Chromatography Coupled With Inductively Coupled Plasma Atomic Emission Spectrometry and Inductively Coupled Plasma Mass Spectrometry

A Review

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Summary of Contents

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Introduction

The various techniques of analytical atomic spectrometry offer the possibility of detecting a wide range of metals and non-metals, although by themselves they only yield information on total concentrations. Thus, with the increasing demand for both qualitative and quantitative information on the form of the metal in a wide range of samples, trace metal speciation studies have increasingly coupled the separatory powers of chromatography with the sensitivity and selectivity of atomic spectrometry for detection. The area has received much attention and has been the subject of many papers. Two major reviews covering the direct coupling of gas chromatography (GC)–atomic spectrometry[1] and liquid chromatography–atomic spectrometry[2] were published in the mid-1980s. Together these reviews covered over 250 papers dating back to 1965 and critically evaluated the various types of coupling then available. However, since that time, many developments in coupled techniques have been made, particularly in response to the need for versatile systems which facilitate the obtainment of better detection limits and which lend themselves to routine laboratory operation. One of the major advances in atomic spectrometry since the reviews were published has been the introduction and widespread adoption in many laboratories of commercial inductively coupled plasma mass spectrometry (ICP-MS) systems. Such instruments provide significantly lower detection limits than inductively coupled plasma atomic emission spectrometry (ICP-AES) instruments, and, when coupled with either gas or liquid chromatography offer on-line operation in real time. In addition, ICP-MS also offers a multi-element mode which can be used for trace-metal speciation in real samples.

This review covers the use of coupled liquid and gas chromatography with both ICP-AES and ICP-MS systems, with an emphasis on applications to real samples. Every effort has been made to avoid duplication of material covered in the previous reviews. However, some early high-performance liquid chromatography (HPLC) couplings with an ICP-AES system have been included, since, in many cases, the nature of the coupling with an ICP-MS system is essentially the same, although the chromatography *e.g.*, mobile phase, may have to be modified for use with ICP-MS. Although only a modest number of GC–ICP-AES couplings have been reported, the use of capillary GC with ICP-MS offers some exciting potential use for the future.

High-performance Liquid Chromatography–Inductively Coupled Plasma Atomic Emission Spectrometry

When used as a detector for HPLC, the ICP offers good sensitivity, a dynamic range of over five orders of magnitude and multi-element detection capabilities. However, conventional HPLC–ICP couplings *i.e.*, direct connection between the end of the HPLC column and the nebulizer, can suffer from poor transport efficiency, particularly when pneumatic nebulizers are used. Such couplings also demonstrate low tolerance to many of the organic solvents commonly employed in mobile phases for HPLC. Investigations have therefore been performed to characterize the effects of mobile-phase composition and flow rates on HPLC–ICP methods.[3,4] In addition, workers have reported studies on modified nebulizer and spray chamber arrangements in an attempt to maximize analytical performance; *e.g.*, the effects of nebulization chamber position using both Meinhard[5,6] and fixed cross-flow[7,8] nebulizers for liquid HPLC–ICP couplings. These studies revealed that, for aqueous eluents, peak broadening and distortion occurred when the chamber was placed inside the ICP gas box due to extended liquid transport. However, when the chamber was

placed outside the gas box, a loss in signal commensurate with aerosol transport over an equivalent distance occurred, thus emphasizing the importance of keeping the dead volume associated with the coupling to a minimum. More recently a number of other workers have tried ultrasonic nebulizers,[9] thermospray vaporizers[8,10,11] and glass-frit nebulizers[12] for sample introduction in HPLC–ICP-AES. In all cases improvements in sample transport efficiency have been reported when compared with pneumatic nebulization, particularly for organic solvents. The solvent load of the plasma (important in terms of plasma stability) can be decreased by aerosol thermostating,[13–15] cooling of the spray chamber,[15,16] and application of a condenser.[17–19] The amount of solvent introduced into the plasma may also be reduced by employing micro HPLC systems for the separations.[20,21] In a brief communication, Lawrence *et al.*,[22] described a total injection, microconcentric nebulizer that was reported to yield up to 100% nebulization and transport efficiency for HPLC–ICP-AES. Later, this group under Fassel extended the study and the direct injection nebulizer (DIN) was again used in HPLC–ICP-AES studies,[12] although this time the range of organic solvents was extended to include up to 100% methanol, acetonitrile, isobutyl methyl ketone and pyridine in the HPLC eluent. In addition, it was reported that detection limits using HPLC–DIN-ICP-AES for a number of elements were better than those obtained by other workers using HPLC–ICP-AES with other nebulizer arrangements. From our own experience the fragility of such devices can be a disadvantage, although the recent availability of commercial designs might encourage their more widespread application.

In all of the above developments, the principal aim has been to minimize band spreading in the interface following separation by the chromatographic column. Various types of HPLC columns have been used, including thermal gradient applications.[23] However, supercritical fluid chromatography (SFC) has also been used recently in conjunction with ICP-AES detection.[24–26] The unique properties of supercritical fluids totally eliminate the need for the nebulizer–spray chamber interface since, as the fluid leaves the chromatographic column and restrictor, it becomes a gas at atmospheric pressure and will transport essentially 100% of the sample in a readily atomized form. In one of the first papers in this area Fujimoto *et al.*[25] reported the interfacing of an ICP to a packed column SFC system and evaluated its performance with ferrocene and its derivatives. An ICP coupling to a capillary SFC has also been reported and, in this case, applied to the separation of organosilicon compounds.[27] A short review of this interesting area, discussing techniques for coupling SFC to ICP-AES has also been prepared by Li,[26] although in all reported cases the ICP suffers from the same limitations for elemental speciation in SFC as in other forms of chromatography *i.e.*, poor response for many non-metallic elements.

The following tables (Tables 1–4) list the various applications reported for HPLC–ICP-AES. The four categories used for the tables, *i.e.*, environmental, clinical, industrial, and general applications, are only meant as a guide to aid the reader, since many publications describe several applications that might fit one or more of these sections. Publications dealing with development work using laboratory chemicals as samples are described in Table 4 under general applications. It should also be noted that a surprising number of workers do not give details of the detection limits achieved in their work, and this is reflected in the tables.

Table 1 HPLC–ICP-AES applications (environmental)

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
ICP all argon plasma, 1.05–1.9 kW FP. HPLC coupled to ICP *via* Teflon tubing into a cross-flow nebulizer	Zorbax C_8 column (250×4.4 mm i.d.). Mobile phase, linear gradient of 55% ethanol up to 80% EDTA	Separation of iron carbonyl and molybdenum carbonyl compounds	Fe 0.7 ng Mo 0.3 ng	—	3
ICP all argon, 1.3 kW FP. HPLC coupled to ICP *via* Teflon tubing into a cross-flow nebulizer	Anion-exchange column, μ-bondpak-NH_2. Mobile phase, oxylate–Mg buffer	Separation and quantitative analysis of orthophosphate diphosphate and triphosphate	Ortho 0.5 μg, di 1.0 μg, tri 3.0 μg	ATP and ADP also analysed	28
All argon ICP HPLC coupled to ICP *via* Teflon tubing into a cross-flow nebulizer	30 cm columns packed with 3 types of ion exchanger: bondpak-NH_2; Nucleosil CH_3-10; and Nucleosil SO_3H-10. Mobile phase, 0.05 mol l^{-1} phosphate buffer	Separation and quantitative analysis of As compounds in biological samples	As 2.6 ng	Other detection also employed (HPLC–AA and DCP)	29
Bausch & Lomb ARL 34000 48 channel. HPLC coupled *via* PTFE tubing into cross-flow nebulizer	Hamilton PRB 1 reversed-phase column. Mobile phase, 0.002 mol l^{-1} hexadecyltrimethylammonium bromide (HTAB) pH 9.6	Arsenic, selenium and phosphorous compounds	As 130 μg l^{-1}	—	30
PlasmaTherm HFP2500D ICP 1.5 kW FP. HPLC coupled *via* Teflon capillary tubing into a concentric nebulizer	Various columns: C_{18} ODS Spherisorb; C_8 Ultrasphere; C_1 5 mm; and C_2 LiChrosorb RP-2. Mobile phase, various water and alcohol mixtures were studied	Demonstration of the suitability of HPLC–ICP to the separation of tetramethyl and tetraethyllead in gasoline	TML 42 mg l^{-1} TEL 212 mg l^{-1}	Optimum HPLC conditions: C_2 LiChrosorb column; butanol–ethanol–water (15+35+50) mobile phase	31

Table 1—*continued*

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
PlasmaTherm HFP2500D all argon ICP. HPLC coupled *via* Teflon capillary tubing into a cross-flow nebulizer	Various reversed-phase and ion-exchange columns	Determination of alkyllead compounds	TML 33 pg s^{-1} TEL 100 pg s^{-1}	Glass frit nebulizer incorporated to increase ICP ability to accept organic solvents with high evaporation rates	32
Jarrell-Ash 975 AtomComp ICP 1.2 kW FP. HPLC coupled *via* PTFE tubing into a cross-flow nebulizer	Either TSK3000SW (600 × 7.5 mm i.d.) or TSK2000SW (500 × 7.5 mm i.d.) size-exclusion columns. Mobile phase, distilled, de-ionized water	Fractionation and measurement of metal species at ambient levels in natural waters	Not reported	By coupling SEC with ICP it was possible to determine if metal peaks would co-elute with ultraviolet absorbing dissolved organic matter	33
Plasma 100 all argon ICP	Paired ion reversed-phase C_{18} type columns (250 × 4.6 mm i.d.). Mobile phase, 0.005 mol l^{-1} paired-ion chromatography (PIC) reagent (Waters)	Trace analysis and speciation for arsenic anions in environmental drinking water supplies	Not reported	Hydride generation derivitization successfully interfaced with paired ion reversed-phase HPLC	34
All argon ICP	Short column packed with a porous polyacrylate-based anion-exchange resin. Mobile phase, 5.0×10^{-4} mol l^{-1} potassium hydrogenphthalate solution pH 6.5	Determination of Cr^{III} and Cr^{VI} as a method for the fractional determination of Cr species in waste waters	Cr^{III} 7.5 ng Cr^{VI} 22.0 ng	Improved sensitivity and shortened retention time of Cr^{VI} was attained by the formation of tetrathiocyanato-chromate(III) prior to injection	35
Jarrell-Ash ICAP-575 ICP 1.0 kW FP. HPLC coupled *via* Teflon-PTFE tubing into a conventional nebulizer	Ion-exchange preconcentration column (100 × 1.6 mm) packed with iminodiacetate chelating resin. Mobile phase, 0.1 mol l^{-1} sodium citrate	Determination of cadmium in certified biological reference materials and waste water samples	Cd^{2+} 0.05 ng ml^{-1}	Ion-exchange preconcentration allowed a 25-fold improvement in sensitivity and detection limits over direct aspiration of the aqueous solution	36
Bausch and Lomb 34000 1.6 kW FP. HPLC coupled *via* Teflon tubing into a concentric nebulizer	Hamilton PRP-1 column (250 × 4.1 mm). Mobile Phase, Methanol–0.05 mol l^{-1} ammonium acetate	Detection of sulfur containing surfactants in waste waters	Sulfur 15 ng	—	37
Bausch and Lomb ARL 34000 argon ICP	Hamilton PRP-1 reversed-phase column (25 × 4 mm)	Quantitative determination of arsenobetaine in crabs	3 ng methylarsonic acid	—	38
Leeman Laboratories PlasmaSpec 1 ICP 0.98 kW FP	Ion-exchange chromatography using cation-exchange columns (Bio-Rad AG50W-X8 resin). Mobile phase, 1.7–6.0 mol l^{-1} HCl, dependent on procedure	Separation of lanthanide series elements in marine Fe–Mn crusts	Not reported	Major (Fe and Mn) and minor constituents (Al, Co, Cu, Ni, Ca, Mg) eluted with 1.7–2 mol l^{-1} HCl; the rare earth elements (REE) then eluted from the resin with 4.0 or 6.0 mol l^{-1} HCl	39
PlasmaTherm ICP 1.0 kW FP. HPLC coupled *via* PTFE tubing to a hydride generation system. The nebulizer was replaced with a gas–liquid separator	Nucleosil SB anion-exchange column (200 mm). Mobile phase, 50 mmol l^{-1} $NaH_2PO_4 \cdot H_2O$ buffered to pH 6.75 with $Na_2HPO_4 \cdot 2H_2O$	Determination and speciation of arsenic in aquatic media	As^{III} 3.5 $\mu g\ l^{-1}$ of As, MMA 3.8 $\mu g\ l^{-1}$ of As, DMA 21.3 $\mu g\ l^{-1}$ of As, As^{V} 9.2 $\mu g\ l^{-1}$ of As	A gas–liquid separator was used to impede the entrance of the mobile phase into the plasma torch	40
Jobin-Yvon JY24 ICP 1.3–1.7 kW FP. HPLC interfaced into a concentric nebulizer	Gel permeation SEC column (TSK G 3000SW). Mobile phase, phosphate buffer pH 7.5	Investigation of organometallics in the marine ecosystem (Zn, Cd, Cu)	Not reported	—	41

Table 1—*continued*

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
JY 48P 36 channel argon ICP 1.1 kW FP. *Concentric* glass nebulizer	Ion-exchange 8 PSCX 10 μm radial pak LC cartridge. Mobile phase, 0.1 mol l^{-1} $NaNO_3$, 0.02 mol l^{-1} $MgCl_2$	Determination of Y and selected REE in geological samples	Yttrium 1–2 $\mu g\ g^{-1}$	—	42
PlasmaTherm HFS5000d ICP 0.85 kW FP. HPLC coupled *via* heated transfer line directly into the ICP torch assembly	SFC: fused silica capillary column coated with poly(dimethylsiloxane). Mobile phase, SFC-grade carbon dioxide	Evaluation of SFC–ICP-AES as a selective detector for organosilicon compounds	5.8 ng of Si injected	—	43
Perkin-Elmer 5500 ICP 1.25 kW FP. Column effluent line inserted directly into a cross-flow nebulizer	Waters Z module ion-exchange column containing Bio-Rad Aminex resin. Mobile phase, gradient from water to ammonium carbonate	Separation of biologically important As species	Sensitive to 60 ng As injected onto the column	—	44
All argon ICP-AES	Econosphere C_{18} reversed-phase column (25 cm × 4 mm). Mobile phase, stepwise aqueous, methanol gradient (10–70%)	Determination of inorganic lead and several alkyllead compounds	74–317 ng	—	45

2.1 Environmental Applications

The majority of publications to date employing HPLC–ICP-AES have described work that can be placed under the broad heading of environmental applications. Of these, there is a notable emphasis on the determination of specific organometallic compounds, and in particular organoarsenic and organolead compounds. However, although the detection systems and interface designs are often very similar, the nature of the mode of separation is often different. For example, Morita *et al.*[29] have described the separation of arsenite, arsenate, methylarsonic acid (MMA), dimethylarsinic acid (DMA) and arsenobetaine (AsB) with both anion- and cation-exchange chromatograpy with phosphate buffers as mobile phases. The detection limit for As using the As I 193.6 nm line was reported as 2.6 ng s^{-1} (2σ). The same arsenic species have also been determined by Irgolic *et al.*,[30] although phenylarsonic acid was determined instead of arsenobetaine and a reversed-phase column was used. Slightly poorer detection limits ($\approx$13 ng) were obtained. A similar variety of chromatographic approaches is also found for the determination of organolead compounds with both reversed-phase[31] and ion-exchange columns being used.[32]

A wide range of environmental samples have been investigated using HPLC–ICP-AES. These include natural waters;[33,34] waste waters;[35–37] marine samples (*e.g.*, crabs,[38] marine crusts[39] and other marine organisms;[40,41] petroleum products;[31,32] geological samples;[42] and certified reference materials.[36] The elements determined include: As, Cd, Cr, Cu, Fe, Mn, Mo, P, Pb, S, Se, Si, Y and Zn, although a number of other elements of environmental interest are discussed in Section 2.4 (Table 4). Details of reported environmental applications of HPLC–ICP-AES are presented in Table 1.

2.2. Clinical Applications

This section discusses applications of HPLC–ICP-AES to clinical samples and includes publications that have used the technique to determine trace elements in amino acids, blood, pharmaceutical products, proteins, vitamins and other biological matrices. One of the most commonly determined elements in this section is phosphorus. Since the terminal phosphate groups found in nucleotide molecules can be separated using anion-exchange chromatography, the use of HPLC–ICP-AES provides an attractive means of determining individual monomeric units. The technique also overcomes some of the problems encountered when using more conventional detection techniques such as spectrophotometry, since nucleotides tend to be hygroscopic and unstable, and, in addition, require individual calibration graphs to take account of the unique extinction coefficients associated with each type of nucleotide. In one of the first studies in this area, Hiene *et al.*,[46] assessed the capabilities of ICP-AES as a selective detector by observing the P I emission at 213.6 nm. The nucleotides were separated on an anion-exchange column using acetate buffers, and calibrated using a single calibrant of Na_2HPO_4(aq). A detection limit of 750 ng of phosphorus was obtained with an RSD of 4.5%. Anion exchange has also been used for the determination of ribonucleoside-5′-mono-, 5′-di, and 5′-triphosphates, again monitoring the phosphorus emission by ICP-AES.[47] Other workers have also employed gel-permeation columns, *e.g.*, for the determination of C, Co and P in vitamin B_{12}; cation-exchange columns, *e.g.*, in the determination of amino acids (monitoring the C and S emission); reversed-phase columns;[9] and more recently size-exclusion chromatography, as in the determination of ferritin in pharmaceutical products.[48] Table 2 gives details of these applications, together with other published work in this area.

2.3 Industrial Applications

Directly coupled HPLC–ICP-AES has also been reported for a number of industrial applications such as the determination of trace elements in petroleum products, coal process streams and oil shares,[12,55–58] the characteriza-

Table 2 HPLC–ICP-AES applications (clinical)

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
Jobin-Yvon 38 Type III ICP 1.27 kW FP. HPLC coupled *via* Teflon tubing into various nebulizers including a continuous-flow ultrasonic nebulizer	Various columns: Vydac 201TP C_{18} (250×4.6 mm i.d.); Partisil 5 ODS3 (250×4.6 mm i.d.); Hamilton PRP-1 (15×4 mm i.d.). Mobile phase, various eluents were used including the ion-pairing reagent tetrabutylammonium phosphate	Speciation of ionic compounds containing As, Se and Cr	Se 10–14 mg l^{-1} As 30–40 mg l^{-1} Cr 8–10 mg l^{-1}	The analytical figures of merit using an ultrasonic nebulizer were comparable to, or better than, conventional nebulization in terms of organic solvent tolerance, sensitivity, detection limits and repeatability	9
Jarrel Ash 500S argon ICP. HPLC coupled *via* stainless-steel tubing into a cross-flow nebulizer	Develosil 100-5 capillary column (230×0.35 mm i.d.). Mobile phase, toluene and chloroform	Organometallic speciation in petroleum and biological samples	Not reported	Micro-column LC using a no spray chamber nebulization system	20
All argon ICP 1.0–3.0 kW FP. HPLC coupled *via* PTFE tubing into a Babington principle nebulizer	MicroPak AX-10 anion-exchange column (300 mm). Mobile phase, A 0.007 mol l^{-1} $NaC_2H_3O_2$ pH 4 and B 0.3 mol l^{-1} $NaC_2H_3O_2$, 0.3 mol l^{-1} NaCl pH 3. Linear gradient from A to B of 5 min	Determination of nucleotides by analysing the total P concentration	750 ng of P	A Babington type nebulizer was used to aspirate the high percentage salt solutions with a 6% efficiency	46
Jarrel-Ash ICAP-50 ICP 1.3 kW FP. HPLC coupled *via* Teflon tubing into a cross-flow nebulizer	Stainless steel anion-exchange columns (500×4 mm i.d., 250×4 mm i.d.). IEX-260-SA-SIL column packing. Mobile phase, 0.1–0.73 mol l^{-1} $HCOONH_4$, pH 3	Determination of ribonucleoside 5′-mono-, 5′-di- and 5′-triphosphate by analysing the integrated emission intensity of P	Concentration as P 0.37–0.56 μg ml^{-1}	Column temperature maintained at 60 °C with a column oven	47
Jobin-Yvon 38VHR ICP 2.2 kW FP. HPLC coupled *via* PVC tubing into a concentric nebulizer	Either TSK G4000SW or TSK G 5000PW Superose 6HR 10/30 size-exclusion chromatography columns. Mobile phase, KH_2PO_4 0.07 mol l^{-1} $NaClO_4$ 1 mol l^{-1}, NaN_3 10^{-4} mol l^{-1} pH 6.8	Analysis of ferritin in pharmaceutical products	Fe 1.1 ng	—	48
Jarrell-Ash AtomComp all argon ICP 1.25 kW FP. HPLC coupled *via* Teflon tubing into a cross-flow nebulizer	TSK GEL 3000SW (600×2 mm) gel-permeation column. Mobile phase, 0.9% NaCl aqueous solution	Determination of C, Co, and P in vitamin B_{12} and the multi-element analysis of proteins	Not reported	Vitamin B_{12} was not recovered completely possibly owing to adsorption onto the stainless-steel tubing	49
Plasma 100 all argon ICP	Paired ion reversed-phase C_{18} type columns (250×4.6 mm i.d.). Mobile phase, 0.005 mol l^{-1} PIC reagent	Qualitative and quantitative analysis of various metal cations or anions	Cr^{III} 220 mg ml^{-1} Cr^{VI} 450 mg ml^{-1}	—	50
As above	Reversed-phase C_{18} type column. Mobile phase, NaCl or LiCl saturated with tributyl phosphate buffered to pH 3.9–6.0	Cd, Zn, Hg	Not reported	—	51
Sequential ICP atomic emission spectrometer 1.04 kW FP. HPLC coupled *via* Teflon tubing into a Fisher cross-flow nebulizer	Nucleosil-$NH(CH_3)$ strong anion-exchange column. Initial mobile phase, 0.002 mol l^{-1}–ammonium dihydrogen phosphate (ADP) 0.005 mol l^{-1} ammonium acetate pH 4.6. Second mobile phase, 0.08 mol l^{-1} ADPpH 6.9	Speciation and quantification of arsenate, arsenite, selenate and selenite	Absolute, 52 ng As^{III} 140 ng Se^{IV} 57 ng As^{V} 91 ng Se^{VI}	—	52

Table 2—*continued*

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
Jarrell-Ash ICAP-50 ICP 1.2 kW FP. HPLC coupled *via* small diameter Teflon tubing into a cross-flow nebulizer	Stainless-steel column (300×4 mm i.d.) packed with a strong cation-exchange resin. Mobile phase, gradient elution from 0.2 mol l^{-1} NaH_2PO_4 pH 3.2 to 0.2 mol l^{-1} NaH_2PO_4 pH 4.3	Determination of amino acids	30–50 $\mu g\ ml^{-1}$ and 1–3 $\mu g\ ml^{-1}$ detection limit obtained by detecting emission intensities of C and S, respectively	C I emission intensity at 193.09 nm. S I emission intensity at 180.73 nm	53
ARL 3520 all argon ICP 1.05 kW FP. HPLC coupled *via* PTFE tubing into a GMK nebulizer	TSK G3000SW SEC column. Mobile phase, 0.1 mol l^{-1} HEPES, 0.1 mol l^{-1} NaCl pH 7.4	Study of the distribution of Cu, Fe, Zn and Co in various biological samples, including milk and blood	Not reported	—	54

Table 3 HPLC–ICP-AES applications (industrial)

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
Plasma Therm HFS5000D ICP 1.8 kW FP. HPLC coupled *via* stainless-steel tubing into a direct injection nebulizer	Partisil 5 ODS-3 C_{18} reversed-phase column (250×4.6 min i.d.). Mobile phase, 5 mmol l^{-1} aqueous tetrabutylammonium phosphate	Various samples, including gravimelt process stream materials and crude shale oils	Relative detection limit 0.74–39 ng ml^{-1} arsenite, 42 ng ml^{-1} selenite	Evaluation of the application of a direction injection nebulizer	12
R.f. Plasma Products HFP 2500f ICP 1.4 kW FP. HPLC coupled *via* Teflon tubing into a concentric nebulizer	H-P 5710A GC used to generate temperature gradient. HPLC column placed inside oven. Carbosphere ODS (150×2 mm) for non-aqueous. Microsorb C_{18} (100×4.6) for aqueous	Sulfur (aqueous), silicon (non-aqueous)	S 4 ng s^{-1} Si 0.2 ng s^{-1}	Application of thermal gradient LC	23
Bausch and Lomb 3580 all argon ICP	Two analytical sciences SEC UltraGel MXL columns connected in series	Molecular size distribution of specific elements in petroleum crudes and 650+ (S and Vn)	Not reported	—	55
R.f. Plasma Products HFP 2500F ICP 1.4 kW FP. HPLC coupled *via* Teflon tubing into a concentric nebulizer	Size-exclusion chromatography	Study of the behaviour of V, Ni and S during heavy crude oil conversion processes	Not reported	—	56
AtomComp 975 ICP 1.75 kW FP. HPLC coupled *via* PTFE tubing into a cross-flow nebulizer	SEC columns: 300×7.5 mm PL-Gel; and 250×9.5 mm GP250. Four mobile phases	Molecular size speciation of V and Ni complexes in oil	3.5 ng of Ni 0.5 ng of V	—	57
ICP all argon	Column-exchange chromatography columns prepared with tri(2-ethylhexyl)phosphate (TEHP) or dihexyl-*N*,*N*-diethyl-carbamoyl-methylenephosphate (DHDECMP)	Characterization of selected nuclear fuel materials materials	Not reported	—	58
Shimadzu V1000 ICP 1.2 kW FP. A hydrofluoric acid-resistant sample introduction system was used	Anion-exchange column packed with either Dowex 1-X4 or Dowex 2-X8. Mobile phase, 2 mol l^{-1} nitric acid	Determination of B in iron disilicide and high-purity iron	B, 0.01 $\mu g\ ml^{-1}$ in solution, 0.05 $\mu g\ g^{-1}$ in high-purity iron	—	59
ARL 3520 ICP 1.22 kW FP. HPLC coupled *via* direct connection of HPLC eluent into a concentric nebulizer	Sulfite ion exclusion column (100×7.8 mm) of polystyrene-divinylbenzene with 10% cross linking. Mobile phase, 0.1% HCl v/v pH 1.84	Detection of sulfite with reference to the determination of sulfite in beverages and foods	Sulfite as S 0.08 mg ml^{-1}	—	60
Jarrell Ash all argon ICP 1.2 kW FP. HPLC coupled *via* Teflon tubing into a cross-flow nebulizer	Stainless-steel column (250×4 mm) packed with strong cation-exchange resin. Mobile phase, 0.4–1.0 mol l^{-1} ammonium lactate	Determination of rare earths elements	0.001–0.3 $\mu g\ ml^{-1}$	15 rare earths determined	61
Sequential ICP-AES	Ion chromatography	Determination of Cr, Mo, Mn and Ni in certified steel samples	Not reported	—	62

Table 4 HPLC–ICP-AES applications (analytical)

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
Jarrel-Ash 975 AtomComp ICP 1.2 kW FP. HPLC coupled *via* Teflon capillary tubing into the ICP nebulizer	Anion-exchange column (100 mm × 2.1 mm i.d.) packed with Aminex A-14 anion-exchange resin. Mobile phase, aqueous 0.05 mol l^{-1} $(NH_4)_2SO_4$	Evaluation of ICP as a detector for HPLC peaks containing specific elements	Cu 6.9 ng. Detection limits also determined for 25 other elements	ICP compared with AAS for the detection of HPLC peaks composed of H_4edta and H_3nta (nitrilotriacetic acid) chelates of copper	4
PlasmaTherm 2500 ICP 1.2 kW FP. HPLC coupled *via* Teflon capillary interface into a concentric nebulizer	50 × 4.1 mm i.d. stainless-steel anion-exchange column	Mg	Not reported	Examined the properties of the location of pneumatic nebulizer spray chamber systems on transport mechanisms	5
Perkin-Elmer Plasma II ICP 1.4 kW FP for aqueous solution. 1.9 kW FP for organic solution. HPLC coupled *via* a thermospray vaporizer into a cross-flow nebulizer	Waters IC-PAK anionic column (150 × 4 min i.d.). Mobile phase, ammonium citrate 0.08 mol l^{-1} pH 3.3.	Speciation of Se in $(CH_3)_3Se^+$, SeO_3^{2-} and SeO_4^{2-}	A detection limit of 44 μg l^{-1} was achieved with 25% methanol in the Se standard solution	Using a thermospray nebulizer, a threefold increase in sensitivity was achieved, along with a 33% increase in the methanol addition to the plasma	8
Jobin-Yvon 38 Type III ICP 1.27 kW FP. HPLC coupled *via* Teflon tubing into various nebulizers including a continuous-flow ultrasonic nebulizer	Various columns: Vydac 201TP C_{18} (250 × 4.6 mm i.d.), Partisil 5 ODS3 (250 × 4.6 mm i.d.), Hamilton PRP-1 (150 × 4 mm i.d.). Mobile phase, various eluents were used including the ion-pairing reagent tetrabutylammonium phosphate	Speciation of ionic compounds containing As, Se and Cr	Se 10–14 mg l^{-1} As 30–40 mg l^{-1} Cr 8–10 mg l^{-1}	The analytical figures of merit using an ultrasonic nebulizer were comparable to or better than conventional nebulization in terms of organic solvent tolerance, sensitivity, detection limits and repeatability	9
ARL 137000 ICP 1.4 kW FP. HPLC coupled *via* Teflon or 316 stainless-steel tubing into a Pyrex glass nebulizer	100A μ-Styragel size-exclusion chromatography column. Mobile phase, toluene	Determination of organometallic species in synthetic mixtures	Detection limits in toluene were found to be comparable to those found in aqueous static operation of ICP-AES	A Pyrex spray chamber to facilitate the interface, and to be compatible with volatile solvents, was developed	16
Jarrell Ash 500S all argon ICP 1.2–2.0 kW FP	Teflon columns either reversed phase (120 × 0.5 mm) or normal phase (150 × 0.5 mm i.d.). Mobile phase, methanol–water	Cu–acac Cu–ddtc Zn–ddtc Co–ddtc Cr–ddtc Fe–ddtc	Not reported	Micro-HPLC coupled to ICP-AES for analysis of organometallics	21
PlasmaTherm argon ICP. HPLC coupled *via* stainless-steel tubing into a micro-concentric nebulizer	Ion pairing reversed-phase (500 × 1 mm i.d.) C_{18} microbore column (HRSM-50-C_{18}). Mobile phase, water	Reference solution of Mg, Mn, Cd, As, Se, Hg, Sr, Co Ba, Pb and Cr	Absolute detection limit Cr^{III} 2.2 ng As 13.0 ng	—	22
ICP all argon 1.3 kW FP. HPLC coupled *via* Teflon tubing into a cross-flow nebulizer	Anion-exchange column, μ-bondpak-NH_2. Mobile phase, oxylate–Mg buffer	Separation and quantitative analysis of orthophosphate diphosphate and triphosphate	Ortho- 0.5 μg Di- 1.0 μg Tri- 3.0 μg	ATP and ADP also analysed	28
PlasmaTherm ICP 1.0 kW FP. HPLC coupled *via* PTFE tubing to a hydride generation system. The nebulizer was replaced with a gas–liquid separator	Nucleosil SB anion-exchange column (200 mm). Mobile phase, 50 mmol l^{-1} NaH_2PO_4–H_2O buffered to pH 6.75 with Na_2HPO_4–$2H_2O$	Determination of As speciation in aquatic media	As^{III} 3.5 μg l^{-1} As MMA 3.8 μg l^{-1} As DMA 21.3 μg l^{-1} As As^{V} 9.2 mg l^{-1} As	The use of a gas–liquid separator impedes the entrance of the mobile phase into the plasma torch	40
Jarrell Ash 500S argon ICP 2.2 kW FP. HPLC coupled *via* Teflon tubing into a cross-flow nebulizer	Teflon microcolumn (200 × 1 mm i.d.) packed with Fine Gel SC220. Mobile phase, distilled water	Analysis of carbon containing compounds	800 ng of C	—	63

Table 4—*continued*

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
Jarrell-Ash 955 Plasma Atomcomp ICP 0.8–1.2 kW FP. Ion-exchange column coupled *via* PTFE flow injection manifold into a cross-flow nebulizer	Single or parallel preconcentrating ion-exchange columns (20 × 2.3 mm i.d.) packed with Chelex-100 resin. Mobile phase, 2 mol l^{-1} nitric acid	Ba, Be, Cd, Co, Cu, Mn, Ni and Pb standards	Ba 0.04 $\mu g\ l^{-1}$ Be 0.008 $\mu g\ l^{-1}$ Cd 0.04 $\mu g\ l^{-1}$ Co 0.1 $\mu g\ l^{-1}$ Cu 0.2 $\mu g\ l^{-1}$ Mn 0.04 $\mu g\ l^{-1}$ Ni 0.02 $\mu g\ l^{-1}$ Pb 2.0 $\mu g\ l^{-1}$	FI–ion exchange ICP-AES gave a detection limit 20 times better than for conventionally aspirated systems	64
Shimadzu ICPQ-100 ICP 1.3–1.4 kW FP. Ion-exchange column coupled *via* PTFE flow injection manifold into a concentric nebulizer	Preconcentrating ion-exchange microcolumn (20 × 3.2 mm i.d.) packed with Muromac A-1 resin. Mobile phase, 2 mol l^{-1} HNO_3	Determination of Cr^{III}, Ti, V, Fe^{III} and Al	Al 1.5 $\mu g\ l^{-1}$ Cr^{III} 0.21 $\mu g\ l^{-1}$ Fe^{III} 0.11 $\mu g\ l^{-1}$ Ti 0.08 $\mu g\ l^{-1}$ V 0.15 $\mu g\ l^{-1}$	Signal enhancements of 34–113 times better than conventionally aspirated systems were achieved using this system	65
Instrument Laboratory Model 200 ICP. HPLC coupled *via* Teflon tubing into an all glass spray chamber	Two C_{18} columns in series (150 × 3.9 mm i.d.). Mobile phase, 0.06 mol l^{-1} ammonium acetate, 0.005% v/v mercaptoethanol	Determination of inorganic and organomercury compounds	32–62 mg l^{-1} based on a signal-to-noise ratio of 2:1	Post-column cold vapour generation used to improve detection limits	66
Jarrell-Ash 975 AtomComp ICP 1.2 kW FP. HPLC coupled *via* PTFE tubing into the ICP nebulizer	Anion-exchange column (250 × 1.6 mm) packed with sub-400 mesh AGI × 4 anion-exchange resin. Mobile phases, 0.05 mol l^{-1} $(NH_4)_2SO_4$	Determination of NTA and EDTA chelates of Cu, Zn, Ca and Mg	Not reported	For the species studied, the sensitivity of ICP-AES detection was better than, or virtually equal to that of UV detection at 254 nm	67
All argon ICP-AES	Cation-exchange chromatography. Mobile phase, α-hydroxyisobutyric acid or ammonium lactate	Determination of lanthanoids in standard rock samples	Not reported	—	68

tion of selected nuclear fuel materials,[58] impurities in high-purity iron,[59] and, by monitoring sulfur emission, the determination of sulfite in beverages and foods.[60] In a study by LaFreniere *et al.*,[12] a direct injection nebulizer was used for elemental speciation studies on coal process streams and various oil-based samples. The limits of detection achieved using the HPLC–DIN-ICP-AES system for a range of elements (As, Cd, Co, Cr, Cu, Ni, S, Se and Zn), were compared with other coupled techniques. These workers reported that the limits of detection obtained using HPLC–DIN-ICP-AES were either comparable to those obtained by continuous-flow sample introduction into the ICP or inferior by only a factor of four (As), and concluded that this was due to the low dead volume (1.5 μl) associated with the DIN interface, which resulted in low or negligible extra-column analyte dispersion. However, despite this obvious benefit, there have been few subsequent publications in this area, possibly reflecting the practical problems associated with this device as discussed above.

The chromatography associated with the various industrial application has once again been diverse with both anion- and cation-exchange, reversed-phase, and size-exclusion chromatography all being reported. Table 3 gives details of the columns used for these studies together with an overview of the industrial applications reported to date.

2.4 General Analytical Approaches

This section includes publications which do not readily fit into the three categories described in Section 2.1, 2.2 and 2.3. Many of these publications report development work and so do not include 'real' samples. This section covers papers describing work using laboratory standards and synthetic mixtures. However, many of the approaches described could readily be used in one or more of the application areas discussed above.

Once again various types of chromatography have been explored although the interface–detection systems are often evaluated more fully than in some of the applications papers discussed above. Spray chamber construction for example has been investigated with respect to the organic solvents used in HPLC mobile phases[16] and in terms of sample transport mechanisms.[5] The use of different types of nebulizer such as cross-flow micro-concentric,[22,63] ultrasonic[9] and thermospray[8,10,11] have also been evaluated. The use of both flow injection techniques[63,64] and post-column cold vapour generation[40,66] are also included. In some papers two or more of these factors are incorporated into the system used. For example, in one of the more recent papers by Elgersma *et al.*,[11] the performance of a low consumption thermospray nebulizer is described for specific use with micro-HPLC and general use in flow injection with ICP-AES detection.

Table 4 gives further details of the publications that fall into this more general section, and includes work on the element specific detection of over 20 elements.

3 High-performance Liquid Chromatography–Inductively Coupled Plasma Mass Spectrometry

The use of ICP-MS as an element specific detector for HPLC offers both exceptional sensitivity and multi-

element capability. Although ICP-MS can handle the same types of chromatographic eluents as ICP-AES, the better sensitivity often eliminates the need for additional techniques such as post-column derivatization. In addition, the capability of ICP-MS for isotope ratio determinations can also be exploited, thus allowing isotope dilution analyses to be used, where techniques such as spark source mass spectrometry were used in the past. The use of isotope dilution also saves on the time required to prepare multiple chromatograms from which to obtain calibration graphs and compensates for matrix effects. Finally, the ability of HPLC to remove troublesome matrix interferences on-line offers a potential generic advantage for all ICP-MS applications.

The coupling of HPLC with the ICP-MS instrument has been investigated by a number of workers. In one of the first papers in this area by Dean *et al.*,[69] the characteristics of HPLC–ICP-MS couplings were investigated using the number of theoretical plates, peak tailing, rise time and wash-out time as criteria of merit. The HPLC flow rates used in this work were limited to between 0.5 and 1.5 ml min^{-1} in order to remain compatible with the normal range of uptake rates of the cross-flow nebulizer. It was found that the optimum coupling consisted of a short aerosol line with extended liquid transport tubing. More recent papers have tended to adopt a similar approach.

As stated above, ideally the choice of mobile phase to achieve optimum chromatographic separation should not be compromised. In general, although flow rates might be restricted, good separations with relatively short retention times have been reported. However, problems can arise when using ICP-MS with mobile phases containing certain buffers or high concentrations of organic solvent. For example, Heitkemper *et al.*[70] reported that the phosphate buffer system, used in their work on the speciation of arsenic in urine, caused rapid erosion and clogging of the nickel sampling cone. After about 2 h the nickel sampler became badly pitted and salt deposits started to clog the sampling orifice. In this case, a solution was found using an aluminium sampler with a 0.7 mm orifice, which tolerated the phosphate buffer solution well.

The use of mobile phases with high concentrations of organic solvent can be a bigger problem, since they lead to elevated reflected powers, even at high forward powers (FP), which can lead to generator cut-out with extended use. Furthermore, soot deposits on the faces of the sampler and skimmer cones within the ICP-MS interface region result in elevated noise and decreased signals. These problems can be overcome by introducing oxygen into the nebulizer gas,[70,71] although the reflected powers can still be greater than 100 W. An alternative approach is to replace the standard torch supplied with most commercial instruments with a low argon flow torch. This approach was employed by Branch *et al.*,[72] who used a Fassel torch design with 1.3 mm jets in the outer and intermediate gas flow and a configuration ratio of 0.82; this contrasts with gas inlets of 6 mm and a configuration ratio of 0.78 in the standard Fassel torch. When operated at a total argon flow of 10.55 l min^{-1}, the reflected power was less than 25 W and no soot deposition was observed on the cones.

To reduce the amount of organic solvent from the mobile phase actually reaching the plasma, most workers reduce the temperature of the spray chamber,[70,73] although more efficient desolvation can be achieved by passing the aerosol through a heating chamber prior to the cooling condenser.[19,74] A range of desolvation systems have been described, which are capable of removing a large percentage of the organic solvent (up to 80%) prior to its reaching the plasma.[19,75–80] The advantages of such desolvation systems in terms of HPLC–ICP-MS are the increase in plasma stability and the availability of detection limits that are comparable to those obtained during aqueous operation.

3.1 Environmental and General Applications

A number of reports describing off-line preconcentration of trace metals in matrices such as sea-water,[81] and the removal of matrix elements by ion exchange[82] using ICP-MS detection were published in the mid 1980s. However, the first work to look at the feasibility of using ICP-MS as an on-line multi-element detector for HPLC was published by Thompson and Houk in 1986.[83] In the original study, ion pair reversed-phase liquid chromatography was used and sample introduction was achieved by ultrasonic nebulization with aerosol desolvation. The work concentrated on arsenic and selenium species and gave detection limits of the order of 0.1 ng. This study also reported on the precision (<2%) and accuracy (≈1%) when using isotope ratio measurements, and concluded that HPLC–ICP-MS had considerable potential for speciation studies using stable tracer isotopes. Jiang *et al.*[74] also reported on the removal of various ionization interferences by utilizing chromatographic retention of metal complexes in ICP-MS studies.

As with HPLC–ICP-AES, various forms of chromatography have also been employed with ICP-MS. Micellar liquid chromatography has been used for example in the speciation of alkyltin compounds.[71] Trimethyltin chloride, triethyltin bromide and tripropyltin chloride were separated with a 0.1 mol l^{-1} sodium dodecyl sulphate (SDS) micellar mobile phase and C_{18} stationary phase. Detection limits reported for the three tin species were 27, 51 and 111 pg, respectively. Three other tin species were also separated; monomethyltin trichloride, dimethyltin dichloride and trimethyltin chloride. In this case a 0.02 mol l^{-1} SDS mobile phase was used and detection limits of 46, 26 and 126 pg, respectively, where obtained. The maximum SDS concentration for use in this work was shown to be 0.1 mol l^{-1} if clogging of the torch and sampling orifice was to be avoided. Other workers have used ion-exchange resins to separate organotins. Branch *et al.*[72] employed a column packed with Partisil (10 μm) for the determination of tributyltin species in waters. This study also presented the results from a 'blind-trial' of water samples spiked with tributyltin and concluded that HPLC–ICP-MS offered a sensitive and accurate method of determining the tributyltin ion at normal environmental levels. More recently, SFC coupled with ICP-MS has been reported,[84] again for the determination of organotins. In this work, separation of tetraalkyltin compounds gave detection limits in the sub-pg range (0.034 pg for tetrabutyltin and 0.047 pg for tetraphenyltin). The system used was linear over three orders of magnitude (1–1000 pg) and gave an RSD of better than 5%.

Considering the relatively short period of time that ICP-MS has been available in many laboratories, there are a surprising number of publications reporting a range of applications of HPLC–ICP-MS. These include mercury speciation in tuna fish,[85] arsenic in various marine reference materials,[86–88] tin in natural waters[71,72,89,90] and harbour sediments,[91] metals in soil leachates[92] and tellurium compounds in waste water streams.[93] Various applications of HPLC–ICP-MS in marine analytical chemistry have also been reviewed by McLaren *et al.*[91] This publication discusses the speciation of mercury and tin in some detail as well as the application of isotope dilution studies for metal speciation in marine samples. Details of the various environmental applications of coupled HPLC–ICP-MS are presented in Table 5.

3.2 Clinical and Industrial Applications

In terms of clinical and industrial applications for HPLC–ICP-MS, arsenic has been one of the elements to receive most attention. This reflects both the widespread interest in this element and the problems of determining

Table 5 HPLC–ICP-MS applications (environmental and analytical)

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
VG PlasmaQuad 1.65 kW FP. HPLC coupled to ICP *via* Teflon tubing into a standard nebulizer	Spherisorb ion pair ODS-2 column or Adsorbosphere SCX ion-exchange column	Speciation and detection of organotin compounds	ICP-MS, 0.4–1.0 ng Sn ICP-AES, 200–1700 ng Sn	Major Sn isotope measured at 120	71
VG PlasmaQuad ICP-MS 1.0–1.8 kW FP. HPLC coupled to ICP *via* silicon rubber tubing into a standard nebulizer. Survey scan data acquisition mode	Partisil STX column (250×4.6 mm i.d.). Mobile phase, 80+20 methanol–water, 0.1 mol l^{-1} with respect to ammonium acetate	Monitoring TBT in waters	Low flow torch 500 ng ml^{-1} Standard torch, 25 ng ml^{-1}	Standard and low flow torches used	72
SCIEX Elan 250 ICP-MS 1.25 kW FP. HPLC effluent from column coupled to ICP-MS *via* an ultrasonic nebulizer Multiple-ion monitoring mode	Hamilton PRP-1 column (150×4.1 mm i.d.). Mobile phase, *N*-methyl-fluorohydroxamic acid, de-ionized, distilled water with 2% ethanol	Study of the retention of complexes of Mo^{VI} and Ti^{IV} in 1% HNO_3 in distilled water using chromatographic retention	Cu 2 $\mu g\ l^{-1}$ Zn 1 $\mu g\ l^{-1}$ Cd 1 $\mu g\ l^{-1}$	—	74
SCIEX-Elan 250 ICP-MS 1.2 kW FP. HPLC coupled to ICP-MS *via* stainless-steel tubing into an ultrasonic nebulizer. Operating in peak hopping mode	Econosphere C_{18} column (250×4.6 mm i.d.). Mobile phase, 5% methanol in water, 0.005 mol l^{-1} PIC-135 pH 3.0	Elemental speciation of 30 elements, particularly As and Se	Near 0.1 ng (as element) for six species of As and Se	—	83
VG PlasmaQuad ICP-MS 1.35 kW FP. SFC coupled to ICP-MS *via* a stainless-steel heated transfer line directly into the ICP injector	SB-Octyl-50 capillary column housed in a gas chromatograph. Mobile phase, bone dry grade carbon dioxide	Separation of tetraalkyltin compounds	TBT 0.034 pg TPT 0.047 pg	—	84
VG PlasmaQuad ICP-MS 1.3 kW FP. HPLC coupled to ICP *via* Teflon (FEP) tubing into nebulizer inlet	Waters PicoTag C_{18} column. Mobile phase, 0.06 mol l^{-1} ammonium acetate, 3% acetonitrile and 0.005% v/v 2-mercaptoethanol pH 5.3–6.8	Hg speciation in NBS RM-50 Albacore Tuna sample and thimerosal in contact lens solution	LC–ICP-MS, 0.6–1.2 ng ml^{-1} for three mercury species LC–cold vapour ICP-MS, 7–20 ng ml^{-1} for three mercury species	(*i*) For post column Hg cold vapour generation, spray chamber replaced with glass chamber. (*ii*) Optimized at *m/z* 201 to minimize background at 202	85
SCIEX Elan 250 ICP-MS 1.4 kW FP. HPLC coupled to ICP *via* Teflon tubing into a standard nebulizer. Single-ion monitoring mode	Pierce C_{18} column (300×4.6 mm i.d.). Mobile phase, 1.0 mmol l^{-1} sodium dodecyl sulfate 5% methanol, 2.5% acetic acid	Quantification of As species in Dogfish Muscle reference material (DORM-1)	Arsenobetaine 300 pg of As	FI–ICP-MS detection limits were compared. Arsenobetaine 30 pg of As	86
SCIEX Elan 250 ICP-MS 1.4 kW FP. HPLC coupled to ICP *via* Teflon tubing into a standard nebulizer. Multi-element analysis mode	Columns either anion pairing, anion exchange, or cation pairing	Determination of As species in DORM-1	Absolute detection limit 50–300 pg	Anion pairing found to be more sensitive to changes in matrix, anion exchange more tolerant. Cation pairing more suitable for DMA and AsB in biological samples with high salt content	87
Yokogawa PMS100 ICP-MS 1.3 kW FP. HPLC coupled to ICP *via* Teflon tubing into a concentric nebulizer	Asahipak GS220 reversed-phase gel permeation column (500×7.6). Intersil ODS-2 reversed-phase column (250×4.6) Mobile phase, anionic As, TRA pairing ion pH 7; cationic As, alkylsulfonate pH 3	Separation and detection of 15 As compounds from natural samples including human urine after eating fish	Arsenobetaine (VIII) and cacodylate (IV) 20–50 pg of As	—	88

Table 5—*continued*

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
VG PlasmaQuad ICP-MS 1.3 kW FP. HPLC coupled to ICP *via* Teflon capillary tubing into a standard concentric nebulizer	Spherisorb ODS-2 column (500 × 4.6 mm i.d.) Mobile phase, prepared by addition of the appropriate modifier to the stock solution and diluted with 3% v/v propanol	Speciation of alkyltin compounds	TMT–Cl 27 pg TET–Br 51 pg TPrT–Cl 111 pg MMT–TCl 46 pg DMT–DCl 26 pg	Micellar LC applied using 0.1 or 0.02 mol l^{-1} SDS micellar mobile phase	89
VG PlasmaQuad ICP-MS 1.35 kW FP. SFC coupled to ICP *via* insulated copper tubing from the GC oven into the ICP torch	Octyl-50 capillary column (2.5 × 50 mm i.d.) fitted into a Hewlett-Packard 5890 series II GC oven. Mobile phase, bone dry grade liquid CO_2	Determination of ultra-trace levels of organotin compounds	Tetrabutyltin 0.034 pg Tetraphenyltin 0.047 pg	—	90
SCIEX Elan 500 ICP-MS 1.2 kW FP. Fitted with a thermostated nebulizer spray chamber	Strong cation-exchange column	Determination of tributyltin and dibutyltin in the harbour sediment reference material PACS-1	Tributyltin 5 ng g^{-1} Sn Dibutyltin 12 ng g^{-1} Sn	—	91
SCIEX Elan 500 ICP-MS. 1.2 kW FP. HPLC coupled to ICP-MS *via* 0.5 mm i.d. tubing into the nebulizer	Superose-12 size exclusion column. Mobile phase, 0.2 mol l^{-1} ammonium acetate pH 3.6–5.2	Determination of organic and inorganic Al, Mn, Fe, Ni, Cu, Zn, Cd and La in soil leachates	Not reported	At a higher pH more organic material was dissolved, whereas the total metal concentration was usually lower	92
SCIEX Elan 500 ICP-MS 1.5 kW FP. HPLC coupled to ICP *via* PTFE tubing into a Meinhard type nebulizer	Dionex ion chromatography AG4A + AS4A column. Mobile phase: eluent 1, 200 mg l^{-1} NaOH eluent 2, 500 mg l^{-1} Na_2CO_3 eluent 3, 500 mg l^{-1} $NaHCO_3$ Eluent 4, H_2O	Determination of Te compounds in waste water streams	Not reported	—	93
SCIEX Elan 250 ICP-MS 1.25 kW FP. HPLC coupled to ICP *via* stainless-steel tubing into an ultrasonic nebulizer	Hamilton PRP-1 or Vydal 201TP. Ion-pairing reagent and mobile phase dependant on compound to be separated	Detection of P and S compounds	0.4–4.0 ng P 7.0 ng S	Analyte sensitivity decreases as organic modifier concentration in mobile phase increases	94
SCIEX Elan 500 ICP-MS	Anion-exchange chromatography using SGE 250GL-SAX columns (250 × 2 mm). Mobile phase, ammonium acetate buffer and acetonitrile	Analysis of target and non-target pollutants in aqueous leachates, including Cl, other halogens, P and S	Not reported	Preliminary data presented on an anion-exchange chromatography particle beam–MS based technique for the detection of the target compound, 4-chlorobenzene sulfonic acid	95
VG PlasmaQuad ICP-MS 1.3 kW FP. HPLC coupled to ICP-MS *via* Teflon FEP tubing into the nebulizer	Waters PicoTag C_{18} column (isocratic separation). Mobile phase, 0.4 mol l^{-1} 2-hydroxy-2-methylpropanoic acid, 0.02 mol l^{-1} octanesulfonic acid (pH 3.8). BakerBond WP C_{18} column (gradient separation). Mobile phase, 0.05–0.4 mol l^{-1} 2-hydroxy-2-methyl propanoic acid	Determination of rare earth elements in SRM 1633a Fly Ash	Ho 0.4 ng ml^{-1} La 5.0 ng ml^{-1}	Spray chamber cooled to 8 °C	96
SCIEX Elan 250 ICP-MS 1.3 kW FP. HPLC coupled to ICP-MS *via* a direct injection nebulizer (DIN)	Metal free GLT column packed with Intersil ODS-2 (5 μm). Mobile phase, 5 or 25% methanol in water with ion-pair reagent	Charged species of Sn and As separated as ion pairs	Sn 16–20 μg l^{-1} As 0.4–1.2 μg l^{-1}	The use of DIN improved the detection limit by 1–2 orders of magnitude	97
VG PlasmaQuad ICP-MS 1.35 kW FP. HPLC coupled to ICP-MS *via* Polyplex tubing into a type C-1 concentric nebulizer	Wescan Anion/R-IC ion-chromatography column (250 × 4.1 mm). Mobile phase, ammonium carbonate and ammonium hydrogen carbonate buffered to pH 7.5	Speciation of As in urine, club soda and wine	As^{III} 0.063 ng As^{V} 0.037 ng DMA 0.032 ng MMA 0.080 ng	Sensitivity was improved by using an He–Ar mixed-gas ICP as the ionization source	98

Table 5—*continued*

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
All argon ICP-MS. HPLC coupled to ICP-MS *via* a Tefzel transfer line	Dionex AS4A anion-exchange column. Mobile phase, 6 mmol l^{-1} ammonium sulfate or 10 μmol l^{-1} $HClO_4$ buffered to pH 9	Determination of hexavalent Cr	Cr^{VI} 0.4 μg ml^{-1}	This method was compared with a method using the same ion-chromatographic separation coupled with colorimetry. Detection limits were comparable for both techniques.	99
All argon ICP-MS	Ion pair reversed-phase chromatography	Pb speciation in a lead fuel reference material and a water quality control sample	Inorganic Pb 0.37 ng TEL 0.14 ng TPhL 0.17 ng TTEL 3.9 ng	—	100

arsenic species using more traditional forms of analysis. Whilst hydride generation is well suited to the reducible forms of arsenic, species such as arsenobetaine are not suited to this approach and so were often estimated by subtraction once the reducible forms and total arsenic had been determined. The HPLC–ICP-MS method overcomes this problem and allows both the reducible and non-reducible forms of arsenic to be determined with good sensitivity. Heitkemper *et al.*[70] have used this technique to determine arsenic in urine. Four arsenic species were determined: arsenic; arsenate; dimethylarsinate; and monomethylarsonate, using an anion-exchange system. The determination of the arsenite (As^{3+}) was however complicated by the presence of $^{40}Ar^{35}Cl$ ions ($m/z=75$) resulting from the correlation of chlorine-containing species. In a later work the same group reduced the interference by employing ion chromatography to resolve the chloride from the arsenic compounds.[73] A 20-fold dilution of the urine samples was necessary to avoid column overloading from chloride and subsequent argon chloride interference. Recently Hill *et al.*[101] have shown that the ArCl interference can be eliminated by the addition of nitrogen to the outer and nebulizer gas flows in the presence of 1% m/v chloride. These workers have also shown that the addition of nitrogen aids the determination of selenium and vanadium in the presence of chloride and in addition promotes the reduction of Mo^+ and ArO^+ interferences and the background response.

Several studies in this area have utilized HPLC–ICP-MS for studies of metalloprotein species. Dean *et al.*[69] investigated the characteristics of HPLC–ICP-MS couplings for this sort of application using the number of theoretical plates, peak tailing, rise time and wash-out time as criteria of merit. They found that a short aerosol connection line was optimal and, when compared with on-line UV monitoring, ICP-MS gave a comparable number of theoretical plates. In another study on metalloproteins, Mason *et al.*[102] used size-exclusion HPLC coupled with ICP-MS and concluded that the technique had considerable potential for the rapid quantitative analysis of metals associated with cytosolic metal-binding ligands. The greatest limitation encountered was the ability to effectively separate the various metal binding moieties, although the workers suggest that this might be overcome using tandam HPLC systems, *e.g.*, size exclusion followed by ion exchange.

Other studies that can be placed under the general heading of clinical and industrial applications include the determination of lead and other trace element species in blood by size-exclusion chromatography–ICP-MS,[103] the determination of cadmium species in kidney,[104] the determination of gold-based drug metabolites in human blood,[105] the use of reversed-phase chromatography for the separation of zinc species in chicken meat,[98] the determination of thiomersal (thimerosal) in biological products[106] and, in one of the few industrial applications, the determination of rare earth impurities.[107] Details of these application are presented in Table 6.

4 Gas Chromatography–Inductively Coupled Plasma Atomic Emission Spectrometry

The first couplings of a gas chromatograph to an ICP were reported in the late 1970s. In one of the first studies, Windsor and Denton[111] explored the capabilities of ICP-AES for the elemental analysis of organic compounds using an all argon plasma. In this work various organic and organometallic compounds were determined utilizing the simultaneous multi-element capabilities of the coupling. The interface employed for the study used a T-junction which enabled an argon make-up gas to be added to the eluent from the packed column gas chromatograph which was connected to a demountable ICP torch. The optical system incorporated a 0.35 m scanning monochromator and a 1.5 m, 0.02 nm resolution multichannel direct-reading spectrometer.

In a later report the same group extended their work to derive empirical formulae for a number of organic compounds, although with limited success.[112] During the same period, Sommer and Ohls used a GC–ICP technique employing both all-argon-and nitrogen-cooled plasmas for the determination of tetraalkyllead compounds[113] and nickel and zinc diethyldithiocarbamates (ddtc),[114] whilst Fry *et al.*[115] investigated a large number of fluorine atom lines for the selective detection of various fluorine-containing organic compounds. This latter group of workers also monitored near-infrared oxygen emissions to enable oxygen-specific detection.[116]

Despite this early activity, the ICP has never been widely adopted as a GC detector and there have been very few papers on the subject since the early 1980s. This is in contrast to the adoption of ICPs for detection in HPLC monitoring and the use of microwave induced plasmas (MIPs) for GC work.[117] The use of an ICP does offer the advantage of withstanding organic solvents more readily than does an MIP because of its higher gas temperature. In addition, oxygen or nitrogen does not have to be added to the plasma to reduce deposits, since, although deposits can sometimes form on the inside of an extended ICP coolant tube, they are formed well above the observation zone. However, these advantages are outweighed by the fact that the performance levels for non-metals are much inferior to those using an MIP, and so whilst GC–ICP couplings are now very seldom used, GC–MIP has seen something of a revival in recent years with the introduction of a second generation of commercial instruments.

Table 7 gives details of the various applications that have been published for GC–ICP-AES.

Table 6 HPLC–ICP-MS applications (clinical and industrial)

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
VG PlasmaQuad ICP-MS 1.35 kW FP. HPLC coupled to ICP-MS *via* PTFE tubing into crossflow nebulizer. Single-ion monitoring mode	Superose-12 SEC column capable of separating proteins of relative molecular mass 1000–300000. Mobile phase, 0.12 mol l^{-1} Tris·HCl pH 7.5	Study of metallo-proteins in gel filtration standard and solutions of metallo-thionein and ferritin	Not reported	Physical coupling was studied in detail particularly involving minimum liquid transport and extended aerosol transport, and *vice versa*	69
VG PlasmaQuad ICP-MS 1.5 kW FP. HPLC coupled to ICP *via* Flexon HP tubing into a concentric nebulizer	Weak anion-exchange column (250×4.6 mm i.d.). Mobile phase, 30% methanol–15 mmol l^{-1} $NH_4H_2PO_4$–1.5 mmol l^{-1} CH_3COONH_4 pH 5.75	Speciation of As in urine	20–91 pg in aqueous media 36–96 pg in urine	Determination of As^{3+} complicated by interference from co-elution of Cl-containing species forming $ArCl^+$ ions	70
VG PlasmaQuad ICP-MS 1.35 kW FP. HPLC coupled to ICP-MS *via* Polyplex tubing	Wescan anion R-IC column (250×4.1 mm i.d.) Mobile phase, 5 m mol l^{-1} phthalic acid	Elimination of $AgCl^+$ interference from As speciation in urine samples	A^{III} 340 pg As^V 420 pg DMA 700 pg	—	73
VG PlasmaQuad Ar–ICP-MS 1.35 kW FP. He–ICP-MS 1.55 kW FP. Type C-1 concentric. nebulizer	Wescan anion R-IC column (250×4.1 mm i.d.). Gradient programme using 2% propan-1-ol and 50 mmol l^{-1} carbonate buffer, pH 7.5	As in urine	As^{III} 4.95 μg l^{-1} As^V 6.0 μg l^{-1} DMA 1.2 μg l^{-1} MMA 3.6 μg l^{-1} (100 ml injection)	Paper also contains results for As speciation in club soda and wine	108
VG PlasmaQuad ICP-MS 1.25 kW FP. HPLC coupled to ICP *via* Teflon capillary tubing into a standard concentric nebulizer	Spherogel TSK SW 2000 size-exclusion column (600×7.5 mm). Mobile phase, 0.06 mol l^{-1} Tris·HCl, 0.05% NaN_3 pH 7.5	Separation and elemental analysis of metallo-proteins in biological samples	Absolute: 240–350 pg of protein (calculated from the peak areas of the Cd signal)	The techniques' versatility has been demonstrated by quantitative multi-element analysis of cytosolic metal-binding proteins separated from a species of polychaete worm	102
SCIEX Elan 250 ICP-MS 1.3 kW FP. HPLC coupled to ICP *via* PTFE tubing into a cross-flow nebulizer	TSK G 3000 SW size-exclusion column (300×7 mm). Mobile phase, 0.1 mol l^{-1} Tris·HCl pH 7.2	Determination of lead and other trace element species in blood	Pb in protein fraction 0.15–0.05 μg l^{-1}	—	103
VG PlasmaQuad ICP-MS 1.3 kW FP. HPLC coupled to ICP *via* Teflon tubing into a cross-flow nebulizer. Single-ion monitoring mode	Superose-12 SEC column. Mobile phase, 0.12 mol l^{-1} Tris·HCl pH 7.5	Investigation of Cd speciation in kidney	Not reported	—	104
SCIEX Elan 250 ICP-MS 1.3 kW FP. HPLC coupled to ICP *via* PTFE tubing into a concentric nebulizer. Multi-element mode	(*a*) Altech WAX300 anion-exchange column. Mobile phase, 15 min gradient from 20–200 mmol l^{-1} Tris buffer (*b*) TSK 250 SEC column. Mobile phase, aqueous 25 mmol l^{-1} Tris buffer	Determination of Au drug metabolites in human blood	Cu 3.0 pg Cd 7.0 pg Zn 8.0 pg Au 10.0 pg	—	105
VG PlasmaQuad PQ2 Turbo Plus ICP-MS 1.35 kW FP. HPLC coupled to ICP-MS *via* a V7 manual valve into a de Galan nebulizer	Both size-exclusion and reversed-phase chromatography	Size exclusion chromatography was used to separate known proteins. Reversed-phase chromatography was used to separate Zn-containing species in chicken meat	Not reported	—	98
VG PlasmaQuad ICP-MS. Procedure as per ref. 82	Waters PicoTag C_{18} column Procedure as per ref. 82	Determination of thimerosal and biological products	Not reported	Spray chamber cooled to 8 °C	106
Yokogawa PMS200 ICP-MS 1.4 kW FP. HPLC coupled to ICP *via* PTFE tubing into a Meinhard concentric nebulizer	Yokogawa Excelpak ICS-C35 (150×4.6 mm) and ICS-C15 (125×4.9) ion-chromatography columns. Mobile phase, either, lactic acid or hydroxyisobutyric acid. Both adjusted to pH 4.3	Determination of rare earth elements as impurities in other rare earth materials	1.0–5.0 pg ml^{-1} for 14 rare earth elements	—	107
All argon ICP-MS	Gel permeation liquid chromatography	Determination of Fe-containing proteins	Ferritin 0.01 μg Haemoglobin 1.0 μg Myoglobin 0.7 μg Cytochrome *c* 0.4 μg	—	109
SCIEX Elan 250 ICP-MS 1.4 kW FP. HPLC coupled to ICP *via* a narrow bore Polysil tubing into a direct injection nebulizer (DIN)	PEEK micro-bore column packed with reversed-phase C_{18} material. Mobile phase, ammoniun salts of S5, S7 and S12	Speciation of Hg and Pb compounds in human urine	MePb 0.2 pg Pb EtPb 0.2 pg Pb MeHg 18 pg Hg	—	110

Table 7 GC–ICP-MS/AES applications

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
All argon ICP. GC coupled *via* stainless-steel tubing into a demountable ICP torch	6 ft × 1/8 in o.d. column packed with 8% Carbowax 1540 on 80/100 mesh firebrick	Simultaneous multi-element analysis of GC effluents	Br 2×10^5 ng C 12.0 ng Cl 7×10^3 ng Fe 5.9 ng Pb 33.0 ng	—	111
Jarrell-Ash 66-100 ICP 0.8 kW FP. GC coupled to ICP *via* stainless-steel tubing into the sample tube of the plasma torch	6 ft × 3.175 mm o.d. column packed with 8% carbowax 1540 on 80/100 mesh firebrick	Determination of the elemental compositions and empirical formulae of hydrocarbons and halogens	Not reported	—	112
PlasmaTherm 250 ICP 1.5 kW FP. GC coupled to ICP *via* heated stainless-steel tubing	6 ft × 1/8 in capillary column packed with Amine 220. Carrier gas argon	Determination of F	F 1 mg	—	115
PlasmaTherm 2500 ICP 1.75 kW FP. GC coupled to ICP *via* heated stainless-steel tubing	122 × 0.46 mm capillary column packed with 10% Carbowax on 80–100 mesh Chromosorb P. Carrier gas argon	Selective quantitative determination of O in volatile liquid mixtures	O 650 ng	The detection limit for the GC–ICP system was considerably worse than for direct gas sampling loops (20 ng) owing to band spreading on the GC column	116
PlasmaTherm 2500 all argon ICP 1.85 kW FP. Heated transfer line connecting GC to ICP-AES	4 ft × 1/8 in nickel tube column packed with 80–100 mesh Chromosorb WHP. Stationary phase, 20% amine 220. Carrier gas argon	Detection of N-containing compounds	N 0.25 μg	—	118
All argon plasma ICP 1 kW FP	3.5 ft × 3 mm i.d. column packed with chromosorb 102	Ge, As, Sn, Sb hydrides generated, cold trapped and passed through plasma	Ge 4 ng As 50 ng Sb 50 ng	—	119
PlasmaTherm HFP2500 ICP 1.5 kW FP. GC coupled *via* glass lined stainless-steel capillary tubing directly into the plasma torch	1.8 m × 2 mm i.d. borosilicate column packed with 5% OV-101 on Chrom W-HP 80–100 mesh. Carrier gas argon	Determination of volatile organometallic species in complex mixtures such as the products of coal conversion	Pb 6 pg Sn 25 pg Fe 15 pg Se 100 pg Si 40 pg Cr 60 pg C 75 pg	A number of organoselenium compounds were observed in the gasification by-products of a spiked coal sample	120
R.f. plasma detector consisting of a helium r.f. plasma doped with a small amount of oxygen in a 1 mm i.d. quartz tube. GC coupled directly to the system	200 μm i.d. fused silica column coated with methyl or biphenyl polysiloxane. Carrier gas, oxygen	Detection of S compounds in fossil fuels	S 0.5 pg s^{-1}	Detection limits, selectivity and linearity were all considerably better than those achieved using flame photometric detection	121
Daini Seikosha ICP-AES 0.5–1.1 kW FP. GC coupled to ICP *via* PTFE tubing, heated with a tape heater to 150 °C	Fused silica capillary column coated with methylsilicone. Carrier gas, helium. Flow rate, 7.5 ml min^{-1}	Determination of methylmercury species	Methylmercury as Hg 3 pg	Methylmercury species were converted into the iodide form	122
VG PlasmaQuad 2 ICP-MS 1.5 kW FP. GC coupled to ICP *via* heated transfer line with an aluminium core through which the capillary is passed	25 m × 0.32 mm high-temperature column packed with a siloxane carborane stationary phase. Carrier gas, helium	Analysis of alkyllead species in fuel	TEL 0.7 pg s^{-1}	This method is also applicable to the analysis of relatively non-volatile organometallics	123
All argon plasma ICP-MS 1.35 kW FP. GC connected to ICP *via* glass lined stainless-steel tubing	Molecular sieve adsorbent column. Stationary phase, 10% didecyl phthalate–10% carbowax 20 mol l^{-1} Carrier gas, argon	Multi-element analysis and isotope ratio determinations in individual organic compounds	Range 0.001–400 ng s^{-1}	—	124

Table 7—*continued*

Detector	Chromatography	Sample	Detection limits	Comments	Ref.
SCIEX Elan ICP-MS 1.25 or 1.5 kW FP. GC coupled to ICP *via* heated stainless-steel tubing (0.5 m)	Column, 3% OV-1 on Chromosorb W. Carrier gas, argon 8 ml min^{-1} and oxygen 2 ml min^{-1}	Separation and determination of pentylated Sn compounds	Me_3SnPe 6 ng Me_2SnPe 16 ng $MeSnPe_3$ 10 ng	Limits of detection achieved in this preliminary work were worse by over 2 orders of magnitude than electrothermal atomic bsorption detection	126
All argon axially viewed ICP-AES	Fused silica capillary column coated with methylsilicone	Determination of methylmercury species in air	Methylmercury 3 pg as Hg	—	127

5 Gas Chromatography–Inductively Coupled Plasma Mass Spectrometry

The analytical capabilities of using a mass spectrometer to monitor ionic species from an ICP have been well known since the mid-1980s. Now that many laboratories have ICP-MS available, it is perhaps not surprising that once again workers are starting to re-evaluate the elemental analysis of individual compounds eluting from a gas chromatograph using this state-of-the-art detection system. One of the first papers to report a GC–ICP-MS coupling was by Chong and Houk in 1987.[124] In this work a GC with a packed column was interfaced to an ICP-MS in order to yield atomic mass spectra of a number of organic compounds. The detection limits obtained were in the range 0.001–500 ng s^{-1}, depending on the ionization energy of the element and its abundance in the background spectrum. This study also exploited the possibility of isotope ratio work using ICP-MS, although the precision reported was not adequate to study the effects of isotopic fractionation by natural physiochemical processes such as those occurring in geological samples, food products and biological tissues.

To date however, little work has been published on GC–ICP-MS, although a number of research groups have recently reported developments using capillary GC–ICP-MS at conferences. Capillary GC provides good efficiency and rapid separation but the mass loading that is possible, without overloading the column and, hence, degrading resolution, can restrict detection limits. The most recently published work in this area[123] described the construction of a capillary GC–ICP-MS interface and its application to the speciation of alkylleads in fuel. However, the technique lends itself to the determination of a range of organometallic compounds, and Kim *et al.*[127] have successfully used the interface for a retention index window (volatility range) in excess of 3400 (C_{34}). Published applications of GC–ICP-MS are presented in Table 7.

6 Conclusions

It is clear that with the growing demand for species-specific information on many elements, present in a wide range of matrices, many laboratories have adopted the approach of coupling the separatory powers of chromatography with the element-specific detection offered by atomic spectroscopy. The reluctance of many laboratory managers in the past to bring together the necessary equipment, often traditionally sited in different sections of the laboratory, has been overcome by the wealth of evidence that is now available to support the use of directly coupled techniques to obtained unequivocal information for speciation studies. The use of plasmas to monitor not only metal emission lines, but also carbon lines could, providing non-carbon containing eluents are used, offer a universal HPLC detector. Many of the early problems associated with the use of ICP-AES as the detector have now been alleviated, although, for many environmental samples, detection limits are still a problem. The use of ICP-MS however not only provides a means of obtaining significantly lower detection limits but also provides the facility for isotope dilution studies and, by utilizing the simultaneous multi-element capabilities, gives a truly versatile detection system.

Most of the interface systems currently in use are relatively cheap and easy to construct, require few (if any) modifications to existing instrumentation, have short installation times and can be readily demounted when not in use. Much work has also been conducted on sample introduction systems, *e.g.*, novel desolvation devices, which might also aid the construction of coupled liquid chromatography–plasma systems since they greatly reduce the problems associated with high solvent loadings in the plasma. Most work to date has utilized the versatility of HPLC for separating the species of interest, although more recent developments in coupling capillary GC with ICP-MS offer some exciting possibilities for the future.

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