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Sample preparation using molecularly imprinted polymers

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Contents

Trends in polymerization methods	4
Choice of the reagents	4
Towards green approaches	6
Synthesis of MIPs for proteins.....	6
MIP in SPE.....	8
Preparation of MIP for SPE.....	8
Applications of MIP-SPE	10
Optimization of the SPE procedure	11
MIP-SPE performances	11
MIP in dispersive SPE (dSPE)	14
Preparation of the MIP particles	15
Applications of MIP in dSPE.....	19
Optimization of the dSPE procedure.....	20
Evaluation of the dSPE performances	21
MIP in SPME and related techniques	24
Preparation of the MIP fibers.....	24
Optimization of SPME procedures and applications.....	24
Evaluation of the SPME performances.....	25
SBSE and related techniques	26
Extraction devices combining MIP with membranes or plates.....	27
Dispersive extraction on membranes or plates	27

Membrane protected solid-phase extraction	28
Concentration of target by deposition on membrane/plate surface.....	28
Conclusion	29
Author informations.....	30
Corresponding Author.....	30
ORCID	30
Author Contributions	30
Notes	30
Biographies.....	30
References.....	31

Despite the advances in the development of new instruments and highly sensitive analytical methods based on gas, liquid or supercritical fluid chromatography coupled to various detectors including high resolution mass spectrometry (MS) that can be associated with different ionization sources, a pre-treatment is usually necessary in order to extract and isolate the analytes of interest from complex samples before their determination. Solid-phase extraction (SPE) is routinely used for the extraction or purification of compounds from liquid samples or solid matrix extracts. Despite their attractive features, the classical SPE sorbents retain analytes by non-selective hydrophobic (with alkyl-bonded silicas, polymers, carbonaceous sorbents,...) or polar interactions (with silica, amino-bonded silica, alumina,...) that lead to partial co-extraction of interfering substances that may cause matrix effects even with a specific detector such as a mass spectrometer.

To enhance the extraction selectivity of the target analytes, new materials involving a mechanism of molecular recognition were developed. They include immunosorbents based on the high affinity and selectivity of antigen-antibody interactions allowing a selective extraction of the target analyte and compounds having a similar structure.¹⁻⁴ Nevertheless, the development of an immunosorbent is time-consuming and relatively expensive. A similar behavior can also be obtained using aptamers, *i.e.* DNA or RNA sequences with high specificity towards given compounds. The resulting oligosorbents were recently successfully applied to the selective extraction of different target analytes from biological fluids and food samples.⁵⁻⁸ Once the sequence is available, the development of an oligosorbent is less expensive than an immunosorbent. However, despite their high potential, a limited number of sequences is, to date, available.

An alternative is to develop molecularly imprinted polymers (MIPs). These sorbents are synthetic polymeric materials possessing specific cavities designed for a template molecule involving a retention mechanism based on molecular recognition. The MIPs have been already successfully used in several fields, such as sensors,^{9,10} biomimetic catalyst in organic synthesis,¹¹ drug delivery,¹² and separation of structural analogs or enantiomers¹³ in liquid chromatography (LC)¹⁴⁻¹⁶ and capillary electrophoresis.¹⁵⁻¹⁸

The use of MIPs as selective sorbents for sample pretreatment was described for the first time by Sellergren and co-workers in 1994 and concerned the development of a MIP for the solid-phase extraction of pentamidine from urine ¹⁹, there has been a growing interest in these polymers for extraction purposes. Initially mainly developed for the selective recognition of small molecules, such as drugs, pesticides or other environmental pollutants,^{20–23} they are now developed, as illustrated in recent reviews, for the recognition of proteins^{24–26} or even microorganisms.²⁷ While the nature of the targets for which MIPs have been developed has evolved, so has the format of the extraction devices. Indeed, although MIPs have been mainly applied to the selective extraction or cleaning of target analytes from various complex samples by introducing them in a cartridge to carry out off-line SPEs, a strong trend towards miniaturized extraction devices has been observed over the past decade. The tendency is to develop new synthesis pathways to obtain particles of controlled sizes, fibers, stir-bars or membranes thus allowing their use in dispersive SPE (dSPE), solid-phase microextraction (SPME) or stir bar sorptive extraction (SBSE). This change of format is not only a reduction in size, but also implies changing the polymerization modes, which, despite the small size of the devices, must make it possible to maintain sufficient binding capacity. The modification of the polymerization conditions is also required when developing MIPs for proteins because of their lack of stability in conventional polymerization solvents. Based on the works published over the past two years for numerous target molecules, as reported on Figure 1, this paper aims to review the new strategies of development of MIPs in different formats dedicated to various extraction methods (whose distribution in terms of published work is given in Figure 2), often treated independently in the previously mentioned reviews, for both small organic molecules and proteins for which there are high expectations for replacing antibodies.

Figure 1: Groups of molecules for which MIPs have been recently developed. NSAIDs: Nonsteroidal anti-inflammatory drugs.

Figure 2: Distribution of extraction methods using MIPs in the works published over the past two years.

Trends in polymerization methods

Choice of the reagents

The synthesis of a MIP usually consists first in the complexation of a template molecule with functional monomers in solution, through non-covalent bonds. A cross-linker and an initiator are then introduced to generate the polymerization of the monomers around the template. After polymerization, template molecules are removed by extensive washing steps thus making available the binding sites, *i.e.* cavities, complementary to the template in size, shape, and position of its functional groups. MIPs are generally prepared using methacrylic acid (MAA), acrylic acid (AA), vinylpyridine (VP), itaconic acid (IA) or styrene as functional monomer and ethylene glycol dimethacrylate (EGDMA) or divinylbenzene (DVB) as cross-linker.

A non- to moderately polar and aprotic solvent, such as toluene, dichloromethane, chloroform, and acetonitrile or a mixture of them is used as porogen. Thus, polar interactions such as hydrogen bonds and electrostatic interactions can take place in these organic media. A few studies reported the use of polar and protic media, such as methanol, ethanol, and even water, for the synthesis of MIPs specific of compounds able to develop strong electrostatic interactions.²⁸ Nevertheless, the most common approach used to produce a MIP in polar solvent is the sol-gel approach based on the use of organosilanes, mainly 3-aminopropyltrimethoxysilane (APTMS), 3-aminopropyltriethoxysilane (APTES), and P phenyltrimethylsilane (PTMS), plus tetraethyl orthosilicate (TEOS) as cross-linker and by adding an acid or a basic molecule as catalyst.^{29–37} This approach is particularly attractive when polar compounds used as template are not soluble in organic solvents, which are traditionally used as porogen.

Other polymerization methods based on less conventional monomers were recently reported, such as the synthesis of a MIP by a condensation reaction between 1,3,5-triformylphloroglucinol and 2,6-diaminopyridine (Schiff based reaction),³⁸ between formaldehyde, melamine, and urea in the presence of a triblock copolymer of polyethylene glycol acting as porogen,³⁹ or between formaldehyde and phenol.⁴⁰ The synthesis of photoresponsive polymers prepared with azobenzene derivatives as monomers⁴¹ or thermosensitive polymers using acrylamide derivatives were also recently reported.^{42–45} At

last, a mercapto-alkynyl click polymerization to produce a MIP at the surface of magnetic Fe₃O₄ nanoparticles (NPs) was reported.⁴⁶

If the non-covalent approach is the most commonly used to obtain MIP extraction sorbents, as it facilitates the removal of the template molecule at the end of the synthesis, the covalent approach was recently used to produce a MIP for bisphenol A by synthesizing first a template molecule by reaction between an analog of bisphenol A and an organosilane.⁴⁷ This was also achieved by synthesizing a polymerizable template, a phenolic R-amphetamine sulfonamide derivative, that was combined with phenol and formaldehyde, the sulfonamide linkage being further hydrolyzed to provide cavities for the trapping of R-amphetamine.⁴⁰ Boronic acid was also used for its ability to form a reversible covalent complex with cis-diol compounds such as luteolin,^{48,49} vitamin B12,⁵⁰ sialic acid,⁵¹ or for the specific trapping of glycans of glycoproteins as discussed in more detail below.

Many works reported the screening of different synthesis conditions by preparing MIPs using different types of monomers, cross-linkers, template/monomer or monomer/cross-linker ratios, natures of the porogen,^{28,30,39,43,52–65} and even the pH when boronic acid is involved.^{50,66} The evaluation of the resulting MIPs consists mainly in comparing the binding capacity of the MIP for the target analyte with the one obtained with the corresponding non-imprinted polymer (NIP) synthesized with the same conditions as the MIP but in the absence of the template molecule. To limit the number of MIPs to be prepared and characterized, a computational approach was as an help to select the monomer or template/monomer ratio.^{67–69}

A MIP is usually synthesized for a specific analytical use that implies the choice of a given template molecule, whose the structure and the functionalities define the subsequent properties of the binding sites. In most of the cases, the molecule selected as template is the molecule that has to be extracted next by the MIP thus ensuring an optimal recognition during the extraction process. The selection of the template is also particularly crucial when the objective is to develop a MIP for class-selective extraction, such as it was the case for natural products,^{70,71} antibiotics,^{60,72,73} drugs,^{74–77} industrial products,^{38,68,78,79} pesticides,^{30,54,80,81} and estrogen receptor-active compounds.^{82–85} To improve the ability of the polymer to selectively trap as many structural analogs as possible, a mixture of two templates was reported for the trapping of four plant growth regulators,⁸⁶ six phthalate esters³³ or seventeen triazines.⁸⁷ A mixture of two target molecules was also used as template for their simultaneous extraction from real samples.^{61,65,88}

The complete removal of the template molecules from the MIP is difficult to achieve and necessitates extensive washing steps with large volumes of organic solvents in basic or acidic conditions. Recently, the efficiency of Soxhlet extraction and ultrasound to remove the template was compared, showing the higher efficiency of ultrasound to remove hydroxybenzoic acid from the MIP.⁸⁹ The use of a dummy molecule as template, i.e. a compound that resembles the target analyte in terms of shape, size, and functionalities and that can be selected by computational approach,⁹⁰ prevents from the risk of residual template leakage from the polymer, thus causing false quantification when it is applied to trace analysis. This

can be illustrated by a recent work related to the application of a MIP for the selective extraction of carbamazepine (CBZ) at trace level in river water.⁹¹ CBZ and methoxyCBZ, taken as dummy molecule for the MIP synthesis as it is never recovered in real waters, were detected in the elution fraction of the MIP at a concentration level of 80 and 1010 ng.L⁻¹, respectively. The presence of methoxyCBZ resulted from its leakage from the MIP during the extraction procedure. This concentration represents only 0.000047% of the amount of the template molecule introduced during the synthesis. Even if this value remained low, it clearly demonstrates the importance of the use of a structural analog as template during the MIP synthesis in order to avoid false positive responses during its subsequent use, particularly when trace level concentrations are investigated. In addition to this advantage, the dummy approach was also considered for an expensive or difficult-to-achieve template molecule.^{29,55,90–93}

Towards green approaches

Several groups also put forward the necessity to develop greener synthesis approaches, by using water as porogen. In this way, MIPs were produced in aqueous media using different types of monomers such as dopamine,^{94,95} chitosan,^{96,97} acrylamide derivatives,⁹⁸ melanine and resorcinol combined with methylenetetramine,⁶⁴ nylon-6^{99,100} or aniline.^{101,102} To provide a green synthesis process, another approach consists in preventing the direct use of a toxic cross-linking agent by producing it directly in the polymerization solution, such as it was done for formaldehyde through the hydrolysis of hexamethylenetetramine.⁵⁵ The use of ionic liquids as monomer^{28,73,80,88} or porogen^{103,104} can also be considered as a greener approach than the used of conventional monomers. Deep eutectic solvents (DESs) are also considered as a green-like material. They resemble ionic liquids with low vapor pressure, low toxicity, good biocompatibility, and good biodegradability with an easier preparation than that of ionic liquid. DESs were used as monomers for the synthesis of MIPs specific to transferrin,¹⁰⁵ bovine hemoglobin,¹⁰⁶ quercetin,¹⁰⁷ and catechins.¹⁰⁸ A DES whose composition had to be optimized to adapt its liquid state and viscosity¹⁰⁷ was also used both as template and monomer for the synthesis of a MIP for 3,4-dihydroxybenzoic acid.¹⁰⁹

Synthesis of MIPs for proteins

While many applications of MIPs in the field of extraction have mainly focused on small molecules, their development in recent years for the protein extraction has grown very rapidly. These MIPs were mainly synthesized in aqueous media, for example by cryopolymerization for myoglobin¹¹⁰ or using water soluble reagent such as melanine and resorcinol as monomers and methylenetetramine as cross-linker for bovine serum albumin (BSA).⁶⁴ Dopamine for horseradish peroxidase (HRP)¹¹¹ and metallothionein,⁹⁵ aniline for ovalbumine (OVA),¹⁰² and DES for bovine hemoglobin^{105,106} were also recently used as monomers. The synthesis of imprinted silica materials by sol-gel approach using organosilanes^{35,112} or a mixture of organic monomers and organosilanes¹¹³ was also proposed. It was achieved using water soluble and photo-switchable monomers such as azobenzene

derivatives¹¹⁴ or preparing thermo-sensitive polymer using N-isopropylacrylamide (NIPAM).⁴⁴ A similar approach was proposed to prepare a MIP for other macromolecules, heparin oligosaccharides.⁴³

To enhance the affinity of MIPs towards glycoproteins, many authors proposed the use of boronic acid. As an example, this ligand was first immobilized onto core particles and put in contact with the target protein that was trapped by its glycan residues before initiating the polymerization around the protein. This was done for transferrin that was immobilized on boronic acid-functionalized NPs to achieve an oriented surface imprinting by self-polymerization of either 2-anilinoethanol or 4-aminobenzylalcohol around the immobilized template.⁶⁶ A similar approach was applied to OVA, the MIP layer being produced by a redox polymerization of aniline around the immobilized template.¹⁰² A combination of boronic acid and dopamine was also proposed to develop a MIP for OVA.¹¹⁵ The grafting of boronic acid on the surface of a particle was also used to trap HRP protein by its glycan moieties before the synthesis of a MIP layer in the presence of an organosilane or aniline around the particle.^{111,112} The *in situ* digestion of the protein using trypsin and then pronase E was also proposed to isolate glycan-linked short peptides further used as templates to produce a MIP toward this glycoprotein.¹¹² A schematic diagram of this approach is reported on Figure 3. The use of metal chelation to immobilize the protein onto NPs before initiating the surface imprinting in the presence of a boronic acid derivative was also proposed for selective trapping of OVA.⁷¹

Figure 3: Schematic diagram of the precision imprinting strategy by combining the *in situ* dual enzymatic digestion and boronate affinity controllable oriented surface imprinting approach, Reproduced from Bie, Z.; Xing, R.; He, X.; Ma, Y.; Chen, Y.; Liu, Z. *Anal. Chem.* 2018, 90 (16), 9845–9852 (Ref ¹¹²). Copyright 2018 American Chemical Society.

MIPs for proteins or large peptides can also be prepared using the epitope approach. Indeed, a nonapeptide fragment derived from the C-terminus domain of cytochrome C was used as template molecule to prepare a MIP specific to Cytochrome C, by conventional radical polymerization of MAA and EGDMA in organic solvent.¹¹⁶ The epitope approach was also used to prepare a MIP for amanitine, an octopeptide, by thiol-ene click reaction in an organic solvent.¹¹⁷ A similar approach using dual-template epitope, *i.e.* C- and N-terminal peptides of the targeted protein, and combining metal chelation and distillation precipitation was also proposed.¹¹⁸ At last, the synthesis of a MIP using a tetrapeptide DYKD contained in the FLAG epitope (DYKDDDDK) used to tag proteins was developed to purify tagged proteins from crude

cell lysates, the epitope approach again allowing the use of conventional monomers and organic porogen for the MIP synthesis.¹¹⁹

MIP in SPE

In the extraction field, MIPs were initially mainly developed in SPE format¹²⁰ and several ones are already commercially available. The principle of SPE with MIP is the same as with conventional SPE sorbents. The MIP particles (60 to 400 mg) are packed into disposable cartridges between two frits. Some works recently reported the introduction of 5-70 mg of MIP particles in 100-1000 μL pipette tips^{29,39} or of 2 mg into the needle of a syringe.¹⁰⁹ After a conditioning step, the sample is percolated through the MIP and a washing solution can be applied to remove the interfering compounds that are not strongly retained by the MIP cavities. The desorption of analytes is achieved by percolating a solvent able to develop interactions with the sorbent inducing the elution of the analytes.

Preparation of MIP for SPE

Most of the reported MIPs were prepared in bulk, by far the most widely used method owing to its simplicity.²⁰ The bulk polymer monolith is then crushed, ground, and sieved to obtain particles, with a non-regular shape, mainly in the 25-100 μm size range. A sedimentation step is then achieved to remove fine particles.

Particles of MIP can also be directly obtained by precipitation polymerization that takes place in the presence of a larger amount of porogen (typically 2 to 10 times higher than for bulk polymerization).^{54–56,87,90,121,122} As the polymerization proceeds, the growing polymer chains become insoluble in the liquid phase and precipitate. Micro- or nanospheres can be generated when accurate control of the parameters governing the precipitation polymerization is achieved (*i.e.* temperature, cross-linker nature ...). Then, RAFT was recently combined with reflux precipitation polymerization to obtain water-compatible MIP particles for sulfonamides.¹²³

MIPs can also be obtained by suspension polymerization that consists in the introduction of the organic-based polymerization mixture as droplets into an excess of a continuous dispersion phase (water or perfluorocarbon fluids) by agitation in the presence of a stabilizer (suspending agent), each droplet acting as a mini bulk reactor. This method is suited for the production of spherical beads in a broad size range from a few micrometers up to a few millimeters. In return, the polymerization mixture must contain higher molar concentrations of template and monomers to compensate the partial loss of these reagents in the dispersion phase. Inversed suspension polymerization was recently reported, the polymerization solution being drop-wise in an *n*-heptane solution containing a surfactant.⁵⁷ Pickering emulsion using silica was also proposed to produce particles in the 19-44 μm ¹²⁴ or 30-80 μm range,⁸² that are well-adapted to the flow-rate of liquids during the extraction process in a SPE cartridge.

In order to better control the size distribution and shape of the MIP particles, while decreasing the amount of waste materials, polymerization methods based on the coating of preformed particles (with a more or less uniform size) was reported to produce SPE sorbents. They consist of the dispersion of these cores in the MIP polymerization solution, containing the monomer, the template, and the cross-linking agent. These particles can be silica particles of various sizes^{73,125,126} or mesoporous silica spheres^{104,127} (that can also be used as sacrificial supports),^{119,128} polystyrene beads,¹²⁹ polystyrene-divinylbenzene beads,²⁸ or polymeric cores prepared by dispersion polymerization.¹³⁰ To improve the rigidity of the MIP particles while increasing the adsorption capacity, polyhedral oligomeric silsesquioxanes were combined with nano mesoporous molecular sieve thus providing a dendritic effect.¹⁰⁴ A MIP was also recently produced by combining graphene oxide (GO) selected for its high surface area and β -cyclodextrin to enhance its adsorption capacity.¹³¹ At last, to increase the flow-rate of percolation for large sample volumes, a mix of MIP particles and filter paper pulp was placed between commercial cellulose filters to prepare a disk of paper-based MIP of 47 mm of diameter. This disk was used as a MIP-SPE cartridge, the large size diameter allowing the percolation of a large volume (300 mL) of water at a high flow-rate (30 mL/min).¹³²

The direct *in situ* synthesis of a monolith by bulk polymerization to prepare different extraction devices, thus avoiding the grinding step, were also recently reported. A monolith was directly prepared in a 100 x 4.6 mm stainless steel column using ionic liquid as porogen to control the monolith permeability¹⁰³ or in a 8 cm x 530 μ m internal diameter capillary using acryloyl- β -cyclodextrin and MAA as dual-functional monomers and in the presence of silanized multi-walled carbon nanotubes (CNTs), to enhance the specific surface area of the resulting sorbent.¹³³ A MIP monolith prepared in a 6-mL cartridge in the presence of GO particles was also recently proposed.⁸⁸ Permeable monolithic MIPs were also obtained in a 2-mL extraction cartridge by the *in situ* synthesis with a sol-gel approach.⁷² The production of MIP particles by emulsion polymerization in a cryogel directly into a cartridge reservoir was also recently reported to circumvent the problem of high back pressure generated by small-size particles.¹³⁴ The direct *in situ* synthesis of a permeable monolith in a 200 μ L-pipette tip by adding dodecanol as porogen in toluene was also reported.⁶⁰ Obtaining a good permeability by optimizing the proportion of porogen; i.e. dodecanol, in acetonitrile was also the objective of Bouvarel et al. when synthesizing a monolithic MIP *in situ* in a 100 μ m internal diameter fused-silica capillary for its further on line coupling with nanoLC.¹³⁵

The scanning electron microscopy (SEM) pictures of the resulting different types of MIP sorbents used in SPE, are reported on Figure 4. If the shape of the MIP particles prepared by bulk polymerization depends on the grinding and sedimentation process, the size of the particles generated by precipitation polymerization, coating of a core sorbent or Pickering emulsion strongly varies, which has a strong impact on the MIP flow-through properties during the SPE procedure. For *in situ* synthesis, the perfect anchoring of the MIP to the surface of the device chosen for its synthesis (pipette tip, capillary...) as well as a sufficient permeability of the monolith to limit back pressure during sample percolation have to be controlled.

Figure 4: MIP sorbents used in SPE and obtained by various approaches of synthesis: (a) surface of particles obtained by bulk polymerization; (b) precipitation polymerization; (c) MIP layer coating of polystyrene divinyl benzene beads; (d) Pickering emulsion; (e) *in situ* synthesis of a monolith in a 530 μm internal diameter capillary. Reproduced from (a) Sorribes-Soriano, A.; Esteve-Turrillas, F. A.; Armenta, S.; Amorós, P.; Herrero-Martínez, J. M. *Anal. Chim. Acta* 2019, 1052, 73–83 (ref ⁷⁴); (b) Li, Z.; Qian, Z.; Hu, S.; Gong, T.; Xian, Q. *Chemosphere* 2018, 212, 872–880 (ref ⁹⁰). (c) Zhu, G.; Cheng, G.; Wang, P.; Li, W.; Wang, Y.; Fan, J. *Talanta* 2019, 200, 307–315 (ref ²⁸) (d) Tang, J.; Wang, J.; Yuan, L.; Xiao, Y.; wang, X.; Yang, Z. *Steroids* 2019, 145, 23–31.(ref ⁸²); (e) Liang, G.; Guo, X.; Tan, X.; Mai, S.; Chen, Z.; Zhai, H. *Microchem. J.* 2019, 146, 1285–1294 (ref ¹³³). Copyright 2018 and 2019, with permission from Elsevier.

Applications of MIP-SPE

MIP-SPE was recently applied to the trace analysis of target analytes, mainly pesticides, industrial contaminants, and drugs, from real waters,^{28,81,83,90–92,131,132,134,136} soil and sediment extracts,^{67,73} and food extracts or beverages.^{38,54,60,72,82,87,123,124,129,130,133,137,138} It was also used to extract natural products from food or plants^{39,55–57,70,86,103,121,127,139} to control their occurrence, such as for toxins, or to purify them. It was also largely applied to the determination of drugs^{29,60,74,75,88,93,122,135,140,141} or proteins^{110,119,126}, mainly in biological fluids, and of various compounds in manufactured products.^{125,128}

Aqueous samples are often filtered before their percolation through the MIP. For more complex samples, such as biological fluids, different methods were reported to limit the risks of matrix effects during this percolation step. This can consist of a simple dilution of the sample with a buffer, a centrifugation step or a precipitation of the proteins (further removed by centrifugation), which can be also followed by a liquid-liquid extraction (LLE) procedure.^{54,122} For solid samples, the final dry extract is often diluted in the solvent used for the MIP synthesis, that should favor the selective interactions, or in a buffer. A preliminary purification step by LLE³⁰ or on conventional SPE sorbent was also reported.^{103,124}

If MIP can be applied to the purification of a target analyte from low sample volumes of biological fluids or extracts from solid matrices, they can also be used to selectively concentrate target analytes from samples. Indeed, enrichment factors (EFs) between 50 to 2000 can be calculated from papers describing the percolation of 500 mL¹²⁹ to 1 L^{90,92} of the sample and a final volume of the extract of 0.2-0.5 mL.

Optimization of the SPE procedure

In MIP-SPE as with conventional SPE sorbents, different parameters have to be optimized, particularly when high EFs are expected, such as the amount of sorbent and the composition and volume of the sample to avoid breakthrough of the target analyte. Several studies reported the existence of an optimal pH range to favor electrostatic interactions between the ionized form of the monomer residues and the basic or acidic analyte, thus improving the extraction recoveries.^{75,90,92,110,131} The effect of temperature on the MIP retention capacity was also reported for protein extraction, as the use of a basic aqueous saline solution for elution to replace organic solvents generally used to desorb the small organic molecules.¹¹⁰ Many works reported the optimization of these different parameters to obtain high extraction recoveries on MIPs.^{75,88,90,122,123,127,128,131} Nevertheless, when using a MIP, the objective is to reach an optimal selectivity. Therefore, the study in parallel of the extraction recoveries of the target analyte on the NIP must be done during the optimization of the extraction parameters, as it is often the case.^{39,55,60,72,74,81,81,90-93,110,124,135,136,140} These recoveries must be as low as possible on NIP to ensure that the retention on MIP is mainly due to the presence of specific cavities and then to ensure an optimal selectivity. A control molecule with a different structure from the target analytes(s) can also be studied on both sorbents. This was done recently by Shao *et al.* who prepared a MIP for the selective extraction of fluoroquinolones (FQs) from infant formula powders.⁷² In order to evaluate the selectivity of the MIP, a mixture containing 6 FQs and a control compound was tested. The MIP showed a good capture ability for the six FQs with recoveries ranged from 84.3 to 96.0%, while the recoveries on the NIP was only around 30%. For the control compound, very similar recoveries (around 36.2%) were observed on both MIP and NIP. The higher recoveries for FQs on the MIP than on the NIP and the low retention of the control molecule confirmed both the specific recognition generated by the imprinted cavities.

MIP-SPE performances

The validation of analytical methods involving MIP as SPE sorbent was achieved by the calculation of day-by-day and inter-day recoveries and by the estimation of the LOD and LOQ in real samples,^{30,38,60,72,81,82,93,125,130,140} which is a real evolution these last years. Indeed, previous works mainly reported the measurement of recoveries in a single spiked sample. The reproducibility of the synthesis was only recently reported, when comparing results from different batches for a MIP prepared by combining reversible addition-fragmentation chain

transfer (RAFT) with reflux precipitation polymerization (RPP)¹²³ and for a MIP monolith synthesized in situ in a 100 μm capillary.¹³⁵

MIP-SPE methods were also evaluated by comparing the extraction recoveries obtained using the MIP and other commercially available SPE sorbents^{30,39,60,92,131} or obtained with methods such as QuEChERS for food samples.¹³⁷ The comparison with conventional SPE sorbents was also carried out to demonstrate the selectivity brought by the MIPs. Indeed, the removal of matrix components from final extracts with MIPs gave rise to a cleaner baseline in UV⁸¹ or fluorescence³⁹ and a higher sensitivity (higher S/N ratios in MS)⁹¹ than using conventional sorbents. They also allow to limit ion suppression effect in MS.⁸³ It was also recently reported that the potential remaining matrix effects were reduced with MIPs in comparison with conventional sorbents.^{30,82,93,123}

The clean extracts obtained by MIP-SPE are usually analyzed by chromatographic methods (mainly LC or gas chromatography –GC–) associated to various types of detectors. Owing to the high clean-up effect brought by the MIP, these methods were sometimes replaced directly by ion mobility spectrometry (IMS) to shorten the analysis duration.^{132,137,140} The direct on-line coupling of a MIP with MS was also recently described, allowing thus a complete automation of the entire analytical procedure. In this case, MIP particles were packed in a precolumn (10 x 4.6 mm) connected to a LC switching valve and, after the transfer of the sample via a loop through the MIP, the desorption of the target analyte was achieved by a solution that allows both effective desorption and ionization in MS. This was done for the extraction of tricyclic antidepressants from diluted serum, their identification being ensured by a triple-quadrupole mass analyzer.¹⁴¹ To limit interferences, the MIP was coated with BSA allowing the exclusion of proteins during the extraction procedure. As previously mentioned, the high selectivity brought by a MIP can also be ensured by a careful optimization of the SPE procedure by comparing the retention on MIP and on NIP in real media. This was done for the extraction of cocaine from biological fluids, plasma and saliva, on a miniaturized on-line set-up by coupling of a MIP monolith (prepared in a 100 μm diameter capillary) on line with reversed phase nanoLC-UV (see the scheme on the top of Figure 5). As illustrated by the chromatograms on Figure 5, the very clean-baseline obtained using the MIP and the lack of retention of cocaine using the NIP highlight the high selectivity brought by the MIP that allows the easy determination of the cocaine analyte in this plasma with a limit of quantification of 14.5 ng/mL with UV detection while injecting 100 nL of a diluted plasma sample.¹³⁵

Figure 5: Set-up of the on-line coupling of the monolithic MIP/NIP (50 mm x 100 μm i.d.) with nanoLC-UV (Top) and chromatograms obtained after the extraction on MIP (a) and NIP (b) of 50 nL of plasma spiked with cocaine (equivalent to 100 ng mL^{-1} in plasma) compared to the blank plasma (c) on MIP. Reproduced from Bouvarel, T.; Delaunay, N.; Pichon, V., *Anal. Chim. Acta* 2019. <https://doi.org/10.1016/j.aca.2019.10.046> (Ref ¹³⁵). Copyright 2019, with the permission from Elsevier.

The removal of matrix components also enabled the direct analysis of the MIP elution fraction by UV detection,^{103,138} amperometry,²⁹ by assays that are often affected by matrix effects, such as an immunochromatographic assay,¹³⁶ or by assays measuring the bioactivity of an extract containing natural products⁷⁰ or the activity of compounds towards estrogen receptors.⁸³ A recent example reported by Yagishita *et al.* illustrates perfectly the interest of MIP to remove the matrix effect that can affect the response of sophisticated and expensive instruments such as MS or bioassays.⁸³ Indeed, they synthesized a MIP for the selective extraction of estrogen receptor(ER)-active compounds from surface water and they compared the chromatograms obtained by the LC-MS analysis of the fractions concentrated with a conventional styrene-divinylbenzene (SDB) sorbent or the MIP (defined as SDB-Conc, MIP-Conc, respectively). They also analyzed the solution recovered after percolation on the MIP that contained the non-retained compounds (defined as MIP-Pass) (see Figure 6). Pictures of the tubes containing these different concentrated fractions show that most of the colored compounds in SDB-Conc are also present in the MIP-Pass fraction, which demonstrates that they are interfering compounds not retained by the MIP cavities. The ER activity values measured with the bioassay for each fraction, also reported on Figure 5 show that some ER-active compounds were detected in both SDB-Conc and MIP-Conc. The detected concentration was much higher in MIP-Conc than in SDB-Conc, with values of 3.7 and 3.1 ppt, respectively, whereas the activity of the MIP-Pass fraction was 0. All these data showed that the MIP decreased interference by ion suppression in LC-MS and identified the presence of a

few ER-active compounds, which could not be detected by commonly used hydrophobic sorbents.⁸³

In addition to these performances, the greenness of an analytical method involving a MIP was recently evaluated by giving penalty points while considering solvent or energy consumption.¹³⁷ At last, in order to reduce the analytical cost, the reusability of some MIP was evaluated showing the possibility to use them 5,^{70,131,140} 6,¹²⁷ 10,¹³⁹ 12,¹¹⁰ 20^{38,60} to 25 times⁸⁷ without observing a loss of recovery higher than 5%.

Figure 6: LC-MS chromatograms of the environmental water sample and physical appearance of the fractions (a) concentrated by SDB cartridge, (b) concentrated by MIP, (c) collected after the percolation of the sample through the MIP (non-retained compounds). Each chromatogram corresponds to the overwriting signals of all the peaks of the detected compounds. Reproduced from Yagishita, M.; Kubo, T.; Nakano, T.; Shiraishi, F.; Tanigawa, T.; Naito, T.; Sano, T.; Nakayama, S. F.; Nakajima, D.; Otsuka, K. *Chemosphere* 2019, 217, 204–212 (ref ⁸³). Copyright 2019, with the permission from Elsevier.

MIP in dispersive SPE (dSPE)

The use of MIPs in dSPE has increased significantly in recent years, accounting for 53% of the works published in the field of MIP extraction in the last 18 months. In this case, the extraction is carried out by introducing a given amount of MIP particles into the sample. After a sufficient extraction time under stirring, the particles are recovered mainly by centrifugation or magnetic field (if magnetic core particles are used) and then introduced into a suitable desorption solvent after a possible washing step.¹⁴² MIP-dSPE can be achieved using conventional beads, magnetic beads but also NPs. As with conventional dSPE sorbents, the key-parameters to be optimized are the sample volume/sorbent amount ratio, the volume

and nature of desorption solvent, but also the extraction time, the stirring rate, and the desorption time.

Preparation of the MIP particles

As for MIP-SPE, MIP particles for dSPE can be obtained by bulk polymerization that gives a monolith that must be crushed and possibly sieved.^{53,58,64,143–146} More homogenous MIP microspheres can also be obtained by precipitation polymerization,^{63,65,147–149} suspension polymerization,^{45,89} and emulsion polymerization.¹⁵⁰

Another option is surface imprinting, which mainly consists in dispersing a core sorbent in the polymerization solution as described in detail in recent reviews.^{151,152} With this approach, the recognition sites are located on the surface of the supporting material, thus displaying a sufficient binding capacity, a fast mass transfer, and rapid binding kinetics due to the easy accessibility of the analytes to the binding sites.¹⁵³ In the recent works, these core sorbents were activated-SiO₂ microspheres or NPs,^{31,32,66,101,115–117,154,155} hollow mesoporous silicas,⁴⁷ carboxyl-activated polystyrene colloids,¹⁰⁰ ZnO NPs coated with SiO₂ and further vinylized,¹⁵⁶ poly(styrene-glycidyl methacrylate (GMA)) NPs,⁷¹ tryptamine-activated sepharose beads³⁵ or vinylized GO nanosheets.¹⁵⁷ A poly(GMA) grafted on a styrene macroporous resin was also put in contact with the template and a diamine thus providing an imprinting process synchronized with a cross-linking method.¹⁵⁸

Fe₃O₄ microspheres coated with a silanized carbon shell (Fe₃O₄/C) also served as core sorbent to produce MIP particles, the hollow surface of the MIP being then generated by dissolving the Fe₃O₄/C microspheres that served as sacrificial material.¹⁵⁹ A similar approach consisted in the use of silica nanospheres, the hydrolysis of the SiO₂ cores giving rise to a hollow shell structured MIP of 480 nm diameter with a shell thickness of 40 nm.⁴¹ A zeolite imidazolate framework-8 (ZIF-8) was used as a stabilizer and sacrificial material in a Pickering emulsion polymerization procedure, the further dissolution of ZIF-8 leading to hollow spherical polymer microspheres too.¹⁶⁰ Some examples of particles that were prepared by some of these different approaches are reported on Figure 7 a-d. Those various procedures gave rise to particles of different sizes whose homogeneity was studied for three of them. Indeed, the size of particles prepared by suspension, precipitation polymerization or by using SiO₂ nanosphere as a core were in the range 1-8 μm, 100-350 nm, and 20-250 nm, respectively.

Figure 7: Non-magnetic particles prepared for dSPE by (a) suspension polymerization, (b) precipitation polymerization, polymerizing a MIP layer on (c) SiO₂ nanosphere or (d) a hollow mesoporous silica surface and (e) SEM (and TEM in insert) picture of magnetic MIP particles produced using Fe₃O₄@SiO₂ NPs as core particles. Part (a) reproduced from Liu, X.; Wu, F.; Au, C.; Tao, Q.; Pi, M.; Zhang, W. *J. Appl. Polym. Sci.* 2019, 136 (3), 46984 (ref ⁸⁹) – Copyright 2019, with the permission of John Wiley and Sons; Part (b) (c) and (d) reproduced from Lu, W.; Liu, J.; Li, J.; Wang, X.; Lv, M.; Cui, R.; Chen, L. *Analyst* 2019, 144 (4), 1292–1302 (Ref ⁶⁵), from Li, D.; Tu, T.; Wu, X. *Anal. Methods* 2018, 10 (36), 4419–4429. (Ref ⁶⁶) and from (d) Li, L.; Yu, K.; Tian, M.; Wang, Y.; Zhang, Z.; Jiang, G.; Li, L. *Anal. Methods* 2018, 10 (32), 3926–3932. (Ref ⁴⁷) respectively by permission of the Royal Society of Chemistry; Part (e) reproduced from Zhang, Y.-Z.; Zhang, J.; Tan, L.; Xia, Z.; Wang, C.-Z.; Zhou, L.-D.; Zhang, Q.; Yuan, C.-S. *J. Sep. Sci.* 2018, 41 (15), 3060–3068 (Ref ⁴²) - Copyright 2018, with the permission from John Wiley and Sons.

To avoid the tedious centrifugation step after each step of the dSPE procedure, magnetic MIP particles can be prepared by various polymerization methods using different types of magnetic core (particles, nanotubes, nanosheet, porous structures...) as recently reviewed for MIPs developed for various types of molecules¹⁶¹ or only for biomacromolecules.¹⁵² In the most recent works involving MIP in dSPE, different types of magnetic sorbents were dispersed in the polymerization solution such as Fe₃O₄ NPs,^{34,98} silanized Fe₃O₄ NPs,^{43,106,162,163} vinylized Fe₃O₄ NPs,^{52,59} PEG-Fe₃O₄ NPs,⁹⁶ acrylic acid-,¹⁰⁵ methacrylic acid-,¹⁶⁴ boronic acid-,^{50,112} or oleic acid-Fe₃O₄ NPs,¹⁶⁵ and chitosan-Fe₃O₄ NPs.⁶² Microspheres of Fe₃O₄ NPs covered by a layer of poly(GMA),¹⁰² microporous SiO₂,^{42,68,69,113,114,116,166–176} or TiO₂¹¹¹ were also recently reported. An example of particles produced using Fe₃O₄@SiO₂ NPs as core particles is provided in Figure 7e. Among these studies, Li *et al.*, who produced a layer of MIP by polycondensation of melamine, resorcinol, and formaldehyde in the pores of a mesoporous silica layer, used as sacrificial support, showed the effect of polymerization time on the adsorption capacity as well as on the selectivity of the MIP particles which reached an optimum after 3 h.¹⁷³ Other types of particles, such as silanized-hollow Fe₃O₄ microspheres,⁴⁴ graphite flakes coated by Fe₃O₄ NPs and further silanized,³³ Fe₃O₄ NPs covered by a mesoporous silica layer and further covered by GO¹⁷⁷ or GO coated with Fe₃O₄ NPs⁹⁴ and further vinylized¹⁷⁸ or covered by a mesoporous silica layer before being vinylized,¹⁷⁹ graphene-CNTs grafted with Fe₃O₄ NPs,¹⁸⁰

CNTs covered by a SiO₂ layer,¹¹⁸ silanized magnetic mesoporous carbon particles,¹⁸¹ cobalt-based magnetic nanoporous carbon prepared from MOF,¹⁸² and modified- β -cyclodextrin silanized Fe₃O₄ NPs¹⁸³ were also recently reported.

Magnetic properties were also obtained by the grafting of Fe₃O₄ NPs at the end of the synthesis of the MIP previously prepared at the surface of mesoporous silica⁵¹ or by the *in situ* growth of Fe₃O₄ NPs in the pores of the mesoporous imprinting silica prepared by a sol-gel approach with the presence of a surfactant.³⁷ The introduction of silanized Fe₃O₄ NPs in the polymerization mixture before bulk polymerization¹⁸⁴ or by mixing Fe₃O₄ NPs with the reagents used for precipitation polymerization¹⁸⁵ was also proposed. The use of Janus silica nanosheets grafted with Fe₃O₄ NPs on one side and activated on the other side for the MIP coating by dispersion in the polymerization mixture¹⁵³ or of silica nanobottles with a hydrophobic exterior surface used to produce a MIP layer and a hydrophilic internal surface functionalized by magnetic NPs were also reported.⁴⁹ Some examples of magnetic particles prepared by some of these different approaches are reported on Figure 8.

Figure 8: SEM images of (a) MIP prepared on silanized magnetic mesoporous carbon particles, (b) cobalt-based magnetic nanoporous carbon coated with MIP, (c) MIP prepared on the surface of hollow Fe₃O₄ microspheres (TEM picture in insert) and TEM pictures of CNTs (d-a), CNTs@SiO₂ (d-b), vinylized CNTs@SiO₂ (d-c) and CNTs@MIP (d-d). Part (a) (c) and (d) reproduced from Ge, Y.-H.; Shu, H.; Xu, X.-Y.; Guo, P.-Q.; Liu, R.-L.; Luo, Z.-M.; Chang, C.; Fu, Q. *Mater. Sci. Eng. C* 2019, 97, 650–657 (Ref ¹⁸¹), Zhou, J.; Wang, Y.; Ma, Y.; Zhang, B.; Zhang, Q. *Appl. Surf. Sci.* 2019, 486, 265–273. (Ref ⁴⁴) and Qin, Y.-P.; Wang, H.-Y.; He, X.-W.; Li, W.-Y.; Zhang, Y.-K. *Talanta* 2018, 185, 620–627 (ref ¹¹⁸) respectively – Copyright 2018 and 2019, with permission from Elsevier. Part (b) reproduced from Wu, C.; He, J.; Li, Y.; Chen, N.; Huang, Z.; You, L.; He, L.; Zhang, S. *Microchim. Acta* 2018, 185 (11), 515. (Ref ¹⁸²) – Copyright 2018, with the permission from Springer Nature.

The objectives of these different approaches of synthesis are to obtain particles with a high specific surface area and a large amount of specific cavities while maintaining sufficient magnetic properties when magnets are used in the extraction procedure. Specific surface area

values were measured by BET (N_2 adsorption) and were, for example, 243 m^2/g for MIP developed on SiO_2 NPs,¹¹⁵ 326 m^2/g for 3D graphene-CNT hybrid composites¹⁸⁰ or 320 m^2/g for MIP particles obtained by bulk polymerization.¹⁴³ To improve the surface area of dSPE-MIP particles, SiO_2 nanospheres were coated by a covalent organic framework (COF) based on triformylbenzene and diaminobiphenyl as monomers and produced by heterogeneous nucleation and growth method.¹⁵⁵ The improvement was demonstrated by the preparation in parallel of a COF-MIP by homogeneous nucleation, *i.e.* without the introduction of SiO_2 nanospheres that led to a lower adsorption capacity, 152 instead of 322 m^2/g . In the same way, the use of a 2D boron nitride (BN) scaffold dispersed in the polymerization mixture in the presence of Fe_3O_4 NPs allowed to produce MIP NPs with a binding surface of 50 instead of 30 m^2/g without the BN scaffold.¹⁰⁷ Wang *et al.* recently compared different polymerization methods to produce a MIP for capsaicin such as bulk, precipitation polymerization, that give rise to non magnetic particles, and surface imprinting technology based on silanized Fe_3O_4 NPs, showing that the latest possess the best affinity and adsorption capacity.¹⁷¹ At last, to prepare a HRP-MIP, boronic acid was grafted on Fe_3O_4 NPs covered by a porous TiO_2 layer instead of a silica layer before the polymerization with dopamine in order to improve the specific surface area of the sorbent, since the surface of $Fe_3O_4@TiO_2$ is much rougher, which is beneficial to offer more binding sites.¹¹¹

The measurement of the specific surface area is a parameter indicating the potential binding capacity of the MIP but it is also important to check for the presence of cavities. For this, as for other fields of application of MIPs, binding at equilibrium is studied on both MIP and NIP, and differences between MIP and NIP values indicate the presence of cavities. Those values are often given in mg/g thus rendering difficult the comparison of MIPs specific of molecules of different sizes. Moreover, more than the capacity value itself, it is the ratio between the values obtained with the imprinted and non-imprinted supports, named the imprinting factor, which is important for assessing the presence of specific cavities. Recently, a careful optimization of several parameters affecting the binding properties of a glycoprotein on a MIP, prepared with boronic acid, by a comparison of the IFs obtained in various conditions of synthesis has been reported.⁶⁶ An imprinted factor of 17.3 was obtained for the most promising sorbent for the target glycoprotein with IFs lower than 1.23 for 6 other proteins including glycoproteins, thus highlighting the very high selectivity of this MIP.

To improve the adsorption capacity while obtaining a high selectivity, different approaches were recently proposed. As an example, silica NPs were replaced by mesoporous silica NPs and by adding a surfactant in the sol-gel polymerization mixture thus improving the binding capacity of the MIP from 13.42 to 21.1 mg/g , the imprinting factor being about 2.15.³¹ A high value of 108.1 mg/g was also reported for MIP particles for an acidic herbicide obtained by Pickering emulsion stabilized by a zeolith imidazolate framework, with only a value of 22.22 mg/g for the NIP thus highlighting the imprinting effect.¹⁶⁰ The use of metal chelation to immobilize the glycoprotein OVA onto NPs before initiating the surface imprinting in the presence of a boronic acid also led to a MIP having a higher adsorption capacity and selectivity than the MIP prepared with only boronic acid.⁷¹

At last, it is worthwhile to notice that the thickness of the MIP layer resulting from the different approaches described above to produce magnetic MIP particles is rarely given. If it affects the binding capacity, it also affects the final magnetic properties of the resulting particles. Indeed, for MIPs prepared on the surface of silanized Fe₃O₄ NPs, saturation magnetization values (SMVs) decrease only slightly in some cases, by a factor of 1.2 to 2,^{94,106,174,181} but much more in other cases with losses by a factor of 3-5.3,^{113,114,168,169,185} 7,^{167,179} and even 11.4.⁴² In one of these studies, the decrease by a factor of 5.3 was correlated to a too large thickness of the MIP layer (15 nm) covering NPs of 520 nm.¹¹⁴ The SMV decrease was lower for a MIP layer on the surface of magnetic GO particles.⁹⁴ Indeed, these particles of 16 nm gave rise to MIP particles of 40 nm (thickness of the layer about 12 nm) causing only a decrease of the SMV by a factor of 1.7. The final SMVs belong to a wide range of values that have an impact on the time required to recover the particles with the magnet. Indeed, 5-30 s are required to recover particles with SMVs from 12.2 to 19.88 emu.g⁻¹,^{33,62,113,114,163} and 50-60 s with SMVs less than 5.33 emu/g.^{37,42} It can be noticed that commercialized magnetic MIP particles have a low SMV of 1.52 emu/g.¹⁸⁶

Applications of MIP in dSPE

MIP-dSPE was recently applied to the selective extraction, prior to their analysis, of biomarkers,^{50,51,149,153,174} glycoproteins,^{66,71,105,111} and drugs^{62,69,147,164,165,178,184} from biological fluids, proteins from blood or serum,^{35,106,114,118} from urine,^{64,113} or from cell culture,³² and of drugs from environmental waters,^{61,65,155,187} sediment¹⁷⁵ or food.⁵⁹ It was also applied to the extraction of natural products from plant extracts,^{42,45,46,107,108,169-171,177,188} foodstuff,^{58,146,148,154,163} bacteria extracts,⁴⁸ human serum,¹⁷³ waste,¹⁷² and environmental¹⁷³ waters. Another application field is the monitoring of toxins or natural hormones in waters,⁹⁴ food^{117,168,182} and biological fluids.¹⁸¹ At last, recent works reported the use of dSPE-MIP for the extraction of pesticides from waters,^{160,167} soil,¹⁶⁷ and food extracts,^{144,162,185} and of industrial pollutants from waters,^{31,33,37,47,158,166,179,183,186} food,^{34,68,96,98,180,183} or samples collected in an industrial bioreactor.⁵³

Another objective of sample purification using MIP is the removal of a class of compounds that interfere with the analysis of the target analytes. For example, MIP particles prepared using β -carotene were used to remove this molecule and other carotenoids from food, in replacement of conventional SPE sorbent in QuEChERS procedure, to improve the reliability of the analysis of pesticides in this sample, showing a limited loss of the pesticides compared to conventional sorbents.¹⁴⁶ It is interesting to note that if in some cases a MIP can trap several analogs of the template molecule, it is not always the case. As an example, a MIP developed for the selective trapping of microcystin-LR using this target molecule as template has shown to be very specific to this microcystin, which is a very different behavior from that of antibodies able to recognize and then trap several structural analogues.⁹⁴

In most of the cases, 5-100 mg of particles are dispersed in the samples. The ratio between the amount of MIP particles and the volume of the sample, that has only been optimized in some cases,^{68,180} can be lower than 1,^{32,33,44,94,143,158,169,179} between 1 and 10,

45,50,58,59,61,64,65,89,98,106,107,111,114,117,147,154,155,163–165,170,177,178,185 or up to 50 34,66,69,144,149,168,174,181,188 and even 250 mg/mL.⁴³

Environmental waters were filtered¹⁷² or directly put in contact with the MIP particles for the extraction of target analytes. A direct extraction was also applied to an apple juice.¹⁷³ However, viscous liquid samples such as honey, milk, juice, or olive oil were diluted in a buffer^{50,148,185} or in a solvent.¹⁴⁴ Wine samples were first treated by LLE to remove some interfering compounds.¹⁵⁴ Urine samples were extracted without any treatment,^{113,164,173} or after pH adjustment,¹⁶⁵ filtration,¹⁷⁴ centrifugation,¹⁴⁷ dilution by a factor of 25,¹⁵³ or a complex sample pretreatment involving a dilution with a buffer (1:1, v/v) and a first SPE extraction step on C18 silica.¹⁴⁹ For serum samples, a direct extraction,¹⁷³ a dilution by a factor 50,¹¹¹ 100,^{105,106} 150,¹¹⁴ 200¹¹⁸ or 250,⁶⁶ or a protein precipitation step⁶⁹ that can be followed by a dilution with a buffer was proposed.^{51,147,165} For solid samples, as for MIP-SPE applications, which are subjected to a first treatment with a solvent, the resulting liquid extracts are put in contact with MIP particles either directly¹¹⁷ or after a dilution with a buffer or a hydro-organic mixture.^{34,59,96,180,182,185} While all these sample pretreatment procedures are varied and aim to make the sample less viscous or to eliminate certain interfering compounds such as proteins, the conditions are rarely, if ever, really justified.

The desorption of small molecules is mainly achieved using organic solvents that may contain some acids to help desorption. The addition of DES in methanol to desorb a nephrotoxin was also recently reported.¹⁸¹ Concerning large molecules, some works described the desorption of glycoproteins from boronate-MIP with 5% acetic acid combined with up to 30% acetonitrile in water¹¹¹ or a solution with a high salt content.⁶⁴ For thermo-sensitive MIPs, this solution with a high salt content was combined with a decrease in the temperature from 32 and 35 to 20 and 25°C for BSA⁴⁴ and some alkaloids,⁴⁵ respectively. Desorption of protein was also ensured by the use of a surfactant combined with acetic acid¹¹⁸ or with UV irradiation for a MIP prepared with photo-switchable monomers,¹¹⁴ but only a partial release was reported in this last case. Irradiation at two different wavelengths was also applied to a photo-responsive MIP prepared for cyclodextrine.⁴¹

Optimization of the dSPE procedure

A dSPE is based on an equilibrium during the extraction but also during the desorption step and this procedure can be achieved with an extraction time that can be close to those of the SPE-MIP method, from 10 to 30 min.^{32,107,111,155,167,168,179,180,182,183} However, many studies reported very long durations, up to 1 h,^{33,34,51,69,94,98,102,163,177,181} 2 h^{44,50,61,149,170} or even more.^{35,41,43,45,65,106,172} These long times concern in some cases the extraction of macromolecules that have low molecular diffusion coefficients or the use of thermo- or photo-responsive MIPs whose structural modifications require longer times. It is also interesting to note that in some studies the duration of the extraction and desorption steps was not optimized. Some authors also reported the use of ultrasound to shorten the dSPE duration time.^{147,155,156,165,174}

The optimization of the extraction conditions with real samples is very rarely described. In most of the cases, it is worthwhile to notice that the optimization was achieved by studying the binding of the target molecule(s) in pure media, in very few cases with also a comparison with the NIP, and then the optimal conditions were applied for real samples without any additional study of matrix effects. However, Gast *et al.* recently reported that this MIP/NIP comparison can be helpful for optimizing the selectivity in real samples. Indeed, they studied the effect of the dilution rate of cell culture supernatant on the fixed amount of a viral hexon protein, showing that the dilution improved the selectivity of the trapping by decreasing the amount retained by the NIP.³²

As with conventional dSPE sorbents, the key-parameters to be optimized are the sample volume, the ratio of the sample volume and the amount of sorbent, the extraction time, the agitation rate, the pH of the sample, the nature of the solvent, and the time required for desorption.¹⁸⁹ In MIP-dSPE, a washing step was in some cases introduced before desorption to remove some interfering compounds,^{50,62,162,164,165,170,173} but no real optimization of this step was reported. Some other parameters can also be studied such as the number of extraction or desorption steps or the use of shaking devices (rotary shaker, ultrasonic bath). When their optimization was done, it focused only on finding the conditions leading to the highest extraction recoveries, but without verifying the binding on the NIP that should be as low as possible to ensure an optimal selectivity of the extraction process. Indeed, there are only a few cases studying the effect of the polymer amount,^{50,185} loading time^{117,184} and volume, nature,⁶⁸ and pH of the sample^{50,113,185} on the binding on both MIP and NIP to find conditions giving rise to the best selectivity.

Most of the authors, who reported some optimization of extraction conditions, used a one-variable-at-a-time approach, while keeping the others fixed. They mainly studied the effect of pH,⁹⁸ time of extraction and desorption^{68,98,180}, and nature¹⁸⁰ and volume of the desorption solution^{33,65,94,149,155,165,174,177,181} on the binding properties. The major drawback of this approach is that it cannot completely consider the collaboration effects among the factors and subsequently is incapable of attaining the true optimum level, *i.e.* the optimal extraction recoveries on MIP. To overcome this drawback, an experimental design can be used to first identify the main influencing factors. This was done for example with a Plackett-Burman approach and considering the NIP and MIP as a “polymer type” factor to evaluate the impact of the imprint on the results.¹⁸⁶ A box-Behnken design was also applied to optimize the elution conditions (frequency, time, and volume) of carbamazepine.⁶² A central composite design (CCD) with four parameters, selected after having set some other parameters, and a response surface methodology (RSM) or, in case of multi-criteria optimization, a desirability function were also employed to help optimize the dSPE conditions.^{96,147,169,178}

Evaluation of the dSPE performances

In most of the reported studies, EFs are very low, even lower than 1, the objective being more the purification than the concentration of the analytes. An example of purification effect is given by the comparison of chromatograms provided in Figure 9 that corresponds to the

analysis of grape (Figure 9a) and apple (Figure 9b) juices before (black) and after the desorption of MIP (red) or NIP (blue) particles dispersed in the same samples.¹⁷³ The complexity of these juices is demonstrated by their direct LC-UV analysis with coelution of GA with some interferences. The use of MIP-dSPE allows the selective extraction of GA, no interferences being observed, whereas no GA peak was observed in the elution fraction from the NIP thus highlighting the contribution of the MIP cavities in the extraction process.

Figure 9: Chromatograms corresponding to the analysis of gallic acid (GA) in grape juice (a) and apple juice (b) (black line), and of the desorption fraction after dSPE on MIP (red line) and on NIP (blue line). Reproduced from Li, H.; Long, R.; Tong, C.; Li, T.; Liu, Y.; Shi, S. *Talanta* 2019, 194, 969–976 (Ref¹⁷³) – Copyright 2019, with the permission from Elsevier.

Nevertheless, EFs of 20¹⁷⁰ and even 60-75 without evaporation for urine samples or food extracts,^{147,169} and higher than 150 after an evaporation of the desorption solution to concentrate it were obtained.^{34,96,178} If most of the studies concern the trapping of a target molecule and one or two analogs in some cases, Li *et al.* reported EFs from 16 to 20 for 6 NSAIDs in waste water with IFs between 2 and 2.3 using ibuprofen as template.¹⁵⁵ As for SPE-MIP, the validation of a dSPE procedure was mainly based on the intra- and inter-day studies of the extraction recoveries, measured mainly in pure media^{59,96,180,184} but also in real samples, in their native form^{62,181} or spiked at different concentration levels.^{37,45,50,51,62,65,69,94,96,113,149,163,165,168,172,174,178,183,184}

Li *et al.* compared MIP and C18 silica particles to evaluate their difference in term of adsorption capacity of drugs from environmental waters, that was higher with the MIP (factor 2.6).¹⁵⁵ A similar comparison was reported by Lu *et al.* that observed a higher selectivity, with a better clean-up effect with the MIP.¹⁶⁷ Liang *et al.* also compared the binding of a natural product on MIP and NIP particles immersed in real samples showing an extraction capacity of the MIP 2.5 higher than that of the NIP, thus illustrating the contribution of specific cavities in real conditions, even in the presence of a large amount of interfering compounds.¹⁸⁸ Similar conclusions were obtained by Ge *et al.* as a higher binding capacity was obtained in urine samples with the MIP particles than with other sorbents such as NIP but also magnetic mesoporous carbon particles (used as core for the production of the MIP particles), or bare silica and C18 silica particles. The lower binding on NIP showed again the contribution of the specific cavities for the binding of the target in real samples.¹⁸¹

The matrix effect in the HPLC-UV analysis of carbamazepine in urine and serum was evaluated and matrix effect factors ranged from 88.14 to 97.45% with SD within 7.59% thanks to the MIP clean-up.⁶² Similar results were obtained for the extraction of 6-mercaptopurine from human plasma and its analysis by LC-MS,⁶⁹ perphenazine from non treated urine and its analysis by HPLC or HPTLC,¹⁶⁴ and folic acid from lettuce and cookies and its analysis by LC-MS.⁵⁸ As already reported for MIP-SPE, thanks to the clean-up effect brought by the MIP, chromatographic methods typically used to analyze the dSPE extract can be replaced by a direct analysis by IMS as it was done for example for cocaine in saliva, which is a faster but also greener method compared to LC-MS often used for this application.¹⁸⁴

The study of the reusability of the dSPE particles was often reported. The possibility to use them in 3,^{53,105,185} 5,^{31,45,46,50,62,96,117,153,154,175,179,188} 6,^{43,94,94,111,113,167,172,182} 7,^{49,115} 8,^{37,44,102,159,180} 9,¹⁵⁶ 10,^{35,47,163,170} 20¹⁷⁸ and even 30¹⁵⁵ cycles, was mainly studied in pure media and resulted in a difference in binding efficiency between 3 and 15% between the first and the last use. A loss of capacity efficiency of 15% after the treatment by dSPE of four urine sample extracts was also reported.¹⁴⁹

Concerning the MIP particles produced by bulk (by introducing silanized Fe₃O₄ NPs in the polymerization mixture), their non-reusability was mentioned, but a good repeatability of their synthesis, which favors their single use, was reported.¹⁸⁴ It is interesting to note that the repeatability of the synthesis is very rarely studied, leading authors to often characterize their media with great precision and to evaluate the performance of their methods without verifying that the synthesis of these media is repeatable. However, two¹⁶² or five^{50,173} independent synthesis of magnetic MIP particles led to RSD values lower than 6 % for adsorption capacity.⁵⁰ In addition, highly reproducible recoveries of sialic acid in pure samples were obtained using a hollow magnetic MIP, with RSD values of 1.6 and 5.5% for intra- and inter-batch measurements, respectively.⁵¹ At last, Wang *et al.* compared the binding properties of MIPs obtained with three independent syntheses and they were very close, this study being also achieved on the corresponding NIP in order to also check the repeatability of the selectivity.⁴⁶

MIP in SPME and related techniques

Other methods based on the partition equilibrium of the target between the sample and MIP were developed by replacing particles by other formats such as fibers or rods of different sizes, resulting in selective extraction methods named solid-phase microextraction (SPME) and stir-bar sorptive extraction (SBSE). Mostly developed for the extraction of the volatile compounds before their analysis by GC after their thermodesorption, the application of SPME has been extended to biological fluids with an off-line coupling with LC. In this case, the desorption is achieved with a solvent, which no longer requires the use of sorbents stable at high temperature.

SPME generally consists in the extraction of compounds by immersing a fused silica fiber (100 μm diameter) usually coated with polydimethylsiloxane (PDMS), divinylbenzene (DVB), polyacrylate (PA) or a combination of them, into a sample. As recently reviewed, numerous groups work on the replacement of conventional coating material to improve its potential to a larger range of compounds,¹⁹⁰ recent reviews focusing particularly on the use of MIPs as coating material.^{120,191} This part of the review summarized the last developments in this field.

Preparation of the MIP fibers

Among the different approaches allowing the preparation of MIP-fibers recently reviewed,^{120,191} recent works have shown that MIP fibers can be prepared by coating a stainless steel fiber (6 cm x 200 μm diameter)¹⁹² or a silica glass fiber (1.8 cm x 300 μm diameter)⁷⁹ by immersing them in a 1 mm diameter glass capillary filled with the polymerization solution. The capillary acts as a mold to form the MIP layer around the fiber. Another approach involved a pre-activation step of a stainless steel fiber by dipping it in an acidic solution before its immersion for a controlled time in a polymerization solution to coat it with a MIP layer, the immersion being achieved three times to ensure a sufficient coating of the fiber.¹⁹³ A MIP fiber can also be *in situ* synthesized in a capillary filled with the polymerization solution and acting as a mold. In this case, the capillary size defines the fiber size and fibers of 2.5-2 cm x 530 μm diameter^{76,80} or 4 cm x 300 μm diameter¹⁹⁴ were synthesized. A larger mold, 3 cm x 3.5 mm diameter, was used to prepare four fibers then tied up together to form a fiber bundle.⁸⁵

Optimization of SPME procedures and applications

MIP-SPME was applied to the extraction of pollutants from waters,⁷⁹ of drugs from diluted biological fluids⁷⁶ or food extracts,⁸⁵ of pesticides from juices after their filtration and their dilution in water^{80,194} and of flavonoids from green tea or coffee.¹⁹³ A MIP fiber was also applied to *in vivo* sampling of a flavonone and its metabolites for uptake studies from a liver of an anesthetized rat.¹⁹² It is interesting to note that to improve the selectivity of the MIP-SPME procedure when it is used with biological samples, BSA was coated at the surface of the MIP after its preparation to limit the extraction of macromolecules from biological samples during the extraction of the targets.^{76,192}

As for conventional sorbents, the extraction efficiency of the MIP-SPME device depends on different parameters such as the sample nature, the amount of extraction sorbent, the extraction time, the stirring rate, and the extraction temperature. Due to the instability of MIPs at high temperatures, desorption is achieved by immersing the fiber in a solvent, which also involves optimizing its nature and volume, and desorption time. The optimization of these parameters was mainly achieved by studying the amount of target molecule fixed on the MIP fiber, but without studying the NIP that is only used as control after this optimization with the exception of only two cases where the MIP/NIP comparison was achieved to set the extraction time.^{80,192} As for d-SPE, experimental designs can help optimize these numerous parameters. For example, a Box-Behnken design (BBD) with 3 variables and RSM allowed to optimize six parameters affecting the extraction (sample pH, amount of salt in the sample, and duration) and desorption (nature and volume of the solvent and duration) steps.⁸⁵ As dSPE, the MIP-SPME method is based on a partition equilibrium during the extraction but also the desorption step. Therefore, this procedure is quite long compared to SPE and requires from 50 min-1 h^{85,193,194} up to 2h.⁷⁹

Evaluation of the SPME performances

The reproducibility of the fiber preparation was evaluated for the GO/MOF/MIP fiber, showing RSD values on the extracted amount of 3.4-4.1% for consecutive extractions on one fiber and of 4.3-5.2% for five similarly prepared fibers.⁸⁵ These values are very satisfactory and only slightly higher (difference of 1%) than for a MIP prepared by the same group without adding GO/MOF nanocomposite in the polymerization solution.¹⁹⁴

If MIP-SPME was mainly applied to the selective extraction of target molecules from samples without any focus on the concentration effects, large enrichment factors were reported for some applications. Indeed, EFs of 200 and about 440 for an initial volume of 20 mL of diluted food extracts⁸⁰ or 4 mL of waters (including a concentration step of the desorption solution by evaporation)⁸⁵ were reported, respectively.

The potential of the MIP-SPME fibers was studied by comparing their efficiency to extract target analytes with fibers based on PA,⁷⁹ DVB¹⁹² and PDMS.^{79,192} In all cases, higher extraction efficiencies were obtained with the MIP-SPME fibers. However, it should not be forgotten that the amount of extracted analyte is proportional to the amount of extracting phase and that the MIP fibers have larger dimensions than those commercialized, that are coated with no more than 0.5 μ l of polymer. At last, as for the previous extraction techniques, the selectivity brought by the MIP was exploited to facilitate the direct analysis of the extract by IMS.¹⁹⁴ When the reusability of the fiber was studied, it was high, with up to 25¹⁹³ or 100 cycles.⁷⁹

To improve the extraction efficiency and stability of a MIP-fiber, the fiber was prepared by dispersing a nanocomposite of GO and of metal-organic framework (MOF, ZIF-8) in the polymerization solution.⁸⁵ At last, a polymerizable β -cyclodextrin was used as monomer to form a so-called supramolecularly imprinted polymeric SPME coating for the extraction of phenols, including bisphenol A, from waters leading to a higher binding capacity than the MIP

prepared with the conventional MAA monomer.⁷⁹ This MIP was also selective as IFs between 1.4 and 2.3 depending on the target molecules were measured using a β -cyclodextrin based-NIP. Unfortunately, the IF values with the MAA-NIP were not provided, which prevents the evaluation of the selectivity contribution of the β -cyclodextrin-based approach compared to the single use of MAA.

SBSE and related techniques

Recently the inner and outer surfaces of a silica capillary (15 x 1 mm) was immersed in a polymerization solution leading to a capillary both filled and coated with a MIP, thus increasing its binding capacity compared to the previously described MIP-SPME devices.⁸⁴ This in- and out-tube coating-SPME device was applied to the extraction of endocrine disrupting chemicals from waters in less than 30 min. The reproducibility of the binding amount of one fiber is 2.4–6.6% (RSD, n=5) and fiber-to-fiber is 4.5–8.1% (RSD, n=5) and authors did not observed a significant change in the binding properties over 100 cycles, which indicates an excellent stability and reusability of this coating approach.

If the objective of this work was to increase the amount of MIP sorbent by filling the capillary inside, the same objective motivated other groups to developed MIP-SBSE type devices, as for conventional SBSE devices whose potential has been recently reviewed.¹⁹⁵ For this an iron bar (15 x 2mm diameter) was activated in surface and immersed in the polymerization mixture.⁷⁸ Despite the good performances obtained for the extraction of naphthalene sulfonates from sea waters in terms of recoveries, selectivity, and reusability (50 cycles), no data related to the dimension of the layer were provided. In the same way, a sealed glass tube containing an iron wire (30 x 5 mm) was introduced in a second glass tube containing 3 mL of the polymerization mixture.¹⁹⁶ In this case, the resulting MIP layer thickness was estimated to 1.41 μm . Extraction recoveries higher than 80% with variations of 4.11% (RSD, n=5) from batch-to-batch indicate a good efficiency and reproducibility of the preparation procedure. This device was applied to the extraction of semicarbazide from fish samples. A similar approach was used by introducing a sealed glass tube (20 x 2 mm) containing a 16 mm iron rod in 0.4 mL of the polymerization mixture to prepare a MIP stir bar for the extraction of six β -agonists from food extracts previously treated by TCA and LLE.⁷⁷ This MIP-stir bar was reused more than 60 times and was very selective towards the target compounds giving rise to higher recoveries on the MIP (40–90%) than on the NIP (<20%) in 70 min.

In a recent work, Alvani-Alamdari *et al.* compared a MIP-dSPE procedure with a MIP-SBSE procedure for the extraction of carbamazepine from precipitated serum.¹⁷⁶ The MIP-SBSE was prepared by introducing a 30 mm magnetic core coated with glass in the polymerization solution. The same polymerization mixture was used to immerse $\text{Fe}_3\text{O}_4@\text{SiO}_2$ NPs to prepare MIP-dSPE particles. The MIP-stir bar (MIP amount not mentioned) or 40 mg (optimized amount) of magnetic MIP NPs were immersed during 15 min in a 500 μL plasma sample (after a precipitation step) and desorbed for 20 min. A better sensitivity was obtained in dSPE, since NPs have a higher surface-to-volume ratio.

A stir bar was also prepared by introducing magnetic NPs as magnetic cores in a glass insert (3 cm x 4.5 mm) containing the polymerization mixture (35 mg NPs in 0.5 mL of the polymerization mixture) and used as a mold.¹⁹⁷ After its removal from the glass insert, a thin PTFE strip was wrapped around the middle of the stir bar to ensure a correct rotation under stirring. This MIP-SBSE device was used for the extraction of fungicides from orange extracts. An EF of about 16 was obtained after 50 min of treatment that included a 10 min washing step to remove the interfering compounds, thus providing a high degree of clean up.

To prepare a larger device, the *in situ* bulk polymerization of a MIP at the surface of a vinylized-PTFE membrane (with a 25.3 mm diameter using 1 mL of polymerization mixture) placed between two magnet rings was recently proposed.¹⁸⁷ This MIP-disk was then immersed during 30 min in a 200 mL water sample for the selective extraction of a cocaine metabolite. After washing with 50 mL of water, the desorption was achieved in 30 min with 5 mL of acidified methanol further analyzed by IMS.

In contrast to the increase in the dimensions of the extraction devices generally sought by moving from SPME to SBSE, the development of MIP nanofibers has been recently proposed. Indeed, MIP nanofibers were successfully fabricated by electrospinning while introducing Nylon 6 in the sol-gel polymerization mixture. Fibers with diameters in the 80–145 nm range were obtained and applied to the extraction of bisphenol A from pure aqueous media.¹⁰⁰ A binding capacity of 103.8 mg/g was obtained, the selectivity being proven with recoveries on MIP and NIP of 83.5% and 36.8 %, respectively.

Extraction devices combining MIP with membranes or plates

Dispersive extraction on membranes or plates

Other formats complementary to particles, fibers, stir bars or magnetic disks previously described, have been proposed to carry out extraction under equilibrium. As an example, a membrane was prepared using MIP particles (15 mg) and agarose.¹⁹⁸ The resulting membrane (1 x 10 mm diameter) was placed into a 12.5 mL sample for the extraction of sulfonamides from waters. A small volume of 250 μ L was sufficient for the desorption and EFs higher than 20 were reported. Agarose was also involved in another reported work related to the use of a fiber glass paper (disk of 0.5 x 6 mm diameter) put in contact with MIP particles and agarose and the resulting MIP-disk was introduced in 250 μ L urine for 2 h for the extraction of cotinine.¹⁹⁹ MIPs were also recently produced at the surface of polyethylene filter plates (no data provided related to their size) previously treated by multi-walled CNTs.³⁶ Four plates were mixed with 5 mL cosmetic product extracts for the selective extraction of prednisone in just over 2.5 h.

A RAFT polymerization method, often chosen to control the thickness of the MIP layer, was selected for the synthesis of a MIP at the surface of hydroxylated-PDMS plates (1 x 1mm) and 10 mg of these MIP-PDMS plates were mixed with 5 mL orange juice for 60 min for the selective extraction of folic acid.²⁰⁰ Another way to prepare such a membrane consisted in

applying the polymerization mixture to a 1.26 cm diameter paper. Three repetitive deposits (with drying step between the deposits) were required to obtain a sufficient MIP thickness. This device was immersed in a soda drink for the selective extraction of quinine.⁹⁹ Imprinted membranes of 40 μm -thickness were prepared by the cross-linkage of chitosan around methylparaben (MP) used as template on the top of a glass plate.⁹⁷ These membranes were involved in a matrix solid phase dispersion procedure: 150 mg of MIP-membranes were mixed with 50 mg of powder sunscreen sample and sea sand. The mixture was further introduced in polypropylene cartridge between frits and a washing step with hexane was applied before the elution of MP by acidified methanol. No data related to the reproducibility of the synthesis of these different devices were reported.

Membrane protected solid-phase extraction

Recently, MIP spherical particles prepared by emulsion polymerization were encapsulated in a polypropylene (PP) porous membrane for the direct extraction of triazines from tea extracts.¹⁵⁰ The amount of MIP introduced in the membrane and the size and number of membranes used for one extraction were optimized by a Box-behnken design. Three bags of 1.5 x 1.5 cm containing each 50 mg of MIP particles allowed the extraction of triazines in 35 min from a hexane extract of tea (10 mL). This method was compared to a conventional SPE procedure with C18 silica showing the higher efficiency of the MIP-bag approach to limit matrix effects. A similar approach using a smaller amount of MIP, 50 mg of MIP introduced in a unique cone-shaped PP membrane, was applied to the extraction of cathinones from 1 mL urine in 4 min.²⁰¹ This device was used 27 times without observing loss in recoveries. At last, 10 mg of MIP particles were packed in a dialysis bag (21 x 15 mm) to extract luteolin from bacteria extracts in 200 min, the bags being reusable for 5 extraction cycles.⁴⁸ No data related to the reproducibility of the synthesis of these different devices were reported.

Concentration of target by deposition on membrane/plate surface

MIP-membranes were also produced to selectively concentrate target analytes on their surface. For example, metalloproteins (MPs) were selectively concentrated from plasma sample deposited on the surface of a MIP-MALDI plate, prepared by polycondensation of dopamine in the presence of an MP on the plate.⁹⁵ After 1 h of extraction (contact time) and three washing steps, the MPs were analyzed by MALDI-TOF-MS. This procedure is summarized on Figure 10.

A strong enhancement of their MS signal and a low intensity of the albumin peak was reported thus demonstrating the selectivity of the concentration process that took place on the plate. A MIP for a glycopeptide antibiotic was also recently prepared in the pores of a microporous membrane of polyvinylidene fluoride (2.5 x 3 cm) and applied to the extraction of this target from fetal bovin serum.²⁰² After 2 h of extraction (contact time) and a washing step, the glycopeptide was recovered in 5 mL of methanol further analyzed by UV. Some matrix effects being observed, a protein precipitation step was first applied to the sample thus allowing to

obtain accurate results. Again, no data related to the reproducibility of the synthesis of these devices were reported.

Figure 10: Overall workflow of MIP formation, sampling and MALDI-MS detection of an MP, metallothionein. Reproduced from Vaneckova, T.; Vanickova, L.; Tvrdonova, M.; Pomorski, A.; Kręžel, A.; Vaculovic, T.; Kanicky, V.; Vaculovicova, M.; Adam, V. *Talanta* 2019, 198, 224–229 (Ref ⁹⁵) – Copyright 2019, with the permission from Elsevier.

Conclusion

Throughout the review, we highlighted the diversity of approaches leading to the preparation of MIPs as selective extraction media for targeted molecules from complex samples. These sorbents have proved their worth for the selective trapping of molecules with very varied physico-chemical properties. Recent results obtained for proteins, targets that are currently particularly studied, suggest that they will in the near future be an alternative to antibodies that are still widely used in the clinical field.

Significant progress has been made by the authors in validating these materials for use in real samples, although it appears that it is still necessary to continue studies on the validation of synthesis, with little works highlighting this aspect.

Particular emphasis was also placed on so-called green synthesis to limit the consumption of toxic reagents, as well as on the removal of conventional chromatographic methods, since the removal by the MIP of interfering compounds from the extracts allows the direct detection of the target analyte in the extract by detection methods such as direct UV detection and MS without observing matrix effects.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Nathalie Delaunay holds a Ph.D. degree in analytical chemistry from the University of Pierre et Marie Curie Paris and a Master degree from ESPCI Paris. She is a CNRS researcher at the LSABM (ESPCI Paris). She focuses her research on the development of analytical methods for trace analysis by liquid chromatography and capillary electrophoresis in complex samples. She also works on electrokinetic or selective preconcentration techniques (immunosorbents, ion-imprinted polymers). The targeted compounds can be lanthanide or polyoxometallic ions, PAHs, explosives or glycoproteins. She is the author of about 60 publications. She is currently President of Club Ile-de-France of AfSep (Francophonie Association of Separation Sciences).

Audrey Combes received her Ph.D of University Pierre and Marie Curie (Paris, France) in Biochemistry, with Jean-Michel Camadro in the Department of Mitochondria, Metals and Oxidative stress at Jacques Monod Institute. Her research interest involve sample treatment based on molecular recognition and LC/MS analyses for developing targeted, and quantitative approach, and untargeted approach (metabolomic) for small molecules in different type of environmental or biological samples.

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