On-line sample-pre-treatment schemes for trace-level determinations of metals by coupling flow injection or sequential injection with ICP-MS

Jianhua Wang, Elo Harald Hansen

Within the last decade, the first generation of flow injection (FI) has been supplemented by sequential injection (SI), also termed the second generation, and, recently, by the third generation, i.e., SI-Lab-on-Valve (SI-LOV). As apparent from the literature, FI and/or SI have become dominant as substitutes for labor-intensive, manual, sample-pre-treatment and/or solution-handling procedures prior to analyte detection by inductively coupled plasma mass spectrometry (ICP-MS). The present review presents and discusses the progress of the state of the art in implementing miniaturized FI/SI systems for on-line matrix separation and pre-concentration of trace levels of metals with detection by ICP-MS. It highlights some of the frequently applied on-line, sample-pre-treatment schemes, including solid phase extraction (SPE), on-wall molecular sorption and precipitate/(co)-precipitate retention using a polytetrafluoroethylene (PTFE) knotted reactor (KR), solvent extraction-back extraction and hydride/vapor generation. It also addresses a novel, robust approach, whereby the protocol of SI-LOV-bead injection (BI) on-line separation and pre-concentration of ultra-trace levels of metals by a renewable microcolumn is interfaced to ICP-MS, as conducted in the present authors' group. It discusses the future outlook in this field.

Keywords: Flow injection (FI); Inductively coupled plasma mass spectrometry (ICP-MS); Lab-on-Valve (LOV); Matrix removal; Pre-concentration; Separation; Sequential injection (SI)

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1. Introduction

ICP-MS has been widely accepted as one of the most attractive technique for trace-metal analyses, because of its high sensitivity, low limits of detection (LODs) and its capability of multi-element and isotope ratio measurements [1,2]. Despite early claims that ICP-MS is relatively free from interferences [3,4], a prominent feature in most publications in this field is their focus on the problems of interference [5], which fall into two categories:

- the inherent low tolerance limit of ICP-MS to total dissolved salts (TDS) – which should not exceed 0.2% (m/v) – tends to result in severe matrix effect/signal suppression; and, in addition,
- spectral interferences make its applications difficult [1].

The production of low levels of interfering molecular ions and the attenuation of matrix effects are, therefore, the two major goals in establishing multi-element screening procedures with detection by ICP-MS.

Spectral interferences can be reduced by employing a shielded torch [6,7], a cold plasma [8,9], a mixed gas plasma [10,11] and a dynamic reaction cell [12–14].

 0165-9936/03/$ - see front matter © 2003 Published by Elsevier B.V. doi:10.1016/S0165-9936(03)01207-X

However, the applications of these approaches are still rather limited. In addition, a cold plasma causes a much lower sensitivity [15], a shielded torch increases the oxide level [16], and a mixed gas plasma adversely affects both the sensitivity and the LODs [17,18]. A high-resolution (HR)-ICP-MS eliminates most polyatomic ion interferences encountered in quadrupole ICP-MS [15,19], yet the cost for the high resolution is a sacrifice in sensitivity [20]. Moreover, HR-ICP-MS suffers from parallel matrix effects, similar to those experienced with quadrupole ICP-MS [21].

Arithmetic correction is required in some cases, although a certain amount of error is always introduced when applying it [15]. In practice, it is recommended for controlling corrections to within 10% of the total signal [22], but this is not always the case. Thus, one publication even derived an excessively high correction factor of up to 90% of the value [23].

Being the most important source of error, the matrix effect is very difficult to measure and quantify. Nevertheless, a number of methods have been used to alleviate or to compensate non-spectral interferences. Sample dilution reduces the matrix concentration [24,25], yet it leads to unduly high limits of quantification (LOQs), which are further degraded by polyatomic ion interferences. Internal standardization [26,27] requires the internal standard and the analyte to be closely matched in both mass and ionization energy [23,28]. Matrix matching of standards and samples might be useful in specific situations [23,29], but it is not feasible in the real world, where frequently the matrix content is unknown. The standard addition technique produces precise and accurate data, yet it is time consuming and thus best suited to a relatively small number of elements or samples [30,31].

It can therefore be concluded from the above discussions that the most effective way to eliminate the non-spectral interferences or matrix effects and overcome or attenuate the spectral interferences is to separate the analytes from the matrix components prior to ICP-MS detection. At the same time, the analytes can be pre-concentrated. When pre-concentration is practiced manually in the batch mode, there is a high risk of sample contamination that constitutes an important source of error when considering the extremely low LODs of ICP-MS instruments. Special care should, therefore, be taken in order to minimize sample contamination during the sample-pre-treatment process.

In this respect, it is especially noteworthy that the three generations of FI — the first generation (FI), the second (SI) and the third (SI-LOV) — have played very important roles as replacements for the labor-intensive manual operation of various separation and pre-concentration techniques *via* on-line manipulations [32–35]. In automated, miniaturized closed systems, sample or reagent consumption, waste production and sample-preparation times are considerably reduced in comparison with batch-mode operation. Besides, and most importantly, the risks of sample contamination from the environment are also minimized, and that is especially critical for samples with very low levels of analytes in complex matrices [32,33].

This review presents an up-to-date report on progress with the implementation of the three generations of FI in the on-line matrix removal and the pre-concentration of trace levels of metals with detection by ICP-MS. We emphasize the first two generations that incorporate some of the frequently employed, on-line, sample-pre-treatment schemes. We also provide a pertinent discussion about the newly developed SI-bead injection (BI)-LOV approach applied to SPE.

2. On-line separation or pre-concentration schemes coupled to ICP-MS

Extensive studies have shown that, besides separation of interfering matrix components and pre-concentration of ultratrace levels of analytes, FI/SI/SI-LOV on-line sample-pre-treatment procedures also offer a number of benefits compared with their manual operational counterparts [32,33], including:

- high efficiency in terms of sample throughput or sampling frequency;
- reduced sample and reagent consumption and waste production;
- improved precision (RSD);
- low LODs/LOQs;
- minimal risk of sample contamination;
- potential improvement of selectivity through kinetic discrimination under chemically non-equilibrated conditions; and,
- automation.

Theoretically, an FI/SI/SI-LOV on-line sample-pre-treatment system can be interfaced with any kind of spectrometric detector. Its interface with an ICP-MS detector is, in most cases, quite straightforward because of the compatibility between the continuous operation feature of the ICP-MS instrument and the on-line flow system. It is evident from the literature that great efforts have recently been made to develop suitable on-line sample-pre-treatment procedures coupled to ICP-MS, based on using various separation and pre-concentration techniques [36]. These are summarized in Fig. 1, and pertinent details of the diverse protocols are discussed in the following sections. Some of the major techniques presented in this review include the most important up-to-date developments in SPE,

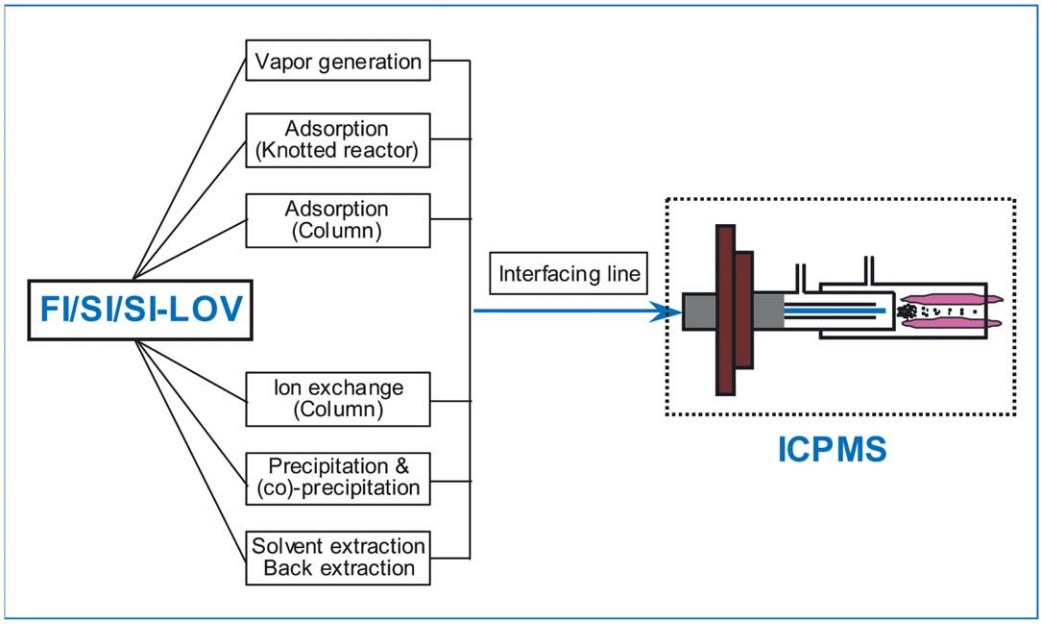

Figure 1. Illustration of the FI/SI/SI-LOV on-line separation and pre-concentration schemes interfaced to ICP-MS.

on-wall retention *via* molecular sorption and/or precipitation/(co)-precipitation, solvent extraction/back extraction, and hydride/vapor generation.

2.1. On-line, column-based separation or pre-concentration systems

Column-based SPE has proved to be one of the most efficient on-line sample-pre-treatment approaches [33,35,37], and various sorbent materials have been investigated for on-line column separation or pre-concentration coupled to ICP-MS. The broad range of choice for sorbent materials along with various chelating reagents and eluents makes this technique very attractive for on-line sample pre-treatment.

For preparing packed columns, a number of factors that might influence the performance of an on-line column separation or pre-concentration system should be taken into account. Some of the most important comprise:

- the sorption (break-through) capacity of the sorbent material for both the analyte and the other constituents that might act as interferents;
- the extent of interference effects and the level of the interferents; and,
- the particle size of the sorbent.

In order to achieve a higher enrichment efficiency, the dispersion of the pre-treated sample zone in an FI/SI/SI-LOV on-line system should be kept at a minimum, and this remains true equally well in column pre-concentration systems. So far, most of the on-line pre-concentration systems described employ time-based sample loading, where dispersions are not significant [34].

As to the sorbents used for on-line, column-based SPE, chelating, ion-exchange resins are the most frequently applied column-packing materials, among which the two most popular functional groups are iminodiacetate and quinolin-8-ol. Although chelating resins generally offer better selectivities in comparison with normal cation- or anion-exchange resins, there is virtually no discrimination between the individual transition or heavy metals when chelating resins are used as sorption media (i.e., they tend to chelate a variety of transition or heavy metals onto the surface of the resin at the same time, which is of great importance for group pre-concentration, and this feature makes them suitable for multi-element measurement by ICP-MS). Hence, a number of FI on-line column separation and pre-concentration procedures coupled to ICP-MS have been developed by using resins with iminodiacetate [38–45] and quinolin-8-ol [38,39,46–50] as functional groups, having been employed for multi-element determinations in various sample matrices, including estuarine water [38,39,50], seawater [39,41–45, 48–50], blood or serum [40], natural waters [46] and urine [47]. Instead of employing a pre-packed column as sorption medium, in some cases, miniaturized chelating resin disks containing iminodiacetate functional groups have been used for on-line pre-concentration of multi-elements followed by ICP-MS detection [51,52].

In addition to the two resins mentioned above, some others with diverse functional groups have been employed for on-line matrix separation or column

pre-concentration with detection by ICP-MS, including TRU resin (a support material impregnated with a liquid ion exchanger) [53], AG50W-X8 [54], AG1-X8 [55], and SP Sephadex C-25 [56]. One distinct advantage of using chelating and cation-exchange resins is that, in many cases, the retained analytes can be eluted by using nitric acid [41,43,51,52,56]. This is beneficial for overcoming the detrimental effects of organic eluates on ICP-MS detection, which tend to cause rapid loss of sensitivity and even blockage of the sampler orifice as a result of carbon deposition on the sampling cone, and generation of polyatomic ion interferences attributed to the combination of carbon with oxygen, argon, sulfur and chlorine [56,57].

Non-polar bonded or immobilized octadecyl (C_{18}) functional groups on silica gel provide another kind of sorbent that has been widely used for on-line column separation and pre-concentration [35,37,58]. Surprisingly, in contrast with its applications in on-line sample pre-treatment coupled to electrothermal atomic absorption spectrometry (ETAAS), where a large number of procedures are available [58], there are only a few reported procedures based on the employment of bonded C_{18} functional groups on silica gel as sorption medium coupled to ICP-MS. They have exploited diethyldithiocarbamate (DDTC) [59], diethyldithiophosphate (DDPA) [60,61], and 2-(5-bromo-2-pyridylazo)-5-(N-propyl-N-sulfopropylamino)phenol (5-Br-PAPS) [62] as chelating reagents. This might be attributed to the fact that the retained, non-charged metal complexes in these cases are mostly eluted with organic solvents, which exclude the direct interface of the pre-concentration systems to ICP-MS [59,60] because of the detrimental effects of organic solvents on ICP-MS determinations [56,57].

Microcolumns packed with activated alumina have also been used for FI, on-line pre-concentration of trace metals. Thus, platinum and palladium [63,64], and arsenic, chromium, selenium and vanadium [65] were retained as anions onto the acidic form of an activated alumina-packed column; they were afterwards eluted with ammonia and the eluates were ultimately directed into the ICP-MS for quantification.

A PTFE bead-packed microcolumn has very recently been introduced for SI, on-line separation and pre-concentration of trace cadmium and lead *via* adsorption and elution of the Cd- and Pb-DDPA complexes, with subsequent detection by ICP-MS [66]. This novel column not only substantially improved the retention efficiency of the metal complexes (i.e., quantitative sorption of cadmium and lead), as compared with the widely employed PTFE KRs, but also allowed the elution of the retained analytes with nitric acid [66,67], which facilitated ICP-MS measurement. Furthermore, as the PTFE beads do not undergo any volume change during operation, they have the advantage of low flow resistance. In fact, using hydrophobic column materials imparts some specific advantages, because it is possible, *via* intelligent choice of the chelating reagent, not only to obtain increased selectivity, but also, by playing on clever chemistries, to gain higher tolerance for potentially interfering ions, plus eliminating inert ions in samples with high salt content.

In practice, a smaller particle size of the sorbent, corresponding to a larger surface area, will result in a higher break-through capacity. However, finer particles tend to cause progressively tighter packing of the column material and hence create flow resistance/back pressure, which will inevitably adversely affect the performance of the system in long-term operation. Moreover, some sorbent materials undergo volume changes (i.e., swelling or shrinking) at different experimental conditions, which make the situation even more complicated [68]. In conventional analytical procedures based on column operations, the solid phase is always treated as a stationary component, being used repetitively and renewed only after numerous analytical runs. In this format, the deterioration in analytical performance, associated with malfunctions of the reactive surface as caused by contamination and/or deactivation of the surface, or even the loss of functional groups, is eventually unavoidable. This effect is particularly critical when analyzing biological samples.

A solution to this problem was very recently presented, comprising a SI-BI system with a LOV microconduit incorporating a renewable microcolumn [69–71]. Here, the microcolumn is renewed for each analytical run, which effectively eliminates the flow resistance and any potential changes or malfunctions of the surface properties encountered in the traditional approaches. By using SP Sephadex C-25 cation-exchange resin as sorption material, this novel scheme has successfully been applied to separation and pre-concentration of nickel and bismuth in biological and environmental samples with detection by ICP-MS [56], yielding significantly improved precision and LODs, when compared with conventional counterparts. The operating protocols of this renewable surface scheme are illustrated in Fig. 2.

2.2. On-wall adsorption or retention of non-charged metal complexes

Since they were first employed for FI, on-line collection of co-precipitate without filtration [72] and on-line sorption of neutral metal complexes [73], PTFE KRs have been widely recognized as a trouble-free, very efficient collecting medium, facilitated by the secondary flow created in the KR [33,72,73], which also holds true in its applications with detection by ICP-MS.

There are two main approaches to executing on-line KR sorption or retention pre-concentration followed by ICP-MS detection. In most cases, pre-concentration is

achieved through on-line merging of the sample solution and a complexing or precipitating/(co)-precipitating reagent, followed by the sorption or retention of the neutral metal complexes or the precipitate or (co)-precipitate on the interior surface of the KR. After a washing step, the neutral metal complexes or the precipitate or (co)-precipitate are eluted or dissolved with an appropriate eluent. By using this approach, pyrrolidinedithiocarbamate (APDC) [57,74,75] has been used for FI, on-line formation and sorption of neutral metal complexes, while DDTC [76,77] and ammonia buffer [78] were employed as precipitating reagents for collecting precipitates of transition metals and rare-earth elements.

Another approach, which in practice is effective only for on-line sorption of metal complexes, is to pre-coat the complexing reagent directly onto the interior surface of the KR, followed by sample loading, thus executing the separation or pre-concentration process. After a washing step, the analyte is eluted and ultimately transported into the ICP-MS. This approach has so far been employed for only FI, on-line separation and pre-concentration of rare-earth elements with pre-coated 1-phenyl-3-methyl-4-benzoylpyrazol-5-one (PMBP) [79], but the figures of merits reported appear to indicate an improved sensitivity and overall efficiency compared to that of on-line merging of the sample and the reagent solutions.

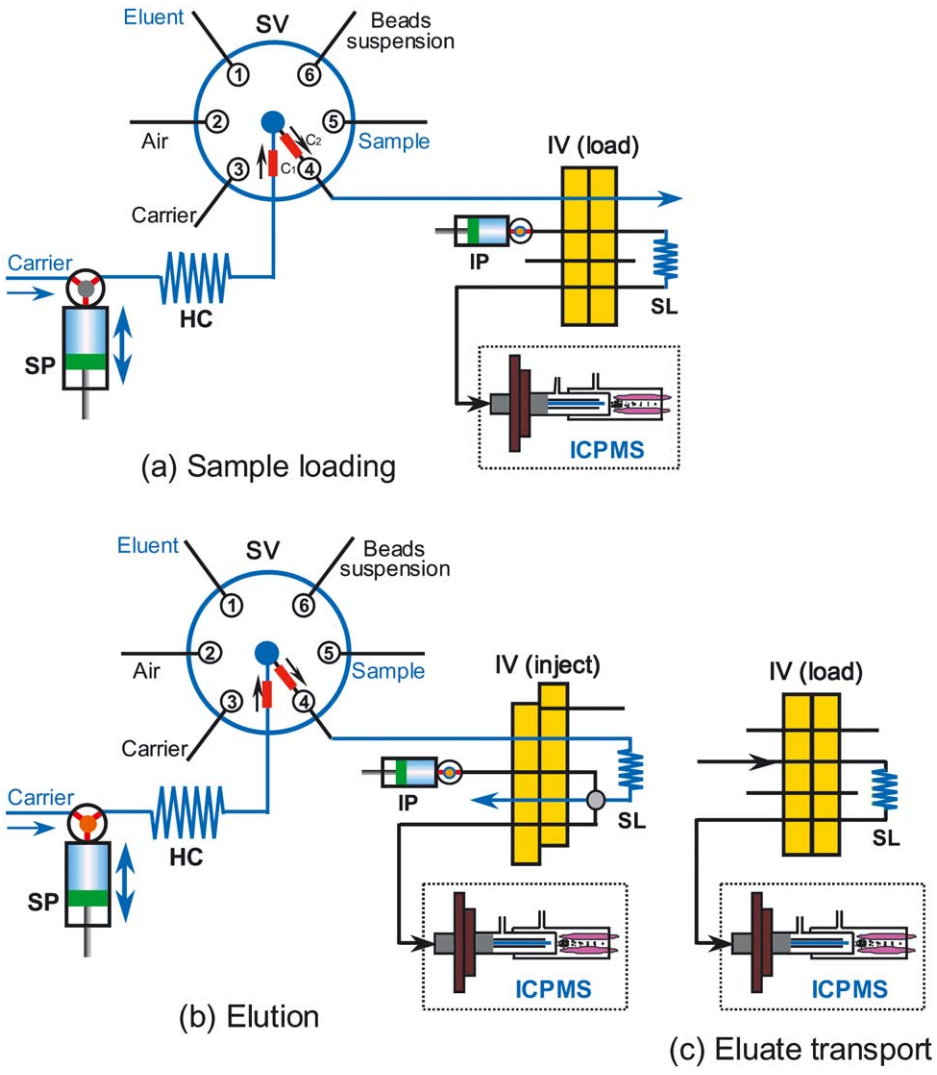

Figure 2. SI-LOV renewable surface scheme for ultra-trace-metal pre-concentration and matrix separation using Sephadex C-25 cation-exchange beads. SV, LOV mounted on top of a 6-port selection valve; SP, Syringe pump; HC, Holding coil; IV, Injection valve; IP, Infusion pump; SL, Sample loop; C_1 and C_2, Renewable column positions. (a) Sample solution is first aspirated into HC, followed by about 20-µl suspension of beads of Sephadex C-25 resin which are entrapped in column position C_1. Thereafter, the beads are transferred to C_2, where they are captured to pack a renewable column, followed by sample solution (i.e., pre-concentration takes place in this position). Carrier solution is continuously delivered to the ICP by the IP. (b). With IV in the inject position, the retained analytes on the column are eluted and stored in SL. (c) Finally, IV is switched to the load position and the content in SL is propelled into the ICP by the continuously operating infusion pump.

As to molecular sorption schemes, neutral metal complexes adsorbed onto the interior surface of the KRs are often eluted with organic eluents, such as isobutylmethyl-ketone (IBMK), ethanol and methanol. In order to eliminate the adverse effects of organic solvents on the ICP-MS measurements, it is therefore compulsory either to employ an ultrasonic desolvation nebulization system [57,79] or to use a mineral acid, preferentially nitric acid, as eluent [74,75]. In our experience, neutral metal complexes adsorbed onto the PTFE surface can, in many cases, be eluted with nitric acid [66,67].

However, with on-line precipitation or (co)-precipitation systems, the retained precipitates or (co)-precipitates on the interior surface of the KRs are generally dissolved with nitric acid of appropriate concentrations [76–78], which can afterwards be introduced directly into the ICP-MS instrument for quantification. However, so far this approach has not been employed much for coupling to ICP-MS.

Open-ended KRs entail the clear advantage of low hydrodynamic impedance, so they allow high sample-loading flow rates and obtain better enrichment factors. A limiting factor in using KRs as collecting media are their low retention efficiency for most metal complexes [80], which restricts significant improvements in their pre-concentration capability. This drawback can be eliminated by employing a PTFE bead-packed column [66] as sorption medium instead of a KR.

2.3. On-line solvent extraction-back extraction, sample-pre-treatment schemes

Liquid-liquid solvent extraction is among the most effective sample-pre-treatment techniques in the separation of interfering matrices and pre-concentration of metals. When using ICP-MS as the detection device, it is a prerequisite to eliminate the adverse effects of organic solvents on ICP-MS measurements. In this respect, an ultrasonic desolvation nebulization (USN) system was employed to eliminate organic solvent after the analytes were extracted into an organic phase (choloroform) and prior to introduction into the ICP [81]. Although this proved to be a useful tool, the most effective approach is, in our experience, employment of a back-extraction procedure that appears to eliminate the organic solvent completely [82].

Surprisingly, there have been scarcely any reports on attempts to interface FI, on-line solvent extraction-back extraction systems with ICP-MS in recent decades. So far, only one single procedure has been located in the literature [83]. This might be attributed to the lack of robustness of conventional FI systems, the difficulty in manipulating organic solvents and the trouble associated with most on-line phase separators. In this respect, the simplicity, robustness and versatility of a SI system make it most suitable for executing on-line, solvent extraction-back extraction operations. The hyphenation of SI and FI further facilitates the manipulation of more complicated manifolds [82].

The practicability of this approach has been demonstrated by a novel FI/SI, on-line solvent extraction-back extraction procedure coupled to ICP-MS by using two newly designed PEEK dual-conical gravitational phase separators [84]. Illustrated for the determination of copper and lead *via* complexation with ammonium APDC, the metal chelates were first extracted into IBMK, and subsequently successfully back extracted into an aqueous phase containing dilute nitric acid by using Pd(II) as a stripping agent to accelerate the slow back-extraction process. The aqueous phase was then introduced into the ICP for quantification. In this case, analyte enrichments were obtained in both stages of the extraction.

2.4. On-line hydride/vapor generation coupled to ICP-MS

The interface of an FI/SI, on-line hydride/vapor generation system to ICP-MS is straightforward. The compatibility between the two set-ups allows the hydride/vapor to be introduced directly into the ICP by using an Ar flow. There are two main approaches for obtaining the hydride and/or the vapor. The most widely employed is the chemical hydride/vapor-generation scheme using a suitable reductant (such as sodium tetrahydroborate) in acidic medium. So far, this approach has been applied extensively for FI, on-line separation/pre-concentration of hydride/vapor-forming elements in various sample matrices [85–96]. A second approach is the recently reported FI, on-line electrochemical hydride generation (EcHG) technique, where the hydride is generated on-line by an appropriate electrolysis current [97]. Both schemes can completely eliminate the matrix components, and are thus most favorable for analyses of hydride/vapor-forming elements in biological samples, where serious matrix effects and consequently signal suppression are very often encountered.

Although hydride/vapor generation is a clean, elegant approach to separation, the sensitivity by direct introduction of the hydride/vapor into the ICP is, in some cases, not sufficient. Thus, by employing electrothermal vaporization (ETV) after on-line hydride/vapor generation, the hydride/vapor was successively sequestrated in a palladium pre-coated graphite tube, which offered appropriate pre-concentration of the analytes, and it could therefore substantially improve the sensitivity [98].

The major drawback of the hydride-generation technique is that the presence of transition metals, such as Ni(II), Co(II), Cu(II) and Fe(III), can severely suppress the formation and the release of the analyte hydride, because of the interaction of hydrides with the reduced forms of these metals [91,92]. Fortunately, the forma-

Table 1. The main on-line sample-pre-treatment schemes coupled to ICP-MS for determination of trace levels of metals

Separation/pre-concentration schemes	Reaction medium/functional group	Analytes	Samples	References
Solid phase extraction				
permanent column approach				
- chelating ion exchange resins	Iminodiacetate	Cd, Cu, Ni, Zn, Mn	Estuarine water	[38]
		Mn, Co, Cu, Zn, Cd	Estuarine/coastal water	[39]
		Fe, Ni, Cu, Zn, Pb	Blood/serum	[40]
		Pb, Mn, Cu	Seawater	[41]
		Cd, Co, Cu, Mn, Ni, Pb, U, Zn	Seawater	[42]
		Mn, Ni, Cu, Cd, Pb	Seawater	[43]
		Cr(III)/total Cr	Seawater	[44]
		Al, U, Mn, Co, Ni, Cu, Zn, Mo, Cd, Pb, U	Seawater	[45]
	Quinolin-8-ol	Cd, Cu, Ni, Zn, Mn	Estuarine water	[38]
		Mn, Co, Cu, Zn, Cd	Estuarine/coastal water	[39]
		Pb, Mn, Ni, Cu	Natural water	[46]
		Bi	Urine	[47]
		Rare-earth elements	Seawater	[48]
		Ti, V	Seawater	[49]
		Multi-elements	Estuarine/coastal water	[50]
- sorption	Immobilized C_{18}	Cd, Co, Cu, Mn, Ni, Pb, Zn	Seawater, riverine water, urine, bovine muscle	[59]
		Cu, As, Se, Cd, In, Hg, Tl, Pb, Bi	Bovine liver, bovine muscle, riverine water, urine	[60]
		Ag, Tl, U, Au	Riverine water, apple leaves, milk powder	[61]
		Mn, Fe, Ni, Cu, Zn, Cd, Pb	Seawater	[62]
	Activated alumina	Pt	Natural water, car exhaust	[63]
		Pd	Urban water	[64]
		As, Cr, Se, V	Dogfish muscle/liver tissue	[65]
	PTFE bead surface	Cd, Pb	Urine, natural water, sea lettuce	[66]
renewable column approach				
- cation-exchange resin	Sulfopropyl	Bi, Ni	River sediment, urine	[56]
- chelating resin disks	Iminodiacetate	Rare earth elements	Natural water	[51]
		V, Mn, Co, Ni, Cu, Mo, Cd, U	Seawater	[52]
On-wall adsorption/retention				
- molecular sorption	PTFE KR inner surface	Cu, Ni, Sb, Co, Ag, Cd, Mo, In, Pb	Fresh water, coastal water, cod muscle, mussel tissue	[57]
		Fe(II)/Fe(III)	River water, groundwater, tap water	[74]
		As(III)/As(V)	Riverine water, pore water	[75]
		Rare-earth elements	Riverine water, coastal water, estuarine water, fresh water	[79]

(*continued on next page*)

Table 1 (*continued*)

Separation/pre-concentration schemes	Reaction medium/functional group	Analytes	Samples	References
- precipitation/co-precipitation	PTFE KR inner surface	Cu	Estuarine water	[76]
		Cr, Mn, Fe, Co, Ni, Cu	Estuarine water	[77]
		Rare-earth elements	River water, pore water, basalt	[78]
Solvent extraction/back extraction	HDEHP* + H_2MEHP*/ octyl alcohol + HNO_3	Rare-earth elements	Seawater, rocks	[83]
	IBMK/Pd(II) + HNO_3	Cu, Pb	Natural water, sea lettuce, river sediment, urine	[84]
Hydride/vapor generation	Chemical hydride/vapor generation	As	Seawater, riverine water, urine	[85]
		Tl	Seawater	[86]
		Pb	Natural water, plant tissue, pond sediment	[87]
		As, Sb, Bi, Hg	Seawater, tap water, riverine water	[88]
		Se	Estuarine water	[89]
		As, Bi, Ge, Hg, Sb, Se, Sn	Urine	[90]
		Se	Dogfish liver/muscle tissue	[91]
		Tl	Nickel-based superalloy	[92]
		As, Se	Plant leaves, water	[93]
		Se	Water, serum	[94]
		As, Sb, Hg	Seawater	[95]
		Se(IV)/Se(VI)	Synthetic aqueous solution	[96]
	Electrochemical hydride generation	As, Bi, Ge, Hg, Sb, Se	Fresh water	[97]

*HDEHP: bis(2-ethylhexyl) hydrogen phosphate; *H_2MEHP: 2-ethylhexyl dihydrogen phosphate

tion rates of these free metal ions are slow when compared with those of the hydride-generation process. Thus, in a FI system, the short reaction time and rapid separation of the hydride effectively attenuate the adverse effect of transition metals. However, in some systems, the effect of the transition metal ions is still quite pronounced, and masking agents are required to alleviate their interferences [92]. Recently, a novel FI system, with a 60-ms reaction time for hydride generation and rapid separation of the reaction products with a modified Scott spray chamber serving as a gas-liquid separator, effectively suppressed the effect of transition metals and substantially improved the performance of the system when coupled to ICP-MS [91].

As a summary of the above discussions, the main FI/SI/SI-LOV on-line sample-pre-treatment schemes coupled to ICP-MS for the determination of trace levels of metals are highlighted in Table 1.

3. Eluate delivery from on-line pre-concentration system to ICP-MS

In most FI/SI on-line separation/pre-concentration procedures, the final volume of the concentrate is usually very limited (i.e., at the µl level). When making the coupling to ICP-MS, the dispersion of the concentrate during its introduction to the ICP might cause a severe loss of sensitivity. This is particularly critical with a conventional cross-flow nebulization system. In such cases, the introduction of small air segments at both ends of the concentrate can help to minimize the dispersion during its transport [57,79,99] with careful optimization of the ICP-MS system. However, the low sample-transport efficiency of the conventional nebulizers, typically 1–2% for a cross-flow nebulizer, does not make it appropriate for transporting the very limited amounts of concentrate after an FI/SI, on-line pre-concentration procedure. It is beneficial to use a micro-flow, high-efficiency nebulizer. A direct-injection, high-efficiency nebulizer (DIHEN) has therefore been applied to the interface of FI/SI, on-line sample-pre-treatment procedures [56,66,84] with an Elan 5000 ICP-MS. The use of (liquid) carrier segmentation along with a very short, narrow-bore connection (250 µm i.d.) between the on-line system and the DIHEN caused insignificant dispersion of the concentrate. This might be attributed to the very narrow diameter of the sample capillary in the DIHEN (75 µm i.d.) and the low flow rate (typically 40–60 µl/min) employed.

4. Perspectives

The above FI/SI/SI-LOV on-line separation and pre-concentration procedures effectively alleviate the interference effects in ICP-MS determinations, and, at the same time, offer sharp improvements in the sensitivity. However, when compared with other spectrometric techniques, the coupling of on-line sample-pre-treatment schemes to ICP-MS has resulted in practical problems that have not been investigated much, thus leaving some topics in need of further exploration.

As mentioned in the section for on-line hydride-generation systems, the sensitivities achieved by direct introduction of the hydride into the ICP are, in many circumstances, not sufficient for determination of ultra-low levels of metals. This might be further improved upon by employing an on-line pre-concentration step, such as precipitation/(co)-precipitation and SPE, followed by hydride generation, to achieve complete elimination of interfering matrices.

SI-LOV—the third generation of FI — is still in its infancy. There is, therefore, much to be explored in coupling in-valve, on-line, sample-pre-treatment protocols with detection by ICP-MS. In this respect, further explorations could be directed towards investigations of SI-LOV separation/pre-concentration *via* solvent extraction and precipitation/(co)-precipitation, and/or in-LOV matrix removal and pre-concentration of hydride/vapor-forming elements by precipitation/(co)-precipitation/SPE followed by a second-stage separation (i.e., post-hydride generation).

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