

Extraction and stirring integrated techniques: examples and recent advances

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Abstract Extraction techniques, which focus on selectivity and sensitivity enhancement by isolation and preconcentration of target analytes, are essential in many analytical methods. Because many extraction techniques occur under diffusion-controlled conditions, stirring of the sample solution is required to accelerate the extraction by favoring diffusion of the analytes from the bulk solution to the extractant phase. This stirring may be performed by use of an external device or by integrating extraction and stirring in the same device. This review focuses on the latter techniques, which are promising methods for sample treatment. First, stir-bar-sorptive extraction, the most widely used method, is considered, paying special attention to the development of new coatings. Finally, a general overview of novel integrated techniques in both solid-phase and liquid-phase microextraction is presented; their main characteristics and marked trends are reported.

Keywords Stir-bar-sorptive extraction · New coatings · Rotating disk-sorptive extraction · Stir-rod-sorptive extraction · Stir-membrane extraction · Liquid-phase microextraction

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Rafael Lucena has been Associate Professor (“Contratado doctor”) in the Analytical Chemistry department of the University of Cordoba (Spain) since 2010. His main research interests are the development of new microextraction techniques and the evaluation of ionic liquids and carbon nanostructures in this context. Apart from this main topic, he also works on the development of mid-IR sensors and their applications in industrial process control. He has co-authored approximately 40 scientific articles and three book chapters on these topics.

Introduction

Despite advances in instrumental analysis, isolation and preconcentration of target analytes from a sample matrix are still important aspects of many analytical methods to improve selectivity and sensitivity, respectively. Extraction techniques have been the focus of intensive research in the last 15 years, with automation, miniaturization, and simplification being the forces driving this evolution [1]. Microextraction techniques, in both the solid- and liquid-phase formats, have become a reality in analytical laboratories and their transfer to routine laboratories will depend on their efficient integration in commercial instruments.

Thermodynamic and kinetic aspects are crucial aspects of the efficiency of a given microextraction technique. Both must be considered, because the main objective of these techniques is to achieve efficient analyte extraction in a reasonable time. On the one hand, the distribution constant for a given analyte determines the maximum amount that

can be transferred to the extracting phase in accordance with thermodynamics. Different variables, for example extraction temperature, use of secondary reactions, selection of the appropriate pH, among others, may be varied to increase this potential transfer. Kinetic properties, on the other hand, determine the rate at which equilibrium is reached [2]. With regard to the kinetics, the contact surface between the sample and the extracting phase, and stirring of the solution may be emphasized.

Extraction techniques occur under diffusion-controlled conditions. According to the Nernst law, diffusion through the boundary layer between the bulk solution and the extractant phase is rate controlling, and this can be enhanced by efficient stirring of the solution. In practice, this stirring may be performed with an external device, assisted by an external energy source or by integrating the extraction and stirring elements in the same device. The latter techniques will be considered in depth in this article.

Stir-bar-sorptive extraction

Stir-bar-sorptive extraction (SBSE), first proposed by the Sandra's research group in 1999 [3, 4], is based on the same general principles as solid-phase microextraction (SPME) [5, 6], because extraction occurs as a consequence of distribution of the analytes between the sample and a small amount of sorptive material immobilized on an inert

support. In this case, the inert support also enables stirring of the sample by the extracting phase; SBSE can therefore be regarded as an example of those extraction techniques which integrates the extraction phase and the stirring element in the same device.

Although SBSE does not usually operate as an exhaustive extraction technique, extraction recovery is higher than that of conventional SPME because the volume of sorptive phase is 50–250 times higher [7]. Moreover, integration of extraction and stirring in the same device avoids potential analytes losses because of introduction of an external stirring device. The latter effect usually occurs when polymeric stir-bars are used in SPME.

Classic SBSE is mainly focused on extraction of non-polar or moderately polar analytes from samples of different nature, although moderately polar compounds usually require prior derivatization to promote their transfer to the extracting phase [8, 9]. This aspect is a direct consequence of the non-polarity of polydimethylsiloxane (PDMS), the classic SBSE coating, commercialized under the name Twister. Intensive research has been conducted in recent years to overcome this potential limitation by modification of PDMS coatings or the development of special and new ones. In this context, use of molecularly imprinted polymers (MIPs), monolithic materials, and polyurethane foams should be emphasized. These novel coatings, which will later be described in depth, are depicted in Fig. 1. The general advantages and disadvantages of each coating are critically

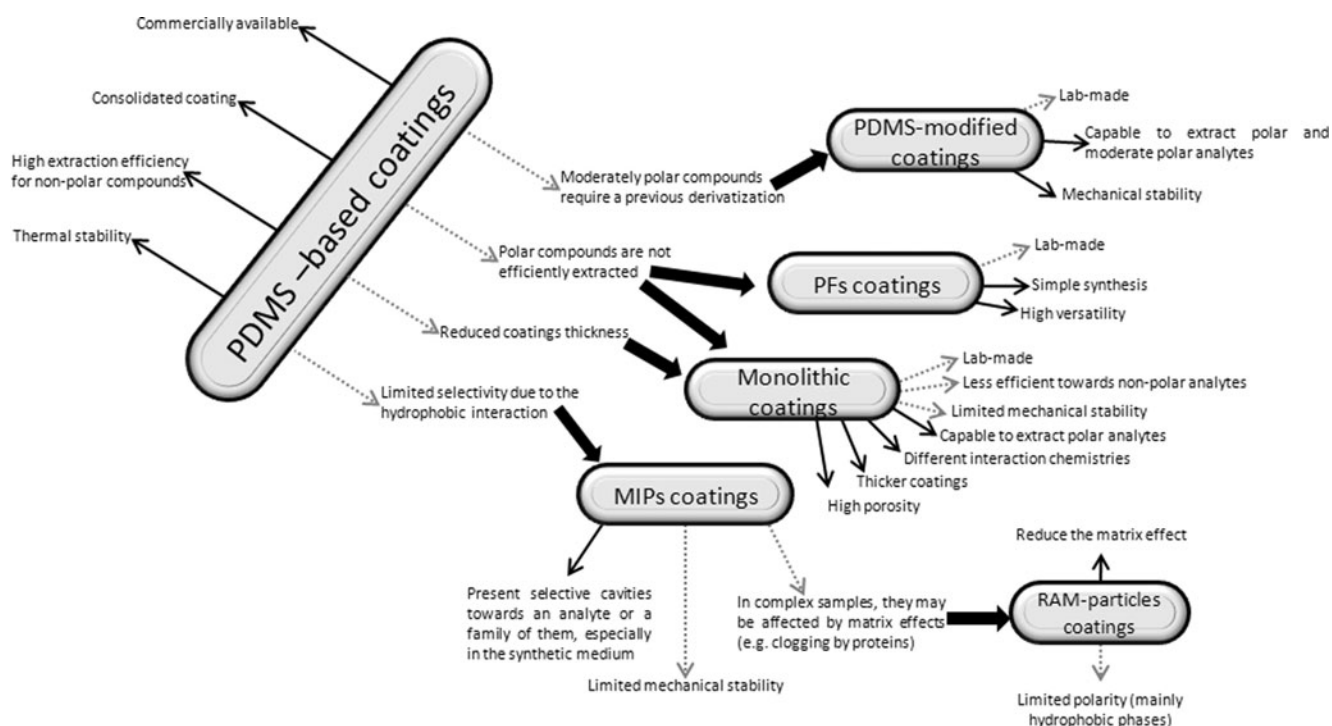


Fig. 1 Schematic and critical diagram summarizing the advantages (solid black lines) and disadvantages (dotted grey lines) of the main coatings used in SBSE. *PDMS*, polydimethylsiloxane; *PFs*, polyurethane foams; *MIPs*, molecularly imprinted polymers

presented in the figure, which also shows the evolution of the research on this topic.

Trends in SBSE coatings

PDMS-modified coatings

The fabrication of PDMS coatings modified with different additives has been proposed to extend the applicability of SBSE to more polar compounds. The main applications developed in this context are summarized in Table 1.

The synthetic process, usually based on a sol–gel reaction, enables the efficient chemical immobilization of the coating into the surface of a glass stir-bar. This chemical binding results in coatings of high mechanical, thermal, and chemical stability, which are important in the extraction and elution steps. The sol–gel reaction is based on different, well defined reactions. In the first step the coating precursors are hydrolyzed and the hydroxylated compounds generated then participate in a polycondensation process which produces a three-dimensional network [10]. The mechanical and thermal stability of the final coating is controlled in two different steps. On the one hand, the glass bar is chemically treated to promote the generation of superficial silanol groups that will participate in the polycondensation reaction, enabling chemical attachment of the final coating. On the other hand, the final gel is submitted to thermal treatment, consisting of a slight temperature gradient under an inert atmosphere, which provides mechanical strength to the coating. The chemical properties of the final coating can be adjusted by selecting the precursors in the sol–gel reaction, as summarized in Table 1. In this context, Hu et al. proposed an SBSE coating

consisting of PDMS and β -cyclodextrin (β -CD) for extraction of estrogens and bisphenol A [11], taking advantage of the well known affinity of PDMS– β -CD for the target analytes [12]. The coating has a homogeneous and rough surface with a thickness in the range 30–150 μm depending on the synthetic conditions. According to the results, PDMS– β -CD results in better extraction recovery than PDMS for those analytes with $K_{o/w}$ (octanol–water partition coefficient) lower than 3.5 and gives comparable results for the non-polar analytes. This general approach, based on two active components, has been exploited in other applications, with good results. Yu and Hu proposed the combination of PDMS and poly(vinyl alcohol) (PVA) for successful extraction of organophosphorus pesticides (OPPs) from honey [13]. In this case, the coating has a BET surface area of 21.248 $\text{m}^2 \text{g}^{-1}$, which is 500 times higher than that of commercial PDMS. Moreover, analysis of this complex matrix requires only previous dilution of the sample with water.

Yu et al. have developed a sol–gel coating consisting of three different compounds, PDMS, β -CD, and divinylbenzene (DVB), for extraction of polycyclic aromatic hydrocarbons (PAHs) and polycyclic aromatic sulfur heterocycles from water and soil samples [14]. The new coating provides better results than those obtained with PDMS, PDMS– β -CD, and PDMS–DVB coatings.

Besides these coatings, Ibrahim et al. have synthesized inorganic–organic hybrid coatings for SBSE by using tetraethoxysilane (TEOS) [15] and cyanopropylethoxysilane (CNPrTEOS) [16] as inorganic modifiers. With both approaches, extraction of polar OPPs and non-steroidal anti-inflammatory drugs (NSAIDs) were successfully accomplished.

Polymeric coatings based on PDMS and an appropriate modifier can also be prepared by following a special synthetic process different from the sol–gel procedure. In

Table 1 Application of PDMS-modified coatings in stir-bar-sorptive extraction

Analytes	Sample	Modifiers	Reaction	RSD (%)	Thickness	Reuses	Comments	Ref.
Estrogens and bisphenol A	Drinking water and leachates	β -CD	Sol–gel	3.6–8.6	30 μm	—	·Homogeneous and rough surface ·Thermal stability up to 315 $^{\circ}\text{C}$ ·Improved extraction of polar compounds	[11]
Organophosphorus pesticides	Honey	PVA	Sol–gel	4.3–13.4	30 μm	50	BET surface of 21.248 $\text{m}^2 \text{g}^{-1}$	[13]
Polycyclic aromatic compounds	Water and soil	β -CD–DVB	Sol–gel	3.2–15.2	100 μm	40	Unsmoothed and porous surface Better results than PDMS, PDMS/ β -CD, and PDMS/DVB.	[14]
Organophosphorus pesticides	—	TEOS	Sol–gel	—	2.8 μm	—	Homogeneous and rough surface BET surface of 3 $\text{m}^2 \text{g}^{-1}$	[15]
Non-steroidal anti-inflammatory drugs	—	CNPrTEOS	Sol–gel	—	Variable	—	Thermal stability above 230 $^{\circ}\text{C}$	[16]
Antidepressants	Plasma	PPY	Polymerization	—	22 μL	40	Porous surface	[17]
Pesticides	Sugarcane juice	ACB	Polymerization	—	90 μL	150	Homogeneous surface	[18]

this case, the PDMS is mixed with the modifier and an elastomer curing agent, avoiding bubble formation. The resulting mixture is introduced into a polytetrafluoroethylene (PTFE) mold in which a magnetic rod has previously been located, and submitted to controlled thermal treatment to form the desired coating. By use of this procedure, stir-bars based on PDMS and polypyrrole (PPY) [17] or activated carbon (ACB) [18] have been prepared. The PDMS–PPY coating has high porosity and efficiency compared with PDMS, enabling efficient extraction of anti-depressants from plasma, with excellent extraction recovery despite the complexity of the matrix. PDMS–ACB coating enables extraction of pesticides from sugarcane juice.

Molecularly imprinted polymers coatings

Selectivity, a crucial issue in any extraction procedure, becomes critical when complex samples are analyzed. Despite their usefulness, hydrophobic coatings do not interact selectively with analytes and, therefore, new approaches have been developed to overcome this limitation. In this context, molecularly imprinted polymers (MIPs), which are polymeric materials with selective cavities for an analyte or a family of chemically related compounds, have attracted much attention as sorptive materials. Zhu et al. proposed the use of MIPs as coatings in SBSE for selective extraction of monocrotophos, an OPP, from soil [19]. The proposed MIP consists of a 6-Nylon polymer network with selective extraction cavities for the analyte. The MIP is synthesized by a phase immersion method taking advantage of the inherent ability of Nylon chains to form intra and inter-molecular hydrogen bonds through the amide group. Briefly, synthesis of this MIP is performed by dissolving Nylon pellets and an appropriate amount of the template in formic acid. A PDMS stir-bar is subsequently immersed in the mixture and later the wet bar is placed in pure water. The solvent change causes the Nylon to come out of solution, leaving a polymeric network around the template, which is finally removed. The phase-inversion synthesis gives the final MIP very attractive properties, for example high porosity (pores in the range of 1 to 2 μm) and faster extraction and elution. With regard to selectivity, the MIP enables discriminated extraction of monocrotophos and structurally related analytes. The selective interaction of 6-Nylon-based MIPs has also been proved in the enantioselective extraction of L-glutamine in the presence of D-glutamine [20].

MIP stir-bars can be also fabricated by a process of wrapping a pretreated silica cylinder of minimal dimensions (1 cm in length) [21]. In this case, the MIP coating is synthesized by polymerization of the monomer, using as starting material an active compound that has been covalently bonded to the silica surface. Once synthesized, the

MIP–silica cylinder is coupled to a hex screw by means of a nut to enable magnetic stirring. These MIP-based stir-bars have been proposed for extraction of cyanide exposure markers from urine samples. They have high extraction and elution efficiency with moderate selectivity compared with the non-imprinted material.

However, in the classic approach MIPs are synthesized by co-polymerization of an appropriate monomer and a cross-linker in a bulk organic solution in the presence of the target analyte (template) or a mimic. A silica capillary with a metallic core is used as inert support for construction of the bar. The capillary should be previously treated, by successive silanization and silylation reactions, to achieve strong immobilization of the coating. In a parallel step, the template and the monomer are incubated, inducing their self-assembly by hydrogen-bonding, which is fundamental for creation of the final selective cavities. Finally, the capillary is immersed in this mixture, the cross-linker and the initiator being added subsequently. Polymerization occurs at a fixed temperature leaving an MIP coating on the silica bar surface. The resulting bar is eluted to remove the template and aged at a high temperature to enhance its mechanical stability, which is the main shortcoming of these coatings. Xu et al. used this strategy to fabricate MIP-based bars for selective extraction of ractopamine from complex samples such as pork, liver, and feed [22]. In this case, a coating thickness of 20 μm was obtained, resulting in high extraction recovery with a negligible effect on extraction rates. The synthesized bars can be fabricated reproducibly, with bar-to-bar relative standard deviation below 17.1%, and they can be reused 40 times. As was previously mentioned, the mechanical stability of the MIP coating is limited, which may be problematic in SBSE because the coating is in close contact with the bottom of the extraction vessel. To minimize loss of coating during extraction, Hu et al. proposed a dumbbell stir-bar format for MIP-based extraction of terbutylazine from rice, apple, lettuce, and soils [23].

The classic synthetic approach has been extensively used for construction of MIP-based stir-bars for selective extraction of sulfa drugs [24] and bensulfuron-methyl [25] from complex samples. However, a novel alternative has recently been proposed for selection of more appropriate reagents for MIP synthesis. In this sense, Gomez-Caballero et al. used molecular modeling for monomer selection to achieve enantiospecific extraction of (*S*)-ciropralam in the presence of the *R* isomer [26]. The synthetic material has excellent selectivity for separation of the enantiomers. Despite interest in enantioselective extraction, a few examples using SBSE have been described to date [20, 26]. However, SBSE in combination with special instrumental techniques, for example enantioselective multidimensional gas chromatography–mass spectrometry, has been proposed for this purpose [27, 28].

Although MIP coatings can be used to improve extraction selectivity, in most cases this enhancement is less than the theoretical value. On the one hand, maximum selectivity of the MIPs is achieved in the solvent (usually organic) used for their synthesis. This selectivity and efficacy is reduced in an aqueous medium which is, in fact, the usual matrix medium. On the other hand, some matrix components may reduce the extraction efficiency. In this sense, proteins in biological samples usually clog the sorbent, hindering its interaction with the analytes. In these cases, previous sample treatment, including a sample dilution or even its deproteinization, is required before use of an MIP.

The selectivity of extraction from a complex environment can be also enhanced by limiting interaction of the matrix components with the active sites of the sorbent. Restricted access materials (RAMs) can be used to overcome this shortcoming by using a size-exclusion mechanism. RAMs have a controlled pore size which acts as physical barrier to large biomolecules, protecting the extraction cavities. The extraction cavities consist of non-polar groups (C_4 , C_8 , or C_{18}) different from the selective cavities present in MIPs. RAM have been also used in SBSE for extraction of caffeine and related metabolites from biological fluids [29]. In this case, a hollow glass tube with a magnetic core is covered by an epoxy binder and subsequently coated with commercial RAM particles. The RAM-based stir-bars can be re-used up to 50 times because interaction with the sample matrix is avoided. Excellent sensitivity and selectivity are achieved by this approach, especially compared with the classical deproteinization process.

Monolithic based coatings

In classic SBSE, based on use of PDMS as coating material, the theoretical recovery can be calculated by use of the equation [30]:

$$TR = \left(\frac{\left(\frac{K_{o/w}}{V_s/V_{PDMS}} \right)}{1 + \left(\frac{K_{o/w}}{V_s/V_{PDMS}} \right)} \right)$$

where TR is the theoretical recovery, V_s the volume of the sample, V_{PDMS} the volume of the PDMS coating, and $K_{o/w}$ the octanol–water partition coefficient. This equation, which assumes that the $K_{o/w}$ defines the partition of a given analyte between a water solution and a PDMS coating ($K_{o/w} \approx K_{PDMS/w}$), shows the importance of the volume of the extractant phase in any extraction. As calculated theoretically, the greater the amount of extractant the greater the recovery obtained. However, because this equation is based on distribution constants, it only considers the thermodynamic aspects of the extraction. In fact, when thick coatings are used, higher recovery is obtained at the expense of extraction and elution kinetics, because diffusion of the analytes through the coating

is limited. Monolithic materials, which consist of a rigid macroporous structure, are very attractive in this context, because they enable the amount of the extractant to be increased with a minimum effect on extraction rates. In addition, the monolith can be prepared easily from relatively inexpensive materials and adjusted by combination with different monomers for task-specific extraction of analytes. The usual synthetic procedure is based on in-situ polymerization using, most often, azobisisobutyronitrile as initiator. In this procedure, the monomers and the porogen solvents should be selected in accordance with the final application, because they affect the physical and chemical properties of the monolith. On the other hand, the monomers define the chemistry (polar, non-polar, ion exchange, or mixed modes) of the extraction and the porogen solvent determines the mechanical stability and porosity of the coating.

Huang and Yuan were the first to propose the use of monolithic materials in SBSE [31]. Table 2 summarizes the main contributions in this context, showing the synthetic variables (monomers and porogen solvents) and analytical aspects (preconcentration factors) for each material. In the first approach, a monolithic material based on octyl methacrylate and ethylene dimethacrylate was synthesized to extract PAHs from water and anabolic steroids from urine, covering therefore a wide range of polarities and sample complexity. The monolithic coating has better chemical stability toward acid reagents and can be fabricated with bar-to-bar reproducibility better than 5.2%. By following a similar approach, a monolithic stir-bar was fabricated for extraction of steroidal hormones from urine samples [32]. In this case, dilution of the sample is required to avoid matrix effects. The monolith was physically characterized; it had a surface area of $4.25 \text{ m}^2 \text{ g}^{-1}$ and pores of different sizes (one of 1100 nm which results in the high porosity to the material and another at 73.4 nm which results in a high surface area).

Classic SBSE is mainly focused on the extraction of non-polar compounds, because of the hydrophobic nature of PDMS coating. Polar analytes should be derivatized to increase their hydrophobicity prior to their extraction. However, derivatization is an extra step which can be tedious or may involve the use of expensive or harmful reagents. Moreover, derivatization is not always possible. The task-specific character of monolithic materials can be exploited in this sense, by selecting the most appropriate monomers for a given analyte. In this context, Huang et al. proposed a new monolithic stir-bar for extraction of phenols, avoiding the previous derivatization step [33], simplifying the extraction procedure, and protecting the stir-bar from the negative effects of derivatizing reagents. In a similar way, different monolithic stir-bars have been proposed for extraction of analytes covering a wide range of polarity [34–37]. Moreover, use of a monolithic stir-bar can simplify the overall extraction procedure, as is reported for extraction of

Table 2 Application of monolithic materials as coatings in stir-bar-sorptive extraction

Analytes	Sample	Monolithic material synthesis		Analytical feature	Ref.
		Monomers	Porogen solvents		
PAHs, anabolic steroids	Water, urine	Octyl methacrylate and ethylene dimethacrylate	1-Propanol, 1,4-butanediol, and water	134–189, PAHs; 40–51, anabolic steroids	[31]
Steroid sex hormones	Urine	Methacrylic acid stearyl ester and ethylene dimethacrylate	1-Propanol and 1,4-butanediol	21–81 ^a	[32]
Phenols	Lake and sea waters	4-Vinylpyridine and ethylene dimethacrylate	1-Propanol and 1,4-butanediol	4.1–15 ^b	[33]
PAHs, hormones, aromatic amines, and phenols	Water samples	Vinylpyrrolidone and divinylbenzene	Cyclohexanol and 1-dodecanol	80–98, PAHs; 38–55, hormones; 9–73, aromatic amines; 23–50, phenols	[34]
Aromatic amines	Water samples	Vinylimidazole and divinylbenzene	Cyclohexanol and 1-dodecanol	9.4–19 ^b	[35]
Phenols	Wastewater	Vinylpyrrolidone and divinylbenzene	Cyclohexanol and 1-dodecanol	9.1–16 ^b	[36]
Emerging pollutants	Water samples	Vinylpyrrolidone and divinylbenzene	Cyclohexanol and 1-dodecanol	4.5–50 ^b	[37]
Sulfonamides	Milk	Vinylimidazole and divinylbenzene	Cyclohexanol and 1-dodecanol	–	[38]
Anions	Water	2-(Methacryloyloxy)ethyltrimethylammonium and divinylbenzene	Cyclohexanol and 1-dodecanol	–	[39]
Quinolones	Wastewater	Methacrylic acid-3-sulfopropyl ester and divinylbenzene	Cyclohexanol and 1-dodecanol	10.7–12.1 ^b	[40]
Nitroimidazole	Honey	Methacrylic acid-3-sulfopropyl ester and divinylbenzene	Cyclohexanol and 1-dodecanol	9.6–18.9	[41]
Pharmaceuticals	Complex water samples	Methacrylic acid and divinylbenzene	Cyclohexanol and 1-dodecanol	6.5–50 ^b	[42]

^a Data expressed as sensitivity enhancement factor

^b Data calculated from the reference taking into account the absolute extraction recovery and the volumes of the sample and the final extract

sulfonamides from milk [38]. In this case, prior removal of fats and proteins, as required for classical SBSE, is avoided; only 1:10 dilution with water was necessary.

The extreme versatility of monolithic materials also enables ion-exchange and mixed mode mechanisms of interaction with the analytes. Use of 2-(methacryloyloxy)ethyltrimethylammonium and divinylbenzene as monomers enables the final polymer to extract anions from waters [39], whereas use of methacrylic acid-3-sulfopropyl ester and divinylbenzene as monomers enables mixed (cation exchange and hydrophobic) interaction, enabling extraction of quinolones from water [40] and nitroimidazole residues from honey [41]. Recently, combination of methacrylic acid with divinylbenzene has been proposed for extraction of polar pharmaceuticals from complex water samples [42].

According to the literature, monolithic materials are highly versatile compared with the classic PDMS coating, because different “interaction chemistry” (including polar, ionic, or mixed modes) can be developed by selecting the appropriate monomers. Moreover, the porosity of these materials enables the thickness of the coating to be increased with negligible effect on extraction rates. The main disadvantage of the materials is their “laboratory-made” nature, although their synthesis reproducibility is acceptable.

Monolithic materials are mainly based on acrylates and these materials are commercially available as SBSE coatings (e.g. PA-Twister). Use of polyacrylates in SBSE, originally proposed by Rodil et al. [43], has recently been applied to the determination of benzothiazole in untreated wastewater samples [44].

Polyurethane foams

Polyurethane foams (PFs) are plastic materials, synthesized by reaction of polyisocyanates and polyols in the presence of other additives (chain extenders, cross-linkers) and catalysts, in which a proportion of the solid phase has been replaced by gas in the form of bubbles [45, 46]. Because of their exceptional properties, PFs have been used as packaging material and in thermal and acoustic insulating systems. In analytical chemistry, PFs have been proved to be promising materials for metal extraction. Taking into account the great variety of available monomers (including aliphatic and aromatic structures) and the importance of these compounds to the final chemical and physical properties of the synthesized polymer, PFs can be regarded as very versatile extraction materials. In fact, PFs can be modified to furnish task-specific sorbents. Moreover, their good mechanical

properties, and thermal and chemical stability makes them attractive materials in SBSE.

The use of PFs in SBSE was proposed for the first time by Neng et al. in 2007 [47], who used a very simple synthetic procedure. Appropriate amounts of polyol, water, modifiers, and catalyst were vigorously mixed for 1 min in a polyethylene flask then the isocyanate was added. After vigorous stirring (ca 15 s), the final mixture was left to stand (1 min) and finally heated for 1 h. The synthesized polymer is used to coat a commercial PTFE bar for SBSE.

PFs with a wide range of polarity can be prepared for SBSE, overcoming the main shortcoming of the commercial PDMS coating. In fact, for polar analytes the extraction efficiency is two orders of magnitude higher for PFs than for PDMS, whereas the latter has higher efficiency for non-polar compounds [48]. This aspect has been exploited for extraction of very polar compounds, unapproachable by classic SBSE, for example triazinic compounds [49] and related metabolites [50].

Novel stirring/extraction integrated devices for solid-phase (micro)extraction

In recent years, exhaustive research has been focused on the development of new stirring/extraction integrated devices. Some of these new techniques overcame the main limitations

of classical and novel coatings, especially their mechanical instability. These new techniques have also widened the field of application of stir-based extraction by use of novel materials (for example polymeric membranes) and principles (solid and liquid-phase extractions). The main approaches proposed in recent years are shown schematically in Fig. 2, which also shows their advantages and limitations. Each approach will be considered in depth in the next sections.

Rotating disk-sorptive extraction

Rotating-disk-sorptive extraction (RDSE) was proposed by Richter et al. in 2009 with the objective of minimizing damage to the bar coatings when high stirring velocities are used [51]. The novel technique is based on a dedicated device which consists of two main parts as indicated in Fig. 3. On the one hand a PTFE disk with an integrated bar magnet is used as the base of the device, enabling magnetic stirring of the unit while preventing the deterioration of the coating, because it is not in direct contact with the extraction vessel walls. On the other hand, a PDMS film, which enables extraction of the target analytes, is attached to the PTFE disk by use of silicone. The thin PDMS film, which is synthesized by a sol-gel process, has a high surface-to-volume ratio enhancing surface contact with the sample. The inherent characteristics of the extraction unit enable stirring at higher velocities (up to 1,600 rpm) than in

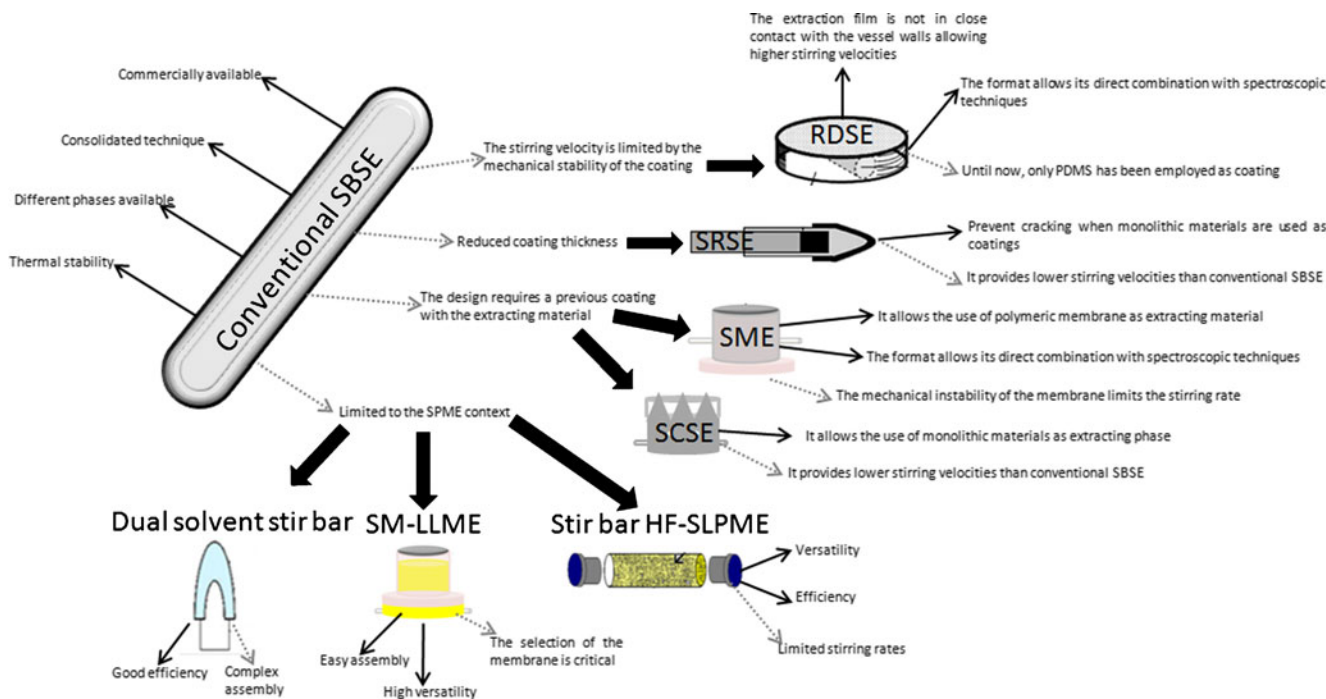


Fig. 2 Schematic and critical diagram summarizing the advantages (solid black lines) and disadvantages (dotted grey lines) of the novel extraction techniques that integrate extraction and stirring in the same device. SBSE, stir-bar-sorptive extraction; RDSE, rotating-disk-sorptive

extraction; SRSE, stir-rod-sorptive extraction; SME, stir-membrane extraction; SCSE, stir-cake-sorptive extraction; SM-LLME, stir-membrane liquid-liquid microextraction, HF-SLPME, hollow fiber solid-liquid-phase microextraction

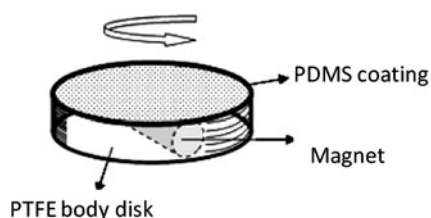


Fig. 3 Schematic diagram of a rotating-disk-sorptive extraction device. Reproduced, with permission of Elsevier, from Ref. [51]

conventional SBSE. This aspect and the high surface-to-volume ratio of the coating makes RDSE faster than conventional SBSE. In addition, the device is easily fabricated, with good disk-to-disk reproducibility (relative standard deviation <10%) and high extraction factors are achieved.

The overall extraction method is similar to that in SBSE. The extraction unit is introduced into the previously treated sample and it is stirred at a defined velocity for a fixed time. After the extraction, the unit is recovered, dried, and submerged in an appropriate solvent for elution of the analytes. Following this general procedure, RDSE has recently been proposed for extraction of pesticides from river samples for subsequent determination by gas chromatography–mass spectrometry (GC–MS) [52]. In this work, limits of detection in the very low $\mu\text{g L}^{-1}$ range were obtained by using only 25 mL sample. Moreover, RDSE enables better extraction of the target analytes than PDMS-based SBSE.

RDSE is a very versatile technique, because of its potential coupling with different analytical instrumentation including solid-phase spectrophotometry [53]. In this case,

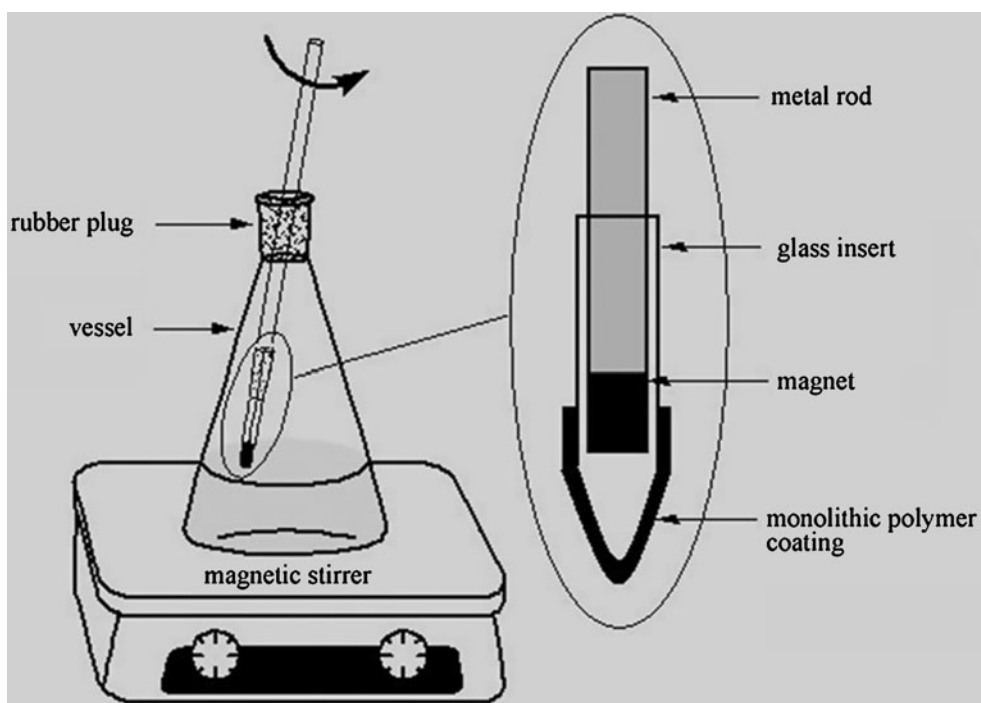
the analytes are monitored on the surface of the coating, avoiding the elution step. A special PDMS coating should be synthesized for this purpose, because it should have high transparency to UV–visible radiation.

Stir-rod-sorptive extraction

Stir-rod-sorptive extraction (SRSE) was proposed in 2010 by Luo et al. to minimize damage to monolithic materials when they are used as coatings in classic SBSE [54]. In fact, monoliths may crack when high stirring velocities are used, as a consequence of the friction between the coating and the vessel walls. The extraction unit, which is depicted in Fig. 4, consists of a metal rod with a magnet in one of its ends. This end is covered by a glass insert to the surface of which a monolithic polymer coating is attached. The stir-rod device is introduced and fixed to the extraction vessel by a rubber plug which enables its rolling in the sample. This novel approach enables re-use of the extraction units at least 60 times, with use of 300 rpm as optimum stirring rate. In the first proposal, SRSE was used for determination of fluoroquinolones in honey by use of a mixed-monolithic coating involving hydrophobic and ionic interactions. An anion-exchange mode has been also proposed for extraction of NSAIDs from environmental water samples [55].

Use of monolithic materials, as already indicated, increases the versatility of the extraction because different interaction chemistry can be developed. In this sense Lao et al. have prepared monolithic composites containing graphene for extraction of PAHs from water samples [56]. The synthetic

Fig. 4 Schematic diagram of stir-rod-sorptive extraction. Reproduced, with permission of Elsevier, from Ref. [54]



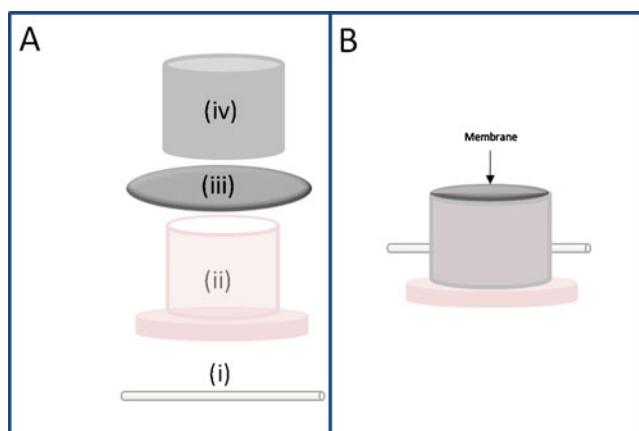


Fig. 5 Schematic diagram of the stir-membrane extraction device. **(a)** Main elements: *(i)* iron bar, *(ii)* upper part of a commercial solid-phase extraction cartridge, *(iii)* PTFE membrane, and *(iv)* section of a 5-mL pipette tip. **(b)** Final assembly of the unit

process is similar to that previously described but in this case graphene is added as extraction modifier. In addition, the polymerization process is accelerated by use of microwave energy, to avoid deposition of the graphene during synthesis. Inclusion of graphene results in a composite of greater surface area, therefore enhancing its extraction capability.

Stir-membrane extraction

Polymeric membranes (PMs) are useful extraction materials because of their good sample-to-adsorbent contact surface ratio, their potential affinity for different analytes, their porosity, and their mechanical stability. Moreover, the large number of commercially available membranes, and their potential chemical modification, makes them very versatile tools. PMs in different formats (flat, hollow fiber) have been extensively used as active sorbents, inner supports, or protecting materials for microextraction.

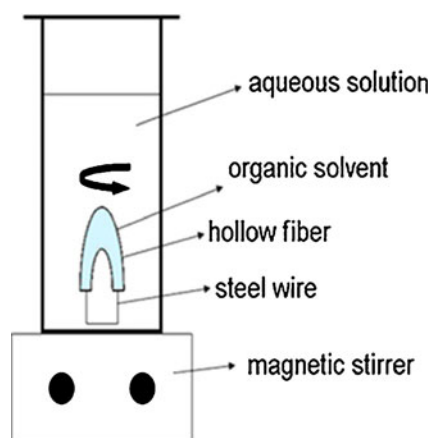


Fig. 6 Extraction unit used for dual solvent-stir-bar microextraction. Reproduced, with permission of Elsevier, from Ref. [60]

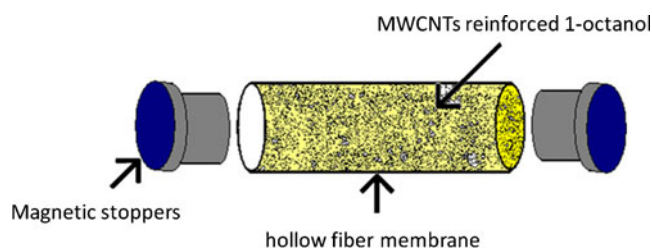


Fig. 7 Carbon nanotubes-assisted pseudo-stir-bar for solid-liquid micro-extraction. Reproduced, with permission of Elsevier, from Ref. [61]

The first stir-membrane format, called stir-membrane extraction (SME), was proposed by our research group in 2009 [57]. The new technique is based on a dedicated device that integrates the extraction capabilities of PMs and the stirring element. The extraction device, presented schematically in Fig. 5, consists of four basic and commercially available elements. This aspect, besides the easy assembly process, enables good unit-to-unit reproducibility to be achieved (RSD <12.5%). In the conventional procedure, the extraction device is stirred in the sample at the optimum rate and for a time promoting extraction of the analytes. Extraction occurs as a consequence of sample flow through the membrane, by a filtration process, which clearly enhances rates of extraction and elution. After the extraction, the unit is withdrawn from the sample and analysis is performed by an appropriate technique. SME is compatible with chromatographic and spectroscopic techniques. In the first approach, only simple chemical elution with an appropriate solvent is required. For the second approach, special considerations, mainly related to the PM used, must be taken into account.

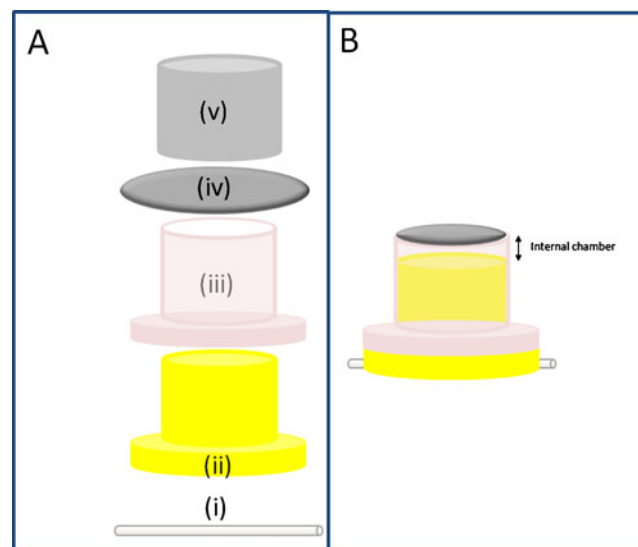


Fig. 8 Schematic diagram of the stir-membrane liquid-phase extraction device. **(a)** Main elements: *(i)* iron bar, *(ii)* PTFE top-cap, *(iii)* upper part of a commercial solid phase extraction cartridge, *(iv)* PTFE membrane, and *(v)* section of a 5-mL pipette tip. **(b)** Final assembly of the unit. Adapted from Ref. [62]

SME has been proposed for determination of the hydrocarbon index in water by infrared spectroscopy (IR) [58] after an extraction procedure similar to that previously described. Considering the low sensitivity of IR detection, determination of the analytes directly on the membrane surface was preferred, avoiding an elution process which involves inherent loss of material. PTFE membranes 40 μm thick were used in this application, for which the method detection limit was as low as 18 $\mu\text{g L}^{-1}$. The new approach was more sensitive than its ASTM counterpart.

In 2011 Huang et al. proposed a new extraction approach, called stir-cake sorptive extraction (SCSE) [59], which shares some aspects of the RDSE, SME, and SRSE devices. In fact, SCSE use a monolithic material (as SRSE) in a disk format (similar to RDSE) as sorptive phase. To protect the disk from cracking it is assembled in a dedicated device (similar to that in SME) avoiding its contact with the walls of extraction vessel. The first application was devoted to the determination of steroid hormones in milk by liquid chromatography with diode-array detection. For this purpose a poly(vinylimidazole-divinylbenzene) monolithic phase was used. The general extraction procedure was very simple, not requiring previous removal of fat and proteins. Only dilution in water was necessary before extraction.

Novel stirring/extraction integrated devices for liquid-phase (micro)extraction

In liquid-phase microextraction (LPME), the first approach of integrating stirring and extraction, the so-called dual solvent-stir-bars microextraction, was proposed by Yu et al. [60]. The extraction device, depicted in Fig. 6, consists of a stainless-steel stir-bar to which two hollow fibers containing the appropriate solvent are attached, to promote their agitation. The novel device enabled more rapid extraction than conventional U-shaped hollow-fiber LPME for extraction of Sudan dyes from food samples. In the same way, Es'haghi et al. recently proposed carbon nanotubes-assisted pseudo-stir-bar solid-liquid microextraction in which a special stir-bar, shown schematically in Fig. 7, is used [61]. In this technique a polypropylene hollow fiber is used as support, and a dispersion of carbon nanotubes in an appropriate solvent, located in its lumen and pores, is used as extractant. The hollow fiber is closed by use of two iron caps, which enables magnetic stirring of the unit. With this approach, the extraction of brilliant green from fish pond water was easily accomplished.

The versatility of SME has been also exploited in the LPME format. In this case, the extraction device is modified with a fifth element, also commercially available, to create a small chamber of reduced volume (ca 50 μL) in which the extraction solvent is located. A schematic view is presented in Fig. 8. The so-called stir-membrane

liquid-liquid microextraction (SM-LLME) technique can be used in two or three-phase mode depending on the analytical problem. In the simplest approach, the inner chamber is filled with an organic solvent which also wets the PM. The organic solvent has properties such as affinity for the target analytes, immiscibility with water, and compatibility with the final instrumental technique. By following this general procedure, GC-MS determination of selected chlorophenols in water was achieved [62]. In addition, SM-LLME can be also performed in three-phase mode by using an aqueous extraction phase in the inner chamber and an appropriate organic solvent wetting the PM as a supported liquid membrane (SLM) [63]. This extraction mode is especially useful for liquid chromatographic analysis of ionizable analytes. The driving force of the extraction is the pH gradient established at both sides of the SLM, which may result in a high enrichment factor (up to 395 for phenols in water samples) in a reasonable time.

Conclusions

Integration of stirring and extraction in the same device, a concept that emerged in 1999, is continuously evolving. Current research is focused on two different lines of investigation. On the one hand new coating materials, different from the classic PDMS, are being developed to make the principle of SBSE applicable to more polar compounds. In this context, use of MIPs or RAMs has also been proposed to enhance the selectivity of analyte isolation. On the other hand, new extraction formats covering both solid and liquid-phase microextraction have appeared in response to the limitations of classic SBSE, for example potential damage or low surface areas of the coatings. In this review the current state of the art of those extraction techniques was presented. The main examples and trends have been outlined and described.

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