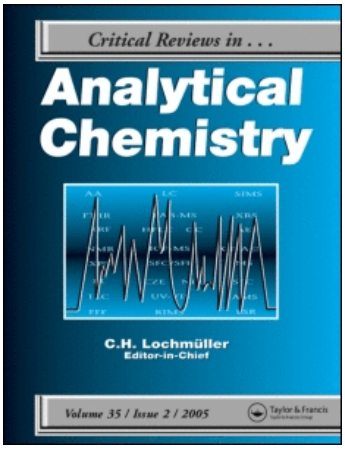

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Progress in Development of Molecularly Imprinted Polymers as Sorbents for Sample Preparation

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Sample preparation has been one of the most often investigated steps in analytical procedures. These investigations are focused on problems such as isolation of analytes from the sample matrix, matrix simplification, analyte enrichment to the level above the detection limit of the instrumentation used, and the removal of interfering species to improve the final determination. Techniques based on solid (adsorption) and pseudo liquid (absorption) media play an important role in sample preparation because of their universal applicability, possibility of automation and low cost of implementation. The use of these techniques reduces or even completely eliminates organic solvents from analytical procedures.

Solid phase extraction (SPE) and its special mode, solid phase micro-extraction (SPME), are among most commonly used sample preparation techniques. The search for novel sorbents characterized by their unique sorption properties aims at expanding the applicability of SPE and SPME. One of such novel groups of sorbents are molecularly imprinted polymers—MIPs. The purpose of this paper is to review recent publications on synthesis and applications of MIPs as well the procedures used to study MIPs.

Keywords Molecularly imprinted polymers, sample preparation, solid phase extraction, adsorbents

INTRODUCTION

Despite the development of new, increasingly more efficient and sensitive analytical techniques, such as hyphenated techniques, sample preparation remains one of the key steps of any analytical procedure. The objectives of this step include analyte enrichment and isolation from interferences as well as matrix replacement to make it compatible with the selected technique of final determination. As a result of the recent trend to limit or completely eliminate organic solvents from analytical procedures, an increasingly more important role is played by solid phase extraction techniques, such as solid phase extraction (SPE), solid phase micro-extraction (SPME), and stir bar sorptive extraction (SBSE). This interest also results from the fundamental limitation of liquid-liquid extraction (LLE), i.e., limited availability of solvents having high affinity for analytes and at the same time insoluble in sample matrix, which is especially evident in the case of water analysis.

Due to their favorable mechanical properties, solid sorbents can be used in a number of different configurations: as packings in columns or sorption traps in the form of grains, granules, monoliths, thin film on a support, coatings or particles in filtration media. As a result of ready availability of a wide range of adsorbents, the use of adsorption for analyte isolation allows the determination of a variety of compounds with widely different polarities, such as pesticides, phenols, chlorophenols, pharmaceuticals and their metabolites, polycyclic aromatic hydrocarbons and heavy metals (1–9). Solid sorbents have been successfully used for sample preparation of gaseous, aqueous, food and biological samples (10–14) as well as in clinical, forensic and drug analysis (15, 16). The extraction process depends on the type of sorbent used and can make use of simple adsorption or chelation, ion exchange and molecular exclusion. Adsorption can be non-specific, in which case weak dispersive interactions (van der Waals forces) will dominate. However, for the types of analytes mentioned above, adsorbents utilizing specific interactions resulting from analyte polarity, ionic nature

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or the presence of specific functional groups are preferred. It should be pointed out that specific interactions do not eliminate non-specific interactions, thus enabling isolation of highly hydrophobic compounds. The effect of both factors on the purity of extracts is different and depends mostly on the kind and composition of primary sample.

Among commercially available solid sorbents, there are many types that, due to their chemical composition and structure, can be involved in specific (polar sorbents), non-specific (non-polar sorbents) and ionic (ion exchangers) interactions. Most commonly used sorbents include: C_8-C_{18} bonded silica, polymeric sorbents (primarily styrene-divinylbenzene copolymers), zeolites, carbonaceous sorbents, and amino-bonded silica. At the same time, there is a continuing need for the development of novel sorbents with improved selectivity towards groups of compounds or even individual compounds. Examples include immunosorbents, where selectivity is accomplished through the specificity of interactions of antigen-antibody (17). A less expensive and time-consuming solution of great potential are MIPs. The principle of operation of MIPs is similar to that of immunosorbents—they exhibit molecule-recognition selectivity (18–20), but in the case of MIPs the selectivity is controlled by the person designing the adsorbent. This is achieved by the proper selection of a template compound and polymerization conditions (solvent, initiator, monomer). MIPs are characterized by high chemical and thermal stability as well as good mechanical properties. The synthesis and operation of MIPs are depicted schematically in Figure 1.

Although the reasons for development of novel sorbents mentioned above are also valid for SPME, in the latter case the focus is on improved mechanical properties of coatings. In SPME, due to fiber size and the fact that in the majority of cases fused silica is used as a fiber material, the key factors are mechanical stability and the strength of binding sorbent to the fiber. In addition, it should be pointed out that the number of fiber coatings available commercially, particularly polar ones, is very limited (21). Consequently, the sol-gel method of producing coatings has recently gained considerable attention. The coating is formed through hydrolysis and condensation of appropriate alkoxides. The coating formed is chemically bonded to the fiber. Furthermore, adsorbents with desirable physico-chemical properties can be obtained through a judicious selection of the alkoxide and modifier (22).

The procedures discussed above are not the only ways of developing novel sorbents. The search for new adsorbents continues. The possibility of adapting for analytical purposes materials known from other areas of chemistry, such as nanotubes, is also under consideration (23, 24).

The objective of this review is to present the state-of-the-art in the area of preparation of MIPs intended for analytical applications. The papers published over the last two years are discussed in more detail. Due to certain transferability of MIPs among different analytical techniques, the focus of the paper is on properties and significant application parameters of the sorbents without assigning them to specific sample preparation techniques.

MOLECULARLY IMPRINTED POLYMERS

Although the idea of polymer synthesis by introduction of compounds with specific properties and molecular parameters has long been known, it was the first MIP application in chemical analysis (25) that brought about an increased interest in materials of this type. An exponential growth in the number of papers on new synthetic procedures and applications of MIPs has been observed ever since (26). These investigations have been competently discussed in a number of reviews dealing with both methods of MIP synthesis (27–30) and their applications (31–36). Examples of MIP applications can also be found in publications describing sample preparation techniques for specific groups of analytes (37–40).

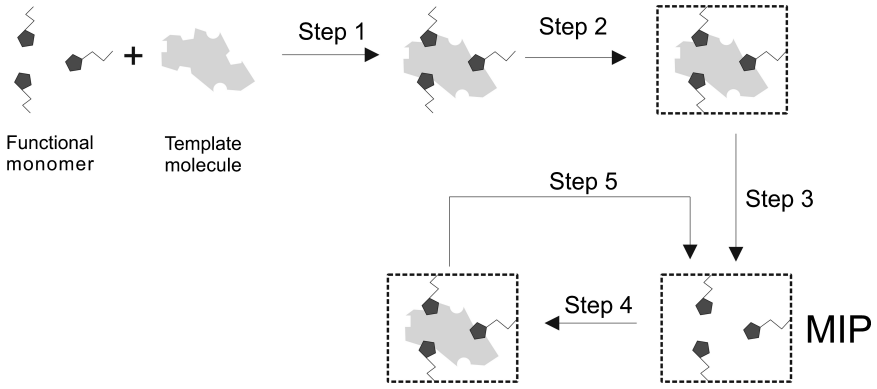

FIG. 1. Synthesis and isolation of a target compound using a molecularly imprinted polymer. Step 1 – prearrangement of functional monomers around the target molecule, in their most favorable geometry; Step 2 – polymerization in presence of the cross-linker leading to "frozen" monomer geometry; Step 3 – washing out the template compound; Step 4 – rebinding process with template analogous compounds; Step 5 – extraction of absorbed analytes.

Preparation Procedures

The development or selection of an appropriate method of synthesis and its optimization are critical factors in the production of sorbent with desirable properties. It should be pointed out that the desirable effects are not limited to the formation of cavities suitable for retaining target analytes, but also optimization of extraction efficiency through an increase in accessibility of active sites (pore structure), limitation of interactions with interfering substances, producing a sorbent with the optimal form, mechanical properties, chemical resistance and, in some cases, high thermal stability. An additional problem in the synthetic procedure is the need to account for the composition of sample matrix, and particularly the presence of polar compounds and/or those capable of forming hydrogen bonds (41). MIPs can be obtained in many different forms:

- particles—compact polymeric material produced through synthesis is further ground and sieved to obtain a desired fraction with a narrow range of particle diameters (42–46),
- beads—this term is generally used for adsorbent particles formed during the synthesis step. The procedure is usually carried out by one of the two techniques: suspension and precipitation polymerization (47, 48),
- monolithic packings—polymer synthesis is performed *in situ* in a column, which is ready for use right after the removal of template (49,50,51),
- coatings—generally coated onto an appropriate support already during the synthesis step (52–55),
- monolayers of specifically interacting compounds bound to the surface of support made of other materials (56–58),
- fibers—synthesis is performed as for monolithic packings. After synthesis the capillary is destroyed and the remaining polymer constitutes a fiber (59).

The most important factor determining properties of an MIP is the selection of appropriate reagents, i.e., template compound, functional monomer, cross-linking agent, initiator and solvent (porogen), in which the reaction is carried out.

Characteristics of Intermolecular Interactions MIP-Template

Proper selection of reagents, reaction medium and conditions should take into consideration the complexity of formation of selective sites in the polymer structure so as to obtain a polymer capable of not only highly selective recognition of target analytes but also having good kinetic parameters. A good starting point in designing an MIP is elucidation of the nature of intermolecular forces both during polymerization of functional monomers in the presence and absence of template (non-imprinted polymer analogue—NIP) and in the subsequent rebinding of target analyte. Three approaches are used in practice (60).

The first approach involves the methods based on the data obtained from adsorption/desorption processes. The simplest example of this approach is analysis of chromatographic data (61) (including the use of theory of non-linear chromatography [62, 63]) obtained using a column packed with an MIP, in which various analytes were separated. Additional information is provided by using eluents of various compositions in the separation process (64, 65). This approach also includes direct measurement techniques, in which equilibrium adsorption is carried out. In this case, the amount of adsorbed analytes as a function of sample matrix and the kind of solvent used for template removal from the polymer are investigated (66–68). The data acquired in these experiments can also be used to find the best adsorption model by fitting to known adsorption isotherms (69–71).

The second approach includes techniques enabling direct determination of the kind of intermolecular forces in the reaction mixture as well as in the template-MIP complex (72). Spectroscopic techniques, such as UV-VIS (73, 74), FTIR (73, 75, 76), and NMR (73, 77–79) are commonly used for this purpose.

The third approach allowing elucidation of the nature of intermolecular interactions is based on *ab initio* calculations through formulation of appropriate algorithms, followed by comparison of the results with experimental data. Molecular orbital calculations using Gaussian 03 software are an example of this approach (74). The calculations revealed that in the nickel(II) phthalocyanine tetrasulfonic acid tetrasodium—poly(allylamine) hydrochloride (template-functional monomer) system, the polymer forms a cage around the nearly planar, rigid template molecule. The terminal amino groups were spatially oriented such that there were strong interactions between the terminal amino groups of the polymer and the sulfonate groups of the template (Fig. 1). Other authors used molecular dynamics simulation procedure accounting for the presence of hydrogen bonding between the template and various types of functional monomers to design MIPs (77). In these calculations, 17β-estradiol was used as a template, while compounds with various acidities were used as potential functional monomers. These included: methacrylic acid (MAA), 2-(trifluoromethyl)acrylic acid (TFMAA), 2-(diethylamino)etyl methacrylate (DEAEMA), 4-vinylpiridyne (4-VP), 2-vinylpiridyne (2-VP), methacrylamide (MAAM), N-vinylpyrrolidone (NVP), 4-acetoxystyrene (AST) and 2-hydroxyethyl methacrylate (HEMA). The effect of porogen on the structure of polymer was also taken into account in the calculations. The results of the calculations revealed that the monomers most complementary with the template with respect to intermolecular interactions are MAA, DEAEMA and MAAM. The results were confirmed by 1H-NMR, which confirms their usefulness in designing MIP synthesis. The usefulness of simulation methods for the system template - functional monomer - porogen was also demonstrated in other works, where different modeling protocols were used (80–83).

Another way to obtain the optimum composition of the reaction mixture, not involving elucidation of the nature of intermolecular interactions, is the use of combinatorial chemistry

(84). The proposed procedure involves synthesis of many different kinds of MIP and their evaluation by screening. In their investigations, the authors used a drug substance containing aromatic, hydroxyl and -O-$CONH_2$ functional groups. The synthesis was carried out using all possible combinations of the four most popular functional monomers (MAA, 4-VP, acrylamide, styrene) and two porogens (ACN, toluene). The amount of cross-linking agent (ethylene glycol dimethacrylate—EGDMA) was maintained constant. A solvent solubility study was carried out on the drug substance prior to polymerization to find which of the 36 solvents tested provided the highest extraction yield of the substance from the polymer matrix. The results of these studies allowed choosing the optimum set of reagents for MIP synthesis as well as the optimum solvent to recover the analyte from the MIP. It should be pointed out that minimum amounts of chemicals were used: for a single synthesis 0.4 mmol of a functional monomer were combined with 0.1 mmol of the template, 2 mmol of the cross-linker and no more than 0.5 mL of a porogen.

Optimization of MIP Synthesis Procedures

It should be evident that the methods described above are for now complementary and cannot replace detailed experimental studies for specific applications. Several examples of optimization of conditions of MIP synthesis are described below.

One such example can be comprehensive studies on digoxin as a template compound (85). Using bulk polymerization, the effect of such factors as kind of functional monomer (MAA and EGDMA), kind and amount of the porogen (ACN, dichloromethane) used, and the method of polymerization initiation (UV lub thermal) were investigated. The template was removed using Soxhlet extraction with a mixture methanol:acetonitrile or microwave extraction using acetonitrile, dichloromethane and a mixture of methanol:acetonitrile. The surface morphology was investigated by scanning electron microscopy. The studies revealed that an excess of functional monomer results in a significant increase of non-specific interactions, thus lowering the polymer selectivity. It was also found that more microporous structures were obtained when using acetonitrile rather than dichloromethane as the porogen and that the larger porogen volumes produced better defined spherical polymer microparticles.

Chemometric techniques, such as the Doehlert experimental design, can also be used to optimize the polymerization process (86). The influence of kind and degree of cross-linking on template recognition was studied using S-propranolol as the template. The same functional monomer (MAA) and porogenic solvent (ACN) were used, so to vary the degree of cross-linking and the kind of cross-linker, two cross-linkers based on the same monomer were selected: ethylene glycol dimethacrylate (EDGMA, two polymerizable double bonds) and trimethylolpropane trimethacrylate (TRIM, three polymerizable double bonds). The degree of cross-linking was controlled by varying the ratio of the EDGMA:TRIS mixture with respect to the functional polymer. The response factor was the percent of ^{3}H-labeled propranolol adsorbed at equilibrium. The studies revealed that the non-specific binding increased with the concentration of polymer or analyte. For low polymer and analyte concentrations, binding increased with the degree of cross-linking.

METHODS OF MIP SYNTHESIS

The variety of procedures of sorbent synthesis methods makes it difficult to come up with a simple classification of these procedures. However, since the synthesis is the key for producing MIPs with desirable properties, several examples of preparative methods for the production of MIPs for specific analytical purposes are described in this review.

The first example is an MIP developed for a flow-injection system for the determination of carbamate pesticide carbaryl in complex biological matrices (47). The MIP imprinted with carbaryl as the template was obtained by suspension polymerization. A polymeric surfactant synthesized from 2-(N-ethylperfluorooctanesulfonamido)ethyl acrylate and acryloyl polyethylene 1000 monomethyl ether was used as a reaction medium providing conditions for suitable dispersion of polymer beads. The use of saturated solution of the porogen (chloroform) in perfluoro(methylcyclohexane) was required for the synthesis. The amount of surfactant used in the polymerization mixture influenced the size of the beads, and also determined the degree of cross-linking. To elute carbaryl from the binding sites on MIP, the pH of the elution solution was changed to 2.0, which resulted in protonation of the secondary amine group and release of the analyte. The pH change at the flow cell generated by the deprotonation of carbaryl in alkaline medium was used to determine the carbaryl concentration.

An example of another solution is the use of MIP as a monolithic bed. It is a fairly recent approach (87, 88). This technology was developed to eliminate problems associated with traditional methods of polymerization, in which the obtained polymer had be crushed, ground and sieved prior to use. These additional steps are not only time consuming, but also result in the reduction of number of active sites and, if used for the separation of mixtures, significantly deteriorate efficiency of this process. Monolithic MIPs are produced by *in situ* polymerization directly in a cartridge or column. The procedure involves a single step and is very reproducible. Furthermore, preparation of monolithic polymers requires smaller amounts of templates, which substantially reduces their cost.

An example of this procedure is the preparation of a monolithic column used for the separation and quantitation of caffeine and theophylline in various kinds of green tea (51). The morphological characteristics of monolithic MIP were investigated by scanning electron microscope, which revealed that both mesopores and macropores were present in the monolith. The former increase adsorption capacity of the polymer, while the latter are responsible for a high external porosity and a high permeability of the column. The authors also performed a thorough analysis of thermodynamic parameters of adsorption process, which

revealed the mechanism of analyte retention. Hydrogen bonding and hydrophobic interaction play an important role in the retention and separation. The two analytes differ in substitution of hydrogen in the amino group (theophylline) by the methyl group (caffeine). Since the template for the MIP was theophylline, whose hydrogen from the amino group can participate in hydrogen bonding, the selectivity of adsorption was determined by the higher tendency of theophylline to form a stable system with the polymer than that of caffeine. Thermodynamic data obtained by Van't Hoff plots (logarithm of retention factor vs. reciprocal temperature) revealed an enthalpy-controlled separation, while the entropy effect for the two analytes was very similar.

To some extent, sorbents whose selectivity was increased by introducing on the support surface compounds capable of specific interactions, such as chelating agents, can be considered a form of MIPs. Surface imprinting is particularly attractive if we consider diffusional limitations associated with extraction using classical MIPs. If active sites are placed on the surface of sorbents, the diffusional path of analytes to the active sites is substantially reduced, thus resulting in a considerable shortening of time of extraction (89, 90).

A good example of MIP of this type is an ion-imprinted polymer for the isolation and enrichment of dysprosium Dy(III) (56). Silica gel was used as a support. Silica gel with activated hydroxyl groups was placed in solution of 3-aminopropyl trimethoxysilane, yielding aminopropyl silica gel. Thenoyltrifluoroacetone (TTA) was used as the compound selectively binding Dy(III). In order to generate active sites, TTA was bonded to the aminopropyl silica gel already as a complex with dysprosium $(TTA)_3Dy(III)$. An analogous procedure in which TTA was bonded to the amino groups in the absence of Dy(III) resulted in preparation of a non-imprinted polymer.

The above approach to surface imprinting, however, has some limitations related to a restricted number of active sites. This is primarily due to the limited surface of supports used. In addition, binding of active groups to the support surface takes place through covalent bonds, and the reaction is difficult to carry out and control, which precludes the optimum filling of the surface. Moreover, as a result of restricted access to active sites, rebinding capacity is lower than would follow from the amount of the template compound used. Consequently, recent research has been focused on the use of nanoparticles as supports (91, 92). As a result of a favorable surface/volume ratio for nanoparticles, the majority of chemically active groups are located on the surface, where they are easily accessible to reagents. Increased dispersion of sorbents results in an increased interfacial surface area, thus improving extraction kinetics. An example of this approach is the preparation of a sorbent through coating of a layer of MIP onto the surface of silica nanoparticles 100 nm in diameter (93). A two-step procedure was used to obtain the acrylamide-monomer-capping silica particles. First, aminopropyl modification of silica nanoparticles was carried out with 3-aminopropyltriethoxylsilane (APTS). Then, the amino end groups of APTS monolayer were further acryloylated with acryloyl chloride (CH2=CHCOCl). The MIP layer was synthesized in acetonitrile using 2,4,6-trinitrotoluene (TNT) as the template compound, acrylamide (AA) as the functional monomer, EGDMA as the cross-linking agent and azo-bis-isobutyronitrile (AIBN) as the initiator. The thickness of imprinted polymer shells could be controlled by varying the ratio of AA-APTS-silica to the functional monomer and cross-linking agent and ranged from 10 to 40 nm. The authors observed that decreasing the shell thickness increased rebinding capacity, but only to some extent. Decreasing the shell thickness below 25 nm did not result in an increase in adsorption capacity, which suggests that 25 nanometers may be a critical scale to meet the requirements that provide the complete removal of templates and the best site accessibility to target molecules, forming the highest average density of effective imprinted sites in imprinted polymer shells. Under optimum conditions, this polymer had a five-fold higher adsorption capacity than an analogous MIP obtained by traditional methods.

The procedures discussed above constitute just a small fraction of methods of synthesis of MIPs described in the literature. In addition to the most commonly used bulk, precipitation, *in-situ* and suspension polymerization, novel methods of preparation of MIPs are being sought, which is at least partly due to various ways of their implementation into analytical procedures. As follows from the data compiled in Table 1, in addition to the polymerization techniques mentioned above, multi- and one-step swelling and polymerization method (94), electrochemical polymerization (95), electrodeposition (96–98), grafting on monolithic column (99), photografting (100, 101), and sol-gel method (102) have been also employed.

APPLICATIONS

The data listed in Table 1 reveal that MIPs have been synthesized for isolation/enrichment of a great variety of analytes: pesticides (47), phenols (50), antibiotics (103, 104), drugs of abuse (105) and heavy metals (106, 107). The range of samples from which target analytes have been extracted is also impressive and includes blood (108, 109), urine (43, 110), food (95, 111, 112), hair (113), and environmental samples (94, 97, 114). MIPs have also found application in other areas of chemistry, such as catalysis (115) or in refolding of proteins (116). A few selected applications of MIPs are described below, including information on optimization of sample preparation conditions.

A good example of application of MIP to isolate analytes from matrices as complex as milk and its products is the determination of the antibiotic chloramphenicol and its residues (111). The authors demonstrated that the only preliminary step required prior to extraction is centrifuging, which allowed the sample preparation time to be reduced several fold compared to classical LLE. In order to fully realize the possibilities of molecularly imprinted polymers, detailed planning and optimization of analytical procedure is required.

An example of a well planned and optimized sample preparation step is the procedure for determination of 4-aminophenol in

TABLE 1
Compilation of literature data on preparation and analytical applications of MIPs

		Reagents						Extraction		
Analyte	Sample	Template	Functional monomer	Cross-linker	Solvent	Polymerization method	Polymer form	Washing step	Elution	Reference
4-Aminophenol	Water	4-aminophenol	Hemin MAA	EGDMA	Chloroform/ DMSO	Bulk	Particles	MeOH:HAc	Tris-HCl (buffer)	42
Sulfamethazine	Milk	Sulfamethazine	MAA	EGDMA	ACN	Bulk	Particles	MeOH:HAc	MeOH:HAc	119
Dy(III)	Water (buffer)	$(TTA)_3Dy(III)$	-	-	MeOH	Bulk	Surface imprinting on silica gel	6 mol/L HCl	1.5 $molL^{-1}$ HCl	56
Cotinine	Urine	Cotinine	MAA	EGDMA	Cl_2CH_2	Bulk	Particles	MeOH:HAc	ACN:TFA	43
Diethylstilbestrol	Water	Diethylstilbestrol	MAA	EGDMA	ACN	Bulk	Particles	MeOH:HAc	MeOH:ACN	44
Carbaryl	Plasma	Carbaryl	MAA	EGDMA	PFPS[a]: chloroform: perfluoro (methylcyclo-hexane)	Suspension	Beads	Acetone	ACN:phosphate buffer	47
Caffeine theophylline	Green tea	Theophylline	Acrylamide	EGDMA	Toluene: dodecanol	In situ	Monolithic	THF, MeOH:HAc	CH_2Cl_2:MeOH:HAc	51
Metformin	Water, blood serum	Metformin	MAA	EGDMA	ACN	Bulk	Particles	MeOH:HAc	oxidation solution: H_2O_2, cupric polyphosphate	45
Benzodiazepines	Hair	Diazepam	MAA	EGDMA	Chloroform	Bulk	Particles	MeOH:HAc	HAc:ACN	113 120
Sinomenine	Plasma	Sinomenine	MAA	EGDMA	Toluene	Bulk	Particles	MeOH:HAc	MeOH:HAc	46
Paraoxan parathion	2-propanol	Paraoxan parathion	Methacryloyl-antipyrine	EGDMA	2-propanol water toluene	Surface imprinting	Beads	NaOH:MeOH	—	48
Paraoxan parathion	2-propanol	Paraoxan parathion	Methacryloyl-antipyrine-gadalonium	EGDMA	2-propanol water toluene	Surface imprinting	Beads	NaOH: MeOH	—	48
DL-tetrahydro-palmatine	Herb	L-tetrahydro-palmatine	MAA	EGDMA	toluene: dodecanol	In situ	Monolithic	MeOH:HAc	ACN	49
Phenolic compounds	River water	Bisphenol a	4-VP	EGDMA	Toluene: dodecanol	In situ	Monolithic	MeOH:HAc	ACN-HAc	50
Reserpine	Chloroform	Reserpine	MAA	EGDMA TRIM	Chloroform	Bulk	Particles	MeOH:HAc	MeOH:HAc	73
Triazines	Soybean corn lettuce	Prometryn	MAA	TRIM	Toluene	In situ	Coating	MeOH:HAc	MeOH:HAc	53
Bisphenol A	Water	Bisphenol a	4-Vp	TRIM	ACN	Precipitation	Particles	MeOH	MeOH:water	121
α-lactam antibiotics	Water	Penicillin G procaine	1-(4-vinylphenyl)-3-(3,5-bis-(trifluromethyl) phenyl)urea	EGDMA	MeCN	Bulk	Particles	MeOH:HCl	TBA[b]:MeOH	104

L-tryptophan	Citric acid buffer	L-tryptophan	Acrylamide	TRIM	ACN:TFA: HAc	In situ	Coating	EtOH:HCl	EtOH:HCl	52
Ochratoxin A	Red wine	Ochratoxin A	CN:QD:Py[c]	EGDMA	ACN	In situ electrode-position	Coating	Triethylamine: ACN: ammonia buffer	Triethylamine	96
Pinacolylmethyl-phosphonic acid	Water	Methylphospho-nic acids	MAA	TRIM	ACN	Bulk	Particles	HCl:Water: MeOH	Water	122
Al(III)	Water	8HQS[d]: $AlK(SO_4)_2$	Acrylamide 2-hydroxyethyl methacrylate	EGDMA	MeOH:water	Bulk	Particles	NaF	NaF	123
Organotin compounds	Biota	TBTCl	Sodium methacrylate	EGDMA	ACN	In situ	Particles	HCl:MeOH	HCl:MeOH	124
Organotin compounds	Biota	Divinylbenzoin-DBT	Sodium methacrylate	EGDMA	ACN	In situ	Particles	HCl:MeOH	HCl:MeOH	124
Hg(II)	Water	Hg(II):CTAB[e]	TPED[f]	Tetraethoxy-silane	Water	Suspension	Particles	EtOH/HCl	HCl:water	125
Emodin	Acetonitrile	Emodin	Acrylamide	TRIM	THF	In situ	Coating	MeOH:HAc	MeOH	126
L- PAA D-PAA	-	L- PAA D-PAA[g]	MAA	EGDMA	Non-polar solvents	Bulk	Coating	MeOH:HAc	MeOH:HAc	127
Bilirubin	Rat serum and bile	Bilirubin	MAA	EGDMA	CH_2Cl_2	Bulk	Particles	NaOH	NaOH	128
Thiabendazole	Citrus	Thiabendazole	MAA	EGDMA	Toluene: *iso*-octane	In situ	Monolithic	MeOH:HAc	ACN:H_2PO_4Citric acid:ACN	65
Xylenes	-	O-xylene	Hydrogels of chitosan	Genipin	HAc:MeOH: glucosamine	Bulk	Particles	HAc	HAc	129
Pazufloxacin mesilate	Human urine	Pazufloxacin mesilate	MAA	EGDMA	CH_2Cl_2	Bulk	Particles	ACN:HAc	ACN:HAc	130
Atrazine	Ground water	Atrazine	MAA	EGDMA	Toluene	Bulk	Particles	HAc:chloroform	-	114
Dansyl-phenylalanine	-	Dansyl-L-phenylalanine	4-VP MAA	EGDMA	ACN	Precipitation	Microspheres	MeOH:HAc: acetone	ACN	131
Chloramphenicol	Milk shrimp	Chloramphenicol	DEAEM[h]	EGDMA	Polyvinyl alcohol:water	Suspension	Microspheres	MeOH:HAc	MeOH:HAc	111
Fenbendazole	Beef liver	Fenbendazole	MAA	EGDMA	DMSO	Bulk	Particles	MeOH:HAc	MeOH:HAc	132
Bilirubin	Human serum	Bilirubin	B-cyclodextrin	1,6-diisocyanato-hexane	DMSO	Bulk	Particles	THF. EtOH	-	133
Uric acid	Human blood serum	Uric acid	Melamine	Chloranil	DMF	Bulk	Surface imprinting on silica gel	Hot water	Hot water	57
Zearalenone α-zearalenol	Cereal swine feed	CHDB[i]	1-allyl-piperazine	TRIM	ACN	Bulk	Particles	MeOH:HAc	MeOH:HAc	134

(Continued on next page)

TABLE 1
Compilation of literature data on preparation and analytical applications of MIPs *(Continued)*

		Reagents						Extraction		
Analyte	Sample	Template	Functional monomer	Cross-linker	Solvent	Polymerization method	Polymer form	Washing step	Elution	Reference
Triazine herbicides	River water	Atrazine	MAA TFMAA	EGDMA	Toluene	Multi-step swelling	Particles	MeOH:THF	Potassium phosphate buffer:ACN	94
Methylthio-triazine herbicides.	River water	Ametryn irgarol	MAA TFMAA	EGDMA	Toluene	Multi-step swelling	Particles	MeOH:THF	Potassium phosphate buffer:ACN	94
Bupivacaine mepivacaine *S*-ropivacaine	Acetonitrile	Bupivacaine mepivacaine *S*-ropivacaine	MAA	EGDMA	Toluene	Grafting on monolithic column	Surface	MeOH	ACN	99
Theophylline	MeOH	Theophylline	MAA	EGDMA	MeOH	Photografting	Film	MeOH:ACN	MeOH:ACN	100
Hydroquinone	ACN	Hydroquinone	MAA	TRIM	ACN:toluene	Precipitation	Microspheres	MeOH:HAc	MeOH:HAc	135
Ochratoxin A	Red wine	Ochratoxin A	Py	EGDMA	ACN	Electrochemical polymeriza-tion	Coating	Triethylamine: MeOH	Triethylamine: MeOH	136
Cholesterol	Cheese products water	Cholesterol	MAA	EGDMA	Chloroform	Bulk	Particles	THF:HAc	ACN	95
Mycophenolic acid	Human plasma	Mycophenolic acid	4-Vp	EGDMA	ACN:toluene	Bulk	Particles	MeOH:HAc	MeOH:HAc	108
Sulfamethoxa-zole	Water	Sulfamethoxa-zole	4-VP MAA acrylamide	EGDMA	1-dodecanol	In situ	Monolithic	MeOH:HAc	water:ACN	137
Fluoroquinolone antibiotics	Soil	Ciprofloxacin	MAA	EGDMA	MeOH	Suspension	Particles	MeOH:HAc	MeOH:HAc	138
Sodium dodecyl sulfate	River water	Sodium dodecyl sulfate	Py	-	Buffer solution	Electrochemical polymeriza-tion	Coating	Water	Water	139
Uracil	Water	Uracil	MAA	Acrylonitrile	Liquid CO_2	In situ	Membrane	HAc	-	140
Diacetylmorphine	Water	Diacetylmorphine	MAA	EGDMA	ACN	In situ	Monolithic	MeOH:HAc	Thermal	69
Daminozide	Apples	Daminozide	MAA	EGDMA	MeOH	Precipitation	Microspheres	NaOH:HAc	MeOH:HAc	118
Alkyl alkylphos-phonic acids	Soil	Pinacolyl methylphospho-nic acid	MAA	TRIM	ACN	Bulk	Particles	HCl:MeOH	Water	141
Nicotine	Hair	Nicotine	MAA	EGDMA	CH_2Cl_2	Bulk	Particles	MeOH:HAc	MeOH:HAc	142
Bisphenol A	Pig urine tap water human plasma human plasma	Bisphenol A	4-VP	TRIM	ACN:toluene	Precipitation	Particles	MeOH:HAc	MeOH	143

Cholesterol	Biological matrixes	Cholesterol	MAA	EGDMA	Chloroform: toluene	Bulk	Particles	Chloroform: HAc	Chloroform: EtOH:HAc	66
Tebuconazole	Water biological	Tebuconazole	MAA 4-VP	TRIM	ACN	Precipitation	Particles	MeOH:HAc	MeOH	64
Diethylstilbestrol	Fish water	Diethylstilbestrol	APTES[j]	TEOS[k]	MeOH	Surface imprinting	Particles	HCl:MeOH	MeOH	75
Triazines	Soil vegetable	Propazine methacrylate	MAA	EGDMA	Toluene	Precipitation	Particles	NaOH:MeOH HCl	ACN:MeOH HAc	144
Bisphenol A	River water	BPA-d_{16}	4-VP	EGDMA	Toluene	Multi-step swelling	Particles	MeOH THF	Water:ACN	97
Benzotriazole	Chloroform	Benzotriazole	MAA	Triallyl isocyanurate	Chloroform	Bulk	Particles	MeOH:HAc	MeOH:HAc	145
Carbamazepine	Urine wastewater	Carbamazepine	MAA	DVB-80	CH_2Cl_2	Bulk	Particles	MeOH	MeOH	67
Zn(II)	Celery	-	Zn(II)-8-AOQ[l]	EGDMA	MeOH chloroform	Bulk	Particles	EDTA	EDTA	146
EGCg ECg GCgm	Green tea	EGCg ECg GCg	2-VP	EGDMA	Cyclohexanol	Multi-step swelling	Particles	MeOH THF	50% EtOH	147
Nicotine	Cigarette smoke	(*S*)-nicotine	MAA TFMAA	DVB	Toluene: ACN	Precipitation	Microspheres	ACN	ACN	148
Metsulfuron-methyl	Water	Metsulfuron-methyl	4-VP MAA	EGDMA	Chloroform: ACN	One-step swelling	Beads	MeOH:THF	ACN	98
Ciprofloxacin	Human urine	Ciprofloxacin	MAA	EGDMA	MeOH:water	Bulk	Particles	MeOH:HAc	MeOH: trifluoracetic acid	149

[a]Perfluoro polymeric surfactant obtained by polymerization of 2-(N-ethylperfluorooctanesulfonamido)ethyl acrylates, acryloyl polyethylene 1000 monomethyl ether, 1,1′-azobis(cyclohexanecarbonitrile) in chloroform.
[b]Tetra-n-butylammonium hydrogen sulfate.
[c]CN—carbon nanotubes, QD—Nanometer-sized semiconductor quantum dots (CdSe core and ZnS shell), Py—pyrrole.
[d]8-hydroxyquinoline-5-sulfonic acid.
[e]Cetyltrimethylammonium bromide.
[f]*N*-[3-(trimethoxy-silyl)propyl]ethylenediamine.
[g]Phenylalanine anilide.
[h]2-(diethylamino) ethyl methacrylate.
[i]Cyclododecanyl-2,4-dihydroxybenzoate.
[j]3-aminopropyltrimethoxysilane.
[k]Tetraethylorthosilicate.
[l]8-acryloyloxyquinoline complex monomer.
[m]EGCg - (−)-epigallocatechin gallate, ECg -epicatechin gallate, GCg—gallocatechin gallate.

water. The procedure is significantly different from traditional ways of sample preparation (42). In a nutshell, the sorbent used played the role of a catalyst rather than a classical medium for analyte isolation. During the "sample collection" step, a peroxide solution in buffer was passed through the system to catalytically activate the polymer and obtained oxidized hemin groups. In the second step, called by the authors injection, a sample containing phenols was passed through the bed prepared in this manner. Under these conditions, phenols were oxidized to quinones or their free radicals, which allowed their amperometric determination. It is interesting to note that due to the role played by the sorbent bed in this procedure, the classical step of elution of adsorbed analytes from the sorbent was not used. The efficiency of the entire procedure expressed as the current measured was optimized using fractional factor analysis, where the factors considered were: buffer flow rate, buffer concentration, pH, H_2O_2 concentration and sample volume. Under optimum conditions the detection limit was 0.21 μmol/L, and the limit of quantitation 0.71 μmol/L.

The next example demonstrates the use of MIP for on-line enrichment and determination of metformin (oral antihyperglycemic agent) with chemiluminescence as a detection technique (45). A metformin-imprinted polymer was synthesized using MAA and EGDMA as monomers. Bulk polymerization was carried out in acetonitrile. The method was based on hydroxyl radical chemiluminescence—the hydroxyl radical generated by reaction of Cu(II) and hydrogen peroxide oxidized rhodamine B (RhB) to produce weak chemiluminescence which can be enhanced by metformin. The procedure involved four steps. In the first step, the metformin solution (or serum sample) flowed through the MIP column, and metformin was selectively adsorbed on the MIP. Next, the sorbent bed was washed with ultra-pure water to remove interfering substances. The next step involved several simultaneous processes. A mixture of hydrogen peroxide and cupric polyphosphate was passed through the MIP column and reacted directly with the adsorbed metformin. The metformin was quickly oxidized by the newly generated hydroxyl radical. In a polyphosphate medium the oxidized metformin transferred its energy to RhB, leading to the chemiluminescence process. The amount of metformin could therefore be quantitatively determined by recording the change in chemiluminescence intensity at 580 nm. The detection limit was as low as 4×10^{-9} g/mL when using 10 mg of MIP. During the oxidation process the structure of metformin was destroyed, resulting in weakened affinity for MIP and easy removal of the analyte before subsequent sampling.

Another approach illustrating potential applicability of MIPs is the polymer developed to isolate viruses. An MIP was synthesized targeting tobacco mosaic virus (TMV) (117). Various solutions, including water, 1M NaCl, 6M urea and 1M NaOH, were compared for their ability to remove the virus template from the MIP. The studies were carried out by the stationary method: freshly prepared MIP containing TMV was placed in solvents. Every 6 hours, a sample of solution was taken out of the mixture and analyzed for the TMV content. The use of 1 M NaOH as the eluent resulted in over 80% TMV template removal after five wash cycles. Viral binding studies were carried out in a similar manner. The MIP from which the template had been previously removed was placed in the TMV solution. The TMV virus binding capacity was expressed as the amount of virus adsorbed per gram MIP. The dependence of binding capacity on the monomer ratio (PAA:EGDMA) in the reaction mixture and the amount of TMV used in the polymerization process was investigated. The studies revealed that the highest binding capacity was obtained when using PAA:EGDMA in a ratio of 35:15% (v/v) with the amount of TMV in the reaction mixture being 0.4 mg/mL.

Another example of MIP application is the developed sorbent having catalytic properties (42). To this end, two types of monomers were used: MAA, which formed recognition sites and ferriprotoporphyrin IX (hemin), which formed catalytic sites. The sorbent was prepared to determine 4-aminophenol (4-Aph), which was used as the template. The obtained polymer mimicked catalytic properties of peroxidase.

The diversity of MIP uses in analytical procedures should also be mentioned. An example of such a diverse application is the use of MIP obtained by precipitation polymerization (MAA and EGDMA as functional monomer and cross-linker, respectively), and then the polymer particles were immobilized as a thin film on the surface of the electrode of the quartz crystal (118). The MIP was prepared to determine daminozide (DM) and its metabolite. A measure of the amount of adsorbed analyte was the frequency shift measured with the electrochemical quartz crystal microbalance. An NIP was used as a reference in the investigations. The studies revealed the relationship between the DM concentration in standard solutions and the frequency shift over a wide range of analyte concentrations. There was no linear relationship between the frequency shift and the logarithm of DM concentration in the entire concentration range, but in the range of 10^{-9} up to 10^{-6} mg/mL and from 10^{-6} up to 10^{-1} mg/mL, separately. The sensor has been applied to determine DM in spiked apple samples.

As mentioned earlier, one of the ways to reduce the amount of template compound used is *in situ* polymerization to obtain a monolithic column. Sorbents of this type are ideally suited for on-line applications. The procedure of isolation and enrichment of bisphenol A (BPA) and other phenols from water samples is an example of such an application (50). The MIP was prepared using BPA as the template and 4-VP and EGDMA as the functional and cross-linking monomers, respectively. Polymerization was carried out directly in a stainless-steel tube, which was then connected to an HPLC pump. The studies revealed the effect of composition of the eluent (water:ACN ratio) on the analyte retention. The imprinting factor, defined as the ratio of the analyte retention factor on the MIP column to that on the NIP, was used to evaluate the recognition ability of the MIP. The results obtained revealed that at lower water content in the mobile phase (up to about 40% v/v), all of the analytes

tested (BPA, hydroquinone, phenol, 4-tert-butylphenol [t-BPA]) had similar values of the retention factors, thus indicating similar adsorption capacities of the MIP and NIP columns. On the other hand, at the limiting content of water in ACN (80% v/v), the retentin of BPA and t-BPA was so strong that these analytes practically were not eluted from the column. In turn, at the water content above 50%, a clear separation of components of the standard solution was observed. These results reveal the effect of solvent on the interaction of the analytes with the polymer. In this case, already at lower water content in acetonitrile, the hydrogen bonding practically had no effect on retention and therefore the mixture components were not separated. However, since the BPA and the polymer are relatively hydrophobic, the hydrophobic interaction came to play when the percentage of water was increased, the retention began to increase. It has been shown that intermolecular hydrogen-bonding between BPA and the polymer is weak in aqueous solution because of the competition from the high concentration of water molecules. Consequently, the analysis of samples of river water spiked with target analytes was carried out using gradient elution. The detection limit and limit of quantification for BPA were 0.06 and 0.2 μg/L, respectively.

The few examples of application of MIPs in analytical chemistry discussed above do not provide a comprehensive guide and are only intended to illustrate practically unlimited possibilities of this technique. Table 1 provides the compilation of literature data on MIPs covering the period 2006–2008.

CONCLUSIONS

Molecularly imprinted polymers are finding increasing applicability both in analytical chemistry and in other areas of chemistry. Their potential has been noticed by numerous research centers in the world, where novel methods of their synthesis are being developed. New areas for their applications are being explored. In addition to suitable extraction properties, MIPs currently in use are characterized by high chemical and mechanical stability. In most cases, they are thermally stable as well. The greatest challenge facing adsorbents of this type seems to be their adaptation to a larger degree to the analyte isolation/enrichment step from environmental samples, mainly from water. Thus far, there are no procedures available for synthesis of MIPs that would be fully compatible with this matrix. It should also be pointed out that although MIPs have been known for a dozen or so years, they have not been commercialized yet. Paradoxically, the reason for this seems to be what is considered their greatest strength: high selectivity towards specific analytes. Consequently, a unique MIP reveals its usefulness only for the determination of a compound used as template. A significant decrease in extraction yield is observed even for template analogues. New research should focus on the synthesis of molecularly imprinted polymers with good adsorption properties towards not only single compounds but classes or groups of analytes.

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