

# Molecularly Imprinted Polymers: Developments and Applications of New Selective Solid-Phase Extraction Materials

Florence Chapuis, Valérie Pichon and Marie-Claire Hennion,

Department of Environmental and Analytical Chemistry, Ecole Supérieure de Physique et de Chimie Industrielles, Paris, France.

Molecularly imprinted polymers (MIPs) are synthetic polymeric materials possessing specific cavities designed for a target molecule. By a mechanism of molecular recognition, MIPs are used as selective sorbents for solid-phase extraction of target analytes from complex matrices. The various parameters affecting extraction selectivity are discussed and the potential of MIPs as selective sorbents is reviewed through recent applications.

## Introduction

Trace determination of organic contaminants in complex matrices requires a sample pretreatment. Solid-phase extraction (SPE) is routinely used for the extraction of compounds from liquid or solid matrices. Despite their attractive features, classic SPE sorbents retain analytes by non-selective hydrophobic interactions that lead to a partial coextraction of interfering substances. To enhance extraction selectivity new selective materials based on molecular recognition were recently developed. These are composed of immunosorbents (ISs) whose affinity and selectivity stem from antigen-antibody interactions. Therefore, they allow a selective extraction of the target analyte and of similarly structured compounds. Several reviews have recently highlighted the interest in immunosorption as a selective sample pretreatment method.<sup>1-3</sup> However, the development of ISs is time consuming and relatively expensive. These drawbacks have contributed to the recent development of molecularly imprinted polymers (MIPs).

MIPs are synthetic polymeric materials with specific cavities designed for a template molecule. The retention mechanism involved is based on molecular recognition. MIPs have been successfully used in several fields including sensors, organic synthesis and enantiomeric separation.<sup>4</sup> They are often called synthetic antibodies in comparison with ISs. Indeed, both have comparable selectivities but MIPs offer better handling and stability and are cheaper and easier to prepare.<sup>5</sup>

The use of MIPs as selective sorbents for SPE is a recent development. The first application was performed by Sellegren et al. in 1994 for the extraction of pentamidine from

urine.<sup>6</sup> Today, MIPs are being applied to the selective extraction or clean-up of target analytes from various complex matrices (Table 1). Many examples in the pharmaceutical domain deal with the extraction of a drug from plasma,<sup>7-13</sup> serum<sup>14-15</sup> and urine.<sup>6,16-19</sup> In the environmental field, MIPs were mainly developed for the selective extraction of a particular class of pollutants including phenolic compounds in river water,<sup>20-21</sup> triazines and phenylureas from soil or plant extracts,<sup>22-25</sup> surface waters<sup>23,25-29</sup> and food matrices.<sup>24-25,30</sup>

The principle of selective extraction on MIPs is the same as with an immunosorbent. After a conditioning step, the sample is percolated through the MIP and then a washing step removes interfering compounds that were partially retained. The desorption of analytes is achieved by percolating a solvent able to disrupt the selective interactions involved between the MIP and the target analyte. The principle of synthesis is presented in this article and parameters affecting the selectivity are discussed. For this, the sorbent capacity and choice of extraction solvents were studied. Finally, the selectivity obtained with MIPs is illustrated by various applications.

## Choice of the Reagents

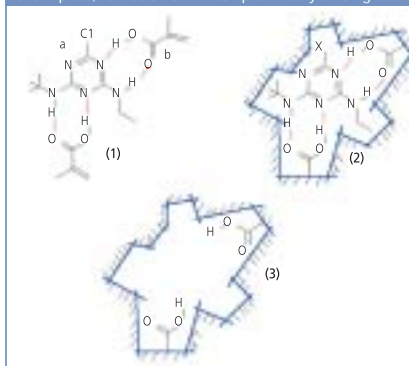
The molecular imprinting step is crucial for obtaining optimal selectivity. Specific cavities must be designed for the template molecule. For this reason, monomers are chosen to develop strong interactions with the target analyte (or a structural analogue) acting as the template in a porogen solvent. In the presence of a large amount of cross-linking agent, polymerization takes place around the template molecules. At the end of the polymerization process, the templates are

removed to produce a polymer with binding sites complementary to the template in size and shape. In solid-phase extraction, the most common approach consists of a non-covalent imprinting. Only an MIP was synthesized by semi-covalent approach for the extraction of phenolic compounds from river water<sup>20</sup> but the authors underlined no clear imprinting effect of this MIP by comparison with the non-covalent MIP synthesized with the same monomers and template. Figure 1 illustrates the principle of non-covalent synthesis of a triazine MIP used for selective SPE. The polymerization solvent is weakly polar and aprotic allowing the generation of polar interactions between the template and the monomers, such as hydrogen bonds or electrostatic interactions.

Most of the reported MIPs have been prepared by bulk polymerization. Nevertheless, other methods of polymerization can be used including suspension, emulsion, two-step swelling and precipitation. These various methods were recently compared under the same conditions to assess rebinding characteristics.<sup>31</sup> Concerning the use of MIPs for the extraction, two MIPs were prepared by suspension for the extraction of triazines<sup>32</sup> and phenobarbital<sup>33</sup> and one extraction of bisphenol A was performed with an MIP prepared by two-steps swelling.<sup>34</sup>

In non-covalent imprinting, the porogen solvent is one of the most important factors determining effective molecular recognition<sup>35</sup> because the accuracy of the assembly from the template and monomer is related by the physical and chemical parameters of the solvent. For most MIPs used in SPE, weakly polar and aprotic solvents, such as dichloromethane, chloroform or toluene are used for obtaining a relatively stable complex between template and monomers. Furthermore, the template must be carefully selected because its removal can be incomplete. A "bleeding" of this molecule during the SPE process can then be observed leading to false positives in the quantification of the template in real samples. This problem can

Figure 1: Principle of synthesis of a non-covalent MIP. (a) triazine, (b) methacrylic acid. (1) Complexation between monomers and template, (2) polymerization of functional monomers with cross-linkers around the template, (3) removal of template, formation of the complementary binding sites.



MIPs have been successfully used in several fields including sensors, organic synthesis and enantiomeric separation.

be overcome using a "dummy template", which is structurally related to the target analyte.<sup>10,14,33-34,36-38</sup> As Spivak et al. proved,<sup>39</sup> there is a real shape selectivity in non-covalent MIP. Consequently, the choice of template is particularly important for producing MIPs dedicated to the selective extraction of a group of structurally related compounds. This was clearly demonstrated for the selective extraction of triazines.<sup>24</sup> Extraction recoveries obtained with terbutylazine MIPs and an ametryn MIP are reported in Table 2. The ametryn MIP strongly retains all the triazines including their two metabolites with extraction recoveries between 72 and 100% for each analyte (with the exception of terbutryn). In contrast, low extraction recoveries were obtained for thiotriazines on the terbutylazine MIPs. By molecular modelling of studied triazines, these results could be directly related to the structure of the compounds and to the electric charge distribution.<sup>24,40</sup>

Although the synthesis of MIPs is mainly based on the use of methacrylic acid monomer (MAA) or vinyl pyridine monomer (VP), other polymers have been developed for a better optimization MIP selectivity. Sellegren et al. recently established a technique for high-throughput synthesis and evaluation of large groups of polymers.<sup>7</sup> The principle of this new procedure is described in Figure 2. The synthesis is performed *in situ* in the reaction vessels of a 96-well plate. A library of 80 polymers can thus be prepared in a very short time and a complete evaluation of binding properties can be assessed in one week. This technique was applied to the optimization of MIP synthesis for the extraction of bupivacaine. A computational method for a custom synthesis of MIP can be considered as another approach. By using molecular modelling software, a virtual library of functional monomers was designed and screened against the template to identify the best monomers for imprinting. A microcystin MIP and tylosin MIP were synthesized by selecting monomers in this way.<sup>41-42</sup>

## Binding Characteristics of the MIP

When using MIPs in SPE, it is important to estimate the capacity value that corresponds to the maximum amount of a compound that can be retained on the MIP for a given extraction procedure. These binding characteristics can be evaluated by constructing a saturation curve. This curve is obtained by loading constant volumes of a sample spiked with increasing amounts of target analyte through the MIP cartridge. The amount of extracted analyte is reported as a function of the amount of analyte present in the percolated sample. Figure 3 is a binding saturation curve obtained on a terbutylazine MIP with a percolated volume of 5 mL.<sup>24</sup> The curve presents a linear part corresponding to an extraction with a recovery of 100% for a sample containing up to 60 µg of target analyte and tends to reach a plateau corresponding to the saturation of binding sites. The amount of atrazine bound to the MIP was estimated at 2 µmol of atrazine per gram of polymer. By comparison with immunosorbents, the capacity value for MIPs is thirty times higher.<sup>1</sup> In an attempt to estimate the binding properties of the MIP, equilibrium binding experiments can be performed and the obtained data can be

processed with Scatchard equations.<sup>43–45</sup> In each instance, the Scatchard analysis confirmed the heterogeneous population of binding sites for non-covalent polymers resulting from the low association constant between the monomer and the template.

Recently, researchers have used a method based on the Freundlich adsorption isotherms to assess the affinity distribution of MIPs by introducing a heterogeneity parameter, assuming a continuous range of affinity constants.<sup>46–47</sup>

**Table 1:** Applications of MIPs for solid-phase extraction used in off-line or on-line procedures. AA: acrylamide, AMPSA: 2-acrylamido-2-methyl-1-propanesulphonic acid, CHCl<sub>3</sub>: chloroform, CH<sub>2</sub>Cl<sub>2</sub>: dichloromethane, DEAE: diethylamino ethyl methacrylate, EtOH: ethanol, H<sub>2</sub>O: water, MAAM: methacrylamide, MAA: methacrylic acid, MASE: microwave assisted solvent extraction,

Target analytes	Template	Matrices	Monomer/solvent
Alkyl-phosphonates	Pynacoliii-methylphosphonate	Human serum	MAA/MeCN
Bisphenol A	Terbutylphenol	Surface water	4-VP, two steps swelling polymerization
Bupivacaine	Bupivacaine	Plasma	MAA/toluene
Caffeine	Caffeine	Urine, coffee, drinks	MAA/MeCN
Cephalexin	Cephalexin	Plasma, serum	TFMAA/MeCN
Ceramide	Ceramide	Yeast	Monomers mixture/ toluene-heptane, <i>in-situ</i>
Chloramphenicol	Chloramphenicol	Ophthalmic solution, milk	DEAE/THF
Chlorophenols, nitrophenols	4-chlorophenol, 4-nitrophenol	River water	4-VP/MeCN
Chlorophenoxy acetic acids	Trichlorophenoxy acetic acid	River water	4-VP/ MeOH-H <sub>2</sub> O
Clenbuterol	Clenbuterol	Urine	MAA/MeCN
	Clenbuterol	Liver, urine, milk	MAA/MeCN
Darifenacin	Darifenacin	Plasma	MAA/ THF, ethyl acetate
Harmine, Harmaline		Seeds	MAA/ toluene-MeCN, MeCN, THF
Ibuprofen	Naproxen	Plasma	4-VP/ hydro-organic mixture, RAM-MIP
Metformin	Metformin	Plasma	TFMAA/MeCN
Nicotine	Nicotine	Nicotine chewing gum	MAA/CHCl <sub>3</sub>
Pentamidine	Pentamidine	Urine	MAA/propanol
Phenobarbital	Amobarbital	Urine, medicines	MAA/CHCl <sub>3</sub> suspension polymerization
Phenytoin	Phenytoin	Plasma	MAAM/ MeCN-THF
Phenylureas	Isoproturon	Surface water	MAA/toluene
	Fenuron	Plant samples	MAA/toluene
Quercetin	Quercetin	Red wine	4-VP/MeCN
	Quercetin	Plasma	AA/THF
	Piceatannol	Medicinal herb	4-VP/MeCN-THF
Sameridine	Sameridine	Plasma	MAA/toluene
Scopolamine	Hyoscyamine	Urine, serum	MAA/toluene
Sulfonylureas	Metsulfuron-methyl	Water and soil	TFMAA/CH <sub>2</sub> Cl <sub>2</sub>
Theophylline	Theophylline	Serum	MAA/CH <sub>2</sub> Cl <sub>2</sub>
Triazines	Atrazine	Beef liver	MAA/CHCl <sub>3</sub>
	Terbutylazine	Water surface and sediment	MAA/CH <sub>2</sub> Cl <sub>2</sub>
	Terbutylazine	Humic acid	MAA/toluene
	Terbutylazine	Water surface	MAA/toluene
	Terbutylazine	Water surface, grape juice, soil	MAA/CH <sub>2</sub> Cl <sub>2</sub>
	Pirimicarb	Water surface	MAA/CHCl <sub>3</sub>
	Propazine	Water, soil, corn	MAA/toluene
	Simazine	Humic acid, urine	MAA/CH <sub>2</sub> Cl <sub>2</sub>
Tylosin and metabolites	Tylosin	Broth samples	Monomers mixture/ THF
Verapamil	Verapamil	Urine	MAA/CHCl <sub>3</sub>

### Applications

It has been largely demonstrated that MIPs offer the highest selectivity when samples are dissolved in the solvent used for the MIPs preparation.<sup>35</sup> As most MIPs are synthesized in

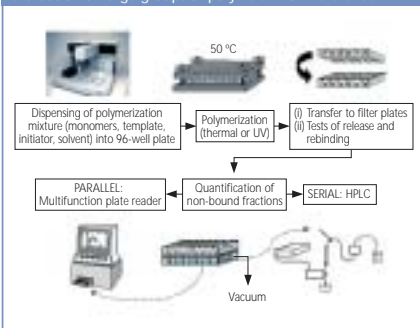
organic solvent, MIPs seem to be well adapted to the clean-up of complex matrices. During the percolation of organic sample, the target analyte develops specific interactions in the cavities similar to those developed during MIP synthesis. A washing

Sample pretreatment	mode	ref
Centrifugation and liquid–liquid extraction with MeCN	off	54
No	off	34
Dilution in citrate buffer	off	7
Dilution in water	on	16
SPE (C <sub>18</sub> )	on	8
Extraction in CHCl <sub>3</sub> /MeOH	on	55
Sol.: dilution in phosphate buffer. Milk: precipitation with acid, centrifugation	on	56
Acidification	on	20, 21
Acidification	off	57
No	off	17
Liquid–liquid extraction (On column, elution hexane/CH <sub>2</sub> Cl <sub>2</sub> )	off	18
Precipitation with MeCN, centrifugation	off	9
Soxhlet extraction (EtOH)	on	37
No	on	10
Precipitation with MeCN, centrifugation	on	11
Extraction in ethyl acetate/NH <sub>3</sub>	off	58
Dilution in buffer, MeCN	off	6
Dilution in water	off	33
No	off	12
SPE (PS-DVB)	off	26
Extraction in MeCN, centrifugation	off	22
No	off	59
Dilution in acetic acid	off	60
Extraction by EtOH, liquid–liquid extraction (various organic solvents)	on	61
Liquid–liquid extraction (heptane)	off	13
Serum: precipitation with MeCN, centrifugation	off	14
Urine: acidification		
Addition of EDTA	off	50
Liquid-liquid extraction (CHCl <sub>3</sub> )	on	15
Extraction in CHCl <sub>3</sub>	off	30
Water: no. Soil: soxhlet extraction (MeOH)	off	23
SPE (RAM)	on	49
SPE (C <sub>18</sub> )	off	27
Soil: MASE	off	24, 28
Liquid: no		
No	off	29
Water: SPE (PS-DVB). Soil, corn: extraction in MeCN	off	25
SPE (C <sub>18</sub> )	on	48
Dilution in MeOH	off	42
SPE (RAM)	on	19

step is generally achieved by the same solvent and compounds are further desorbed by a protic and polar solvent, such as methanol, for disrupting hydrogen bonds. An organic acid can be added to the polar elution solvent to disrupt the residual electrostatic interactions. The biggest problem in the establishment of an extraction procedure on MIPs is to have a specific retention. To evaluate the rate of non-specific retention on MIPs, the extraction procedure is also applied on a non-imprinted polymer. The latter is obtained by performing the synthesis procedure without a template. Consequently, a real optimization must be performed to remove the overall interactions on the non-imprinted polymer while retaining high extraction recoveries on the MIP. The extraction recoveries in Table 2 were obtained by percolating a dichloromethane sample containing 1% MeOH. MeOH prevented the initiation of non-specific interactions during the extraction and thus highlighted the effect of the template on selectivity. Without 1% MeOH, both MIPs retain all studied compounds with an extraction recovery close to 100% because a large part of interactions are non-specific. It is also very important to assess a specific retention and not overestimate the capacity value. The saturation curve from Figure 3 was established by applying the previous optimized procedure. It thus allowed the estimation of specific binding sites. It must be kept in mind that the advantage of using MIP in SPE is selectivity. Therefore, if the applied procedure on MIPs is not selective, their use is not justified over a hydrophobic sorbent.

Feng et al. introduced an alternative method to minimize non-specific interactions by percolating picric acid during the washing step of a metformin extraction from plasma using metformin MIP.<sup>11</sup> Others adapted the volume and nature of the washing solvents. The potential of the MIPs for the purification of solid matrices is illustrated in Figure 4 for the clean-up of a soil extract containing triazines on a terbutylazine MIP when compared with an immunosorbent. It is interesting to compare MIPs and ISs in terms of selectivity because ISs have largely been used for multiresidue analysis of pesticides. The interfering compounds are easily removed by purification through the MIPs allowing an easy identification and quantification of the three spiked compounds. In addition, the chromatogram obtained following immuno clean-up showed

Figure 2: Procedure for high-throughput synthesis and evaluation of large groups of polymers. From reference 7.



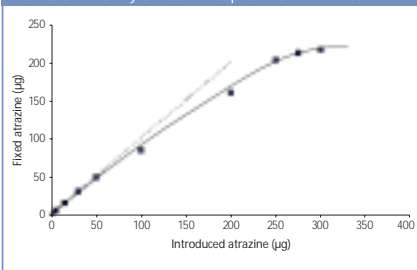
### The use of combinatorial screening is certainly an efficient tool to develop more selective MIPs with new monomers.

that the selectivity benefits of MIPs are similar to those using IS. The MIP cavities can be considered as synthetic antibodies for this application.

As is shown in Table 1, many MIPs have also been used for the purification of extracts from various aqueous matrices, such as surface waters or biological samples. The same principle is adopted here, as it is for the solid matrices: a pretreatment step using classic SPE sorbent or liquid-liquid extraction is performed before percolation on the MIP to dissolve the compounds in an appropriate organic solvent. As an example, Brambilla et al. used a clenbuterol MIP for the clean-up of this drug from urine following its liquid-liquid extraction on column.<sup>18</sup> The resulting chromatogram is shown in Figure 5. With an extraction recovery close to 100% on the MIP and no retention on the non-imprinted polymer, this application confirms the real potential of MIPs for purification. In most instances, the MIP is packed in a cartridge or a column and used off-line. However, applications in on-line mode using a multidimensional on-line sample preparation were developed for the extraction of triazines<sup>48,49</sup> or drugs from biological fluids<sup>8,19</sup> using conventional sorbent such as C<sub>18</sub> silica,<sup>48,8</sup> or RAM (restricted access material)<sup>49,19</sup> before their on-line clean-up on the MIP.

The direct extraction of compounds from aqueous matrices on MIPs is more difficult. During percolation of the water sample, trace compounds can not be retained by the polar selective interactions that are developed in the solvent of synthesis (specially by hydrogen bonds that are too weak in aqueous medium). The retention mainly occurs by non-selective hydrophobic interactions with the polymeric matrix. However, Ferrer et al.<sup>23</sup> proposed a procedure to directly extract triazines from real water using a MIP synthesized in dichloromethane with methacrylic acid as monomer. In this procedure non-specific interactions are transformed into specific hydrophilic interactions (hydrogen bonds) by applying

Figure 3: Curves of capacity obtained after the percolation of 5 mL dichloromethane-methanol (99:1) mixture spiked with increasing amount of atrazine on the terbutylazine MIP (130 mg). The dotted line corresponds to a slope of 1, meaning an extraction recovery of 100%. Adapted from reference 24.

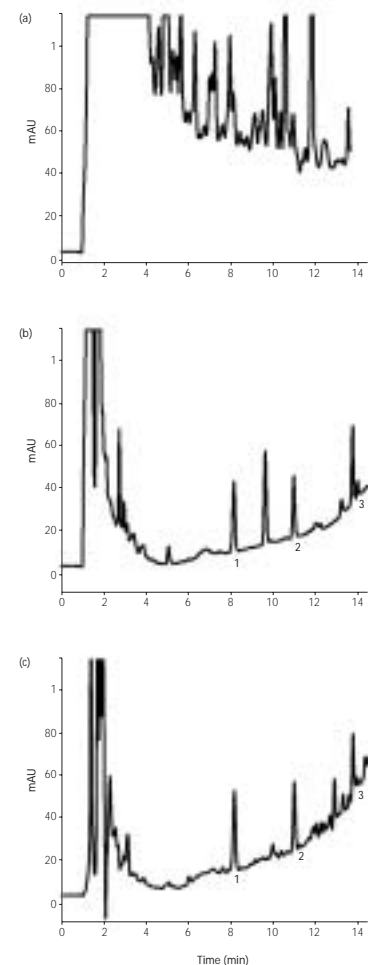


a small volume of a weakly polar and aprotic solvent after aqueous sample percolation. Though the selectivity of MIPs was demonstrated with real samples, poor recoveries were obtained compared with those obtained with pure water samples. Other groups have attributed this matrix effect to the presence of divalent cations in real water and, in particular, calcium ions that cause an ion-exchange with the hydrogen of the carboxyl groups of the MIP, thus preventing subsequent specific interactions.<sup>28</sup> This matrix effect has been removed by introducing an acid washing step after the percolation of sample water or by adding EDTA to complex inorganic cations.<sup>50</sup> Figure 6 presents the results of the direct and selective extraction of triazines from an industrial effluent on a terbutylazine MIP after including an acid washing. The results obtained on MIP were compared with those obtained using a classic PS-DVB (polystyrene divinylbenzene) sorbent. The sample was also spiked with phenylureas that are similar pesticides to triazines in terms of size and polarity, to demonstrate the specificity of the MIP. The extraction recoveries of triazines are virtually 100% on the MIP indicating the complete removal of matrix effect. Using the PS-DVB sorbent many interfering substances and phenylureas have been retained and can be seen in the chromatogram [Figure 6(a)]. By using MIPs, a significant portion of interfering compounds has been removed and phenylureas do not show up demonstrating the high selectivity of MIPs [Figure 6(b)]. For instance, the direct extraction of triazines from real waters by MIP coupled on-line to HPLC was not performed. Only phenolic compounds were directly extracted by MIP in on-line mode.<sup>20,21</sup> In pharmaceuticals, a preliminary extraction step is necessary to remove proteins from samples. Hence, literature describes extractions with MIP in on-line mode only for clean-up.

Table 2. Extraction recoveries (%) obtained on the ametryn and terbutylazine MIPs and on the non-imprinted polymer for triazines after the percolation of 10 mL of a dichloromethane-methanol (99:1) mixture spiked with 500 ng of each analyte (n = 3, RSD varied between 0 and 8%). DET: deethylterbutylazine. DIA: deisopropylatrazine. Adapted from [24].

MIP	Ametryn	Terbutylazine	Non-imprinted
Ametryn	78	26	0
Prometryn	81	31	0
Terbutryn	60	25	0
Chlorotriazines			
Simazine	93	100	1
Cyanazine	82	100	1
Atrazine	88	100	0
Sebutylazine	72	98	1
Propazine	87	100	0
Terbutylazine	77	100	1
Metoxytriazines			
Prometon	100	100	1
Metabolites			
DET	100	100	2
DIA	98	97	9

Figure 4: Chromatograms obtained after microwave assisted extraction of a soil containing 20 ng/g of triazines. (a) direct injection of the extract, (b) extract dissolved in CH<sub>2</sub>Cl<sub>2</sub>/MeOH (99:1) mixture and purified on terbutylazine MIP, (c) extract dissolved in water/MeOH (98:2) mixture and purified on antitriazines immunosorbent.



Peaks: 1 = atrazine, 2 = simazine, 3 = terbutylazine. UV detection at 220 nm. Adapted from reference 24.

The only direct extraction in on-line mode was performed by Haginaka et al. who had prepared a RAM-MIP to simultaneously remove proteins and extract ibuprofen from plasma.<sup>10</sup>

### Prospectives

Many successful applications have proved that the use of molecularly imprinted polymers for selective solid-phase extraction is a powerful method for the clean-up and the direct selective extraction of trace level compounds from various complex matrices. The commercial availability of MIPs is imminent; in fact, a Swedish start-up company (MIP Technologies AB, Lund, Sweden) is already producing a clenbuterol MIP and proposes to develop custom-made phases. In parallel, many academic research teams synthesize their own MIPs for the development of new selective extraction methods of various molecules of interest, such as drugs for the pharmaceutical industry or organic micropollutants for environmental purposes. In contrast, MIP can be limited in terms of selectivity because of the nature of selective interactions that take place during the extraction. The MIPs are commonly synthesized with vinyl or acrylic monomers and generate selective interactions based on hydrogen or electrostatic bonds. Consequently, the use of MIP for direct extraction from aqueous samples requires a comprehensive investigation into the retention mechanism to optimize the extraction procedure. In addition, polar compounds that reach the specific cavities and develop interactions with the binding sites can be retained on MIPs. The use of combinatorial screening is certainly an efficient tool to develop more selective MIPs with new monomers. Nowadays, we tend to develop short time analysis and MIPs should find room in analytical chemist's toolboxes if they can be used in throughput analysis. The use of MIPs in on-line mode is already established and a MIP was recently conditioned in 96-well plates for the solid-phase extraction of a pharmaceutical compound from plasma.<sup>51</sup> At last, by their high capacity value, MIPs have a high potential to be used in miniaturized system, such as the coating on a SPME (solid-phase microextraction) fibre<sup>52</sup> and in electrochromatography<sup>53</sup> where promising results can be seen.

Figure 5: Chromatograms resulting from the extraction on clenbuterol MIP from (a) blank urine and (b) urine spiked with 5 ppb clenbuterol. Adapted from reference 18.

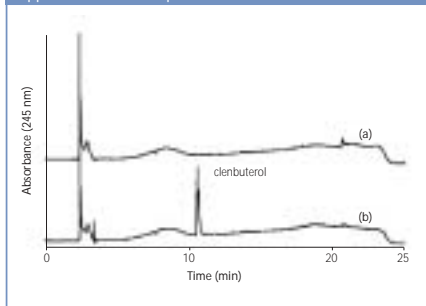
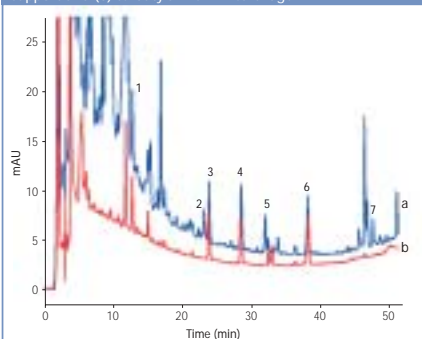


Figure 6: Chromatograms obtained after the preconcentration of 50 mL of a diluted industrial effluent spiked at 1 µg/L with a mixture of triazines and phenylureas through the (a) PS-DVB support and (b) terbutylazine MIP cartridge.



Peaks: 1 = DEA, 2 = monuron, 3 = DET, 4 = atrazine, 5 = diuron, 6 = terbutylazine, 7 = neburon. UV detection at 220 nm. From reference 28

### References

- M.C. Hennion and V. Pichon, *J. Chromatogr. A*, **1000**, 29 (2003).
- D.S. Hage, *J. Chromatogr. B*, **715**, 2 (1998).
- V. Pichon, M.C. Hennion, in: J. Pawliszyn (Ed.), *Sampling and Sample Preparation for Field and Laboratory, Comprehensive Analytical Chemistry*, Vol. XXVII, (Elsevier, Amsterdam, The Netherlands, 2002) p 1081.
- K. Haupt, *Anal. Chem.*, **75**, 376 A (2003).
- J. Svenson and I.A. Nicholls, *Anal. Chim. Acta*, **435**, 19 (2001).
- B. Sellergren, *Anal. Chem.*, **66**, 1578 (1994).
- B. Dirion et al., *J. Am. Chem. Soc.*, **125**, 15101 (2003).
- E.P.C. Lai and S.G. Wu, *Anal. Chim. Acta*, **481**, 165 (2003).
- R.F. Venn and R.J. Goody, *Chromatographia*, **50**, 407 (1999).
- J. Haginaka and H. Sanbe, *Anal. Chem.*, **72**, 5206 (2000).
- S.Y. Feng, E.P.C. Lai et al., *J. Chromatogr. A*, **1027**, 155 (2004).
- A. Berezcki et al., *J. Chromatogr. A*, **930**, 31 (2001).
- L.I. Andersson, A. Paprica and T. Arvidsson, *Chromatographia*, **46**, 57 (1997).
- G. Theodoridis et al., *J. Chromatogr. A*, **987**, 103 (2003).
- W.M. Mullet and E.P.C. Lai, *Anal. Chem.*, **70**, 3636 (1998).
- G. Theodoridis et al., *J. Chromatogr. A*, **1030**, 69 (2004).
- C. Berggren et al., *J. Chromatogr. A*, **889**, 105 (2000).
- G. Brambilla et al., *J. Chromatogr. B*, **759**, 27 (2001).
- W.M. Mullet et al., *J. Chromatogr. B*, **801**, 297 (2004).
- E. Caro et al., *J. Chromatogr. A*, **963**, 169 (2002).
- E. Caro et al., *J. Chromatogr. A*, **995**, 233 (2003).
- F.G. Tamayo, J.L. Casillas and A. Martin-Esteban, *Anal. Chim. Acta*, **482**, 165 (2003).
- I. Ferrer et al., *Anal. Chem.*, **72**, 3934 (2000).
- F. Chapuis et al., *J. Chromatogr. B*, **804**, 93 (2004).
- E. Turiel et al., *Anal. Chem.*, **73**, 5133 (2001).
- A. Martin-Esteban, E. Turiel and D. Stevenson, *Chromatographia Supplement*, **53**, S434 (2001).
- T. Pap et al., *J. Chromatogr. A*, **973**, 1 (2002).
- F. Chapuis et al., *J. Chromatogr. A*, **999**, 23 (2003).
- M.L. Mena et al., *Anal. Chim. Acta*, **451**, 297 (2000).
- M.T. Muldoon and L.H. Stanker, *Anal. Chem.*, **69**, 803 (1997).
- N. Perez-Moral and A.C. Mayes, *Anal. Chim. Acta*, **504**, 15 (2004).
- J. Matsui et al., *Anal. Commun.*, **34**, 85 (1997).
- S.G. Hu, S.W. Wang and X.W. He, *Analyst*, **128**, 1485 (2003).
- T. Kubo et al., *J. Chromatogr. A*, **987**, 389 (2003).
- K. Yoshizako et al., *Anal. Chem.*, **70**, 386 (1998).
- J. Matsui, K. Fujiwara and T. Takeuchi, *Anal. Chem.*, **72**, 1810 (2000).
- J. Xie, L. Zhu and X. Xu, *Anal. Chem.*, **74**, 2352 (2002).

- B. Dirion et al., *Chromatographia*, **56**, 237 (2002).
- D.A. Spivak, R. Simon and J. Campbell, *Anal. Chim. Acta*, **504**, 23 (2004).
- N. Delaunay-Bertoncini, V. Pichon and M.C. Hennion, *J. Chromatogr. A*, **999**, 3 (2003).
- I. Chianella et al., *Biosens. Bioelectron.*, **18**, 119 (2003).
- S. Piletsky et al., *Anal. Chim. Acta*, **504**, 123 (2004).
- Q. Z. Zhu et al., *Anal. Chim. Acta*, **468**, 217 (2002).
- J. Matsui et al., *Anal. Chem.*, **67**, 4404 (1995).
- T. Zhang et al., *Anal. Chim. Acta*, **450**, 53 (2001).
- C. Baggiani et al., *Anal. Chim. Acta*, **504**, 43 (2004).
- A.M. Rampety et al., *Anal. Chem.*, **76**, 1123 (2004).
- B. Bjarnasson, L. Chimuka and O. Ramström, *Anal. Chem.*, **71**, 2152 (1999).
- R. Koeber et al., *Anal. Chem.*, **73**, 2437 (2001).
- Q.Z. Zhuf et al., *Environ. Sci. Technol.*, **36**, 5411 (2002).
- C. Chassaing et al., *J. Chromatogr. B*, **804**, 71 (2004).
- E.H.M. Koster et al., *Anal. Chem.*, **73**, 3140 (2001).
- P. Spiegel, L. Schweitz and S. Nilsson, *Electrophoresis*, **24**, 3892 (2003).
- M. Zi-Hui and L. Qin, *Anal. Chim. Acta*, **435**, 121 (2001).
- M. Zhang et al., *J. Chromatogr. A*, **984**, 173 (2003).
- M.L. Mena et al., *Anal. Bioanal. Chem.*, **376**, 18 (2003).
- C. Baggiani et al., *J. Chromatogr. A*, **938**, 35 (2001).
- A. Zander et al., *Anal. Chem.*, **70**, 3004 (1998).
- A. Molinelli, R. Weiss and B. Mizaikoff, *J. Agric. Food Chem.*, **50**, 1804 (2002).
- J. Xie et al., *J. Chromatogr. B*, **788**, 233 (2003).
- L. Zhu, L. Chen and X. Xu, *Anal. Chem.*, **75**, 6381 (2003).

Florence Chapuis is a PhD student in the Department of Environmental and Analytical Chemistry at the Ecole Supérieure de Physique et de Chimie Industrielles, Paris, France. Her main area of interest is the development of new SPE selective sorbents involving artificial antibodies (molecular imprinted polymers) to extract various molecules from complex matrices, such as organic micropollutants or pharmaceutical compounds.

Valérie Pichon is Assistant Professor in the Department of Environmental and Analytical Chemistry at the Ecole Supérieure de Physique et de Chimie Industrielles, Paris, France. Her research focuses on the development of new analytical methods dedicated to sample pretreatment: extraction methods for solid matrices (supercritical fluid extraction, microwave assisted solvent extraction...) and solid-phase extraction (SPE) applied to liquid samples (development of SPE for polar micropollutants, development of immunosorbents and on-line coupling of SPE with LC).

Marie-Claire Hennion is Professor and Head Director of the Department of Environmental and Analytical Chemistry at Ecole Supérieure de Physique et de Chimie Industrielles, Paris, France. Her current research includes liquid chromatography, gas chromatography and the development of new analytical methods for environmental monitoring.