achieved using 0.1 *M* oxalic acid in 0.19 *M* LiOH with a Dionex CS5 mixed bed column. The lanthanides were found to elute in order of increasing atomic number. Röllin et al. [99] recently published a study for the determination of fission product isotopes in irradiated nuclear fuels using the same technique. High U and Pu concentrations in such samples are known to suppress the signals of trace elements and this study offers a method for the measurement of Nd, when high concentrations of U and Pu are present and, similarly, a method of eliminating isobaric overlaps by separating U, Am and Pu. An IonPac CS10 analytical column was used for these separations with 1 *M* HCl as an eluent. Separation of the lanthanides was achieved using an 18 min gradient from 0.04 to 0.26 *M* HIBA. The method proved to yield a very reliable and efficient separation, comparable to standard techniques for the calculation of the burn-up of a nuclear fuel.

Cation-exchange chromatography has been used to determine 20 elements including the rare earths and Co, Cu, Mn, Ni, Zn, Pb and U with ICP-MS at ultra-trace levels [100]. Multielement standards were used for calibration of the analytical system in order to increase sample throughput. The detection limits for the elements were in the range 1–50 pg ml^{-1}.

2.6. Size-exclusion chromatography

2.6.1. Introduction

Size-exclusion chromatography (SEC) is a separation method where the retention of a solute depends on molecular size. In addition, the retention of a particular compound may be controlled by molecular interactions between the solute and the mobile and stationary phases. If the solute has an equivalent affinity for both phases, then the selectivity and retention of the system will only be dependent upon the physical characteristics of the stationary phase, such as pore size distribution. If the chromatographic system is suitably calibrated it also may be possible to identify the approximate molecular masses of the particular components being separated.

In SEC, smaller molecules are able to sample a larger effective pore volume compared to bigger solute molecules. Larger particles of higher molecular mass therefore spend relatively less time in the stationary phase pores and so are eluted before the smaller particles. Solvent molecules are normally the smallest molecules in the eluent system and are thus eluted last at a retention time known as the 'dead-time', t_0. This is in contrast to the liquid chromatographic methods described previously where the components are eluted after the t_0 peak.

Size-exclusion chromatography has a number of advantages over other LC methods. First, samples of unknown molecular mass are known to elute before t_o and so the end of a chromatographic run may be predicted. Second, the retention time of an unknown compound is predictable in a calibrated chromatographic system. Third, SEC is a 'gentle' method of chromatographic separation and does not normally result in sample analyte loss or on-column reactions.

Conversely, SEC has a number of disadvantages associated with the technique. The separation is determined upon molecular size; therefore, the whole separation must be eluted within the excluded volume and the dead volume. To obtain an adequate separation, the peaks must be sufficiently narrow as the column exhibits limited peak capacity. For a complex multicomponent system, complete resolution of the peaks is normally not achieved. A further disadvantage is that the method is only applicable to certain samples that are not of similar size and do not absorb onto the column packing materials.

SEC has been used frequently to separate and identify biological macromolecules using hydrophillic column packings and aqueous mobile phases. In addition, hydrophillic packings and organic mobile phases have been used to separate small organic molecules and to obtain the molecular mass distribution of some polymers.

2.6.2. Applications of size-exclusion chromatography

A number of studies investigating the metal content of metalloproteins have been performed using SEC–ICP-MS [32,101–108]. Dean et al. [103] used a Superose-12 'prep grade' SEC column and

Tris HCl mobile phase to separate metallothionein and ferritin in horse kidney in an attempt to determine the cadmium content in the two metalloproteins. In a following paper, the same group used SEC for the speciation of Cd in retail pig kidney samples [107]. Three discrete peaks were observed in uncooked kidney, and their molecular masses calculated. Samples of cooked kidney and a simulated gastric digestion of the cooked kidney were also analyzed, and it was found that the majority of soluble cadmium in retail pig kidney is associated with a metallothionein-like protein which survives cooking and simulated in vitro gastrointestinal digestion.

Mason et al. [104] used SEC for the analysis of metallothionein protein standards of known elemental composition for Cd, Zn and Cu. Zn was displaced from the protein molecule during chromatography and substituted with Cu. Full recovery of Cd was obtained. The technique was used for the analysis of the metal content of cytosolic metal binding proteins from the polychaete worm *Neanthes arenaceodentata*. Cu, Zn and Cd were determined, using EDTA complexation and a Tris-HCl mobile phase, at levels of 42.178 μg Cd, 4.523 μg Zn and 2.368 μg Cu per mg of protein. The same group [106] also used directly coupled SEC–ICP-MS for the quantitative analysis of environmentally induced perturbations in cytoplasmic distributions of metals in *Neanthes arenaceodentata*. Specific binding patterns in the marine organisms were identified and it was concluded that ligands in metallothioneins preferentially bind Cu>Cd>Zn.

Owen et al. [101] described a preliminary study of metals in proteins using SEC–ICP-MS where multielement and multi-isotope determinations were made using time resolved software. A mixture of known proteins was separated on a Superose 12 column and the distribution of associated elements was measured. Isotope retention times were found to be reproducible.

Three papers by Takatera and Watanabe [102,109,110] have described studies for the analysis of Zn(II), Cd(II), Cu(II) and Hg(II), in induced metallothionein compounds of the metals, found in cyanobacterium. Temperature and light conditions were optimised for metallothionein biosynthesis. Valuable information regarding the preferred incorporation of the metals and interactions during metallothionein synthesis was obtained using the SEC–ICP-MS system. The same authors [108] used the technique to determine sulphhydryl groups (SHs) in chicken ovalbumin (OVA) after the conversion into mercaptides using organomercury compounds. SEC–ICP-MS may be used to separate excess organic mercurial reagents that are not consumed in the reaction. Five commercially available organic mercurial reagents were compared regarding their reactivity towards SHs in OVA.

SEC may yield significant information regarding protein bound metal distributions in blood plasma and serum samples. Shum and Houk [32] described the separation of proteins in human serum, without the need for sample pretreatment, using a direct injection nebuliser. Pb, Cd, Cu, Fe and Zn metalloproteins were separated using a SynChropak SEC column and 0.1 *M* Tris–HCl mobile phase at pH 6.9. Six metal binding molecular mass fragments were observed of viscosity 15 000–650 000. Possible proteins responsible for these molecular mass fractions were postulated, e.g. ceruloplasmin at 130 kDa, however some are still unidentified. Detection limits for the metals in the metalloproteins ranged from 0.5 to 3 pg of metal and are superior by two orders of magnitude to previous values obtained by ICP-MS.

Lyon and Fell [105] used ^{63}Cu:^{65}Cu isotope ratio measurements to measure blood plasma and serum by ICP-MS. Polyatomic species such as $ArNa^+$ and PO_2^+ were found to 'swamp' the Cu measurements. As copper is principally bound to proteins in blood, SEC was used to overcome the interferences.

Gercken and Barnes [111] also used the technique for the determination of lead and other trace element species in human blood. Lead was found in at least 3 molecular mass fractions, the major fraction being coincident with the copper signal at M_r 140 000. This fraction was attributed to ceruloplasmin. Analysis of rat serum samples was also performed and both iron and zinc concentrations were quantified. The detection limit for lead in the protein fractions was 0.15 $\mu g\,l^{-1}$ with a precision of ±10%.

A study attempting to separate Au, Zn and Cu bound immunoglobulins in blood plasma was investigated by Matz et al. [112]. No conditions could be found using SEC–ICP-MS where the metals were released from the column in a single run. Resolution

was poor and low MW fragments were retained on the column. Anion-exchange studies were more effective.

Rottmann and Heumann [113] used SEC–isotope dilution-ICP-MS to determine the interactions of different molecular mass fractions of dissolved organic matter with Cu and Mo in a water sample. Three Mo species, which interacted with the humic substances, were identified and were of high molecular mass. Two species of Cu were detected and were found to interact with the low-molecular mass fraction. Total elemental levels were found to agree well with the sum of the concentrations of the speciated fractions, emphasising the reliability of the method.

The various applications of size-exclusion chromatography are listed alphabetically in Table 1 according to sample type. The chromatographic parameters, instruments used for detection and elements analyzed are summarised.

3. Gas chromatography

3.1. Introduction

The technique of gas chromatography (GC) involves vaporisation of a sample, injected onto a GC column which is then eluted by a gaseous mobile phase. This mobile phase does not interact with the sample analyte—its only function is to transport the analyte through the column. There are two common types of gas chromatography: gas-liquid chromatography and gas-solid chromatography, depending on the physical state of the mobile phase. Gas-solid chromatography is seldom used and the studies reported in this review all employ the technique of gas-liquid chromatography, where the analyte is partitioned between the mobile phase (gas) and a liquid phase which is retained onto a finely divided inert solid support such as a diatomaceous earth. The liquid phase should ideally possess a low volatility (so that it does not volatilise with the analyte), be thermally stable, be chemically inert and have solvent characteristics such that k' is favorable. The mobile phase gas must be chemically inert so that no interaction occurs with the analyte. Common gases included, helium, argon, nitrogen and carbon dioxide and the choice of gas is principally determined by the detection system used. For an argon ICP, argon would be used as the mobile phase.

The sample is injected via a microsyringe through a rubber septum into a flash vaporiser port situated at the top of the GC column. This vaporiser port is maintained at a temperature high enough to quickly vaporise the sample, normally 50°C higher than the boiling point of the least volatile analyte in the sample to be separated.

There are two basic types of GC column commonly used in coupled techniques: the packed and capillary column (otherwise known as an open tubular column). The latter type is becoming more popular and several studies will be described where such columns have been utilised. Columns are usually between 2 and 50 m in length and are coiled for practical insertion into the GC oven where the temperature is controlled. Temperatures commonly used should be just above the boiling point of the sample so that elution of the analytes occurs in a reasonable time whereas in LC separations may be optimised by using gradient elution. In GC, temperature gradients may be programmed to improve chromatographic resolution.

Earlier reviews concerning GC–ICP-MS [2,4] reported the limited use of GC–ICP-MS as an analytical tool due to the limited sample applications associated with the technique. The number of studies published recently, however, indicates that the technique is gaining popularity, probably due to the fact that speciation information is now often required when analysing samples.

There are a number of advantages associated with the use of GC–ICP-MS for the separation of volatile species and these are summarised in an excellent paper by Peters and Beauchemin [114]. Due to the gaseous state of the sample being introduced into the plasma, there is approximately 100% sample transport efficiency from the GC to the plasma. This results in low detection limits and excellent analytical recoveries. The analyte is also more efficiently ionised in the plasma as it is already in the vapour form thus requiring no desolvation and vaporization upon aspiration into the ICP. Due to the absence of an aqueous mobile phase, GC suffers less isobaric interferences than LC. Water and organic solvents in LC also increase the load on the plasma and as solvents are physically separated before the analyte

reaches the plasma. Buffers containing a high salt content are also not required in GC; therefore, erosion of the sampler and skimmer cones is not as prevalent.

3.2. Interface designs and GC–ICP-MS applications

One of the first reported couplings of GC–ICP-MS was by Van Loon et al. [115], who used a coupled system for the speciation of organotin compounds. A Perkin-Elmer Sciex Elan quadrupole mass filter instrument was used as the detector with 1250 or 1500 W forward power. The GC system comprised a Chromasorb column with 8 ml min^{-1} Ar/2 ml min^{-1} O_2 carrier gas flow with an oven temperature of 250°C. The interface comprised a stainless-steel transfer line (0.8 m long) which connected from the GC column to the base of the ICP torch. The transfer line was heated to 250°C. Oxygen gas was injected at the midpoint of the transfer line to prevent carbon deposits in the ICP torch and on the sampler cone. Carbon deposits were found to contain tin and thus proved detrimental to analytical recoveries. Detection limits were in the range 6–16 ng Sn compared to 0.1 ng obtained by ETAAS, but the authors identified areas for future improvements in detection limits and scope of the coupled system.

The next reported use of GC coupling with ICP-MS was by Chong and Houk [116]. A special interface oven was used which involved connecting the end of a packed GC column to the innermost tube of the ICP torch with glass lined stainless-steel tubing. The thermal conductivity and inert surface of this tubing prevented adsorption of analytes and condensation. The authors found that a stable plasma was obtained if the tip of the stainless-steel tubing was placed 2 cm below the tip of the injector tube (positioning of the tube higher into the load coil caused arcing). Volatile organic compounds were analyzed and elemental ratios of C, N, Cl, Br, S, B and Si were calculated. Detection limits for the various elements were in the range 0.001–400 ng s^{-1} with the best detection limits reported for elements with relatively low ionisation energy.

Two papers by Kim et al. [117,118] described the use of a capillary column for the speciation of organometallic compounds. The first paper [117] described the construction of a capillary GC–ICP-MS heated transfer line. The central cone of the transfer line was made of an aluminium rod with a longitudinal slot for column insertion. The transfer line was grounded and the temperature monitored using four thermocouples. The length was kept to a minimum to limit dead volume. Helium was used as the carrier gas for capillary GC and argon was added as a make-up gas for efficient sample transport into the plasma. Again, the distance of the capillary column from the tip of the injector was important, along with alignment of the torch and transfer line. The quantitative analysis of five alkyllead compounds in a complex naptha hydrocarbon mixture was described (Fig. 9). The detection limit was 0.7 pg s^{-1} (measured at 50 pg) and the authors stated that the method was applicable for the analysis of more involatile organometallic compounds.

In the second paper [118] tin, iron and nickel organometallic compounds were separated using aluminium-clad high temperature columns coated with 0.1 μm films of HT-5. Various column lengths and temperature gradients were used to separate the species. Helium was used as the carrier gas. The same GC–ICP-MS set up was used as in the previous paper with slight modification of the transfer line for the analysis of nickel diethyldithiocar-

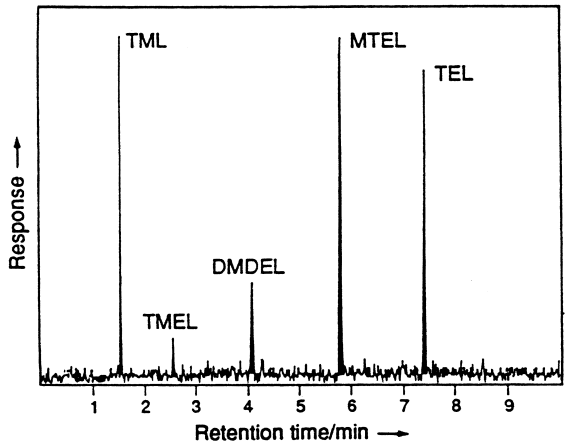

Fig. 9. GC–ICP-MS chromatogram (^{208}Pb) of naptha sample containing five alkyllead components: TML (tetramethyllead), TMEL (trimethylethyllead), DMDEL (dimethyldiethyllead), MTEL (methyltriethyllead) and TEL (tetraethyllead). Reprinted from Kim et al. [117] by permission of The Royal Society of Chemistry.

bamate ($Nidt_2$). Separation of six organotin chlorides was achieved with detection limits in the range 3–6.5 pg s^{-1} and retention times of 4.4–12.4 min. The method was applied to the analysis of a harbour sediment sample. Ferrocene gave a detection limit of 3.0 pg s^{-1} in hexane (mean retention time 7.75 min) and $Nidt_2$ a detection limit of 6.5 pg s^{-1} (mean retention time 10.45 min).

Peters and Beauchemin [114] described the use of a novel design interface for GC detection which allowed the analysis of nebulised solutions using a 'zero dead-volume' switching T-valve. The valve could be rotated to permit standard aerosol introduction into the plasma. The transfer line was constructed from glass-lined stainless-steel tubing which was heated with heating tape. A 'sheathing' (make-up) gas was again used and introduced tangentially into the device. Ion lenses were optimised using solution nebulisation. This interface was used to separate dichloromethane, 1,1,1-trichloroethane and trichloroethylene while detecting the $^{35}Cl^+$ ion. Detection limits of 2.6, 2.2 and 2.6 ng were obtained for the three compounds, respectively. The performance of the interface for the direct aspiration of aqueous solutions was also assessed and degradation of detection limits for most elements was observed.

In a further paper [119], the authors stated that the interface constricted aerosol flow from the spray chamber to the plasma torch resulting in condensation in the sheathing device, reduced aerosol flow to the torch and ultimately poor sensitivity. A new sheathing device was constructed with an enlarged inner diameter which reduced the aerosol constriction and improved sensitivity. The central channel was also extended to overcome 'pooling' of water and sputtering. Detection limits for 1,1,1-trichloroethane and trichloroethylene were much improved compared to the previous paper.

Pretorius et al. [39,120] described the development of a high temperature GC–ICP-MS interface for the analysis of geoporphyrins. The first paper described a modification of the system used by Kim et al. [117,118]. The retention index (I) of the established system for most retained analytes was approximately 3400 (due to cooling effects of the argon nebuliser gas flow) whereas metalloporphyrins have typical I values in the region of 5000. This established the need for a modified interface. The main requirement for improved Is demands heating of the argon which is difficult owing to its low heat capacity. An argon heater was constructed from nichrome wire inside a silica tube which was heated to 'red-heat' with the argon gas passing through the heater. Dead volume was kept to a minimum where possible. This GC interface with ICP-MS proved to be a selective and sensitive method for profiling metalloporphyrins in geological samples. In the next paper by the group [39] a second interface was described which gave similar chromatographs and detection limits but eliminated potential 'cold spots' by uniformly heating the entire interface.

The use of GC–ICP-MS with a 'purge-and-trap' method for the analysis of methylmercury species in sediment samples has been described by Hintelmann et al. [121]. The ICP-MS detector was used to measure specific isotopes in methylmercury compounds after GC separation. Detection limits were 1 pg (as Hg) or 0.02 ng g^{-1} Hg in dry sediment with an R.S.D. of 4%. Accuracy of the method was verified by analysis of a certified reference material harbour sediment.

In a recent paper by Prange and Jantzen [122], the development of a GC–ICP-MS interface was described for the determination of organometallic species. A quartz transfer line, heated to 240°C was used to direct a capillary column to a short distance in front of the argon plasma. Helium was used as the carrier gas in the gas chromatograph, and a temperature gradient was used for the separation of organotin, lead and mercury compounds. Limits of detection for tetraethyllead, diethylmercury and tetrabutyltin were 100, 120 and 50 fg, respectively, which were at least 3 orders of magnitude superior to previously reported detection limits. This highlights the excellent applicability of GC–ICP-MS for the analysis of volatile organometallic compounds. Van Loorn et al. [115] used a short stainless-steel tube interface in a similar study.

De Smaele et al. [123] described the coupling of GC and ICP-MS via a commercial transfer line and a custom-made transfer line (Fig. 10). The former consisted of a stainless-steel tube, a teflon tube and a fused-silica capillary tube — the teflon served to prevent capillary breakage. A variable voltage supply was employed to heat the stainless-steel tube and the

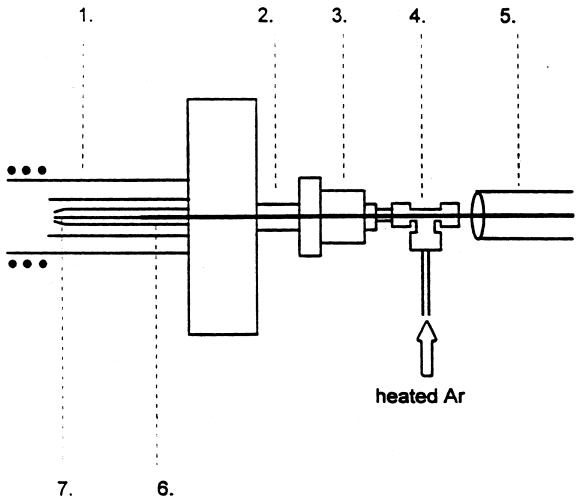

Fig. 10. Scheme of coupling of the GC with the ICP-MS instrument: 1, torch; 2, injector supply; 3, PTFE piece+PTFE Swagelok adapter; 4, Swagelok T-joint; 5, commercial transfer line; 6, stainless-steel transfer tube; 7, transfer capillary. Reprinted from De Smaele et al. [123] by permission of Elsevier Science.

temperature monitored using a built-in thermocouple. The end of the transfer line was situated 5 cm from the torch injector tip to prevent arcing. Again, a heated Ar tube was used to heat the Ar make-up gas which was introduced via a T-joint at the base of the torch. The use of this T-joint caused peak broadening due to solvent condensation from insufficient heating, therefore a custom made transfer line was constructed using a miniaturised T-joint design where heating was more isothermal. In addition, the initial transfer line was of 'stiff' construction and the capillary was prone to breakage. The transfer line was bent over 360° to obtain flexibility for easy coupling of the GC and ICP-MS. In a further paper by the same workers [124], the 'flexible' interface was used for the analysis of alkyltin compounds. This time Xe was used as a make-up gas. A 30 m capillary column was used for the separation of several organotin compounds. Results were not reported for a certified reference material therefore no indication of the accuracy of the method could be ascertained. Detection limits were very low and in the 15–35 fg range.

A recent paper by Pritzl et al. [125] described a convenient interface for capillary GC–ICP-MS which could be set up in under a minute. The transfer line was, again, a stainless-steel capillary tube, thermostated between 20–350°C and connected to the torch injector. To enable easy coupling, the GC oven was placed on a guide way sledge. The performance of the system was evaluated using various phosphorus, arsenic and tin species along with a certified marine sediment sample. Speciation of three organotin species gave detection limits in the range 0.1–1.0 pg.

The various applications of GC–ICP-MS are shown in Table 2. Samples are listed alphabetically according to sample type and it can be seen that the technique may be utilised for the analysis of a range of environmental and geological samples.

4. Supercritical fluid chromatography

4.1. Introduction

A supercritical fluid exists when a substance is heated above its critical temperature and pressure and is unable to be condensed to a liquid by pressure alone. A typical supercritical fluid is carbon dioxide, which, at temperatures above 31°C and pressures above 73 atm, exists in a supercritical fluid state where individual molecules of the compound are held by less restrictive intermolecular forces and molecular movement resembles that of a gas (1 atm=101 325 Pa).

Supercritical fluid chromatography (SFC) has gained increasing popularity in recent years as an alternative to liquid chromatography and gas chromatography. SFC is faster than LC due to the lower viscosity of the mobile phase and high diffusion coefficients of the analytes. It also yields chromatographic peaks which have less band broadening when compared to GC. Many LC techniques require the use of organic solvents and have relatively long on-column residence times which are improved by the use of SFC. In addition, compounds which are traditionally difficult to separate by GC such as thermally labile, non-volatile and high-molecular-mass compounds may be separated with relative ease.

SFC has been performed using instruments similar in design to those used with HPLC with provision for pressure control, the primary variable. Gradient

Table 2
Gas chromatography applications

Sample	Chromatography	Detector	Elements	Limits of detection	Reference
Fuel	Aluminum clad high-temp. column with siloxane carborane stationary phase (25 m×0.32 mm I.D.) Temperature program: 40°C–180°C Helium carrier gas, 6 ml min^{-1} at 150°C	VG Plasma Quad 2. 1500 W FP <5 W RP In-house transfer line constructed	Pb (as alkyllead compounds)	0.7 pg s^{-1} for various species	[118]
Geo-porphyrins	High-temperature gas chromatography. HT-5 aluminum clad fused-silica column (12 m×0.32 mm I.D.) or DB-1 HT polyimide-coated fused-silica (15 m×0.32 mm I.D)	VG Plasma Quad 2 1500 W FP <5 W RP Stainless-steel transfer line	Co, Cr, Fe, Ni, Ti, V, Zn (metallo-porphyrins)	Not reported	[39]
Harbour sediment	25 m×0.32 mm I.D. aluminium-clad high-temperature column Helium carrier gas, 2 ml at 200°C Temperature gradient (40–320°C)	VG Plasma Quad 2 1500 W FP <5 W RP Stainless-steel transfer line at 190–337°C (depending on compound)	Sn (organotin compounds) Fe (ferrocene) Ni ($Nidt_2$)	3.0–6.0 pg s^{-1} (retention time 4.4–12.4 min) for organotin compounds 3.0 pg s^{-1} (ret. time 7.75 min) for ferrocene 6.5 pg s^{-1} (ret. time 10.4 min) for $Nidt_2$	[87]
Harbour water	RSL–150 capillary column (30 m×0.25 mm I.D.) Gradient temperature program used H_2 carrier gas at 30 p.s.i. inlet pressure[a]	Perkin-Elmer Elan 5000 ICP-MS 1300 W FP Heated transfer line at 250°C	Sn (as organotin compounds)	15–35 fg	[124]
Metallo-porphyrins	Aluminium clad high-temp. column (10 m×0.32 mm) Helium carrier gas, 3 cm min^{-1} Temperature gradient program used	VG Plasma Quad 2 1500 W FP <5 W RP Stainless-steel transfer line at 190–337°C (depending on compound)	V, Mn, Fe, Ni, Cu, Zn (as metalloporphyrins)	0.10–0.55 ng on-column for various species	[109]
Sediment (PACS–1)	DB1701 quartz capillary column (30 m×0.32 mm I.D.). 80–280°C, 30°C min^{-1} He carrier gas used	Perkin-Elmer Elan 5000 ICP-MS 1000 W FP Heated transfer line at 240°C	Sn (as organotin compounds)	50–120 fg absolute for various species	[122]
Sediments	J&W 22 m DB5 0.25 mm×0.25 μm column used	PE Sciex Elan 5000 1200 W FP	P, As, Sn, Sb, Sn (as organo compounds)	0.1–1.0 pg for organotin compounds	[125]
Sediments	OV-3 on carbowax column (40×0.4 cm) at 105°C. Ramp heating to 200°C	PTFE transfer line Perkin-Elmer Elan 5000 ICP-MS 1200 W FP	Hg (organomercury speciation)	1 pg (as Hg) absolute	[121]

[a] 1 p.s.i.=6894.76 Pa.

elution may be achieved by adjusting the pressure in SFC as well as using mobile phase gradients and temperature gradients to achieve an optimum separation with good k' values and resolution. Both packed and open tubular columns may be used, although the latter generally lead to better column efficiency. Columns are longer than those used with LC (10–20 m length, 50–100 μm diameter) and are commonly made from fused-silica with chemically bonded polysiloxane coatings. The most commonly used mobile phase for SFC is carbon dioxide, although ethane, pentane, dichlorodifluoromethane, diethylether and tetrahydrofuran have also been employed.

Most preliminary SFC-plasma coupled techniques employed microwave-induced plasmas (MIPs), however the use of ICP-MS is now increasing in popularity. Carey and Caruso [126] have discussed in detail the use of plasma spectrometric detection for SFC. Flame ionization detection has been traditionally used with SFC, however ICP-MS detection offers improved sensitivity and is element selective,

so speciation information may be easily obtained. Detection is performed after the decompression zone of the system. At this point the supercritical fluid changes state to a gas. A restrictor, a length of fused-silica tubing (30–120 cm long) with a porous frit end, is connected to the end of the SFC column to maintain a linear mobile phase velocity so that significant band broadening does not occur [20].

Carey and Caruso [126] also summarised the two main approaches to interfacing the SFC restrictor with the ICP torch. The first method, used with packed SFC columns, introduces the restrictor into a heated cross-flow nebuliser and the nebulised sample is subsequently swept into the torch by the nebuliser gas flow. Where capillary SFC systems are used, a second interface design is commonly employed where the restrictor is directly introduced into the central channel of the torch. This interface is more widely used with SFC–ICP-MS coupling [20]. The restrictor is passed through a heated transfer line which connects the SFC oven with the ICP torch. The restrictor is positioned so that it is flush with the inner tube of the ICP torch. This position may, however, be optimised to yield improved resolution. The connection between the transfer line and the torch connection must be heated to prevent freezing of the mobile phase eluent after decompression when exiting the restrictor. A make-up gas flow is introduced to transport the analyte to the plasma. This flow-rate is normally similar to traditional nebuliser gas flow-rates. The make-up gas flow-rate and temperature must be optimised for improved analytical sensitivity and resolution.

The introduction of the SFC mobile phase into the plasma has the effect of reducing sensitivity due to quenching of the plasma, rather like the effect of introducing organic solvents with LC. Polar modifiers, however, do not have a serious deleterious effect on the plasma which enables the polarity of the mobile phase to be changed with no significant loss of sensitivity or resolution. This enables the analysis of compounds which are too polar for adequate separation with pure CO_2 as the mobile phase [126]. It should be noted that the use of CO_2 may cause background interference from $^{12}C^+$, $^{12}C^{16}O_2^+$ and $^{40}Ar^{12}C^+$ [20].

4.2. Applications

The first instance of SFC coupled to ICP-MS was reported by Shen et al. [127] for the speciation of tetraalkyltin compounds. Liquid CO_2 was used as the mobile phase and the SFC column was completely inserted through the transfer line and connected to a frit restrictor (Fig. 11). The restrictor was heated to approximately 200°C by a copper tube inserted into the ICP torch. Tetramethyltin (TMT), tetrabutyltin (TBT), tetraphenyltin (TPT), tributyltin acetate

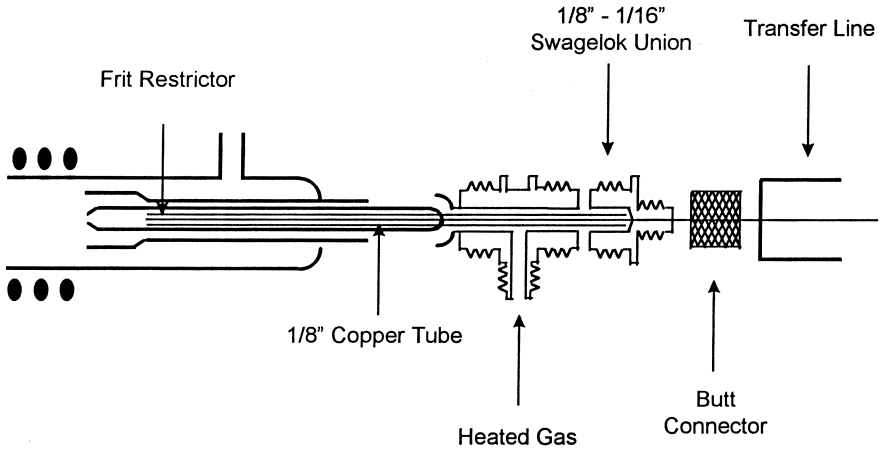

Fig. 11. SFC–ICP-MS interface. Reprinted from Shen et al. [127] by permission of the American Chemical Society.

(TBTA) and dibutyltin diacetate (DBTDA) were separated. CO_2 was introduced as the auxiliary flow to the ICP torch. The Sn signal was found to decrease with increasing CO_2 flow and increase with increasing forward power and so was optimised to give an optimum signal with minimal carbon deposition on the sampler cone. Only TBT and TPT could be separated, despite pressure gradients being applied, due to insufficient interaction with the stationary phase (Fig. 12). Detection limits were 0.034 pg TBT and 0.047 pg TPT. The addition of an organic modifier to increase solvent polarity, increasing the solvent strength, use of an alternative stationary phase and a longer column were postulated as potential areas for future studies.

A further study by Vela and Caruso [128] evaluated the effects of interface temperature, oven temperature, CO_2 pressure, mobile phase composition and column length in order to optimise the separation of several tetra and tri organotin compounds. The same interface, described by Shen [127], was used. It was found that the introduction of CO_2 did not require nebuliser flow-rate and RF power optimisation if the ion lenses were tuned sufficiently. The addition of a polar solvent to the non-polar mobile phase did not yield any improvement in resolution. Longer columns were found to yield broader chromatographic peaks. Absolute detection limits for TBT, tributyltin chloride, triphenyltin chloride and TPT were in the range 0.20–0.80 pg Sn.

The same workers [129] compared flame ionisation and ICP-MS as methods of detection for organometallic compounds separated by capillary SFC. TBT, tributyltin chloride, triphenyltin chloride and TPT were separated using the same SFC–ICP-MS interface, used for the previous studies [127,128]. Resolution, detection limits, linear dynamic range and reproducibility were all compared for the two detection systems. Fluctuations in transfer-line temperature resulted in degradation of resolution for ICP-MS. Detection limits were improved by an order of magnitude using ICP-MS and were in the range 0.20–0.80 pg Sn. Reproducibility was also improved using SFC–ICP-MS compared to SFC–flame ionization detection (FID) (1.3–3.4% compared to 3.2–6.4%). Temperature control of the SFC–ICP-MS interface was found to be critical which was not the case with SFC–FID.

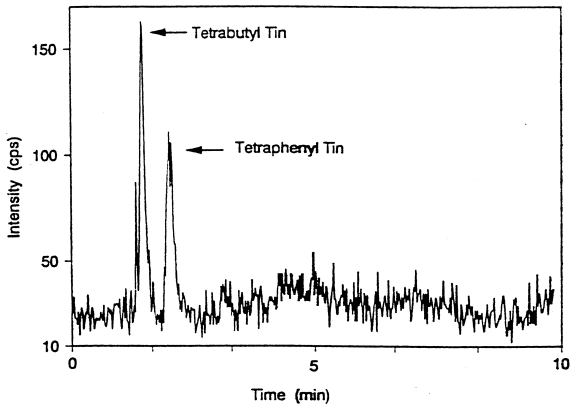

Fig. 12. SFC-ICP-MS chromatogram for a 1 pg injection of tetrabutyltin and tetraphenyltin. Reprinted from Shen et al. [127] by permission of the American Chemical Society.

Kumar et al. [130] used SFC–ICP-MS for the speciation of organometal compounds of arsenic, antimony and mercury. The study was performed using the interface developed by Shen et al. [127]. Trimethylarsine (TMA), triphenylarsine (TPA), triphenylarsenic oxide (TPAO), triphenylantimony (TPSb) and diphenylmercury (DPHg) were all separated in a single chromatographic injection. A mixed gas He/Ar plasma was used to improve detection limits of As compounds by reducing the $^{40}Ar^{35}Cl^{+}$ interference and methanol was used as the solvent instead of methylene chloride. SFC parameters such as pressure and temperature were optimised for ICP-MS detection. The element selective detection of ICP-MS enabled the TMA peak to be distinguished from the solvent peak, a feat not possible using FID. Detection limits were in the subpg–pg range.

Carey et al. [131] also investigated the feasibility of multielement detection for organomercury and organolead compounds. Simultaneous multielement detection of chromatographic peaks was compared to results obtained by single ion monitoring using the Shen interface [127]. Detection limits using the two modes of data acquisition were always better when single ion monitoring was used. This difference was attributed to the large mass differences between the elements which results in increased scan time of the quadrupole and lower duty cycle for each element during multielement analysis.

The same authors used SFC–ICP-MS for the separation of a pair of β-ketonate chromium com-

pounds and a thermally labile organochromium dimer [132]. Flame ionisation detection and ICP-MS detection were again compared. In this instance the thermally labile complex was only detectable using FID. ICP-MS gave superior detection limits for the separation of the β-ketonate complexes. The labile dimer may have thermally decomposed in the restrictor and could have been irreversibly bound to the capillary tube walls. The use of CO_2 as a mobile phase resulted in the formation of $^{40}Ar^{12}C^+$ which isobarically interfered with the major isotope of chromium at m/z 52. Nitrous oxide, was, therefore, chosen as an alternative mobile phase and yielded a simpler background spectrum.

Two papers by the Raynor group [133,134] described a capillary SFC–ICP-MS system for organometallic analysis. In the former paper [133], an interface was described in detail which was easy to assemble and caused minimal disruption to the SFC or ICP-MS instruments. The SFC oven was placed as close to the ICP as possible, in order to keep chromatographic efficiency at a maximum, and the restrictor temperature was optimised. Tetrabutyl and tributyl tin were separated using a CO_2 mobile phase with a pressure gradient. The mobile phase change did not interfere with the analysis. Detection limits were 0.025 pg and 0.035 pg for tributyltin and tetrabutyltin, respectively. These results compared well with those reported by Shen et al. [127]. The addition of small amounts of a modifier such as formic acid may improve the peak tailing exhibited in the chromatograms. In the second paper [134], the same interface was used to analyze a series of organotin, organoarsenic and organoiron compounds. The effect of analyte concentration and, again, restrictor temperature on peak intensity was investigated along with the effect of the CO_2 mobile phase.

5. Capillary electrophoresis

5.1. Introduction

The coupling of capillary electrophoresis (CE) to ICP-MS is a technique that has started to receive attention in recent years; the first papers describing the technique were written in 1995 [135–137] by the Olesik, Barnes and Lopez-Avila groups. CE is sometimes known as high-performance capillary electrophoresis (HPCE) since it has far greater efficiency of separation in comparison with conventional slab-gel electrophoresis. The most widely used mode in CE is capillary zone electrophoresis (CZE) since it offers ease of operation and can be used for a wide range of analytes. Other modes of CE include capillary gel electrophoresis (CGE), micellar electrokinetic chromatography (MEKC), capillary isoelectric focusing (cIEF) and capillary isotachophoresis. The separation of analytes depends upon the solutes' mobilities in an electric field as opposed to distributions between a mobile and stationary phase. The technique offers the analyst a valuable separation tool suitable for the separation of ionic and neutral compounds with many potential applications.

The general mechanism for CE separations is based upon differences in the mobilities of solutes which are transported along a capillary tube by a high DC voltage. Both ends of a fused-silica capillary, filled with a suitable buffer, are immersed in two reservoirs of the same buffer. The capillary is normally 50–100 cm long with an I.D. of 25–100 μm. A high potential difference of 20–30 kV is applied across two platinum electrodes in the reservoirs. The sample (several nl) is injected into the capillary and the components of the sample migrate toward the negative electrode. Owing to the small cross-section of the capillary, a high surface to volume ratio is achieved which dissipates heat, generated by joule heating, to the surroundings. Convective mixing within the capillary is, therefore, not significant and band broadening is minimised resulting in efficiencies of several hundred thousand plates.

Electroosmotic flow (EOF) of the solvent occurs in the capillary in the direction of the positive to negative electrode. It arises due to the electric double layer that is formed at the silica capillary surface/solution interface. The capillary surface has a net negative charge owing to the dissociation of the functional groups on the capillary surface. Positive ions are attracted from the buffer solution and a double layer scenario results. Mobile positive ions, present at the capillary surface, are attracted to the negative electrode and solvent molecules are transported concurrently. Capillary electrophoresis flow profiles are flat rather than parabolic owing to this

phenomenon and peak broadening contributions from the EOF are not problematical.

Separations in CE arise from differences in electrophoretic mobilities of the analytes which are principally determined by the mass-to-charge ratios of the analyte, physical dimensions of the analyte, viscosity of the medium and the interaction of the analyte with the buffer [21]. Positive species are attracted to the negative electrode and therefore migrate at a velocity greater than the EOF. Conversely, negative species are repelled by the cathode and migrate more slowly than the EOF. Neutral species move with the EOF and are generally unseparated unless some modification to the surface charge of the analyte is made, for instance by the addition of a surfactant.

Traditional detectors used in CE are genuinely the same as those employed with HPLC. However, for high resolution, the volume of sample injected onto the capillary must be small relative to the capillary volume and usually is in the 5–50 nl range. Detection of these very low levels of separated analytes requires a method that is both sensitive and specific. ICP-MS is potentially suitable, however two major challenges for coupling of the technique need to be addressed and have been described by Tomlinson et al. [21]. The flow-rate (typically of the order of $\mu l\,min^{-1}$) and low sample volume of a typical CE separation is the first potential problem, as most nebulisers for ICP-MS are designed to operate at flow-rates in the $ml\,min^{-1}$ range. Glass frit, direct injection, oscillating capillary and ultrasonic nebulisers are suitable for such low flows. Another factor to consider is that the end of the capillary will no longer be immersed in a buffer reservoir upon coupling to ICP-MS and a method of 'grounding' the electrode must be achieved. The construction of such an interface is an important consideration so that a high transport efficiency is achieved.

5.2. CE–ICP-MS interfaces and applications

Olesik et al. [135] reported the first instance of a CE–ICP-MS coupled system for rapid elemental speciation. The paper is a very comprehensive study which may be used as a guide for any analyst attempting CE–ICP-MS for the first time. The aim of the study was to develop a technique for 'quantitative elemental speciation in less than 1 min with detection limits in the low $ng\,ml^{-1}$–sub-$ng\,ml^{-1}$ range for a range of sample types'. In addition, the authors sought to determine the concentrations of free ions with different charge states, metal-ligand complexes and organometallic species.

It was noted that there is no need to electrophoretically separate species that contain different elements from each other as the ICP-MS detector serves to individually identify the metals present. Speciation studies are of primary interest for CE–ICP-MS as only 'ions, complexes or molecules containing the same element need to be separated'. Therefore, for different element ions of similar mobilities, electrophoretic resolution will be poor but the ions will be adequately identified by the ICP-MS element specific detector. It was identified that for CE–ICP-MS there is a need for an interface with low dead volume to reduce peak broadening. The actual interface used was simple in construction and the capillary was ground by coating the last 5 cm with silver paint to complete the electrical connection. The thickness of the paint layer was controlled. Contamination of the capillary effluent may occur using this method of grounding. The EOF was ~0.05 $\mu l\,min^{-1}$ and, due to the formation of a slight vacuum from the gas exiting the nebuliser, a natural aspiration rate of 2 $ml\,min^{-1}$ was achieved and no make-up flow was required. This increased laminar flow resulted in peak broadening due to the formation of a parabolic shaped velocity profile but could have been minimised using a capillary with smaller internal diameter. A smaller capillary may, however, degrade detection limits. The effect of conductivity of the electrolyte upon resolution was discussed along with the choice of electrolyte, the effect of nebuliser gas flow-rate and the effect of injection volume on peak width and peak area. Detection limits for ions were in the range 0.06–2 $ng\,ml^{-1}$ for all elements investigated. These were a factor of 20 worse than those obtained using continuous sample introduction and may have been principally caused by the use of a spray chamber which had significant dead volume and low sample transport efficiency.

Liu et al. [136] used a direct injection nebuliser (DIN) in a CE–ICP-MS interface where the CE capillary was placed concentrically inside the DIN

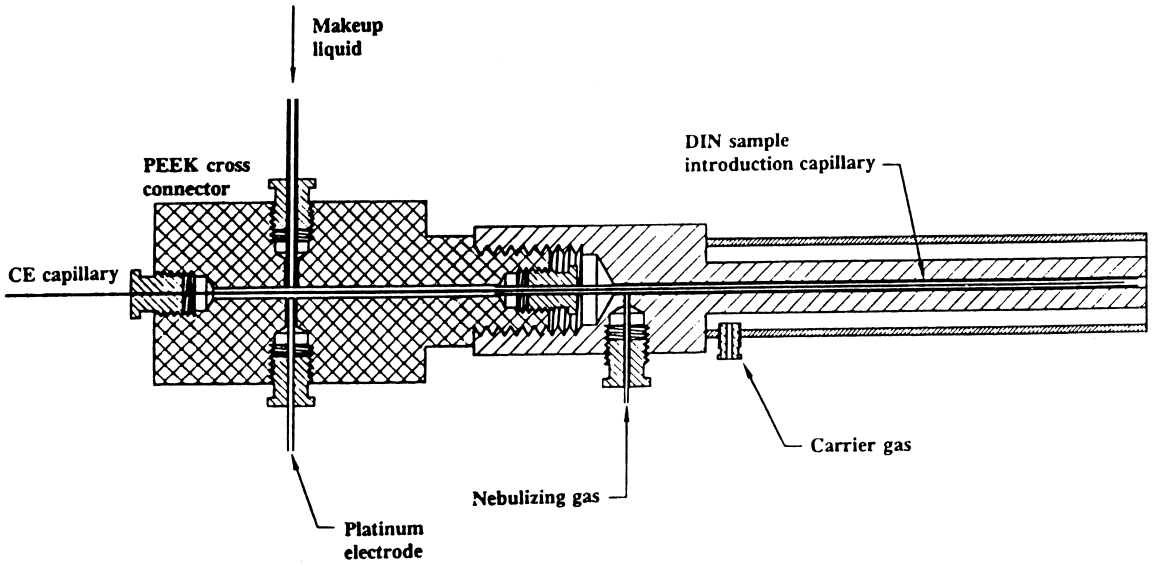

Fig. 13. Block diagram of the CE–ICP-MS interface. Reprinted from Liu et al. [136] with permission of the American Chemical Society.

sample introduction capillary so that the liquid sample was directly nebulised into the central channel of the ICP torch (Fig. 13). In this way 100% sample transport efficiency may be achieved and low sample flow-rates (10–100 μl) may be accommodated. In addition, memory effects are minimal due to fast sample washout and a small internal volume. A three-port PEEK cross-connector was specially made to accommodate the DIN sample introduction capillary (through which the CE capillary was inserted), a platinum grounding electrode and a make-up liquid which flows outside the CE capillary to establish the electrical contact. The make-up liquid was directly nebulised, along with the EOF, into the ICP torch and ensured that operation of the DIN was independent of the EOF.

The EOF and make-up flow were combined at the exit of the capillary before nebulisation. In this way, no suction was observed and band broadening was not significant. Alkali, alkaline-earth and heavy metal ions were analyzed at concentrations of 2–100 ng ml^{-1}. Detection limits were worse for CE–DIN-ICP-MS compared to continuous DIN-ICP-MS although the authors did not explain why this should occur. The feasibility of using the system for speciation studies of As and Se was demonstrated with excellent resolution of peaks and sensitivity.

Lu et al. [137] used a concentric glass nebuliser interface, similar to that used by the Olesik group, for their CE–ICP-MS studies along with a conical spray chamber. A conductive co-axial liquid sheath of electrolyte solution in the nebuliser was used to provide ground contact to the capillary. It was found that the CE capillary position inside the glass nebuliser had a significant influence on signal intensity, resolution and migration time. Peak widths narrowed and migration times shortened as the CE was inserted into the nebuliser. The technique was used to separate metal-binding proteins and to determine bound metal concentrations. Metallothionein isoforms and ferritin concentrations were determined. Detection limits were in the subpg range.

A further study by the Olesik group [138] used an interface with a laminar flow in the direction of the detector. The interface was a stainless-steel tee with the capillary threaded through the colinear ends of the tee. A sheath electrolyte was delivered through the lower arm of the tee with a peristaltic pump. Both a high efficiency nebuliser (HEN) and a concentric glass nebuliser were used in the study; the former was used with a conical spray chamber and the latter with a Scott double-pass spray chamber. Increasing the sheath electrolyte flow-rate enabled the laminar flow to be eliminated, therefore improv-

ing electrophoretic resolution. With higher sheath flow-rates, the laminar flow direction was reversed (away from the detector), effectively retarding migration of charged species. This may be useful where high injection concentrations are required to obtain low detection limits as band broadening may decrease, resulting in resolution enhancement, by reversing the laminar flow. The sheath flow-rate should therefore be optimised to obtain ideal resolution with satisfactory analysis times. The HEN had a lower sheath flow-rate than the concentric nebuliser for elimination of the laminar flow. Improved aerosol transport efficiencies were obtained with a lower sheath flow-rate so this nebuliser was used preferentially.

An ultrasonic nebuliser has been described by Lu and Barnes [139] for a CE–ICP-MS interface. As in their previous paper [137] the CE ground path was provided using a sheathing electrolyte flow around the capillary. Modification of the USN was required to accommodate the CE assembly of the two capillaries. Also described previously, the position of the CE capillary was variable inside the outer capillary. The arrangement gave improved separation resolution and sensitivity compared to a concentric nebuliser. Detection limits were not improved significantly, however, as the signal background with the USN was noisy. The authors postulated that the interface may be altered in order to transport a more uniform aerosol, yielding lower noise levels.

Preliminary studies by Michalke and Schramel [140] employed a Meinhard nebuliser interface for CE–ICP-MS. The interface was not described in significant detail. A co-axial sheath flow provided the electrical connection and no detectable ‘suction’ flow was identified. The method was used for the separation of Se compounds and adequate electropherograms were obtained.

A recently published paper by Magnuson et al. [141] described the use of a CE hydrodynamically modified electroosmotic flow with hydride generation ICP-MS for arsenic speciation. This modified EOF was similar in operation to the ‘sheath electrolyte flow’ described by Kinzer et al. [138]. The electroosmotic flow was modified by applying hydrodynamic pressure in the opposite direction to the EOF. This enabled the injection of large quantities of analyte, which normally cause peak broadening, by offsetting the EOF thus yielding improved peak resolution. Four hydride species were separated using this technique with post capillary hydride generation to convert the species to their hydrides before analysis by ICP-MS. Detection limits were in the range 6–58 ppt for four arsenic species. Two drinking water samples were analyzed using this technique.

6. Other plasma mass spectrometric systems used as chromatographic detectors

Although ICP-MS is the most commonly used plasma mass spectrometric technique in the analytical laboratory, other plasma sources have been used as mass spectrometric detectors and will be briefly discussed.

6.1. Use of the helium microwave induced plasma as a chromatographic detector

A number of papers by the Caruso group [142–147] have highlighted the attributes of a He-MIP as an alternative ion source for chromatographic detection by mass spectrometry. A review by Olson and Caruso [142] discussed instrumentation, chromatographic techniques and the advantages associated with He-MIP plasmas. The main advantages of using MIPs as alternative plasma sources are principally the reduced gas flows and power consumption needed to sustain the plasma. Alternative plasma gases may also be used which form plasmas of more efficient excitation and ionisation energies, thus improving sensitivity for elements with higher ionisation potentials. For non-metals this is significant as Ar-ICPs only ionise approximately 50% of the sample in the plasma. Isobaric interferences from polyatomic species are also problematical in Ar ICPs and may prevent the detection of lower mass elements due to argon, oxygen, nitrogen and hydrogen combinations [142]. These interferences are essentially eliminated when helium is used as the plasma gas.

The most common method of sample transport into the He-MIP is by gaseous introduction. The use of MIP-MS as a gas chromatographic detector has been well described by the work of Caruso et al.

[142,143,145–147]. Both non-metals and metals have been analyzed by GC–MIP-MS. The GC–MIP-MS interface used in these studies was made from a 1/6 in. stainless-steel tube, wrapped with heating cord and insulated with fibre glass tape (1 in.=2.54 cm). The transfer line was maintained at 300°C.

Helium MIP-MS has also been used as an element selective detector for supercritical fluid chromatography of halogenated compounds [144]. Compared to the Ar-ICP, the He-MIP offers spectral simplicity and, for halogens, more efficient ionisation. The design of the interface is important [144] as the temperature of the frit restrictor must be maintained above 100°C to avoid condensation of the analytes. Again, a heated stainless-steel transfer line should be used. Typical plasma power settings for such a coupled system are in the region of 100 W with a low (5 l min^{-1}) plasma gas flow-rate. To date, liquid chromatography has not been coupled with He-MIP-MS as the high liquid flow-rates involved tend to quench the plasma. The use of microbore LC coupled to MIP-MS may be a more promising technique [148].

6.2. Use of low-pressure helium ICP-MS as a chromatographic detector

Another alternative ion source for mass spectrometry is the helium low-pressure ICP [149–151]. Again, this helium plasma gas has a higher ionisation energy (24.6 eV) compared to the argon ICP (15.8 eV) and isobaric interferences are minimised. The use of a low-pressure plasma eliminates air entrainment and consumes less gas than an atmospheric pressure ICP ($<$500 ml min^{-1}) and radio frequency (RF) powers (100 W) may be used.

Evans and Caruso [152] developed a low-pressure argon ICP with a water-cooled low-pressure torch interface for gaseous sample introduction. Further studies by the same workers [149–151] realised the potential of He as the plasma gas. These plasmas were coupled to GC systems for the analysis of organotin and organohalide compounds [149–153]. Recent papers have realised that it is possible to sustain the plasma using the carrier gas from the gas chromatograph alone [150,151]. In addition, mass spectra may be obtained that yield more molecular information as the degree of fragmentation of the organic species may be controlled by altering the plasma gas flow and forward power [150,151].

Castillano et al. [154] investigated the feasibility of using solution nebulisation with a low-pressure He-ICP with mass spectrometric detection. The importance of reduced solvent loading to avoid quenching of the plasma was realised. Multielement solutions containing As, Se, In, Cs and Pb were aspirated and detection limits were in the low ppb region. Obviously this technique has great potential for direct coupling of microbore liquid chromatography to the low-pressure plasma for speciation studies.

6.3. Use of ion spray mass spectrometry as a chromatographic detector

Corr and Anacieto [155] recently described the successful separation of a mixture of ions by capillary electrophoresis and ion-exchange chromatography with mass spectrometric detection using an ion-spray atmospheric pressure ionisation source. Ion-spray is similar to electrospray except that the ionisation of the analyte is pneumatically assisted. Such an atmospheric pressure ionisation technique is able to produce analyte ions in the gaseous phase directly from solution [155]. Using an ion-spray source, ion-adduct declustering and molecular fragmentation may be controlled selectively, thus yielding both elemental and molecular information depending on the instrumental settings.

7. Conclusions and future directions

From the volume of papers published in recent years it is apparent that users of ICP-MS are increasingly employing the instrument for chromatographic detection. Several modes of liquid chromatography, gas chromatography, supercritical fluid chromatography and capillary electrophoresis have all been hyphenated with ICP-MS for improved detection limits compared to other traditional methods of detection such as UV–Vis spectroscopy.

There is a significant demand for speciation information for many elements and the separation ability of chromatography coupled to ICP-MS offers the analyst a versatile tool for such studies. Both

metals and non-metals may be speciated, therefore compounds containing elements such as the halogens may be separated. It is now evident that certified reference materials for speciation studies of various elements must be developed and made available so that speciation techniques may be evaluated for environmental and toxicological studies.

Sample preparation is also an area for future research. Common digestion and extraction procedures are time consuming and may result in the loss of volatile elements. Extraction procedures such as microwave-assisted extraction and supercritical fluid extraction may be employed and even coupled on-line so that samples for chromatographic analysis may be prepared.

Capillary electrophoresis is a technique that offers the analyst potential benefits for speciation analysis. Although capillary electrophoresis is now widely used to perform routine separation of compounds, the coupling of CE with ICP-MS is relatively new and interface designs are still being developed and evaluated. The use of direct injection nebulization and other 'low flow' nebulizers are, without a doubt, the way forward if electropherographic resolution is to rival that obtained with UV detection.

Microbore liquid chromatography is a technique where low flows and small diameter columns may be used to obtain chromatograms of resolution comparable to traditional analytical performance LC columns. These columns may be suitable for performing separations with ICP-MS detection as lower organic solvent concentrations and buffer concentrations would be transferred to the ICP-MS, via a transfer line. This may enable the analyst to use gradient elution of organic solvents for reversed-phase and other modes of LC, without significant loss of plasma stability, an area of chromatography which has proved problematical in the past.

Modern ICP-MS instruments are invariably computer-controlled and chromatograms are usually obtained with on-board time resolved analysis software. This software is often cumbersome and is the limiting factor with regard to resolution and ease of chromatographic data acquisition. Owing to the increasing use of ICP-MS as a chromatographic detector, instrument manufacturers must now meet the demands of the chromatographer and find improved ways for data information acquisition that employ software programs compatible with everyday word processing and presentation packages.

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