Microchimica Acta (2018) 185: 247
https://doi.org/10.1007/s00604-018-2735-4

REVIEW ARTICLE

Molecularly imprinted polymers for the detection of illegal drugs and additives: a review

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Received: 23 October 2017 / Accepted: 16 February 2018 / Published online: 4 April 2018

Abstract

This review (with 154 refs.) describes the current status of using molecularly imprinted polymers in the extraction and quantitation of illicit drugs and additives. The review starts with an introduction into some synthesis methods (lump MIPs, spherical MIPs, surface imprinting) of MIPs using illicit drugs and additives as templates. The next section covers applications, with subsections on the detection of illegal additives in food, of doping in sports, and of illicit addictive drugs. A particular focus is directed towards current limitations and challenges, on the optimization of methods for preparation of MIPs, their applicability to aqueous samples, the leakage of template molecules, and the identification of the best balance between adsorption capacity and selectivity factor. At last, the need for convincing characterization methods, the lack of uniform parameters for defining selectivity, and the merits and demerits of MIPs prepared using nanomaterials are addressed. Strategies are suggested to solve existing problems, and future developments are discussed with respect to a more widespread use in relevant fields.

Keywords Illicit drugs · Molecular imprinting · Polymerization · Sports doping · Surface imprinting · Trace substance

Introduction

Illegal drugs are defined as drugs that are not related to the purpose of medical treatment, prevention and health care. Illegal drugs have been prohibited by regulations of the state administration because they are believed to present unacceptable risks of addiction to users [1]. Illegal drugs include illicit drugs and doping agents as used in sports. Illicit drugs are addicted pharmaceutical drugs generally which can cause mental disorder or irritability and lead to a series of abnormal behavior [2, 3]. The use of illegal psychoactive drugs is commonplace in many parts of the world, and this phenomenon seems to be widespread and may be increasing [4–6]. Doping in sports are drugs that athletes take to improve performance in competition [7, 8]. Illegal food additives refer to the non-food substances which are prohibited in human food. The harm of illicit drugs which pose a threat to human survival and development has spread to food safety, sports, medical and health field, becoming a globalization problem. Considering that illegal drugs have developed rapidly, detection of illicit drugs in the human body and illegal additives in food has become a priority. However, there exist some problems such as complicated composition, low quantity, serious matrix interference, high labor intensity and poor selectivity in the enrichment and detection of illicit drugs and additives. Hence the traditional extraction materials and analysis methods have been unable to meet the actual needs. To overcome these obstacles, we require new high selectivity materials and rapid analysis method which can simplify sample pretreatment steps, improve the detection sensitivity and realize the automatic detection.

Molecular imprinting [9] is a method for creating, in a polymer matrix, an imprinted cavity that has a shape matched to a template molecule. The concept of molecular imprinting appeared due to the development of molecular immunology antibody formation theory proposed by L. Pauling, whose history can be traced back to the 1940s [10]. The recognition

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00604-018-2735-4) contains supplementary material, which is available to authorized users.

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of MIPs mainly imitates the biological processes such as ligand-receptor binding, substrate-enzyme reactions and translation and transcription of the genetic code. Molecularly imprinted polymers (MIPs) are obtained by assembly of a cross-linked polymer matrix around a template molecule that is held in dispersive medium, either covalently or non-covalently, by judiciously chosen functional monomer, and subsequent removal of the template molecular from the prepared polymer matrix produces a molecularly imprinted cavity with a shape matched to the template molecule. In the final MIPs, the imprint cavity remains when the imprint molecule is removed, and is able to interact with template molecular or the molecular that as same as the template through any combination of size, shape, and functional group matching. Fig. S1 shows the principle of molecularly imprinting polymers [11].

The Molecular Imprinting Organization was established at Lund University in 1997. Ever since, molecular imprinting has become one of the most impressive materials with high selectivity and high concentration [12]. Owing to their advantages, MIPs have been widely utilized as molecular recognition and separation materials in different fields particularly as selective adsorbents for solid-phase extraction (SPE) [13–17], chromatographic [18–22] and chemical sensor [23–28]. As technology progresses, MIPs gradually have also become essential for determination of illicit drugs and additives [29–34]. Fig. 1 shows the timeline of the advances in MIPs used for detection of illicit drugs.

In all analytical methods of detecting illicit drugs and additives, MIPs possess incomparable superiority relative to traditional analysis methods. Firstly, the content of illegal drugs is usually too low to be detected by traditional analysis methods, while this requirement can be achieved with help of MIPs. Secondly, due to high matrix interferences of some complex samples, severe masking caused by components existing in the form of compounds, and interfering effects of protein substances on the detection of illegal drugs, there is a pressing need for an enrichment method with high selectivity and a highly sensitive detection method like MIPs. Otherwise, it is extremely apt to result in missed and false detection [57]. Thirdly, with the continual development of illegal drugs, a wide variety of illicit drugs and additives have appeared on the market. For example, because of the increasing supervision to clenbuterol hydrochloride, the structural analogue, ractopamine has been used as succedaneum of clenbuterol hydrochloride. Therefore, the single detection method designed for a single drug cannot overcome its limitations. Due to the procedure of metabolism and elimination, the content of the prototype drug decreases gradually until it fails to be detected. There is an urgent need for a multi-sample and multi-index identification and detection system [58] to simultaneously enrich the prototype drug and its metabolin. The specific cavities and action sites of MIPs can realize the simultaneous enrichment of some illegal drugs, their structural analogues and metabolin.

Fig. 1 Timeline showing the advances in MIPs used for detection of illicit drugs and additives in the literature. Reproduced from Refs. [35–59]

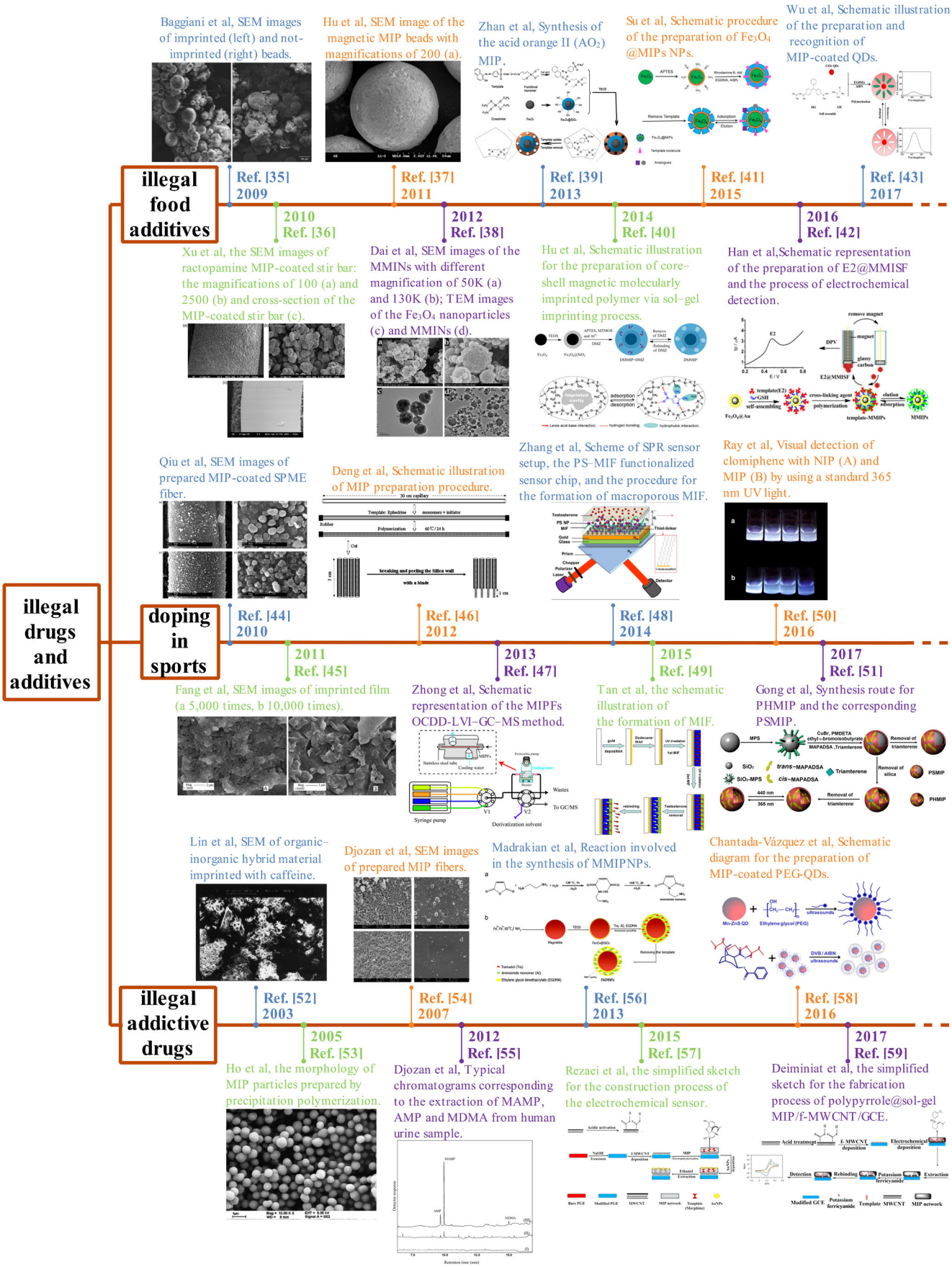
Although MIPs enjoy significant benefits in detecting illegal drugs and additives, they confront many challenges such as the lack of convenient preparation methods, template leakage, the recognition in aqueous environment, the balance of adsorption capacity and selectivity factor, lack of convincing characterization methods, absence of uniform parameters for selectivity and so on. In this article, we give a comprehensive overview of the advances in MIPs used for detection of illicit drugs, which covers the main approaches to the design, synthesis, characterization and application of MIPs in the determination of illicit drugs. Furthermore, we place more emphasis on the challenges and existing solutions in the field of molecularly imprinted polymers for the detection of illicit drugs.

Polymerization method of MIPs using illicit drugs and additives as templates

Free-radical polymerization is that the monomer by means of light, heat, radiation and initiator agent forms active radicals and then polymerization of monomers forms a chemical reaction chain polymer. Owing to its advantages of mild reaction conditions, tolerant of functional groups in the monomers and impurities in the system and fast response,free-radical polymerization is widely used in synthesis of MIPs.

Blomgren et al. [60] prepared a MIP by radical polymerization using brombuterol, a structural analogue of clenbuterol as the template for the extraction of clenbuterol from calf urine samples. Compared with the non-imprinted polymer, the MIP has higher selectivity for clenbuterol. The result shows that the MIP coupled with HPLC–UV is superior to routine analytical methods in bioanalysis at trace levels. Harun et al. [61] synthesized an anti-ketamine MIP by free radical polymerization for solid-phase extraction and isolation of ketamine and norketamine from human hair extracts prior to LC-MS/MS analysis. The MIP columns can simultaneously detect ketamine and its main metabolite, norketamine and a range of different pH and solvent conditions are unaffected for the performance of MIPs.

So far, MIPs synthesis methods mainly are bulk polymerization, in-situ polymerization, suspension polymerization and surface imprinting free radical polymerization as the basic principles.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2010 Ref. [36]
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2012 Ref. [38]
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Dai et al, SEM images of the MMINs with different magnification of 50K (a) and 130K (b); TEM images of the Fe_3O_4 nanoparticles (c) and MMINs (d).
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2015 Ref. [57]
Ref. [58] 2016
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Lump MIP synthesis

Lump MIP synthesis refers to that the MIP prepared by this method has no fixed shape and stacks together without rules. This method includes bulk polymerization and In-situ polymerization. Because of the roughness, the MIP forms irregular shapes and has large specific surface area.

Bulk polymerization, which is also known as mass polymerization, is the most conventional method for preparing MIPs due to its attractive properties, such as simple operation and low production costs. This method generally is dissolving the template molecule, functional monomer, crosslinking agent and initiator in accordance with a certain proportion in an inert solvent, and then adding initiator to initiate the reaction. After crushing, grinding, sieving and other processes, the molecule with desired particle size is obtained. Although the MIPs prepared by bulk polymerization provide adequate selectivity, there are still some shortcomings including time-consuming preparation procedure, low-affinity binding, high diffusion barrier, low-rate mass transfer, and poor site accessibility.

In-situ polymerization means that monomers are filled into the interlayer and polymerization occurs between the layers. In-situ polymerization is generally pouring polymerization mixture solution into an empty column or capillary firstly and then ending with a plug. After initiated at a certain time, column or capillary will be connected to the column or capillary chromatography or electrophoresis. When the template is washed out, the MIP column or MIP capillary can be used directly in chromatographic or electrophoretic separation. This method greatly simplifies the experimental process because they are prepared and packed in one step. However, the suitable porogen which is added to make the column with good permeability can form hydrogen bonds between the porogen and functional monomers and influence the hydrogen formed between template and functional monomer, thus the affinity and selectivity of MIPs decrease. Furthermore, the degree of in-situ polymerization reaction is difficult to control.

A. Sorribes-Soriano et al. [62] prepared a cocaine-based MIP using bulk polymerization for solid-phase extraction of cocaine in saliva samples by ion mobility spectrometry. The result of MIP coupled with ion mobility spectrometry is comparable to that of a confirmatory gas chromatography-mass spectrometry method statistically, indicating that MIP-IMS is a practical choice of immunoassay procedures to screen cocaine in biological fluids. Kaisong Yuan et al. [63] sensitively determined rose bengal in brown sugar by molecularly imprinted solid-phase extraction (MISPE) coupled with capillary electrophoresis laser-induced fluorescence detection. The rose bengal imprinted monolithic column prepared by in-situ polymerization shows higher specificity, recognition ability, recovery and stability than HPLC and capillary electrophoresis coupled with traditional SPE. The comparison of SEM images of MIPs synthesized by two methods is shown in Fig. 2. As shown in Fig. 2A and 2B, A. Sorribes-Soriano et al.[62] produced cocaine MIPs and Zhengzhong Lin et al.[65] synthesized malachite green MIPs by bulk polymerization. They are both in the form of small globules. As shown in Fig. 2C and 2D, Haiyun Zhai et al.[63] prepared rhodamine B MIPs and Ting Du et al.[66] synthesized difenoconazole MIPs by in-situ polymerization. Compared with bulk polymerization, the MIPs prepared by in-situ polymerization are rounded, beaded and filled in the glass capillary.

Spherical MIP synthesis method

Spherical MIP synthetic method is a MIP synthetic method that the MIP has regular spherical shape and a particle size within a certain range, including precipitation polymerization, suspension polymerization and emulsion polymerization. Table 1 compares the three spherical MIP synthesis methods.

Precipitation polymerization uses a polymerization reaction to form a polymer in an organic solvent and the occurrence of polymer phase separation, and the resulting precipitates are nearly spherical MIPs. In this approach, polymerization takes place in a large excess of an organic solvent (where the monomers are soluble, but the resulting polymer is not), at monomer concentrations typically in the range of 2–5% (*w*/*v*). In such conditions, the polymer nuclei formed by aggregation of highly cross-linked oligomer radicals do not overlap or coalescence but continue to grow individually by capturing new oligomers in this diluted reaction system. The growing polymer has little affinity for the surrounding solvent and phase separation occurs, and nonporous polymer microspheres are obtained. Zhongcan Zhang et al. [69] prepared MIPs by precipitation polymerization for selective extraction of melamine in daily products. When 7.48 mmol crosslinker was used, the perfect microspheres were obtained. According to the MIPs images, it is evident that the MIP microspheres are rather homogeneous with no significant aggregation. Peilong Wang et al. [67] synthesized molecularly imprinted polymer microspheres by precipitation polymerization for the treatment of pork samples to detect clenbuterol and other β-agonists. The results indicate that the method coupled with ultra-performance chromatography coupled tandem mass spectrometry detection offers high recoveries, low detection limit and good repeatability, providing a reliable method of determining β-agonists in real pork tissue samples.

Suspension polymerization is one method for preparing polymer microsphere. The monomers used in suspension polymerization are usually hydrophobic and dispersed phase is usually water or highly polar organic solvent. Because of the shortcomings of the MIP synthesized by suspension polymerization, it is difficult to prepare MIPs by conventional aqueous suspension polymerization process. But there are some reports of the success of suspension polymerization. Zi-Ru Lian et al.

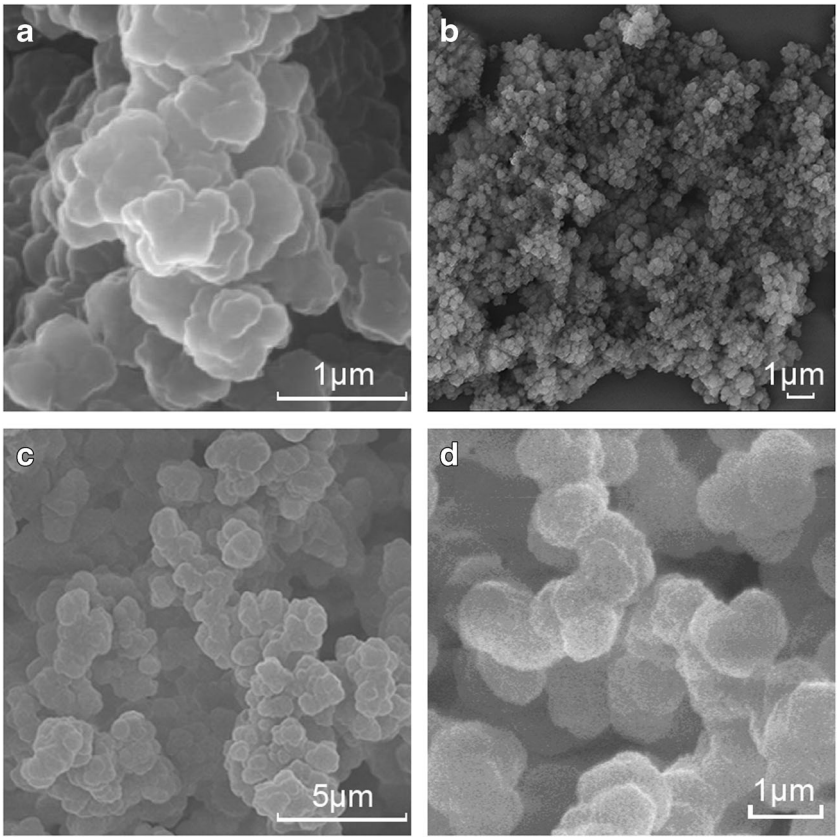


Fig. 2 The SEM images of MIPs synthesized by two methods. **a** cocaine MIP synthesized by bulk polymerization [62]; (**b**) malachite green MIP synthesized by bulk polymerization [64]; (**c**) rose bengal MIP synthesized by in-situ polymerization [63]; (**d**) difenoconazole MIP synthesized by in-situ polymerization [65]

[68] used caffeine as the dummy template molecule and polyvinyl alcohol as the dispersive reagent in water to prepare MIPs as a selective sorbent for the solid-phase extraction of gonyautoxins 2,3. The MISPE can eliminate the influence of interference matrix in the extract. Hongyuan Yan et al. [70] prepared new ionic liquid modified dummy molecularly imprinted microspheres by aqueous suspension polymerization as the sorbent of solid-phase extraction to detect clenbuterol and clorprenaline in urine. The molecularly imprinted microspheres were synthesized using phenylephrine as dummy template and 1-allyl-3-ethylimidazolium bromide as co-functional monomer. According to the results, the ionic liquid modified polymers have regular shapes, high adsorption capacity and mechanical strength, which brings about high selectivity and adsorbability to clenbuterol and clorprenaline and avoids the effect of template leakage on quantitative analysis.

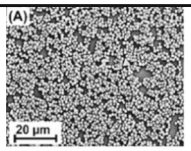
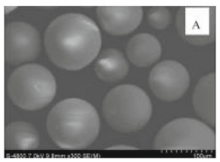
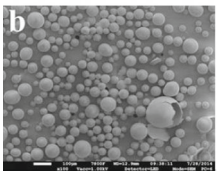
The emulsion polymerization is another method for preparing the MIPs microspheres. The template molecule, functional monomer and crosslinking agent are dissolved in an organic solvent, and typically a certain amount of surfactant is added. Then this solution is transferred into water for stir and emulsification, and polymerization occurs by adding the initiator. Compared to precipitation polymerization, it usually requires a larger number of chemicals including surfactants, buffer components and stabilizers which have to be removed after the synthesis, making washing procedures more sophisticated and sometimes reducing the purity of MIPs.

A so-called Pickering emulsion is an emulsion stabilized by solid particles. It was firstly described by Pickering in 1907. As reported previously, the emulsion type (O/W or W/O) and droplet sizes of Pickering emulsion can be easily controlled by adjusting the hydrophilic–hydrophobic properties and mass concentration of the used solid particles. Pickering emulsion polymerization, a promising alternative for preparing desired MIP materials for SPE applications, benefits from their advantages of simplicity, high yields of polymer and good control of final particle size. Li et al. [71] prepared MIPs by emulsion polymerization for extraction of malachite green in fish. The MIP particles were synthesized using MAA as functional monomer, EGDMA as cross-linker, and a combination of Span-80 and Tween-80 as an emulsifier. The detection method based on MIPs is successfully established to selectively analyze malachite green residue in fish samples.

Surface imprinting

Surface imprinting has increasingly attracted the most attention in the field of molecular imprinting because its advantages overcome the traditional shortcomings of MIPs slow mass transfer and increase the uniformity of the binding site. Surface imprinting technique and technology continue to be

Table 1 The comparison of three common spherical MIP synthesis methods

Spherical MIP synthesis method	Particle size	Initiator	Advantage	Disadvantage	SEM image	Ref.
Precipitation polymerization	wide particle size distribution	no special requirement	1 quick, straightforward and cheap 2 mono-disperse spherical polymer particles in high yield and purity.	1 higher cost 2 environmentalhazard		[67]
Suspension polymerization	micron grade, uniform-sized particle	oil-soluble initiator	1 most convenient 2 most common	1 Highly polar solvents will affect the selectivity of the polymer to the template. 2 Hydrophilic acidic monomer cause the no rules copolymerization difficult. 3 water-soluble molecular imprinting will loss		[68]
Emulsion polymerization	nanometer grade, uniform-sized particle	water-soluble initiator	1 Sizes uniform 2 Exhibit imprinted surfaces with improved binding site homogeneity and accessibility	1 Large variability in the particle size. 2 Poor purity		[14]

innovative and grow to maturity. Surface molecular imprinting creates recognition sites on the surface of the matrix material to increase the bonding speed of imprinting molecular recognition site, more suitable for solid-phase extraction and the stationary phase packing. Moreover, the matrix materials have considerable mechanical stability and different MIPs needed can be achieved by adjusting the matrix material itself. However, due to the incomplete or uneven coating of matrix materials, surface imprinting may have higher nonspecific adsorption than conventional imprinting methods.

Generally surface imprinting is divided into two methods, the traditional surface imprinting and hollow imprinting. Traditional surface imprinting includes modified imprinting surface method, and imprinted sites strictly controlled in MIPs surface method. The general process of modified imprinting surface method is that template molecule and functional monomer are dissolved in porogen for prepolymerization, and then this pre-polymer is grafted onto the matrix materials treated with surface activation, such as silica, polymer particles, glass, and carbon nanotubes. Fangdi Wei et al. [72] anchored MIPs on the surfaces of two different color quantum dots (QDs) to simultaneously detect norepinephrine and epinephrine. Two kinds of QDs@MIPs were both synthesized by the surface modification method. The process of imprinting on the surface of QDs is shown in Fig. S2. With good dispersibility, uniform morphology, high selectivity and binding affinity, the QDs@MIPs can realize simultaneous detection of norepinephrine and epinephrine.

As the concept of the hollow MIPs was proposed, the single hole hollow capsules were first synthesized in 2007 [73]. Like previous surface imprinting, hollow imprinting methods also enjoy the advantages of high selectivity, high stability to harsh chemical and physical conditions, and excellent reusability. In addition, the controllable hole structure of hollow polymers favors faster mass transfer. Qi Zhao et al. [74] prepared single-hole hollow molecularly imprinted microspheres to extract triazine pesticides in cereal samples. They used carboxylated polystyrene particles as the core. The process of synthesizing the MIP is shown in Fig. S3. The results indicate the specific surface area and binding capacity of MIPs prepared by hollow imprinting are superior to those of MIPs prepared by precipitation polymerization and surface imprinting.

But the hollow imprinting has obvious shortcomings. The MIP shell has to be thick because the polymer outside is easy to collapse and break when dissolving and removal of the soft core. However, the thick imprinting shell leads to a low mass transfer and low utilization ratio of the binding sites. Dong

Ren et al. [75] developed a new approach to the preparation of hollow MIPs with thin and solid shells. With polystyrene/SiO_2 particles as the core, only the polystyrene part was sacrificed, and the SiO_2 part was kept in the hollow MIPs as the support to make it possible to get a thin but solid MIP shell. This method not only avoids deformation and breaking but increases the surface area of matrix materials.

Free-radical polymerization cannot stay in an intermediate stage and cannot separate the stable product, and thus the particle size of the MIP is heterogeneity. Many efforts have been devoted to addressing this issue in the past years and some progress has been made in this field [76–79]. Controlled radical polymerization (CRP) is defined as the process that the balance between growth radicals and various dormant species is used for controlling polymer molecular weight, the distribution of molecular weight and terminal functional groups in radical polymerization system. The CRP includes iniferter, stable free radical polymerization, atom transfer radical polymerization and reversible addition fragmentation chain transfer polymerization. The advantage of CRP is that the molecular weight of the polymer, end-group functionalization, molecular weight distribution, three-dimensional structure, block copolymers and graft copolymers can be controlled which exactly solves the problem mentioned above. But its disadvantages of harsh polymerization conditions and polarity sensitive groups limit the wide range of applications.

As a CRP, atom transfer radical polymerization (ATRP) has been a popular method to graft polymer brushes because of the wide applicability of monomers, good compatibility of functional groups and excellent controllability for product molecular weight and dispersity. Yongliang Liu et al. [80] prepared surface molecularly imprinted Fe_3O_4@MIP nanoparticles by surface initiated ATRP to selectively enrich pefloxacin mesylate in egg samples. The overall preparation of Fe_3O_4@MIP nanoparticles is shown in Fig. S4. Due to the advantages of specific recognition and high affinity for pefloxacin mesylate in aqueous media, the Fe_3O_4@MIP nanoparticles are proved to be effective in concentrating pefloxacin mesylate from real samples.

Application

MIPs usually act as a vehicle for preconcentration and separation of samples, which is widely used in the detection of trace compounds, such as stimulants, environmental pollutants, food additives, etc. In the last years, MIPs have been shown to be effective in such areas, therefore the relevant articles have been increasing in quantities. The great potential applications of MIPs utilized for sample separation are summarized in Ref. [81–113], where the application of MIPs in the detection of illicit drugs is enumerated in particular. Tables 2, 3 and 4 summarize the highlighted applications of MIPs prepared by different polymerization processes as the separation media for the determination of various illegal additives in food, doping in sports and illicit addictive drugs, respectively. A variety of trace compounds are extracted from different samples for detection, such as tetracycline antibiotics, malachite green, clenbuterol, triamterene, testosterone, morphine, methamphetamine and so on.

The detection of illegal additives in food

In accordance with law, use of illegal food additives shall be prohibited in human food as a result of the fact that these non-food substances pose a great threat to human health. The β-agonist ractopamine and azo dye basic orange II are both classified as illegal food additives when they are used in food.

Compared with traditional sensor detection methods for determination of trace compounds which are hard to avoid the interference of analogs, MIPs developed as imprinted sensing membrane coupled with sensor measurement technology may improve the detection efficiency. Hongcai Zhang et al. [114] prepared a novel amperometric sensor based on screen-printed electrode modified with multi-walled carbon nanotubes (MWCNT) and molecularly imprinted membranes (MIM) for the determination of ractopamine in pig urine. Fig. S5 shows a scheme of screen-printed electrode modified with MWCNT and MIM. The MIMs were prepared on the screen-printed electrodes via in-situ thermal polymerization, and the electrodes were modified with MWCNT beforehand. Helped by the replacement of new screen-printed electrodes modified with MWCNT-MIM, it is convenient to realize multiple or successive determination of ractopamine.

Solid-phase extraction is the most widely used pretreatment technology at present. However, the traditional sorbents such as bonded silica gel, ion exchange resin are lack of enough selectivity. MIPs as a novel sorbent with high selectivity can be applicable for solid-phase extraction. Xiaoyan Li et al. [115] developed a novel MIP with modified rosin as a cross-linker for the determination of basic orange II in food. The synthesized MIPs possess a highly imprinting capacity and significant selectivity in comparison with those prepared by traditional cross-linkers.

The detection of doping in sports

There are many examples of domestic and international athletes taking punishment because of taking illegal drugs. Common illegal drugs are about 100 kinds which can be divided into the following seven categories, including analgesics, tranquilizers, stimulants, anabolic steroids, peptide hormones, thiazide diuretics and aldosterone drugs, masking agents and β- blockers.

Table 2 Selected application examples of MIPs for the determination of illegal food additives

Polymerization process	Target molecule	Template molecule	Monomer/cross-linker/porogen	Application/detection	Sample source	Ref.
Precipitation polymerization	Tetracycline antibiotics	Tetracycline	MAA/TRIM/MeOH–ACN	MISPE–LC–MS/MS	Foodstuffs	[80]
Precipitation polymerization	Malachite green, gentian violet and their metabolites	Malachite green	MAA/EGDMA/ACN	MISPE–HPLC	Aquatic products	[81]
Emulsion polymerization	Acephate	Acephate	MAA/EGDMA/chloroform	Extraction	Contaminated water	[82]
Emulsion polymerization	Florfenicol	Florfenicol	AM/EGDMA/DMSO	MISPE–LC–MS/MS	Milk	[83]
Suspension polymerization	Clenbuterol hydrochloride	Tert-butylamine and 2-chloroaniline	MAA/EGDMA/chloroform	MI–MSPD–HPLC	Chicken samples	[84]
In-situ polymerization	Rhodamine B	Rhodamine B	MAA/EDMA/MeOH–toluene–dodecanol	GO/SiO_2–MISPE monolithic column	Chili powder	[85]
Bulk polymerization	Dichlorvos	Dichlorvos	MAA/TRIM/ACN– toluene	MISPE–HPLC	Cucumber, lettuce	[86]
In-situ polymerization	Tetracyclines	Tetracycline	MAA/EGDMA/ cyclohexanol–dodecanol	MISPE–HPLC	Milk, honey	[87]
In-situ polymerization	Quinolones	Norfloxacin	MAA/EGDMA/DMF–DMSO	MISPE–HPLC	Pork	[88]
Bulk polymerization	Sudan I	Sudan I	MAA/TRIM/ acetone	MIP–coated SPME–HPLC	Hot chili powder, poultry feed samples	[89]
Surface imprintig	Aflatoxins	5,7–dimethoxycoumarin	MAA,4VP/EGDMA/DMSO–ACN	Extraction, UHPLC-MS/MS	Tea–leaves, corn	[90]
Thermal polymerization	Ractopamine	Ractopamine	MAA/EGDMA/ chloroform–MeOH	MIP membrane–aptasensor	Feed, beef	[91]

Table 3 Selected application examples of MIPs for the determination of doping in sports

Polymerization process	Target molecule	Template molecule	Monomer/cross-linker/porogen	Application/ detection	Sample source	Ref.
Thermal polymerization	Tamoxifen	Clomiphene	MAA/ EGDMA/ ACN	MISPE–HPLC–UV	Urine	[92]
Precipitation polymerization	Triamterene	Triamterene	MAA/DVB/ ACN- toluene	MISPE–HPLC–UV	Human serum	[93]
Bulk polymerization	Testosterone glucuronide	1,2,3,4-tetra-O-acetyl-β-glucuronic acid	1-(4-vinylphenyl)-3-(3,5-bis(trifluromethyl)phenyl)urea/ pentaerythritol triacrylate/ MeCN	MISPE-HPLC-UV	Urine	[94]
Precipitation polymerization	Propranolol	Propranolol	MAA/DVB-TRIM/ACN	MIP–based sensor	Pharmaceutical samples	[95]
Bulk polymerization	Carvedilol	Carvedilol	MAA/EGDMA/chloroform-ACN-MeOH	PT–MISPE–HPLC–DAD	Human urine	[96]
Precipitation polymerization	Testosterone	Methyltestosterone	MAA/EDMA/ACN	Extraction	Hydrolyzed urine samples	[97]
Bulk polymerization	Methadone	Methadone	MAA/ EGDMA/anhydrous ACN	MISPE–GC–FID	Plasma, saliva	[98]
Reversible addition-fragmentation chain transfer polymerization	Clenbuterol	Clenbuterol	MAA/EDMA/toluene-dodecanol	MIP monolithic column	Complex samples	[99]
Bulk polymerization	Metoprolol	Metoprolol	MAA/EGDMA/chloroform	MIP based PVC–membrane–coated graphite electrode	Human urine and plasma	[100]
Bulk polymerization	Acetazolamide	Acetazolamide	4-VP/ EGDMA/ acetone	MISPE–DPV	Human plasma	[101]
Electro–polymerization	Hydrochlorothia-zide	Hydrochlorothiazide	Pyrrole/−/ ethanol	MIP–modified MWCNTs/ PGE	Human serum	[102]

Table 4 Selected application examples of MIPs for the determination of illicit addictive drugs

Polymerization process	Target molecule	Template molecule	Monomer/cross-linker/porogen	Application/detection	Sample source	Ref.
Precipitation polymerization	Methamphetamine	Methamphetamine	MAA/EGDMA/ACN	MISPE–DLLME	Human urine	[103]
Photopolymerization	Ketamine	Ketamine hydrochloride	MAA/EGDMA/water–MeOH	MIPH	Human urine and saliva	[104]
Photopolymerization	Cocaine	Cocaine	MAA,2-VP/EGDMA, DVB, TRIM/ACN	MISPE–LC–MS	Hair	[105]
Precipitation polymerization	Buprenorphine	Buprenorphine	AA/EGDMA/ACN-MeOH	Extraction, HPLC–UV	Human urine and plasma	[106]
Bulk polymerization	Norephedrine	Norephedrine	MAA/EGDMA/ACN-MeOH	MISPE	Khat samples	[107]
Precipitation polymerization	Δ^9-tetrahydrocannabinol	Catechin	4-Vpy/ EGDMA/TRIGLYME	MISPE–LC–MS/MS	Urine, oral fluid	[108]
Radical polymerization	Δ^9-tetrahydrocannabinol	11-hydroxy-Δ^9-tetrahydrocannabinol	MAA, HEMA, 4-VPy/EGDMA/ MeOH	MISPE–GC–MS	Urine	[109]
Thermal radical copolymerization	Diacetylmorphine	Diacetylmorphine hydrochloride	MAA/ EGDMA/ACN	SPME–GC or GC/MS	Aqueous samples	[110]
Bulk polymerization	Tramadol	Tramadol	MAA/EGDMA/chloroform	MISPE–HPLC	Plasma and urine	[111]
In-situ polymerization	Tramadol	Tramadol	MAA/EGDMA/chloroform	MIP monolithic column–HPLC	Human plasma and urine	[112]
Bulk polymerization	Tramadol	Tramadol	MAA/EGDMA/chloroform	MISPE–HPLC	Human plasma and urine	[113]

In comparison to different nonspecific extraction methods, the selective extraction based on MIPs tends to be more precise. Testosterone is the primary male sex hormone. Due to its anabolic effects that lead to increases in muscle mass and strength, it is often illegally used to enhance athletic performance in sports. Bernadette Tse Sum Bui et al. [116] prepared MIP, with methyltestosterone as template, to clean up the hydrolyzed urine samples for quantification of testosterone via LC-MS/MS. After a one-step extraction on the MIP, a solution containing 2 ng mL^{-1} testosterone can be obtained, which meets the conditions set by the World Anti-Doping Agency for the minimum required performance limits for doping controls, between 2 and 10 ng mL^{-1}.

β-blockers have a relaxing effect on muscle function, which are known as an illegal, performance-enhancement drug for athletes. Sonla Morante-Zarcero et al. [117] developed a new method based on a new polysaccharide-based stationary phase by MIP extraction, to detect the four pairs of β-blockers simultaneously by HPLC, including propranolol, metoprolol, pindolol, and atenolol. The MIP-SPE-HPLC-UV method shows the advantages of good linearity, selectivity, precision and sensitivity.

The detection of illicit addictive drugs

Drugs refer to the narcotic and psychotropic substances which can lead to drug addiction, such as opium, heroin, methamphetamine, morphine, marijuana, cocaine and so on. Drugs are usually divided into two categories of narcotic drugs and psychotropic drugs, the most commonly including marijuana, opium and cocaine in narcotic drugs. Cocaine is taken as an example to compare the LOD and LOQ of the determination of cocaine by different methods which is shown in Table 5.

Coupled with sensor technologies, MIPs can also be installed on the carbon paste electrode to form a novel electrode for specificity identification. Caffeine is an alkaloid causing many physiological effects including stimulation of the central nervous and cardiovascular systems. Taher Alizadeh et al. [133] 7prepared a novel voltammetric sensor for the determination of caffeine based on MIT. They embedded the caffeine-selective MIP in the carbon paste electrode to recognize caffeine selectively and prepare for the caffeine preconcentration. Compared to NIP carbon paste, the electrode has the capacity to identify caffeine precisely.

Solid-phase microextraction (SPME), whose principle is different from solid-phase extraction, is utilized for pretreatment and can achieve ultratrace analysis associated with HPLC or GC. Methamphetamine is a central nervous system stimulant producing the feelings of euphoria, hallucinations, wakefulness and inappetence which may result in agitation and violence. Djavanshir Djozan et al. [134] synthesized a monolithic solid-phase microextraction fiber on basis of a MIP by gas chromatography to extract, pre-concentrate and detect methamphetamine. The fabricated fiber possesses the advantages of good firmness, stability and durability, high selectivity and great recognition ability. The result shows the fiber is compatible with for determination of methamphetamine from human saliva samples.

Table 5 The LOD and LOQ of the determination of cocaine by different methods

Method	LOD	LOQ	IF	Sample	Ref.
LC-MS/MS	3 ng mol^{-1}	5 ng mol^{-1}	3.436	whole blood	[118]
Label-free DNA hairpin biosensor	1.517 ng ml^{-1}	–	6.409	human serum	[119]
HPLC/MS	0.003 ng mg^{-1}	0.008 ng mg^{-1}	2.729	0.200 g whole blood or 50 μl urine were mixed with 200 μl water and 100 μl 0.10 mg l^{-1} IS in acetonitrile	[120]
UPLC–MS/MS	2.2 ng ml^{-1}	7 ng ml^{-1}	2.729	urine	[121]
Label-free electrochemical cocaine aptasensor	91,020 ng ml^{-1}	–	1.394	cocaine aptamer	[122]
HPLC	32 ng ml^{-1}	100 ng ml^{-1}	2.14	plasma	[123]
GC	0.02 ng mg^{-1}	0.04 ng mg^{-1}	2.14	hair	[124]
Label-free fluorescence aptamer-based sensor	57,646 ng ml^{-1}	–	–	cocaine aptamer	[125]
MIP	0.049 ng ml^{-1}	0.0081 ng ml^{-1}	4.513	urine	[126]
Complementary strand of aptamer	145.632 ng ml^{-1}	–	6.409	Cocaine	[127]
Microfluidic affinity sensor	3.034 ng ml^{-1}	–	–	blood serum	[128]
Electrochemical aptasensor based on single-walled carbon nanotubes	31.857 ng ml^{-1}	–	6.409	rat serum	[129]
A novel fluorescent aptasensor based on hairpin structure of	63.4106 ng ml^{-1}	–	6.409	cocaine aptamer	[130]
Chemiluminescence aptasensor	145.632 ng ml^{-1}	–	3.436	Cocaine aptamer	[131]
Reversed-phase HPLC	1 ng ml^{-1}	–	4.169	plasma and human hair	[132]

Limitation and challenge

Despite the great progress of the development that has been achieved in MIPs used for enrichment and determination of illegal drugs, there still remain substantial development challenges to be tackled, such as the lack of convenient preparation methods, template leakage, the recognition in polarity and aqueous environment and so on. In order to improve the situations of MIPs in this field, certain achievements have been attained up to now.

Optimization of preparation methods for MIPs

It is obvious that only a small part of MIPs applied in the determination of illegal drugs and additives has realized industrialization for the moment. Because the preparation of MIPs is affected by various factors, the research on most of MIPs is still in the experimental stage. Currently, a trial-and-error method is seemed as the general approach to selecting functional monomer [135]. Namely, a portion of molecularly imprinted polymers are synthetized with different common functional monomers, and the experimental results decide the optimal molecularly imprinted polymer [136]. The choice of functional monomer, cross-linker and polymerization method depends on experience, which carries significant limitations. It is both time consuming and tedious to screen an imprinted system by experience.

Molecular simulation is simulating molecular motion by theoretical method and computing technology for improvement of cycle time spent on designing new materials and cost reduction. Molecular simulation technology, has been utilized for explanation of recognition mechanism, selection of functional monomer, determination of ratio of target molecule to functional monomer, and the design of molecular imprinting system. Although the combination of molecular simulation and mathematical methods is regarded as a convenient approach [137], the technology as still shown some defects. Therefore, its main studies are qualitative research rather than quantitative study. Farhad Ahmadi et al. [138] designed a MIP by aid of computational methods, and the MIPs were successfully used to extract metaproterenol in human plasma. The computer assisted-design of MIP is proven to be effective in the screen of the most suitable functional monomers for a specified template molecule. According to the results, the best functional monomer is AA. The best MIPs show high selectivity, sensitivity, reproducibility and accuracy for quantification of metaproterenol in complex biological samples.

The development in the respect of novel techniques and methods for MIPs preparation is also rapid, such as electropolymerization [139, 140], the epitope approach to molecular imprinting [141], self-assembly [142, 143], microwave-assisted method [144] and so on.

Applicability in aqueous solution

It is generally known that the samples used in the detection of illegal drugs and additives are usually organic small molecules in aqueous solution. However, most MIPs using organic small molecules as template molecule only show great molecular recognition property in organic solution. MIPs in organic solution recognize objective molecules via hydrogen bonding, while in aqueous solution, hydrogen bonding is weakened greatly because of strong hydration action, which affects MIPs molecular recognition property. In order to overcome limitations of existing MIPs whose template molecule is organic small molecule identification strategies in aqueous solution, research on MIPs in aqueous solution is imperative.

For the sake of weak hydrogen bonding, other intermolecular forces such as metal ion chelation, electrostatic interaction should be taken in consideration. Metal ion chelation is not influenced by water molecules, which is stronger than hydrogen bonding in aqueous solution. Stable specific binding sites between metal ion and template molecule are formed in aqueous solution for selective recognition. As a bond interaction, metal ion chelation facilitates the mild generation and cleavage of the interaction between metal ion and imprinted molecule in aqueous solution. Zhong Zhang et al. [145] prepared novel Hg^{2+} ion-imprinted polymers based on dithizone–Hg^{2+} chelation by a sol–gel process. The template molecule and functional monomer were dithizone–Hg^{2+} chelate and 3-aminopropyltriethoxysilane, respectively. The method shows great potential for the determination of Hg^{2+} in aqueous, solid and semi-solid biological samples.

Surface modification is another rational choice apart from enhancing the intermolecular forces, which is mentioned in section 2.3. Chiyang He et al. [146] grafted testosterone-imprinted polymer film on the surface of porous silica successfully to selectively detect testosterone. The composite is seemed as a rational method for separation of testosterone.

Leakage of template molecules

When MIPs are prepared by noncovalent bond, template molecules can form molecular complexes in presence of functional monomers. MIPs binding sites established tend to be inhomogeneous, resulting in non-specific binding. Then, it is difficult to remove template molecules from the molecularly imprinted polymers, which causes the leakage of template molecules. At present, the leakage of template molecules is a serious distraction to the detection in the detection of illicit drugs and additives.

To resolve the problem, structural analogs which possess similar parent structure or the same functional groups, are utilized as dummy template molecules. The analogous binding sites and spatial structure of dummy template molecules can avoid the leakage of template molecules and poor solubility of template molecules. Xiao-Yun Zhao et al. [147] prepared a MIP monolithic column by in-situ thermal-initiated polymerization to detect triamterene. Because the structure of melamine is similar to that of triamterene, it is chosen as a dummy template molecule, which can avoid leakage of the template and improve the efficiency of detection. The monolithic columns are effective in analysis of triamterene in biological samples.

Porous MIPs are endowed with highly crosslinked microporous structure, narrow hole sizes and large specific surface areas. Numerous effective recognition sites bring about high adsorption capacity for target molecules and rapid adsorption kinetics. Furthermore, the porous structure can avoid the poor results of incomplete template molecule removal from the polymers during subsequent treatment. Shoufang Xu et al. [148] developed three types of porous MIPs, including single-hole hollow MIPs, multihole hollow MIPs and porous solid MIPs, for the preconcentration and detection of triazines in soil samples. In the respect of the imprinting capacity, single-hole hollow MIPs and multihole hollow MIPs are better than porous solid MIPs. The MIPs have higher binding capacity and faster mass transfer in favor of template removal.

Balance of adsorption capacity and selectivity factor

Adsorption capacity is usually used as an evaluation index of MIPs adsorption performance. Selectivity factor refers to special selectivity for target molecule and high selectivity factor makes target molecule easier to be identified in complex samples. For the sake of the best results, large adsorption capacity and high selectivity factor are both needed to improve the materials performance. Nonetheless, influenced by surface functional groups, different temperature, various concentration of the solutions, diverse ratio of functional monomers to template molecules and so forth, adsorption capacity and selectivity factor cannot reach the best value simultaneously. Namely, there exists a balance relationship between the two indexes. How to balance the relationship between adsorption capacity and selectivity factor depends on the specific requirements in actual application.

Lack of convincing characterization methods

In general, the characterization of MIPs consists of morphology characterization, structural characterization, recognition behavior recognition, property characterization, hydrophilic characterization and so on. The adsorption capacity can be selected to characterize the surface area of MIPs. Besides, various kinds of microscopes including transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic microscopy(AFM) and so forth, are applied for morphology characterization of prepared MIPs, obtaining the size and morphological characters. The physical property and the structure of product are investigated by fourier transform infrared (FT-IR) spectroscopy and elemental analysis, and thermogravimetric analysis(TGA) is used to evaluate thermal stability. Analysis of equilibrium data with kinetic model and thermodynamics model can show the assessment of recognition behavior. The maximum adsorption capacity, selectivity factor and bioconcentration factor are all significant parameters in the performance measurement for MIPs. The evaluation of hydrophilic property of MIPs is carried out by means of their dispersity in aqueous solution and contact angle with water. In spite of the fact that there are a large number of characterization methods in all aspects, an efficient characterization method is still lacking when researchers wonder whether it really formed imprinted holes as respected.

Absence of uniform parameters for selectivity

The concept of selectivity is used to quantify the extent to which a given sorbent (MIP) binds two different compounds (template and referent). However, there have at least two description method:

a. The interrelated absorbed coefficient was evaluated by the following equations. [149]:

Static distribution coefficient: $K_d = \frac{C_p}{C_s}$

where *Cp* is the concentration on the absorbed medium and *Cs* is the final free concentrations of the solution. For comparison of the MIP beads selectivity, the selectivity coefficient *k* was calculated as the following formula:

Selectivity coefficient: $K = \frac{K_{d(Template)}}{K_{d(Referent)}}$

where $K_{d(Template)}$ and $K_{d(Referent)}$ are the static distribution coefficients of template and referent molecules, respectively.

b. The equilibrium adsorption capacity (Q, μg mg^{-1}) of template or referent bound to the imprinted polymers are calculated as the following formula [150]:

$$Q = (C_0 - C_1) \cdot V/m$$

Where C_0 and C_1 represent the initial solution concentration and the final solution concentration (μg mL^{-1}) of template or referent. *V* represents the volume of the solution (mL) and *m*

represents the weight of the polymer (mg), respectively.

The imprinting factor is defined as follows:

$$\alpha = \frac{Q_A}{Q_B}$$

where Q_A and Q_B are the capacities of MIP and NIP to adsorb the template or referent. The selectivity factor is defined as follows:

$$\beta = \frac{\alpha_1}{\alpha_2}$$

where α_1 is the imprinting factor with respect to the template and α_2 is the imprinting factor with respect to referent.

There is not a uniform parameter for assessment of the selectivity for the moment. Different authors used various kinds of parameters because MIPs are widely used in a large range of scientific applications. Hence, it is difficult to compare the synthetized MIPs whose selective recognition ability are measured by diverse parameters.

Merits and demerits of MIPs prepared using nanomaterials

Using nanostructure materials as template, many MIPs with nanometer size have been synthesized for detection of illegal drugs and additives. In the preparation of MIPs, nanostructured MIPs need no comminution and screen, which avoids damaging the recognition sites. Compared with MIPs with micron structures, nanostructured MIPs has higher specific surface area to increase the proportion of effective binding sites. Most of the binding sites are located at or near the surface of nanomaterials so that nanostructured MIPs show higher adsorption capacity. Besides, template molecules can easily attach to the molecular recognition sites, resulting in fast binding kinetics. The comparison of nanosized and microsized MIPs is shown in Table 6.

However, the preparation process of nanosized MIPs has high requirements on instruments and technology. Nanosized MIPs still have the problems of high cost of production, irregular shape, uneven particle size, and decreased affinity due to high polymerization temperature. Therefore, the preparation of nanostructured MIPs is still a research direction in the future.

Conclusion

The development of new enrichment materials with high selectivity, and sensitive analysis methods for the determination of illicit drugs and additives has become a significant research subject. In this review, polymerization methods, highlighted

Table 6 The comparison of nanosized and microsized MIPs

Nanosized MIPs				Microsized MIPs			
Ref [79]	Fe_3O_4@MIP NPs	particle size	500 nm	7–15 μm	particle size	Fe_3O_4@MIP MPs	Ref [151]
		adsorption capacity	28.3 μmol g^{-1} for pefloxacin mesylate	16.0 μmol g^{-1} for dicofol	adsorption capacity		
		equilibrium time	10 min	9 min	equilibrium time		
Ref [152]	SiO_2@MIP NPs	particle size	200 nm	2.7 μm	particle size	SiO_2@MIP MPs	Ref [153]
		adsorption capacity	94.4 μmol g^{-1} for rhodamine B	88.3 μmol g^{-1} for rhodamine B	adsorption capacity		
		equilibrium time	15 min	60 min	equilibrium time		
Ref [70]	MIP NPs	particle size	150 nm	35–75 μm	particle size	MIP MPs	Ref [154]
		adsorption capacity	5.2 μmol g^{-1} for malachite green	7.4 μmol g^{-1} for malachite green	adsorption capacity		
		equilibrium time	no more than 15 min	–	equilibrium time		

applications, limitations and challenges of MIPs in the detection of illegal drugs and additives are summarized. Comparing with traditional analytical methods, MIPs demonstrate incomparable superiority in view of easy preparation, high sensitivity, good selectivity, and so on. Significant efforts have been made to further accelerate the development of MIPs. The preparation methods for MIPs can be optimized with the help of molecular simulation and computer-aided designing system. The intermolecular force is enhanced by means of metal ion chelation and surface modification in response to the limitation of poor identification strategies in aqueous solution. As the result of the fact that the leakage of template molecules has been impeding the pace of development of MIPs, dummy molecule imprinting and porous polymers are selected to solve the problem. However, there are still some challenging problems in this field. In order to satisfy the requirements of practical applications, the relationship balance of adsorption capacity and selectivity factor is worthy of research. The characterization of MIPs is unilateral in absence of convincing characterization methods. There are no uniform parameters for selectivity factor so that the MIPs are hard to compare by various parameters and indicators. Nanosized MIPs are increasingly popular, but there are also advantages of irregular shape, uneven particle size, and so on. These problems open a new line of inquiry that should be pursued by research laboratories in the field for more widespread use in relevant fields.

Acknowledgements This work was supported by the National Natural Science Foundation of China (Grant No. 81402899) and Shandong Provincial Natural Science Foundation, China (No. ZR2014HP020).

Compliance with ethical standards The author(s) declare that they have no competing interests.

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