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REVIEW

HYPHENATED FLOW INJECTION SYSTEMS AND HIGH DISCRIMINATION INSTRUMENTS

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Summary—An overview of the state-of-the-art in flow injection analysis (FIA) coupled to instruments capable of providing either multidetection and/or multi-information is reported. The versatility of FIA endows the hyphenated instruments with analytical capabilities which increase from simple sample introduction to more complex sample handling such as automatic dilution and calibration, solvent exchange, derivatization reactions and on-line separation processes, among others. Unexplored aspects of these powerful problem solvers are also discussed.

Unaffordable analytical problems have found proper solutions since the appearance of 'hyphenated techniques', a term coined by Hirschfield at the beginning of the last decade[1] to name the coupling of two or more powerful techniques or instruments to achieve a synergistic effect of their overall performance with respect to their separate use. Liquid,[2,3] gas[4] and supercritical fluid[5] chromatographic techniques interfaced with mass spectrometric or with atomic spectrometric instruments[6] are examples of the excellent performance of these complex systems, as is the mass spectrometry–mass spectrometry tandem.[7] Most of the cases of hyphenated techniques entail powerful, large, expensive units, whose capabilities compensate for both high acquisition and maintenance costs.

Flow injection analysis (FIA)[8–10] is a simple and inexpensive technique the versatility of which affords for developing steps of the analytical process of rather different complexity. The simplest use of FIA is as a way for introducing samples into a detector, which is far from demonstrating the capabilities of this technique. Nevertheless, this simple use enables the sampling frequency to be dramatically increased and reduce the sample and reagent consumption. More interesting is the use of FIA to implement on-line derivatization reactions,[11] separation processes[12,13] as well as a number of sample handling modes to fit the initial sample conditions to the most suitable for single and multidetection[14,15] or implementation of flow-through (bio)chemical sensors,[16–18] among others.

Most of the detectors coupled to FI manifolds, either for sample introduction or for more complex sample handling, have been conventional instruments (e.g. molecular, atomic optical or electrochemical) capable of providing only two dimensional information. As happened with chromatographic techniques,[19] the first attempts to obtain three dimensional information in FIA were performed using either fast scan electrochemical[20] or diode array detectors,[21] thus enlarging the scope of application of FIA to more complex chemical systems. In a parallel but delayed development of hyphenated systems in chromatography, the coupling of FIA with high discrimination instruments pointed out the maturity of this dynamic technique. This last step in FIA started with the FIA–ICP-AES coupling. The capability of ICP-AES for multidetermination has been aided by FIA in different aspects since the earliest 1980's as listed in Table 1[41–103] and has been reviewed by different authors.[22–24] More recent and less numerous have been the arrangements of FI manifolds with instruments which enable three dimensional information and high

Table 1. FIA–ICP coupling

Technique	FIA contribution	Analyte(s)	Sample(s)	Sample volume (μl)	Sampling frequency (hr^{-1})	Detection limit	Other aspects	Ref.
ICP-AES	Sample introduction	Ca	Synthetic, water, cements	25–300	90–320	40–400 *ng/ml*		41–43
		B	Water	300	320			44
		Organometallic Cd, Pb, Zn		50		0.139 *μg/ml*	Interface performance studies	45
		Non-metals (Br, C, Cl, S)	Gaseous samples (SF_6, CF_2Cl_2, CF_3Br in Ar)	15–500		50, 30, 80, 20 *pg*		46
		Metal Acetylacetone complexes		50 *μl*			Complex stability studies. Optimization SFC–DAD–ICP system. Supercritical FI system	47
		Trace elements (Cu, Fe, Mg)	Fine chemicals				FI slurry atomization	48
		Sc	Technological processing solution (containing ~ 30 *mg/ml* Fe and 10 *mg/ml* Ti)	500		8.4 *ng/ml*		49
		Ca, Mg	Synthetic	114			Interference studies. Kalman Filter	50
		Multielements	Synthetic	100–500		0.5–6 *ng/ml*		43, 51
			Used lubricating oils	500	45	0.02–1.3 *μg/g*	Robotics	52
			Alloys				On-line electrolytic dissolution	53
			Biological samples	20–50		10–340 *ng/ml*	Reduced sample volume	54, 55
			Synthetic (aqueous and organic solutions)	10–300	60	0.3–500 *ng/ml*	Interface studies	56–60
	Sample handling		Synthetic Reference oils	500			Interference studies	61, 62
		Sc		22.2–88.8			FI slurry automization	63
		Si	85% phosphoric acid sample	177			On-line dilution	64
		Cu	Burt filtrates (from Zn plant)	150	110		On-line standard addition	65
		Rare-earth	Metal samples				On-line matrix matching calibration	66
		Cu, Ni, Zn	Alloys	500			On-line standard addition. Reverse-FIA	67
		Zn, Mn, Ca	Plant digests	100	132		On-line standard addition	68
		Multielements	Lubricating oils		80		On-line standard addition	69
			Water		60		On-line dilution	70
							Standard salinity matching	71

		Botanical SRM	15			Time-based injection	
		Botanical SRM	15			On-line standard On-line standard addition (computer-guided). Time-based injection	
		Rocks RM	500	120		addition (zone sampling)	73
On-line separation process (I). Liquid–solid interfaces	Au	Refinery effluent water	10 *ml* (250 eluent)	6	1 *ng/ml*	Amberlyst A-26, mercaptoacetoxy-cellulose	74
	Mo	Seawater	10–50 *ml*		0.2 *ng/ml*	Activated alumina	75
	Cr(III)	Human urine	10 *ml*		0.05 *ng/ml*	Activated alumina	76
	Al	Potable waters and haemodialysis fluids	1000 (100 eluent)		3 *ng/ml*	Chelex 100, Amberlite, Dowex	77–78
	B		250			Amberlite XA-743 resin. Time-based injection	79
	Cu	Synthetic seawater	1 *ml*	30	0.16 *ng/ml*	C_{18} bonded silica MIP*–AES	80
	P	Steels	200	45	0.6 *μg/ml*	Activated alumina	81
	I^-, IO_3^-		10 *ml*		0.75, 31 *ng/ml*	Anion-exchange (AGI-X8 resin). On-line oxidatin to I_2	82
	SO_4^{2-}	Natural waters, seawater, boiler-feed water	2 *ml* (200 eluent)		2.8 *ng/ml*	Acidic alumina	83
	Oxyanions		200			Activated alumina	84
	Organotin compounds	River water	10–50 *ml* (250 eluent)		0.15–0.2 *pg*	C_{18} bonded silica. Speciation by chromatography–MIP*–AES	85
	Multielements	Synthetic	6–30 *ml*	30	0.008–20 *ng/ml*	Chelex 100. In parallel columns	86
		Waters	7.5–80 *ml*	12–20	0.009–2 *ng/ml*	Chelating resin, basic alumina	87–89
		Serum	0.5–2.5 *ml*		0.3–5.1 *ng/ml*	Desolvation device	90, 91
		Alkali metal salts	35 *ml*	20	0.0021–0.12 *μg/g*	Chelating-cellulose	92
		Aluminium alloys				Chelating-cellulose Al and Na removal	93

continued

Table 1. *continued*

Technique	FIA contribution	Analyte(s)	Sample(s)	Sample volume (μl)	Sampling frequency (hr^{-1})	Detection limit	Other aspects	Ref.
		Metals	Salts solutions	350–500 *ml*	2–8	*pg/ml*	Donnan dialysis preconcentration	94
	On-line separation process (II). Liquid–liquid interfaces	F^-	Waters	200	36	30 *ng/ml*	Indirect determination liq–liq extraction (La-alizarin complexone fluoride complex)	95
		Be	Mg–Al alloys, Cu alloys	500	25	50 ng/ml	Liq–liq extraction. Microporous PTFE tubing separator	96
		Cu	SRM water	3 *ml*	25	0.1 *ng/ml*	Liq–Liq extraction (dithizone in CCl_4)	97
		Cd	SRM (biological)	5 *ml*	20	0.4 *ng/ml*	Liq–liq extraction. Suction-cup sampling	98
	On-line separation process (III). Gas–liquid interfaces	Organic C	Water (containing 500 *mg/l* of carbonate carbon)			5 *mg/l*	Evaporation of inorganic C	99
		As	Synthetic, SRM, glycerine, geological, NaCl and $AlCl_3$	40–374	120–200	0.025–5.2 *ng/ml*	Hydride generation (with and without microporous PTFE membrane/tubing separator)	100–105
		Ge	Single-crystal gallium arsenide (non-, Zn- and Si-dop Al) and poly(ethylene-terephthalate)	1000	150	0.4 *ng/ml*	Hydride generation. Microporous PTFE separator	106
		Sb(III), Sb(V)	Copper metal, waste water			0.19 *ng/ml*	Hydride generation. Continuous flow system	107
		As, Sb, Se	Surface waters	750		3.5, 7.0, 3.6 *ng/ml*	Hydride generation	108
		As, Sb, Bi	Ore rock			0.2, 0.2, 0.1 *μg/g*	Hydride generation	109
		Multielements	SRM (steel, coal fly ash, urban particulate, river and seawaters)				Hydride generation	110
	Speciation	Cr(III), Cr(IV)	Reference waters	2 *ml* (200 μl eluent)		1.4, 0.2 *pg/ml*	Acidic alumina column	111, 88
		Sb(III), Sb(V)	Waste waters				Hydride generation	107
		PO_4^{3-}, total P	Waste waters	200	40–80	5, 0.6 *μg/ml*	In serial detectors (spectrophotometer UV-visible and ICP-AES)	112, 113

*Microwave plasma torch AES.

Table 2. FIA ICP–MS coupling

Technique	FIA contribution	Analyte(s)	Sample(s)	Sample volume (μl)	Sampling frequency (hr^{-1})	Detection limit	Other aspects	Ref.
ICP/MS	Sample introduction	Mo	Synthetic	10	30			114
		U	Nuclear material					115
		Au	Seawater	120	4	10 *fM*	Off-line preconcentration $[Au(CN)_2^-]$	116
		In	Synthetic	100	45	*ng/g*	Ion lens tuning strategies	117
		Organomercury	SRM (biological)	100		2.7 *ng/ml*	Avoidance interface clooging	118
		Thimerosal	Biological					119
		Trimethylgallium etherate	Human faeces				Simplex optimization	120
		Pt-group metals	Peridotite			sub-*ng/g*	Solid content: 5–10%	121
		U, Th	Aluminium	250	30	0.2 *ng/g*	Comparison with laser-ablation	122
		Ba, In	Synthetic seawater	500			Ion lens tuning strategies	123
		Pb, Zn	Powdered, blood plasma					124
		Re, Pb, Ir	Natural water, sediments	250, 500		5–14 *pg*	Off-line ion-exchange and isotope dilution	125
		Tl, Pb, Bi	Nickel-base alloys	200		1 *ng/ml*		126
		Au, Zn, Cu	Blood plasma, serum	<1000		0.2 *ng/ml*		127
		Zn-64/Zn-67 ratio	Human faeces				Feeding experiments	128
		Multielement	Synthetic	10–25	60	0.01–0.1 *ng*	Optimization study prior to HPLC–ICP-MS coupling	129, 130
			SRM (rock)	500			Minimized matrix deposition	131
			Organometallic compounds, sediments, alloys	25, 100		0.52–2.0 *ng/ml*	Special interfaces	132–136
			Trace metals	50		*ng/ml*	Interface introduction volatile organic solvents	137

continued

Table 2. *continued*

Technique	FIA contribution	Analyte(s)	Sample(s)	Sample volume (μl)	Sampling frequency (hr^{-1})	Detection limit	Other aspects	Ref.
	Sample handling	Pb (isotopes)	NIS SRM 983	1075	240		Isotopic dilution	138, 139
		Multielement	NIS SRM 991 Undiluted urine	500	10		On-line standard addition method	140
			Highly conc. H_3PO_4 and NH_4NO_3	200	10–15		On-line standard addition method	141
			High purity Ni	200		*ng/g*	Continuous sample standard mixing, high solid content	142
	On-line separation process (I). Liquid–solid interfaces	Re	Seawater	10–50 *ml*		0.27 *pg/ml*	Dowex 1-x-8 (ReO_4^-) Isotopic dilution	143
		Pt	Airborne particulate	800	12	0.1 *ng/ml*	Dowex 50 W-X8 (matrix retention)	144
		Trace metals	Concentrated brines (30%)	10 *ml* (0.2 *ml* eluent)			On-line proconcentration matrix removal	145
			SRM (seawater)			2 *ng/ml*	In-parallel columns	146
		Multielement	Hair, SRM	50 *ml*		27 *pg/ml* (Cu)	On-line anodic stripping voltammetry	147
		Cu, Cd	SRM (urine)	1000		545 *pg/ml* (Cd)		
	On-line separation process (III). Gas–liquid interfaces	Bi	SRM (rock)	40		1.8 *ng/ml*	Hydride generation	148
		Pb	SRM, galene			40 *ng/ml*	Hydride generation Isotopic dilution PTFE tubing separator	149
		Hydride-forming elements, Hg	Seawater	500	20	4–6 *pg/l*	Hydride generation–vapour generation	150, 151

Table 3. Other FIA/high discrimination detector couplings

Technique	FIA contribution	Analyte(s)	Sample(s)	Sample volume (μl)	Sampling frequency (hr^{-1})	Detection limit	Other aspects	Ref.
FTIR	Sample introduction	Phenyl isocianate	Synthetic	25	60	4 $\mu g/ml$		152
		o-Xylene	Xylol	200	20	0.02% *v/v*	Comparison flow cells	153
		Ibuprafen	Pharmaceuticals	320	20	80 $\mu g/ml$	Partial dissolution in Cl_4C	154
		Carbaryl	Pesticide formulations	300	53	1.6 $\mu g/ml$	Flowing or stop-flow modes	155
		Allyldiisopropylamine oxide	Synthetic		60		Carrier: supercritical CO_2	156
		Aliphatic esters	Synthetic	130	25	14 *mM*	Comparison flowing and stop-flow modes	157
		Choline compounds	Pharmaceutical preparations		60	0.02 fg/ml	μ-CIRCLE cell	158
		Xylene compounds	Commercial xylol	200	20	0.02% *v/v*	μ-SPEAC cell	159
	Sampling handling	Benzene	Gasoline	300	18	0.02% *v/v*	On-line standard addition	160
		tert-Butyl ether	Unleaded gasolines	320	45	0.035% *v/v*	First order derivative	161
MS	Sample introduction	Tributyltin	Sediment, SRM	500	50	0.2 μg *Sn/g*	Ion spray MS–MS Selected reaction monitoring	162
		Acetic acid, acetoin, 2,3-butanediol, ethanol, CO_2, O_2	Fermentation broth	250	15		MS–MS gas diffusion	163, 164
		Toxins	Plankton			2 $\mu g/ml$	Ion spray MS/MS Selected ion monitoring	165
		β-Blocking drugs	Pharmaceuticals			0.2 *ng*	Study prior to LC-MS coupling	166
	Sample handling	Acetaminophen, glutathione, cysteine	Synthetic	100			On-line electrochemical and chemical reactions	167
	On-line separation process	As, Se, Sb, Sn	Synthetic	100		0.1–1 $\mu g/ml$	Hydride generation	168, 169
		Chloroform	Synthetic			1 $\mu g/ml$	Gas diffusion	169
MECA	Sample introduction	Organophosphorous compounds, insecticides	Synthetic	2	100	0.5–50 μg *P*	No cavity cooling between injections	170, 171
		Sulphide, sulphite, sulphate	Synthetic	5	20	1 *ng S*	No cavity cooling between injections	172
	On-line separation process	Arsenic	SRM (vegetal)	120	100	80 ng/ml	Hydride generation	173
NMR	Sample introduction	Toluene	Acetonitrile	50		130 $\mu g/ml$	Evaluation flow-cell	174
Flame IRES	Sample introduction	Total inorganic carbon, saccharides	Tap water	25, 250	60		Design purge-cell FI and continuous modes	175

discrimination capabilities like MS (by direct coupling or through an ICP source), FTIR and NMR, among the most important, which have also been reviewed,[35-40] and whose most significant features are listed in Tables 2[114-151] and 3.[152-175]

Figure 1 shows the dissimilar use of flow injection analysis–high discrimination instrument (FIA–HDI) couplings. For this reason the aim of this work is to give to the analytical community, but particularly FIA users, an overview of the present situation of these hyphenated techniques, emphasizing the advantages involved in them, criticizing their negative aspects and showing the unexplored availabilities of one of the most promising uses of FIA.

INTERFACES

The connection between a flow injection system and a high resolution detector has a decisive influence on the performance of the hyphenated system, as analytical quality parameters such as reproducibility, accuracy, sensitivity and selectivity are highly dependent on how this coupling is accomplished. The complexity of the interface is very different depending on whether the measurement is performed in solution, plasma or vacuum.

Inexpensive flow-cells (either conventional or demountable micro-flow cells) with KBr windows and different thickness spacers (0.015–0.22 mm, 0.15–9 μl cell volume) are used in FIA–FTIR coupling when organic solvent carriers are involved.[143-145,159-161] The use of thick spacers yields a higher contribution to the blank measurement from the carrier solvent, so poorer detection limits are obtained. More sophisticated cells are used with uncommon solvents. A 25 μl-micro-Circle cell equipped with a zinc selenide crystal (0.318 cm diameter) has been used for aqueous samples in FIA–FTIR;[157,158] and a high pressure flow cell (2 μl, 1 mm optical path length and 2 mm^2 cross sectional area) when supercritical CO_2 was the carrier.[156]

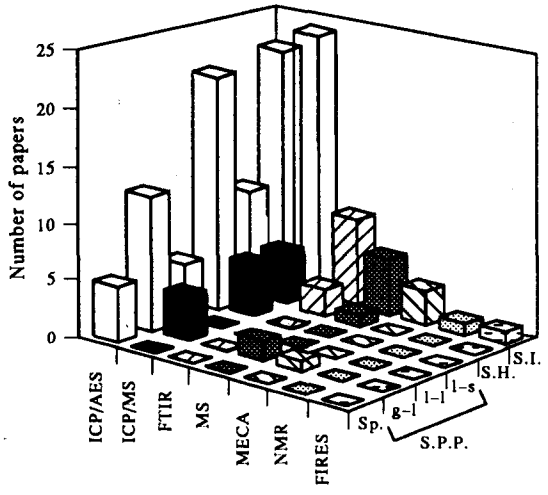

Fig. 1. Tridimensional plot of the main contributions of flow injection analysis coupled to high discrimination detectors. (Sp) Speciation; (g–l) gas–liquid; (l–l) liquid–liquid; (l–s) liquid–solid; (S.P.P.) on-line separation processes; (S.H.) sample handling and (S.I.) sample introduction.

The design of an NMR flow cell should provide rapid sample displacement without significant degradation of resolution. Cells similar to those in Fig. 2, with a 50 μl observed volume work well at 1 ml/min flow-rate. The FIA injector can be connected directly to the NMR flow cell with 0.01-in i.d., 1/16-in o.d. tubing.[174] Sufficient premagnetization time of the sample can be accomplished by placing the injector and connectors within the magnetic field.

Special attention has been paid to interfacing FI systems and ICP.[42,44-46,56,57,59,60,132,176-179] A general interface to introduce a liquid into a plasma consists of a nebulizer, a spray chamber and a separator. The main shortcomings of using conventional interfaces in FI–ICP and in LC–ICP couplings related to continuous sample aspiration are the large dead volume and the sample loss involved as well as the band broadening. Efforts have been focused on producing interfaces with high analyte transport efficiency and minimal solvent loading and dead volume in order to decrease detection limits. Low analyte transport efficiency of conventional pneumatic nebulizer/spray chamber systems (only 1–2% of the analyte aspirated actually reaches the plasma) limits the ability to analyse small sample volumes. Miniaturized interfaces have been designed[42,44,45] in order to overcome this drawback. The direct injection nebulizer (DIN)[60] is another approach to minimize the dead volume: a microconcentric nebulizer fits into the central aerosol tube of a conventional ICP torch. Solutions are nebulized directly at the base of the plasma and there is no spray chamber or separator. The microconcentric nebulizer[46,59,60] and thermospray nebulizer[57,176,179] have been the most used. In addition, miniaturized glass-frit nebulizers[45] have been reported to couple FIA and ICP. Solvent loading is identified as a major contributor to plasma instability and poor detection limits. A jet separator,[177] a condenser[57,179] or a membrane dryer separator[132,178] can be used to remove the majority of

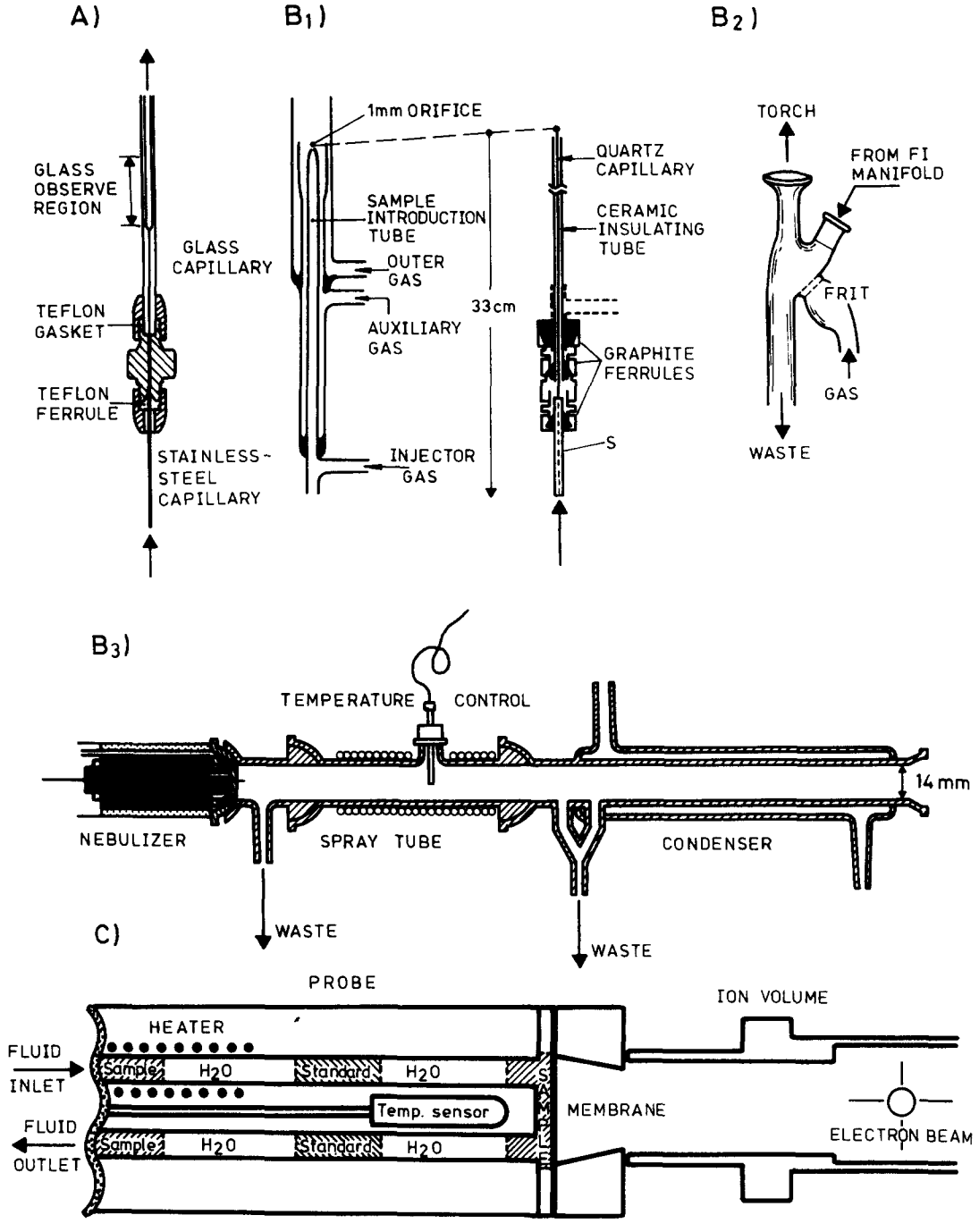

Fig. 2. FIA–HDI interfaces. (A) NMR flow-cell and interface. (B) FIA–ICP interfaces. (B_1) Direct insertion of a microconcentric nebulizer (right) into the ICP torch (left). (B_2) Miniaturized glass-frit nebulizer. (B_3) Thermospray interface consisting of a thermospray nebulizer, a heated spray chamber and a condenser. (C) FIA–MS–MS interface. Sheet membrane probe with membrane temperature control.

the solvent and convert the sample into a dried and desolvated aerosol in a flow of argon. Membrane separators are especially useful for organic solvents.

Flow injection and mass spectrometry have been interfaced either by membrane introduction and ion spray systems. The former consists of a membrane probe directly inserted into the mass spectrometer ion source. The carrier solution flows across the inside surface of the membrane while the outside surface is exposed to the vacuum of the mass spectrometer. This interface is suitable for volatile analytes capable of diffusing through the heated membrane.[163,180]

In ion spray MS the carrier solution is allowed to flow at a rate of 1–500 μl/min, through a very narrow bore capillary tubing (50–200 μm) polarized to a high voltage (2–3 kV). Spraying is facilitated by a coaxial flow of nitrogen. The electrically charged droplets found evaporate during their flight to the sampling plate (counter-electrode). The analyte must be present as an ion in solution because there is no ionization process. This injector has been connected to the ionspray interface via a 1 m × 50 μm i.d. fused-silica tubing.[162]

SAMPLE INTRODUCTION

Despite the FIA capability to carry out a series of chemical processes, the major use of flow injection-high discrimination instruments (FI–HDI) has been to transport a few μl of sample to the detector. In addition to this application other more interesting uses are commented on in the following sections.

An extensive use of FIA as a sample introduction tool has been done when coupled to ICP-AES[41–63] and ICP-MS.[114–137] Nevertheless, FIA–ICP hyphenated systems have profited from many other FIA capabilities.

The use of flow injection as a means of sample introduction endows the methods with a number of advantages, namely: reduced sample and reagent consumption, increased sample throughput, higher reproducibility and better detector performance.

The sample saving achievable in FI–ICP is remarkable. Sample volumes in continuous aspiration ICP are usually between 2 and 5 ml, which decreases to 10–500 μl when coupled to FIA. Continuous aspiration of the sample is too wasteful to be feasible when only a limited sample volume is available (*i.e.* biological, clinical and forensic analysis); so the reduction of sample consumption achievable by FIA is of paramount importance in these fields. By way of example, FIA combined with ICP-AES has been successfully applied to the simultaneous determination of eight elements in 20-μl serum samples,[54] and acceptable detection limits for the analysis of several metals in biological samples were obtained with the use of *ca.* one-hundreth of the minimum sample volume required for continuous aspiration.[55]

The high sample throughputs achievable by FIA are a consequence of the simple and automatic way of sample introduction, as this can be inserted into the flowing stream and monitored within few seconds, whereas standard NMR methods require at least 45–60 sec before starting monitoring.[174] Flow injection couplings enable near-real time monitoring thus avoiding fraction trapping, which is time-consuming and capable of sample contamination. FI sampling with membrane introduction MS–MS has been used for fully automated monitoring and feedback control of bioreactors.[163] It allows quantification of the major products and metabolites of fermentation and even detection of trace metabolites.

Flow injection is a very reproducible means to introduce a precise volume of sample and also to improve the performance of the detector by minimizing blockage drawbacks in the interface thus favouring the detector stability. The precision of transient signal integration measurements as compared to steady-state integration measurements was found to be at least one of magnitude better for all of the wear metals.[52] The significant improvement in precision is due to reduced carbon build-up (more stable plasma; improved torch stability (no air pockets), constant sample solution flow-rate (use of a pump to avoid problems with viscosity changes) in the coupled FIA–ICP-AES. The ability to use small sample volumes reduces the loading of undesirable matrices on nebulizers and torches, particularly in high salt content samples or organic solvent solutions. An injection volume as low as possible without increasing detection limits must be chosen in order to minimize solid sample deposition on the torch injector tip and on the mass spectrometer sampling interface. Thus, no matrix deposition occurs and therefore reproducibility of a particular measurement is improved. This also provides better long-term stability of the instrument. The flow injection technique enables determinations in samples with total dissolved solid concentration 20–30 times higher than those handled by conventional solution aspiration. The precision of an FIA–ICP-MS approach reported by Vickers *et al.*[114] was found to be *ca.* twice that of a continuous flow mode, whereas Stroh *et al.*[131] have found a mean long-term stability better than 5% RSD for all the elements (10 ng/ml) they have studied in a 3% m/v NaCl matrix.

Memory effects are also minimized in an FIA–HDI coupling as the carrier immediately follows each sample plug, which results in a continuous rinsing effect that dramatically reduces clogging of the interface by deposition of

solid. The rinsing effect of the carrier decreases wash-out times, so the sampling frequency is improved as a result. Since the carrier system is flowing continuously, plasmas which normally extinguish at the air–water interface will no longer do so. In addition, injection of the sample avoids its passage through the flexible tubing of peristaltic pumps, which can adsorb the analyte[116] causing diminished signals and memory effects that severely degrade precision; at the same time, a close control of the flow-rate is accomplished in this way.

The use of FIA–FTIR systems provides simple and rapid sampling and easy cleaning of the flow-cell, and enables the continuous monitoring of the baseline of spectra. Pharmaceuticals[154,158] and pesticide formulations[155] have been determined successfully by FIA–FTIR thus demonstrating the usefulness of this approach.

Detection limits and spectroscopic resolution of FIA–NMR are also better than for static sample measurements.[174] The FI carrier solution provided a suitable medium where stable ion-spray could take place in MS sample introduction.[163]

Solid[181–184] and gaseous[185] samples can also be introduced in FIA–HDI couplings. Despite the capability of FIA for direct introduction of solid and gaseous samples, this potential has not been exploited. Only the direct analysis of solid samples by FIA–ICP-AES has been carried out by electrolytic dissolution[48] and FIA–slurry atomization.[63] Simultaneous determination of Zn, Si, Fe, Mn, Cr, Mg and Cu in aluminium alloys has been accomplished in a few minutes. Gaseous mixtures of compounds containing the elements Br, C, Cl and S were introduced by FIA with various sample loops (15–250 μl) on the injection valve.[46] Sample gas was added to the loops at *ca.* 10 ml/min, then the sample carrier gas (Ar) was switched through the loops to transport their contents into the ICP.

SAMPLE HANDLING

This section deals with some simple operations such as automatic mixing of the sample with a dilution, standard or reagent thus completing the step within a short period of time with less sample and diluent, standard or reagent consumption. An additional advantage of the automatic performance of this step is a decrease of sample manipulation and thus of the human errors arose from it.

Dilution is an FIA capability which can be performed in an automatic way, thus achieving dilution factors for samples of standards ranging between 0 and 200. This fact justifies its coupling to HDI instead to other less versatile continuous dilution systems.[70] Different ways have been used to achieve this goal, namely the insertion of a short piece of wide-bore tubing, a delay coil, merging streams, zone sampling approach by using an unstirred or stirred chamber. A dilution step can be mandatory in order to minimize matrix effects in the determination of major components in a complex sample, or to fit the concentration of the analyte(s) within the linear range of determination in concentrated samples. A significant reduction of the mass-dependent interference effects without substantial sacrifice in sensitivity can be achieved by appropriate dispersion in the FI system. Vickers *et al.*[114] have demonstrated the almost complete elimination of signal suppression by using a FI manifold which provides dispersion factors up to 25. Martin and Ihrig[72] have developed an FI–ICP-AES approach for the automatic determination of widely varying elemental composition and concentration in a series of liquid samples without operator intervention. All the samples were appropriately diluted before determination by ICP–AES by using computer-guided sequential dilutions to place all elements within the optimum range. Sample dilution was accomplished by injecting the sample for shorter periods of time (time-based injection). The tandem-injection and merging-streams have also been employed to achieve on-line dilution and steady-state concentrations for ICP-AES and ICP-MS.[64]

Automatic calibration

The ability for on-line development of relatively time-consuming sample pretreatment procedures such as standard additions, internal standard, isotope dilution, and matrix-matching calibration in a simple way, saving both time and sample makes FIA a useful tool for this sample handling.

The standard-addition method has proved to be effective in overcoming matrix effects, one of the main sources of loss in both accuracy and sensitivity in certain types of samples. The FI manifold can be designed either to add the standard to the sample (before, in, or after injection) or to inject the standard into the sample (reversed FIA), among others, thus

avoiding sample and standard contamination and the time-consuming preparation step.

In the reverse-FIA mode the standard-addition method is accomplished by continuous sample pumping to the detector instead of the carrier solution, the detector is zeroed for this baseline value, and the standard solutions are injected in the sample stream. The calibration curve can be run by injecting equal volumes of standards of different concentration; different volumes of the same standard solution, or using any of the FIA alternatives for dilution prior to injection. This method has been proposed to determine benzene in gasoline by FIA–FTIR,[160] and Si in an 85% phosphoric acid sample[65] and rare earth in metal samples[67] by FIA–ICP-AES.

Sample–standard merging before injection is an easy way to implement the standard addition method. A third stream of internal standard can merge after the sample and standard confluence.[141] The standard addition stream is used to add multielement standard solutions of variable concentrations. A complete standard addition can be performed in each sample by changing the standard solution. Unlike the reversed-FIA standard addition method, continuous introduction of the sample matrix into the detector is avoided by the sample standard merging method, which has been successfully used in FIA–ICP-MS[142,113] couplings.

The merging-zone approach has also been used for calibration purposes in the determination of Ni, Cu and Ni in alloys.[68] The system utilized successive injections of the sample, each one accompanied by the injection of a different standard. The limitations of this system include the relatively low sampling rate and the necessity of preparing a series of standards. The latter shortcoming might be overcome by using the zone-sampling mode, which enables controlled dilution of a given standard before its injection into the final standard carrier stream. Standard addition in plant digest samples has been implemented in an FIA–ICP-AES system by merging the sample zone with an aliquot delivered from a trapped standard zone in a modified version of the zone sampling approach. Eleven additions ranging from 3 to 32% of only one standard solution were performed in 5 min.[69] Nine toxic elements in undiluted urine were determined in less than 5 min using an FIA–ICP-MS approach[140] in which the FI manifold, which included a splitter tee, two in-parallel injection valves with different size loops (40 and 500 μl for standard and sample, respectively) and a mixing tee, was used to inject sequentially three standard solutions into the same sample plug.

Isotope dilution was used by Lasztity, Viczian *et al.* for the determination of lead in various matrices using a merging zones approach with programmable time-based injections.

Matrix matching of sample and standards was implemented in FIA–ICP-AES by Giné *et al.*[71] to minimize the interferences due to easily ionizable elements. Initially the ICP determines the sodium content in the sample and thereafter the computer selects the appropriate sodium addition to match the saline concentration with that of the standards. After having received a suitable amount of sodium, the sample reaches the ICP and the elements are determined.

Derivatization

Flow injection is a suitable tool to carry out on-line chemical reactions in a reproducible and automatic way with a noticeable saving of both sample and reagents. The analyte can be converted into a more suitable form for detection (*e.g.* a volatile species which enhances the selectivity, sensitivity and scope of application of the coupled system). The chemical reactions most widely used in FIA–ICP-AES, FIA–ICP-MS and FIA–MS have been hydride generation and vapour generation.[100–110,148–151,168,169] Getek *et al.*[167] have reported an FIA–MS coupling in which electrochemical and chemical reactions took place. On-line formation and detection of glutathione and cysteine conjugates of acetaminophen were accomplished by interfacing a coulometric cell with a thermospray mass spectrometer in the flow-injection system. The electrochemical information enables the confirmation of *in vivo* reaction mechanisms.

ON-LINE SEPARATION PROCESSES

One of the more advantageous aspects of FIA is its availability for the development of non-chromatographic continuous separation techniques with minimal complication of the experimental set-up. Flow injection takes advantage of its dynamic nature for an easy, inexpensive implementation of separation techniques involving any of the possible interfaces (liquid–solid, liquid–liquid or gas–liquid). All of them have been implemented in on-line helped by an FI manifold, then hyphenated to a high

capability instrument. The goal of the separation step has been to enhance either the sensitivity of the method by preconcentration of the target analyte(s) or the selectivity by removal of the matrix thus avoiding both its interference on the analytical signal and its passage through the detector, which is of a paramount importance in cases of insufficient or non-discrimination capability. The use of switching valves makes it feasible to lead undesirable species to the waste after separation without passing through the detection point. An additional benefit is an increased reproducibility as distortion of the signal from the analyte is minimized or avoided.

Liquid–solid interfaces have been established in FIA–HDI systems mainly by the use of solid-phase columns packed with either ion-exchange or adsorptive material, particularly with preconcentration purposes. This previous step can improve dramatically the sensitivity of a given method by one or two orders of magnitude. By way of example, the preconcentration FIA–ICP systems described by Hartenstein *et al.* are capable of increasing the signal by 10–15-fold and 20–75-fold per minute of sample loading time for simultaneous multielement integrated and simple element peak height, respectively, giving nearly 100% recovery of spiked analytes in tap and rain run-off waters.[89] Nevertheless, there are two negative aspects of these separation processes, namely: (a) The sample volume used is higher than in the absence of this step (see Tables 1–3). Depending on both the concentration of analyte in the sample and the enrichment factor to be attained the sample volume ranges between 2 and 100 ml, far from the μl range usual in FIA. (b) The sampling frequency decreases by a factor which depends on the working conditions. In the above example[89] this parameter decreased from 30–60 determinations/hr to 12–20 determinations/hr. This shortcoming can be minimized by using several columns arranged in parallel which work simultaneously and deliver sequentially the eluates to the flow manifold. The location of the column(s) in the dynamic system dramatically affects the overall performance and thus the results obtained. When the column is located in the transport zone of the flow manifold, a switching valve after the column is mandatory in order to waste undesirable sample components, thus avoiding their passage through the detector (SV_2 in Fig. 3A) (see Refs 81, 91, 92 and 143 as examples). The main drawback of this arrangement is the continuous

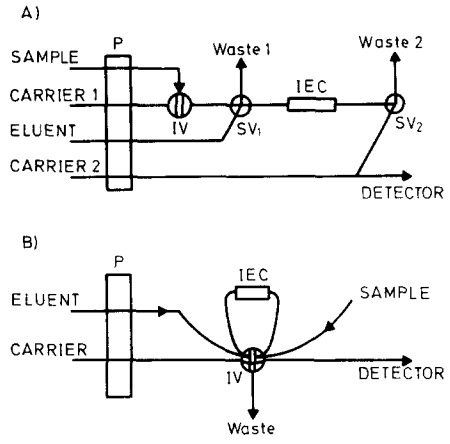

Fig. 3. Schemes of flow injection solid phase separation column coupled to high discrimination detectors. (P) Peristaltic pump; (IV) injection valve; (SV) selecting valve and (IEC) ion-exchange column.

circulation of the liquid in the same direction which tends to compact the packed material in the column and hence increases the pressure within the system. This problem can be overcome by placing the column upright and passing the solution upstream or by carrying out elution in the opposite direction of retention. The implementation of the latter approach is easy if the column is located in the loop of an injection valve (Fig. 3B). (A detailed description of the use of microcolumns in continuous flow systems can be found in Refs 12 and 13.)

In addition to the microcolumn located in any of the commented on above points, other units can be included on-line in the FI manifold to improve the efficiency of the overall process. Such is the case with the desolvation device connected to a microcolumn by Peng *et al.*[91] in the development of a method for the determination of trace elements by FIA–ICP-AES with on-line preconcentration. The authors achieve a desolvation efficiency of 73% at a desolvation temperature of 120 C and apply the method to

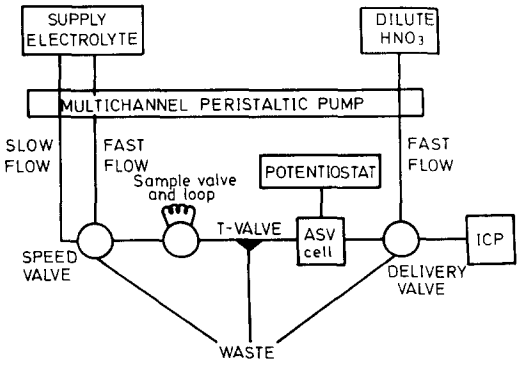

Fig. 4. Scheme of the flow injection-anodic stripping voltammetry inductively coupled plasma (FI-ASV-ICP) approach.

the determination of Al, Cu, Cd, Fe and Mn in serum by separation of the target analytes from various co-existing elements.

A less common liquid–solid interface in FIA–HDI is that created by using an on-line voltammetric stripping cell in the flow manifold such as the arrangement depicted in Fig. 4 which has been used to deposit Cu and Cd at a working electrode, then releasing the analytes for detection by ICP-AES.[147] The deposition step enables the elimination of the sample matrix components that are not electroactive and do not deposit during passage of the sample through the cell, thus being sent to waste by switching the delivery valve. The target analytes were preconcentrated from sample volumes as large as necessary, then stripped for detection into a small volume of liquid of the appropriate characteristics. Detection limits of pg have been achieved for 1-ml urine samples. It must be emphasized that the sampling frequency affordable by a stripping technique is usually higher than by solid columns as both the retention and elution steps are faster. Another additional advantage of stripping is the higher efficiency of the deposition process, which can be 100%.

Liquid–liquid interfaces have seldom been established in FIA–HDI by the use of both extraction and dialysis techniques and in all of the cases the detector has been ICP-AES. In continuous liquid–liquid extraction processes the efficiency of the separation strongly depends on the aqueous–organic flow-rate ratio. One of the earlier papers in this field[98] reported an increase in sensitivity of *ca.* 250-fold in comparison with direct aspiration of an aqueous solution for the determination of Cd by ICP–AES after extraction of its diethyldithiocarbamate into carbon tetrachloride with a detection limit of 4 ng/ml and a sampling frequency of 20 hr^{-1}. Indirect methods have also been established in this area, as is the case with the determination of fluoride in water by formation of the lanthanum/alizarin complexone/fluoride ternary complex and its extraction into hexanol containing *N*,*N*-diethylaniline. The introduction of the organic layer into the plasma and measurement of the emission intensity of La III 333.75-nm line enables the determination of the target analyte in a 0.03–1.3 μg/ml linear range with a sampling rate of 36 samples/hr.[85] Two in-series phase separators are used in order to obtain a pure organic phase to be transferred to the detector.

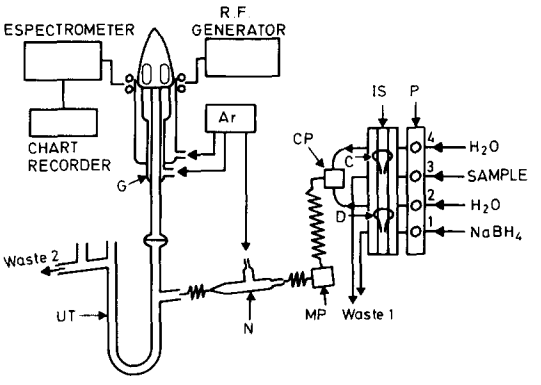

Fig. 5. Scheme of a flow injection–hydride generation–ICP-AES system. (P) Peristaltic pump; (IS) injection system; (CP) confluence point; (MP) mixing point; (N) nebulizer and (UT) U-tube.

A recent combination of flow injection Donnan dialysis with inductively coupled plasma atomic emission spectrometry has proved to yield enrichment factors of over 200 for cations with an 8-min dialysis time, allowing ng/ml level detection limits. These results were obtained for receiver solutions consisting either of Sr(II) or Mg(II), providing complementary free spectral ranges and the applicability of the hyphenated system to trace metal cation analysis for both transition and rare earth elements. The enrichment factors obtained were linear over a wide range of concentrations and limits of detection approximately 100 times lower than for direct aspiration. Additional improvements in enrichment factors were obtained with increases in the dialysis time and/or final sample solution temperature. A signal enhancement factor of 650 with a detection limit of 11 ng/ml for monovalent silver cation was obtained using a 30-min dialysis.[94] These results call for greater attention to be paid to Donnan dialysis as a powerful tool to manipulate the sensitivity of FIA–HDI methods.

Despite the small number of species capable of yielding a gas after reaction, gas–liquid interfaces have gained extensive use in FIA–HDI. Within gas–liquid separation, techniques based on hydride generation are the most common in hyphenated systems, particularly in FIA–ICP-AES and FIA–ICP-MS, where vapour generation has proved considerable enhancement of the analytical capabilities for multielemental determination of volatile vapour-forming elements at ultratrace levels in environmental samples. Very good accuracy and precision in addition to increased sensitivity and avoidance of espectral interferences caused by high salt matrix, as demonstrated in ocean

water samples.[150] An arrangement such as that depicted in Fig. 5 was used in one of the earlier hydride generation–FIA–ICP-AES methods. The determination of arsenic as arsine was performed at a rate of 200 injections/hr with detection limits of 1.4 ng arsenic.[102] Subsequent contributions have been the determination of arsenic in glycerine,[103] that of antimony in waste water,[107] and the simultaneous determination of As, Sb and Se,[108] among others. The simultaneous method,[108] as compared with continuous sample introduction, provides detection limits three times poorer. By contrast, the precision is approximately 150% better with FI due to the reduced pump pulsations. Other advantages of the FI system are the reduced sample size necessary for analysis (<750 μl *vs.* 4–5 ml for the continuous introduction system) and the potential for a greatly increased rate of sample throughput.

One of the scarce contributions on FIA–MS dealing with hydride generation is that reported by Canham and Pacey and consists of preliminary studies of the behaviour of such a system with very promising results.[169] A more complex FIA–ICP-MS arrangement has also been reported for the determination of hydride-generating elements and for the determination of mercury. Several pre-reduction techniques were investigated and applied to the determination of the target analytes (namely, B, Sb, Se, Te, Hg and As) at ultra-trace levels in environmental samples. The detection limits found were in the range 0.5–7.0 pg/ml.

On-line preconcentration and oxidation by hydrogen peroxide were combined to improve the atomic emission limit of detection for iodine. The process was automated by FIA and hyphenated to both ArICP-AES and HeICP-AES for evaluation of the performance of the overall system as a way to circumvent the drawbacks encountered in the batch method, to which I_2 is adsorbed onto the peristaltic PVC pump tubing causing a memory effect, and the mixed reagents were only stable for 1 hr. To minimize the memory effect in the batch method, the transfer line was rinsed with a 0.02% solution of sodium thiosulphate in an attempt to reduce I_2 (adsorbed on the transfer line) to I^-. Although this procedure was effective in reducing the memory effect, its use in routine analysis was limited because of cross-contamination and increased analysis time. To eliminate the cited limitations in the batch method, the reagents were mixed on-line and the formation of I_2 took place along the reactor, thus avoiding its passage through the pump tubing. The iodine signal at 183.04 nm was enhanced by a factor of 33 and 100 for ArICP and HeICP, respectively, with detection limits of 5 and 9 ng/ml.[82]

SPECIATION STUDIES

Speciation has been implemented in FIA–HDI using different capabilities of such arrangements. One of the simpler but more expensive ways to develop speciation is by the use of a detector which allows direct discrimination of the different forms of a given element or compound. This is the case with the FIA–MS–MS tandem, with ion-spray sample introduction and discrimination by selective reaction monitoring of daughter–parent pairs, which has been used for speciation of organotin compounds in sediment and SRM,[162] or the use of molecular emission cavity analysis (MECA) for the speciation of sulphur anions (as sulphide/sulphite/sulphate)[172] and that of phosphorus insecticides[171] and organophosphorus compounds,[170] based on the parameter t_M (t_M is the time elapsed between introduction of the cavity into the flame and analytical achievement of the maximum peak intensity). Speciation can also be implemented in FIA systems coupled to twin in-series detectors with non-capability for speciation. Such is the case with the speciation of phosphorus compounds (as phosphate and total phosphorus) in waste water by FIA and sequential spectrophotometry and ICP-AES. Phosphate was determined as molybdovanadophosphoric acid using a colourimetric method and the solution from the flow cell of the spectrophotometer was directly introduced to an ICP. The determination of total phosphorus was performed by measuring the emission intensity at 177.499 nm. Chromium caused a positive error in the colourimetric determination, but ions commonly existing in waste water did not interfere with the determination of total phosphorus. The sampling throughput was 80 samples/hr. The contributions of FIA to improve the features of the method were the on-line derivatization and the increased sampling frequency.[112]

Discrimination can also be achieved in the FI manifold. Such is the case with speciation of antimony [as Sb(III)/Sb(V)].[107] Antimony was reduced to stibine and determined in 1 *M* malic

acid or 0.5*M* tartaric acid, whereas in either of these media antimony(V) gave little or no signal. Total antimony was separately determined in the presence of 0.1*M* thiourea as pre-reductant.

An on-line separation step can also endow the method with discriminating capability, as in the method proposed for the sequential speciation of chromium [as Cr(III)/Cr(VI)] based on the use of microcolumn of activated alumina in an FIA–ICP-AES arrangement. The column was used to separate and preconcentrate Cr(VI) from Cr(III) before ICP detection at 267.72 nm. Thus, determination limits of 1.4 and 0.20 ng/ml for Cr(III) and Cr(VI), respectively, were obtained.[111]

More complex separation techniques as GC have also been hyphenated to FIA and microwave-induced plasma (MIP) atomic emission spectrometry for organotin speciation analysis. The method was based on the preconcentration of ionic organotin compounds by sorption on bonded silica with octadecyl functional groups followed by on-column ethylation using sodium tetraethylborate. The derivatized species were eluted with 250 μl of methanol, separated by gas chromatography and detected by MIP–AES. The method was applied to the determination of the target analytes in river samples which were also analysed using a manual liquid–liquid extraction method. The results agreed within 10–15% for concentrations of a few pg/ml.[85]

CONCLUSIONS

From Tables 1–3 the more extensive use of FI coupled to ICP can be stated. The first of such arrangements exploited the FI manifold only as a means of reproducible transport of the sample into the instrument, with the sole aim of increasing sample frequency. Later it was realized that periodical washing of the nebulizer is beneficial, allowing handling of concentrated samples. These features, together with the feasibility of automated dilution and calibration led to the realization that FIA is the cure of the 'Achilles heel' of ICP. From more recent developments such as FIA preconcentration/separation, FIA speciation and FIA conversion it becomes apparent that FIA can be a more useful problem solver.

The long way ran for full implementation of FIA–ICP coupling seems also to be the way followed by other high discrimination systems, as can be inferred from Tables 2 and 3. In this respect it is noticeable the scarce number of FI–RMN methods proposed so far, despite the fact that interface problems are successfully solved as a result of the previous coupling of RMN with other hydrodynamic systems as is the case with LC-RMN.

Some isolated attempts have been made using these hyphenated systems and should be exploited as they offer interesting perspectives, namely: (a) use of robotic stations for sample pretreatment steps such as weighing and dissolution. The pretreated sample can be introduced directly into the FI manifold,[186,187] thus achieving full automation of the analytical process. (b) Direct introduction of solid samples into the FIA–HDI arrangement. A first attempt has been made in this respect by use of electrical energy for leaching the sample.[181,182] Electrolysis is not the sole way of using solid samples in these dynamic systems, as ultrasounds have also proved their great potential in this context.[183,184] (c) Use of FIA as a 'hyphen' allowing different instrumental techniques to be linked together. The use of a stripping flow-cell for preconcentration purposes is a partial example of this potential, which can also be expanded to its use for preconcentration/determination prior to the high discrimination instrument, thus increasing the information level. Also FIA could be linked to apparatus such as a supercritical fluid extractor and an HDI with accomplishment of the intermediate step (derivatization, separation, *etc.*), which no doubt would improve the overall performance of the method. (d) The scope of non-chromatographic continuous separation techniques coupled to FIA–HDI should be broadened by including prevaporation[188] and continuous precipitation[189] as both have proved their capabilities when coupled to FIA. (e) More attention must be paid to the use of FIA to obtain information in the development of theoretical studies of the dynamics in membrane and membraneless instruments,[180] and to the FIA–HDI coupling interfaced by an autosampler.[190] All these slightly or unexploited aspects of FIA in hyphenated systems can undergo suitable development with the present trend of some manufacturers, which integrate FIA systems in HDI as a means, in principle, of sample handling.

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