

Newest applications of molecularly imprinted polymers to sample preparation for determination of contaminants in environmental and food matrices: a review

Andrea Speltini*, Andrea Scalabrini, Federica Maraschi, Michela Sturini, Antonella Profumo

Department of Chemistry, University of Pavia, via Taramelli 12, 27100 Pavia, Italy

**Corresponding author. Tel.: +39 0382-987349; fax: +39 0382-528544.*

E-mail address: andrea.speltini@unipv.it (A. Speltini)

Abstract

This paper presents an overview of the recent applications of molecularly imprinted polymers (MIPs) to sample preparation. The review is thought to cover analytical methods for determination of organic/inorganic contaminants (mainly illegal/noxious compounds) in food and environmental matrices, with a particular focus on the various pre-concentration/cleanup techniques, that is offline and online solid-phase extraction (SPE), dispersive SPE (d-SPE), magnetic SPE (MSPE), solid-phase microextraction (SPME) and stir-bar sorptive extraction (SBSE), applied before instrumental quantification. The selectivity and extraction efficiency of MIP-based sorbent phases are critically discussed, also in relation to the physical-chemical properties resulting from the various synthetic procedures. A variety of molecularly imprinted sorbents is presented, including hybrid composites embedding carbon nanomaterials and ionic liquids. The analytical performance of MIP materials for sample preparation is commented as function of the complexity of the matrix, and compared to that exhibited by (commercial) aspecific and/or immunosorbent phases.

Keywords Cleanup; Environmental samples; Extraction; Food; Molecularly imprinted polymers; Selectivity

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References

Acronyms

AA, acrylic acid

ABPA, 3-amino-1-propanol acrylate

ACN, acetonitrile;

AIBN, 2,2-azoisobutyronitrile;

AM, acrylamide;

APTES, 3-aminopropyltriethoxysilane;

ASE, accelerated solvent extraction;

BPA, bisphenol A;

C[4], 5,11,17,23-tetra-tert-butyl-25,27-dicyanomethoxyl-26,28-dihydroxy calix[4]arene;

CAR, carboxen;

CE, capillary electrophoresis;

CNTs, carbon nanotubes;

CW, polydimethylsiloxane carbowax;

DCM, dichloromethane;

1 DMF, dimethylformamide;
2 DMSO, dimethyl sulfoxide;
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4 d-SPE, dispersive solid-phase extraction;
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6 DVB, divinylbenzene;
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8 EAMA, *N*-(2-aminoethyl)methacrylamide;
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10 ECD, electron capture detection;
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12 ECL, electrochemiluminescence;
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14 EDMA, ethylene dimethacrylate;
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16 EF, enrichment factor;
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18 EGDMA, ethylene glycol dimethacrylate;
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20 ELISA, enzyme linked immunosorbent assay;
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22 EtOH, ethanol;
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24 FA, formic acid;
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26 FD, fluorescence detection;
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28 FID, flame ionization detection;
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30 FPD, flame photometric detection;
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32 FQ, fluoroquinolone;
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34 GC, gas chromatography;
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36 GMA, glycidilmethacrylate;
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38 GO, graphene oxide;
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40 HAc, acetic acid;
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42 HLB, hydrophilic–lipophilic-balanced reversed phase;
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44 HPLC, high performance liquid chromatography;
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46 HRCS-AAS, high resolution continuum source atomic absorption spectrometer;
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48 IF, imprinting factor;
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50 IL, ionic liquid;
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52 KH570, 3-(methacryloxy)propyltrimethoxysilane;
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54 LIF, laser-induced fluorescence detection;
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1 LLE, liquid-liquid extraction
2 MAA, methacrylic acid;
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4 MAC, methacryloyl chloride;
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6 MCX, mixed-mode strong cation exchange reversed phase;
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8 MeOH, methanol;
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10 MIP, molecularly imprinted polymers;
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12 MPS, 3-metha-criloxypropyltrimethoxy-silane;
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14 MS, mass spectrometry;
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16 MSPE, magnetic solid phase extraction;
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18 MTMS, methyltrimethoxysilane;
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20 NIP, not imprinted polymers;
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22 NOBE, *N,O*-bismethacryloyl ethanolamine;
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24 NPD, nitrogen phosphorus detector;
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26 PA, poly(acrylate);
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28 PBS, phosphate buffer saline;
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30 PCB, polychlorinated biphenyls;
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32 PDMS, polydimethylsiloxane;
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34 PMMA, polymethyl methacrylate;
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36 POSS, polyhedral oligomeric silsesquioxane;
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38 PP, polypropylene;
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40 PS, polystyrene;
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42 PVA, polyvinyl alcohol;
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44 RAM, restricted access material;
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46 SBSE, stir-bar sorptive extraction;
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48 SERS, surface-enhanced Raman spectroscopy;
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50 SPE, solid-phase extraction;
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52 SPME, solid-phase microextraction;
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54 TBA, tetra-*n*-butylammonium hydrogen sulphate;
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TEOS, tetraethoxysilicate;

TFA, trifluoroacetic acid;

THF, tetrahydrofuran;

TRIM, trimethylolpropane trimethacrylate;

VP, vinylpyridine

1. Introduction

Selectivity is probably the most important goal in analytical chemistry. It becomes imperative in the case of trace analysis of target species in real matrices, often quite complex, as environmental, biological and food samples. Ideally, a working analytical method should be accurate, reproducible and highly selective (or specific) toward the target analytes. In particular, selectivity should be pursued both in the instrumental detection method (i.e. by mass spectrometry, MS) and in the sample preparation step. Since the latter is strictly connected with potential matrix effects occurring in the final quantification, and thus with the overall method sensitivity, it appears that selectivity is particularly important in the sample pre-treatment.

Depending on the matrix, sample preparation is necessary for extraction/enrichment/cleanup of trace compounds in aqueous samples, e.g. environmental waters [1], or in solid samples like food [2]. To date, the most used pre-concentration technique is solid-phase extraction (SPE) – which has almost totally replaced the traditional liquid-liquid extraction (LLE) – but also its related branches are gaining increasing popularity, that is dispersive SPE (d-SPE), magnetic SPE (MSPE), stir-bar sorptive extraction (SBSE) and solid-phase microextraction (SPME). Despite these techniques greatly enhance the sample throughput in terms of extraction time, solvent consumption, reproducibility and enrichment factor (EF), the conventional sorbents generally used (e.g. octadecyl silica, polymeric reversed-phase materials) suffer from lack of selectivity. This is an analytical drawback, and requires extensive optimisation of the procedures to minimize adsorption and co-elution of matrix interferences/not target compounds [3].

It is clear that the development and application of selective sorbent phases are of primary importance. Different selective materials have been tested to date, including restricted access materials (RAMs), immunosorbents, and oligosorbents. The former are able to separate small molecules from biomolecules *via* hydrophobic interactions and size exclusion effects but, since small molecules are aspecifically retained,

1 such materials are mostly applicable to biofluids in clinical and toxicological analyses; immunosorbents and
2 oligosorbents are synthesized by derivatization of inert solid supports with antibodies and aptamers,
3 respectively, and have found several applications for various matrices. Despite the highest selectivity level
4 assured by antibodies, immunosorbents are expensive, similarly to oligomers, and characterized by poor
5 stability outside optimized pH, ionic strength, temperature, and pressure conditions [4].
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10 A powerful, smart generation of selective sorbent phases is represented by molecularly imprinted polymers
11 (MIPs), synthetic materials able to specifically rebind a target molecule in preference to other closely related
12 compounds. The ultimate goal in molecular imprinting is the synthesis of materials providing binding
13 properties comparable to those of natural receptors. Experimentally, MIPs are prepared by co-polymerization
14 of functional and cross-linking monomers in presence of a template molecule (that is the target analyte). The
15 reaction between the monomers, chosen basing on their affinity with the functional groups of the template,
16 yields a highly cross-linked three-dimensional network polymer binding sites with shape, size and
17 functionalities complementary to the target analyte. MIPs synthesis is relatively cheap and easy, and the as-
18 prepared imprinted polymers show good stability and robustness in a wide range of pH, solvents and
19 temperature, and are a valid alternative to natural receptors [3].
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33 In view of these considerations, MIPs have found application in various fields of analytical chemistry, such
34 as chromatographic separation of enantiomers, binding assays, sensors and sample preparation [4, 5-8].
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37 As discussed in previous review articles, MIP-based materials have been tested for pre-concentration/cleanup
38 of a number of analytes in environmental [3, 4, 9], biological [10, 11] and food [12, 13] samples, and in
39 particular their use in SPE is by far the most advanced technical application [3]. Although a relevant number
40 of papers, collected and discussed in recent reviews [3, 11, 13, 14] about the use of MIPs in various pre-
41 concentration techniques have risen in recent years, this review aims to gather their latest applications
42 focusing on the determination of harmful substances (pesticides, residual drugs and metabolites, dyes, etc.)
43 in food (2014-2016) and environmental matrices (approximately 2015-2016).
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53 The selected applications are presented and discussed in relation with the different enrichment techniques,
54 i.e. SPE, d-SPE, MSPE, SPME, SBSE. After a general description of the preparation routes, described in
55 detail in previous works [9, 15], the physical-chemical properties of the as-prepared materials and their
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1 analytical performance have been critically commented and compared with immunosorbents, commercial
2 and other sorbent materials.
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6 **2. Synthetic routes and materials properties: general aspects**

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8 Molecular imprinting can be carried out by different approaches, as described in the following, but always
9 entails three steps: a) formation of a pre-polymerization complex between the template molecule and the
10 monomer; b) polymerization in the presence of a cross-linker, usually triggered by a radical initiator; c)
11 removal of the template to give the imprinted polymer.
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17 Once the template is eliminated, the obtained material consists of a three-dimensional network presenting
18 pores with geometry and position of the functional groups complementary to those of the template. This
19 means that the polymer is endowed with specific recognition sites.
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24 Three different approaches have been proposed for MIPs preparation, that is the covalent, non-covalent, and
25 semi-covalent routes, differing from the way the template is linked to the functional monomer, and thus from
26 the resultant binding sites.
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31 The covalent approach involves the formation of reversible covalent bonds between template and monomer
32 in step a); this procedure yields an imprinted polymer characterized by homogeneous distribution of binding
33 sites due to the strong template-monomer interaction; the stoichiometric reaction ensures that functional
34 monomer residues exist only in the imprinted cavities and allows to minimize aspecific sites. On the other
35 hand, the covalent approach is limited because both formation and cleavage of the covalent bond should
36 occur under mild conditions. Similar is the semi-covalent option, but in this case the template rebinding
37 (hence the analyte uptake) is driven merely by non-covalent interplays.
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46 The non-covalent approach, the most used in molecular imprinting processes, appears the straightforward
47 procedure, as a number of commercially available monomers can be used; indeed, this process involves
48 formation of weak, non-covalent interactions between the template and the monomer in the reaction mixture
49 (ionic interactions, hydrogen bonding, van der Waals forces and π stacking). Formation of stable pre-
50 polymerization complexes (governed by an equilibrium process) is the crucial step of this route. The need for
51 high amounts of functional monomers to favour the formation of the template-monomer complex
52 unavoidably leads to a higher density of non-selective binding sites compared to the covalent approach.
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1 Therefore, a careful optimisation of the experimental conditions, primarily with regard to the template :
2 functional monomer : cross-linker ratio, strictly related to the overall selectivity, is required [4].
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4 The imprinting technique can be also adopted to recognize metal ions obtaining ion-imprinted polymers,
5 characterized by low selectivity; a novel, more efficient strategy for this type of analytes is the use of ligand-
6 ion complex as the template, that ensures better results compared to the use of free metals [15].
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9 Due to the relatively high number of factors involved in MIPs synthesis, computational models, theoretical
10 calculations and multivariate analysis can be of great convenience to design/develop high-selectivity
11 materials. Indeed, in order to develop those working sorbent phases, template, functional monomer, cross-
12 linker and reaction solvent (named porogen) should be accurately selected.
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15 In principle, the target compound is chosen as the template molecule, but often it can be replaced by a
16 structural-related molecule (dummy templating, also named surrogate), as much as possible resembling the
17 analyte for size and chemical groups. This strategy is particularly useful in the determination of very low
18 concentrations of analyte, because any potential leaching of residual template (that generally cannot be
19 wholly removed after polymerization) would not interfere in the quantification of the target species. In any
20 case, it is important that the template is able to form stable complexes with the functional monomer. This
21 usually contains a recognition unit and a polymerizable moiety, and should involve specific donor-receptor
22 complexes with the template; a typical monomer is methacrylic acid (MA) due to its hydrogen bond donor-
23 acceptor properties. Since the formation of the template-monomer complex is affected by the solvent
24 polarity, the solvent plays a major role in addressing molecular recognition and acts as dispersion medium
25 and pore-forming agent in the reaction mixture. Being related to the analyte diffusion, density of recognition
26 sites and mechanical stability of the prepared material, nature and amount of cross-linker are as well
27 important.
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30 With regard to polymerization, different methods can be used. The conventional technique is the *bulk*
31 *polymerization*, the most immediate procedure that anyway requires the final product to be crashed,
32 grounded, sieved and sedimented from a proper solvent (to eliminate the finer particles) before use. These
33 steps are potentially detrimental for the binding sites, and lead to partial recovery of useful solid phase and
34 large distribution of the beads particle size, thus limiting the applications to off-line extractions.
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Other strategies, developed to improve the binding efficiency and mass transfer properties are the *suspension* and *precipitation polymerization* that yield spherical, mono-dispersed particles (from nanometers-micrometers to millimetre size). The former entails the suspension of droplets of the polymerization mixture in a liquid phase (e.g. water, perfluorocarbon and mineral oil), while the latter consists of a polymerization carried out in a large excess of porogen in which the polymeric phase gradually precipitates.

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MIPs can be prepared with high yields by *emulsion polymerization* in oil/water biphasic systems, and by the multi-step swelling method, viz. *seed polymerization*, that is based on the swelling of preformed uniform particles and provides mono-dispersed spherical microparticles. A completely different route is the *in situ polymerization*, that minimizes the amounts of template and functional monomer, resulting particularly useful to prepare MIP monolith stationary phases for liquid chromatography and capillary electrochromatography, but also SPME fibres. Simple preparation at ambient conditions and use of more eco-friendly solvents, including water, are provided by the sol-gel process, that relies on polycondensation of tetraalkoxysilane precursors to form highly cross-linked silica gels [3, 4, 9, 15].

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Other smarting strategies are the *Pickering emulsion polymerization* and the *surface molecular imprinting*. The former involves the polymerization in presence of suspended nanoparticles that prevent emulsion droplets coalescence by surrounding their interface; MIP particles with proper size can be obtained by tuning the amount of nanoparticles and their hydrophilic/hydrophobic properties [16]. The second approach consists in forming a MIP layer on the surface of solid supporting beads; these can be removed after the formation of the imprinted phase (*solid phase* or *hard template method*) leaving a highly channelled or hollow MIP beads with accelerated mass transfer kinetics compared to, for instance, bulk polymerization [17, 18].

46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 **3. Use of MIPs in sample preparation**

Various MIPs have been recently developed and applied for selective determination of residual pesticides, drugs, organic dyes, mycotoxins and persistent organic pollutants in food and environmental matrices. Different synthetic approaches have been practiced, involving various polymerization techniques and/or supporting substrates, to prepare (hybrid) materials with different physical-chemical properties, selectivity/cross-selectivity, chemical stability and analytical applicability. Depending on the analytical task

to be solved, the advantages offered by MIPs can combine i) selective separation of the target from the bulk matrix, ii) analyte pre-concentration, and iii) interferences abatement (reduction of matrix effect).

3.1. *Solid-phase extraction (SPE)*

Most of the applications of MIPs to sample preparation refers to SPE, as summarized in Table 1.

	Template/monomer/ cross-linker/solvent	Analyte(s)	Matrix	Extraction	Description	Recovery (%)	EF ^a	Determination	Reuse (times)	Ref.
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5	Levofloxacin/MAA/EGDMA/DMSO-	Levofloxacin,													
6	[BMIM]BF ₄ -CHCl ₃	Ciprofloxacin,	Milk, lake water	10 mL (pH 6-8), 100 mg MIP, 0.5 mL/min	82-98	2	5 mL MeOH-NH ₃ (96:4)								[30]
7	(8:1.6:5)	Enrofloxacin,													
8		Gatifloxacin													
9															
10															
11	Congo red/ beta-cyclodextrin-maleic	Congo red	Pork, beef, jelly, hawthorn	50 mL (pH 4.5), 100 mg MIP	84-105	10	5 mL MeOH-NH ₃ (7:3)								[31]
12	anhydride + [2-														
13	(methacryloyloxy)ethyl]trimethylammonium														
14	chloride/N,N-														
15	methylenebisacrylamide/H ₂ O														
16															
17															
18	Clenbuterol/MAC/EGDMA/DCM+MeOH	Clenbuterol	Pork, potable water	50 mL (pH 7), 100 mg MIP, 1 mL/min	74-108	~3.3	15 mL MeOH-HAc (8:2)								[32]
19															
20															
21	4-dihydroxy-2-naphthoic acid/2-														
22	dimethylaminoethyl	Citrinin	Corn	1 mL, 300 mg MIP	82-91	-	5 mL MeOH-HAc (98:2)								[33]
23	methacrylate/TRIM/acetone-ACN (1:3)														
24															
25		Melamine,													
26	Melamine/MAA/EGDMA/EtOH-H ₂ O (4:1)	dicyandiamide,	Animal tissue foods	3 mL, 60 mg MIP, 0.3 mL/min	89-107	-	3 mL HAc-MeOH (7:3)								[34]
27		cyromazine													
28															
29															
30	proheptadine/MAA/EGDMA/DCM	Cyproheptadine	Pig, poultry feeds	5 mL, 50 mg MIP, 1 mL/min	86-96	5	1 mL MeOH-NH ₃ (95:5)								[35]
31															
32															
33	<i>Surface molecular imprinting polymerization</i>														
34															
35	permethrin/MAA/EGDMA/ACN:acetone	Pyrethroid	Fish	15 mL, 2 min vortex, 15 min sonication (membrane SPE)	84-101	20	0.75 mL hexane (40 °C), 30 min, 600 rpm								[36]
36	(80:50)	insecticides													
37															
38	actopamine/MAA/EGDMA/DMSO	β ₂ -agonists	Pork	5 mL, 50 min (membrane SPE)	83-97	-	10 mL MeOH-HAc (9:1)								[37]
39															
40															
41	Malachite green/MAA/EGDMA/ACN-	Malachite green	Sea and river water, fish	100-250 mL (pH 7), 50 mg MIP, 2.5 mL/min	95-98	50-125	2 mL MeOH-H ₂ O (5:95), 0.25 mL/min								[38]
42	CHCl ₃	and fuchsine													
43															
44	propazine/MAA/EGDMA/toluene	Triazine herbicides	Maize, water, soil	20-30 mL, 200 mg MIP, 0.5 mL/min	78-103	10-15	2 mL MeOH								[39]
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5	Chrysoidine/APTES/TEOS/MeOH (0.1 M HAc)	Chrysoidine	Oil bean curd, yellow croaker, paprika	50 mL (pH 6.3), 2.5 mL/min, 50 mg MIP (online SPE)	MeOH-ammonium acetate (65:35), 1 mL/min, 2 min	89-98	-	HPLC-UV	-	[40]				
8														
9	Florfenicol/APTES/TEOS/THF	Florfenicol	Fish, chicken	15 mL (pH 6), 150 mg MIP, 0.5 mL/min	2.5 mL 0.1 M ammonium acetate-MeOH (70:30)	86-97	6	HPLC-UV	5	[41]				
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12														
13	Okindole/APTES/TEOS/MeOH	Patulin	Fruit-derived foods	50 mL (pH 4), 50 mg MIP, 1.5 mL/min (online SPE)	0.1% HAc-ACN (9:1), 1 mL/min (2 min)	60-98	25	HPLC-UV	-	[42]				
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17	2,2-Bis(4-(hydroxyphenyl)hexafluoropropane)/TEOS/MeOH	Bisphenol A	Potable and surface waters	7 mL (5% MeOH), 600 mg MIP	2 mL MeOH	97-106	3.5	HPLC-UV	20	[43]				
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22	Tetracycline/MAA+TEOS+KH570/ACN	Tetracyclines	Eggs, milk, milk powder	0.8 mL/min (online SPE)	MeOH-ACN-10 mM oxalic acid (5:2.5:75), 0.8 mL/min	85-98	-	HPLC-UV	-	[44]				
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24														
25	8,9-trihydroxy-dibenzol[b,d]pyran-6-one	Alternariol	Tomato	15-50 mL, 100 mg MIP, 0.093 mL/min	1 mL MeOH-TFA (99:1)	81-103	15-50	HPLC-FD	-	[17]				
26														
27	Grolithin C/EAMA-MAA/EDMA	Triazine pesticides	Cereal samples	7 mL, 125 mg MIP, 0.8 mL/min	1.5 mL ACN-HAc (95:5)	81-101	4.7	HPLC-MS	-	[18]				
28														
29	Prometryn/MAA/DVB/H ₂ O-toluene													
30														
31	Precipitation polymerization													
32														
33	[CH ₃ Hg] ⁺ /MAA/EDMA/ACN-H ₂ O (4:1)	[CH ₃ Hg] ⁺	Fish	5 mL, 150 mg MIP, 0.5 mL/min	10 mL 1 M thiourea 1 M HCl, 0.5 mL/min	100	-	HRCs-AAS	5-10	[45]				
34														
35														
36	4,4'-dichlorobenzhydrol/ glyoxal-urea-formaldehyde/H ₂ O	Organochlorine pesticides	Spinach	1 mL, 5 mg MIP, 0.05 mL/min	0.6 cyclohexane-ethylacetate (9:1)	89-102	~2	GC-ECD	-	[46]				
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39	fenarimol/MAA/EGDMA/ACN	Fenarimol	Apple, banana, tomato	10 mL, 150 mg MIP, 0.5 mL/min	5 mL ethylacetate-HAc (9:1)	91-100	2	HPLC-UV	-	[47]				
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43	5-chloro-DDT/AM/DVB/ACN+1-allyl-3-(4-ethylimidazolium bromide	Dicofol	Celery	1 mL, 2 mg MIP	1 mL acetone-HAc (9:1)	87-102	-	GC-ECD	7	[48]				
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6	Malathion/MAA+GMA/EDMA/CHCl ₃	Organophosphorus pesticides	Honey	25 mL (pH 6), 100 mg MIP, 1 mL/min	1 mL MeOH	91-98	25	-	GC-FPD				[49]
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9	Ivermectin/VP/EGDMA/CHCl ₃	Ivermectin	Meat	3.9 mL, 100 mg MIP, 1 mL/min (online SPE)	ACN-MeOH-H ₂ O (6:3:1), 1 mL/min, 100 s	52-93	-		HPLC-UV		48		[50]
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12	Monolithic MIP phases												
13													
14	Salbutamol/MAA/EGDMA/DMF	Salbutamol, clenbuterol	Pork	5 mL, 0.5 mL/min	1 mL MeOH-HAc-H ₂ O (7:2:1)	72-92	5	-	GC-MS				[51]
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19	Saltaquinoxaline/MMA/EGDMA/DMF-p-xylene-isooctane	Antimicrobials	Chicken, pork, egg	25 mL, 0.15 mL/min (online-SPE)	0.4 mL ACN-H ₂ O-HAc (20:79.8:0.2), 0.15 mL/min	71-108	63	> 100	HPLC-UV				[52]
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23	Phloxine B/MAA/EDMA/MeOH-toluene-dodecanol	Phloxine B	Coffee beans	4 mL, 0.02 mL/min (capillary monolithic column SPE)	0.04 mL MeOH-HAc (9:1), 0.1 mL/min	~90	100	50	HPLC-LIF				[53]
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25													
26	Rhodamine B/MAA/EDMA/MeOH-toluene-dodecanol (17:33:50)	Rhodamine B	Chili powder	8 mL, 0.02 mL/min (capillary monolithic column SPE)	0.08 mL MeOH-HAc (9:1), 0.1 mL/min	84-88	100	30	HPLC-FD				[54]
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30	Isoprocarb/MAA+MTMS+KH570/EGDMA	Isoprocarb	Rice	3 mL, 0.05 mL/min	0.15 mL MeOH-ACN (6:4), 0.05 mL/min	91-107	20	-	HPLC-UV				[55]
31													
32													
33	Other routes for preparation of MIP phases												
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36	Aflatoxin B ₁ /MAA/EGDMA/H ₂ O-CHCl ₃	Aflatoxin B ₁ and Aflatoxin M ₁	Barley, peanut oil, beer, beans/corn/formula feeds	sample pH 6.5, 200 mg MIP, 2 mL/min	6 mL MeOH-HAc (9:1), 1 mL/min	83-96	-	6	HPLC-FD				[56]
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38													
39	9,9'-(1-phenylethylidene)bisphenol	Bisphenols	Sediments	10 mL, 300 mg MIP, 1 mL/min	5 mL MeOH-TFA (98:2)	75-105	2	-	HPLC-UV				[16]
40	VP/EGDMA/toluene												
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42													
43	Basic orange II/acrylamide/ maleic rosin	Basic orange II	Sausage, dried beancurd stick, dried shrimp, stewed tofu	2 mL, 300 mg MIP, 0.2 mL/min	2 × 3 mL EtOH	68-80	-	-	HPLC-UV				[57]
44	VP/acrylate/ethylacetate-soybean oil												
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5	Sulfadiazine/MAA/EGDMA/PVA-H ₂ O	Sulfadiazine	Egg yolk	10 mL, 100 mg MIP, 0.25 mL/min	1 mL MeOH, 0.25 mL/min	78-86	10	HPLC-UV	-	[58]			
6													
7	Diethylstilbestrol/MAA/EGDMA/PVA-H ₂ O	Diethylstilbestrol	Seawater	5 mL, 100 mg MIP	1 mL MeOH-ACN (65:35)	77-85	5	HPLC-UV	5	[59]			

^a EF: referred to MIP-extraction, calculated as the ratio sample volume/eluent volume

Table 1 Use of MIPs for SPE in food and environmental samples.

1 The great potentiality of molecular imprinting is corroborated by various MIP sorbent phases currently
2 available on the market and routinely used according to standardized protocols. In this context, commercially
3 available MIP cartridges were employed for the selective SPE of seven bisphenol A (BPA) analogues from
4 beverages and canned food samples [19]. The analytes were adsorbed from aqueous extracts with good
5 selectivity, as demonstrated by binding tests in presence of other compounds with different molecular
6 structure but similar polarity. The seven targets were retained on the sorbent but in a different extent,
7 requiring addition of formic acid (FA) to methanol (MeOH) for quantitative desorption of the strongly
8 bounded molecules; at the same time, the specific interaction analyte-sorbent allowed washings steps to
9 remove the non-specifically extracted polar/apolar matrix interferences, with no loss of the target
10 compounds. Higher selectivity was observed compared to the commercial HLB phase (hydrophilic-lipophilic
11 balanced aspecific sorbent) that, on the contrary, was able to retain selected non-structurally related probes
12 but also matrix interferences. As a matter of fact, the application of the MIP sorbent resulted in a better
13 sample cleanup, providing lower signal suppression in MS detection.
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16 Commercial MIP sorbents proved to be useful for the cleanup of nine aminoglycosides antibiotics in honey
17 samples [20]. This is particularly important when capillary zone electrophoresis based on field-amplified
18 sample stacking is adopted to enhance sensitivity, before instrumental detection (MS in this case). It should
19 be underlined that, for such highly polar compounds, use of selective sorbent with strong binding sites can
20 really improve recovery from aqueous solution, and thus method sensitivity.
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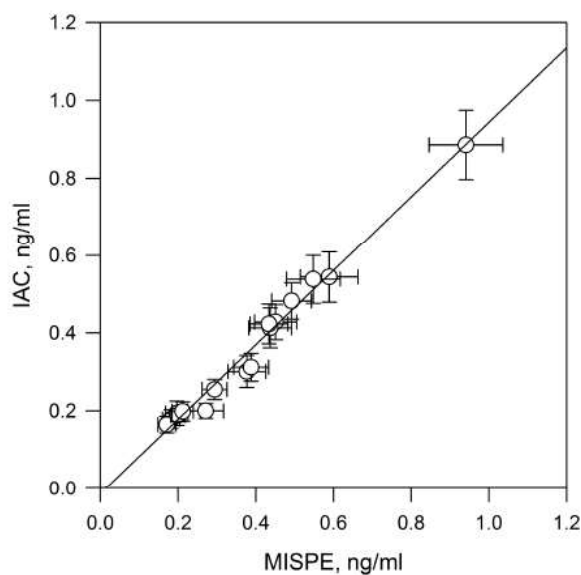
23 As reported in the following paragraphs, lots of lab-made MIPs are now under study to develop selective,
24 robust and performing sorbents by means of various synthetic approaches, ranging from the conventional
25 bulk polymerization to the most innovative surface molecular imprinting strategies.
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28 *3.1.1. Bulk polymerization MIPs preparations*

29 The imprinted materials prepared by conventional bulk polymerization have found recent application for off-
30 line SPE of mycotoxins, pesticides and residual drugs from various foods. As hereafter commented, new
31 achievements were reported in terms of analytical performance, strictly connected with the material
32 synthesis.
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1 Appell et al. [21] designed MIPs for cleanup of fusaric acid mycotoxin in maize. The sorbent ($322 \text{ m}^2 \text{ g}^{-1}$, 38-
2 $75 \text{ }\mu\text{m}$) was prepared by radical bulk polymerization using picolinic acid as the template molecule, and was
3 used in conventional SPE tubes. The best results were found using 2-dimethylaminoethyl methacrylate as
4 functional monomer, while using methacrylic acid (MAA) the behaviour of the sorbent was quite
5 comparable to the not imprinted polymer (NIP) phase. Quantitative recovery was observed in corn ($1\text{-}100 \text{ }\mu\text{g}$
6 g^{-1}).

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13 Another off-line molecularly imprinted SPE procedure was proposed for the pre-concentration of the
14 mycotoxin ochratoxin A in red wine prior high-performance liquid chromatography coupled with
15 fluorescence detection (HPLC-FD) [22]. After quantitative uptake of the target compound from diluted/pre-
16 treated samples, hydro-organic mixtures were tested to refine the ability to wash away the interfering
17 matrices from the cartridge, and the best results were found with water-acetonitrile (ACN) (80:20). As
18 clearly shown in Fig. 1, the reliability of the proposed procedure was demonstrated by comparing the results
19 found in a variety of red wines with those obtained using commercial immunosorbents, employed according
20 to a standardized protocol.



52 **Fig. 1.** Comparison of ochratoxin A determination in 17 red wine samples by immunoaffinity SPE (IAC) and
53 MIP-based SPE (MISPE). Reprinted with permission from [22]. Copyright (2014) American Chemical
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1 MIPs were also used for determination of two organophosphate pesticides in vegetables [23]. The authors
2 synthesized two MIP solid phases, one using trichlorfon and the other using monocrotophos as the template
3 molecules, that were successively mixed in a SPE column. Each imprinted material showed two-fold
4 sorption capacity for the target compared to the NIP, and considerable affinity for both analytes, reasonably
5 due to the similar molecular structures (sorbed amounts 15-20 mg g⁻¹). However, the use of the mixture of
6 trichlorform-MIP and monocrotophos-MIP improved the limits of detection of both organophosphate
7 pesticides.
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15 Conventional bulk polymerization was adopted to synthesize a terbuthylazine-imprinted MIP material,
16 applied for extraction of the pesticide from olive oil [24]. The product showed a rougher surface and a
17 slightly larger surface area (155 m² g⁻¹) than the NIP, with a mesoporous structure (pore diameter 2-50 nm).
18 Imprinting factor (IF) for the target pesticide was 4.6 in dichloromethane (DCM), but also cross-selectivity
19 for atrazine and ametryn analogues (IF 2.7 and 3.4, respectively). The relatively high IF values for the latter
20 compounds compared to the target can be related to the very similar molecular structures, and to a combined
21 effect of shape/size complementary. Importantly for sample preparation, better sample cleanup was gained in
22 comparison with C18-silica cartridges, especially important when UV detection is used, with quantification
23 limits below the maximum residue limit fixed for terbuthylazine in olive oil (50 ng g⁻¹).
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The same synthetic approach was also chosen by Nezhadali et al. [25] for the MIP-based extraction of
fenvarelate (a pyrethroid insecticide). Polymerization was performed using pyrrole as the monomer in
presence of FeCl₃ as oxidizing agent. The obtained imprinted phase showed a two-fold higher sorption
affinity for the target compared to the NIP aspecific sorbent, and was applied for the determination of
fenvalerate in rice, wheat and bean samples, obtaining recovery as high as 96% (50 ng g⁻¹ spikes).

The organophosphate insecticide fenthion was determined in olive oil by using packed-column MIP SPE
[26]. The imprinted phase (45-100 μm) showed a good loading capacity in apolar solvents, although similar
results were found for the NIP; despite lower sorption capacity, better selectivity was observed in more polar
media such as MeOH and ACN. The sorbent showed specific recognition also for other related pesticides, in
particular for fenthion-sulphoxide, and the selectivity of the prepared material compared to the NIP was
especially evident in terms of binding, that was useful to washout the co-adsorbed interfering species with no
loss of targets, and with better sample cleanup compared to the conventional C18 silica.

1 Ritodrine was selected as dummy template for synthesis of a MIP able to extract ractopamine (a β -antagonist
2 drug) from pig tissues [27]. The product showed a rough and porous structure and was applied in
3 conventional cartridges achieving IF 8.9 for the target, and cross-selectivity for isoxsuprine (another β -
4 antagonist compound), and the structurally analogue clenbuterol. Recoveries of ractopamine and isoxsuprine
5 higher than 70% were achieved in pig liver extracts. Selective extraction coupled with surface-enhanced
6 Raman spectroscopy (SERS) detection led to method quantification limits ($10\text{-}20\ \mu\text{g kg}^{-1}$) lower than the
7 maximum concentrations allowed in swine tissues.
8

9 As often emerged from the here presented literature survey, the care devoted to the synthetic step is of
10 overwhelming importance in addressing selective recognition and sorption capacity. In this context, better
11 recognition properties were seen for an imprinted phase prepared by thermal radical polymerization
12 compared to that obtained by UV-initiated photopolymerization, for determination of erythromycin (a
13 macrolide antibiotic) in sheep milk [28]. Using a high ratio template : cross-linker (1:500), a rigid and
14 mechanically stable material was obtained. This was tested for column SPE (200-355 μm) observing the
15 highest binding ability in ACN (the porogen). Selectivity was satisfactory for the target analyte, with poor
16 recovery for other macrolides (15-35%), with the exception of roxithromycin (recovery ca. 85%), whose
17 structure is indeed very close to erythromycin. The latter was quantitatively recovered from milk after
18 proteins precipitation, and a washing step of the MIP cartridge by *n*-hexane allowed fat removal prior analyte
19 elution. It should be noticed that the sorbent can be reused for more than 200 assays with unchanged
20 analytical performance.
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22 Enhancement of binding ability was gained by double-template imprinting for the determination of melamine
23 and dicyandiamide in powdered milk [29], with a further improvement in comparison with the similar
24 approach employed by Wang et al. [23] for the determination of two organophosphate pesticides by two
25 individual MIPs. The sorbent material, tested in packed cartridges (< 300 mesh, $50\ \mu\text{m}$), showed good
26 selectivity and, in particular, possessed higher sorption capacity than the single-template MIPs, indicating a
27 synergistic effect in terms of imprinting efficiency. The highest binding capability was found in ACN,
28 yielding quantitative recovery ($0.5\text{-}5\ \mu\text{g g}^{-1}$) and cleanup of the matrix non-target compounds, with cleaner
29 extracts that are analyzable by HPLC-UV.
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1 Use of ionic liquids (ILs) as porogen in combination with a particular technique named “molecular
2 crowding” was recently proposed, taking advantage in terms of both binding capacity and selectivity in
3 aqueous solution [30]. Molecular crowding is related to the effect of proteins and polysaccharides, inside the
4 organism, to address the formation of stable 3D structures of biomolecules; in this context, using a crowding
5 agent able to shift the equilibrium towards the formation of template-monomer complex. A MIP SPE sorbent
6 for extraction of four fluoroquinolones (FQs) from surface water and milk samples using polymethyl
7 methacrylate (PMMA) as crowding agent and 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM]BF₄ as
8 porogen was prepared. The material was tested after being crushed and sieved (32-75 μm) showing good
9 selectivity for FQ drugs (IF 2.16-3.22 in water).

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20 As well, good performance in aqueous phase was observed by coupling MIPs with cyclodextrins [31]. In this
21 work cyclodextrins were incorporated into the polymeric phase by using β-cyclodextrin-maleic anhydride
22 and [2-(methacryloyloxy)ethyl]trimethylammonium chloride as co-functional monomers. These molecules
23 were selected in view of their ability to form inclusion interaction and ionic bonds with the target, the illegal
24 synthetic dye Congo red. The aqueous phase polymerization resulted in a good sorption capacity and
25 quantitative recovery in aqueous extracts from pork, beef, jelly and hawthorn samples (IF ~ 1.9).

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33 A particular synthetic strategy was applied by Tang et al. [32] to combine the advantages of covalent and
34 non-covalent imprinting. In this study, firstly the template (clenbuterol) was covalently bound to the
35 functional monomer, and then reacted with the cross-linker to give the bulk MIP phase. After hydrolysis-
36 induced template removal, the MIP particles were able to rebind the target analyte through non-covalent
37 interaction (that allows fast binding). Notice that excess of cross-linker hindered the mass transfer of the
38 analyte. The imprinted material showed homogeneous binding sites distribution, higher sorption capacity
39 than the NIP particles, also due to the higher surface area (~ 80 m² g⁻¹ vs. ~ 25 m² g⁻¹), and high selectivity
40 for the target among other analogues. Quantitative recovery was gained in pork and potable water samples,
41 with comparable results found by an enzyme linked immunosorbent assay (ELISA) test, thus confirming the
42 accuracy of the MIP procedure.

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56 Of course MIPs can be advantageously used for sample cleanup, as reported by Appell et al. [33] for the
57 extraction of citrinin (a nephrotoxic mycotoxin) from corn. Notice that use of a dummy template with radical
58 scavenger properties caused a decrease of surface area of the imprinted phase (269 m² g⁻¹) compared to the
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1 NIP one ($385 \text{ m}^2 \text{ g}^{-1}$), reasonably due to a reduced degree of polymerization. Although with a sorption
2 capacity not remarkably larger than that of NIP, the sorbent provided interferences removal and quantitative
3 recovery (spikes $0.03\text{-}3 \text{ }\mu\text{g g}^{-1}$) from corn MeOH-water extracts.
4

5
6 The key role of MIPs for cleanup of complex matrices is also highlighted in the paper by Ge et al. [34],
7 where MIP cartridges (200-400 mesh, $38\text{-}74 \text{ }\mu\text{m}$) were employed for the selective extraction of
8 dicyandiamide, melamine and cyromazone from animal tissue foods, after accelerated solvent extraction
9 (ASE). In this case the aim was the selective separation of the analytes from the matrix ASE extract.
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15 Better recovery/sample cleanup than commercially cartridges was attained in the determination of
16 cyproheptadine (antihistaminic and antiserotonergic agent) in pig and poultry feed [35]. The proposed
17 sorbent phase ($38\text{-}75 \text{ }\mu\text{m}$) allowed recovery higher than 85% directly from the sample organic extract, while
18 using C18-silica recovery was in the range 5-66% depending on the sample type; MCX (mixed-mode strong
19 cation exchange reversed phase) provided good recovery (75-81%) but worse sample cleanup compared to
20 the imprinted material. This showed the highest binding affinity in MeOH or ACN, two-fold higher than that
21 of NIP.
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31 32 33 34 *3.1.2. Surface molecular imprinting MIPs preparations*

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36 Various imprinted polymers have been recently prepared by surface molecular imprinting by exploiting
37 different organic/inorganic supporting materials (nano/micrometric particle size). Cold plasma-induced
38 grafting polymerization was tested by Zhang et al. [36] to prepare a MIP phase applied to determination of
39 five pyrethroid insecticides in fish. A molecularly imprinted membrane was obtained by grafting a MIP layer
40 onto a dense polypropylene (PP) support by making use of a plasma surface treatment apparatus. After
41 grafting, the modified support showed a homogeneous and rough surface, and a suitable hydrophilicity. The
42 latter feature seems very useful to reduce the matrix-effect of relatively hydrophobic fouling species present
43 in fish samples extracts. Competitive permeation experiments evidenced a markedly different behaviour of
44 the imprinted membrane compared to the not-imprinted and the bare ones, with great affinity and selectivity
45 of the molecularly imprinted membrane resulting in high transport rates of the five analytes, short
46 equilibrium time (30 min), and four-fold higher template sorbed amount. An imprinted membrane-assisted
47 solvent extraction was accordingly developed. Using hexane as the desorption solvent after analytes uptake
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1 from the fish aqueous extracts (10% ACN), the targets were quantitatively recovered and quantified with
2 good accuracy.

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4 In view of the highly ordered hexagonal nanopore array, anodic alumina oxide was used as support for the
5 preparation of a MIP membrane to be used for extraction of β_2 -agonists from pork samples [37]. The
6 channels (200 nm pore diameter) were silanized with 3-aminopropyltriethoxysilane (APTES) and then
7 reacted with 2-bromo-2-methylpropionyl bromide; this is the macroinitiator for the subsequent atom transfer
8 radical polymerization performed in the presence of the pre-polymerization mixture (this procedure can be
9 associated to surface molecular imprinting technology). Higher extraction capacity than the NIP membrane
10 and selectivity make the device useful for determination of ractopamine and other three structural analogues
11 (epinephrine, clenbuterol, terbutaline) in pork samples MeOH extracts, preserving the extraction capability
12 for many reuses.

13
14 Nano- Al_2O_3 was as well utilized as the supporting material [38]. The MIP layer, covalently grafted on the
15 inorganic particles, was functional for the pre-concentration of two triphenylmethane dyes (malachite green
16 and fuchsine) from environmental waters and fish tissues, with quantitative recovery achieved in aqueous
17 solution.

18
19 Triazine residues were determined in maize, soil and water by SPE using a selective sorbent prepared onto
20 TiO_2 nanoparticles [39]. These were acid-activated, silanized with APTES and reacted with acryloyl chloride
21 through formation of an amidic bond. This step was fundamental to chemically anchor the MIP layer onto
22 the TiO_2 support by the subsequent polymerization (co-polymerization acryloyl group with MAA), carried
23 out using propazine as the template. The derivatized supporting particles showed a 3D-structured and a
24 porous surface as a results of the formation of the MIP shell (25-37 nm thickness). A markedly different
25 behaviour in terms of adsorption capacity, adsorption kinetics and selectivity was observed compared to the
26 NIP-modified particles. The resultant adsorption capacity was ca. 16-fold higher on the imprinted material,
27 that proved to own specific recognition for propazine but also cross-selectivity for simazine and atrazine
28 (structurally related herbicides). The MIP cartridge (200 mg) was applied providing quantitative recoveries,
29 higher than those attained using C18-silica cartridges (500 mg).

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31 As hereafter commented, silica is often chosen as the inert supporting phase. Imprinted silica gel
32 microspheres were synthesized by combining surface molecular imprinting with a sol-gel process, for the

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determination of chrysoidine (an industrial dye) in foods [40]. The target compound was used as the template, activated silica (80-120 mesh, 125-175 μm) was the support, APTES and tetraethoxysilicate (TEOS) the functional monomer and the cross-linker, respectively. A strong memory function of the imprinted material for the target was noticed, with sorption capacity four-fold higher compared to that of the NIP, and fast adsorption equilibrium. The MIP-derivatized silica was used for online SPE, with special selectivity for chrysoidine among other structurally related dyes.

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A similar synthetic approach was adopted by Sadeghi and Jahani [41] for the extraction of the antibiotic florfenicol from fish and chicken tissues. The silica beads (70-230 mesh, 62-210 μm) chemically modified with MIPs proved to be highly selective for the target among other antimicrobials (cloramphenicol and metronidazole), with faster sorption kinetics and six-fold higher sorption capacity compared to the non-imprinted material. The sorbent allowed quantitative recovery of florfenicol from the sample extracts, with no need for further sample cleanup.

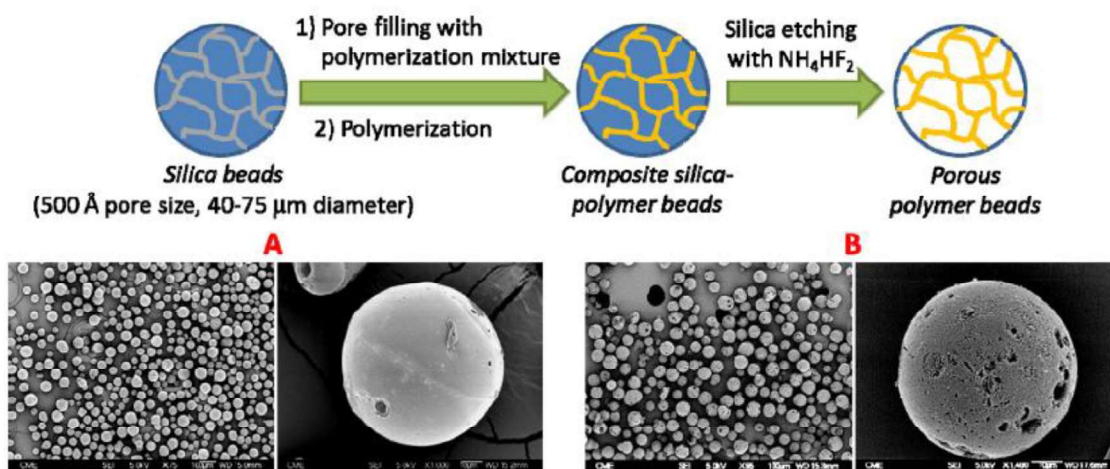
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Surface molecularly imprinted silica gel was prepared also for the online SPE of patulin (mycotoxin) from fruit-derived products [42]. The ratio template : functional monomer : cross-linker strongly affected the adsorption capacity. The best material was selective for patulin (loading capacity 4-fold higher compared to 5-hydroxymethyl-furaldehyde, relative selectivity coefficient 6.6) and was applied for pre-concentration of the target compound prior HPLC-UV analysis.

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A covalently bonded template-monomer complex was formed for the preparation of surface molecularly imprinted silica composites used for the determination of BPA in water samples [43]. The template was removed by thermal cleavage of the urethane bonds, leaving the imprinted cavities at or close to the surface. The porous structure obtained ($\sim 280 \text{ m}^2 \text{ g}^{-1}$, total pore volume $\sim 0.75 \text{ cm}^3 \text{ g}^{-1}$, average pore size $\sim 107 \text{ \AA}$) exhibited very fast analyte uptake (1 min saturation time), also due to the thin (nanometric) MIP layer. Quantitative recovery was obtained also after 20 extraction/desorption runs, with accuracy verified on a certified reference material.

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Tetracycline-imprinted poly(MAA)-silica was prepared starting from TEOS as inorganic precursor and 3-(methacryloxy)propyltrimethoxysilane (KH570) as coupling agent, and applied as online SPE pre-column coupled with HPLC-UV for extraction and separation of tetracycline residues in egg, milk and milk powder [44]. The system allowed selective extraction of three tetracycline antibiotics, with quantitative recovery

1 from the food aqueous extracts and suitable sample cleanup, similar or even better than that achieved on
2 HLB by offline SPE.

3
4 An interesting approach to synthesize porous MIP beads is using sacrificial porous silica beads as the mould
5 for carrying out the polymerization [17]. This route, schematically depicted in Fig. 2, involves the surface
6 molecular imprinting technique but, in this case, the solid supporting material is removed after
7 polymerization, thus leaving a highly channelled MIP material that accelerates mass transfer kinetics
8 compared to conventional bulk polymerization.
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33 **Fig. 2.** Scheme of the preparation of the MIP and NIP microspheres with a silica mould, and SEM images of
34 the intermediate composite material (A) and the same beads after treatment with 3 M aqueous NH₄HF₂ (B).

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36 Reprinted with permission from [17].

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42 Such preparation was tested to obtain imprinted microspheres for the selective extraction of alternariol (a
43 phenolic mycotoxin) from water and tomato samples [17]. Through a combinatorial screening approach
44 testing various dummy templates, functional monomers and cross-linkers, Abou-Hany et al. designed a MIP
45 solid phase with very high selectivity for the target (IF 10.8) and also for the analogue alternariol
46 monomethyl ether (IF 10.4). Polymerization was performed in presence of silica microparticles (40-75 μm,
47 500 Å), thus allowing the polymer to be formed inside the silica pores. The inorganic mould was etched in
48 NH₄HF₂ obtaining MIP beads with a particle size very close to that of the pristine silica. These allowed pre-
49 concentration and cleanup of alternariol from tomato extracts, yielding quantitative determination.
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1 Similarly to the route above described, a hard template method was tested by Zhao et al. [18] to prepare
2 single-hole hollow MIP microspheres. These were obtained by performing the polymerization reaction in
3 presence of carboxylated polystyrene (PS) particles (previously synthesized by emulsion polymerization).
4 The packed-column imprinted beads (1-2 μm) were tested either as-prepared or after removal of the PS
5 support (by using DCM), for pre-concentration of six triazine pesticides in cereal samples. For comparison,
6 MIPs were prepared also by precipitation polymerization. These showed lower surface area compared to the
7 hollow-hole material ($210.5 \text{ m}^2 \text{ g}^{-1}$ vs. $330.5 \text{ m}^2 \text{ g}^{-1}$, correspondingly), that indeed was the best performing
8 sorbent. This is certainly due to the different synthetic approaches, with the hard template route yielding MIP
9 beads characterized by specific sites distributed both on the outer and inner surfaces (after support removal),
10 favouring the mass transfer. The selectivity of the sorbent, as usually verified both on template analogues
11 and structurally different probes, resulted in a better sample cleanup compared to the commercial HLB
12 cartridge, with matrix effect in MS detection not higher than 10% compared to 35% using HLB.
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29 *3.1.3. Precipitation polymerization MIPs preparations*

30 Molecular imprinting by precipitation polymerization was proposed for the determination of methylmercury
31 [45] in two certified reference materials (tuna fish and lobster hepatopancreas), using phenobarbital as the
32 ligand and the formed ligand-ion complex employed as the template. The imprinted material showed
33 satisfactory recovery of both Hg(II) and methylmercury from aqueous solution (pH 7-9) or toluene extract,
34 and higher binding affinity compared to the NIP (+ 30%), with high efficiency for at least 5-10 SPEs.
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42 Polymerization in aqueous media and use of hydrophilic function monomers can surely be good choices to
43 enhance the MIP water compatibility and thus the overall performance in polar solvents. In this context,
44 Yang et al. [46] synthesized a glioxal-urea-formaldehyde MIP for extraction of organochlorine pesticides
45 from spinach samples. The resultant imprinted phase, characterized by high density of hydroxyls, carbonyls
46 and ether linkages, was indeed suitable to be applied in aqueous solution. Size, morphology and sorption
47 capacity were influenced by the synthetic conditions, namely glyoxal : formaldehyde ratio and amount of
48 surfactant (Tween 80) required to solubilise the template. The preparation was reproducible (RSD < 6%) and
49 the MIP beads, employed in pipette-tip format, showed good selectivity for the three organochlorine analytes
50 (dicofol, dichlorodiphenyl dichloroethane, tetradifon), corroborated by the poor affinity observed for atrazine
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1 and 3-indolebutyric acid, highly different from the template. Recovery higher than 89% was gained using the
2 MIP cartridge, although values in the range 75-83% were provided by the NIP, evidence of not negligible
3 aspecific interplays. Anyway, recoveries were far higher compared to those (30-62%) affordable using other
4 non-selective sorbents (e.g. C18-silica, NH₂-silica).
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8 Better binding affinity (and thus higher recovery) than commercial sorbents (C18-silica and HLB) was also
9 achieved by using a MIP cartridge in the extraction of fenarimol, a chlorinated fungicide, from apple, banana
10 and tomato samples [47]. The sorbent showed uniform-size beads (~ 165 nm), IF ~ 2 and cross-selectivity
11 for nuarimol, which can be simultaneously co-extracted (semi-quantitative recovery, 52-72%) from the
12 samples.
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16 Great improvement in sorption capacity and mechanical stability was gained by coupling MIPs with ILs, as
17 reported by Yan et al. [48] for the determination of dicofol, an organochlorine acaricide, in celery samples.
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19 The new type of hybrid imprinted material was prepared by precipitation polymerization using 1-allyl-3-
20 methylimidazolium bromide as auxiliary solvent for a dummy templating synthesis (template α -chloro-
21 DDT). In particular, the IL added in the pre-polymerization mixture was chemically incorporated in the
22 imprinted polymer by electrostatic interactions with the template chlorine atom, and reaction with the
23 functional monomer (acrylamide, AM), resulting in a more mechanically stable material. This proved to have
24 higher adsorption capacity than the NIP material, but also than the IL-free MIP sorbent, due to the
25 electrostatic/ion exchange interactions of the IL fraction exposed to the solution with dicofol. Higher
26 selectivity and affinity were obtained compared to other sorbents, e.g. C18-silica, NH₂-silica and neutral
27 Al₂O₃. The crucial role of the IL is even more evident considering that the IL-free MIP sorbent gave low
28 recovery, similar to that provided by bare silica (~ 65%), while recovery as high as 97% were obtained with
29 the IL-MIP. The sorbent, tested in pipette-tip format, was reusable for more extractions, and the batch-to-
30 batch reproducibility was good (RSD < 5%).
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51 Another smart synthetic route is combining the properties of MIPs with those of RAMs to enhance both
52 extraction capability and matrix cleanup [49]. RAM-MIP microspheres were prepared using
53 glycidilmethacrylate (GMA) as co-monomer, followed by treatment with perchloric acid to open the GMA
54 epoxy ring and forming a hydrophilic external layer on the polymeric phase. As typically observed with
55 RAMs, the modification with GMA allows to reduce the non-specific hydrophobic interactions with the
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1 macromolecules present in the matrix, thus favouring selective binding of the target. The prepared beads
2 showed uniform spherical morphology (about 700 nm diameter) and were tested for the extraction of six
3 organophosphorus pesticides from honey. Comparing MIP with RAM-MIP, it was found that the selective
4 recognition (IF 3.32) is ascribable to the MIP sites (GMA does not significantly interact with the template in
5 the pre-polymerization mixture). The RAM-MIP sorbent proved to be useful for analysis of real samples,
6 yielding higher recovery and precision compared to the RAM-free MIP phase, and also to commercial C18-
7 silica and Florisil (magnesium silicate). Noticed that, due to the restricted access function, the RAM-MIP
8 allows to avoid additional steps for lipids removal, that instead is mandatory using the other three sorbents.
9
10 RAM-MIP proved to be useful also for minimizing the co-extraction of proteins, as reported by de Lima et
11 al. [50] for determination of the antiparasitic drug ivermectin in meat samples. Once synthesized, the RAM-
12 MIP (precipitation method) was firstly derivatized with hydroxyl groups to increase hydrophilicity, then
13 wrapped with a bovine serum albumin (BSA) layer using glutaraldehyde as the cross-linker. The mechanism
14 of protein “exclusion” relies on the electrostatic repulsion between BSA and the proteic fraction of the
15 sample (extraction is done at pH different from the BSA isoelectric point). Indeed, the material used in
16 online SPE allowed direct injection of the meat extracts, providing good performance for about 50 injections.
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18 As an additional advantage, the cost of the RAM-MIP column resulted ten-fold lower compared to a
19 commercial RAM-C18 column.
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40 3.1.4. Monolithic MIP phases

41 Imprinted sorbents with suitable permeability can be synthesized in the monolith format, that is convenient
42 for capillary extractions and online or pipette-tip SPE.
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45 Liu et al. [51] developed a specific sample pre-treatment based on a series of extraction disks consisting of
46 MIP monoliths and C18 adsorbents for pre-concentration of salbutamol and clenbuterol residues from pork
47 samples. The monolithic MIP, prepared by *in situ* polymerization, was assembled downstream a C18 disk to
48 improve the cleanup, and connected with a syringe controlled by an injection pump. The MIP had a
49 relatively irregular and less smooth surface than the NIP, provided IF ~ 1.6 and demonstrated higher
50 selectivity for the target molecules than for ractopamine and *p*-cresol in spite of the similar structure.
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1 A molecularly imprinted monolithic capillary column was tested for the online SPE of trace antimicrobials in
2 chicken, pork and egg samples extracts [52]. The MIP was chemically bonded on the capillary inner wall,
3
4 that showed a loose and microporous surface after polymerization. Uniform morphology, good permeability
5
6 and solvent resistance were obtained using a mixture of isooctane, *p*-xylene and dimethylformamide (DMF)
7
8 as the porogen solvent. The MIP column exhibited high selectivity and sorption capacity towards the targets
9
10 compared to the NIP one, and proved to be reusable for more than 100 extractions. The column-to-column
11
12 reproducibility was good (RSD < 8%).
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15 A hybrid monolith phase was produced by Zhai et al. [53] by coating graphene oxide (GO) with a MIP
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17 prepared in capillary monolith column format by *in situ* polymerization. Using a mixture MeOH-toluene-
18
19 dodecanol as the porogen, the obtained MIP capillary column showed a high density of macropores in the
20
21 network skeleton that allowed fast dynamic transport and low back pressure, enabling to withstand flow rates
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23 up to 0.15 mL min⁻¹. The sorbent was used for selective extraction of phloxine B (a xanthene dye) from
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25 coffee beans, providing IF ~ 6.7 and selective recognition, verified by testing rose bengal as the structural
26
27 analogue probe. GO enlarged the affinity of the material for the target (~ 30% improved sorption capacity)
28
29 likely due to a large platform for the MIP immobilization afforded by the graphene layered structure.
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33 The same group proposed a similar preparation for a chip-based monolithic capillary array columns using
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35 silanized GO as the platform to support the *in situ* polymerized imprinted phase [54]. The chip, designed for
36
37 SPE of rhodamine B from chili powder aqueous extracts, consisted of four capillary tubes (3.5 cm × 500 mm
38
39 i.d.) containing the MIP material. For the synthesis the porogen composition and the template : monomer :
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41 cross-linker ratio were varied, to gain the highest permeability (flow rate up to 0.15 mL min⁻¹) and affinity
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43 for the target (IF 7.07). The GO platform imparted extra sorption capacity to the sorbent optimizing the
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45 surface available for the MIP layer, thus resulting in a more density of binding sites and in improved mass
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47 transfer. Notice that use of the chip provided higher EF compared to single-monolithic column SPE, and
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49 high stability for at least 30 extractions.
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53 Large permeability can be gained by the sol-gel approach to prepare an organic-inorganic hybrid monoliths,
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55 as reported by [55] for pipette-tip SPE of isoprocarb (a carbamate insecticide) from rice extracts. Imprinted
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57 poly(MAA)/SiO₂ was prepared using methyltrimethoxysilane (MTMS) as the inorganic precursor and
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59 KH570 as coupling agent to obtain chemical bonding between the organic and inorganic phases; these were
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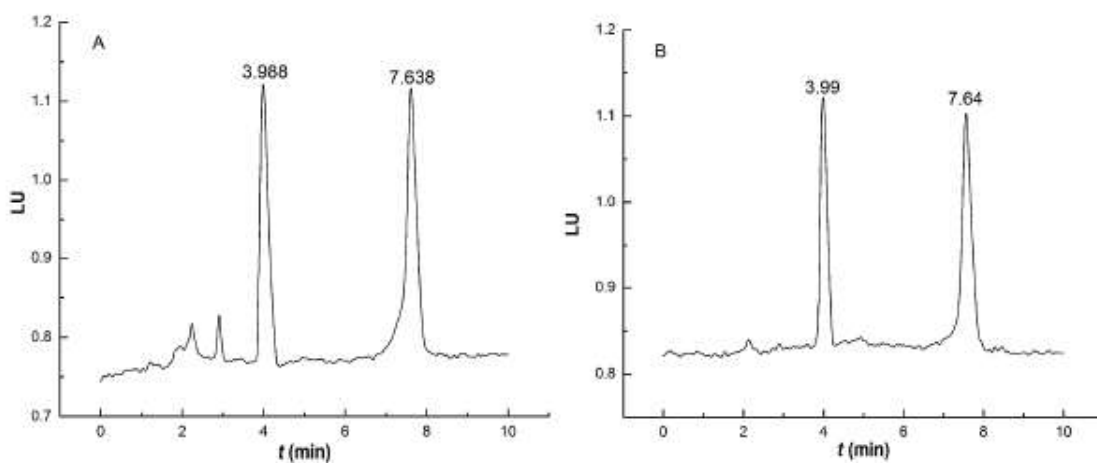
1 balanced to achieve the highest mechanical stability and to avoid shrinkage and excessive backpressure. The
2 material showed macropores and channels that provided large permeability (surface area $25 \text{ m}^2 \text{ g}^{-1}$, pore
3 volume $0.062 \text{ cm}^3 \text{ g}^{-1}$), and successful imprinting (IF 4.41) for selective determination of isoprocab in rice.
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8 3.1.5. Other routes for preparation of MIP phases 9

10 Narrow particle-size distributions and homogeneous polymers, with good selectivity, have been obtained by
11 working strategies, highlighted in the following.
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15 Emulsion polymerization was carried out to obtain a MIP solid-phase for selective SPE/cleanup of aflatoxins
16 prior HPLC-FD analysis [56]. The pre-polymerization mixture was added to the pre-formed aqueous phase
17 emulsion containing a cationic (hexadecyl trimethyl ammonium bromide) and a non-ionic (Span80)
18 surfactants, in addition to *n*-hexadecane as a hydrophobic agent. Spherical particles with an average particle
19 size around $110 \mu\text{m}$ and rough surface were produced. Using aflatoxin B1 as template molecule, cross-
20 selectivity for its structural analogue aflatoxin M1 was observed (IF 1.6 and 1.4, respectively). Selectivity
21 was confirmed by competitive recognition tests in presence of griseofulvin (antifungal drug).
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31 Excellent performance was observed compared to an official method based on immunoaffinity SPE on a
32 commercial immunosorbent (AflaTest). The extraction of the two aflatoxins was applied to barley, peanut
33 oil, beer and other feed samples obtaining cleaner extracts, as apparent from the chromatograms shown in
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38 Fig. 3, recovery higher than 83%, and the possibility to reuse the MIP for 6 extractions.
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1
2 **Fig. 3.** HPLC-FD chromatograms of spiked barley sample extracts obtained from immunoaffinity SPE (A)
3 and MIP-based SPE (B); retention times: aflatoxin M1 3.9 min, aflatoxin B1 7.6 min. Reprinted with
4 permission from [56].
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8 Pickering emulsion polymerization was practiced to synthesize MIP particles selective for bisphenols [16].
9
10 The pre-polymerization mixture was added to silica particles (12 nm) aqueous suspension containing Triton
11 X-100; the polymer-silica mixture was then treated with HF to dissolve the inorganic nanoparticles. A key
12 point was the amount of silica, that strictly affected the shape and size of the imprinted beads; under
13 controlled conditions the material showed high surface area ($\sim 355 \text{ m}^2 \text{ g}^{-1}$) and mesoporous structure (total
14 pore volume $\sim 0.55 \text{ cm}^3 \text{ g}^{-1}$, pore size 2-50 nm), and these characteristics were almost found also in the NIP
15 beads. The narrow diameter distribution obtained (40-70 μm) is advantageous in particular for packed-
16 column SPE applications. Results were satisfactory, with appreciable removal of matrix interferences and
17 recovery higher than 75% for seven bisphenols from sediment samples, without any washing step before
18 analytes elution from the cartridge.
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30 With regard to the chemical stability of the polymer, the work by Li et al. [57] well highlights the importance
31 of the choice of the cross-linker. In this context, modified-rosin as the cross-linker agent was used in a
32 suspension polymerization procedure to obtain a MIP to be used for selective extraction of a banned dye,
33 basic orange II, in foods. The key point of the preparation step was indeed the use of modified rosin, that is
34 maleic rosin glycol acrylate. This, characterized by the ring structure of phenanthrene and large molecular
35 weight, provides a very useful skeleton-supporting effect, resulting in a hard, tough and chemically stable
36 polymer. Under controlled conditions, that is using ethylacetate as organic solvent, soybean oil as porogen
37 and sodium dodecyl sulphate as dispersant, uniform-size polymer particles (180-250 μm) were obtained.
38 Formation of aggregates was avoided also adopting a temperature-programmed mode synthesis, from room
39 temperature to 95 °C. The optimal preparation route yielded spherical MIP particles with a peculiar structure
40 consisting of dense holes that provide inner channels for the target analyte; interestingly, the inner core of the
41 MIP bead showed a honeycomb-like structure, resulting in a largely porous surface available. This resulted
42 in a more specific and higher sorption capacity compared to the NIP particles (IF 2.6), and in a good
43 selectivity for basic orange II in comparison with other azo-dyes (IF 1.3-1.4). Competitive binding tests in
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1 presence of analogue compounds further highlight the role of molecular imprinting, achieving separation
2 factors up to 2.3 and great selectivity, as underlined by comparative SPE tests on C18-silica.
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4 The suspension polymerization technique was also reported by He et al. [58] for preparation of sulfadiazine-
5 imprinted microspheres ($\sim 100 \mu\text{m}$ size), in water-polyvinyl alcohol (PVA) solution. Surface area ($\sim 160 \text{ m}^2$
6 g^{-1}), average pore diameter ($\sim 42 \text{ nm}$), cumulative pore area ($\sim 220 \text{ m}^2 \text{ g}^{-1}$) and cumulative pore volume (\sim
7 0.7 mL g^{-1}) were larger than the NIP control material. The porous surface morphology resulted in a high
8 sorption capacity (ca. $5300 \mu\text{g g}^{-1}$), far higher than that observed on the NIP phase; structurally similar
9 compounds (sulfamerazine and sulfaquinoxaline) were as well retained, though in a lesser extent, evidence
10 of cross-selectivity. Due to the high selectivity of the imprinted sorbent, sulfadiazine was rapidly and
11 quantitatively determined in eggs avoiding any fat-removing step.
12

13 The same research group also proposed a SPE procedure for the synthetic estrogen diethylstilbestrol in
14 seawater [59] using MIP microspheres ($\sim 150 \mu\text{m}$) prepared by the same technique. As well acquired, also in
15 this case higher surface area, faster equilibration time and larger sorption capacity compared to the NIP
16 material provided a good performance of the imprinted SPE cartridge.
17

32 33 34 *3.2. Dispersive solid-phase extraction (d-SPE)*

35 Nanometric MIP sorbents were proposed for the simultaneous extraction of BPA and tebuconazole in
36 vegetables and juice samples [60], as shown in Table 2.
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	Template/monomer/cross-linker/solvent	Analyte(s)	Matrix	Extraction	Desorption	Recovery (%)	EF ^a	Determination	Reuse (times)	Ref.
1	BPA or tebuconazole/4-VP/MAA/ACN	BPA, tebuconazole	Vegetable, juice	5-500 mL, 20 mg MIP, 8 h	1 mL MeOH, 8 h	70-90	5-500	HPLC-UV	2	[60]
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^aEF: referred to MIP-extraction, calculated as the ratio sample volume/eluent volume.

Table 2 Use of MIPs for d-SPE in food and environmental samples.

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2 In order to achieve multi-analyte selectivity, the material was prepared by precipitation polymerization in the
3 presence of both target analytes as the templates. The synthesis conditions were tuned until obtaining
4 nanometric MIP particles that were easily encapsulated in electrospun PVA nanofibres (diameter 0.1-1 μm).
5
6 PVA proved to be a valid, chemically stable supporting polymer matrix, suitable to be treated by
7 electrospinning. Differently from the results reported by Liu et al. [29] where the binary template was used
8 as SPE, in this d-SPE procedure the double-template showed lower binding capacity and selectivity than the
9 corresponding single-template materials, attributable to the interactions between the two templates and the
10 two functional monomers. However, it should be remarked that the nanofibrous MIPs showed high
11 selectivity also in aqueous solution, offering practical advantages in the extraction of the targets from
12 aqueous matrices. Moreover, successful imprinting was observed for the two analytes, that are different in
13 charge and polarity. The role of PVA in molecular adsorption was negligible, highlighting the crucial role of
14 the MIP phase. The fibres (20 mg) were used as affinity sorbent for in-batch SPE of tebuconazole and BPA
15 from juices and vegetable foods extracts. Higher recovery and better sample cleanup than the commercial
16 C18/SCX SPE cartridge (500 mg) were gained, although sorption/desorption require very long time (8 h).
17
18 The synthesis of MIPs coated onto the surface of vinyl-functionalized multi-walled carbon nanotubes
19 (MWCNTs) for the selective separation and determination of dioctyl phthalate in beverage samples was
20 recently proposed [61]. First, the crude nanotubes were oxidized (in sulphuric and nitric acid mixture) to
21 obtain carboxyl-modified nanotubes, successively derivatized with vinyl groups using allyl chloride. Finally,
22 the imprinted film was coated on the vinyl-modified MWCNTs by using MAA as functional monomer and
23 the target molecule as template. The MIP-coated MWCNTs showed a diameter of 70-90 nm, with a MIP
24 thickness of about 15 nm suitable for effective mass transport. The material exhibited good thermal stability
25 (up to 340 $^{\circ}\text{C}$) and IF \sim 3. The adsorption capacity for dioctyl phthalate was about 1.5 and 3 times higher
26 than the two structural analogues dibutyl phthalate and di-(2-ethylhexyl) phthalate, correspondingly.
27
28 Sun et al. [62] reported the synthesis of a series of dummy MIPs for extraction of eight FQs in fish samples.
29 The authors employed different solvent mixtures as porogens for the polymerization, and investigated the
30 effect of the porogen polarity on the affinity and selectivity of the synthesised MIPs. Results showed that less
31 polar porogens yielded the highest IF for the dummy template (daidzein), due to the stronger interactions
32 between the basic π -donor/acceptor monomer 4-vinylpyridine (VP) and daidzein in low-polarity solvents,
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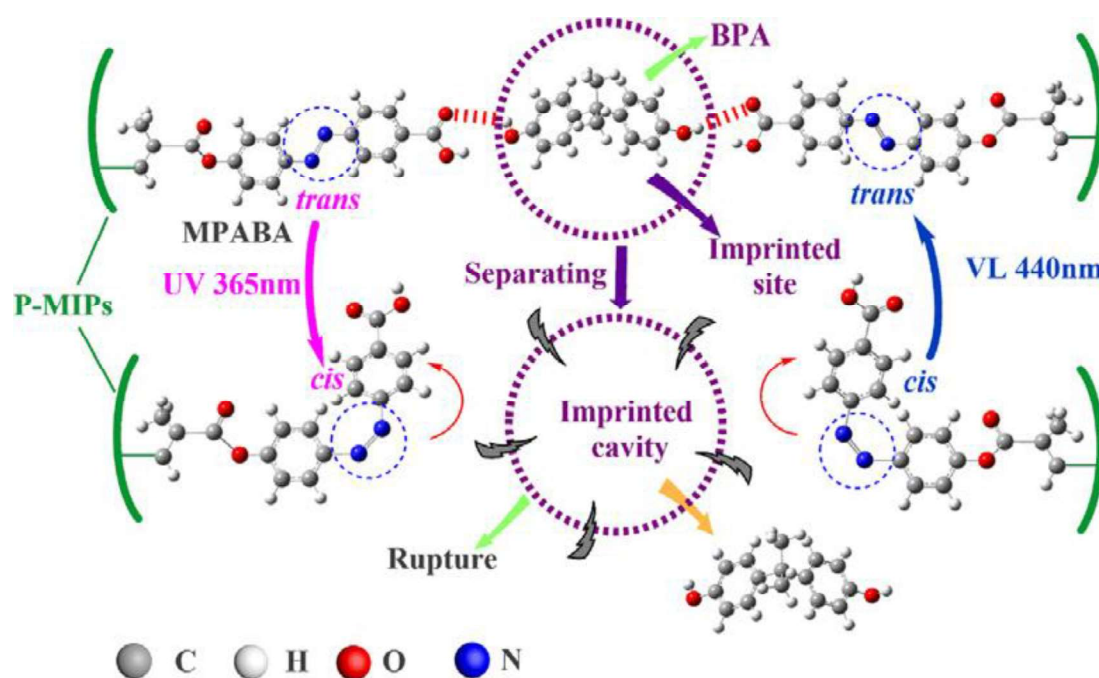
1 thus creating more high-affinity binding sites. Adsorption for the eight FQs was significantly different
2 compared to the template; indeed, the highest IF for FQs was found for MIPs prepared with an intermediate
3 polarity solvent, mixture of ACN and dimethyl sulfoxide (DMSO) (18:10). This was because porogens with
4 low polarity lead to the formation of more rigid cavities for daidzein, not easily accessible to the larger FQ
5 molecules. Recoveries in real samples were acceptable (64-103%), once again with a good sample cleanup
6 due to the intrinsic sorbent selectivity.
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12 Arabi et al. [63] proposed a simple preparation of molecularly imprinted silica nanoparticles *via* sol-gel
13 process, for determination of AM in biscuit and bread samples by matrix solid-phase dispersion. The
14 particles (average diameter around 85 nm) showed uniform, spherical shape. Extraction was performed by
15 blending the sample and the nanoparticles together with sand (to favour powdering) in a mortar, thus
16 allowing the target to easily enter the imprinted cavities by hydrogen bond binding with the functionalized
17 groups of the sorbent. The non-imprinted material showed partial recoveries (39-60%) compared with the
18 imprinted one (86-100%).
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28 Molecularly imprinted hollow spheres for extraction of estrogens from tap water samples were also reported
29 [64]. Silica nanospheres were used as the sacrificial matrix (solid-phase template method) and the
30 polymerization was performed *via* surface imprinting. The obtained MIP particles showed a spherical shape,
31 with uniform diameters of 290 nm and polymer thickness of about 30 nm. Binding tests demonstrated higher
32 affinity for the template β -estradiol (recovery > 90%, IF 1.9) than other estrogens (recovery < 79%).
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40 Nezhadali et al. [65] developed MIPs for extraction of progesterone hormones from biological and
41 environmental samples (e.g. blood and hospital wastewater). MIPs were prepared by oxidative
42 polymerization of pyrrole and showed high porosity, contrary to the NIPs that consisted of larger cluster
43 units with lower porosity/surface area. The greatest extraction efficiency was observed at pH 6.5 and was
44 further improved by “salting out effect” reaching IF ~ 2. MIPs were evaluated on structurally similar
45 compounds (estradiol, testosterone and cholesterol), though singularly tested, and the amounts extracted by
46 the MIP sorbent were much higher compared to the NIPs. In comparison with other extraction techniques
47 (e.g. LLE, SPE, SPME), this method showed acceptable sensitivity, with conventional extraction time and
48 sample volumes.
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1 A particular recognition mechanism was described in a recent work [66] reporting on the synthesis of
 2 photoresponsive MIPs. These, based on mesoporous carriers for recognition of BPA in environmental water
 3 samples, were prepared by a free radical polymerization in presence of modified mesoporous silica, using an
 4 azobenzene-containing monomer. H-bonding interactions between the template and photosensitive monomer
 5 promoted the formation of selective binding sites. The azobenzene chromophore exhibited two isomeric
 6 states, viz. the thermodynamically more stable *trans*-isomer and the meta-stable *cis*-isomer. The *trans* form
 7 was converted into the *cis*-isomer after exposure to UV-irradiation, while the *cis*-isomer can photochemically
 8 return back to the *trans* form under visible light. The photoisomerization of azobenzene produced
 9 considerable changes in molecular geometry and dipole moment to the chromophore, resulting in a
 10 significant alteration of the receptor geometry that affects the host-guest interaction (see Fig. 4).
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50 **Fig. 4.** The possible mechanism of photo-regulated adsorption/desorption of BPA by the photoresponsive
 51 MIP. Reprinted with permission from [66].
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The material adsorbs selectively BPA under visible irradiation and releases it by 365 nm radiation. Recovery was excellent, although a very long equilibration time (24 h) was necessary.

3.3. *Magnetic solid-phase extraction (MSPE)*

As discussed in this section and summarized in Table 3, the application of MIPs for in batch SPE is receiving great attention, in particular with regard to selective adsorption by MSPE, also by design of hybrid sorbents containing carbon nanomaterials.

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	Template/monomer/cross-linker/solvent	Analyte(s)	Matrix	Extraction	Description	Recovery (%)	EF ^m	Determination	Reuse (times)	Ref.
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10	Enrofloxacin/MAA /POSS/CHCl ₃	12 β -estradiol	Milk	20 mL, 100 mg MIP, 10 min shaking	MeOH-HAc (9:1)	89-92	-	HPLC-UV	15	[67]
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14										
15	12 β -estradiol/AA/EGDMA /ACN	12 β -estradiol	Milk	20 mL, 20 mg MIP, 60 min shaking	2 mL MeOH-HAc (9:1)	69-84	10	UV-Vis	-	[68]
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20	Enrofloxacin/MAA/EGDMA/CHCl ₃	FQs	Milk	10 mL, 60 mg MIP, 30 min shaking	2.0 mL MeOH-HAc-TFA (90:9:1), 20 min sonication	76-109	5	HPLC-UV	-	[69]
21										
22	Commercial MIPs (SupelMIPSTM SPE-FQs)	FQs	Milk	2 mL, 20 mg MIP, 1 min vortex	1 mL MeOH-NH ₃ (93:7), 2 min vortex	94-124	2	HPLC-UV	-	[70]
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24										
25		Erythromycin,								
26		oleandomycin,								
27		azithromycin,	Pork, fish,							
28	Erythromycin/MAA/EGDMA / ACN-MeOH	tilmicosin,	shrimp	20 mL, 100 mg MIP, 5 min shaking	10 mL MeOH-50 nM KH ₂ PO ₄ pH 8 (8:2)	64-89	2	HPLC-UV	3	[71]
29		clarithromycin,								
30		roxithromycin								
31										
32										
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37	Sulphonamide template/GMA/DVB/H ₂ O	Sulphonamides	Chicken	1 mL, 15 mg MIP, 10 min shaking	3 \times 0.5 mL MeOH-NH ₃ (98:2)	85-112	-	HPLC-MS	6	[72]
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42	1,7-dioxaspiro [5,5]-undecane/EGDMA	1,7-dioxaspiro [5,5]-undecane	Olive oil	10 mL, 50 mg MIP, 5 min sonicated, 40 min vortex	0.5 mL MeOH	95-99	20	GC-MS	9	[73]
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Various procedures have been developed for pharmaceutically active compounds. Magnetic MIPs were prepared for determination of 17 β -estradiol in milk [67]. Fe₃O₄ nanoparticles were coated with a MIP layer (10 nm thickness) using acryloyl chloride and AM as functional monomers, *via* a surface imprinting procedure. Nanoparticles were almost sphere-shaped, with a narrow particle size distribution (average diameter 100 nm) and high adsorption capacity (12.62 mg g⁻¹), fast equilibrium time (10 min), and satisfactory selectivity for the target, as verified by testing estrone, diethylstilbestrol and estriol as analogues; as expectable, the NIP magnetic material showed no selectivity. The same compound was quantified in milk [68] by a sample preparation step based on a novel nanosized MIP supported onto magnetic GO (GO-Fe₃O₄). The thin single-layer structure of GO provided a suitable platform for anchoring Fe₃O₄ nanoparticles, with the imprinted film coated on the GO-Fe₃O₄ surface. The material provided rapid adsorption and IF 2.46. The binding specificity of the MIP-derivatized sorbent was proved by selectivity tests performed on various structural analogues of 17 β - estradiol.

MSPE-based methods have also been developed to analyze trace antibiotics, as described by He et al. [69]. This paper presented a MIP nanomagnetic polyhedral oligomeric silsesquioxanes (POSS) hybrid material for FQ residues determination in milk samples. The MIP layer was obtained through co-polymerization of active vinyl groups present on the nanomagnetic POSS (Fe₃O₄@POSS) surface and the functional monomer. The material resulted as agglomerated beads made up of sphere-like nanoparticles with average size of about 30 nm. MIPs had superior porosity over the NIPs, such as larger surface area, pore volume and pore size (357 m² g⁻¹, 0.44 cm³ g⁻¹, 4.56 nm). The selectivity of MIPs was investigated on FQ structural analogues and chloramphenicol as reference compound. The results demonstrated much higher adsorption capacity and selectivity toward enrofloxacin and its analogues (IF about 3) than the NIP, and (expected) lower adsorption capacity for chloramphenicol. The extraction resulted pH-dependent (highest affinity at pH 6) ascribed to strong ion-exchange interaction between the MIP deprotonated carboxyl groups and the cationic FQ species.

A simple co-mixing method to fabricate magnetic MIPs was as well proposed for determination of FQs in the same matrix [70]. Magnetic ferrous nanoparticles and commercial MIP SPE beads (SupelMIPs™ SPE-FQs) were co-mixed and vortexed in MeOH, promoting a spontaneous self-assembling into magnetically separable hybrid composites. The obtained powder showed agglomerates, with a mean particle size distribution of about 30-90 μ m. In agreement with the above study [69], extraction resulted pH dependent

1 (best results at pH 6), due to a series of interactions (hydrophobic, ionic and hydrogen bond) with the
2 cationic/zwitterionic forms of the analytes. Moderate sensitivity was gained with respect to other available
3 methods.
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6 A sol-gel approach was undertaken to synthesize a hybrid imprinted material to be used for selective
7 separation of six macrolide antibiotics from pork, fish and shrimp samples [71]. Fe₃O₄ nanoparticles were
8 first coated with SiO₂ *via* a sol-gel process, subsequently modified with the MIP phase, using erythromycin
9 to form hydrogen bond and electrostatic interplays with the monomer (MA). The material demonstrated
10 excellent selectivity (IF 11.9) and also cross-selectivity for the other macrolide antibiotics, differently from
11 not related antimicrobials (e.g. FQs and chloramphenicol). Higher sensitivity and precision were found
12 compared to other MIP column SPE procedures.
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16 Simultaneous determination of 22 sulphonamides in chicken breast muscle by MIP-based MSPE was
17 reported [72]. The imprinted magnetic nanoparticles obtained by ultrasound-assisted polymerization were
18 ringed in shape with inside and outside diameters of 70 and 150 nm respectively, and the polymer layer had
19 an average thickness of approximately 10 nm. The extraction procedure turned out to be strongly pH-
20 dependent, with the best extraction efficiency in the range 5-6. Compared to the NIP material, magnetic MIP
21 demonstrated higher selectivity for most sulphonamides, with better analytical performance than
22 conventional LLE, and other SPE or SPME procedures.
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26 A recent paper deals with synthesis of magnetic MIP nanoparticles for selective extraction of 1,7-dioxaspiro-
27 [5,5]-undecane (sexual pheromone) from olive oil [73]. The nanoparticles resulted spherical, with an average
28 diameter of 20 nm, and grew slightly after the imprinting process, maintaining the same shape. The
29 nanocomposite exhibited short equilibrium time, excellent molecular recognition ability (IF 5.3 in hexane
30 and IF 4 in ACN) but lower sorption capacity in water. The reduced performance in aqueous phase was also
31 encountered by Su et al. [74] for rhodamine B, belonging to the class of organic dyes. Indeed, addition of
32 water or MeOH to the sample extract negatively affected the specific binding, reasonably by hampering
33 hydrogen bond interaction with the target. The material resulted mainly useful for cleanup purposes,
34 allowing detection of the illegal addition of rhodamine B in food (IF 1.9).
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38 With regard to curcumin determination in food, a simple and rapid method for monitoring the dye in food
39 samples using a MIP MSPE combined with UV-Vis spectrophotometry was recently published [75]. The
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1 surface of Fe₃O₄ nanobeads was coated with curcumin-imprinted polymer. The selectivity study, conducted
2 testing several natural structural analogues of curcumin and yellow colorants usually used in foodstuffs (i.e.
3 demethoxycurcumin, bisdemethoxycurcumin, tartrazine, sunset yellow), revealed a much larger adsorption
4 capability for curcumin. The sorbent was applied to actual samples obtaining quantitative recovery.
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8 A novel MIP sorbent based on magnetic phenyl-modified MWCNTs for the same dye determination was
9 applied to ginger powder and kiwi fruit roots [76]. The Fe₃O₄ nanoparticles, grafted on MWCNTs, had a
10 diameter of 100-120 nm, while the MIP thickness was in the range 20-25 nm. The phenyl groups, covalently
11 grafted on the nanotubes skeleton exerted a double role, that is to assist the functional monomer *via* π - π
12 conjugative effect to selectively bind curcumin and, at the same time, to reduce the hydrophilicity of the
13 imprinted system, hence improving adsorption speed. The magnetic composite exhibited a good selectivity
14 for curcumin (IF 2), with higher affinity compared to its analogues demethoxycurcumin and
15 bisdemethoxycurcumin.
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18 The cationic triphenylmethane dye malachite green was quantitatively extracted from fish samples [77] using
19 a core-shell magnetic MIP prepared with Fe₃O₄ nanoparticles derivatized with a silica layer that served to
20 graft 3-methacryloxypropyltrimethoxy-silane (MPS); this was involved in the subsequent polymerization
21 step in presence of the template. The material showed reusability, recognition capability 2.5-fold higher than
22 the magnetic NIP, and a clear selectivity for the target dye compared to crystal violet, a structural analogue
23 dye often detectable in fish tissues.
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26 Analytical methods have been developed for determination of polychlorinated biphenyls (PCBs) in fish [78,
27 79]. The former study involved the preparation of composite consisting of MWCNTs, magnetic particles and
28 MIPs, used as sorbent phase for MSPE of six PCBs. Fe₃O₄ nanoparticles were coated with SiO₂ and then a
29 MIP layer (20 nm) was immobilized on the support (overall particle diameter 500-600 nm). Subsequently,
30 carboxylated MWCNTs were electrostatically linked onto the MIP surface. The material showed good
31 adsorption capacity (~ 0.6 mg g⁻¹) and no interference by other phenyl organic pollutants (i.e. xylenes,
32 chlorophenol, 2,4-dichlorobenzene acetic acid), naphthylamine and inorganic ions commonly present in
33 water.
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36 Another carbon material (GO) was exploited to prepare a magnetic imprinted composite [79]. Reduced GO-
37 Fe₃O₄ nanoparticles were synthesized by *in situ* chemical co-precipitation of Fe²⁺ and Fe³⁺ in presence of
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1 reduced GO and then were coated with a thin polymer film (~ 5 nm) imprinted with a dummy template (3,4-
2 dichlorobenzidine). Thermodynamics tests suggested that adsorption of PCBs was endothermic and
3 spontaneous, and IFs in the range 1.5-2.3 were observed. Compared with C18-silica, the material exhibited
4 large adsorption capacity, high selectivity, and ease of preparation.
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8 Qiao et al. [80] proposed magnetic MIPs for extraction of five phthalates in plastic bottled beverages. The
9 sorbent was fabricated by coating Fe₃O₄ nanoparticles with MIPs *via* aqueous suspension polymerization to
10 improve binding capacity, selectivity, and compatibility of the polymer with water. The morphology of
11 magnetic MIPs was regular spherical, and excellent thermal stability was ascertained (until 240 °C). The
12 ionic strength of the samples did not interfere with extraction efficiency, and compounds commonly found in
13 beverage samples like water-soluble vitamins (e.g. B6, B12, and C and niacinamide) were not absorbed by
14 magnetic MIPs.
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17 Phtalates esters were determined in water and beverages by a magnetic phase consisting of Fe₃O₄ (the core),
18 TEOS-derived SiO₂, “pyrolitic” carbon and MIPs [81]. The multi-step synthesis also involved removal of the
19 silica by strong alkali treatment, and oxidation of the carbonaceous phase in H₂O₂ solution. The carboxylic
20 groups obtained on the magnetic particles were then exploited to chemically anchor the imprinted polymer.
21 This approach resulted smart to enhance the analytes uptake due to the high number of cavities resulting
22 from SiO₂ etching, that was the key feature of the work. This was clearly evidenced by comparison with the
23 same material containing the siliceous fraction, whose sorption capacity was about 4-fold lower. After a
24 rapid extraction, analytes were eluted in pure chloroform with quantitative recovery.
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27 A magnetic hollow MIP for pre-concentration of four triazines from corn, wheat, and soybean samples was
28 described [82]. MIPs were prepared by multi-step swelling polymerization on the surface of PS spheres,
29 followed by *in situ* growth of Fe₃O₄ nanoparticles. Hollow polymers, formed after removal of PS (similarly
30 to the hard template approach used by Zhao et al. [18]), turned out to have average diameter around 1.8 μm,
31 and were advantageous in terms of increased binding capacity and accelerated mass transfer. The sorbent
32 demonstrated good selectivity for the four triazines (IF 5.1-5.7), higher with respect to carbendazim and
33 furazolidone (IF < 1.2).
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36 Ractopamine was extracted from pork samples by a magnetic MIP [83]. This was assembled on the Fe₃O₄
37 core by APTES, yielding a final product (15-40 nm) showing specific binding of ractopamine (IF 2.9) among
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1 other analogues (i.e. isoproterenol, isoxsuprine and terbutaline). It should be noted that the cross-linker
2 played an chief role during polymerization, as excessive amounts resulted in a difficult removal of the
3 template from the polymeric matrix due to steric hindrance. Advantages in term of sensitivity were found
4 compared to the commercial Oasis MCX SPE cartridge.
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8 Selective pre-concentration of four aflatoxins (B1, B2, G1, G2) from food samples was as well achieved
9 exploiting the molecular imprinting technology [84]. Fe₃O₄ nanoparticles were coated with a silica shell by a
10 sol-gel process, then derivatized with the MIP phase. Particles were nearly cubic in shape with an average
11 diameter of 200 nm, and the polymer layer was about 20 nm thickness. The composite showed high
12 adsorption capability for the four aflatoxins, with recovery comparable with those attained using commercial
13 Mycosep-226 columns. Moreover, comparable or superior analytical performance was gained in terms of
14 sensitivity and linear range with respect to existing electrochemical and ELISA-based methods.
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24 The use of MIP magnetic nanoparticles for selective extraction and cleanup of the carcinogenic mycotoxin
25 ochratoxin A in grape juice has been reported [85]. The synthesis was performed on Fe₃O₄ *via* surface
26 initiated atom transfer radical polymerization. The functional monomer (ether methacrylate) demonstrated
27 high affinity for ochratoxin A due to strong hydrogen bonds. The material resulted highly agglomerated
28 before and after molecular imprinting, and the MIP layer showed an average thickness of 18 nm; a water
29 layer on to the hydrophilic surface of nanoparticles was observed. Higher adsorption capacity and greater
30 selectivity were seen for ochratoxin A (IF 3.9) than other mycotoxins (aflatoxin and vomitoxin, IF 2.2 and
31 2.4, respectively), in addition to fast equilibrium time and potential reusability.
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42 Another work reported on the determination of mycotoxin citrinin from rice samples [86]. Surface imprinting
43 of Fe₃O₄ nanoparticles by a “stoichiometric” non-covalent imprinting approach involving the interaction of a
44 urea-based monomer and the template yielded the magnetic MIP sorbent able to recognize citrinin by
45 formation of a complex with stoichiometry 1:1. To facilitate the analyte recognition/uptake, extraction was
46 carried out in aqueous buffered solution (pH 7.5). Overall, the batch-to-batch reproducibility was excellent
47 (RSD < 4%), as well as the chemical stability (reusability for at least 30 cycles). Cleaner extracts and higher
48 specificity were achieved in comparison with SPE pre-concentration using WAX and polyamide cartridges.
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57 With regard to environmental matrices, BPA was determined in seawater by a “temperature-dependent”
58 MSPE [87]. In this work, water-compatible temperature and magnetic dual-responsive MIPs were
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1 synthesized starting from Fe₃O₄ microspheres, capsulated by SiO₂ (to prevent oxidization) and coated with
2 MIPs (layer of 10 nm) able to recognize analyte *via* multiple-point hydrogen bonding. The reversible
3 recognition/adsorption and release of the target molecule can be triggered by tuning temperature; indeed, at
4 20 °C water molecules easily diffuse into the MIP phase that is able to adsorb the analyte by swelling. When
5 temperature increases to 45 °C, most water molecules are expelled leading to a contractive state of the
6 polymer with deformation of the imprinted cavities, responsible for the analyte desorption. The hybrid
7 material showed IF ~ 4 for BPA, and low adsorption for some structural analogues (phenol, estradiol and
8 diethylstilbestrol). It was employed as adsorbent both for MSPE and packed-column SPE: as MSPE it
9 resulted more suitable for simple, rapid, recycled separation and adsorption of BPA, while in the SPE mode
10 was more useful for BPA enrichment and sample cleanup.

11 As compounds of environmental concern, MSPE procedures have been designed for determination of
12 insecticides and herbicides. Qiao et al. [88] prepared a new type of molecularly imprinted IL magnetic
13 microspheres for extraction of dicofol, *p,p'*-dichlorodiphenyldichloroethane (DDD) and tetradifon from
14 water. Synthesis involved aqueous suspension polymerization choosing 1-allyl-3-ethylimidazolium
15 hexafluorophosphate IL and MAA as co-functional monomers. The as-prepared beads resulted spherical,
16 monodispersed, with an average diameter of about 20-50 μm. The aim was to add the IL to establish π-π and
17 electrostatic interactions with the analytes, that were however almost retained also on the IL-free material;
18 moreover, compared to the NIP, selectivity was good only for the template.

19 3.4. Solid-phase microextraction (SPME)

20 Molecular imprinting is under investigation also for SPME applications (see Table 4).

	Template/monomer/cross-linker/solvent	Analyte(s)	Matrix	Extraction	Desorption	Recovery (%)	EF ⁿ	Determination	Reuse (times)	Ref.
10	Beanoate ion/pyrrole/-/H ₂ O (electrosynthesis)	Beanoate	Beverages	25 mL, applied +0.9 V	0.8 mL, applied -1.0 V	-	31	UV-Vis	10	[89]
13	Acetylamine/3-(triethoxysilyl)propylamine/-/ACN-TFA (3:2) (electrospinning)	Acetylamine	Beverages	4 mL, on-line 0.9 mL/min	On-line desorption ACN-0.02 M PBS (85:15)	89-91	-	HPLC-UV	50	[90]
18	Parathion-methyl/C[4]/TEOS/CH ₂ Cl ₂	Fonofos, fenitrothion, parathion, parathion-methyl	Apple, pineapple	4 mL + 1.6 g NaCl, headspace 70 °C, 30 min stirring	Directly in GC injector 250 °C, 8 min	84-109	-	GC-NPD	-	[91]
22	Estradiol/ABPA/ABPA/PBS-ACN (5:20 v/v)	Estrone, estradiol, estriol, ethinylestradiol	Fish, pork	5 mL, 20 min, stirring up and down fibres 160 times/min	7 mL, MeOH-HAc (99:1), stirring up and down fibres 120 times/min 10 min	74-97	-	HPLC-UV	250	[92]
27	Imazethapyr/MAA/EGDMA/EtOH	Imazameth, imazamox, imazapyr acid, imazethapyr, imazaquin acid	Rice, peanut, soil	4.5 mL, 40 min stirring	0.1 mL ACN-0.5% HAc (75:25), 15 min	61-116	45	HPLC-UV	100	[93]
33	Propazine/MAA/EGDMA/toluene	Desethylatrazine, desisopropylatrazine, simazine, cyanazine, atrazine, propazine, ter-butylazine	Water	1.8 mL (10% NaCl), 60 min stirring	0.4 mL MeOH, 15 min shaking	~45	4.5	HPLC-UV	-	[94]
38	Propazine/MAA/DVB-80/ACN-toluene (3:1)	Simazine, cyanazine, atrazine, propazine, ter-butylazine	Surface, ground, tap waters	4.5 mL, 20% NaCl, 45 min stirring	0.45 mL MeOH-HAc (95:5), 30 min stirring	78-103	10	HPLC-UV	-	[95]
43	Benzylparaben	Methyl, ethyl, isopropyl, propyl, benzyl, isobutyl, butylparaben	Soil, sediment	1.7 mL, 60 min stirring	0.4 mL MeOH-HAc (99:1), 30 min	78-109	4.2	HPLC-UV	50	[96]

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4	/NOBE/NOBE/ACN													
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8	Abacavir/AA/EGDMA /DMF	Abacavir	Surface and waste waters	25 mL, 0.3 % NaCl, 45 °C, 40 min stirring	1 mL MeOH-FA (99:1), 10 min sonication	88-99	25	HPLC-MS	-	-				[97]
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^aEF: referred to MIP-extraction, calculated as the ratio sample volume/eluent volume.

Table 4 Use of MIPs for SPME in food and environmental samples.

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With regard to the food matrices, Manbohi et al. [89] reported the preparation of a molecularly imprinted polypyrrole film on the surface of a stainless steel rod for extraction of benzoate ion in beverage samples by electrochemically controlled SPME. The MIP was characterized by a more porous structure and smaller particle diameter (about 90-250 nm) than NIP (250-500 nm). The uptake/release process was based on the electrochemical oxidation/reduction of polypyrrole; during the oxidation, a positive charge was formed on the polypyrrole chain allowing the extraction of the anionic analyte from the solution. Accumulation at pH 6 gave the highest response, because benzoate is mostly anionic and electrostatically is adsorbed to the fibre but, at alkaline pHs, hydroxide ions compete with benzoate decreasing the extraction efficiency. Selectivity was satisfactory as verified with several similar structured ions (salicylate, sorbate, citrate, phosphate, acetate).

A sol-gel process coupled with electrospinning technique was chosen for the immobilization of a MIP nanofibre on the surface of a stainless steel bar [90]. This SPME device was employed for determination of acesulfame in beverage samples. Nylon 6 was used as a backbone to support the MIP precursor in the sol-gel process, and was used to facilitate the electrospinning procedure. Both MIP and NIP SPME fibres showed porous structures, but porosity of the NIP was significantly lower compared to the former; as above commented also for other extraction techniques, the high porosity stands for a largely available surface area, a key factor to improve mass transfer during extraction, as well as analyte desorption. IF 3 was observed, with good selectivity for the target molecule compared to other sweeteners or food additives like saccharine, aspartame and caffeine. The fibre was successfully used in an online HPLC system to facilitate the extraction speed and to reduce solvent consumption.

The sol-gel route was also undertaken to prepare a MIP-derivatized fibre for determination of four organophosphorus pesticides (fonofos, fenitrothion, parathion and parathion-methyl) in apple and pineapple samples [91]. The C[4] calixarene was used as functional monomer for its hydrophobic cavity with plentiful π electrons, which contributed to the bonding force between the coatings and target analytes. The fibre exhibited high extraction ability, selectivity (IF 1.5), excellent solvent and thermal resistance (up to 380 °C). The coating showed a porous and loose structure deriving from the sol-gel layers, that provided a large number of adsorption sites. In comparison with LLE and other SPME-based methods (PDMS, PA,

1 PDMS/DVB and CAR/DVB/PDMS coated fibres), the MIP-SPME technique was competitive in terms of
2 sensitivity and recovery in such complex matrices.
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4 It is noteworthy the great stability and reusability (up to 250 times) shown by the magnetic MIPs designed
5 for the simultaneous automated SPME of estrone, estradiol, estriol, ethinylestradiol from fish and pork
6 samples [92]. Fe₃O₄ nanoparticles were coated with zeolite imidazolate framework-8 and then derivatized
7 with a MIP thin layer (about 5 nm). The particles were immobilized on stain-less steel fibre surface in the
8 presence of a strong magnetic field, and the device was easily integrated with a robotic autosampler. MIP
9 provided the best recovery performing the extraction in *n*-hexane, with good IF (2.3-3.4) and fast adsorption
10 time. Adsorption capacity for estrogens of commercial SPME fibres (85 µm PA, 85 µm CAR/PDMS, 65 µm
11 PDMS/DVB, and 50/30 µm CAR/DVB/PDMS coatings) used for comparison, was affected by the presence
12 of non-target species.
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24 A MIP SPME for determination of herbicides (imazameth, imazamox, imazapyr acid, imazethapyr and
25 imazaquin acid) in food and environmental matrices was developed by Chen et al. [93]. One-step *in situ*
26 polymerization enabled to prepare the MIP coating directly on the surface of a silica fibre. The coated fibres
27 (thickness up to 87.5 µm) showed good intra-batch reproducibility and an excellent thermostability below
28 220 °C. A comparison with commercially available SPME coatings, such as PDMS, PA, PDMS/DVB,
29 CW/DVB and PDMS/CAR, showed superior recovery and selectivity for the targets compounds. The MIP
30 fibre proved to possess higher affinity for the selected analytes compared to non-structural analogues such as
31 4-methylimidazole, 2,4-D butylate ester and nicotinic acid. It was seen that the extraction capability reached
32 the maximum in *n*-hexane, whose apolarity favours hydrogen bond interactions between target molecules
33 and monomer.
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46 The work by Barahona et al. [94] describes MIPs immobilized in the pores of a PP hollow fibre tested for the
47 microextraction of triazines in environmental waters. It was observed that the macropores of the original
48 fibre were completely filled by the MIP and a thin film of toluene was immobilised in the pores of the
49 obtained polymer. Recoveries were lower for the more polar triazines, according to the liquid-liquid
50 repartition between the aqueous solution and toluene film on the MIP surface. Even if addition of NaCl to the
51 sample improved extraction due to salting-out effect, recoveries in water was only partial; moreover, the
52 inter-batch reproducibility showed relatively high RSD (~ 22%).
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1 Better results in terms of trace enrichment and cleanup of triazines in environmental waters are assured by a
2 MIP-derivatized SPME hollow fibre, as shown by Turiel et al. [95]. Using propazine as the template, MIP
3 exhibited good recovery in water sample (78-103%), with the best extraction gained in toluene. The ability
4 of the MIP fibre to selectively recognize structurally related compounds was studied on seven triazines,
5 obtaining recoveries around 70%. A high degree of sample cleanup was noticed compared to a non-selective
6 SPE procedure carried out on commercial C18-silica.

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12 Diaz-Alvarez et al. [96] developed MIP SPME fibres for determination of methyl-, ethyl-, isopropyl-,
13 propyl-, benzyl-, isobutyl- and butyl- paraben in soil and sediments samples. The MIP was prepared with a
14 single bifunctional monomer, *N,O*-bismethacryloyl ethanolamine, replacing the conventional approach based
15 on ethylene glycol dimethacrylate (EGDMA) as cross-linker and MAA as monomer. The comparison
16 between the newly prepared and the conventional imprinted fibres showed that the proposed formulation
17 provided better recognition for the six paraben analogues. These findings can be ascribed to the difference in
18 MIP formats (beads versus fibres), with the greater surface area of the beads providing a larger number of
19 binding sites than the MIPs fibres.

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Another SPME fibre based on MIPs was reported for selective removal/extraction of the antiviral drug
abacavir from surface and wastewaters [97]. The fibre was synthesized by free radical polymerization of
acrylic acid (AA) in glass tubes (2 mm diameter), obtaining a material with a rougher surface and defects
compared to the NIP one. Adsorption was favoured at pH 8, due to non-electrostatic attractive interactions,
i.e. hydrogen bonding, between the carboxyl groups of the MIP fibre (acrylic substrate) and the abacavir
nitrogen atoms. The MIP fibre exhibited a high IF (around 11), and higher selectivity for the analyte
compared to other two drugs, acyclovir and adefovir-dipivoxil. Higher selectivity and affinity were achieved
compared to the commercial HLB SPE sorbent.

3.5. *Stir-bar sorptive extraction (SBSE)*

The most recent applications of MIPs to SBSE are summarized in Table 5.

	Template/monomer/cross-linker/solvent	Analyte(s)	Matrix	Extraction	Description	Recovery (%)	EF ^a	Determination	Reuse (times)	Ref.
1	10lonazepam/MAA/EGDMA/MeOH	Benzodiazepines	Herbal health foods	1.5 mL, 400 rpm, 25 min	1 mL MeOH-HAc (9:1), 20 min sonication	85-103	1.5	HPLC-UV	20	[98]
2	14toluene (9:1)									
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7	13Melamine/MAA/EGDMA/MeOH	Melamine	Powdered milk	10 mL, pH 8.5-9.5, 300 rpm, 50 min	2 mL MeOH- HAc (9:1), 40 min sonication	90-96	5	HPLC-UV	3	[99]
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10	17Cytomazine/MAA/EGDMA/ACN	Melamine	Feed, milk	10 mL, 600 rpm, 180 min	0.4 mL MeOH-NH ₃ (92:8), 20 min sonication	65-113	25	HPLC-UV	13	[100]
11	18Bisphenol A/luminol/0.1 M phosphate 0.1 M KCl	Estrogens	Milk	10 mL, 500 rpm, 20 min (fibre-format SPE)	5 mL MeOH- HAc (99:1), 20 min	83-96	2	HPLC-UV	35	[101]
12	20electrochemical polymerization)									
13	21BPA+diethylstilbestrol/dopamine/0.23 M phosphate	Estrogens	Pork, chicken	50 mL (25% NaCl), pH 6-8, 500 rpm, 20 min (film-format SPE)	5 mL MeOH- HAc (99:1), 15 min	94-108	10	HPLC-UV	20	[102]
14	24electrochemical polymerization)									
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17	28BPA/AM/EGDMA/MeOH	BPA	Surface water	30 mL, 500 rpm, 120 min	0.26 mL MeOH, 5 min sonication	63-99	115	HPLC-UV	100	[103]
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^a EF: referred to MIP-extraction, calculated as the ratio sample volume/eluent volume.

Table 5 Use of MIPs for SBSE in food and environmental samples.

1 A laborious synthetic route was adopted by Li et al. [98] for the preparation of a MIP material for
2 determination of clonazepam and nitrazepam (benzodiazepine drugs) in herbal health foods. Magnetic
3 nanoparticles were prepared by the conventional co-precipitation method (using FeCl₂ and FeCl₃) and
4 successively were derivatized with a silica layer obtained by hydrolysis of tetraethylorthosilicate. The outer
5 silica layer was then treated with two different silylating agents, then a coupling reaction was carried out
6 between the amino-terminating chain deriving from γ -aminopropyltriethoxysilane and diaminobenzoic acid.
7
8 The second silylating agent took part in the subsequent self-assembly pre-polymerization onto a γ -
9 (methacryloxypropyl)trimethoxysilane-modified stir bar, in the presence of clonazepam as the template, and
10 MAA as the optimal functional monomer; polymerization was carried out in MeOH-toluene and relied on
11 hydrogen bonds and π - π conjugation between the template and polymeric phase. The resultant imprinted
12 phase was uniform and homogeneous, with a thickness and sorption capacity that resulted strictly dependant
13 on the amount of intermediate particles (200-250 nm). Notice that an excessive thickness caused an
14 increased mass transfer resistance, with longer contact times to achieve analyte uptake from the solution. Zhu
15 et al. [99] prepared a MIP-SB for determination of melamine in powdered milk. The target compound was
16 used as the template, and the imprinted layer was chemically anchored to the glass surface of the magnetic
17 bar, initially derivatized with 3-(trimethoxysilyl)propylmethacrylate. The obtained coating (~ 4.5 μ m) was
18 uniform, with a compact structure made of small and interconnected globules. The sorption capacity of the
19 MIP-SB was 3.6-folds higher compared to the NIP. This was able to give only physical adsorption, with
20 sorption capacity higher for cyanuric acid compared to melamine, similarly to a commercial PDMS stir bar.
21 The analyte uptake was favoured in the pH range 8.5-9.5, and efficient desorption was gained using acidic
22 MeOH, obtaining quantitative recovery of melamine in powdered milk extracts. Solvent-resistant tests
23 showed good stability, and good efficiency for at least 3 sorption/desorption runs was proved. The MIP-SB
24 preparation was reproducible (RSD around 7%).

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51 Another SBSE procedure for the determination of melamine in animal feed and milk samples was developed
52 by Fan et al. [100] by *in situ* polymerization, using cyromazine as the dummy template; the polymer was
53 chemically bonded to the glass stir bar using γ -(methacryloxypropyl)trimethoxysilane as a bridge agent. The
54 porogen volume directly influences the morphology and mechanical properties of the MIP coating, while the
55 molar ratio functional monomer: cross-linking agent: template plays a key role in the overall recognition
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1 capacity of the material. The best conditions gave a porous structure with a pore size bigger than that
2 observed on the NIP phase, a good stability in various organic solvents, reusability and batch-to-batch
3 reproducibility (RSD < 9%). The high selectivity obtained for melamine, with respect to its metabolites
4 (cyanuric acid and ammeline), poorly retained on the sorbent, was due to the specific recognition sites and
5 matching pore size in the imprinted phase; on the contrary, non-specific adsorption is dominant in the NIP.
6
7 The polarity of the sample solution strongly affected the MIP sorption ability, with the highest selectivity
8 factor observed in MeOH; the best elution solution proved to be alkaline MeOH, able to break down
9 hydrogen bonds between the target analyte and MAA (functional monomer) in the sorbent. Recovery was in
10 the range 65-113% depending on the type of sample.

11
12 Liu et al. [101] practiced the electrochemical polymerization of luminol (5-amino-2,3-dihydro-1,4-
13 ftalazindione) as functional monomer onto a carboxyl graphene-derivatized pencil lead to prepare a novel
14 fibre-type sorbent for the pre-concentration and selective recognition of estrogens (BPA, hexoestrol,
15 diethylstilbestrol) in milk. It should be noted the role of carboxyl graphene that establishes strong
16 electrostatic interaction with polyluminol and, at the same time, provided a large adhesion area for the
17 imprinted layer. This contributes to enhance the sorption ability of the MIP phase toward the target species
18 and facilitates the sorption kinetics. The IF was higher than 4 for the three analytes, that are selectively
19 extracted from the sample due to both specific interactions and complementary size of the imprinted sites;
20 this is supported by the poor affinity observed for phenol and ethynilestradiol, different for size and
21 functional groups. The MIP-fibre was immersed in the sample under stirring, then estrogens were eluted by
22 acidic MeOH prior instrumental quantification, obtaining quantitative recovery in powdered milk extracts
23 (20-100 ng mL⁻¹). The sorbent showed long lifetime (it was reusable for at least 35 extractions) and high
24 selectivity, that resulted in better sensitivity than commercial aspecific sorbents (i.e. polydimethylsiloxane
25 and polyacrylate) in the analysis of real-world samples.

26
27 Qiao et al. [102] produced a MIP-modified 8-electrode array by dopamine electropolymerization for the pre-
28 concentration of estrogens in meat. The device consisted of gold nanoparticles-modified screen printed
29 electrodes supporting a MIP film; this was obtained by drop deposition of the pre-polymerization mixture
30 containing Fe₃O₄@TiO₂ microspheres and dopamine as the functional monomer. Cyclic voltammetry,
31 carried out in aqueous solution, was used to perform polymerization to obtain the imprinted layer, that

1 uniformly coated the magnetic composite surface. Multi-analyte selectivity was achieved by simultaneous
2 imprinting of BPA and diethylstilbestrol as template molecules. The thickness of the polymeric film,
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4 dependant on the number of polymerization cycles, affected the sorption capacity, that was maximized
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6 working with a thickness of about 6 nm. The role of Fe₃O₄@TiO₂ particles is worth noting, enlarging the
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8 base area of the electrode available for the immobilization of the MIP film, thus favouring the sorption
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10 capacity towards the target species (IF 3.7-4.1).

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12 A MIP phase reusable for at least 100 times with no loss of efficiency, and good batch-to-batch
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14 reproducibility, was prepared by capillary *in situ* polymerization, and applied to determination of BPA in
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16 environmental waters [103]. The imprinted polymer, obtained using 4,4'-(hexafluoroisopropylidene)diphenol
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18 as the dummy template, provided a homogeneous coating (thickness ~ 0.4 μm), with a structure
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20 characterized by higher porosity compared to the NIP material, beneficial for molecular adsorption and mass
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22 transfer. Selectivity tests undertaken on various estrogen compounds, proved to be good for BPA, with the
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24 highest IF compared to that observed in the presence of the other probes.
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31 **4. Conclusions and perspectives**

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33 Besides providing an overview of the most recent applications of MIPs to analytical determination of
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35 (banned/harmful) compounds in food and environmental samples, this review highlights the great
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37 potentiality of MIPs for a number of future applications in the various branches of sample preparation (SPE,
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39 d-SPE, MSPE, SPME, SBSE). The literature survey revealed that MIPs are not exclusively used for pre-
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41 concentration purposes, but often their major merit is sample cleanup, especially in the case of very complex
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43 matrices (e.g. meat tissues). Hence, use of such selective sorbents allows separation of the target(s) from the
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45 matrix constituents which represent potential interferences for the instrumental detection/quantification. In
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47 this context, increasing the hydrophilicity of the MIP phases can be of great advantage in minimizing
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49 interfering/fouling species, especially in high lipids samples. Hydrophilic MIPs show also improved water
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51 compatibility, that is advantageous in the case of water samples or aqueous extracts from solid samples. On
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53 the other hand, the reduced performance in aqueous solution the “conventional” MIPs suffer from, needs
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55 alternative synthetic strategies to be further explored, *in primis* polymerization in aqueous media.
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58 Particularly important turned out to be the physical-chemical properties of the imprinted materials, with a
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1 particular emphasis on the porosity, that is a key feature for enhancing mass transfer and analyte uptake, thus
2 gaining short equilibration time and high sorption capacity. In this context, the surface imprinting technique,
3 also coupled to the solid-phase template approach, can be of great usefulness to obtain high surface area
4 materials embedding very thin (e.g. nanometric) MIP layers. Very interesting is also the preparation of
5 hybrid composites containing carbon nanomaterials that contribute to enlarge the surface area available for
6 the formation of the imprinted sites, or in combination with ILs that effectively participate in the analyte
7 uptake. Generally, better performance in terms of recovery and/or cleanup was afforded by using MIP-based
8 materials instead of (commercial) aspecific phases; evidence of specific recognition comes from the
9 excellent results comparable to those achieved by highly specific and selective immunoaffinity sorbents, or
10 ELISA tests. In view of the many parameters involved in the synthesis of imprinted materials (e.g.
11 temperature, template : functional monomer : cross-linker ratio, porogen type), chemometric approaches
12 would be convenient for designing MIPs syntheses. Overall, a huge number of novel/hybrid MIP-based
13 sorbents is expected to be developed and tested in the near future, and a deep, systematic material
14 characterization should be performed and correlated with the synthetic route, in particular with regard to
15 material homogeneity and porosity (total surface area, pores width and volume).
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