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Overview of the novel sorbents available in solid-phase extraction to improve the capacity and selectivity of analytical determinations

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Resum. Aquest article descriu els nous desenvolupaments en materials polimèrics que milloren l'extracció en fase sòlida (SPE) dels anàlits presents en mostres líquides. Se centra principalment en nous sorbents polimèrics, tant els comercialment disponibles com els sintetitzats per grups de recerca, amb propietats millorades per a l'extracció d'analits. Es descriuen diversos tipus de sorbents polimèrics, des dels que milloren la capacitat d'extracció (anomenats *hypercrosslinked*, amb elevada àrea superficial i hidrofilicitat) fins als que milloren la selectivitat del procés (els polímers d'empremta molecular [MIP] sintetitzats amb una cavitat específica per a l'analit d'interès) i també aquells que combinen ambdues propietats (coneguts com sorbents de *mode mixt*, que són sorbents d'elevada capacitat amb un grup d'intercanvi iònic que aporta la selectivitat en el procés d'extracció). També es presenten i es comparen resultats dels diversos sorbents quan s'apliquen a SPE d'anàlits en matrius dels camps d'aplicació analítics més rellevants.

Paraules clau: sorbents · extracció en fase sòlida · capacitat · selectivitat · determinació analítica

Summary. This article provides an overview of the most recent developments in polymer materials that improve the solid-phase extraction (SPE) of analytes from liquid samples. The main focus is on new polymeric sorbents, both commercially available and "in-house" synthesized, whose enhanced properties allow suitable extraction. Several types of polymeric sorbents are described herein. Hypercrosslinked sorbents improve the capacity of the extraction process due to their large specific surface areas and balanced hydrophilicities. Molecularly imprinted polymers (MIPs) are synthesized with a specific cavity for the analyte of interest, improving extraction selectivity. Another type are mixed-mode sorbents that are high-capacity sorbents that contain an ion-exchange moiety that fine-tunes the selectivity of the extraction process. Finally, the results obtained when these sorbents are applied as SPE material to extract analytes in different liquid matrices are presented and comparatively discussed in the context of the most relevant analytical fields.

Keywords: sorbents · solid-phase extraction · capacity · selectivity · analytical determination

Introduction

Solid-phase extraction (SPE) is one of the most successful extraction techniques due to its ability to efficiently enrich and purify analytes from their liquid sample matrices. Another advantage of SPE is its versatility, a result of the different types of sorbents available; it is the choice of sorbent that determines the nature of the interaction during the extraction process. Thus, one of the main aims of SPE research is to develop novel sorbents in order to improve the characteristics of previous ones and thereby the results of SPE [76].

The first SPE materials were silica-based and were modified with C_{18}, C_8, phenyl, CH, CN, or NH_2 groups. However, silica-based materials present several disadvantages, such as instability at extreme pH, low recovery in the extraction of polar analytes, and the presence of residual silanol groups [40]. Recently, carbon-based sorbents have emerged; they include graphitized carbon black (GCB) and porous graphitic carbon (PGC). However, these sorbents are unable to elute certain compounds, and some of them even remain irreversibly adsorbed [40].

Porous polymeric sorbents are another class of SPE materials and they overcome some of the disadvantages of previous sorbents. The traditional polymeric sorbent is macroporous polystyrene-divinylbenzene (PS-DVB), the hydrophobic structure of which has a specific surface area of up to 800 m^2/g. It interacts with analytes —due to the hydrophobic nature of the sorbent— basically through van der Waals' forces and the π-π interactions of the aromatic rings that make up the sorbent structure. However, traditional hydrophobic macroporous PS-DVB still shows poor capacity and selectivity.

To improve capacity, hypercrosslinked sorbents have been developed which, due to their ultra-high specific surface area of up to 2000 m^2/g, provide a greater number of interaction points with the analytes to be extracted [24]. The hydrophobic structure of the original porous polymers has also been improved with the introduction of hydrophilic macroporous and hydrophilic hypercrosslinked sorbents. The hydrophilicity of the sorbents can be introduced either through a hydrophilic precursor monomer or by chemically modifying the PS-DVB polymer skeleton [34].

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To improve selectivity, tailor-made sorbents have been designed that selectively interact with the target compound(s) but remove all other analytes, including interferents. Restricted access materials (RAMs) were one of the first materials developed to improve selectivity. Their biporous structure interacts with analytes by reversed-phase while excluding high molecular weight compounds by size exclusion. However, RAM materials do not always act selectively and when they do their selectivity is low. The first sorbents to be considered as exclusively selective were immunosorbents (ISs), which have an immobilized antibody that allows specific and selective interactions with the target compound (antigen). However, ISs have several limitations: the amount of time needed for their preparation, irreproducibility from batch to batch, instability, and limited use in aqueous medium. To overcome these problems, in the 1990s, molecularly imprinted materials (MIPs) were designed. These synthetic polymers have specific cavities matched to a template molecule and a retention mechanism based on molecular recognition [21].

In the context of the above challenges, research into polymeric sorbents in the last decades has focused on improving capacity and selectivity. This article reviews the latest improvements in SPE polymeric materials that have enhanced the capacity and selectivity of the extraction process. Specifically, the following sorbents are discussed: hypercrosslinked and hydrophilic sorbents, both of which enlarge the capacity of the extraction process; mixed-mode polymeric sorbents, in which both capacity and selectivity are improved; and, finally, MIPs, which have greater selectivity. The morphological and chemical properties of the various polymers are described and their analytical capabilities are compared with those of other SPE sorbents. Examples of the applications of polymeric sorbents in several analytical fields are also presented.

Hypercrosslinked sorbents

In hydrophobic sorbents, the capacity of the sorbent is improved by increasing the specific surface area (i.e., the number of interaction points between sorbent and analyte). In the early 1970s, Davankov introduced a new method in which the precursor polymer (either linear polystyrene chains or slightly crosslinked PS-based copolymer) was extensive post-crosslinked by means of the Friedel-Crafts reaction, which produced various structural bridges between neighboring phenyl groups in a highly swollen state. The resulting resins have a hypercrosslinked structure with high micropore content and very high specific surface area (up to 2000 m2/g) [24].These morphological properties make hypercrosslinked resins much more retentive than conventional macroporous polymers. Previous reviews [34,35] have detailed the structure and properties of several commercially available polymeric hydrophobic sorbents with macroporous and hypercrosslinked structures. However, all of these materials are hydrophobic, which is sometimes problematic, especially in the retention of the most polar analytes.

Apart from commercially available sorbents, several research groups have synthesized hypercrosslinked materials. Among them, Sherrington's research group has focused on the development of hypercrosslinked materials to be applied as sorbents in SPE for the efficient extraction of polar pollutants from environmental samples. They designed two types of hypercrosslinked materials with improved properties in the extraction of polar pollutants: hydrophilic hypercrosslinked sorbents (discussed in the next section) and small (~5 μm) and monodispersed particle size hypercrosslinked sorbents. The benefit of the latest hypercrosslinked sorbents is that they can be effectively packed in precolumns, which have been effectively used in the on-line enrichment of polar pollutants from aqueous samples. This approach has shown greater efficiency and capacity than obtained with the commercially available Lichrolut EN hypercrosslinked sorbent, which has considerably higher particle sizes and broader particle size distributions (40–120 μm) [36].

Hydrophilic sorbents

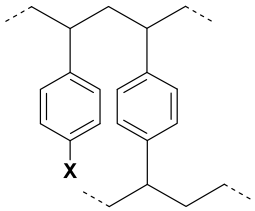
The hydrophobic nature of the hypercrosslinked sorbents enables them to interact with the analytes only through hydrophobic interactions, which leads to poor retention when polar analytes are extracted. One way to overcome this problem is to introduce polarity into the resins, thus favoring polar interactions between analyte and sorbent. There are two strategies to introduce polarity into a sorbent: (i) chemically modifying the PS-DVB based polymers and (ii) copolymerizing hydrophilic monomers.

Chemically modified sorbents. Fritz, in the 1990s, pioneered the chemical modification of resins with the introduction of acetyl [39,71], hydroxymethyl [39,71], and sulfonic [39] groups into PS-DVB resins. Later, Masqué modified the commercial Amberchrom GC-161m resin (PS-DVB, 900 m2/g) with acetyl [53], benzoyl [54], o-carboxybenzoyl [55], 2,4-dicarboxybenzoyl, and 2-carboxy-3/4-nitrobenzoyl [56]. The chemical structures of those moieties have been depicted in previous reviews [34,35]. These modified resins were applied to the extraction of polar organic compounds from water samples, with better results obtained than with their unmodified analogues. However, a limitation of these hydrophilic resins is their low degree of modification, due to the fact that the functional group is more complex. This may lead to less sorbent hydrophilicity.

In spite of this low degree of modification, several commercial chemically modified sorbents have been introduced. Table 1 summarizes the main properties of the commercial sorbents described in this section. Due to their novelty, there are few applications thus far, but the use of these sorbents will no doubt increase, as has been the case of Isolute ENV+ and Strata X, which are being used as SPE sorbents with growing frequency.

In the following, these chemically modified sorbents are compared to other sorbents (from the same or other classifications) in extractions carried out for several applications. Pavlovic et al. [62] developed and optimized a SPE procedure for the determination of a group of antibiotics in water samples. In that study, following the results from a previous study in which

Table 1. Structure and properties of commercially available chemically modified polymeric sorbents

Sorbent	Supplier	Sorbent structure		
		Polymer based	Chemically modified with (X):	Area (m^2/g)
Isolute ENV+	IST		hydroxyl —OH	1100
Strata X	Phenomenex		pyrrolidone 	800
Cleanert HXN	Agela Technologies			600
Speed-Advanta	Applied Separations		carboxyl[a] 	n.d.
Bond Elut Plexa	Varian & Polymer Lab.		hydroxyl —OH	450
Supel Select HLB	Supelco		n.d.	~ 400

[a]Characterized in Sirvent et al. [70]; n.d.: no data

Table 2. Comparison of the pharmaceutical recoveries (%) obtained on the five selected sorbents in sorbent mass formats of 500 and 200 mg. Further information is provided in Pavlovic et al. [62]

	Strata CB	Strata C18-E	Strata SDB-L	Strata-X	Strata X-C	Strata-X-SDB-L	SDB-L-Strata-X
sulfaguanidine	5.0	3.3	17.4	76.1	86.6	40.8	45.8
sulfadiazine	60.2	31.7	97.1	94.1	97.0	97.8	103.2
sulfamethazine	105.7	98.3	96.6	93.3	96.9	92.0	96.3
oxytetracycline	80.7	74.6	90.2	94.7	n.d.	93.8	96.0
penicillin G/ procaine	75.9	83.0	93.0	102.3	n.d.	96.5	103.8
trimethoprim	80.7	80.9	100.4	97.6	n.d.	107.7	110.7
norfloxacin	57.7	72.0	89.4	92.3	n.d.	91.4	94.6
enrofloxacin	89.8	97.9	90.0	96.9	n.d.	85.7	93.1

n.d.: not detected.

Oasis HLB (see details of its morphology and chemistry in next section) failed to extract the most polar analytes of the group, several sorbents were tested in 200- and 500-mg cartridge formats commercialized by Phenomenex: Strata C18, Strata C8, Strata SBD-L, Strata X, and Strata X-C (strong ion-exchange sorbent; see section "Mixed-mode polymeric sorbents" for further details); and using the tandem approach, consisting of 200 mg of Strata SBD-L in tandem with 200 mg of Strata X.

As summarized in Table 2, recoveries were similar for all the sorbents tested, with the exception of sulfaguanidine (the most polar analyte tested and which Oasis HLB failed to retain). Based on sulfaguanidine recovery, the best results were achieved with 500 mg of Strata X. The results presented in Table 2 also show that recoveries for this analyte increased depending upon the mass of the sorbent tested. Another study [64] examined the ability of the recently commercialized Bond Elut Plexa to extract a group of UV filters from water samples. The sorbents tested were Oasis HLB 60 mg and 200 mg, Bond Elut Plexa 60 mg and 200 mg, and Sep-Pak Plus C_{18} ~360 mg. The best results were obtained with Oasis HLB 60 mg, which was therefore selected for further studies. In this case, the two sorbent masses (i.e., 60 and 200 mg) yielded similar results,

but the authors selected the lower-mass sorbent to avoid excessive retention of hydrophobic substances from the matrix, which could mask the analytes, causing matrix interference effects in the subsequent liquid chromatography- mass spectrometry (LC-MS) analysis.

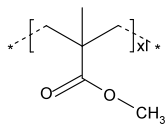
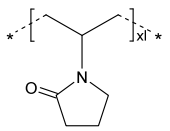
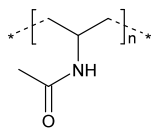
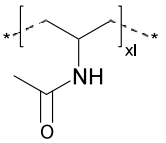
Copolymeric hydrophilic sorbents. The basic structure of these sorbents combines a polar monomer, which promotes hydrophilic interactions and favors interactions with water, with a crosslinking agent, which increases the specific surface area and promotes hydrophobic interactions.

Table 3 lists the details of commercially available sorbents with a polar monomer. The common feature of these sorbents is that they combine a polar monomer with a macroporous structure (specific surface area up to 800 m^2/g). In contrast to the chemically modified sorbents, these sorbents lack the reduced hydrophilicity resulting from the low degree of modification of the polar functional group. However, retention by these sorbents is in some cases compromised due to the need during the polymerization procedure to balance the monomers and the polymerization conditions, thereby yielding resins that are balanced in terms of hydrophilicity and specific surface area.

Among the commercially available sorbents, Oasis HLB has been widely used in SPE to clean up a variety of aqueous, biological, and food samples and to extract analytes with wide-ranging physicochemical properties. In most of its applications, the potential of Oasis HLB for extracting highly polar analytes has been demonstrated; however, this might reflect the fact that it is one of the most frequently included sorbents in comparative SPE studies. Some of these comparative studies were discussed in the previous section. In another study, Oasis HLB was compared to Chromabond HR-P as a preliminary sorbent to extract alkyl methylphosphonic acids, which were then selectively extracted using a MIP designed for these analytes [53]. Chromabond HR-P was unable to retain (0% recovery) some of the most polar analytes studied, while they were partially retained by Oasis HLB (with the lowest recoveries not lower than 30%). From those results, Oasis HLB was selected as the sorbent of choice. When the hydrophilic Speedisk H_2O-Philic DVB and the hydrophobic Speedisk DVB cartridges were compared to other commercially available sorbents, such as C_{18} Empore disk, Amberlite XAD-2, and Abselut Nexus, in the extraction from aqueous samples of fifty semivolatile organic compounds with K_{ow} ranging from 1.4 to 8.3, recoveries by the two Speedisk sorbents were better and were shown to depend on the polarity of the analyte [79]. For the most apolar compounds, recoveries were best with Speedisk DVB, whereas for polar compounds Speedisk H_2O-Philic DVB was better. Therefore, the authors decided to pack a single cartridge with both hydrophobic and hydrophilic materials, allowing quantitative extraction of the entire family of analytes in just one SPE step.

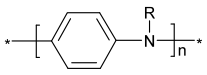
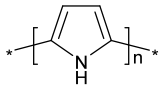
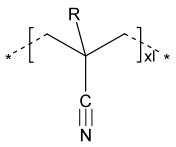
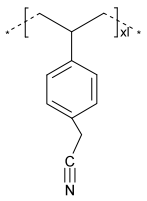
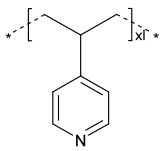
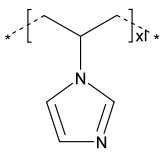
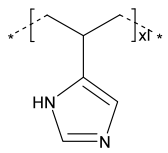
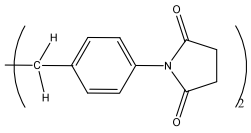
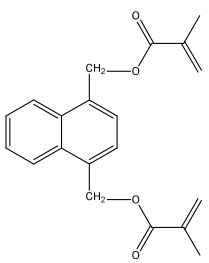
In the last few years, there has been an increasing number of "in-house" prepared sorbents, designed with the aim of improving already available sorbents. Table 4 summarizes these new sorbents, which contain a polar monomer, and lists their

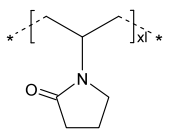
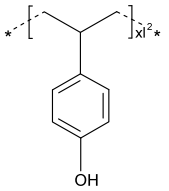
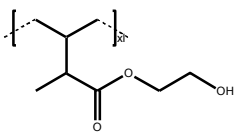
Table 3. Structure and properties of commercially available hydrophilic copolymeric sorbents

Sorbent	Supplier	Copolymeric structure		Area (m^2/g)
Amberlite XAD-7	Applied Separations	Methacrylate-divinylbenzene (MA-DVB)		450
Amberlite XAD-8				310
Abselut Nexus	Varian			575
Focus		n.d.	n.d.	n.d.
Oasis HLB	Waters	N-vinylpyrrolidone-divinylbenzene (PVP-DVB)		830
Porapak RDX				550
Speedisk H_2O-Philic DVB	J.T. Baker	n.d.	n.d.	n.d.
Discovery DPA 6S	Supelco	Polyamide		n.d.
SampliQ OPT	Agilent Technologies	Polyamide-DVB		n.d.

xl: crosslinked with DVB; n: linear polymer; n.d.: no data.

Table 4. Structure and properties of "in-house" hydrophilic copolymeric sorbents

Sorbent	Copolymer structure		Area (m^2/g)	%wt. polar content	References
PANI	R = H; Polyaniline (PANI)		48	n.d.	[3,7]
PNMA	R = CH_3; Poly-N-methylaniline (PNMA)		32	n.d.	[4]
PDPA	R = phenyl; Polydiphenylaniline (PDMA)		38	n.d.	[7]
PPy	Polypyrrolidone		40	n.d.	[5,6]
AN-DVB	R = H; Acrylonitrile (AN)-DVB		460	5.9% N	[77]
MAN-DVB	R = CH_3; Methacrylonitrile (MAN)-DVB		560	4.8% N	[77]
CMPS-DVB	Cyanomethylstyrene (CMSt) – DVB		308	2.6% N	[26]
4VP-DVB	4-vinylpyridine-DVB		710	2.1% N	[29]
NVIm-DVB	N-vinylimidazole-DVB		626	6.3% N	[28]
4VIm-DVB	4-vinylimidazole-DVB		504	8.1% N	[31]
BM-DVB	4,4'-bis(maleimido)diphenylmethane (BM) – DVB		35	n.d.	[12]
DMN-DVB	di(methacryloyloxymethyl) naphtalene (DMN)-DVB		100	n.d.	[12]

Sorbent	Copolymer structure		Area (m^2/g)	%wt. polar content	References
VP-DVB	1-vinyl-2-pyrrolidone-DVB		800	n.d.	[52]
HXLGp	*Hypercrosslinked* (paraVBC-DVB)		908	3.96% O	[32,33]
HXLGmix	*Hypercrosslinked* (mix meta/para-VBC-DVB)		1889	2.95% O	[32,33]
HXLPPpolar	2-hydroxyethyl methacrylate (HEMA)-VBC-DVB		850	~7% O	[14]

n.d.: no data.

optimal properties in terms of specific surface area and the percentage (%) of polar groups contained in these resins.

Most of the studies in which hydrophilic sorbents were prepared involved preliminary attempts to determine the exact ratio between polar monomer and crosslinking agent needed to achieve the best retention properties during the extraction process. For example, Trochimczuk and co-workers prepared resins based on acrylonitrile (AN) [77], methacrylonitrile (MAN) [77], and cyanomethylstyrene (CMSt) [26], all of which are hydrophilic monomers crosslinked with DVB. In those studies, the resins were produced in different degrees for each monomer (hydrophilic and crosslinker), such that they were balanced in terms of hydrophilicity and specific surface area. When the resins were tested in the sorption of phenol, the conclusion was that hydrophilicity and specific surface area are equally important, i.e., resins with a 50:50 ratio of hydrophilic and crosslinker monomer would be the most suitable for extraction. A similar conclusion was drawn when a series of hydrophobic sorbents based on PS-DVB [27] was compared to various hydrophilic (due to the presence of a nitrogen-based moiety) sorbents based on 4-vinylpyridine-divinylbenzene (4VP-DVB) [27,29], *N*-vinylimidazole-divinylbenzene (NVIm-DVB) [30], and 4-vinylimidazole-divinylbenzene (4VIm-DVB) [31] in the SPE of a group of polar pollutants from aqueous samples. The resins prepared by Bagheri's group have the common feature that they contain only one hydrophilic monomer (i.e., polyaniline (PANI) [3,7], poly-*N*-methylaniline (PNMA) [4], polydiphenylaniline (PDPA) [4], and polypyrrole (PPy) [5,6]) and no crosslinker monomer; accordingly, the specific surface area of these resins is only a few square meters per gram. This low specific surface area might explain the low recoveries obtained when they were used as the SPE sorbent to extract polar compounds.

"In-house" sorbents have fared well when compared to similar commercially available sorbents. For instance, in tests of the "in-house" prepared resins NVIm-DVB and 4VIm-DVB against Oasis HLB and Strata X for the on-line-SPE-LC-UV determination of a group of polar pollutants in water samples, the best results in terms of recovery were achieved with NVIm-DVB. This resin combines a high specific surface area with a high polar moiety content [31].

The feature common to the hydrophilic sorbents described so far is their macroporous structure. We prepared hydrophilic sorbents based on a hypercrosslinked structure [32,33]. Firstly, hypercrosslinked resins were generated with different degrees of polarity and specific surface area depending upon the precursor used in their synthesis. Thus, the precursor para-vinylbenzylchloride (VBC)-DVB yielded a hypercrosslinked resin (HXLGp) with an OH loading of 2.35 mmol/g and a specific surface area of 908 m^2/g. When the precursor was a mixture of isomers-VBC, the hypercrosslinked resin (HXLGmix) had half the OH loading (1.47 mmol/g) but double the specific surface area (1889 m^2/g). The differences in the properties of these hypercrosslinked sorbents were also reflected in tests of SPE sorbents in the on-line-SPE extraction of a group of polar analytes. The best recoveries were obtained with HXLGp, which combines the highest number of hydroxyl groups and a high specific surface area.

The same research group generated hydrophilic hypercrosslinked sorbents in the form of low-micron and monodispersed particle sizes. These hydrophilic hypercrosslinked sorbents (HXLPP-polar) were developed from a hydrophilic precursor resin based on 2-hydroxyethyl methacrylate (HEMA)-VBC-DVB, prepared by precipitation polymerization. The sorbents generated were in the form of 4- to 6-μm particles and had a specific surface area of ~900 m^2/g and a hydrophilicity of ~1.5 mmol O content/g. This mixture of properties makes these

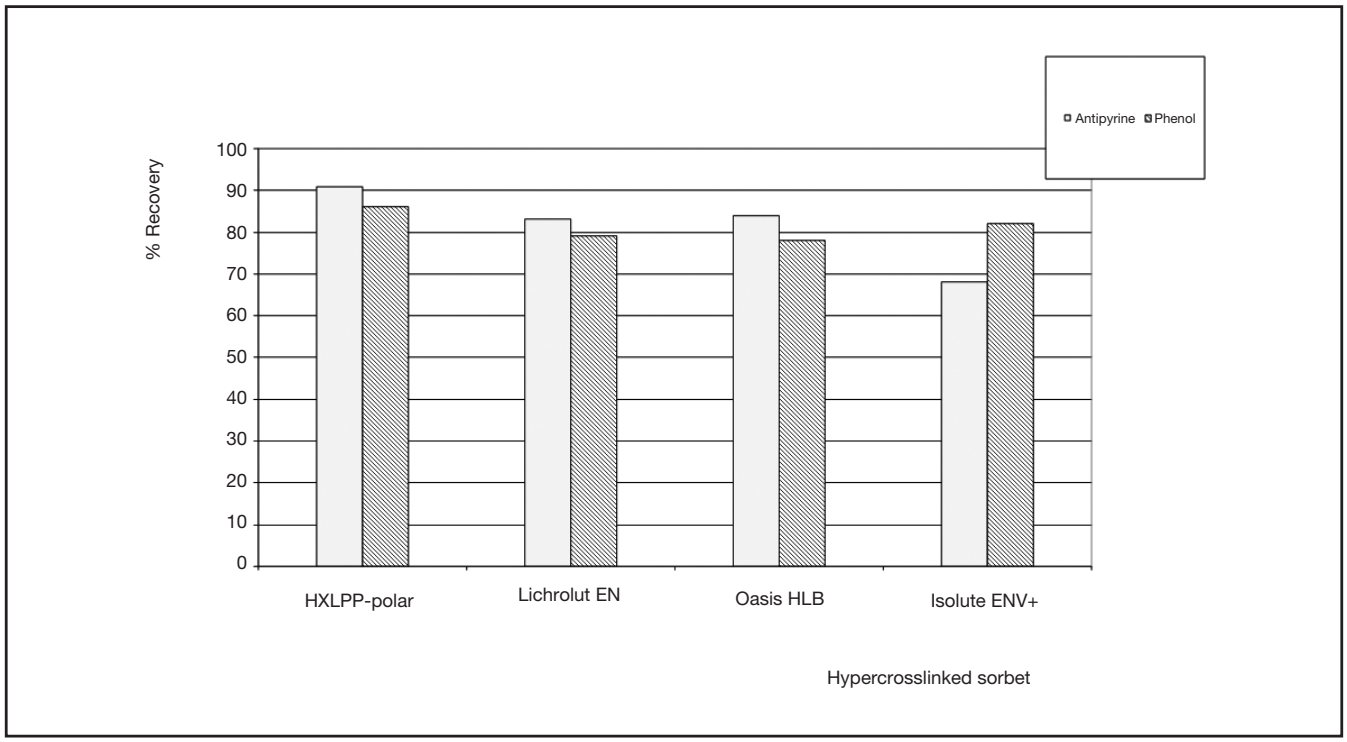


Fig. 1. Recovery values after off-line SPE for 1000 ml of standard solution spiked with 50 μg/l of each compound in Milli-Q water.

sorbents suitable for the SPE of polar pollutants from aqueous samples, since they provide better recovery values than obtained with the commercial Oasis HLB, Lichrolut EN, and Isolute ENV+ [14]. Figure 1 shows the recovery results achieved when 1000 ml of ultrapure water spiked with a mixture of polar analytes was subjected to off-line SPE using the studied sorbents. Based on the results for the two representative analytes, antipyrine and phenol, the best recoveries were achieved with the HXLPP-polar sorbent, which can be attributed to its mixture of enhanced properties: hypercrosslinked structure, high specific surface area, low particle size, and hydrophilicity.

Mixed-mode polymeric sorbents

The section above detailed the different possibilities in sorbent technology that enhance the capacity of the extraction procedure. However, in the analysis of complex matrix samples, another important aim is to obtain clean extracts from the extraction process, removing interferents and, in the process, gaining both sensitivity and selectivity. Moreover, in recent years, highly clean extracts have become more important in attempts to prevent ion enhancement/suppression when the SPE extracts are injected into sensitive detectors, such as tandem mass spectrometry (MS/MS).

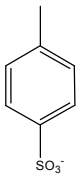
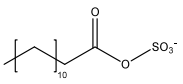
Mixed-mode polymeric sorbents have progressively appeared in efforts to improve the selectivity of the extraction process. These sorbents combine a polymeric skeleton with ionic groups, with two types of available interactions: reversed-phase (from the polymeric structure) and ion-exchange (from the ionic groups). They are mainly used in the extraction of analytes (charged or not) from complex matrices, such as environmental, biological, or food matrices. The philosophy in mixed-mode sorbent technology is that once the sorbent type is selected, careful choice of the pH and solvent in each SPE step allows the matrix components and interferents to be eluted separately from the analytes of interest, in the washing and elution steps, respectively.

Mixed-mode sorbents are commercially available, with most of the recognized sorbent manufacturers nowadays focusing their research efforts on developing new mixed-mode materials. Moreover, several research groups recently started to develop novel mixed-mode sorbents. Consequently, mixed-mode sorbents are being increasingly applied as SPE materials in research laboratories for a variety of applications in different fields.

The typical classification in mixed-mode technology is by the type of ion group attached to the polymeric resin. Thus, these resins are classified as cationic or anionic and as strong or weak. Table 5 lists the strong cationic exchange mixed-mode polymeric sorbents, both commercially available and "in-house" prepared. A full list of all available mixed-mode polymeric sorbents, including their detailed descriptions and applications, was published recently [38]. The acidicty and alkalinity of the moieties modifies the polymeric skeleton and thus also affects the choice of the SPE protocol. In this sense, in applications involving strong ion-exchange sorbents, the aim in the different SPE steps is to switch the chargeability of the analytes or interferents, not that of the sorbent. By contrast, when the application involves weak ion-exchange sorbents, the aim is to switch the chargeability of the sorbent, and, not, if possible, that of the analytes or the interferents.

Studies comparing different mixed-mode polymeric sorbents have been published in the recent literature, including those addressing the performance of neutral, strong, or weak

Table 5. Structure and properties of commercially available and "in-house" prepared mixed-mode polymeric sorbents

Sorbent	Supplier	Polymer based	Ionic group
Strong cation exchange			
Oasis MCX	Waters	Oasis HLB	—SO_3H
Strata X-C	Phenomenex	Strata-X	
Sampli Q SCX	Agilent Technologies	Modified DVB resin	
Speedisk H_2O-Phobic SC-DVB	J.T. Baker	Speedisk H_2O-Phobic DVB	
Bond Elut Plexa PCX	Varian & Polymer Labs.	Bond Elut Plexa	n.d.
Cleanert PCX	Agela Technologies	PS-DVB	n.d.
Evolute CX	Biotage	n.d.	n.d.
Clean Screen DAU	UCT	Silica gel	
HXLPP-SCX	"In-house"	Hypercrosslinked VBC-DVB	

n.d.: no data.

ion-exchange sorbents. For example, Oasis HLB, Oasis MAX, and Oasis WAX were compared regarding the extraction of estrogens in river sediments. The neutral sorbent provided good recoveries for all the compounds, but the extracts contained a large number of interferents, which affect ion-suppression in tandem MS detection. Oasis MAX strongly retained a group of estrogens but was not able to quantify them properly whereas Oasis WAX provided better recoveries and cleaner extracts than its neutral analogue (Oasis HLB) [58]. Kasprzyk-Hordern [46] compared eight different sorbents, Oasis HLB, MAX, MCX, WAX, WCX, Chromabond C_{18}, Isolute ENV+, and Isolute HCX (a silica-based strong cation-exchange sorbent), in the determination of 28 pharmaceuticals and illicit drugs from surface waters. Oasis MCX provided the best extraction, yielding clean extracts (suitable for injection into UPLC-MS/MS) and high recoveries for all the compounds studied.

Another method compatible with mixed-mode sorbents is the tandem approach, in which tandem sorbents are used in series, so as to provide complementary properties and further broaden the fields of application. A tandem approach using Oasis MCX and Oasis MAX in series was also found to be well-suited for the complete extraction of a group of pharmaceuticals (including basic, acidic, and neutral compounds) from complex wastewater samples [49] whereas Oasis MAX alone was unable to extract the basic analytes from the group, and Oasis MCX was only valid for less complex water samples.

Regarding "in-house" prepared mixed-mode polymeric sorbents, to the best of our knowledge, ours is the only research group is working in this field. The mixed-mode sorbents developed in our laboratory have a hypercrosslinked structure, in contrast to the macroporous structure of commercially available ones. This hypercrosslinked structure enhances reversed-phase interactions, thus promoting analyte retention during the SPE process. The hypercrosslinked polymer has been modified with such moieties as piperazine and ethylendiamine, to generate a weak anion-exchange sorbent [37], and with carboxylic groups, to generate a weak cation-exchange sorbent [13]. Both were applied to the extraction of different groups of pharmaceuticals from complex environmental water samples. The results were satisfactory and better than those obtained with commercially available mixed-mode sorbents of the same category.

Molecularly imprinted polymers

These polymers are conferred with a predetermined selectivity for a single molecule or a group of structurally related molecules. This selectivity arises from the synthetic procedure used to prepare the MIP, in which a template molecule is linked to suitable monomer(s) containing functional groups. This link is responsible for the specific binding sites expressed by the MIP. After synthesis of the polymer, the template is removed by extensive washing and the resulting MIPs are stable, robust, and resistant to a wide range of pHs, solvents, and temperatures.

Table 6. Examples of applications of MIPs

Template	MIP synthesis	Target molecules	Sample	Reference
Alfuzosin	Bulk	Alfuzosin	Plasma	[45]
Amoxicillin	Bulk	Amoxicillin, cephalexin	Urine	[8]
Atrazine	Multi-step swelling and polymerization	Atrazine, ametryn, irgarol	River water	[67]
Bensulfuron-methyl	Precipitation	4 Sulfonylurea herbicides	Soybean	[75]
Benzyl paraben	Precipitation	7 Parabens	Soil, sediments	[60]
Carbamazepine	Precipitation	Carbamazepine, oxcarbazepine	Urine	[10]
Cephalexin	Bulk	Cephalexin, amoxicillin	Urine, river water	[9]
Chloramphenicol	Suspension	Cloramphenicol	Milk, shrimp	[69]
4-chlorophenol	Bulk	4-Chlorophenols and 4-nitrophenol	River water	[17]
Clomiphene (dummy)	Bulk	Tamoxifen and 4-hydroxitamoxifen	Urine	[23]
Cyclobarbital	Suspension	Phenobarbital, cyclobarbital, amobarbital, phenytoin	River water	[44]
Diazepam	Bulk	9 Benzodiazepines	Hair	[1]
Enrofloxacin	Bulk	4 Fluoroquinolones	Water	[11]
Enrofloxacin	Bulk	Enrofloxacin, ciprofloxacin	Urine, tissue sample	[19]
Methyltestosterone	Bulk	Testosterone, epitestosterone	Urine	[78]
1-Naphthalene sulfonic acid	Bulk	8 Nahthalenes sulfonic acids	River water	[18]
Nicotine	Precipitation	Nicotine, nornicotine, cotinine, myosmine, β-nicotyrine	Cigarette smoke extracts	[66]
4-Nitrophenol	Bulk	4-Nitrophenol	River water	[57]
4-*n*-Nonylphenol	Precipitation	Nonylphenol and ethoxylated derivatives	Sediment, sludge	[59]
Ofloxacin	Bulk	6 Fluoroquinolones	Serum	[72]
Ofloxacin (dummy)	Bulk	Enrofloxacin, ciprofloxacin	Milk	[80]
Pinacolyl mehtylphosphonic acid	Bulk	3 Alkyl alkylphosphonic acids	Soil extract	[50]
Propazine	Precipitation	5 Triazines	Corn, potato, soil	[15]

As a result, MIPs emulate the interactions established by natural receptors to selectively retain a target molecule (i.e., antigen-antibody) but without the associated limitations on stability, such as cost and storage stability, etc.

This selectivity makes MIPs ideal materials for separation processes, and in recent years they have been widely used as SPE sorbents, namely, in molecularly imprinted solid-phase extraction (MISPE). MISPE was first applied by Sellergren in 1994, for the extraction of pentamidine from urine [68]. More recently, it has been used in the selective extraction or clean-up of target analytes from various complex (environmental, food, and biological) samples [21,44,45,63]. Several MIPs for

extracting a few, specific target compounds are already commercially available.

In the most commonly used approach, MIP synthesis involves solution complexation of the template with the functional monomer or monomers. These monomers must then be polymerized after a crosslinker has been added in the presence of an initiator. Following polymerization, the template molecules are removed by extensive washing steps so that interactions between the template and the functional monomer(s) are disrupted and the cavities, complementary to the template in shape, size, and position of the functional monomer, are made available. Therefore, the synthesis reagents must be carefully selected in order to create highly specific cavities.

The characteristics of the binding sites obtained by molecular imprinting depend on the interactions during polymerization. Interaction between the template molecule and the functional monomer determine the approach by which MIPs are synthesized. The most common is the non-covalent approach, in which interactions between the template and the functional monomer(s) are based on polar interactions, such as hydrogen bonds or electrostatic interactions. After synthesis, the template is easily removed by washing with a solvent or a mixture of solvents, with rebinding of the template to the MIP possible by exploiting non-covalent interactions.

In the semicovalent approach, covalent bonds are established between the template and the functional monomer before polymerization; once the template has been removed from the polymer matrix, the rebinding of the analyte to the MIP exploits non-covalent interactions, as per the non-covalent imprinting approach. When covalent bonds are established between the template and the functional monomer, the binding sites are better defined and more homogeneous than in the non-covalent approach. However, the latter is widely used to prepare MIPs because of the simplicity of the synthesis [15–17].

Several polymerization techniques have been evaluated [15–17,43,47], although most MIPs are prepared by a simple bulk polymerization process, as seen in Table 6. In this kind of polymerization, the polymer monolith is crushed, ground, and sieved to yield a fraction of particles of 25–50 μm in size, which are then packed either into disposable cartridges between two frits or in a small column for on-line MISPE coupled to LC [21]. In spite of its simplicity, this method has its drawbacks, since grinding and sieving are time-consuming and wasteful because only 30–50% of the ground polymer is recovered as useable material, and the particles obtained are of irregular sizes. Nonetheless, bulk polymerization remains the most widely used procedure [15–17].

In recent years, work has been carried out to obtain MIP beads with characteristic physical features, such as size, porosity, pore volume, or surface area. Precipitation [10,66,74], one-step or multi-step swelling [67], suspension [44,69], and grafting [73] polymerization also have been used to prepare MIPs for SPE.

With precipitation polymerization, micro- and nanospheres can be generated by accurately controlling the parameters that govern the polymerization, but this approach is generally not applicable to all polymerization mixtures. Moreover, the crosslinker and the porogen must be compatible if beads are to be generated instead of agglomerates (this may also be due to the influence of the template) [74]. The experimental procedure is quite simple although the disadvantage of this kind of polymerization is that the particle obtained must be large enough to be used in MISPE; however, the method has been successfully employed in the MISPE of propazine [15], nicotine [66], carbamazepine [10], 4-*n*-nonylphenol [59], etc.

Multi-step swelling and polymerization, as proposed by Haginaka's group [67], consists of swelling seed particles (polystyrene latex) using a micro-emulsion of a low molecular weight activating solvent (i.e., dibuthyl phthalate) in water containing a stabilizer in the presence of an initiator. Once the emulsion droplets have been adsorbed onto the seed particles, this dispersion is added to a second dispersion containing porogen, monomers, crosslinker, and the template dispersed in water, in the presence of a polymeric stabilizer such as polyvinylalcohol. This mixture is stirred for a few hours until the droplets are absorbed onto the seed particles. Finally, the dispersion is purged with an inert gas and polymerization starts. This technique is quite time consuming albeit sophisticated, and its applicability is limited to templates that can interact with monomers through strong electrostatic and hydrophobic interactions. However, it allows the production of monodispersed spherical particles over a size range of 5–100 μm and has been successfully used to obtain MIPs for atrazine [67] and other templates [42,43,47].

In all the polymerization techniques, several crucial variables affect the final characteristics of the MIP in terms of its capacity and selectivity for the target analyte. MIPs are usually prepared with methacrylic acid (MAA) [1,45] (other acrylates [80] or urea-based monomers [11] are used to a lesser extent) or 2- or 4-vinylpyridine (VP) [18,57] as the functional monomer, ethylene glycol dimethacrylate (EGDMA) as the crosslinker, and a non- to moderately polar and aprotic solvent, such as dichloromethane, toluene, chloroform, or acetonitrile, as the porogen. Thus, hydrogen-bond and electrostatic interactions are strongly favored in these media. The polar nature of the interactions between template and functional monomers explains the difficulty in applying MIPs directly to aqueous samples. However, recent studies have reported the use of polar and protic media, such as methanol, ethanol, and even water, for the synthesis of MIPs targeted for compounds able to engage in strong electrostatic interactions, such as methanol:water (4:1) for 1-naphthalene sulfonic acid [64] or methanol:water (9:1) for ofloxacin [72].

The ratio between reagents is also very important, and determination of the optimum MIP may take several weeks of trial-and-error experiments, using different ratios of template, monomer, and crosslinker [67,74], although combinational or computational approaches have also been used [22]. A study of the effects of reagents on the synthesis of a MIP for digoxin [61] revealed that an excess of functional monomer increases non-specific interactions and lowers polymer selectivity. The typical ratio is 1:4:20 (template:monomer:crosslinker molar ratio) but this may not be the optimal ratio.

One problem that has been pointed out in the MISPE literature on trace analysis is template bleeding. Despite the fact that in most of the papers dealing with MISPE, no template bleed-

ing has been described at the concentration levels under study. Therefore, although template bleeding may exist, it cannot be considered as being of any real importance for most applications. Regardless, one way of preventing the bleeding problem is to use a dummy molecule, which is a template analogue that resembles the target analyte in terms of shape, size, and functionalities but differs in chromatographic separation, in which case template bleeding does not interfere with quantification of the target analyte. This approach is currently used not only to prevent the template from leaking [23], but also to decrease synthesis costs when the template is expensive or difficult to achieve [48]. Another very interesting alternative is to use a stable-isotope-labeled compound as template. This was first proposed by Sambe et al. [65] for the preparation of a RAM-MIP for bisphenol A-d16 and applied to the direct injection of bisphenol A in serum combined with column-switching LC-MS. MIP can show cross-selectivity for compounds structurally related to the template molecule. Therefore, these polymers can be used for MISPE in compound-specific and group-specific extraction modes. Template selection is particularly crucial when the aim is to develop a MIP for class-selective extraction, as in the MISPE of triazines [15], organophosphorus nerve agent degradation products [50], benzodiazepines [1], sulfonylurea herbicides [75], fluoroquinolones [72], or parabens [60].

Prior to the use of a MIP in MISPE, its recognition properties for the target analyte or a group of structurally related analytes are usually checked. Chromatographic evaluation [11,75,80] and equilibrium batch experiments [11] are the most common methods to evaluate MIP selectivity. To do so, a non-imprinted polymer (NIP) is synthesized in the same way as the MIP but in the absence of template, so that the imprinting effect can be evaluated. The selectivities of the MIP and NIP are then compared. Since MISPE is no different from other SPE procedures, the common steps of conditioning, sample loading, clean-up, and elution are performed. During the conditioning step, the cavities of the MIP are activated in order to maximize the interactions with the target analyte in the sample.

The loading solvent is selected so that the analyte can rebind to specific sites, whereas the elution solvent must be capable of disrupting the analyte-polymer interaction. Before the elution step, a washing step is usually carried out to maximize the specific interaction between the analyte and MIP, with the simultaneous elution of interfering compounds that are non-specifically retained.

In the loading step, the loading solvent has a direct influence on the recognition properties of the MIP, and selectivity is higher when the sample is dissolved in the porogen solvent used in synthesis of the MIP [8,50]. As most MIPs are synthesized in non- to moderately polar and aprotic solvents, during percolation the target analyte can develop specific interactions in the cavities. These mainly hydrophilic interactions are typically of the hydrogen-bond and/or electrostatic type. Moreover, a washing step is generally carried out with the same solvent or with the addition of a small amount of a polar modifier in order to limit non-specific interactions of the target analyte with the external surface of the MIP.

Most samples (water, plasma, urine, etc.) are in aqueous media and since the majority of MIPs are prepared in non-aqueous media, the analyte and other interfering compounds are generally retained non-specifically on the polymer. Therefore, to achieve selective extraction, a washing step with an organic solvent is introduced prior to the elution [21,63]. Low-polar solvents, such as dichloromethane, toluene, and chloroform [17], are the most common, but polar solvents, such as acetonitrile and methanol, have also been used [9]. The elution solvent is usually a protic and polar solvent, such as methanol, with the possible addition of an acid or basic modifier to disrupt hydrogen bonds and electrostatic interactions [11,19,21].

In recent years, an increasing number of studies have involved the direct application of water-compatible MIPs to water samples [18,23]. Figure 2 compares the chromatogram of 50-ml extracts of human urine after SPE with Oasis HLB and a MIP synthesized for carbamazepine, in which the higher selectivity of the MIP is clearly demonstrated.

When the MIP is not water compatible and aqueous samples are to be analyzed, a two-step MISPE can be carried out. In the first step, the sample is extracted with a conventional SPE sorbent (polymeric, silica, RAM) while in the second the

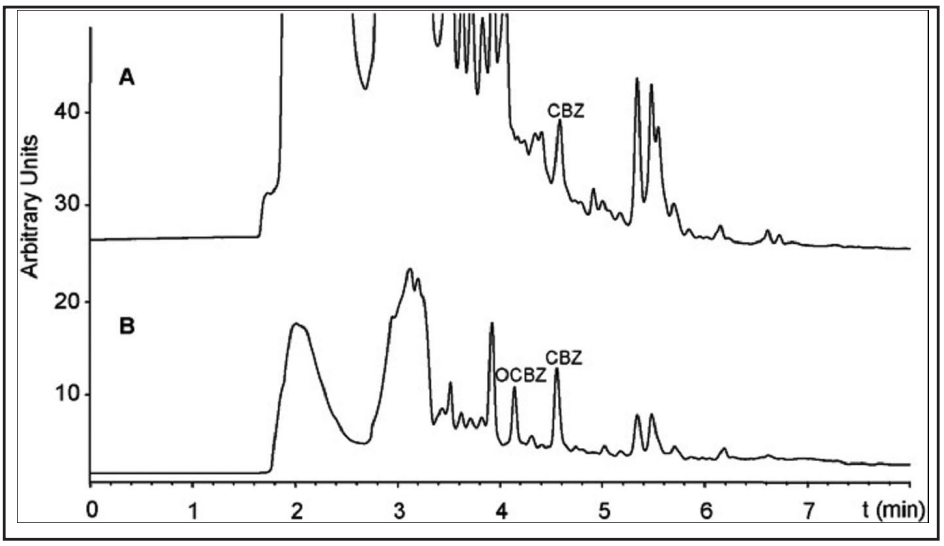


Fig. 2. Chromatograms of SPE extracts obtained after percolation of 50 ml of human urine spiked with 0.05 mg each of carbamazepine and oxocarbamazepine/l through Oasis HLB (**A**) and MIP (**B**) with a clean-up step using 10 ml of water (pH ~12) [10].

analytes are eluted with a MIP-compatible solvent, which is passed though the MIP for selective extraction. Several examples of a conventional sorbent combined with MIP are described in the literature [9,19,23].

When the MISPE (one- or two-step) is highly selective, there is no need for commonly used chromatographic techniques as, instead, the extract can be directly analyzed with the detection system. This was possible for the direct determination of pentamidine in urine samples and detection by UV [68], and of ciprofloxacin from urine by MS, after a two-step extraction using an Oasis HLB cartridge and a MIP synthesized with ciprofloxacin as template [20].

The selectivity of MISPE is also a clear advantage when LC-MS is further applied for quantification, since it reduces the typical ion suppression usually present in electrospray ionization. For instance, when a hydrophilic-lipophilic balanced sorbent, a mixed-mode sorbent, and a MIP were compared for the extraction of amphetamines from wastewater, the best performance was achieved with the MIP in terms of selectivity, resulting in lower matrix effects as well as better limits of detection (LODs), accuracy, and precision [41]. Another recent example, in which antidepressants in environmental waters were determined [25], also showed cleaner extracts with MIP and lower ion suppression.

Most of the MISPE-based analytical methods are performed in the off-line mode, but there are some that are performed on-line coupled to LC [17,45,57]. The first on-line application [57] was described for the selective extraction of 4-NP from river water samples. However, the elution solvent required elution of the analytes from the MIP precolumn, which is not always compatible with the mobile phase required to separate the analytes.

MIPSE has been applied in the determination of a wide range of compounds in samples as varied as water, soil extract, urine, serum, plasma, blood, hair extract, tissue, food, medicinal plants [21,43,47,78], etc. Table 6 lists several examples of applications involving different types of samples. It is not exhaustive but does provide an overview of the many recent applications. As can be seen in the table, in some cases the template molecule used in MIP synthesis is the target analyte [45,57]. In most cases, however, the MIP shows cross-selectivity and both the template and several structurally related molecules are extracted [1,18,25]. An interesting example is the cross-selectivity of MIPs synthesized using 4-chlorophenol, with cross-selectivity for 4-chlorophenols and 4-NP in the extraction of river water and using a washing step of dichloromethane [17].

Another interesting application is the use of MIPs to clean up complex matrices after a previous extraction step. In solid matrices, the dry extract obtained after Soxhlet extraction, microwave-assisted extraction, ultrasonic, or pressurized liquid extraction is diluted in a solvent close to the porogen and is percolated through the MIP. For example, when nonylphenols and ethoxylated derivatives were determined in sediment and sludge, MIPSE was applied after microwave-assisted extraction [59]; after sonication, to determine clortriazines in soil, potato, and corn [15] and parabens in soil [60]; or after hot pressurized water extraction, to determine the degradation products of an organophosphorus nerve agent in soils [50].

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About the group

The Chromatography and Environmental Applications research group belongs to the Department of Analytical and Organic Chemistry, located within the Faculty of Chemistry at the Rovira i Virgili University in Tarragona (Catalonia). From the group's beginning, in the 1990s, its aims have been to determine and control organic pollutants in environmental and biological samples, using new extraction techniques combined with latest-generation chromatographic techniques. From 2000, the group has been awarded as a Consolidated Research Group honorary mention by the Government of Catalonia, and it has been certified according to the ISO 9001-2008 regulations of May 2009 by TÜV Rheinland Iberica for the introduction of a Quality Management System in its research laboratories.

The group's research focuses on four different lines: (a) the development of new methods for the determination of pollutants in solid, aqueous, and atmospheric environmental samples, applying new extraction techniques combined with chromatographic separation techniques and mass spectrometry; (b) the development and application of new polymeric materials for extraction techniques in order to improve their capacity and/or selectivity; (c) the application of capillary electrophoresis to the determination of different compounds in biological or environmental samples; and (d) the development of new methods for the determination of different radioisotopes in environmental samples. Web site of the group [http://www.quimica.urv.es/~gcroma/].