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REVIEW

Recent Advances in Molecularly Imprinted Polymers in Food Analysis

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ABSTRACT: Food security as a world issue has received increasing concern, and therefore, effective analytical methods and technologies have been continuously developed. However, the matrix complexity of food samples and the trace/ultratrace presence of targeted analytes require highly efficient cleanup and enrichment materials and procedures. Molecularly imprinted polymers (MIPs) with specific recognition abilities as versatile materials are being increasingly developed for diverse species in various fields, especially in food analysis. In this review, we mainly summarize the recent advances in MIPs used for food matrices over the last 5 years. We focus on toxic and harmful substances, such as pesticide/drug residues, heavy metals, microbial toxins, and additives. Some relatively new preparation methods involving surface imprinting, composites, and stimuli responsiveness are reviewed. Different MIPs as solid-phase adsorbents in solid-phase extraction, solid-phase microextraction, matrix solid-phase dispersion, stirring bar sorptive extraction, and magnetic material extraction and as stationary phases in chromatographic separation for foodstuff have been comprehensively summarized. MIP-based biomimetic sensing and enzymelike catalysis receive special attention. Moreover, some limitations and comparisons related to MIPs performances are also discussed. Finally, some significant attempts to further promote MIP properties and applications to ensure food safety are discussed. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40766.

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INTRODUCTION

Food safety is directly related to human health and nutritional excellence and also produces higher market competition. So the food industry is rapidly changing its quality control practices for wider quality assurance and management system compliance with national and international legislation to ensure food safety and quality, and the modern food industry (including minimally processed products, modified-atmosphere-packaged foods, specialist dietary formulas, and products with few or no additives) is increasingly aware of consumer demands for wholesome manufactured foods. For example, the melamine incident of 2008 severely impacted the Chinese milk industry and caused panic among customers. From a food safety perspective, it is especially important to accurately assess analytes in rough environments, such as the freshness of raw materials and the nutritive values of processed food, food additives, microbial toxins (e.g., mycotoxins and bacterial toxins), antibiotic residues, and artificial hormones. It is well known that herbicides and insecticides are mainly used in agricultural products (fruits, vegetables, cereals, etc.), and these chemicals can lead to bioaccumulation. Moreover, increasing demands and regulations from authorities in more areas, such as the European Union, the United States, and China, together with the enhanced public understanding, are incentives for the better control of produced food and especially in monitoring food processes. However, this is not a simple task as foodstuffs contain a broad range of components. Therefore, the demand is inevitable for the establishment of a food safety guarantee system by means of cost-effective special interest methods that combine one-step isolation, preconcentration, and quantitative determination of analytes (which are usually present at trace levels) independent of the complexity of the matrix.[1] However, these are generally not robust because of interference from background food components and the turbidity of food homogenates. So, materials with a high selectivity for sample pretreatment are in high demand, and thereby, molecularly imprinted polymers (MIPs) have appeared in response to this demand.

MIPs, attractive polymeric materials specially designed to offer highly selective recognition to specific templates, have received

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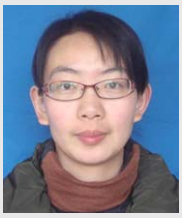

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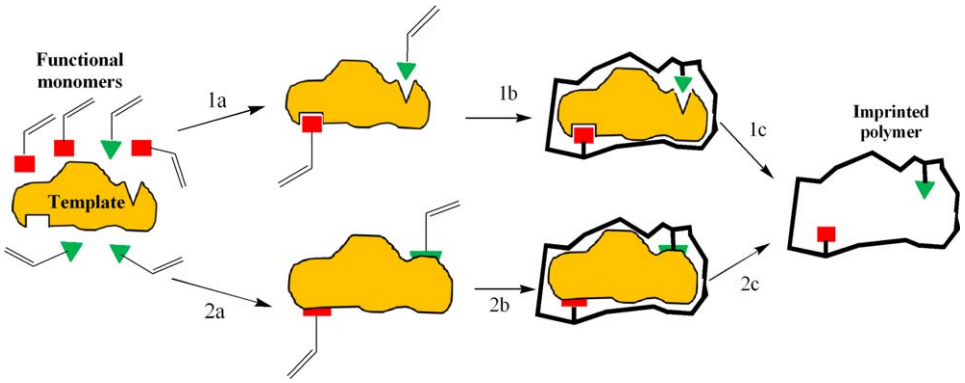
great attention and have become a research hotspot.[2] Molecular imprinting technology (MIT), as a burgeoning powerful technology, is gaining increasing attention for its prospect of creating synthetic polymers with highly specific recognition capabilities in complicated samples.[2–4] A typical MIP synthesis protocol contains template molecules, functional monomers, crosslinkers, polymerization initiators, and solvents. The method of molecular imprinting involves the polymerization of functional monomers and crosslinkers around molecular templates and the subsequent removal of the template molecules. Molecular recognition is most likely the way natural antibodies work;[5] the lock-and-key notion developed by Emil Fisher in 1894[6] has today become one of the most frequently mentioned concepts regarding molecular recognition. To create specific recognition sites for a target molecule within a synthetic polymer, the molecular imprinting process starts by positioning the functional monomers around the template molecule to polymerize and crosslink around the template to fix their position and to freeze the geometry of the pores in the network. This method offers several advantages to the food chemist, so it is possible to design and produce tailor-made, stable recognition matrices for a wide range of analytes. These matrices can be subsequently used in a multitude of analytical formats. In recent years, MIPs have been used in many fields, including isolation and



Scheme 1. Schematic overview of the MIT. The steps of noncovalent imprinting are (1a) self-assembly, (1b) polymerization, and (1c) solvent extraction of the template. The steps of covalent imprinting are the (2a) synthesis of the polymerizable template, (2b) polymerization, and (2c) extraction of the template by chemical cleavage. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

purification,[7,8] chiral separation,[9] catalysis,[10] and sensors.[11] In this review, we mainly summarize the recent advances in MIPs used for food analysis over the last 5 years. Some relatively new preparation methods involving surface imprinting, composites, and stimuli–response are also reviewed. MIPs as extraction adsorbents in solid-phase extraction (SPE), solid-phase microextraction (SPME), matrix solid-phase dispersion (MSPD), and magnetic material extraction (MME) and as a stationary phase in the chromatographic separation for foodstuffs have been comprehensively summarized. Special attention is paid to MIP-based biomimetic sensing and enzymelike catalysis. In addition, some limitations and comparisons related to the performance of MIPs are also discussed. Finally, some significant attempts are proposed to further promote MIP properties and applications to ensure food safety.

SURVEY OF MIPs

MIPs are functional polymers generated from MIT, which is an efficient method for producing functional materials with specific recognition sites that are complementary in shape, size, and spatial arrangement to the template molecule. It is important to note that the polymers need to be rigid enough to retain a permanent memory of the imprint, and the imprinted sites need to be macroporous to allow the template molecules to easily diffuse in and out.[12–14] The variety of approaches for generating synthetic receptors can be divided into reversible covalent or noncovalent (including hydrogen, ionic, Van der Waals, *n–n*, etc.) methods, depending on the interaction between the monomer and template. Scheme 1 illustrates the basic imprinting process and mechanism.

Traditionally, most MIPs prepared by bulk polymerization have poor site accessibility to the target molecules and a low rebinding capacity because of the thick polymeric network.[15] To overcome these drawbacks of bulk polymerization, more sophisticated and complex polymerization techniques have been proposed to obtain MIPs with different forms, such as beads, monolithic forms, and coatings. First, the beads are generally used for packing columns for chromatography or SPE, and they are usually synthesized by suspension polymerization, emulsion polymerization, seed polymerization, and precipitation polymerization. Monolithic packings–polymers are used for *in situ* columns, which are ready for use right after the removal of the template.[16–18] Next, coatings are also a general form, and these materials are opposite to the structure on an appropriate support of fibers, beads (magnetic nanoparticles,[19] quantum dots,[20] or gold nanoparticles[21,22]), carbon nanotubes,[23] or films for hybrid materials with silane chemistry or surface-grafting-to approaches. Additionally, multistep or one-step swelling and polymerization methods,[24] electrochemical polymerization,[25] electrodeposition,[26–28] grafting on monolithic column,[29] photografting,[30,31] and sol–gel methods[32] have also been used. Furthermore, surface imprinting over nanosized sphere support materials with a large specific surface area is very appropriate for target analytes to develop smart MIP nanospheres.[33] Intelligent materials mimic natural receptor characteristics; for example, stimuli-responsive MIPs have been prepared with stimuli-responsive polymers as the matrix for molecular imprinting. Stimuli-responsive MIPs, including magnetic responsive MIPs, temperature-responsive MIPs, pH-responsive MIPs, photoresponsive MIPs, dual or multi stimuli-responsive MIPs, and so on, have received widespread attention, and significant progress has been achieved in recent years and was recently reviewed by our group.[34] Each of the representative synthetic procedures and morphologies has their own advantages and limitations; these are highlighted in Table I.[2,35–45]

HIGHLIGHTED APPLICATIONS OF MIPs IN FOOD ANALYSIS

MIT consists of the self-assembly of functional monomers and template molecules in solution followed by the copolymerization of the functional monomer with an excess of an appropriate crosslinking monomer, and the resulting polymer exhibits a high affinity for the template molecule or group of structural analogs. Furthermore, MIPs as sorbent materials compared with conventional sorbents may lead to the selective enrichment and separation or cleanup of the analytes. Intense ongoing studies have proven that MIPs can be efficiently used in food and

Table I. Advantages and Limitations of Representative Synthetic Strategies and Morphologies of MIPs

MIPs (or method)	Advantages	Limitations	Reference
Noncovalent approaches	Experimental simplicity, easy removal of the template from the MIP, and fast mass-transfer rate to analytes	Nonselective binding sites may form because of the excess of free monomers and their random incorporation into the polymeric matrix.	35
Covalent approaches	Formation of a more homogeneous population of binding sites and the minimization of the number of nonspecific sites during the polymerization process	Template rebinding or release is difficult because covalent bonds between the templates and monomers will be formed or destroyed.	36
Bulk polymerization	Rapidity and simplicity of preparation and no requirement for sophisticated or expensive instrumentation	The binding site distribution is inherently heterogeneous, and there are wasteful chemicals. The binding sites are mostly deeply buried, and the diffusion methods for the guest molecules are long (to obtain small particles, mechanical grinding and sieving steps must be included).	2
MIP nanoparticles	Higher surface-area-to-volume ratios, suitability for surface imprinting, templates that are easily accessible to imprinted cavities, and improved binding kinetics	Strong template–monomer interactions are needed, and the fabrication of MIPs is not easy.	37
Solid-phase synthesis of MIP nanoparticles	Multiple reuse of molecular templates, automated synthesis of imprinted polymer nanoparticle,; precisely controlled batch-to-batch reproducibility, and nano-MIPs with size, specificity, and solubility characteristics	Polymer precipitation needs to be prevented. The template should be immobilized on glass beads. High-affinity nanoparticles are separated from low-affinity materials and unreacted monomers. There are too few usable solid phases for template immobilization.	38
Suspension polymerization	Improvement in the specificity and avoidance of complicated posttreatment procedures and the usual regular spherical shapes and sizes of the particles	They are polydisperse in size (a few micrometers to a few hundred micrometers) and display poor recognition (the reason may be that water can weaken the noncovalent interactions).	39
Miniemulsion polymerization	Homogeneous structures and nanoparticles, high droplet-to-particle conversion rate, and suitability for surface imprinting	Water and interfering chemicals (e.g., surfactants) are present. There is a broad affinity distribution. The synthesis and purification steps are long and tedious.	40
Precipitation polymerization	Simple techniques, good yields, less time needed than for other techniques, no need for any stabilizer, and suitability for imprinting different compounds (e.g., peptides)	There are high dilution conditions, and careful adjustment of the synthetic parameters (e.g., temperature, pressure, and composition of the polymerization mixture) is needed.	41

Table I. *Continued*

MIPs (or method)	Advantages	Limitations	Reference
Core–shell approaches: grafting polymerization	Better control over the size and shell thickness, suitability for surface imprinting, possible use of the core with particular properties (e.g., magnetic), and no need for surfactant or stabilizers	Depending on the grafting reaction, interfering compounds may be present. The formation of nanoparticle aggregates is possible. Poor imprinting in the shell is too thin.	42
MIP microgels and nanogels	Good solubility and flexibility, large specific surface area, easily tunable size, and ability to be effectively functionalized to achieve variations in characteristics	A reduction in the size of the MIPs to the nanoscale has problems. The presence of the surfactant can interfere during polymerization.	43
Magnetic responsive MIPs	Magnetic MIP beads with magnetic properties and large specific surface area, improvements in the binding capacity and kinetics and favorable selectivity for the target molecule, more convenient and economical magnetic separation	Surface modification is time-consuming and laborious. The magnetic susceptibility of the embedded beads may decrease. Imprinting in the shell is not easy. There is poor compatibility of the reaction solvent (water) under optimal molecular imprinting conditions.	44,45

agricultural areas, and MIPs have attracted extensive attention as affinity chromatography stationary phases, for selective SPE, and as recognition layers in chemosensors/biosensors. In essence, derived molecularly imprinted solid-phase extractions (MISPEs), biomimetic sensors, and other potential utilities have been successfully applied to solve various challenging issues in food analysis and food processing, mainly including widespread pesticide residues,[46] drug residues,[47] mycotoxins,[48] poisonous substances (e.g., toxic metal ions),[49] additives/preservatives,[50,51] and constituents.[17] The highlighted application of MIPs as selective sorbents for separation and cleanup or determination of food samples are summarized as follows; this is important, particularly when the sample is complex, and impurities can interfere with targets in food matrices.

MIP-Based Sample Preparation for Food Analysis

It is well known that most methods, such as high performance liquid chromatography (HPLC), gas chromatography (GC), and capillary electrophoresis, cannot handle sample matrices directly because the analytes are often present at low concentrations in food matrices, so sample pretreatment is usually required to extract, isolate, and concentrate the analytes of interest from complex matrices. In 1994, Sellergren[52] first reported sample pretreatment with MIPs for the direct determination of drug pentamidine. In that study, MIPs were used as sorbents for the extraction, purification, and concentration in diluted urine samples, and the selective elution allowed the successful detection of pentamidine free of co-extractives. Because MISPE has emerged fast as a popular tool to achieve selective extraction procedures. A quick overview of published methods over the last decades in food analysis revealed that the majority of interest has been focused on herbicides and pesticides, antibiotic residue, endocrine disruptors, toxins, additives, protein substances, trace metals, and pharmaceuticals. Commonly used pretreatment methods in food analysis include SPE, SPME, liquid–liquid extraction, MSPD extraction, supercritical fluid extraction, and column chromatography. Among them, SPE and SPME have been recognized as the most efficient pretreatment techniques for improving the analytical sensitivity. Usually, commercial SPE materials such as C_{18}-bonded silica gel are nonspecific, and they generally have a poor purification efficiency and often result in the coextraction of many other matrix components. Recently, MISPEs and molecularly imprinted polymers used for solid-phase microextraction (MISPMEs) have gained in popularity because they offer the advantages of convenience, time and solvent savings, and selective cleanup of the analytes. Additionally, MISPE and MISPME also can be easily incorporated into automated analytical procedures. Because of the selective absorption of MIPs for a particular analyte or group of analytes, MISPE and MISPME allow the concentrations of these analytes and the removal of the interfering substances from the sample matrix. So far, it is important to stress that the vast majority of MISPE-based analytical methods are performed in offline mode. The three steps for MISPE are (1) sample loading, (2) washing, and (3) elution. The loading solvent is chosen to allow the rebinding of the analyte to specific sites, whereas the elution solvent has to be optimized according to its ability to disrupt the interaction between analytes and polymers. Before the elution step, a washing step is carried out to elute the undesired impurities from the cartridge.[53] In SPME, analytes are thermally desorbed directly onto the injection port of a gas chromatograph or eluted with a suitable solvent for further analysis by

Table II. Summary of MISPE and MISPME Applications in Food Analysis

Imprint species	Analyte	Sample	Method	Reference
	Imidacloprid	Rice	MIP-MSPD	60
	Fenitrothion	Tomatoes	MISPME-HPLC	61
	Triazines	Potato and pea	MISPME-HPLC	18
	Chloroacetanilide	Soybean and corn	SPME/HPLC-UV	62
	Organophosphate	Strawberries	GC-FPD	46
	Cyromazine	Biomatrix samples	MI-SPE/HPLC-UV	63
	Organophosphorus	Fruits	MSPE-GC	64
Herbicides, pesticides	Pyrethroid	Aquaculture seawater	GC-ECD	65
	Atrazine	Lettuce and corn	HPLC-UV	66
	Triazines	Fruits and vegetables	MI-MSPD-MEKC	55
	Chlorpyrifos	Rice	MMIPs/HPLC-UV	67
	Trichlorfon, monocrotophos	Vegetables	MISPE/GC	68
	Bisphenol A	Milk and fish	Offline/HPLC-UV	69,70
	Estrogens	Milk	MSPE/HPLC	71
Contaminants	Acrylamide	Food samples	MIP-SPE/HPLC	72
	Phthalates	Beverages	MAG-MIM-dSPE-GC	73
	PAEs	Beverages	MIP-SPE/GC	41
	Cephalosporins	Milk	MIP-SPE/HPLC	74
	Thiabendazole	Oranges and lemons	Inline MIP-SPE/HPLC	75
	Acyclovir	Pork, chicken, and beef	MI-MSPD/HPLC	76
	Thiamphenicol	Milk	MIP MME/HPLC	77
	Sulfonamides	Chicken meat	Magnetic MIPs/HPLC-UV	78
	Six sulfonamides	Aquatic products	HPLC-UV/multiresidue	79
Pharmaceuticals	Chloramphenicol	Honey, milk, and shrimp	MISPE/LC-MS/MS or LC-UV	37,80
	Pefloxacin, enrofloxacin	Milk	MIP/HPLC-UV	81
	Sulfonamide	Milk	LC-MS/MS	82
	Sulfonamides	Pork and chicken	Online SPE-HPLC	83
	Oxytetracycline	Milk	LC-MS/MS	48
	Clenbuterol	Biological sample	SPME	84
	Quinolones	Eggs, including wildlife eggs	LC-ESI-MS/MS	85
	Copper ions	Wheat flour, corn flour, and barley flour	MIP-SPE/ICP-OES	86
Trace metals	Selenium	Brazil nuts, apricots, milk powder, rice flour, and white beans	Online HG-FAAS	87
	Arsenic	*Laminaria japonica* Aresch juice	MISPE/FAAS	88
	Mercury ion	Tap water	SPE/AFS	89
	Flavonol aglycones	*Moringa oleifera*	MISPE HPLC-UV	90
	PA, caffeic acid, and ferulic acid	*Salicornia herbacea* L.	Offline MISPE/HPLC-UV	91
	(E)-Resveratrol	Wine and fruit juice	MISPE HPLC-UV	92,93
	Huperzine A	*Huperzia serrata*	MISPE HPLC-UV	94
	PA	*Rhizoma homalomenae*	MISPE HPLC-UV	95
Components	Kukoamine A	Potato peels	MISPE HPLC-MS	96
	Fluoroquinolones	Eggs	MISPE HPLC-UV	97

Table II. *Continued*

Imprint species	Analyte	Sample	Method	Reference
	Cytokinins	Soybean sprouts and rape leaves	MI-SPE-LC-MS/MS	98
	Quercetin	*Cacumen platycladi*	SPE/HPLC	99
	Caffeine	Beverages	HPLC-UV	100
	Riboflavin	Beverages	Online SPE-HPLC	101,102
	Plant hormones	Banana	MISPE HPLC-UV	103
	Methylparaben	Canned foods and beverages	SPE-UV	15
	Nicotinamide	Pork liver	MISPE HPLC-UV	104
	Melamine	Milk and egg	MISPE HPLC-UV	105
Additives	Olaquindox	Chicken	SPE/HPLC	57
	Malachite green	Fish	MISPE/ECL	106
	Sudan dyes	Chili sauce	HPLC-UV	107
	Quinoxaline-2-carboxylic acid	Pork muscle	Online SPE/HPLC-UV	108
	Deoxynivalenol, zearalenone	Grains and beverages	SPE/HPLC	109
Toxins	Microsystin-LR	Drinking water	MISPE/piezoelectric sensor	110
	DA;	Shellfish	SPE/HPLC	111

dSPE, dispersive solid-phase extraction; MAG-MIM, magnetic dummy molecularly imprinted microspheres; FPD, flame photometric detector; ECD, electron capture detector; MEKC, micellar electrokinetic chromatography; MMIPs, magnetic molecularly imprinted polymers; ICP-OES, inductively coupled plasma-optical emission spectroscopy; MAA, methacrylic acid; FD, fluorescence detection; DP, differential pulse; DPV, differential pulse voltammetry; DPASV, differential pulse anodic stripping voltammetry; CV, cyclic voltammetry; QCM, quartz crystal microbalance; BPA, bisphenol A; BHb, bovine hemoglobin; Tryp, trypsin; MMA, methyl methacrylate; AM, acrylamide; NAPD, N-acryloyl-pyrrolidine-2, 5-dione; BIS-DMA, bisphenol Dimethacrylate; APB, 3-Aminophenylboronic acid; NHMA, N-hydroxymethylacrylamide; NiPAm, N-isopropylacrylamide; AMPS, 2-Acrylamido-2-methyl-1-propane sulphonic acid; NVP, N-vinyl-2-pyrrolidone; ATRP, atom transfer radical polymerization.
Microcystins have a unique β-amino acid side chain termed Adda, and the variability at the second and fourth amino acid positions in the Adda sequence is the basis of microcystin nomenclature, e.g., LR, LW, RR, YR, etc.

chromatographic techniques. SPME has proven to be a routine tool for its more advantages, such as simplicity of operation, solventless nature, and the availability of commercial fibers. However, the variety of commercially available fibers is rather limited because of a lack of selectivity during the extraction process. So it is imperative to improve the required selectivity for SPME by preparing MIP coatings on fibers. Apart from the offline model, an online system is often used, too. A typical online system is a direct coupling of an MIP column to the detection system. In this way, high-selectivity MIPs would be theoretically possible for simultaneously extracting, enriching, separating, and determining target analytes in complex samples.

In addition to MISPEs and MISPMEs, molecularly imprinted polymers used for MSPDs[54,55] and stirring bar sorptive extractions (SBSEs) are two elements often used in sample pretreatment methods.[56] An MSPD is based on the complete disruption of the sample (liquid, viscous, semisolid, or solid) and allow the sample components to disperse into the solid sorbents. Experimentally, the sample is placed in a glass mortar and blended with the sorbent until a complete disruption and dispersion of the sample on the sorbent is obtained. Then, the mixture is directly packed into an empty SPE cartridge. Finally, analytes are eluted after a proper washing step to remove interfering substances. The main difference between MSPD and SPE is that the sample is dispersed through the column instead of only onto the first layers of sorbent; this typically allows the obtainment of rather clean final extracts and prevents the necessity of further cleanup. To simplify the whole procedure, Zhang et al.[57] established a new method for extracting olaquindox in chicken by MSPD with the olaquindox–MIPs as solid-phase materials. The polymers were prepared with olaquindox as the template, methacrylic acid as the functional monomer, and ethylene glycol dimethacrylate as the crosslinking agent. The prepared material was used as solid-phase materials for MSPD to selectively enrich the olaquindox and then examined by HPLC. The results show that it had good recognition, selective ability, and fast adsorption–desorption dynamics for olaquindox. Under the optimized conditions, the range of recovery spiked with olaquindox at 1.0 and 2.0 μg/g levels was between 85.3 and 93.2%.

SBSE is based on the partitioning of target analytes between a liquid sample and a stationary-phase-coated stirring bar. Furthermore, MIP-coated stirring bars show not only the expected high selectivity but also a rapid equilibrium adsorption thanks to the porous nature of the MIPs obtained combined with the proper thickness of the coated polymer film. In addition, the yield of the extraction process is much greater when a stirring bar rather than an SPME fiber is used because of the larger volume of the extraction phase used. However, the greater coating area of magnetic stirring bars is simultaneously its main

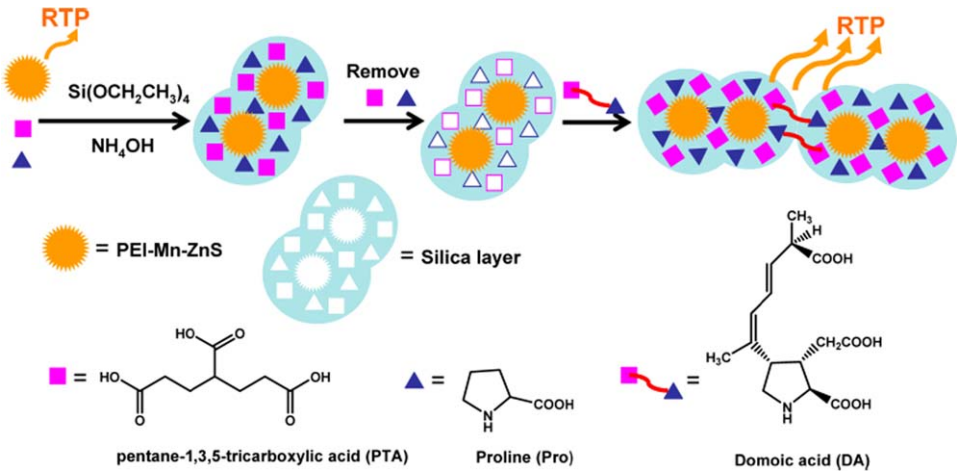
Table III. Representative Examples of MIP-Based Mimetic Sensors

Transduction scheme	Analyte	Functional monomer	MIP preparation procedure	Sample	Reference
UV–visible spectroscopy and EIS	Cholesterol	MAA	UV-initiated radical	Aqueous	140
Diffraction intensity	Diethylstilbestrol	7.5:1 MMA/AM	Thermoradical	Food	141
CL	Fenvalerate	AM	Thermoradical	Fruits and vegetables	142
SERS	BPA	Triethoxysilane template complex (BPA–Si)	Sol–gel process	Beverage	143
SPR	Chlorpyrifos	Dopamine	Oxygen	Apple	144
FD	PAHs	MAA	Thermoradical	Milk	145
FD	Lysozyme	$(NH_4)_2TiF_6$	Liquid-phase deposition	Proteins	146
DP	Oxytetracycline	Prussian blue	Electrochemical	Milk	147
FD	Penicillin G	MAA	Thermoradical	Milk	148
CV and DPV	Melamine	MAA	Thermoradical	Milk	149
BELISA method	Metolcarb	Acrylamide	Thermoradical	Apple juice	150
Chronoamperometry	Hydroquinone	MAAM	UV-initiated radical	Water	151
EIS	BPA	BPA-terthiophene and carbazole	Electrochemical	Aqueous	152
DPV	2,4-Dichlorophenol	MAA	Thermoradical	Tap water	153
DPASV	L-Aspartic acid	NAPD	ATRP	Pharmaceutics	154
Potentiometry	Chlorpyrifos	MAA	Thermoradical	—	155
Potentiometry	BPA	BIS-DMA	Thermoradical	Drinking bottles	156
Potentiometry	Clenbuterol	MAA, MMA	Thermoradical	Pig urine	157
CV	Horseradish peroxidase	AM, APB	Oxidative	Proteins	158
QCM	BHb, Tryp	NHMA, NiPAm	Catalyzed	Proteins	159
QCM	L-Nicotine	MAA	Thermoradical	Saliva	130
QCM	Melamine	Bis(2,2′-bithienyl)-benzo-[18-crown-6]methane	Electrochemical	—	160
Impedometric detection	Desmetryn	AMPS	UV-initiated radical	Drinking water	131
Interdigitated capacitance	Hevein allergenic proteins	6:2 MAA:NVP	Thermoradical and oxidative	Latex rubber	161

PAH, polycyclic aromatic hydrocarbon; SERS, surface-enhanced Raman scattering; EIS, electrochemical impedance spectroscopy; MAA, methacrylic acid; FD, fluorescence detection; DP, differential pulse; DPV, differential pulse voltammetry; DPASV, differential pulse anodic stripping voltammetry; CV, cyclic voltammetry; QCM, quartz crystal microbalance; BPA, bisphenol A; BHb, bovine hemoglobin; Tryp, trypsin; MMA, methyl methacrylate; AM, acrylamide; NAPD, N-acryloyl-pyrrolidine-2, 5-dione; BIS-DMA, bisphenol Dimethacrylate; APB, 3-Aminophenylboronic acid; NHMA, N-hydroxymethylacrylamide; NiPAm, N-isopropylacrylamide; AMPS, 2-Acrylamido-2-methyl-1-propane sulphonic acid; NVP, N-vinyl-2-pyrrolidone; ATRP, atom transfer radical polymerization.

drawback because the extraction kinetics are slower than for SPME fibers, and a high amount of interfering matrix compounds are co-extracted with target analytes. At this regard, Li et al.[58] developed a sulfamethazine MIP-coated (ca. 20 μm thickness) stirring bar by sorptive extraction coupled with HPLC. It has been successfully applied to the simultaneous analysis of eight sulfonamides in spiked pork, liver, and chicken samples with satisfactory recoveries. It is obvious that MIP-coated stirring bars would extend the applicability of SBSEs in sample preparation.

Furthermore, the achievement of optimum specific recognition conditions for target analytes, especially for multiple target analytes, is also a significant challenge. To realize this goal, MIPs synthesized for specific analytes or groups of structurally related species in contrast to conventional SPE sorbents, have been successfully used as sorbents for SPE.[59] In this study, an MISPE with thiamphenicol as the template molecule was developed and optimized by chromatographic methods for specific, simultaneous, qualitative, and quantitative analyses of chloramphenicol, thiamphenicol florfenicol, and florfenicol amine in



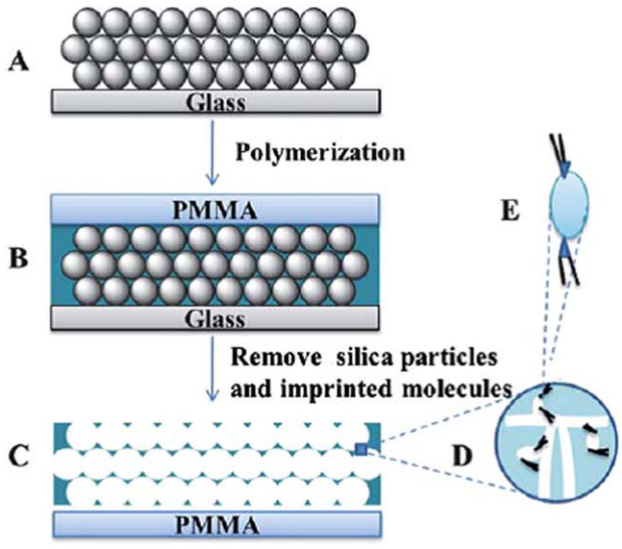
Scheme 2. Schematic illustration of the construction of Mn–ZnS quantum dot (QD)-embedded two-fragment imprinting silica for an enhanced RTP assay of DA. PEI, Polyethyleneimine. (Adapted with permission from ref. 137. Copyright 2013 American Chemical Society.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

aquaculture samples coupled with liquid chromatography–mass spectrometry/mass spectrometry (LC–MS/MS). The significant progress of MIPs in SPE and SPME in food analyses is summarized in Table II.[15,18,37,41,46,55,57,60–111]

MIP-Based Chromatographic Stationary Phase for Food Analysis

Molecular imprinting as a very interesting technique applied in chromatographic separation has the prominent advantage of its predictable elution order.[112] The MIP chromatographic stationary phase needs several conditions to serve as MIP HPLC stationary phases: high selectivity, good hydrodynamic behavior, and high capacity. Another important criterion is the homogeneity of the particles used as packing materials in HPLC. Chromatographic separation based on MIPs is often used for chiral separation, isomer separation, and enantioseparation in the food field, such as for ephedrine and pseudoephedrine,[9,113] blockers,[114] amino acid and its derivatives,[115] ibuprofen,[116] and propranolol.[117] Recently, HPLC and capillary electrophoresis has been used for enantiomeric separation.[40] Because of the ease of validation and assessment, the chiral resolutions of chromatographic separation have been paid special attention by numerous studies. For a specific enantioseparation, the main problem in chromatography is to predict whether analytes and their enantiomers are separated or not. The greatest advantage of the use of chiral molecularly imprinted stationary phases is the easy choice of the elution order of the analytes, and strong elution conditions can be avoided. Yue et al.[118] successfully prepared a water-compatible surface molecularly imprinted silica nanoparticle with L-tryptophan as the template. The resulting MIPs can be used as enantioselectors in electrokinetic chromatography for the enantioseparation of tryptophan. Tryptophan enantiomers can be fully resolved with symmetric peak shapes, mainly because of the fast mass transfer and good accessibility of the sites located at the surface of the surface of molecularly imprinted silica nanoparticles with well-imprinted shapes.

Monolithic stationary phases are also separation media in a format that some chromatography researchers regard them as fourth-generation chromatography adsorbents. Matsui et al.[119] first used *in situ* polymerization for the preparation of molecularly imprinted monoliths in 1993. Recently, monolithic molecularly imprinted supports as stationary phases have attracted significant interest in HPLC and capillary electrochromatography.[120] Combining the advantages of MIT and monolithic columns, these monolithic materials are typically prepared directly inside stainless steel columns or capillary columns without the tedious procedures of grinding, sieving, and column packing.



Scheme 3. Schematic illustration of the preparation of an imprinted photonic hydrogel of cholesterol: (A) silica colloidal crystals on a glass substrate, (B) infiltration of the complex solution into the colloidal crystal template followed by photopolymerization, (C) MIPH film after the removal of silica microspheres and template molecules, (D) imprinted cavities with a complementary shape and binding sites to the template molecule, and (E) complex of the monomer and the template molecule. (Adapted with permission from ref. 140. Copyright 2011 Royal Society of Chemistry.). PMMA, polymethyl methacrylate. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

This *in situ* monolithic MIP synthesis technique has many advantages, including the ease of preparation, high reproducibility, versatile surface chemistry, cost effectiveness, and rapid mass transport, especially ideal for enantiomeric separation. The target component (which can be one of the two enantiomers) is added as a template during polymerization. After extraction of the template, an imprint site is left in the formed material; this was complementary to the shape and functionality of the template molecule.

The use of molecularly imprinted monolithic columns as a stationary phase for rapid separation has been increasingly reported.[121–123] The process seems to have greater flexibility than packing a column with particles. However, such monolithic MIP columns often suffer from high backpressure and low efficiency;[124–126] this limits their application in practical separations. Some methods, such as an increase in the amount of cyclohexanol and the addition of latex beads to the polymerization mixture, can overcome this problem by increasing its permeability. For example, the diastereomers of cinchonine and cinchonidine were fully separated by both isocratic and gradient elutions on the chiral monolithic column obtained.[127] Because of the large pores in the chiral monolithic column, backpressure was low during the separation process, and a separation factor of 3.18 was achieved at 1.0 mL/min. When the flow rate was 2.0 mL/min, the backpressure reached only 1.08 MPa.

MIP-Based Mimetic Sensors for Food Analysis

Complex food matrices are hard to detect by traditional analytical methods, so a complicated pretreatment procedure is required. MIP-based mimetic sensors with good accuracy and a simple pretreatment procedure have been an active research area in recent years. MIP-based sensing systems offer great advantages over conventional analytical techniques; these include a high specificity for real-time analysis in complex mixtures, low cost, and simple operation without the need for extensive sample pretreatment. MIPs have already been applied to many different kinds of optical sensors,[128] such as field effect devices,[129] quartz crystal microbalances,[130] impedance determination,[131] conductometric measurements,[132] capacitance measurements,[133] amperometric measurements,[134] fluorescence measurements,[135] spectroscopic measurement,[136] chemiluminescence (CL),[11] modified CdSe/ZnS Quantum dot (QDs),[20,137] and biomimetic enzyme-linked immunosorbent assay (BELISA) method.[138,139] The MIP-based mimetic sensors are ongoing, and some highlighted applications in food are listed in Table III.[130,131,140–161]

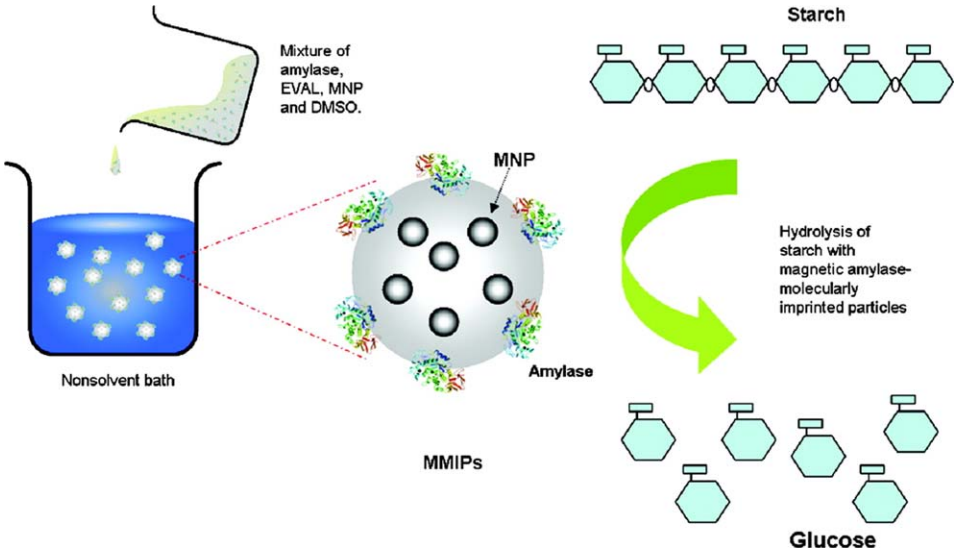
However, one difficulty for sensors based on traditional MIPs is that MIPs usually contain no inherent signaling elements, or the analyte must contain a chromophore or a fluorophore or be electroactive to generate a readable optical or electronic signal.[162] Otherwise, the analyte must be modified or tagged; this may be complex and time consuming. Some new strategies have been proposed to solve those limitations. For example, an MIP-based room-temperature phosphorescence (RTP) probe has been presented to construct enhanced MIP–RTP sensors,[137] as illustrated in Scheme 2. In this study, two fragments or structurally similar parts of the target analytes were used as dummy templates. The developed methodology was applied to construct a highly selectively enhanced MIP-based RTP probe for domoic acid (DA) detection. The two-fragment imprinting silica exhibited linear RTP enhancement to DA in the range 0.25–3.5 μM in buffer and 0.25–1.5 μM in a shellfish sample. The precision for 11 replicate detections of 1.25 μM DA was 0.65% (relative standard deviation), and the limit of detection was 67 nM in buffer and 2.0 μg/g wet weights (w/w) in the shellfish sample.

The development of MIP-based label-free and rapid analytical methods for the onsite determination of analytes in foods is highly desirable. Surface plasmon resonance (SPR),[144,163] reflectometric interference spectroscopy,[164] and molecularly imprinted photonic hydrogels[165] are all promising label-free optical sensing elements, which allow for the setup of sensors for almost all kinds of analytes. For instance, a sensing platform of molecularly imprinted photonic hydrogels (MIPH) has been fabricated by our group[140] on the basis of the combination of a colloidal crystal templating method and MIT, as displayed in Scheme 3. Herein, the response of MIPH to targeted cholesterol molecules in an aqueous solution was detected through a readable Bragg diffraction redshift; this was due to the lattice change of molecularly imprinted photonic polymer structures responding to their rebinding to the target molecules. MIPHs have also been prepared for detection of vanillin,[166] tetracyclines[162] and others. For example, the Bragg diffraction peak shifted from 451 to 486 nm when the concentration of the vanillin was increased from 10^{-12} to 10^{-3} mol/L within 60 s, and it proved that the MIPHs had a high selectivity and rapid response for vanillin.[166] The application of such a label-free sensor with a high selectivity, high sensitivity, high stability, and easy operation might offer a potential strategy for the rapid real-time detection of trace vanillin.

Another attractive flow-injection CL sensor[167] for the determination of quercetin has been established. In this study, quercetin MIPs were synthesized by precipitation polymerization with acetone as a solvent, acrylamide as a functional monomer, ethylene glycol dimethacrylate as a crosslinker, and 2,2-azobisisobutyronitrile as an initiator. Flow-injection CL optimized experiments were obtained, and the possible mechanism was discussed. The CL intensity responded linearly to a concentration of quercetin ranging from 1.4×10^{-6} to 1.6×10^{-4} mol/L, with a detection limit of 9.3×10^{-7} mol/L. The relative standard deviation for determination ranged 2.72 to 3.31%. On the basis of speediness and sensitivity, the sensor was reusable and showed a great improvement in selectivity. As a result, the new sensor was successfully applied to the determination of quercetin in drug samples. As for electrochemical sensors, they can easily be fabricated and miniaturized in a most economical way. The fields of MIP-based chemosensors and biosensors featuring artificial receptors have received broad attention and has shown pronounced progress.

MIP-Based Applications for Food Processing

About MIPs, more attention has been paid to their robust molecular recognition elements. In recent years, the fabrication of specific binding sites via MIT has become the main objective of many studies and the major interest of some researchers.

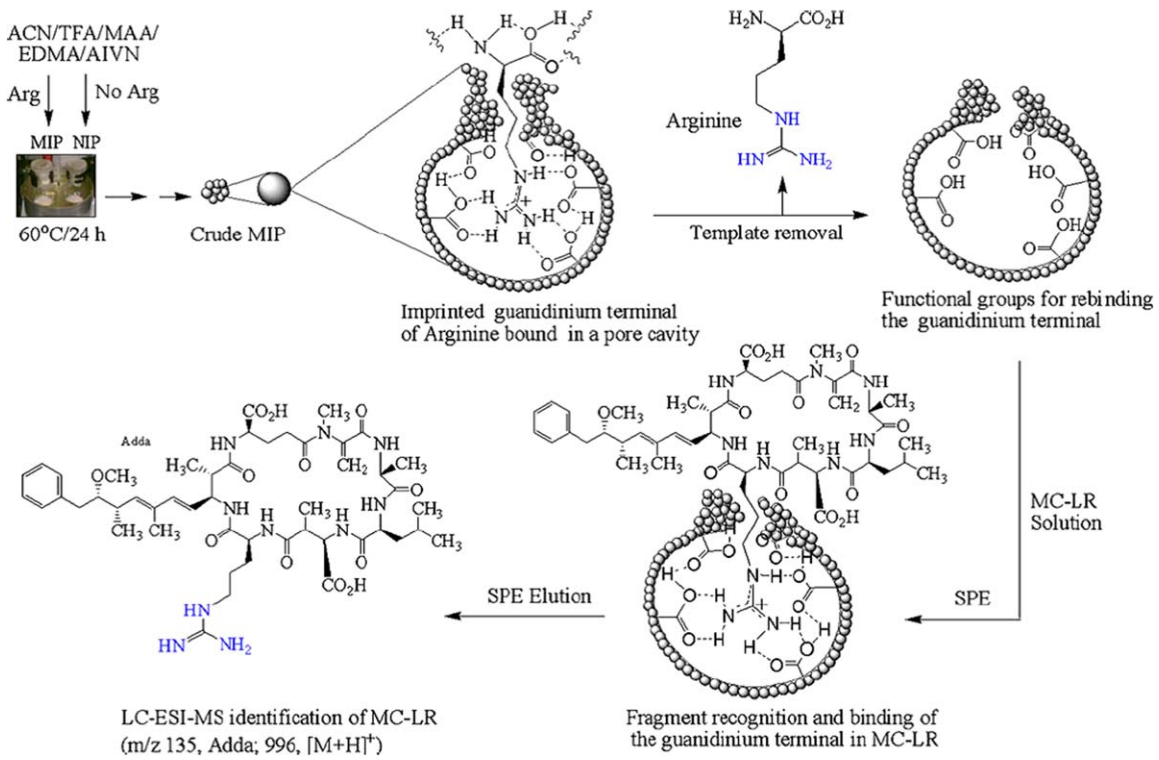


Scheme 4. Synthesis and hydrolysis of the magnetic amylase-imprinted EVAL composite nanoparticles. (Adapted with permission from ref. 179. Copyright 2012 American Chemical Society.). MNP, magnetic nanoparticle; EVAL, poly(ethylene-co-vinyl alcohol). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Affinity-based separation is the most developed area for molecularly imprinted materials. Compared with immunoaffinity materials, MIPs with a high selectivity demonstrate better applicability in harsh chemical media. First of all, more effort in recent studies has been put into the use of MIPs in column separation, in which a sample of low concentration can be dramatically enriched by the passage of a large volume over a molecularly imprinted material, and the target compounds are then extracted into a small volume in the separation process. Thus, the bulk matrix can be washed away without affecting the bound compounds. These advantages of MIPs over other sorbents have made column separation technology become one of the most important technologies for selective sample separation in the food field.

It is well known that various synthetic protocols have been developed for the preparation of MIPs; these include suspension polymerization, grafting procedures, and precipitation polymerization. Generally, the resulting MIP spheres have diameters ranging from microspheres to submicrospheres; however, submicrospheres are not suitable for SPE because of the leaking of resulting small particles from the frit of the SPE cartridge. Therefore, MIP-based column separation technology shows potential value for selectively isolating specific compounds or their structural analogs from a complex food matrix. To date, MIPs have often been applied to extract and separate the active ingredients from traditional Chinese herbs.[8,168] That mainly involves the qualitative separation of some compounds with simple structures, such as alkaloids,[169–171] flavones,[100,172,173] esculine,[174] glycyrrhizin,[175] rographolide,[176] and polyhydric phenols.[177] Good results were obtained thanks to the selective recognition of specific analytes or a group of structural analogs. This could be partly attributed to its efficient, stable, and distinct selectivity characteristics with the simultaneous control of the porous properties, morphology, and other structural features of the polymers. Chen et al.[95] developed an MISPE protocol using protocatechuic acid (PA), a phenolic acid, as the template molecule. Six structurally similar phenolic acids, including *p*-hydroxybenzoic acid, gallic acid, salicylic acid, syringic acid, vanillic acid, and ferulic acid, were selected to assess the selectivity and recognition capability of the MIPs. The MISPE sorbent selectively extracted almost 82% of PA from the extract of *Rhizoma homalomenae*. Additionally, to reduce lactose intolerance (lactase deficiency) symptoms in humans, Hadizadeh et al.[8] applied MIPs as sorbents for the separation of lactose from milk and produced low-lactose milk. In their study, the MIPHs synthesized by a noncovalent imprinting method could be considered for the molecular recognition and separation of lactose from aqueous media, and it could be considered as a sorbent for producing low-lactose milk. Although the feasibility of these applications has been demonstrated, their commercial applications are few. This could be partly ascribed to difficulties in generating high-affinity binding sites while simultaneously controlling the porous properties, morphology, and other structural features of the polymers. Fortunately, direct routes to spherical particles, such as the use of microfluidic reactors[178] and solid-phase synthesis,[38] which are suited for industrial production, would be highly beneficial for applications such as chromatography and SPE. Future work should investigate the scope of these methodologies and evaluate the performances of these uniform MIP beads in SPE and other flow-through applications in comparison with conventional materials.

By contrast, valuable results of MIPs have been obtained with particular regard to binding polymers in analytical applications, but the generation of efficient catalytically imprinted polymers remains a challenge. Because of the insolubility of molecular imprinting materials, the enzymes as catalysts can be easily filtered off after a reaction, and this advantage would bring the use of imprinted polymers for food analysis to the fields of production and processing. Nowadays, MIPs have been increasingly used for the binding and immobilization of active enzymes. Lee



Scheme 5. Preparation of guanidinium-terminus MIPs and hypothetical presentation of the fragment recognition and binding of the guanidinium terminal in [Arginine (Arg)]–MCs for the selective SPE/LC–ESI–MS analysis of [Arginine]–MCs in water. (Adapted with permission from ref. 187. Copyright 2004 Springer.). MC, microcystin; MC-LR, microcystin-LR; ESI, electrospray ionization; TFA, trifluoroacetic acid; EDMA, ethylene glycol dimethacrylate; ACN, acetonitrile; AIVN, 2,2'-azobis(2, 4-diethylvaleronitrile; NIP, non-imprinted polymers. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

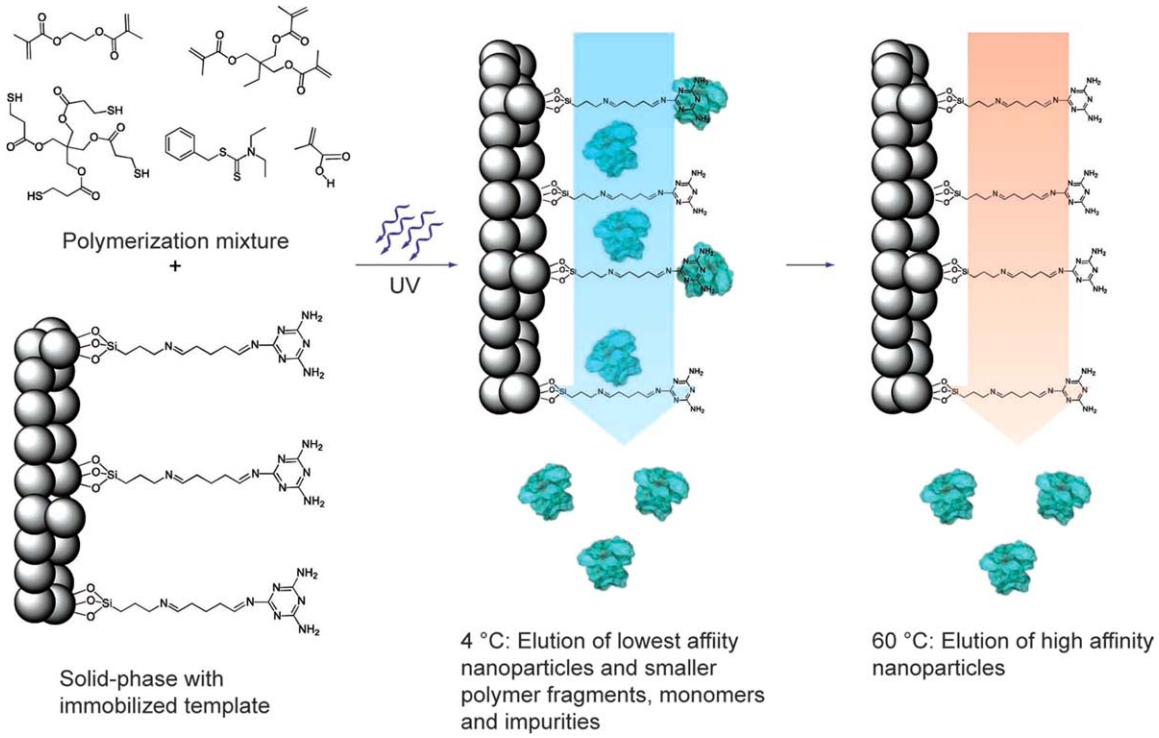
et al.[179] prepared magnetic MIPs to recognize the enzyme amylase with the phase inversion of poly(ethylene-*co*-vinyl alcohol) (EVAL) solutions with 27–44 mol % ethylene in the presence of amylase, as illustrated in Scheme 4. The results show that the highest hydrolysis activity of magnetic MIPs (obtained with 32 mol % ethylene) was up to be 1545.2 U/g. Compared to the conventional catalysis process, magnetic MIPs presented advantages of a high surface area, suspension, an easy removal from reactions, and the rapid reloading of enzyme. The good activity of amylase magnetic MIPs persisted after 50 cycles of starch hydrolysis.

CHALLENGES OF MIPs IN FOOD ANALYSIS

At present, the exciting and promising MIT is being increasingly adopted as a platform for food analysis. In addition to their suitable extraction properties, MIPs currently in use for new areas are being explored, and novel synthesis methods are being developed. In fact, because of the excellent performances of MIPs as selective sorbents for SPE, there are already several companies selling MISPE cartridges for the extraction of certain analytes; this will ease the implementation of MISPE in analytical laboratories.[112] In most cases, a refinement of its use in MISPE or its combination with others (e.g., chemical sensors and antibody-like receptors) will bring new selective and simple methods for food areas in the near future. In addition, many challenges facing chemists or material scientists seem to be the development of novel materials in this area. However, the limitations on MIPs by conventional synthetic routes lie in the development of novel synthetic approaches to functionalize materials and, thus, to enhance performances of devices. Various simple and efficient means for preparing MIPs in the generation of high-affinity binding sites for all sorts of applications would thus be highly desirable. To overcome the previous challenges, much effort has been expended in an attempt to design and synthesize high-selectivity materials that can be applied in separation processes, chemosensors/biosensors, and so on.[180]

Choice of Target Templates

Generally, an ideal template molecule should satisfy three requirements: (1) it should have no groups involved in or preventing polymerization, (2) it should exhibit excellent chemical stability in the polymerization reaction, and (3) what is more, it should contain functional groups well adapted to assemble with functional monomers. As for the target templates, the imprinting of low-molecular-weight templates has proven to be efficient in providing recognition materials suitable for different analytical applications. Most imprinting templates in the food field can be grouped into four broad categories;[12] these include widespread pesticide/drug residues, poisonous (containing toxic metal ions), additives, and constituents. On the other hand, the large templates, including proteins, can be used an alternative method for generating binding sites on the surface of a supporting material.[181] Even furthermore, imprinted cavities specific for whole cells have been prepared, where the cells act as temporary



Scheme 6. Schematic representation of the solid-phase synthesis of MIP nanoparticles. The monomer mixture is injected into the column reactor with an immobilized template, and polymerization was initiated with UV irradiation. The low-affinity particles and unreacted monomers are eluted at a low temperature. The temperature is then increased, and high-affinity particles are eluted from the column for collection. (Adapted with permission from ref. 38. Copyright 2013 John Wiley & Sons, Inc.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

protecting groups and structural templates during the multistep imprinting process.[182,183]

However, the MIT also has some problems for applications in food samples. First, those highly toxic, high-cost, and/or rare targets cannot be used as template molecules because of the target molecule itself being used. Second, as the templates are often tightly embedded and heterogeneously distributed in the polymer network, template molecule leakage could be a serious problem and could interfere with the accurate quantitative determination and purification. To bypass the undesired leakage of target templates for traditional MIPs, structural analogs of the target molecules have been used as the template molecules, namely, dummy MIPs.[184–186] At this regard, Yan et al.[41] synthesized new dummy imprinted microspheres with diisononyl phthalate as a dummy template with precipitation polymerization and successfully applied them as a special sorbent of dummy molecular imprinting and SPE for the selective extraction of five phthalate esters (PAEs) from plastic bottled beverage products. The results show that the developed extraction protocol eliminated the effect of template leakage on quantitative analysis and could be applied for the determination of PAEs in complicated functional beverages products. With regard to high cost and/or rare targets, the use of fragments, called *fragment imprinting*, seems to be an effective method in which only a part of the target molecule is used as the template,[187,188] as depicted in Scheme 5.[188]

It should be noted that the recognition in a water sample is highly needed because most food samples are related to aqueous media. Selective recognition in aqueous media can, however, be achieved through the use of monomers that form a stronger, and in the ideal case, stoichiometric (1:1) complex with the template [association constant (K_a) $\geq 10^3$ M^{-1}].[185] In one study, a stoichiometric imprinted polymer templated with penicillin G was prepared in the presence of a urea-based monomer. The K_a for this monomer and tetrabutylammonium benzoate in dimethyl sulfoxide (DMSO) was 8820 M^{-1}.

Advances in MIP-Based Immunosensors for Food Safety

With food safety incidents increasingly emerging in the world, the control of poisonous substances in adulterated foods is very crucial, and the accurate and simple analytical methods are urgently required. Many efforts have been devoted to detecting or dealing with challenges. So, a variety of analytical protocols for screening contaminated compounds in food samples have been developed; these include GC, HPLC, GC or LC coupled with mass spectrometry (GC–MS, LC–MS), immunoassay methods, and BELISA.[138] Among them, the GC–MS and LC–MS methods, which are more effective and sensitive, are usually used. However, they have many potential drawbacks, including an investment in expensive instrumentation, extensive cleanup, and a purification pretreatment, and that leads to limitations in their wide utilization and on-spot detection.

In recent years, immunoassay methods have become a popular and useful screening tool with their merits of rapid analysis. However, biological antibodies are relatively unstable and costly, and this results in a limitation of their applications and developments. Recently, some reports have concerned the applications of MIP-based immunoassay methods (i.e., BELISA) in

food safety, and the developed biomimetic immunoassay is an ongoing and exciting application of MIPs.[189–192] For example, Wang et al.[150] developed a novel competitive direct BELISA method for the determination of the *N*-methylcarbamate insecticide metolcarb based on an MIP film as the antibody mimic. Under the optimum conditions, the sensitivity and limit of detection of the competitive direct BELISA were found to be 17 and 0.12 μg/L, respectively. The developed method was applied to the determination of metolcarb in spiked apple juice, cabbage, and cucumber, with mean recoveries ranging from 71.5 to 117.0%. The results suggest that the method has potential for the rapid determination of metolcarb in foods. In the study of Chianella et al.,[193] molecularly imprinted nanoparticles (nanoMIPs) prepared by solid-phase syntheses were used in the development of a clinically relevant enzyme-linked assay for a currently prescribed antibiotic (vancomycin). The sensitivity of the assay was three orders of magnitude better than a previously described enzyme-linked immunosorbent assay based on antibodies. The high affinity of nanoMIPs and the lack of a requirement for cold chain logistics make them an attractive alternative to traditional antibodies used in enzyme-linked immunosorbent assays. However, the structure of enzyme-labeled antigens is quite different from that of template molecules, and poor optical and material properties of MIPs have become major challenges in the development of the biomimetic biosensor format. To promote the application of this approach, there is a need for the development of generic and versatile procedures for the synthesis of MIP nanoparticles for various targets. One potential advance in this area could be the development of an automated nanoreactor for the reproducible synthesis of monodisperse MIP nanoparticles. A reactor similar to that proposed here has recently been produced for the preparation of MIP microparticles, as illustrated in Scheme 6.[38] Therefore, an MIP-based biomimetic immunoassay with good accuracy and a simple pretreatment procedure might well be used to monitor pesticides in agricultural products or antibiotics in milk and animal feed samples in the future.

Production Limitations of MIPs

The implicit challenges of the production of novel MIPs arise chiefly from the fact that all substrates are different and, thus, require different monomer and crosslinker combinations to adequately form imprinted polymers for that substrate.[54] MIPs prepared in traditional formats (e.g., monoliths, membranes, films, beads) are perceived to have a number of drawbacks, including binding site heterogeneity, leaching of the residual template from the polymer, and difficulties involved in their integration with sensors and assay protocols. Many of the perceived disadvantages of MIPs can be traced to the template: soluble templates are in motion, both translation and rotation, during the critical stages of binding site formation. In addition, all of these methods of preparation are labor-intensive, and they are one-off batch processes not suited for industrial production. Poma et al.[38] first reported a significant method for the solid-phase synthesis of MIP nanoparticles. Here, nonporous glass beads, whose surface was modified with template molecules, were, therefore, chosen as the basis of an immobilized template phase for the incorporation into a new reactor design. The use of a reusable molecular template, along with the development of instrumental methods for automating their production, helped to shorten the development time and expedite the synthesis of MIP nanoparticles. This could be of great advantage when dealing with templates that are in short supply or expensive to obtain. With this breakthrough, it is believed that the era of plastic antibodies has begun. The principle of the developed method is schematically outlined in Scheme 6.

CONCLUSIONS AND PERSPECTIVES

In this review, preparation methods for MIPs and their applications in food analysis have been summarized comprehensively. Some relatively new preparation methods involving solid-phase synthesis, surface imprinting, and stimuli responsiveness have been reviewed. MIPs, as solid-phase adsorbents in SPE, SPME, MSPD, and MME and as stationary phase in the chromatographic separation of foodstuffs, have been comprehensively reviewed. MIP-based biomimetic sensing, including optical sensors and electrochemical sensors, and enzyme-like catalysis received special attention.

Although great achievements have been attained in the field of MIPs and they have successfully applied in food analysis, there are still substantial challenges and opportunities. For example, most MIPs are still prepared in organic media, and a lot of organic solvents, such as acetonitrile, toluene, and methanol are used; this results in serious environment pollution. So, green molecular imprinting technology (GMIT) should be popularized. The concept of GMIT is briefed in relation to aqueous phase and other types of novel MITs, and development of novel starting materials. We have pointed out that, along with an increased acceptance of green chemistry, attention should be paid to the deep exploring and development of GMIT to extend the scope of MIT and promote the development of green chemistry. Also, the commercial exploitation of molecular imprinting is still in its infancy by conventional procedures with its own set of pros and cons, and thus, efficient means of preparing MIPs should be highly developed in the generation of high-affinity imprinting materials in terms of the capacity, selectivity, and homogeneity of binding affinity for all sorts of applications. Most sensors cannot achieve on-site, fast, and label-free detection, and expensive and complicated instruments are still needed. Therefore, the development of novel MIP-based sensors, such as MIPH, is becoming a research hotspot of MIT and food safety. Most imprinting targets are small molecules, such as herbicides, additives, and metal ions. Bacteria or protein imprinting are still scarce. Because of the characteristics of food analysis, bacterial detection is highly desired. So the development of a novel method for imprinting bacteria is one important direction in food analysis.

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