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Solid-phase extractions in flow analysis

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ABSTRACT

Coupling solid-phase extraction (SPE) to flow systems has promoted a synergistic development. Whereas SPE mechanization leads to improved precision and higher sample throughput, as well as diminishes systematic errors and contamination risks, analyte concentration and separation from the sample matrix provides a remarkable impact on detectability and selectivity in flow analysis. Historical aspects, main cornerstones, tips for system design, and recent applications are critically reviewed, in the context of analyte(s) separation/concentration, sample clean-up, and release of sorbed chemical species involving both packed (*e.g.* mini-columns, cartridges, and disks) or fluidized (*e.g.* beads and magnetic materials) particles. Novel (bio)sorbents, selective synthetic materials, and stationary phases for low-pressure chromatography are also discussed. Moreover, the feasibility of SPE for sample treatment before chromatographic separation, as well as the exploitation of direct measurements on the solid phase (optosensing) are emphasized.

Key words: beads, flow analysis, in-line analyte concentration, in-line sample treatment, sample clean-up, solid-phase extraction.

INTRODUCTION AND HISTORICAL ASPECTS

Solid phase extraction (SPE) is a widely used strategy for sample clean-up and for enhancement of analytical sensitivity, selectivity or both (Buszewski and Szultka 2012). In general, SPE involves transference of the analyte(s) from a liquid sample to a solid sorbent, usually followed by elution. A typical cycle for analyte separation/concentration comprises: (i) *Conditioning:* a suitable solvent or solution passes through the sorbent to activate its functional groups, and the excess is removed; (ii) *Loading:* a defined sample volume is placed in contact with the sorbent and either the analyte(s) or potentially interfering species are retained; (iii) *Washing:* a rinsing solution removes the residual sample from the sorbent void volume; (iv) *Elution:* the eluent(s) passes through the sorbent for releasing the analyte(s). Equilibrium conditions are generally required when the process is carried out batchwise and, consequently, SPE may become time-consuming.

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In practice, a simplified SPE strategy is preferred, thus the possibility of performing two steps in conjunct (*e.g.* loading and washing) is highly attractive. This aspect is generally attained when SPE is implemented in a flow analyzer. In fact, loading occurs during the transient interaction of the sample zone with the sorbent, whereas washing takes place during passage of the carrier stream through the sorbent.

In segmented flow analysis (Skeggs 1957), few applications exploiting SPE have been reported for analyte separation/concentration, although mini-columns and cartridges with suitable adsorbents were already commercially available in 1973 (van Gemert 1973). Anyway, some applications involving sample clean-up were proposed, and the landmark article focused on sulfate determination in waters (Gales et al. 1968). The unsegmented sample stream was pumped through a mini-column filled with a Dowex-50 W-X8 cation-exchange resin in which the potential interfering ions were retained; the depleted sample merged with a segmented barium chloranilate stream yielding the slightly soluble barium sulfate, and releasing the colored chloranilic acid; the handled sample was then in-line filtered, monitored at 520 nm, and discarded.

The scarce number of SPE applications in segmented-flow analysis is due to the drawbacks of introducing air-bubbles in the sorbent mini-column. This limitation can be overcome by applying a novel extraction principle relying on functionalized magnetic beads (Rendl et al. 2014, Schönberg et al. 2015). The beads are added to every aqueous sample segments, yielding highly reproductive suspensions. After sorption of the species of interest, the beads are retained by a magnet and further exposed to an eluent under unsegmented flow conditions.

Unlike segmented flow analysis, exploitation of SPE in unsegmented flow analyzers has been remarkable. In fact, the implementation of SPE in flow injection analysis (Ruzicka and Hansen 1975, Stewart et al. 1976) and related techniques is worthy for the development of environmental friendly analytical procedures compatible with a large number of samples. Additionally to analyte separation and concentration, monitoring of desorbed chemical species has been proposed for *e.g*. bio-accessibility assays (Vida et al. 2016), estimative of nutrient release from soils (Machado et al. 2017), and speciation analysis (Pons et al. 2005).

The advantages of in-line SPE in unsegmented flow analysis were already noted during the early developments of flow injection analysis (Hansen and Ruzicka 1983). In this context, the pioneer work dealt with ammonium determination in natural waters (Bergamin-Filho et al. 1980). An Amberlite IR-120 resin mini-column replaced the sampling loop of a sliding bar injector. In the loading position, the sample was aspirated through the mini-column, where ammonium was retained, and the sample excess was discarded. Switching the injector to the eluting position intercalated the mini-column into the eluent stream, and the analyte zone was directed towards detection. Thereafter, the zone interacted with the Nessler reagent added by confluence (Bergamin-Filho et al. 1978), and the reaction product was monitored by both radiation absorption and light scattering at 410 nm. Regarding selectivity improvement, interferences of phosphate and sulfate on the determination of calcium by flame atomic absorption spectrometry were circumvented by removal of these anions by in-line ion-exchange (Kamson and Townshend 1983).

Different procedures for in-line SPE involving packed or fluidized sorbents, real-time decisions based on concentration-oriented feedback mechanisms, multi-channel manifolds, and flow reversals, have been implemented in unsegmented flow analyzers. As the involved steps are mechanically accomplished, analytical

precision tends to be enhanced, and human errors are minimized. Risks to the analyst due to exposure to hazardous chemicals are reduced because the entire process takes place inside a closed system. Moreover, sample contamination and/or analyte losses are minimized. The amounts of samples, reagents, and solvents typically diminish, and further reduction can be attained through system miniaturization or some special flow modalities. The above features are in adherence to the concept of Green Analytical Chemistry (Gałuszka et al. 2013).

In flow-based SPE, the time intervals available for the involved physicochemical processes are highly reproducible, allowing the development of analytical methods where equilibrium conditions are not attained. Consequently, non-exhaustive extractions can be precisely carried out, allowing the advantageous mechanization of solid-phase micro-extraction (SPME) in flow analysis (Belardi and Pawliszyn 1989, Arthur and Pawliszyn 1990).

Most applications of SPE in flow analysis aimed at single analyte determinations or sample clean-up. Anyhow, the feasibility of simultaneous determinations relying on sequential elutions was demonstrated in some applications involving *e.g.* successive injections of different eluents (Burguera et al. 1981), concentration gradients (Maniasso et al. 1996) or monolithic columns (Fernández et al. 2012).

In this review, the main aspects inherent to SPE in unsegmented flow analysis are discussed, with emphasis to manifold design, potentialities, limitations, and applications.

MANIFOLD DESIGN

SPE can be implemented in different modalities of unsegmented flow analyzers and the manifold is usually designed either with a packed mini-column or a SPE cartridge. Three basic system configurations (Fig. 1) have been usually exploited (Zagatto et al. 1993).

In the original implementation of SPE in unsegmented flow analysis, the mini-column with the solid sorbent (MC) was placed in the loop of an injector-commuter (Figure 1a, MC in position 1). The main advantage of this configuration is that the mini-column is displaced between two rather different streams, one accountable for the conditioning and loading steps, and the other, for the elution and washing. The depleted sample is discarded without passing through the detection unit. Also, more effective elution under counter-current flow conditions is straightforwardly accomplished. The sample volume is generally defined by the sample aspiration rate and sampling time. With zone sampling (Reis et al. 1981), the sample volume is defined by the sampling loop: the sample zone established into the first carrier stream is directed towards the mini-column, and switching the injector intercalates the sorbent into the eluent stream. The mini-column is then washed after every sorption step.

Another basic configuration (Figure 1a, MC in position 2) involves the placement of the mini-column between the injector and the detector (Burguera et al. 1981). Sample and eluent solutions are sequentially inserted into the carrier stream, and the successive zones flow through the mini-column towards detection. The manifold is simple, but the pronounced concentration gradients can hinder detection. Consequently, the Schlieren effect may impair the detection limit (LOD) in spectrophotometric and luminometric methods (Dias et al. 2006). Moreover, elution may be only partial because of the limited eluent volume. This basic configuration has been preferred in sequential injection analysis (SIA), as shown in Figure 1b (Miró et al. 2000, Economou 2005), because solutions handling is improved by the multiport valve and feasibility of flow programming. In SIA, the solutions are sequentially aspirated towards

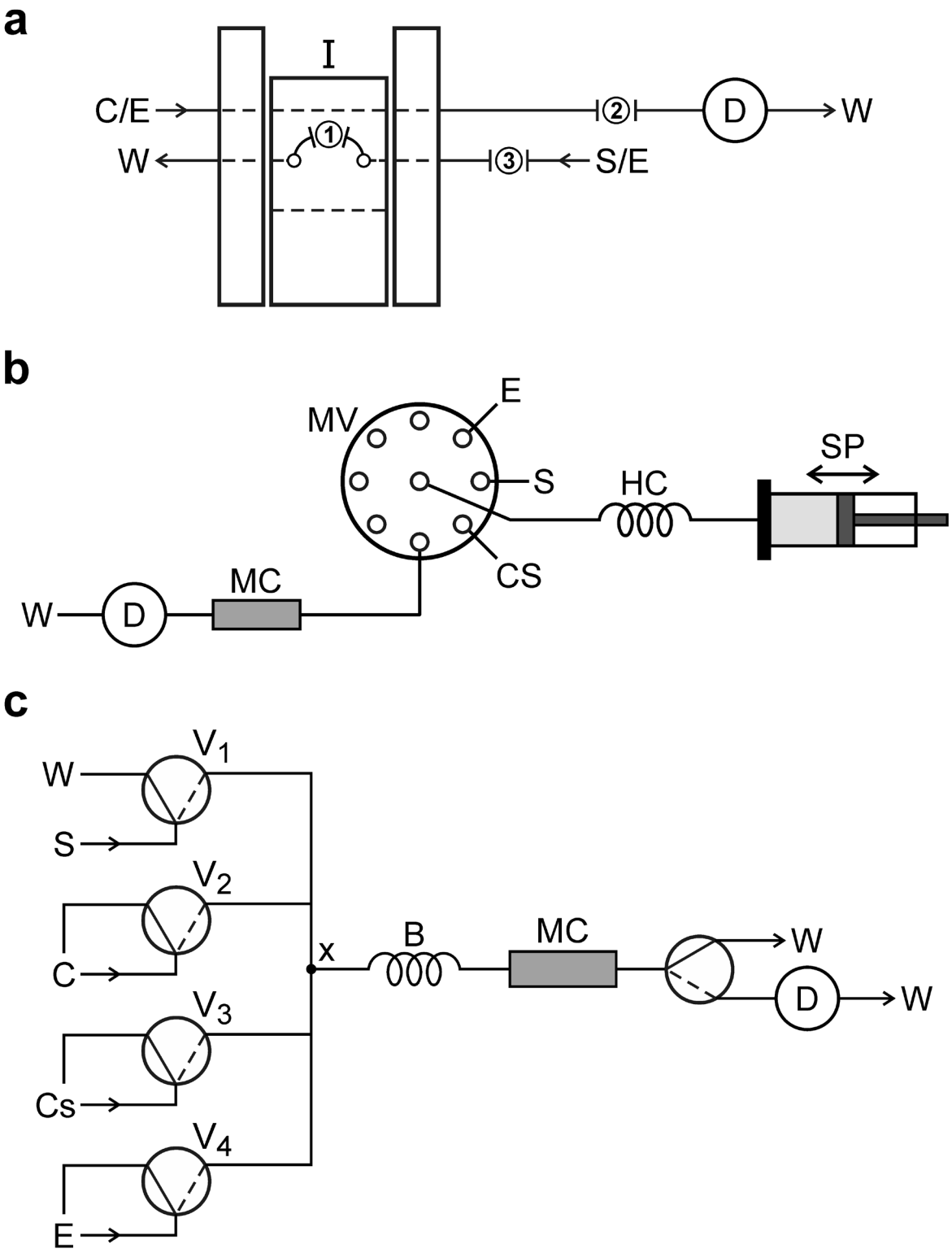

Figure 1 - Flow diagrams of analytical systems with SPE mini-columns (MC): (**a**) FIA with a sliding bar injector (I). MC placed in positions 1, 2 or 3; (**b**) SIA and (**c**) MCFA; S: sample; B: mixing coil; C: carrier stream; CS: conditioning solution; D: detector; E: eluent; HC: holding coil; MV: multi-position valve; SP: syringe pump; Vi: solenoid valves; x: confluence joint point; W: waste recovery vessel.

a holding coil and then driven through the mini-column. The main drawback refers to the mutual dispersion of the aliquots (e.g. sample and eluent; eluent and conditioning solution) at the interfaces, which can hinder the analyte sorption or elution. Some approaches to circumvent this drawback include insertion of an air plug between the carrier and eluent (Chomchoei et al. 2005) and exploitation of programmable flow to complete the sample loading before aspiration of the eluent solutions (Chisvert et al. 2002). The later demonstrates the feasibility of SIA for independent managing of sample, eluent, and conditioning solutions. Other configuration (Figure 1a, MC in position 3) relies on the mini-column placed before the injection port aiming at sample clean-up. Potential interfering species are removed, but a high adsorption efficiency of the sorbent is required. The species in the interstitial phase can also be transferred to the sample loop. Periodic elution is required to avoid sorbent overload, which depends on the sample loaded volume and concentrations of the potential interfering species.

With multicommutation (MCFA), the versatility of the above-mentioned basic configurations is improved (Rocha et al. 2002), as demonstrated by the increasing number of analytical applications. A MCFA flow system designed in the basic configuration is shown in Figure 1c. As previously mentioned in relation to SIA, the efficient solution handling permits the independent implementation of all the steps involved in SPE, *i.e.* sorbent conditioning, sample loading, washing to remove the interstitial solution, and elution (Gonzáles et al. 2009). MCFA also allows coupling of flow-based SPE with inherently discontinuous detection systems, such as ETAAS (Silva et al. 1998). A useful approach is coupling the mini-column at the auto-sampler arm. Sample and conditioning solutions are sequentially driven through the sorbent under reproducible timing and flow rates. Then, a few microliters of eluent are aspirated through the sorbent and the eluate is directly delivered into the atomizer. If necessary, further elution can be carried out before the next measurement cycle. These characteristics, mainly the improved versatility, hold also for the multi-syringe flow systems (Miró et al. 2002). Because of the capability of the syringe pump to deliver low volumes with good precision, the consumption of reagents and eluent can be minimized.

Attention should be given to the column geometry and sorbent characteristics (*e.g.* functional groups, particle size, and breakthrough capacity). Smaller particles are preferred because of the higher surface area, but particle size cannot be decreased at will in order to prevent a pronounced increase in backpressure. Some sorbent materials undergo volume changes due to swelling or shrinking effects. Irreversible contamination, deactivation of the surface or even loss of active sites may also occur. During long-time utilization, preferential pathways may be established inside the mini-column, limiting the interaction of the sample with the sorbent. These aspects can be circumvented by exploiting functionalized moving beads and the number of applications of this approach has increased, especially in the context of bead injection analysis (Ruzicka and Scampavia 1999), including lab-on-valve (Boonjob 2014)), MSFIA (Pons et al. 2005), SIA (Wang and Hansen 2001, Sartini et al. 2002), magnetic beads (Ampan et al. 2002), and fluidized beds (Ribeiro et al. 2006).

Application of stir bar sorptive extraction in flow analysis was recently proposed also aiming at to maximize the sample/sorbent interaction, as well as to minimize backpressure. The sorptive bar was placed inside a chamber and submitted to magnetic stirring in a MSFIA system (Ghani et al. 2016b). Stir bar coatings were prepared from a mixture of montmorillonite and epoxy resin, in which different reagents can be physically or chemically adsorbed. Under suitable experimental conditions, analyte adsorption can be reversible, thus favouring the

reuse of the same sorbent in several retention/elution cycles.

Flow systems have been also exploited for analyte concentration or sample clean-up before chromatographic separation. This hyphenation synergistically enhances the advantages of each process especially in relation to complex samples, analytes at trace levels, or both, with increased sample throughput, good precision, and low reagent consumption and waste generation. Moreover, this approach significantly diminishes the operational costs in comparison to commercially available apparatus for mechanization of SPE. In this sense, MSFIA was used for sample treatment before determination of the beta-blockers atenolol and propranolol in human plasma (Brunetto et al. 2015). The pretreatment involved deproteinization by SPE with a restricted access material and chemical derivatization under microwave-assisted heating to produce volatile trimethylsilated derivatives, which were suitably separated by GC before MS detection. A sampling rate of 7 h^{-1} was attained by performing sample treatment and chromatographic separation simultaneously.

Miniaturization is a fertile research field in flow analysis, with clear advantages in relation to reagent and sample consumptions as well as to portability. Moreover, the large surface-to-volume ratios inherent to microchannels and the dispersion fundamentally caused by diffusion open new perspectives of applications. In this sense, exploitation of solid-phase extraction in microfluidics has been extensively investigated and the main challenges are the risks of excessive backpressure, clogging, and fluid leakage, especially because of swelling of the sorbent. This drawback has been circumvented in different ways, such as use of elastomeric substrates to build up the microfluidic devices (Magalhães and Fonseca 2017), direct preparation of monoliths by photopolymerization in microchannels (Yang et al. 2015), and exploitation of bead sorbents (Verpoorte 2003). Alternatively to the design of dedicated microfluidic devices, SPE has been successfully exploited in lab-on-valve systems (Vidigal et al. 2013). However, under a practical point of view, capability to *in-field* analysis is often hindered by lack of ruggedness.

NON-CHROMATOGRAPHIC SEPARATIONS

Flow-based methods have been usually focused on the selective determination of a single analyte encompassing advantages such as high sample throughput and improved precision. On the other hand, liquid chromatography usually aims at the separation of a group of analytes from each other and from the sample matrix. In this sense, these techniques are complementary and hyphenation can synergistically improve the overall performance including, for instance, in-line sample treatment (clean-up or analyte concentration) in a flow system previously to chromatographic separation (Brunetto et al. 2015, Ghani et al. 2016a). Chromatographic separations have been incorporated to flow analysis by using short (monolithic or fused-core) columns able to operate at relatively low pressures. This topic is further discussed.

In-line separations have been sometimes exploited in flow analysis for improving selectivity and/or for simultaneous determinations. The applications are distinct from typical chromatographic approaches mainly because the flow systems operate at a relatively low pressure (usually < 100 psi), thus requiring more porous materials and/or high particle size, in order to avoid excessive backpressures. This can critically hinder the separation efficiency, leading to significant band broadening in comparison to HPLC. This drawback may limit the applications to separation of a few species or, more usually, a single analyte from the sample matrix. Ingenious approaches have then been proposed to improve the separation capacity in flow analysis, including use of biosorbents, novel

synthetic selective materials (*e.g.* molecularly imprinted polymers), as well as optosensing, which are discussed separately. Illustrative examples of non-chromatographic separations in flow analysis include: (i) separation of Cd(II) from interfering species, *e.g.* Pb(II) and Cu(II), by retaining the corresponding chlorocomplexes in a mini-column packed with an anion exchange resin aiming at determination in foodstuffs (Gomes-Neto et al. 1995); (ii) environmental friendly determination of nitrate in natural waters involving UV spectrophotometry after in-line analyte separation from other absorbing species, *e.g.* organic matter, by ion-exchange (Melchert and Rocha 2005); and (iii) exploitation of polyurethane foam without (Ferreira et al. 1999) or with (El-Shahat et al. 2010) chemical modification for separation of interfering species in nickel determination or for determination of penicillins, respectively. The latter application was based on methylene blue grafted polyurethane foam aiming at analyte concentration and separation from the sample matrix (milk or pharmaceutical formulations), whereas the former exploited the retention of metal ions, *e.g.* Fe(III), Cu(II), Zn(II), and Co(II), as thiocyanate complexes aiming at selective spectrophotometric determination of Ni in alloys and rocks.

IMPROVED SAMPLING RATE AND SAMPLE UTILIZATION EFFICIENCY

Analytical procedures involving analyte separation/concentration are usually time-consuming, mainly because of the time spent at the loading step. Although this aspect is less critical in flow-based procedures, some approaches have been proposed for improving sample throughput without hindering the enrichment factor (EF). As the sample consumption is a limiting factor in some applications of *e.g.* clinical or forensic interest, the loading efficiency also needs to be maximized. These aspects can be evaluated by considering the concentration efficiency (CE) and consumptive index (CI) (Fang 1993), rather than directly from the EF values. The former refers to the EF achieved per unit of time (typically one minute), whereas CI indicates the sample volume required to increase the EF in one unit.

Both CE and CI are inherently improved when several analytes are simultaneously concentrated, a situation typically observed in flow systems involving multielemental detectors (*e.g.* ICPs) and/or unselective sorbents. In this situation, the experimental conditions for sample loading (*e.g.* sample flow rate and sorbent amount), elution, and detection are established as a compromise by considering all the involved analytes.

Some novel sorbents stand out by fast analyte sorption and low backpressure, thus resulting in relatively high CE values. For example, the sorbent based on a poly(vinylpyridine)-supported protoporphyrin yielded a high CE (17.6 min^{-1}) by loading 18.0 mL of sample at a relatively high flow rate (6.0 mL min^{-1}) in a flow injection analyzer (Oliveira et al. 2013). Analytes were efficiently retained and eluted, as demonstrated by the CI of 0.34 mL. The sorbent material was successfully applied to Mn concentration before detection by FAAS aiming at analysis of natural waters, food, and sediments. It should be emphasized that the optimal flow rate at the loading step critically depends on the adsorption kinetics, thus on the physicochemical characteristics of both analyte and sorbent.

More general strategies for improving sampling rate and efficiency of sample utilization (*i.e.* high CE and CI) involve modifications in the system design. In this sense, the simultaneous loading of two mini-columns followed by sequential elution exploiting intermittent pumping of the eluent was proposed (Fang et al. 1984). Even with a sample throughput of 60 h^{-1}, the detectability achieved with FAAS was comparable to that obtained by GFAAS. The strategy was further expanded, with

four mini-columns replacing the sample loops of a sliding bar injector for the determination of Cd by FAAS (Miranda et al. 1995) and the simultaneous determination of Cd, Ni, and Pb by ICP OES in a MCFA system comprising three mini-columns (Miranda et al. 2002). By simultaneously carrying out the loading steps, one expects that CE increases proportionally with the number of mini-columns, but the sample consumption (and thus CI) was not reduced. Other hindrance refers to the need for highly similar mini-columns to achieve reproducible results. In practice, the precision of results obtained in different columns is usually lower than that estimated for a single column. This drawback is not significant when mini-columns are filled with different materials for retention of different species. This approach was exploited for chemical speciation based on the retention of free metal ions in a chelating resin followed by adsorption of complexes on an anion-exchanger (Liu and Ingle 1989), and for the simultaneous in-line concentration of cations and anions exploiting mini-columns placed in series, followed by elutions of the sorbed species in parallel flow channels (Rocha et al. 2004). The latter application exploited the versatility of relocating the mini-columns placed as sampling loops of a sliding-bar injector.

Expert systems are another alternative to improve the analytical productivity in procedures involving SPE, as demonstrated in the sequential spectrophotometric determination of anions in natural waters (Rocha et al. 2001). Chloride, nitrate, nitrite, and phosphate were determined by inserting selective reagents in a continuously flowing sample, which also acted as the carrier of the sample zone. In this way, during the measurement of the transient signals, the sample stream was by-passed through a mini-column filled with an anion exchanger for in-line concentration of the analytes. According to a feedback-oriented mechanism relying on the measured transient signals, a species in concentration lower than LOD by the direct measurement could be measured with improved sensitivity after elution of the analytes previously retained in the mini-column. With this strategy, a 180-s loading time was implemented even with a 50 h^{-1} sampling rate. Further, feedback mechanisms were exploited for real time decision on the need for analyte preconcentration, as well as for performing chemical speciation, as demonstrated in iron determination (Pons et al. 2004). These expert systems exploited the advantages of MCFA for independent solution handling.

BEAD INJECTION

Bead injection analysis involves management of a suspension of beads into a flow system (Fig. 2a). A chromogenic reagent is previously adsorbed on the beads and the sorbent is retained in a specific cell (called a jet-ring cell) where separation, reaction, and detection are in-line carried out. After measurement, the beads are discarded or renewed (Rama et al. 2003).

Poly(styrene-divinylbenzene), agarose or poly(vinylpirrolidone) are commonly used as beads, and uniform spherical shape and size is preferred (Miró et al. 2008). Otherwise, a re-suspension stage is required to promote fluidization, which significantly improves precision in comparison to direct aspiration of suspensions of non-uniform beads, $1.6 < \text{r.s.d.} < 13.8$ and $3.8 < \text{r.s.d.} < 67.6\%$, respectively (Oliveira et al. 2011).

Bead injection allows renewing the solid phase before each loading step, thus avoiding problems of contamination, preferential pathways, and mainly irreversible analyte retention. On the other hand, this implies in higher sorbent consumption. The approach can be suitably combined with optosensing (as further discussed in this review) aiming at improved sensitivity and analyte accumulation in the beads typically yields low LODs (Miró et al. 2008).

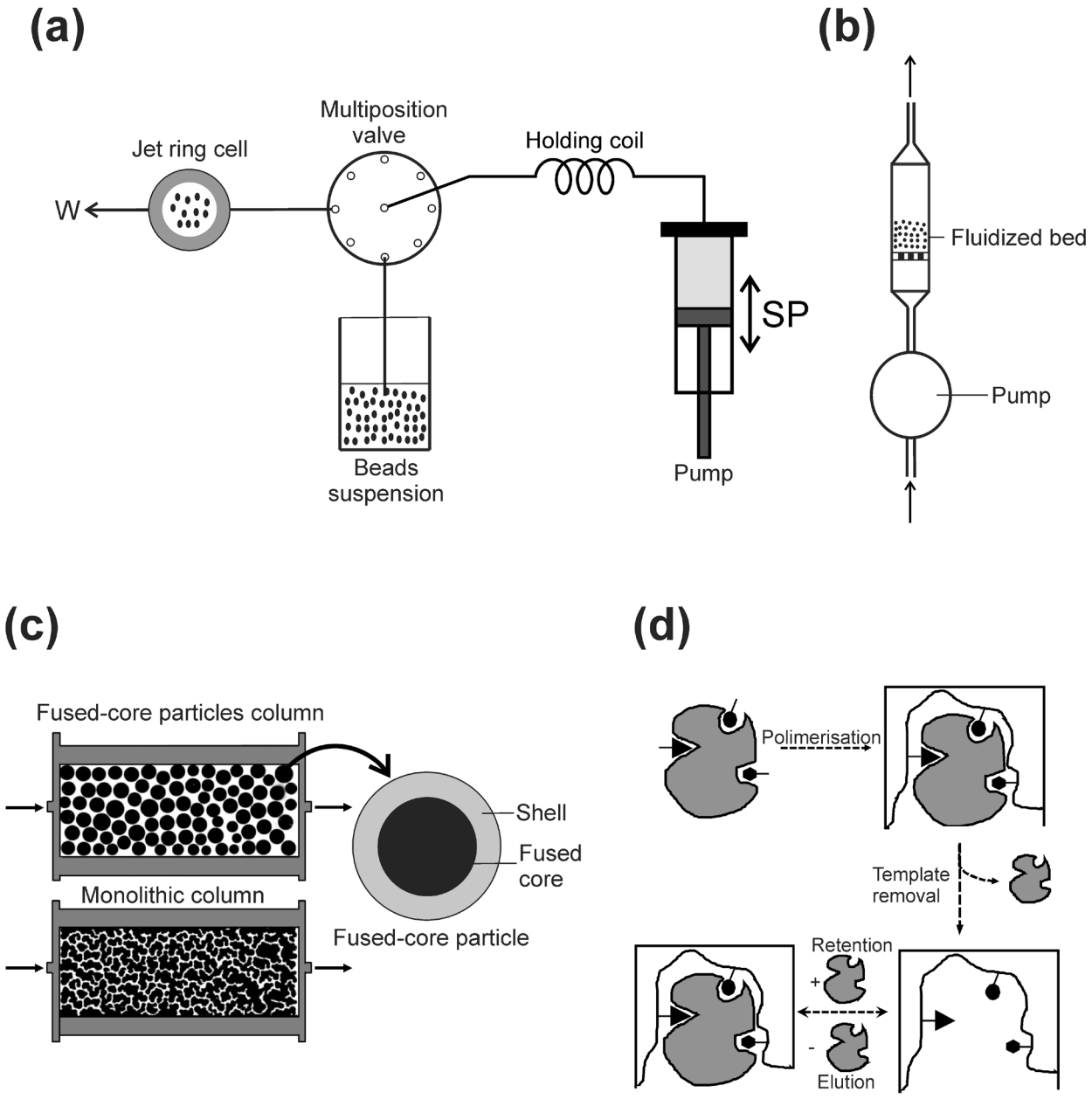

Figure 2 - Some approaches for flow-based SPE: (**a**) bead injection; (**b**) fluidized beads; (**c**) low-pressure chromatography, and (**d**) molecularly imprinted polymers.

Spectrophotometry, fluorimetry or chemiluminescence have been generally used as detection techniques. Coupling with ETAAS is possible by directly introducing polymeric organic beads into the graphite furnace (Miró et al. 2008). Moreover, bead injection has been coupled with amperometric detection and electrochemical jet ring sensor based on enzyme immobilized on the beads surface (Silvestre et al. 2011).

Bead injection has been usually implemented in SIA because of the versatility provided by the multi-position valve and possibility of flow reversal, which is attractive for effective handling of the bead suspensions. The pioneer work involved

a specially designed flow cell, consisting in a tube perpendicular to a flat surface with a narrow circular gap from where the liquid could escape radially. A uniform perfusion and the simultaneous monitoring of the entire bead layer were then accomplished (Ruzicka and Scampavia 1999).

Feasibility of renewal of the ion exchange beads at each measurement cycle in ETAAS was demonstrated by exploiting a six-port selection valve with micro-channels (Wang and Hansen 2001). Tubes with a 10-fold smaller diameter than the beads were introduced within two micro-channels to retain the sorbent. After sample and bead insertion into the mini-column, the analyte was eluted from the beads and the eluate was directed towards the atomizer under segmented flow conditions. The strategy improved precision and selectivity for Ni determination in environmental and biological samples.

Ten β-blockers were determined in environmental samples by coupling a SIA-bead injection analyzer with liquid chromatography-electrospray ionization tandem mass spectrometry (Boonjob et al. 2015). The procedure allowed in-line sample clean-up with bead suspensions, analyte separation/concentration, and detection; EFs within 62–74 and recoveries from 74 to 86% were estimated.

A lab-on-valve system was used for spectrophotometric determination of Fe(II) in acidified seawater samples by 1,10-phenanthroline method, by exploiting a cellulose-based chelating sorbent beads containing 8-hydroxyquinoline (Horstkotte et al. 2016). Before aspiration, air inlet and vortexing were accomplished for re-suspending the beads. System stability was evaluated by repeated analysis over 15 h without significant variations in analytical signals; the coefficient of variation was estimated at 1.6% after 61 determinations.

FLUIDIZED BEDS

Fluidized beds refer to conversion of a solid granular material from a static to a dynamic fluid-like state, establishing a chaotic but reproducible 4π geometry, aiming at improving the solid/liquid interaction. In flow analysis, fluidization can be attained by placing the solid material inside a vertical tubular chamber and letting a pulsed liquid stream to pass through it (Ribeiro et al. 2006), as show in Fig. 2b. Otherwise, mechanical stirring, air inlet, sonication or magnetic beads can be exploited. With fluidized beds, limitations due to the establishment of preferential pathways, high backpressure, bead expansion or compression, and poor accessibility to active sites are minimized. Fluidized beds have been exploited in *e.g.* analytical methods involving in-line SPE (Vakh et al. 2017), relatively slow chemical reactions, and analyte sorption/leaching (Rosende et al. 2010).

The innovation has proved to be also useful for dynamic extraction in metal bioaccessibility assays, evaluation of soil capacity, chemiluminometric determinations, and analytical methods relying on immobilized reagents. The multi-pumping flow system (MPFS) designed for the dynamical evaluation of the soil capacity to adsorb phosphate (Machado et al. 2017) can be mentioned as an example. A phosphate standard solution passed through a fluidized bed column with 50 mg of soil (particles < 0.15 mm), where the analyte was adsorbed. The remaining phosphate was then in-line quantified by the spectrophotometric molybdenum blue method. Excellent figures of merit were attained, in addition to 40, 100, and 180-fold reductions in waste generation, soil amount, and analysis time in comparison to the reference procedure. Other relevant aspect is that soil non-homogeneity becomes less critical, corroborating previous observations (Rosende et al. 2010).

A fluidized-bed reactor was used in a MPFS for the chemiluminometric determination of uric

acid in saliva (Vakh et al. 2017). It consisted of an anion-exchanger placed into a cylindrically-shaped glass tube with inlets at the bottom and top. The pulsed flow delivered by a solenoid pump fluidized the resin and separated the analyte from the sample matrix. The anion-exchanger was used in up to 1500 sorption-desorption cycles, without increasing backpressure.

Stepwise injection analysis with a fluidized-bed reactor was applied to determination of glycerol in biodiesel involving in-line sample preparation (Shishov et al. 2016). After extracting the analyte in a mini-column filled with glass wool covered by adsorbed water, the extract was mixed with a cation exchanger saturated with Cu(II) under fluidized bed conditions. The copper glycerate formed on the surface of the floating particles was spectrophotometrically monitored.

Fluidized beds were also useful in the extraction and spectrophotometric quantification of gossypol in cottonseed meal (Daminato et al. 2017). The fluidized-bed mini-column was coupled to a flow system for the direct analysis of the solid samples under constant stirring, which favored interaction between the extractant and sample (25 mg accommodated in an acrylic mini-column). The coefficient of variation and sampling rate were estimated at 1.9% and 30 h^{-1}, respectively.

OPTOSENSING

Optosensing is a kind of SPE, in which the adsorbed species are measured directly on a solid support, usually by spectrophotometry (either by transmission or reflection), by vibrational spectrometry (Raman or infrared) or by luminescence (fluorescence or chemiluminescence). When spectrophotometric detection is exploited, the process is often termed solid-phase spectrophotometry. Fundamentals, characteristics, and applications of optosensing were critically reviewed (Rocha et al. 2011, Llorent-Martínez et al. 2015).

The higher analytical sensitivity inherent to optosensing results from the analyte accumulation on the solid phase, which usually presents a volume significantly lower than the sample. Measurements are performed before elution, thus avoiding the inherent dilution observed in other approaches for in-line analyte concentration. Other advantages include reduced reagent consumption and waste generation, as well as improved selectivity. The former characteristic is noted especially when the reagents are immobilized on the support and reversible retention of the analyte is feasible – the reagent is then reused in several cycles of analyte retention. The latter is provided by both separation of the analyte from the sample matrix or exploitation of differences on the sorption rates of the species on the solid support (Rocha et al. 2011). Although the process can be carried out batchwise, coupling to flow analysis has been preferred due to the highly reproducible conditioning of the solid support, sample loading, and elution. Analytical precision is then significantly improved and partial (yet reproducible) analyte sorption as well as continuous monitoring of the adsorption process aiming at kinetic discrimination can be exploited. Selection of suitable carrier streams for selective analyte retention can also be exploited for simultaneous determinations (Medina et al. 2000). On the other hand, the increase in backpressure due to the presence of solid particles in the flow cell should be taken into account, as this aspect may limit the flow-rates or the adsorbent amounts to be used. This hindrance has been circumvented either by adaptation of commercially available cells (Yoshimura 1987) or by using specially designed ones (Reis et al. 2000). Selection of suitable adsorbent characteristics (*e.g.* particle size) may also contribute to minimize backpressure.

Recent applications of optosensing include (i) fluorimetric determination of thiamethoxam in vegetables, by measuring the product of the in-line photodegradation, whose reversible

accumulation into C18-bonded silica yielded a 10-fold improvement in sensitivity (Jiménez-López et al. 2016); (ii) direct fluorimetric analysis of urine exploiting molecularly imprinted xerogels as supports for accumulation of the cancer biomarker 5-hydroxyindole or the neurotransmitter serotonin aiming at improving the analytical selectivity and sensitivity (Dios et al. 2013); and (iii) determination of bromate in natural waters involving accumulation of the product of the reaction of the analyte with chlorpromazine on a cation exchange resin. In the latter application, in-line derivatization was carried out in a MSFIA system and, because of the reversible retention of the reaction product, up to 180 determinations were carried out with the same solid support (Oliveira et al. 2012). Other interesting innovation refers to combination of optosensing with bead injection, which permits the renewing of the solid support in every measurement cycle and expands significantly the application of the approach by encompassing irreversible systems. The feasibility of this proposal was demonstrated in the determination of proteins in wines carried out in a SIA-lab-on-valve system (Vidigal et al. 2012).

MONOLITHIC AND FUSED-CORE COLUMNS

SPE mini-columns can be used for low-pressure chromatographic separations for flow-based multicomponent determinations (Masini and Svec 2017). The strategy enhances the analytical potential by combining the versatility of flow techniques with the separation capacity of chromatography. This advance encompasses the use of monolithic and fused-core particles as illustrated in Fig. 2c.

Monoliths are constituted by a porous single piece of ultra-pure silica with macro and micro pores, providing high analyte separation efficiency with low backpressure, which enables their application in flow systems. Selectivity can be improved by bonding specific functional groups to the silica surface, such as octadecyl (C18) and cyano groups. From exploitation of monolithic columns in SIA the term sequential injection chromatography (SIC) was coined and the first application was focused on the determination of salicylic acid and methylsalicylate in pharmaceutical formulations (Huclová et al. 2003). Separation was carried out in a 50-mm long, 4.6 mm i.d. monolithic column with C18 bonded groups. The applications of SIC for analysis of pharmaceuticals and a comparison with HPLC were already reviewed (Chocholouš et al. 2007).

Monolithic phases have been also exploited in FIA systems with peristaltic pumps as fluid propulsion units. Because of the limited torque of these propelling devices in comparison to specially designed syringe pumps used in SIC, separations have been restricted to very short columns thus hindering the separation efficiency. More selective stationary phases are then needed. In the pioneer application, a 5-mm monolithic column was successfully exploited for separation of caffeine, theobromine, and theophylline in coffee (Santos and Rangel 2012).

Applicability of monoliths has been limited by the restricted number of commercially available stationary phases, but ingenious strategies have been proposed to circumvent this drawback. In this regard, stepwise elution allowed the complete separation of eighteen intracellular free amino acids from microalgae *Tetraselmis gracilis* using five different mobile phase compositions (Rigobello-Masini et al. 2008). Additionally, selectivity and detectability were improved by pre-column derivatization and fluorimetric detection. Strategies to modify stationary phase selectivity have also been presented, such as the use of micellar chromatography for in-line sample treatment and separation of melamine in milk (Batista et al. 2014). Chromatographic separation of melamine in C18 stationary phases is a difficult task due to its high polarity. Addition of an anionic surfactant to

the mobile phase modifies the stationary phase by the interaction of their non-polar groups and yields micelles in the mobile phase thus altering the analyte partition and increasing selectivity. An additional advantage is the possibility of direct injection of relatively complex samples, such as milk. In this application, sample treatment involved a simple in-line dilution with the surfactant solution.

Fused-core particles mini-columns also show high separation efficiency, low operational pressure, and are available in a variety of bonded phases. These particles are constituted by a solid core typically of fused silica impermeable to the analytes and to the mobile phase, covered by a thin external porous layer of stationary phase. The chromatographic efficiency is enhanced because of the faster analyte diffusion and the low variation in the particle size as observed with the small particles typically used in HPLC, but with a significant lower backpressure. The selectivity and separation capacity of fused-core columns in SIC were firstly evaluated in relation to seven phenolic acids (Chocholouš et al. 2013). Columns with different bonded phases (30 mm x 4.6 mm, particle size 2.7 μm) were evaluated, and efficient resolution was achieved with RP-amide phase, whereas phenyl-hexyl and C18 mini-columns did not provide enough selectivity, highlighting the importance of appropriate stationary phase to compensate the use of short columns. This aspect was also emphasized by the use of guard (5 mm) fused-core columns in FIA for separation of methyl-, ethyl- and propyl-parabens in daily care products (Batista and Rocha 2014). RP-amide led to the best separation efficiency compared to phenyl-hexyl and pentafluorophenylpropyl phases. Additionally to the low cost of these systems, the potentiality for sample treatment prior to chromatographic separation is a clear advantage.The feasibility of on-column concentration was demonstrated in a SIC procedure for separation of parabens (Batista and Rocha 2015). A high sample volume (up to 5.0 mL) was inserted into a RP-amide fused-core mini-column, followed by water. Because of the low eluent strength, analytes were retained in the top of the column. An acetonitrile plus phosphoric acid solution, pH 2.5 (25:75 v/v) was used for elution and chromatographic separation. Enrichment factors of 435, 405, and 420 were achieved for metyl-, ethyl-, and propyl-parabens, respectively, demonstrating the potentialities of the proposed approach.

Introduction of fused-core columns allowed applications of SIC to more complex analytical problems, such as the determination of antibiotics in freshwaters. In this sense, a procedure coupling in-line extraction and concentration of sulphonamides, followed by chromatographic separation in a fused-core mini-column was developed (Batista et al. 2015). An ion-exchange resin was used for SPE of eight antibiotics, with elution and chromatographic separation on a pentafluorophenylpropyl phase carried out by the mobile phase (acetonitrile plus acetate buffer, pH 5.0).

MOLECULARLY IMPRINTED SOLID PHASE EXTRACTION

Solid phases used in flow systems commonly present poor selectivity and tend to adsorb a group of analytes with similar properties. Selectivity of the related methods has been improved either by exploiting an analyte derivatization reaction or by coupling a selective detector. As the availability of selective derivatization reactions is limited, selectivity needs to be improved by taking advantage of novel solid materials for selective adsorption.

Molecularly imprinted solid phase extraction (MISPE) is based on the use of molecularly imprinted polymers (MIP), which are very selective solid phases with abilities of molecular recognition resulting from the molecular impression during their synthesis. A schematic representation of preparation and operation of a MIP for selective

SPE is shown in Fig. 2d. The use of MIPs solid phases in flow systems was emphasized in a critical review (Dias et al. 2008).

Bulk polymerization is the usual procedure for MIP production, in which functional monomers, template molecules, and a cross-linker reagent are added to form a polymer block. Thereafter, the template molecules are removed from the polymer to create a molecularly impressed site. Methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA) are often used as functional monomer and cross-linker, respectively. Most applications have been focused on the determinations of organic analytes in biological samples, which is a difficult task in flow analysis without a selective sorbent.

As a representative example, a MIP sorbent for epinephrine was developed using MAA and EGDMA (Du et al. 2003), aiming at its chemiluminometric determination. The sorbent was packed into a flow cell placed close to the detector. After selective sorption of the analyte, solutions of luminol and potassium hexacyanoferrate(III) were injected into the system and reacted with the epinephrine adsorbed on the MIP yielding the chemiluminescence. LOD was estimated at 3 nmol L^{-1}, which is suitable for the direct analysis of serum samples. This application illustrates the use of MISPE to improve performance when poorly selective detection is involved or when matrix effects are relevant, such as in the chemiluminometric analysis of biological and environmental samples.

An imprinted polymer for terbutaline extraction prepared with MAA and EGDMA was used in a micro-flow system (He et al. 2006). The chip was built up with two poly(methylmethacrylate) parts with 200 µm wide and 150 µm deep microchannels. The sorbent (2.0 mg) was placed into a 100-mm long chamber. The determination relied on the chemiluminescence produced by the reaction of terbutaline with luminol and potassium hexacyanoferrate(III). With 720 µL of sample, the procedure presented a LOD of 4.0 ng mL^{-1}; the high sensitivity and low sample amount required make the procedure attractive for biological analysis. However, the low flow rate and the need for a cleaning step reduced sampling rate (7 h^{-1}). Additionally, the chip should be replaced after *ca.* 100 determinations due to the lessening of the MIP efficiency.

Because of the improved selectivity, simpler flow manifolds can be achieved by exploiting MISPE. For example, a single-channel manifold was proposed for the fluorimetric determination of 1-hydroxypyrene in urine involving in-line extraction and concentration in a MIP sorbent (Serrano et al. 2017). Because of the complexity of the matrix and the low levels of the analyte in the samples, effective sample clean-up and analyte concentration were needed. The sorbent was prepared with MAA and EGDMA and packed into a 1.8-cm long, 0.8-mm i.d. mini-column. For 250 µL of sample, LOD was estimated at 3.1 µg L^{-1}. Enhancement of selectivity and detectability provided by the selective SPE, the high sensitivity of fluorimetric detection, as well as the versatility and high sampling rate provided by flow analysis make the proposal an outstanding approach.

The advantages of coupling MISPE to flow systems were also highlighted in the determination of florfenicol in liver, pork, chicken, and fish tissues (Ge et al. 2010). The MIP was prepared with acrylamide and EGDMA. After extraction and concentration, the analyte was eluted from the sorbent and quantified by the inhibition of the chemiluminescence from the reaction of 3-p-nitrylphenyl-5-(2'-sulfonophenylazo) rhodamine and bovine serum albumin. Sample treatment included extraction with water and acetone and injection of 1.5 mL of the extract into the flow system. Elution from the MIP mini-column was accomplished with a methanol/acetic acid/sodium dodecyl sulfate (SDS) solution. A LOD of 34 ng mL^{-1} was achieved with a relative standard

deviation of 3.5%. The results agreed with those obtained by HPLC.

MISPE was also exploited in a flow system for in-line concentration of Hg(II) in water and human hair followed by derivatization with dithizone and spectrophotometric detection (Rajabi et al. 2015). The procedure provided an EF of 160 and a LOD of 0.036 ng mL^{-1}. MISPE was also performed with nanoparticles for extraction and concentration of Zn^{2+} (Fereidoonipour and Rajabi 2017). The nanoparticles were synthetized from a stable Zn^{2+} chelate with 3,5,7,2′,4′-pentahydroxyflavone copolymerized with MAA, in the presence of EGDMA. Spectrophotometric detection was carried out after formation of the colored Zn(II) dithizonate complex, with LOD of 400 nmol L^{-1} and EF of 117. Other relevant applications refer to the chemiluminometric determination of isoniazid in urine (Xiong et al. 2007) as well as amperometric determination of 4-nitrophenol in water (Gholivand et al. 2015) and traces of cadmium in jewelry, black and green tea, tobacco and hair (Lago et al. 2016). Additionally to advantages provided by the use of MIP, the performance of these procedures was improved by using MCFA, because of the independent implementation of the steps involved in sample processing.

BIOSORBENTS

Effective analyte separation/concentration and sample clean-up in SPE relies on the suitable choice of the adsorbent material. Usually, solid phases are based on silica or organic polymers functionalized with different ligands, selected in accordance to the target analytes. In general, these materials are relatively expensive and discarded after batchwise procedures. Flow-based techniques usually allow the reuse of the adsorbent material, besides using amounts significantly lower than batchwise. Biosorbents, a suitable alternative to synthetic materials, are usually obtained from plants or microorganisms (*e.g.* seeds and fungi) and some materials are widely available as industrial wastes. Advantages of these materials include low cost, extensive availability, and improved selectivity in comparison to synthetic sorbents. Additionally, consumption of reagents in their synthesis is avoided, although chemical modification is sometimes required to improve selectivity or sorption efficiency.

Biosorbents in flow systems may lead to improved sample throughput. The rigorous time control on the sample processing makes feasible the exploitation of non-exhaustive extractions and kinetic discrimination. Applications have been mainly focused on metal determinations by atomic spectrometry, as recently reviewed (Teixeira et al. 2016). The determination of Cr(III) and Cr(VI) in water involving *Saccharomyces cerevisiae* as sorbent is an illustrative example (Menegário et al. 2005). The fungi cells were immobilized on controlled pore glass and packed into a 2.3-mm long mini-column (4 mm i.d.). Chromium speciation was based on the biosorption of Cr(III) and Cr(VI) retention on pore glass. Selective Cr(III) and Cr(VI) elutions were achieved with 0.05 mol L^{-1} HCl and 2.0 mol L^{-1} HNO_3, respectively. Analyte accumulation provided by biosorption lead to LODs of 0.45 and 1.5 μg L^{-1} for Cr(III) and Cr(VI), with preconcentration factors of 12 and 5, respectively. Biosorbents based on *Saccharomyces cerevisiae* are cheap, easily obtained, and able to be reused for up to 120 analyses without efficiency loss. Other applications of microorganisms as biosorbents in flow systems include the separation/concentration of Pb(II) from tap and seawater by filamentous fungi supported on TiO_2 nanoparticles (Bakircioglu et al. 2010) and use of *Saccharomyces cerevisiae* immobilized on calcium alginate beads for determining Pt(IV) in spiked grass, road dust or water samples in a FIA system with FAAS or chemiluminescence detection (Godlewska-Żyłkiewicz et al. 2008).

Vermicompost is a product of organic matter degradation by earthworms commonly used as a fertilizer. The high content of humic substances provides high cation exchange and sorption capacities. The vermicompost presents a longer lifetime in comparison to other sorbents based on microorganisms. This material is then a suitable option for separation/concentration of metals in flow systems, as demonstrated in the determination of Cd(II) in ethanol fuel by FAAS (Bianchin et al. 2009). With 160 mg of biosorbent, a preconcentration factor of 32, a sample consumption of 10 mL per determination, and a sampling rate of 20 h^{-1} were attained. Additionally, the biosorbent could be reused for more than 150 times without loss of efficiency. Vermicompost was also used for the extraction and concentration of Cd(II) and Pb(II) from mineral waters, pharmaceutical preparations, fruit juices, pig kidney, and beech leaves (Pereira and Arruda 2004). The sorption efficiency was affected by Ca^{2+}, Mg^{2+}, Na^{+}, and K^{+} due to the high cationic exchange capacity of the biosorbent.

Biosorbents based on plant tissues have also been exploited for SPE of metals in flow analysis. In this context, *Moringa oleifera* seeds have been used as an ion-exchanger in the determinations of several metal ions, such as *e.g.* Ag(I) in water in a flow system with FAAS detection (Araújo et al. 2010). Preparation of the biosorbent involved only drying, blending, and sieving of the seeds. An EF of 35 was achieved with 35 mg of biosorbent with a sampling rate of 12 h^{-1} and a sample consumption of 14 mL per determination.

MAGNETIC MATERIALS

Magnetic particles have been efficiently exploited for SPE in flow analysis, as their movement can be efficiently controlled by means of external magnetic fields (*e.g.* dispersion of the sorbent into the sample and removal from the liquid medium). These materials can be dispersed in a large volume of sample, thus increasing the surface area and the number of available adsorption sites (Maya et al. 2017). Magnetic materials have been used with 1-100 nm nanoparticles, particularly of Fe_3O_4, $MnFe_2O_4$, and $CoFe_2O_4$ (Beveridge et al. 2011). Applications involve different analytes (*e.g.* metal ions, estrogens, and surfactants) in a diversity of samples (*e.g.* water, urine, and human hair) with different analytical techniques (*e.g.* UV-Vis, ETAAS, and GC-MS), including *in situ* analysis (Passos et al. 2015). The main characteristics of this approach are illustrated by selected applications.

Magnetic nanoparticles functionalized with 1,5-bis(di-2-pyridil)methylene thiocarbohydrazide were used for in-line separation and concentration of Hg aiming at its determination in biological materials and sea water by ETAAS with a cold vapour generation system (Alonso et al. 2016). Drawbacks such as increased backpressure and manifold clogging were circumvented by the proposed approach. The sorbent lifetime and sampling rate were estimated as 550 cycles and 16 h^{-1}, respectively, demonstrating the potential of magnetic beads exploitation for large-scale determinations.

Flow-injection chemiluminometric determination of chrysoidine in food samples exploited Fe_3O_4@SiO_2 magnetic nanoparticles with MIPs at the particle surface (Lu et al. 2012). The selectivity was up to 100-fold better in relation to the analogous procedure without SPE. Furthermore, the washing step was in-line accomplished, allowing the sensor reuse.

The advantageous reuse of a mini-column was also evident in an automated SIA system with magnetic sorbent extraction coupled to ETAAS for Cd determination in natural waters (Giakisikli and Anthemidis 2013). The mini-column with octadecylsilane functionalized maghemite magnetic particles remained stable during more than 600 cycles, thus reducing the analytical cost and facilitating the use in routine analyses.

A SIA system coupled to GFAAS was proposed for Cd determination by exploiting a modified sorbent based on magnetic multiwalled carbon nanotubes with iron oxide on the surface (Wang et al. 2016). The improvement in sensitivity was noteworthy, with LOD and EF estimated at 1.2 ng L^{-1} and 160, respectively. The sorbent could be reused up to 100 times without degradation.

Magnetic multiwalled carbon nanotubes were used for in-line Cr(III) separation/concentration. A syringe pump was used for insertion of the treated sample solution into a microfluidic chip for in-line derivatization and monitoring of the laser-induced fluorescence (Peng et al. 2017). High selectivity was achieved, EF was estimated at 38, and drastic reduction of the amount of chemical reagent was noted.

Submicrometric magnetic nanoporous carbons derived from metal-organic frameworks were recently proposed as sorbent in SIA (Frizzarin et al. 2016). The set-up included a three-dimensional printed holder with an automatically actuated electromagnet. Extraction of SDS after ion pair formation with methylene blue was selected as a model. The material showed advantages as high contact area and stability; moreover, use of the electromagnet improved the repeatability and the extraction efficiency.

The magnetic porous carbon derived from zeolitic imidazolate frameworks was used in syringe magnetic dispersive micro-solid phase extraction (González et al. 2017). The particles were dispersed in the sample by agitation and further attracted towards a magnetic bar. Sample clean-up and estrogen accumulations required less than 20 min and a low amount (300 µL) of organic solvent.

CONCLUSIONS AND TRENDS

Amazing conceptual, methodological, and applicative advances in flow-based analytical approaches involving in-line SPE were emphasized in this review. These involve the development of novel materials, exploitation of different flow modalities, and applications to solve a diversity of analytical problems, either by analyte separation/concentration or sample clean-up. Some applications have been focused on analyte fractionation or chemical speciation, but studies on this issue are still needed.

In recent years, the number of applications relying on direct measurements on solid supports has been increasing as a consequence of the absence of sample dilution inherent to the elution step, the feasibility of exploiting kinetic aspects related to the sorption processes, as well as the reversible analyte sorption. Novel approaches have been proposed to circumvent drawbacks such as swelling, preferential pathways, and increased backpressure (e.g. by exploiting moving beads or fluidized beds) and to improve sample throughput (e.g. by simultaneously carrying out several processes). Coupling chromatographic solid phases to flow techniques has expanded the applicability range and the analytical selectivity.

Some foreseen trends are: (i) improvement of the sorption efficiency by exploiting nanomaterials or sorbent dispersion by fluidized beds, including use of magnetic sorbents; (ii) development of selective sorbents and/or materials for low pressure chromatographic separations; (iii) exploitation of flow-based SPE for sample treatment before chromatographic separations; (iv) miniaturization aiming at portable devices requiring minute amounts of reagents and eluents, thus despicable waste volumes; and (v) applications involving bioanalysis. In view of this scenario, exploitation of SPE stands out by one of the most fertile field in the future research in analysis.

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