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Molecular imprinting: perspectives and applications

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Molecular imprinting technology (MIT), often described as a method of making a molecular lock to match a molecular key, is a technique for the creation of molecularly imprinted polymers (MIPs) with tailor-made binding sites complementary to the template molecules in shape, size and functional groups. Owing to their unique features of structure predictability, recognition specificity and application universality, MIPs have found a wide range of applications in various fields. Herein, we propose to comprehensively review the recent advances in molecular imprinting including versatile perspectives and applications, concerning novel preparation technologies and strategies of MIT, and highlight the applications of MIPs. The fundamentals of MIPs involving essential elements, preparation procedures and characterization methods are briefly outlined. Smart MIT for MIPs is especially highlighted including ingenious MIT (surface imprinting, nanoimprinting, etc.), special strategies of MIT (dummy imprinting, segment imprinting, etc.) and stimuli-responsive MIT (single/dual/multi-responsive technology). By virtue of smart MIT, new formatted MIPs gain popularity for versatile applications, including sample pretreatment/chromatographic separation (solid phase extraction, monolithic column chromatography, etc.) and chemical/biological sensing (electrochemical sensing, fluorescence sensing, etc.). Finally, we propose the remaining challenges and future perspectives to accelerate the development of MIT, and to utilize it for further developing versatile MIPs with a wide range of applications (650 references).

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1. Introduction

Molecular imprinting is defined as “the construction of ligand selective recognition sites in synthetic polymers where a template (atom, ion, molecule, complex or a molecular, ionic or

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macromolecular assembly, including micro-organisms) is employed in order to facilitate recognition site formation during the covalent assembly of the bulk phase by a polymerization or polycondensation process, with subsequent removal of some or all of the template being necessary for recognition to occur in the spaces vacated by the templating species.”^{1–3} Since the pioneering work of Polyakov in the 1930s using silica matrices,⁴ the continuous development of design, preparation, characterization and application of molecularly imprinted polymers (MIPs) over recent years has reflected the gradual maturation of molecular imprinting technology (MIT) and the broad interest it has attracted from the scientific community in general. The number of articles,^{5–8} reviews,^{2,9–14} and monographs^{15,16} on the topic of molecular imprinting has continued to increase, which directly reflects the rapid development of current trends and areas.

Compared to other recognition systems, MIPs, which possess three major unique features of structure predictability, recognition specificity and application universality, have received widespread attention and have become attractive in many fields, such as purification and separation, chemo/biosensing, artificial antibodies, drug delivery, and catalysis and degradation, owing to their high physical stability, straightforward preparation, remarkable robustness and low cost.¹⁰

Despite the tremendous interest in molecular imprinting, related research studies are still behind compared to the progress made in other technologies such as nanomaterial synthesis and fluorescent probe techniques. One reason is that the number of functional monomers used in molecular imprinting is limited, which restricts the selectivity and the further applications of MIPs to some extent. The other possibility is that MIT for preparing MIPs is usually neglected to a certain degree, which impedes its applications in various fields. In order to stimulate the fast development of molecular imprinting, we think that MIT should be paid particular attention. As a multidisciplinary technology, MIT should develop rapidly along with the advances in polymer technology, nanotechnology, analytical chemistry, environmental science, biotechnology and so on. The borrowing and integration of related technologies/strategies will lead to significant breakthroughs and accelerate molecular imprinting technology development.

A series of excellent reviews give exceptionally thorough accounts of molecular imprinting,^{1–3,12,13,17–29} and most of them have placed more emphasis on the fundamental aspects and characteristic applications of MIPs instead of the MIT technology. To the best of our knowledge, there are few review articles on novel techniques related to the preparation of MIPs.¹⁰ The continuous development of MIT is required for preparation of versatile MIPs with increasing utilization. The recent advances in various smart MITs, the development of novel polymer materials and their versatile applications particularly in sample pretreatment/chromatographic separation and chemical/biological sensing have been reported.

In this critical review, we focus on the recent advances in molecular imprinting comprehensively, emphasizing on literature studies published in the most recent years, including versatile perspectives of MIT and versatile applications of MIPs. Firstly, we provide a brief overview of the fundamental aspects of molecular imprinting including molecular templates, functional monomers, and cross-linkers by emphasizing on the novel polymer materials. Secondly, we highlight various smart MITs for MIPs, including ingenious MIT (surface imprinting, nano-imprinting, click chemistry, microfluidic on-line synthesis, etc.), special strategies of MIT (multi-template/monomer imprinting,

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dummy imprinting, segment imprinting and so on), and stimuli-responsive MIT (magnetic-, photo-, thermo-, pH- and dual/multi-responsive technology). Thirdly, we discuss the development of novel polymer materials and the applications of these MIP materials in various fields, focusing on sample pretreatment and chromatographic separation, and chemical/biological sensing. Finally, we propose the remaining challenges and future perspectives to improve MIT and utilize it for further developing MIPs with versatile applications by fusion of MIT and various technologies and by using special strategies of MIT, including stimuli-responsive MIT.

2. Fundamentals of MIPs

The process of molecular imprinting involves the polymerization of a functional monomer and a cross-linker around a molecular template.³⁰ Firstly, template–monomer complexes are achieved between a chosen template molecule and a complementary functional monomer, the exact constellation of which distinguishes the different types of molecular imprinting technologies from each other,² as illustrated in Fig. 1. A crosslinking polymerization reaction is then performed around the complex. It is important to note that after the template molecule is extracted, the imprinted sites contain a three-dimensional network presenting pores with the geometry and position of the functional groups complementary to those of the templates.

Usually, there are two main methods to produce MIPs, *i.e.*, based on covalent and noncovalent interactions between the template and the functional monomer. Covalent imprinting, being stoichiometric, ensures that functional monomer residues exist only in the imprinted cavities. It is a typical method

and often uses readily reversible condensation reactions involving boronate esters,³¹ ketals/acetals,³² and Schiff's base.³³ However, covalent imprinting is regarded as a less flexible method since the reversible condensation reactions are limited. Moreover, it is very difficult to reach thermodynamic equilibrium since the strong covalent interactions will result in slow binding and dissociation.³ Noncovalent imprinting can proceed by ionic interactions, hydrogen bonding, van der Waals forces and π - π interactions. Most commonly, the dominant interaction is hydrogen bonding, which often occurs between methacrylic acid (MAA) groups and primary amines in nonpolar solvents.¹² Recently, noncovalent imprinting has become the most popular and general synthesis strategy due to the simplicity of operation and rapidity of binding and removal. However, noncovalent imprinting is sensitive to even slight disruption of the interactions holding the complex together (for example, the presence of water), and it is therefore not very robust.² In order to combine the durability of covalent imprinting and the rapid target uptake of noncovalent imprinting, a new method called semicovalent imprinting has emerged. This method offers an intermediate alternative in which the template is bound covalently to the functional monomer, but template rebinding is based on noncovalent interactions.¹⁰

2.1. Essential elements of molecular imprinting

A typical MIP synthesis protocol contains a template, a functional monomer, a cross-linker, a polymerization initiator and a solvent (porogen). In order to prepare MIPs with superior properties, numerous attempts have been made, since polymerization reaction is affected by many factors, such as the type and amount of monomer, cross-linker, initiator and solvent,

Fig. 1 Five main types of molecular imprinting: (i) noncovalent, (ii) electrostatic/ionic, (iii) covalent, (iv) semicovalent, and (v) metal centre coordination. An imprint molecule is combined with an appropriately chosen functional monomer, through noncovalent, covalent, or ligand (L) to metal (M) interactions with complementary functional groups on the imprint. A complex of the imprint and functional monomer (IC) is formed, in which the functional monomer is bound to the imprint molecule (I) by hydrogen bonding or van der Waals interactions, (II) by electrostatic or ionic interactions (the charges on the imprint and functional monomer may be reversed), (III) through a covalent bond, (IV) through a covalent bond with a spacer (orange), or (V) by ligand–metal or metal–ligand coordination. The functional monomer contains a functional group, Y, which undergoes a cross-linking reaction with an appropriate cross-linker. After polymerization of the complex with a cross-linker to form the solid polymer matrix (grey), the imprint functional monomer interactions are intact. The imprint is removed through washing, cleavage of chemical bonds, or ligand exchange, and leaves behind an imprint cavity with functional groups on the walls. Subsequent uptake of a target molecule is achieved by noncovalent interactions (in types i, ii and iv), the formation of a covalent bond (in type iii), or by ligand exchange (in type v) with target molecules that fit into the cavity and possess the correct structure. The matrix may also participate in target recognition and binding through non-specific surface interactions that result from surface features created around the imprint molecule during cross-linking. Reproduced with permission from ref. 2. Copyright © 2014 The Royal Society of Chemistry.

and the temperature and time of polymerization reaction. As we know, the “three-elements of molecular imprinting” include template molecules, functional monomers and cross-linkers, which should especially be investigated.

2.1.1. Target templates. The ultimate goal of molecular imprinting is to generate MIPs with affinity and specificity comparable to those of the biological receptors so that they can eventually replace such biological entities in real applications. Generally, an ideal template molecule should satisfy three requirements: it should contain functional groups that do not prevent polymerization; it should exhibit excellent chemical stability during the polymerization reaction, and what's more, it should contain functional groups that can form complexes with functional monomers.¹⁰ So far, MIPs have been successfully applied for the recognition and detection of a wide range of small organic molecules. And a lot of ion-imprinted polymers (IIPs) have also been prepared and used for selection and enrichment of metal ions, as seen in Table 1. However, low selectivity is often obtained when the metal ion itself acts as an imprinting template, since the metal ions have the same charges, similar ionic radii and properties.³⁴ Now, the method of using a metal ion and a ligand complex as the actual imprinting template is a new trend in ion-imprinting. The metal ion and ligand complex can easily pre-polymerize with functional monomers, and after the polymerization reaction, the metal ion is removed by elution, leaving specific recognition sites for the metal ion, which contributes to the high adsorption efficiency and selectivity for metal ions. For example, Chen *et al.*³⁴ synthesized novel Hg^{2+} IIPs by a sol-gel process using the chelating agent dithizone, with the dithizone- Hg^{2+} chelate as a template and 3-aminopropyltriethoxysilane as a functional monomer. The resultant Hg-IIPs displayed excellent selectivity toward Hg^{2+} over its organic forms and other metal ions. A latest comprehensive review article on IIPs including main group elements, transition elements, actinides, rare earths, metalloids, anion imprinting and ion-mediated secondary imprinting is recommended for reading.³⁵

Additionally, large structured species for MIPs such as proteins, viruses, and cells have also been reported.^{36–39} However, imprinting of proteins and other biomacromolecules is still a great challenge.^{13,40} Table 1 summarizes the various types of target templates.

2.1.2. Functional monomers. The role of the functional monomer is to form a pre-polymerization complex with the template by providing functional groups. So it is important to

select a suitable functional monomer that can strongly interact with the template and form specific donor–receptor or anti-body–antigen complexes prior to polymerization. Some typical functional monomers are shown in Fig. 2.

Among them, MAA has been used as a “universal” functional monomer due to its hydrogen bond donor and acceptor characteristics. Afterwards, Zhang *et al.*⁴¹ explained why MAA is such a versatile monomer for molecular imprinting, and revealed that the dimerization of MAA modestly enhanced the imprinting effect, as illustrated in Fig. 3. Moreover, it is shown that high molar fractions of MAA would result in the large pore size of polymeric materials and further enhance the binding capacity of the polymers.⁴²

As is well known, the number of functional monomers used in molecular imprinting is limited, which restricts the selectivity and the further applications of MIPs to some extent. It is imperative to devise and synthesize new functional monomers capable of forming strong interactions with templates. Generally, a functional monomer is comprised of two types of units. One is the recognition unit and the other is the polymerizable unit, such as a vinyl double bond and silicon hydroxyl, respectively. Thus, some complex ligands modified by the vinyl group and silicon hydroxyl have been designed and synthesized,^{43–51} as shown in Fig. 4. Among them, compound **34**, with the T group as a recognition element for the imprinting of Hg^{2+} , is used in the sol-gel process.⁴⁸ Besides, in order to synthesize chromo- and fluorogenic MIPs, a naphthalimide-based fluorescent indicator monomer is designed by Wagner *et al.*⁴⁹ A 4-amino-substituted naphthalimide (NI) chromophore is used as the scaffold, and the urea group was responsible for the binding of the analyte. And, the styrene moiety has two roles: on one hand, it contains a reactive linker for copolymerization with the MIP matrix. On the other hand, aryl substitution at the urea commonly increases the receptor's affinity toward anionic guests.⁴⁹ More recently, diacetylene monomers have been used for the preparation of MIPs, since this photopolymerization in the absence of any external catalyst or initiator is very practical for the imprinting process. For instance, König *et al.*⁵⁰ embedded photopolymerizable diacetylene tagged dinuclear zinc cyclen receptors (Zn_2PCDA , compound **36**) in the fluid membrane and they were pre-organized in the presence of a peptide as a template to bind simultaneously two receptor sites. Light-induced polymerization of polydiacetylene resulted in the formation of patterns on the vesicle surface with organized arrays of receptor sites.

Table 1 Common target templates used in molecular imprinting

Type	Typical example
Ions	Pb(II) ; Sr(II) ; Hg(II) ; $\text{CH}_3\text{Hg(I)}$; Cd(II) ; Cu(II) ; Cr(III) ; Fe(III) ; Ni(II) ; UO_2^{2+} ; Th(IV) ; Eu(III) ; As(III) ; PO_4^{3-}
Organic molecules	Pesticides: atrazine; 2,4-dichlorophenoxyacetic acid; benzimidazole fungicides Endocrine disrupting chemicals: bisphenol A; estradiol; oestrone; polycyclic aromatic hydrocarbon (PAH) Explosive: 2,4,6-trinitrotoluene (TNT) Pharmaceuticals: tetracycline; quinolones; propranolol; digoxin; sulfonamides Amino acids and peptides: tyrosine; alanine; tripeptides; helical peptides; cinchona alkaloids; N-terminal histidine sequence of dipeptides Sugars: D-fructose; D-glucose; D-galactose
Biomacromolecules	Lysozyme; adenosine; 3,5-cyclic monophosphate (cAMP); bovine serum albumin(BSA)
Cells and viruses	Tobacco mosaic virus; bovine leukemia virus; dengue virus; gut-homing T

Fig. 2 Common functional monomers used in molecular imprinting procedures. (A) Covalent. (1) 4-Vinyl benzene boric acid; (2) 4-vinyl benzaldehyde; (3) 4-vinyl aniline; (4) *tert*-butyl *p*-vinylphenylcarbonate. (B) Non-covalent. (5) acrylic acid (AA); (6) methacrylic acid (MAA); (7) trifluoromethyl acrylic acid (TFMAA); (8) methyl methacrylate (MMA); (9) *p*-vinylbenzoic acid; (10) itaconic acid; (11) 4-ethylstyrene; (12) styrene; (13) 4-vinylpyridine (4-VP); (14) 2-vinylpyridine (2-VP); (15) 1-vinylimidazole; (16) acrylamide (AAM); (17) methacrylamide; (18) 2-acrylamido-2-methyl-1-propane sulfonic acid; (19) 2-hydroxyethyl methacrylate (HEMA); (20) *trans*-3-(3-pyridyl)-acrylic acid; (21) 3-aminopropyltriethoxysilane (APTES); (22) methylvinyl-diethoxysilane (MVDES); (23) 3-methylacryloxypropyl trimethoxysilane (3-MPTS); (24) glycidoxypolytrimethoxysilane (GPTMS). (C) Semi-covalent. (25) 3-Isocyanatopropyltriethoxysilane (IPTS). (D) Ligand exchange. (26) Cu(II)-iminodiacetate-derivatized vinyl monomer; (27) Fe²⁺/MAA complex.

This imprinting strategy surpasses the existing strategies, which are mainly based on employing metal complex fluorophore conjugates, hybrid biosensors, or combinatorial, pattern-recognition-based methods.⁵⁰

Due to their special structures, a series of cyclic oligosaccharides with a hydrophilic exterior and a hydrophobic cavity, such as β -cyclodextrins (β -CDs), have aroused extensive interest as special candidate monomers for molecular imprinting. β -CDs can form complexes with the template through hydrogen bonding, electrostatic interactions and host-guest interactions.

Moreover, the hydroxyl group on β -CDs can act as a polymerization terminal to form a stable polymer matrix in the presence of a suitable cross-linker.¹⁰ For example, Miyata *et al.*⁵² prepared the bisphenol A (BPA)-imprinted hydrogel using β -CD as a ligand and a minute amount of cross-linker. Sandwich-like CD-BPA-CD complexes were formed between β -CDs with a polymerizable acryloyl group (acryloyl-CD) and BPA, leading to an increase in the apparent crosslinking density of the BPA-imprinted and non-imprinted hydrogels, followed by shrinkage in response to BPA.

Fig. 3 Illustration comparing imprinted (a and b) and nonimprinted polymers (c and d) formed from functional monomers that have or lack the ability to dimerize. Reproduced with permission from ref. 41. Copyright © 2010 American Chemical Society.

2.1.3. Cross-linkers. In the process of polymerization, a cross-linker is used to fix functional monomers around template molecules, thereby forming a highly cross-linked rigid polymer even after the removal of templates. The type and the amount of cross-linker have profound influences on the selectivity and binding capacity of MIPs.³⁰ Usually, a too low amount of cross-linker will result in unstable mechanical properties due to the low cross-linking degree, and an extremely high amount of cross-linker will reduce the number of recognition sites per unit mass of MIPs. So far, the commonly used cross-linkers in free radical polymerization and sol-gel processes are shown in Fig. 5. However, their applications are restricted because the currently available cross-linkers are limited and their molecular structures should meet some rigid requirements. In order to synthesize MIPs with strong diffusion-controlled behavior, new cross-linkers are urgently required. Lei *et al.* synthesized compounds **59** and **60** by Diels-Alder addition of the renewable natural product rosin and maleic anhydride, and subsequent esterification with ethylene glycol and acrylic acid. These new cross-linkers have many advantages as follows. Firstly, the characteristic phenanthrene skeleton (Fig. 5) possesses excellent rigidity. Secondly, compound **60** contains three double bonds, which can participate in polymerization reactions and improve the degree of crosslinking to help maintain the structure of the imprinted cavity of the template molecule, even in an organic solvent. In addition, rosin, as a raw material for separating and purifying the effective ingredients of Chinese herbs, is biodegradable and non-toxic.^{53,54}

2.1.4. Porogens. Porogens (porogenic solvents) generally act as dispersion media and pore forming agents in the polymerization process. So they also play an important role in

polymerization. Usually, solvents used for MIP synthesis are 2-methoxyethanol, methanol, tetrahydrofuran (THF), acetonitrile, dichloroethane, chloroform, *N,N*-dimethylformamide (DMF) and toluene.⁵⁵ The polarity of porogens can affect the interaction between the template molecule and the functional monomer, and therefore the adsorption properties of MIPs, especially in non-covalent interaction systems. Non-polar and less polar organic solvents, such as toluene, acetonitrile and chloroform, are often used for non-covalent imprinting to obtain good imprinting efficiency, since the adsorption properties and morphology of polymers are dependent on the types of solvents used. To evaluate the selection processes of monomers and solvents for molecular imprinting and to have an insight into MIP selectivity, the use of theoretical calculations is very important. Saloni *et al.*⁵⁶ studied the effects of solvents on monomer-template binding energy using four solvents: acetone, acetonitrile, chloroform, and methanol. And density functional theory (DFT) had been used for all structural, vibrational frequency and solvent calculations.⁵⁶

More recently, room temperature ionic liquids (RTILs) have been reported as an interesting class of solvents with unique characteristics. The negligible vapor pressure of RTILs can help reduce the problem of MIP bed shrinkage and they can also act as pore templates in the polymerization reaction. Moreover, RTILs can accelerate the synthesis process, improving the selectivity and adsorption of *trans*-asconitic acid imprinted organic polymers.⁵⁷ For example, McCluskey *et al.*⁵⁸ explored the potential use of RTILs as porogens. RTILs including [BMIM][BF₄], [BMIM][PF₆], [HMIM][PF₆] and [OMIM][PF₆] attained satisfactory selectivities and rebinding capacities for propranolol MIPs.⁵⁸

Fig. 4 Chemical structures of new functional monomers used in molecular imprinting. (**28**) Benzo-15-crown-5-acrylamide; (**29**) 1-hydroxy-2-(prop-2'-enyl)-9,10-anthraquinone; (**30**) 1-hydroxy-4-(prop-2'-enyloxy)-9,10-anthraquinone; (**31**) 5-vinyl-8-hydroxyquinoline; (**32**) 4-[(*E*)-2-(4'-methyl-2,2'-bipyridin-4-yl)vinyl]phenyl methacrylate (BSOMe); (**33**) 4-vinylphenylazo-2-naphthol; (**34**) 3-isocyanatopropyltriethoxysilane (IPTS) bearing T bases (T-IPTS); (**35**) *N*-ethyl-4-(*N*-[4-vinylphenyl]hydrazinecarboxamidyl)-1,8-naphthalimide; (**36**) diacetylene tagged dinuclear zinc cyclen receptors (Zn_2PCDA).

2.1.5. Initiators. As we know, the vast majority of MIPs are commonly prepared by free radical polymerization (FRP), photopolymerization, and electropolymerization. FRP can be initiated either thermally or photochemically for a wide range of functional groups and template structures. Aside from the peroxy compounds, azo compounds are extensively used as initiators, such as compounds **61**, **62** and **63**,³⁰ as listed in Fig. 6. Among them, azobisisobutyronitrile (AIBN) is most conveniently used at the decomposition temperatures of 50–70 °C. To ensure the polymerization reaction, removal of the dissolved oxygen from polymerization solutions immediately prior to proliferation is very important. And oxygen can be cleared by bubbling an inert gas like nitrogen or argon.

2.2. Preparation procedures

The selection of an appropriate preparation procedure is critical for the production of MIPs with desirable properties. Generally, the mechanisms of MIP preparation include free-radical polymerization and sol-gel processes. The former is more popular and general. Bulk polymerization, the most widely used free-radical polymerization, includes mechanical grinding and sieving steps to obtain small particles, leading to a lower MIP binding capacity with respect to theoretical values. Moreover, this method needs a large amount of template molecules. In order to overcome these drawbacks of bulk polymerization, more sophisticated and complex polymerization techniques have been

Fig. 5 Chemical structures of common cross-linkers used in free radical polymerization. (A) Covalent; (B) non-covalent; (C) chemical structures of common cross-linkers used in sol-gel process; (D) chemical structures of new cross-linkers. (A) Covalent: **(37)** triallyl isocyanurate (TAIC); **(38)** bis-(1-(*tert*-butylperoxy)-1-methylethyl)-benzene (BIPB); **(39)** dicumyl peroxide (DCP); (B) non-covalent: **(40)** ethylene glycol dimethacrylate (EGDMA); **(41)** *N,N'*-methylene diacrylamide (MBAA); **(42)** divinylbenzene (DVB); **(43)** 1,3-diisopropenyl benzene; **(44)** *N,N'*-1,4-phenylenediacrylamine; **(45)** 2,6-bisacryloylamidopyridine; **(46)** *N,O*-bisacryloyl-phenylalaninol; **(47)** 3,5-bis(acryloylamido)benzoic acid; **(48)** 1,2-diacryloyl piperazine; **(49)** tetramethylene dimethacrylate; **(50)** *N,O*-bismethacryloyl ethanolamine (NOBE); **(51)** glycidylmethacrylate (GMA); **(52)** trimethylpropane trimethacrylate (TRIM); **(53)** pentaerythritol tetraacrylate; (C) chemical structures of common cross-linkers used in the sol-gel process. **(54)** Tetramethoxysilan (TMOS); **(55)** tetraethoxysilane (TEOS); **(56)** phenyltriethoxy silane (PTEOS); **(57)** phenyltrimethoxy silane (PTMOS); **(58)** diphenyldiethoxysilane (DPDES); (D) chemical structure of new cross-linkers: **(59)** maleic rosin glycol acrylate (MRGA); **(60)** ethylene glycol maleic rosin acrylate (EGMRA).

proposed to obtain many different forms of MIPs, such as MIP particles, membranes, *in situ* prepared monoliths, and molecularly imprinted monolayers. Particles have been prepared by

a variety of attractive polymerization methods, such as suspension polymerization, emulsion polymerization, seed polymerization and precipitation polymerization.

Fig. 6 Chemical structures of common initiators used in molecular imprinting. (61) Azobisisobutyronitrile (AIBN); (62) azobisdimethylvaleronitrile (ADVN); (63) 4,4'-azo(4-cyanovaleric acid) (ACID); (64) benzoylperoxide (BPO); (65) dimethylacetal of benzyl (BDK); (66) potassium persulfate (KPS).

A particularly simple procedure for the preparation of porous MIPs is suspension polymerization. For suspension polymerization, the traditional water medium, perfluorocarbon liquid and mineral oil can be used as the continuous phase, however, the method tends to produce a broad size range from micrometers to millimeters and displays poor recognition due to the disturbance of the dispersing medium, which is not suitable for solid phase extraction (SPE) applications.^{59–61} Emulsion polymerization is an effective method to produce high yield, mono-dispersed MIP particles either oil-in-water (O/W) or water-in-oil (W/O), which suffers from the disturbance of remnants of surfactants.^{62,63} Controlled diameter spherical MIPs have been directly prepared and modified *in situ* by using a multi-step swelling method, also called seed polymerization. The particles obtained using this technique are comparatively monodisperse in size and shape and well suited for chromatographic applications, however, the multistep procedure is time-consuming, and the aqueous suspensions used could interfere with imprinting and thus lead to a decrease in selectivity.^{64–66} More uniform sized MIP microspheres can be obtained by the method of precipitation polymerization, since the growing polymer chains can grow individually in the dilute reaction system without overlap or coalescence. As the polymer is formed, microspherical particles will precipitate from the solution. Compared to bulk polymerization, precipitation polymerization needs a large amount of organic solvents and a very strict control of reaction conditions since a few factors like the polarity of solvents, polymerization temperature and stirring speed have great effects on the polymer particle size.^{67–69}

Monolithic MIPs have also been prepared by a simple, one-step, *in situ*, free-radical polymerization process within the confines of a chromatographic column without the need for grinding, sieving and column packing.^{70,71} By using silane chemistry or surface “grafting to” approaches, membranes and molecularly imprinted monolayers are generally formed on an appropriate support of fibers or films. In addition to the polymerization techniques mentioned above, electrochemical polymerization, electrodeposition, grafting on monolithic columns, photografting, and sol-gel methods have also been employed.

In the sol-gel process, tetraalkoxysilane precursors, such as tetramethoxysilane (TMOS) and tetraethoxysilane (TEOS), first hydrolyze to form a colloidal solution (a sol), and then polycondense to form highly cross-linked silica materials (or gels).² Actually, the sol-gel process has distinct advantages such as the ease of fabrication at room temperature without the problem of thermal or chemical decomposition and the use of eco-friendly reaction solvents, such as ultrapure water and ethanol, which is quite different from the general solvents used for free radical polymerization, such as chloroform, acetonitrile and toluene.¹⁰ The typical preparation procedures and imprinting methods of MIPs are summarized in Table 2.

2.3. Characterization methods

Traditionally, the morphologies of MIPs are investigated by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Atomic force microscopy (AFM) and various fluorescence techniques have also played important roles in the characterization of thin-film MIPs. Actually, the use of nuclear magnetic resonance (NMR), infrared (IR) and UV-Vis spectroscopies for characterizing monomer-template interactions is becoming an essential aspect of MIP design, either for the screening of monomers for interaction with the template or for the validation of computational design data. Moreover, the significant increase in the number of spectroscopic studies of ligand-MIP interactions implies a new trend. The use of X-ray absorption fine structures, diffraction studies and X-ray photoelectron spectroscopy (XPS) have become more prominent.¹ The specific surface areas and pore sizes of the polymers can be measured *via* Brunauer-Emmett-Teller (BET) analysis by nitrogen adsorption experiments. Thermal stability is examined by thermogravimetric analysis (TGA). For magnetic materials, such as Fe₃O₄, magnetic properties are analyzed by using a vibrating sample magnetometer (VSM). The typical characterization methods for MIPs are listed in Table 3.

3. Smart MIT for MIPs

The aforementioned traditional preparation procedures and imprinting methods have been continuously used and improved

Table 2 Comparison of different preparation procedures and imprinting methods of MIPs

Mechanism	Imprinting method	Advantage	Disadvantage
Free-radical polymerization	Bulk polymerization	Rapidity and simplicity in preparation; no requirement for sophisticated or expensive instrumentation; purity in the produced MIPs	Time-consuming of grinding, sieving; irregular particles in shape and size; low affinity sites
	Suspension polymerization	Simple process with one step polymerization; spherical particles	Big particle size (a few to a few hundred micrometres); poor recognition
	Emulsion polymerization	High yield, monodispersed polymeric particles; water-soluble polymers	Suffers from the presence of remnants of surfactants; low imprinting capacity
	Seed polymerization	Controllable regular spherical particles; monodispersity; suitable for HPLC	Laborious process; time-consuming
Sol-gel process	Precipitation polymerization	One single preparative step; high-quality, uniform and spherical particles	Large amount of template; high dilution factor
	Sol-gel	Ease of fabrication at room temperature; eco-friendly reaction solvent	Lack of polymerization method and the functional monomer

Table 3 Typical characterization methods and their main purposes for MIPs

Purpose	Characterization method
Morphological evaluation	SEM, TEM, AFM
Screen of monomers for interaction with template or for the validation of computational design data	NMR, IR, UV-Vis
Structure analysis	X-ray absorption fine structure, diffraction and XPS
Measure the specific surface areas and pore sizes of the polymers	Nitrogen adsorption
Thermal stability evaluation	TGA
Magnetic property evaluation	VSM

for synthesizing MIPs with improved performance, however, the resultant MIPs still have many problems, such as template leakage, low binding capacity, irregular material shape, and incompatibility in aqueous media, which have greatly obstructed the applications of MIPs. As a result, various smart preparative technologies and strategies of MIT have emerged to cope with the problems jointly by combining with the developed traditional preparation procedures, and therefore various novel excellent MIPs with a wide range of applications have been prepared. Smart MIT is classified into three main types, *i.e.*, ingenious technologies (surface imprinting technology, nanoimprinting technology, *etc.*), special imprinting strategies (the multi-template/functional monomer imprinting strategy, the dummy/segment imprinting strategy, *etc.*) and stimuli-responsive imprinting technologies (magnetic/thermo-responsive technology, dual/multi responsive technology, *etc.*), and will be emphatically introduced in this section as follows.

3.1. Ingenious MIT for MIPs

With the development of molecular imprinting, various novel technologies have emerged, such as surface imprinting, nanoimprinting, living/controlled radical polymerization, porous polymer synthesis, click chemistry cycloaddition reaction, microfluidic on-line synthesis and solid-phase synthesis. The introduction of these ingenious technologies into the molecular imprinting strategy will open up new opportunities for interesting applications.

3.1.1. Surface imprinting technology. Mosbach^{72,73} first reported the surface imprinting technology to prepare imprinted materials by controlling templates to locate at the surface or in the proximity of materials' surface to create more

effective recognition sites. This attempt resulted in the complete removal of template molecules and provided a good accessibility to target molecules, which is especially suited for imprinting macromolecules, such as proteins,⁷⁴ cells³⁹ and viruses,⁷⁵ since their large sizes usually hinder the templates from both leaving and rebinding the imprinted sites in traditional MIPs. For example, Qian *et al.*⁷⁶ used bovine serum albumin (BSA) as the template protein immobilized on the surface of silica nanoparticles to synthesize the surface modified MIPs. The results showed excellent selectivity and recognition ability for the protein template, as many specific recognition sites for the protein template were generated on the surface of MIPs. Zhang *et al.*⁷⁷ employed hierarchical imprinting, a new kind of surface imprinting technique, to prepare protein imprinted materials for the selective depletion of human serum albumin (HSA) from the human serum proteome. Compared with MIPs prepared by bulk polymerization, the resultant MIPs prepared by the hierarchical imprinting technique showed the advantages of excellent selectivity, high binding capacity, fast adsorption kinetics and good synthesis reproducibility.⁷⁷ However, the surface area of the substrate is so limited that the total amount of the resultant imprinting cavities is always very small. Therefore, finding and preparing large surface area substrates is an important task to attain better performances in surface imprinting.

3.1.2. Nanoimprinting technology. Recently, the development of molecular imprinting nanotechnologies has attracted considerable research interest in that nanostructured MIPs (N-MIPs) show significantly improved characteristics in contrast to bulk MIPs, which are summarized in Table 4. N-MIPs have higher surface area-to-volume ratios, providing a good

Table 4 Comparison of the properties of bulk MIPs and nanostructured MIPs

Bulk MIPs	N-MIPs
Low surface-to-volume ratio, difficult to elute	High surface-to-volume ratio, greater total active surface area per weight unit of polymer
Broad distribution of binding sites with varying affinity, high level of non-specific binding sites	Similar affinity for all binding sites, high level of specific binding sites
Insoluble material, difficult to process, bulk, batch-to-batch variability	Soluble nanoparticles well dispersing in solution, better control of manufacturing process
Difficult to access the empty cavities encased within rigid matrix	Imprinted cavities being more easily accessible to the templates, improving binding kinetics and facilitating the template removal process
High possibility of template leaking from the polymer	Traces of template being easily removed
Limited prospects for <i>in vivo</i> applications	Biological activity showing infinite prospects for <i>in vivo</i> applications

accessibility to target species and leading to the improvement of binding kinetics and binding capacity, as illustrated in Fig. 7A. As seen, the templates located within x -nanometers from the surface can be removed from the bulk materials with a scale of d , and the resultant effective volume of imprinted materials that can rebind target species is $[d^3 - (d - 2x)^3]$. In general, the x value is very small for bulk materials. When the imprinted materials with the same size were prepared in the form of nanostructures with a scale of $2x$ nm, all of the templates can be completely removed from the highly cross-linked matrix, and the resultant sites are all effective for target species.⁷⁸ Thus, nanoimprinted materials are expected to improve the binding capacity, binding kinetics, and site accessibility of imprinted materials.

N-MIPs with different forms such as nanoparticles, nanotubes and nanowires have been synthesized by using different nanotechnologies,^{78–80} as illustrated in Fig. 7B. Zhang *et al.*⁷⁸ reported the surface imprinting of 2,4,6-trinitrotoluene (TNT) molecules at the surface of silica nanoparticles. The uniform core-shell particles with TNT-imprinted polymer nanoshells had a high density of effective recognition sites, which was nearly 5-fold higher than that of traditional imprinted materials. The results provided a new strategy for preparing nanosized imprinted materials. Subsequently, the same group⁷⁹ developed molecularly imprinted silica nanotubes for the recognition of TNT molecules. Most of the recognition sites were situated at the inside and outside surfaces of tubular walls and in the proximity of the two surfaces due to the ultrathin wall thickness of only 15 nm, providing a better site accessibility and lower mass-transfer resistance. Moreover, the maximum uptake capacity of the nanotubes is nearly 3.6 times that of bulk particles, which showed that the density of effective imprinted sites in nanotubes was much higher than that in normal bulk particles. Yang *et al.*⁸⁰ presented a technique for the preparation of polymer nanowires with the protein molecule imprinted and binding sites at the surface. First, the template protein molecule was immobilized on the pore walls of the nanoporous alumina. The nanopores were then filled with a mixture of acrylamide and N,N' -methylene-bisacrylamide. And then polymerization was initiated *via* oxidation with ammonium persulfate. After removing the alumina membrane by chemical dissolution, polymer nanowires were imprinted with the protein molecule and binding sites were generated on the surface. By the use of nanotechnologies and

surface chemistry, N-MIPs with inflexible shape and size have been synthesized and the imprinted sites were located at, or close to, the surfaces, which have greatly improved the removal of templates and the binding capacities and kinetics of molecular recognition, compared with the traditional bulk MIPs. Furthermore, these imprinting protocols may also be employed to imprint biomacromolecules, such as DNA and viruses.

Combining molecular imprinting with nanotechnology has appreciably boosted up both sensitivity and selectivity for the recognition of a wide variety of analytes, ranging from small molecules to large proteins and macromolecules. The large surface area offered by imprinted nanostructures exposed more binding sites to attract the target analyte, which will drive the great development of MIP materials with promising applications. It is not surprising that many research groups have reviewed the development of molecular imprinting nanotechnologies.^{81–83}

3.1.3. Living/controlled radical polymerization technology.

Unfortunately, preparation of regular MIPs is not easy in conventional radical polymerization, since the rate of chain propagation cannot be controlled. The resultant polymers generally have a broad size distribution due to side reactions, including chain transfer and termination.⁸⁴ In order to solve this problem, the living/controlled radical polymerization (LCRP) techniques have emerged, which can thermodynamically control the polymer chain growth processes with negligible chain termination and more constant and much slower rates, resulting in a homogeneous and narrow distribution of polymer networks compared to that of the highly crosslinked microdomains in the heterogeneous polymer networks prepared by traditional free radical polymerization.⁸⁵ Among the LCRP techniques, atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT) polymerization are most promising.

ATRP was discovered in 1995.^{86–88} It originates from the atom transfer step, which is the key elementary reaction responsible for the uniform growth of the polymeric chains. By using transition metal complexes as reversible halogen atom transfer reagents, ATRP can control a fast, dynamic equilibrium between the dormant species (alkyl halides) and active radicals.⁸⁹ In the early stage, ATRP had been successfully applied in the molecular imprinting field for the generation of MIPs.^{90–92} Unfortunately, its application was limited in the preparation of MIP films and the major limitation for this technique in the synthesis

Fig. 7 Schematic representation of nanoimprinting. (A) Schematic illustration of the distribution of effective binding sites in the imprinted bulk materials and the nanosized, imprinted particles after the removal of templates. Reproduced with permission from ref. 78. Copyright © 2007 American Chemical Society. (B) Schematic diagrams of nanoimprinting process for different forms of N-MIPs. (a) Imprinting on the SiO_2 support for the formation of core-shell imprinted nanoparticles. SiO_2 core particles were first modified with the vinyl functional monomer, followed by initiating an imprinting polymerization reaction, leading to the formation of imprinted shells at the surface of silica particles. Adapted from ref. 78. (b) Imprinting on silica nanotubes for the formation of imprinting nanotubes. SiO_2 nanotubes were first modified with APTS, followed by the sol-gel process, leading to the formation of imprinted shells at the surface of SiO_2 nanotubes. Adapted from ref. 79. (c) Imprinting on a sacrificial membrane support by employing an immobilized protein template approach for the formation of imprinted nanowires. The template molecule was firstly immobilized on the inner wall of a porous alumina membrane, followed by imprinting polymerization reaction, leading to the formation of nanowires by removing supporting alumina. Adapted from ref. 80.

of MIPs is the narrow range of monomers used. Typical monomers used for molecular imprinting such as methacrylic acid and trifluoromethyl acrylic acid are incompatible with methacrylamide and vinylpyridine, so it is difficult to achieve high monomer conversion with the metal-ligand complex.⁹³ Very recently, ATRP has succeeded in the preparation of surface initiated and emulsion type MIPs, where acidic monomers like MAA have been employed, which is an important development in the MIP field since it considerably widens the range of functional monomers. For example, Zhao *et al.*⁹⁴ described the controlled synthesis of porous core-shell MIPs for the selective recognition of 2,4-dichlorophenoxyacetic acid (2,4-D) via surface initiated ATRP.

Yan *et al.*⁹⁵ prepared molecularly imprinted nanoparticles through ATRP emulsion polymerization for tetracycline. Using this technique, the time of polymerization was dramatically shortened as compared to that of conventional radical polymerization and the obtained MIPs had a narrow diameter distribution. Besides, Haupt *et al.*⁹⁶ described a new method by using photoinitiated ATRP for the drugs testosterone and *S*-propranolol. The synthesis took place at room temperature and was compatible with acidic monomers, and therefore the two major limitations were overcome for the use of ATRP with MIPs, which widens the range of functional monomers and molecular templates used in ATRP. ATRP can also be used to graft polymer brushes onto the

obtained MIP microspheres to improve their surface hydrophilicity, thus leading to their pure water-compatible binding properties.⁹⁷

The RAFT technique was first reported by Moad and his co-workers⁹⁸ and it is considered to be as simple as introducing a suitable chain transfer agent (also known as a RAFT agent, normally a thiocarbonylthio compound) into a conventional free radical polymerization system. Compared to ATRP, RAFT polymerization has the advantage of readily synthesizing well-defined polymers with a wider range of monomers (almost all monomers suitable for the conventional free radical polymerization) under mild reaction conditions. Furthermore, it can also be used in all modes of free radical polymerization such as precipitation, emulsion, and suspension polymerizations.^{84,99,100} More recently, Chen *et al.* reported the successful synthesis of atrazine MIPs by RAFT precipitation polymerization. The resultant RAFT-MIPs demonstrated a uniform spherical shape with a rough surface containing significant amounts of micropores, leading to an improvement in imprinting efficiency compared with that of the MIPs prepared by traditional precipitation polymerization (TR-MIPs).^{101,102} Zhang *et al.*¹⁰³ used the RAFT technique to synthesize MIPs for vanillin by suspension polymerization. The results showed a smaller particle size, higher molecular adsorption, and considerable binding specificity toward vanillin than those prepared by suspension polymerization. Besides, water-compatible and narrowly dispersed MIPs could be obtained by RAFT polymerization since the functional groups of the RAFT agent could be grafted onto the polymer.^{104,105} All these promising results demonstrate that ATRP and RAFT have great potential in the molecular imprinting field.

3.1.4. Hollow porous polymer synthesis technology. Functionalized hollow porous polymers have gained great popularity in the controlled release of drugs and the removal of pollutants. The main advantage of using porous polymers is that their controllable hole structures, which can readily enhance the mass transfer of target species. The methods for the fabrication of hollow polymer microspheres include self-assembly,¹⁰⁶ templating techniques,¹⁰⁷ suspension polymerization¹⁰⁸ and emulsion polymerization.¹⁰⁹ The introduction of hollow porous polymers into molecular imprinting can provide higher binding capacity and faster kinetics for the target template molecules, as shown in Fig. 8A.¹¹⁰ Hollow structures are superior to core-shell structures or other bulk materials due to a large number of binding sites in the proximity of the interior surface formed by the complete removal of the template molecules through the open interior surface, which is beneficial for the target molecules easily diffusing into the interior sites of hollow spheres. For example, Zhang *et al.*¹¹⁰ reported the TNT-imprinted hollow polymer microspheres by imprinting TNT molecules in the single-hole hollow polymer microspheres. The results suggested that the binding capacity of hollow spheres was almost twice that of pure imprinted shells on the core-shell particles. And it was also found that the imprinted sites on the interior surface or in the proximity of the interior surface played a key role in the enhancement of the rebinding ability of the single-hole hollow spheres.¹¹⁰ Chen *et al.* prepared hollow porous MIPs by swelling polymerization, which were used

for selective and specific recognition of triazines¹¹¹ and Sudan I.¹¹² The obtained hollow porous MIPs displayed excellent characteristics, such as higher binding capacity and faster mass transfer owing to the hollow core with hole(s) in the shell, compared to those of core-shell structures. The same group also prepared another hollow MIP based on surface imprinted hollow vinyl-SiO₂ particles and applied it for the selective recognition and adsorption of estradiol.¹¹³ The resultant hollow MIP demonstrated improvements in the imprinting factor and binding kinetics, which suggested that the hollow imprinted structure not only generated more recognition cavities on the imprinted shell, but also increased the adsorption capacity per unit mass of MIP.¹¹³

3.1.5. Click chemistry cycloaddition reaction technology. Click chemistry was first described in 2001 by Sharpless and co-workers,¹¹⁴ which is a useful and promising synthesis tool owing to its high efficiency with a high tolerance of functional groups and solvents, as well as moderate reaction temperatures.¹¹⁵ Among click reactions, the copper-catalyzed azide-alkyne cycloaddition represents an important contribution, which has been applied to nearly all the areas of chemistry from drug discovery to materials science.¹¹⁶ By introducing a wide range of different functional chains into the polymer, click chemistry attracts great attention to achieve modification of materials and efficient bioconjugation. In 2010, Li *et al.*¹¹⁷ demonstrated an efficient and robust route for the preparation of well-defined MIPs based on RAFT polymerization and click chemistry. The prepared imprinted beads with homogeneous polymer films (a thickness of about 2.27 nm) exhibited obvious imprinting effects towards the template, fast template rebinding kinetics and an appreciable selectivity over structurally related compounds.¹¹⁷ Shannon *et al.*¹¹⁸ developed a method to graft MIP thin films onto Au electrodes using click chemistry. The detection limit of the clicked-on MIP sensor for hydroquinone (HQ) was found to be about four times lower than using the coated-on MIP sensor. In addition, the sensitivity of the clicked-on MIP sensor was found to be approximately three times greater than the coated-on MIP sensor. Ye *et al.* synthesized several multifunctional MIP composites by using alkynyl- or azide-modified MIP core-shell nanoparticles as building blocks.^{119–121} However, these conjugation strategies based on the click reaction need extra processes to introduce a “clickable” shell on the surface of MIP nanoparticles, which are tedious and may affect the surface properties of the MIP nanoparticles and even lead to unexpected nonspecific binding effects. Then, the same group¹²² developed a new and simple conjugation chemistry that allowed unmodified MIP nanoparticles to be easily linked to other functional materials based on photocoupling chemistry, as schematically illustrated in Fig. 8B. Upon light activation, perfluorophenyl azide (PFPA) can be converted to a highly reactive nitrene intermediate that can covalently link to organic materials through C–H insertion. By using this system, ordinary MIP nanoparticles can be conjugated with other types of nanoparticles for preparing multifunctional composite materials by photochemical reactions.

3.1.6. Microfluidic on-line synthesis technology. Since the introduction of the concept of Micro total analysis systems or

Fig. 8 representation of ingenious technologies. (A) The schematic illustration and an experimental example of preparation of MIP nanocapsules with a single hole: single-hole nanocapsules were synthesized by the consecutive two-step polymerization at the surface of carboxyl-capped polystyrene (PS) beads, followed by the dissolution of PS cores with tetrahydrofuran; adapted from ref. 110. (B) Preparation of $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{PAA}@\text{PFP}$ by photoconjugation of MIP nanoparticle with PFP modified magnetic nanoparticle via click reaction. Adapted from ref. 122. (C) Schematic diagram showing microfluidic platform for rapid synthesis of NPs. (a) The NP precursors enter a microfluidic chip with micromixer at different ratios by syringe pumps producing a library of NPs; (b) micromixer in the chip will complete mixing and reacting of streams and (c) image of NPs produced by the system showing from precursors at the beginning to growing/product at the end of the outlet. (D) Schematic diagram showing the mode of operation of the automated solid-phase MIP nanoparticle synthesizer. PC control (pump flow rate, temperature, irradiation time, washing and product collection); syringe pumps, for polymerization mixture and elution solvents; heating rod, up to 60 °C; cooling jacket, down to 0 °C; packed solid phase, immobilizing template. Adapted from ref. 131. Copyright © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

μ TAS in 1990,¹²³ also called lab-on-a-chip or miniaturized analysis systems, the science and technology of manipulating fluids in microchannels has grown explosively and impacted a range of applications including drug delivery, biological analysis and nanoparticle synthesis. A microfluidic chip has been designed for the synthesis of both organic and inorganic materials,^{124,125} which have enabled the synthesis of nanoparticles with narrower size distributions and improved the accuracy and efficiency of processing. The use of microfluidics has great advantages including the simplicity and reproducibility of device fabrication and potentially lower cost of materials owing to the ability to handle small volumes.^{126,127} These advantages make the use of microfluidics ideal for the development of a platform that enables rapid synthesis and optimization of nanoparticles, which can be controlled very precisely through tuning the relative flow rates of immiscible fluids to induce droplet formation, as schematically displayed in Fig. 8C.

More recently, microfluidic devices have been used for polymerization reactions, which can provide a novel route for the preparation of monodisperse molecular imprinting particles with highly controlled size and shape. Choi *et al.* demonstrated a novel microfluidic approach, which presented continuous and uniform MIP particle generation.¹²⁸ Lu *et al.* proposed an improved synthesis method for the preparation of Pb(II) imprinted chitosan (Pb(II)-CS) beads with uniform size and porous morphology by combining the microfluidic technique with crosslinking solidification.¹²⁹ In 2015, Takeuchi *et al.*¹³⁰ synthesized monodispersed submillimeter-sized microgels by inverse suspension polymerization in W/O droplets prepared using a microchannel. By changing the flow rate of the oil phase and using a constant aqueous phase flow rate, the microgel size was easily controlled from 320 to 60 μ m while maintaining monodispersity.

3.1.7. Solid-phase synthesis technology. As we know, the traditional methods for preparing MIPs are labor-intensive and one-off batch processes, which are not suited for industrial production. Piletsky *et al.*¹³¹ first reported the solid-phase synthesis of MIP-NPs. Unlike traditional molecular imprinting employing soluble templates, solid-phase synthesis relies on templates immobilized onto the surface of a solid support. The support is placed in the reactor containing the monomer/initiator mixture, and the MIP-NPs are synthesized on the solid support. The advantage of this method is that all binding sites have the same orientation and are located at the surface of the particle, which can improve the homogeneity of binding sites and their accessibility.¹³² Moreover, the synthesis and subsequent affinity purification can easily be performed using computer controlled instruments, which are applicable in industrial manufacturing. The mode of operation of the automated solid-phase MIP nanoparticle synthesizer is schematically shown in Fig. 8D.¹³¹

Haupt *et al.*¹³³ described a solid-phase synthesis approach to prepare MIP-NPs specific for trypsin. An affinity ligand of the protein was attached to the glass beads and then MIP-NPs were synthesized and purified *in situ* on glass beads packed in a column which served at the same time as a reactor and an

affinity purification column. The advantage of the method was that all binding sites had the same orientation and were located at the surface of the glass beads, thus improving binding site homogeneity and accessibility.¹³³ In 2014, Poma *et al.*¹³⁴ developed an automated chemical reactor for solid-phase synthesis of MIP-NPs in water for proteins such as trypsin, pepsin A and α -amylase. The automatic method offered short synthesis/purification times, thus making it potentially suitable for industrial applications and production.¹³⁴

3.2. Special strategies of MIT for MIPs

During the development process, besides ingenious technologies, some special imprinting strategies have emerged, such as multi-template imprinting, multi-functional monomer imprinting, dummy imprinting and segment imprinting strategies. Related processes and mechanisms are schematically illustrated in Fig. 9. The introduction of special imprinting strategies will effectively push forward the advancement of the molecular imprinting field.

3.2.1. Multi-template imprinting strategy. Generally, the preparation of MIPs primarily involves a single template molecule/ion. However, the single template based MIPs restrict the applications of MIPs in the simultaneous recognition and removal of more than one target.¹³⁵ Actually, by using several targets/species as templates, known as multi-template imprinting, to produce multiple types of recognition sites in a single polymer material, schematically displayed in Fig. 9A, different classes of species can be extracted, separated, assayed, detected, or otherwise analyzed simultaneously, which can greatly widen the MIPs' practical applications.¹³⁶ The simultaneous separation of several compounds on one stationary phase would be of use, for example, in the analysis of pharmaceutical formulations; alternatively, a detector incorporating an MIP into multiple templates would be capable of detecting one (or more) possible contaminants in biological or environmental systems.¹³⁶ In addition, multi-template MIPs can simultaneously recognize and remove multi-targets, which is highly desirable for sustainable development.

The first example of multiple-template imprinting was reported by Sreenivasan and Sivakumar¹³⁷ in 1999, and in 2001 Dickert *et al.*⁷² introduced the idea of "double molecular imprinting". Subsequently, examples of MIPs prepared by multiple-template imprinting have been demonstrated by different groups.^{136,138–141} More recently, three or more templates for preparation of MIPs have been developed. For example, Venkatesh *et al.*¹³⁵ reported the preparation of multi-template MIPs using three p-type pharmaceutical chemicals mixed as the template, which showed significant merits over conventional adsorbents in water purification and wastewater treatment, especially more desirable for the reduction of the cost of treatment compared with single-time-use activated carbon. Krupadam *et al.*¹⁴² described a non-covalent molecular imprinting method to prepare MIPs by using a mixture of six kinds of polycyclic aromatic hydrocarbons (PAHs) as a template. Chen *et al.*¹⁴³ demonstrated a multi-molecular imprinting approach for PAHs by using a mixture of 16 kinds of PAH standards

Fig. 9 representation of special imprinting. (A) Schematic diagram of multiple template imprinting for multi-analyte binding. (B) Schematic diagram of multiple functional monomers imprinting for Pb^{2+} . Adapted from ref. 148. (C) Schematic diagram of dummy imprinting. Using trinitrophenol (TNP) as the dummy template for determination of 2,4,6-trinitrotoluene (TNT) based on the fact that TNT has a similar structure as TNP. (D) Schematic diagram of fragment imprinting. Using part of target molecular as the template, recognition sites were created by the removal of the template molecule, the obtained recognition sites can bind the whole target molecule based on the fact that target molecule has a fragment structure like the template molecule. Adapted from ref. 161.

as a template. Such multi-template imprinting systems could provide great application potential for the simultaneous recognition, enrichment, determination and removal of multiple target analytes, and thus could offer high-throughput methods for target monitoring and elimination. Meanwhile, however, it

should be noted that the selectivity of multi-template MIPs is reduced compared to those synthesized using a single template, which is most probably due to the dilution of the number of binding sites for each template and the increased remixing effects of multiple analytes. Indeed, the imprinting effect of

multi-template MIPs is a balance of the imprinting performances for multiple target templates.

3.2.2. Multi-functional monomer imprinting strategy. Recently, the non-covalent approach has been most frequently used in molecular imprinting. As is well known, the non-covalent binding between the target template molecules and the functional monomers can be enhanced by multipoint interactions.¹⁴⁴ Thus, combinations of two or more functional monomers which are complementary to different regions of the template molecules have become quite necessary to utilize and develop.¹⁴⁴

The first use of two different functional monomers for MIPs was reported by Mosbach *et al.*⁷³ in 1993. Then more examples of MIPs prepared by combinations of functional monomers were demonstrated by different groups.^{145–148} For example, Haruki *et al.*¹⁴⁵ prepared MIPs toward native lysozyme promoting the folding of chemically denatured lysozyme by using acrylamide, MAA, and 2-(dimethylamino)ethyl methacrylate as functional monomers. High refolding yield was achieved due to multi-noncovalent interaction between the template molecule and functional monomers.¹⁴⁵ Zhang *et al.*¹⁴⁷ developed an efficient method for preparation of bifunctional monomer rhein MIPs. By combining MAA with 4-VP, which are complementary to different regions of the template, the synthesized MIPs with bifunctional monomers showed a significantly enhanced imprinting effect and higher adsorption capacity for the template rhein compared with MIPs prepared with a single functional monomer.¹⁴⁷ Chen *et al.*¹⁴⁸ prepared a kind of novel IIP for Pb²⁺ recognition and removal, based on ionic interactions *via* the synergy of dual functional monomers of MAA and 4-VP. 4-VP itself could form coordination complexes with Pb²⁺ ions, but herein its function was more related to its action as a proton acceptor for MAA, that is, it could assist the better dissociation of the carboxyl group through proton abstraction using a base, which would greatly facilitate the binding of the carboxylate with Pb²⁺ ions, as illustrated in Fig. 9B. Therefore, the synergy between 4-VP and MAA played an important role in the improved adsorption efficiency and selectivity of Pb-IIPs for Pb²⁺ ions.

Actually, utilization of dual/multi-functional monomers is a good choice to enhance the selectivity of MIPs/IIPs, and is an effective way to imprint various analytes especially for macromolecule imprinting. However, it is not easy and requires continuous exploration: how to appropriately select and reasonably combine dual/multiple functional monomers commercially available, how to delicately devise and synthesize new functional monomers, and furthermore how to effectively use their synergistic effects in the preparation of ideal MIPs/IIPs.

3.2.3. Dummy imprinting strategy. In earlier studies, MIPs were used successfully as SPE sorbents. However, the leakage of trace amounts of the imprinted molecules from the MIPs hindered the accuracy and precision of the assay.¹⁴⁹ To avoid the risk of template leakage, Andersson *et al.*¹⁵⁰ first used a close structural analogue to substitute the real target molecule as the template in 1997. In 2000, Takeuchi *et al.*¹⁵¹ proposed the concept “dummy template”, and then it was introduced to

produce MIPs by Hosoya *et al.*¹⁵² in 2005. In recent years, the dummy imprinting strategy has been increasingly applied by using structurally analogous analytes of the target compounds as template molecules, which offers an attractive alternative under the following two main conditions: (1) when the original template is very expensive or insecure for its manipulation,¹⁵³ and (2) when the original template degrades easily or when the target analytes have low solubility during polymerization, which is not suitable for the synthesis of MIPs.^{153,154} For example, Chen *et al.* prepared MIPs with trinitrophenol (TNP) as a dummy template molecule for the detection of 2,4,6-trinitrotoluene (TNT), as shown in Fig. 9C, since TNT involves safety concerns and cannot be obtained easily. The resultant MIPs demonstrated highly selective and sensitive recognition and determination abilities.¹⁵³ Wang *et al.*¹⁵⁵ used *N*-vanillylnonanamide as a dummy template to prepare dummy MIPs to simultaneously enrich capsaicin and dihydrocapsaicin due to the high price of the target compound used as the template. The resultant dummy MIPs were found to exhibit good site accessibility, taking just 20 min to achieve adsorption equilibrium with high selectivity toward capsaicin and dihydrocapsaicin.

3.2.4. Segment imprinting strategy. Segment imprinting, also called fragment imprinting, utilizes a partial structure of the target molecule as a pseudo-template to prepare MIPs, as schematically shown in Fig. 9D, which will provide a similar selective recognition ability to the target molecule and broaden the application ranges of molecular imprinting.

In 2000, Minoura *et al.*¹⁵⁶ proposed the use of a compound (as a template), whose structure represents a small fragment of a larger molecule (as an epitope represents an antigen), for the preparation of MIPs by the epitope approach. Subsequently, Kubo *et al.* used a fragment template as part of the structure of the targeting molecule to achieve selective separation of endocrine disrupters.^{157,158} Recently, Wang *et al.*¹⁵⁹ presented a MIP-based probe for domoic acid (DA) by using two-fragment imprinting. Due to the high toxicity and high cost of DA, pentane-1,3,5-tricarboxylic acid (PTA) and proline (Pro), the structurally similar parts of DA were chosen as dummy templates to prepare the two-fragment imprinting silica for highly selective probing of DA. As a result, the probe displayed good selectivity for probing DA. Ueda *et al.*¹⁶⁰ proposed an antibody-based recognition matrix that could be imprinted by a target antigen. Instead of using whole antibody molecules, the isolated antigen recognition domains of antibodies VH and VL were used as templates. The antibody VH/VL fragments have a merit that they can be immobilized at higher density than full-size antibodies to attain a higher signal. The present strategy can be used to detect different antigens *in situ*, which is hard to achieve with a conventional antibody based matrix.

Segment imprinting has broadened the fields of MIPs for a number of target molecules including highly toxic, expensive compounds and biological macromolecules, which can be hardly utilized as the templates or cannot be easily imprinted.¹⁵⁸ Moreover, it can also solve the problem of template leakage. It has to be pointed out that the dummy and segment imprinting techniques have many advantages,

yet the choice of suitable dummy and segment/fragment template molecules is not easy.

3.2.5. Composite imprinting material strategy. The introduction of various functional materials into the molecular imprinting process is an important challenge and a promising opportunity, and the resultant composite imprinting materials gain the advantages of both functional materials and MIPs. At present, common nanomaterials such as SiO_2 ,¹⁶² polystyrene (PS),¹⁶³ titanium dioxide (TiO_2),¹⁶⁴ chitosan¹⁶⁵ and Fe_3O_4 are most frequently used as support cores to prepare core-shell structured MIPs by surface imprinting. Among them, magnetic Fe_3O_4 incorporated into MIPs has the significant advantages of magnetic separation over conventional materials and the detailed discussion of the imprinting process can be found in Section 3.3 "Stimuli-responsive MIT for MIPs". By incorporating nanoparticles (NPs) such as gold nanoparticles (Au NPs), silver nanoparticles (Ag NPs), graphene and quantum dots (QDs) into the MIP matrix, the specific physicochemical properties of the nanoparticles and the recognition specificity of MIPs with electrical or optical properties would be retained by the nanocomposites, which is interesting for the application field.¹⁶⁶

Willner *et al.* introduced imprinted Au NPs as ultrasensitive and selective matrices for the electrochemical or surface plasmon resonance (SPR) analyses of the TNT or RDX explosives,^{167–170} and the imprinting process is presented in Fig. 10A. Liu *et al.* reported a method for the ultra-trace detection of TNT on *p*-aminothiophenol-functionalized Ag NPs coated on silver molybdate nanowires based on surface enhanced Raman scattering (SERS), which offered a highly sensitive, rapid, easy, and reliable means for detecting TNT in environmental samples by measuring the SERS intensity.¹⁷¹ Moreover, semiconductor QDs, recently emerging fluorescent nanomaterials, have received considerable attention because of their special advantages, such as high fluorescence efficiency, good chemical stability and tunable and narrow emission spectral features. The incorporation of QDs can offer the source of fluorescence and enhance the selectivity of MIPs.^{172,173} Chen *et al.*¹⁷⁴ developed QD based mesoporous structurally imprinted microspheres for specific recognition and sensitive detection of phycocyanin by the electron-transfer-induced fluorescence quenching mechanism. As a result, a favorable linearity and a high detectability were observed and the facile preparation and fluorescence sensing processes of QDs-MIPs are schematically displayed in Fig. 10B. More recently, two differently sized CdTe QDs emitting red and green fluorescence were hybridized to develop imprinted polymer coated quantum dot (MIP@QD) ratiometric fluorescence sensors.¹⁷⁵ The fluorescence of green QDs embedded in the imprinted shell can be selectively quenched, whereas the fluorescence of red QDs embedded in silica particles remains constant, which results in a noticeable fluorescence color change and thus facilitates visual detection.¹⁷⁵ High sensitivity with a detection limit down to nM can be achieved by using this ratiometric fluorescence QD sensor.

Carbon-based QDs, a new class of carbon nanomaterials, mainly include carbon QDs (CQDs, C-dots or CDs) and graphene QDs (GQDs). Compared to traditional II–IV semiconductor QDs

and organic dyes, carbon-based QDs are superior in terms of high (aqueous) solubility, robust chemical inertness, low toxicity and good biocompatibility, which endow them with potential applications in sensors.¹⁷⁶ Niu *et al.*¹⁷⁷ reported that CDs were anchored with MIPs for determination of dopamine (DA) *via* fluorescence quenching by DA. Shi *et al.*¹⁷⁸ demonstrated a MIP-coated GQD composite for the determination of *para*-nitrophenol (4-NP) in a water sample *via* fluorescence quenching by 4-NP. The QD-based composite MIPs with high selectivity and excellent detectability will provide more possibilities for sensing applications.

Since molecular imprinting faces severe challenges, development of different types of molecularly imprinted nanomaterials is of tremendous importance. Besides, other significant attempts should be made to improve the performances of MIPs, such as exploration of new types of polymerization methods for molecular imprinting to obtain higher imprinting efficiency and novel optical nanomaterials to synthesize composite MIPs. Moreover, fusion of various technologies and materials into molecular imprinting will bring new opportunities and challenges. For example, Gan *et al.*¹⁷⁹ designed an electrochemical multiplex immunoassay for simultaneous determination of alpha-fetoprotein (AFP) and the carcinoembryonic antigen (CEA) using recombinant apoferritin-encoded metallic nanoparticles (rApo-M) as labels and dual-template magnetic MIPs (MMIPs) as capture probes. The labels were prepared by loading recombinant apoferritin (r-Apo) and separately immobilizing primary antibodies (anti-AFP and anti-CEA) *via* the *in situ* growth of Au NPs on graphene. These results suggested that the proposed multiplexed immunoassay would be potentially applicable for clinical screening of other biomarkers.

3.3. Stimuli-responsive MIT for MIPs

In order to achieve intelligent materials mimicking the natural receptors' characteristics, stimuli-responsive MIPs (SR-MIPs) have been prepared by using stimuli-responsive technology for molecular imprinting. SR-MIPs include magnetic responsive MIPs, thermo-responsive MIPs, pH responsive MIPs, photo-responsive MIPs, and dual or multistimuli responsive MIPs, as schematically shown in Fig. 11, which have benefited from significant advances in polymer science. They have great application prospects as smart materials in many fields such as separation science, chemo/biosensing, drug delivery, biotechnology, and cell encapsulation in biochemistry.¹⁴

3.3.1. Magnetic responsive technology. Incorporation of magnetic components like Fe_3O_4 nanoparticles into MIPs afforded magnetic responsive MIPs (M-MIPs), which show directional movement upon application of an external magnetic field. Mosbach first described the production of magnetite-molecularly imprinted polymer composite beads in 1998.¹⁸⁴ Due to their high magnetic susceptibility, analytes can be easily adsorbed on M-MIPs and separated using an external magnetic field without additional centrifugation or filtration, making the separation of analytes from the medium easier, faster and more efficient.^{185–187} At present, M-MIPs have attracted more and

Fig. 10 Representation of composite imprinting. (A) Schematic representation of the electropolymerization of a composite of bis(aniline)-cross-linked Au NPs for the sensing of PETN or NG using citric acid as an imprinting template. Reproduced with permission from ref. 170. Copyright © 2011 American Chemical Society. (B) Schematic illustrations for the preparation process of SiO₂@QDs@ms-MIPs. Reproduced with permission from ref. 174. Copyright © 2015 American Chemical Society.

more attention in sample pretreatment, magnetic bioseparation, drug delivery and enzyme immobilization.

Usually, the preparation of M-MIPs (using Fe₃O₄ M-MIPs as an example) has been carried out according to the following steps: firstly, synthesis of Fe₃O₄ magnetic nanoparticles by the coprecipitation method or the solvothermal reduction method; secondly, surface modification or functionalization of Fe₃O₄ magnetic nanoparticles; thirdly, molecular imprinting at the surface of Fe₃O₄ magnetic particles to prepare M-MIPs through a sol-gel process or free radical polymerization. To date, the methods used for the preparation of M-MIPs mainly include the grafting method,^{188–207} suspension,^{66,208–221} emulsion,^{222–228} and precipitation polymerization,^{229,230} which offer a wide choice to produce spherical or particle shaped MIPs compared to bulk polymerization.²³¹ Grafting of MIPs on the surface of Fe₃O₄ magnetic particles can result in an ultrathin MIP shell

with controllable shell thickness.^{188–205} Table 5 summarizes related preparation, application and analytical performances of M-MIPs using different preparation methods.

For example, Mei *et al.*¹⁸⁵ prepared M-MIP NPs for recognition of lysozyme. Fe₃O₄ NPs were synthesized by the coprecipitation method and then were coated with a thin SiO₂ film (Fe₃O₄@SiO₂) by a sol-gel process. The formation of the SiO₂ shell provided a biocompatible and hydrophilic surface, prevented the oxidation of Fe₃O₄ and offered many possibilities for surface modification through the covalent attachment of specific ligands on the surface of Fe₃O₄@SiO₂ nanoparticles. Subsequently, a double bond was introduced onto the surface of the SiO₂ shell to ensure the tight growth of MIP film coated onto the surface of the SiO₂ shell. The high saturation magnetization of these multifunctional nanoparticles showed that sufficient magnetite was encapsulated and the magnetic separation process

Fig. 11 Schemes of stimuli responsive MIPs. SR-MIPs are divided into two main types: single responsive MIPs and dual/multi responsive MIPs. Single responsive MIPs mainly include magnetic responsive using Fe_3O_4 as response unit, thermo-responsive using *N*-isopropylacrylamide (NIPAAm) as response unit, adapted with permission from ref. 180; photo-responsive using azobenzene as response unit and pH responsive MIPs using poly(acrylic acid) as response unit, adapted with permission from ref. 181; etc. Dual/multi responsive MIPs mainly include magnetic/thermo responsive MIPs using Fe_3O_4 and NIPAAm as response units, adapted with permission from ref. 182; photo/thermo responsive MIPs using azobenzene and NIPAAm as response units; thermo/pH responsive MIPs using NIPAAm and 4-vinylphenylboronic acid (*p*-VPBA) as response units; thermo/photo/pH responsive MIPs using azobenzene, NIPAAm and 4-((4-methacryloyloxy)-phenylazo)benzoic acid (MPABA) as response units, adapted with permission from ref. 183; etc.

could be performed directly in crude samples.¹⁸⁵ Zhang *et al.*¹⁹² reported a highly controllable and general protocol for coating MIPs on the surface of superparamagnetic Fe_3O_4 NPs to obtain Fe_3O_4 @MIP NPs for rapid enrichment and separation of 2,4-D. Acrylic acid monomers were first anchored at the surface of Fe_3O_4 forming a polymerizable molecule monolayer with polymerizable vinyl end groups, which directed the selective occurrence of molecular imprinting polymerization at the surface of Fe_3O_4 NPs. The modification of magnetic particles is simpler compared to SiO_2 surface modification.¹⁹² Li *et al.*²⁰³ presented a general protocol for the preparation of core-shell magnetic beads *via* RAFT polymerization. Fe_3O_4 NPs were first synthesized by the solvothermal reduction method and then modified by SiO_2 . By using the RAFT agent as the chain transfer agent, the resultant Fe_3O_4 @ SiO_2 @MIPs shell had a thickness of about 22 nm and appeared to be uniform, which is suitable for the fast and magnetic selective removal of endocrine disruptors.²⁰³ Haupt *et al.*²⁰⁴ presented the synthesis of *S*-propranolol M-MIPs using RAFT polymerization. The resulting composites retained both a good imprinting effect and a superparamagnetic behavior. Moreover, the “living” nature of 2-(dodecylthiocarbonothioylthio)-2-methylpropanoic acid fragments present on the surface of synthesized composites was used to further polymerize ethylene glycol methacrylate phosphate, which provided the possibility to finely tune the surface properties of the composite MIPs through the grafting of specific additional layers.²⁰⁴ Shi *et al.*²⁰⁷ prepared MIPs by self-polymerization of dopamine (DA) on magnetic mesoporous silica (Fe_3O_4 @ SiO_2 @m SiO_2 , MMS) using gallic acid (GA)

as a template. Fe_3O_4 NPs were prepared by the solvothermal reaction and then coated with silica. After that, a layer of mesostructured silica was deposited on Fe_3O_4 @ SiO_2 microspheres through a sol-gel process using CTAB as a template. Finally, a thin adherent polydopamine layer with GA embedded on the surface of MMS was initiated by APS under mild conditions, and then MMS-MIPs with surface binding sites were achieved by the removal of the embedded GA. The proposed MIPs were designed by self-polymerization of DA on magnetic mesoporous silica, which is a facile and efficient approach for preparation of hydrophilic MIPs.

The grafting method offers a choice to obtain the desired morphology of the resultant polymers, but low extraction capacity and time consuming and laborious surface modification of Fe_3O_4 sometimes limit its application. Emulsion polymerization usually suffers from the remnants of surfactants.^{211,224} Precipitation polymerization is restricted to accurate reaction conditions during the free-radical polymerization process.²²⁹ Suspension polymerization is a simple method suited to the preparation of porous M-MIPs with spherical or particle shape, since the Fe_3O_4 magnetic particles need no functionalization. Several research groups^{66,211–219} have reported the synthesis of M-MIPs by suspension polymerization. For example, Li *et al.* developed a simple and direct method for the preparation of M-MIP beads, which was based on suspension polymerization, using Fe_3O_4 particles as magnetic cores, atrazine as a template and MAA as a functional monomer.²¹¹ MAA and atrazine were self-assembled through the hydrogen bonding interaction.

Table 5 Summary of M-MIPs

Polymersization method	Preparation of Fe ₃ O ₄	Modification of Fe ₃ O ₄	Template	Application	Recovery (%)	LOD	Ref.
Grafting method	Co-precipitation	Fe ₃ O ₄ @SiO ₂	Lysozyme	—	92.5–113.7	5 ng mL ⁻¹	185
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	E ₂	Dispersive solid-phase extraction	92.7–97.7		186
	Solvothermal reduction method	Fe ₃ O ₄ @SiO ₂	Sildenafil	As the extraction and clean-up materials detection of sildenafil and vardenafil in herbal dietary supplements	70.91–91.75	3.86 µg g ⁻¹	187
	Co-precipitation	γ-MPS-Fe ₃ O ₄	S-Ofloxacin	As stationary phase in capillary electrochromatography for enantioseparation		2.0 µM	188
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	Lysozyme	Solid-phase extraction	90.1–103.7		189
	Co-precipitation		2,4-DCP	As supports	76.3–95.5		190
	Solvothermal reduction method	MWNTs@Fe ₃ O ₄	BSA	As an HPLC stationary phase to separate the template BSA from a binary protein solution	92–97.3		191
	Solvothermal reduction method	Fe ₃ O ₄ -acrylic	2,4-D	Removal of 2,4-D in real water samples			192
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	Sulfadiazine	Urine samples	95–103	1.54 × 10 ⁻⁷ mol L ⁻¹	193
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	CSD	A novel CL sensor applied to determinate the CSD in food samples	96–104		194
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	EE ₂	Magnetic dispersive SPE	87.8, 93.1 and 90.6	5.28, 5.31 and 4.17 ng mL ⁻¹	195
	Co-precipitation	Fe ₃ O ₄ /poly[Stco-MPS]/SiO ₂	E ₂	SPE adsorbent for typical environmental estrogens	93.3–102	4.80 pg mL ⁻¹	196
	Co-precipitation	Fe ₃ O ₄ -CdTe@SiO ₂	P-Nitrophenol	—			197
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	DBP	A microflow CL sensor	102–104	2.09 × 10 ⁻⁹ M	198
	Co-precipitation	Amino-Fe ₃ O ₄	DNase I	—			199
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	HlgG	Detecting human serum specimens by ECLIA	84.15–104.50		200
	Solvothermal reduction	TiO ₂ @SiO ₂ @Fe ₃ O ₄	ENRH	Elective photodegradation of enrofloxacin hydrochlorides residues solution			201
	Solvothermal reduction method	Fe ₃ O ₄ @SiO ₂	E ₂	As fiber coating for detection of trace estrogens in milk powder	81.5–93.3	1.5–5.5 ng g ⁻¹	202
Suspension polymersization	Solvothermal reduction	Fe ₃ O ₄ @SiO ₂	BPA	—			203
	Solvothermal reduction	Amino-Fe ₃ O ₄	S-Propanolol	—			204
	Co-precipitation	Amino-Fe ₃ O ₄	BSA	Applied to bovine serum separation			205
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	Cephalomannine	Enrich and separate four taxoids			206
	Solvothermal reduction	Fe ₃ O ₄ @SiO ₂	Gallic acid	Extraction and determination of GA from grape, apple, peach and orange juices		4.02, 3.91, 5.97, and 0.67 µg g ⁻¹	207
	Co-precipitation	OA-Fe ₃ O ₄	2,4-D	—			208
	Co-precipitation	OA-Fe ₃ O ₄	Oxytetracycline	The separation of tetracycline antibiotics from egg and tissue samples LC-MS/MS	72.8–96.5	0.2 ng g ⁻¹	209
	Co-precipitation	PEG-Fe ₃ O ₄	Atrazine	Integrated MIP extraction and micro-LLE into only one step and applied to the pretreatment of triazines	71.6–118.5	0.20–0.63 µg L ⁻¹	210
	Co-precipitation	PEG-Fe ₃ O ₄	Atrazine	Mag-MIP beads extraction coupled with HPLC in spiked soil, soybean, lettuce, and millet samples	71.6–126.7 72.1–120.2 78.9–119.9 79.6–120.5		211
	Co-precipitation	OA-Fe ₃ O ₄	Albumin, creatinine, lysozyme	Separation and sensing of template molecules in real samples			212
	Co-precipitation	OA-Fe ₃ O ₄	PENV	As sorbent for the extraction of BLAs from milk samples	71.6–90.7	1.6–2.8 ng mL ⁻¹	213
	Co-precipitation	PEG-Fe ₃ O ₄	IAA	Trace analysis of auxins in plant tissues	70.1–93.5	7.4 µg L ⁻¹	214
	Co-precipitation		Chlorogenic acid	Separation of CGA from the extract of traditional Chinese medicine honeysuckle			215

Table 5 (continued)

Polymerization method	Preparation of Fe ₃ O ₄	Modification of Fe ₃ O ₄	Template	Application	Recovery (%)	LOD	Ref.
Emulsion polymerization	Co-precipitation	OA-Fe ₃ O ₄	Ciprofloxacin	As sorbents for the extraction of FQs from water samples	76.3–94.2	3.2–6.2 ng L ⁻¹	216
	Co-precipitation	PEG-Fe ₃ O ₄	B-Sitosterol	Simultaneous determination of three trace sterols in complicated biological samples	71.6–88.2		217
	Co-precipitation	PEG-Fe ₃ O ₄	Ractopamine	As sorbents for the extraction of β -agonists from pork and pig liver samples	82.0–90.0	0.52–1.04 ng mL ⁻¹	218
	Solvothermal method		2-Amino-4-nitrophenol	Applied as a sorbent, the imprinted sorbent was used for the determination of 4-NAP in a mixture solution	80.4–86.8		66
	Co-precipitation	PEG-Fe ₃ O ₄	Tratarzine	Removal of water-soluble acid dyes from water environment			219
Precipitation polymerization	Co-precipitation	TMSMA-Fe ₃ O ₄	Theophylline	Sensors for electrochemical detection of streptomycin residues in food	81–129	10 pg mL ⁻¹	220
	Co-precipitation		Streptomycin				221
	Co-precipitation		Ribonuclease A				222
	Co-precipitation	OA-Fe ₃ O ₄	BSA				223
	Co-precipitation	γ -MPS-Fe ₃ O ₄	BPA	Solid-phase extraction extract BPA from environmental water and milk samples	89–106	14 ng L ⁻¹	224
Bulk polymerization	Co-precipitation	OA-Fe ₃ O ₄	Pyrene	As optical sensing phases	95–101	0.16 μ g L ⁻¹	225
	Solvothermal method	KH-570-Fe ₃ O ₄	Tetracycline	As adsorbents for TC molecules from aqueous medium HPLC analysis	78.1	7 ng mL ⁻¹	226
	Co-precipitation		λ -Cyhalothrin	As sorbents for the selective binding			227
	Solvothermal reduction	OA-Fe ₃ O ₄	Phycocyanin	As sorbents for selective isolation of phycocyanin from protein mixtures and special imaging recognition		1.5 ng mL ⁻¹	228
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	Tadalafil	As DSPE materials coupled with HPLC-UV for the selective extraction and detection of tadalafil from medicines	87.36–90.93	43.46 nmol g ⁻¹	229
Sol-gel	Co-precipitation	OA-Fe ₃ O ₄	1-Naphthylamine	Detection of 1-NA in drinking water	91.6	18 ng mL ⁻¹	230
	Co-precipitation	γ -MPS-Fe ₃ O ₄	Uranium	Sorbents for selective removal of U(vi) from contaminated water	77		231
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	Estrone	Biochemical separation of estrone.			232
	Solvothermal reduction	Amino-Fe ₃ O ₄	BHb				233
	Co-precipitation	Fe ₃ O ₄ @SiO ₂	Benzylpenicillin	Electrochemical sensor	97.96–102.61	1.5 $\times 10^{-9}$ mol L ⁻¹	234
Click reaction	Co-precipitation	Fe ₃ O ₄ @SiO ₂	Cu(ii)	Applied for the removal of Cu(ii) ions from river water			235
	Solvothermal reduction method	Fe ₃ O ₄ @SiO ₂	Pb(ii)	M-SPE	98–104		236
	Co-precipitation	OA-Fe ₃ O ₄	Cu(ii)	Application in the selective separation and enrichment of BSA from a bovine blood sample			237
	Solvothermal reduction method	Fe ₃ O ₄ @SiO ₂	BSA	Enrichment and separation of CIP			238
	Co-precipitation	OA-Fe ₃ O ₄	Ciprofloxacin				239
	Co-precipitation	Fe ₃ O ₄ @SiO ₂ @N ₃	(R,S)-Propranolol				120

Abbreviations: E₂, estradiol; γ -MPS, γ -methacryloxypropyl trimethoxysilane; 2,4-DAP, 2,4-dichlorophenol; BSA, bovine serum albumin; 2,4-D, 2,4-dichlorophenoxyacetic acid; EE₂, ethynylestradiol; CL, chemiluminescence; SPE, solid-phase extraction; DBP, dibutyl phthalate; DNase I, deoxyribonuclease I; ENRH, enrofloxacin hydrochloride; BPA, bisphenol A; OA, oleic acid; PEG, polyethylene glycol; PENV, penicillin V potassium; BLAs, β -lactam antibiotics; IAA, indole-3-acetic acid; DSPE, dispersive solid-phase extraction; BHb, bovine hemoglobin; M-SPE, magnetic solid phase extraction.

Then polyethylene glycol (PEG)-Fe₃O₄ suspension, a cross-linker, copolymer monomers, an initiator, and water were added and mixed, and polymerization was initiated by microwave heating. The resultant M-MIP beads with magnetic properties exhibited superior selectivity for triazines, and gave rather high imprinting efficiency factors.²¹¹

Compared to the above methods, the sol-gel process has distinct advantages such as the ease of fabrication at room temperature and the use of eco-friendly reaction solvents, ultrapure water or ethanol.^{232–239} Zhu *et al.*²³³ combined the grafting method and the sol-gel process to prepare M-MIPs for bovine hemoglobin (Bhb) recognition. Fe₃O₄ nanospheres were directly functionalized with amine groups. Then, a model protein, Bhb, was directly covalently grafted on the surface of modified Fe₃O₄ nanospheres with amine groups by glutaraldehyde. And lastly the polymerization reaction took place on the nanosphere surface by the sol-gel process. The results showed that Fe₃O₄ nanospheres with a diameter of about 50–150 nm were coated with the MIP layer with an average thickness of about 10 nm, which enabled the M-MIPs to show a sensitive and fast magnetic response. This approach is attractive and broadly applicable in bio-enrichment, separation, and sensing, due to easy preparation and high chemical stability.²³³

Tang *et al.*²³⁸ prepared a novel type of uniform magnetic imprinted nanomaterial for the recognition of BSA by anchoring MIP shells on the surface of silica deposited Fe₃O₄ NPs *via* sol-gel polymerization. The method consisted of a two-stage core-shell sol-gel polymerization: the first stage involves the transfer silica shells to the surface of Fe₃O₄ NPs using TEOS to produce Fe₃O₄@SiO₂ with a core-shell structure; and the second stage involves anchoring of MIP shells on the surface of Fe₃O₄@SiO₂ using acetic acid (HAc) as the catalyst to obtain the core-shell Fe₃O₄@BSA-MIPs nanocomposite. The resultant M-MIP nanomaterials exhibited good dispersion, high crystallinity, and satisfactory superparamagnetic properties with a high saturation magnetization (43.82 emu g⁻¹), which allowed them to be easily separated from solution by means of an external magnetic field.²³⁸

As we know, the methods discussed above have a common feature that the Fe₃O₄ NPs as a core material are incorporated into cross-linked imprinted polymers, which will decrease the magnetic susceptibility as the surrounding polymer layer exceeds a certain limit. Recently, Ye *et al.*¹²⁰ reported a new strategy to prepare molecularly imprinted magnetic materials, which used click chemistry to conjugate two types of modular building blocks, MIP-NPs and Fe₃O₄ NPs, surface-functionalized with alkyne and azide groups, to offer both molecular binding selectivity and efficient magnetic separation. The saturation magnetization of MIP@Fe₃O₄ was found to be 29 A m² kg⁻¹. The demonstrated modular assembling approach can be extended to conjugate MIP-NPs with other azide-functionalized nanoparticle building blocks (*e.g.* QDs) or reporter molecules, which will open up further opportunities for MIP-based sensors.¹²⁰

3.3.2. Thermo-responsive technology. Poly(*N*-isopropylacrylamide) (PNIPAAm),²⁴⁰ a temperature responsive polymer, demonstrates a lower critical solution temperature (LCST),

which is near 32 °C in aqueous solution and undergoes a phase separation at temperatures higher than LCST. Above its LCST, the relative equilibrium of hydrophilicity/hydrophobicity is lost because of a thermodynamic transition. Water is expelled from the polymer interior, leading to a drastic decrease in the volume of the polymer. Below its LCST, however, the polymer is soluble in water because the intermolecular hydrogen bonding between PNIPAAm chains and water molecules becomes dominant. PNIPAAm incorporated MIPs are well known to respond to changes in temperature, so PNIPAAm has been applied broadly to develop thermo-responsive MIPs. In 1998, Watanabe *et al.*²⁴¹ first used NIPAAm as a temperature responsive polymer to prepare synthetic polymer gels. Recently, thermo-responsive MIPs have been investigated widely by many groups,^{180,242–250} as listed in Table 6. For example, Zhang *et al.*¹⁸⁰ reported a new approach for the preparation of PNIPAAm-coated molecularly imprinted beads, which were obtained with an external thermo-sensitive PNIPAM layer acting as a thermo-sensitive “gate” and an internal protein-imprinted layer acting as a selective “gate”. PNIPAAm as the outer layer of the coated MIP beads not only increased the thermo-sensitive properties but also improved selectivity for the template lysozyme compared with the MIP beads. As a result, the reference proteins and the template lysozyme could be released at 38 and 23 °C by using the coated MIP beads.¹⁸⁰

As is well known, highly cross-linked materials prepared using typically conventional MIT have relatively rigid structures, which limit the number of binding sites available for the target molecule. Lightly cross-linked polymer gels can undergo reversible swelling and shrinking in response to environmental temperature changes, called thermo-responsive gels, which can be used as smart materials for drug delivery, tissue engineering, and cell encapsulation in biochemistry.^{251–256} This type of thermo-sensitive recognition is very similar to the recognition of proteins in natural systems. Thus, thermo-responsive gels with biocompatibility could have potential applications in the design of protein-imprinted polymer matrices. Several encouraging publications^{253,254,256,257} have focused on the preparation of protein-imprinted materials based on thermo-responsive gels. For example, Li *et al.*²⁵⁴ reported a novel type of thermo-responsive nanogel built by using lysozyme as the protein template and NIPAAm as the major monomer, prepared *via* aqueous precipitation polymerization with the aid of a surfactant and sodium dodecyl sulfate (SDS). The protein-imprinted nanogels in this study were synthesized at human body temperature (37 °C) so that potential volume phase transition-associated affinity loss induced by temperature changes could be avoided in *in vivo* applications.²⁵⁴ In 2013, Li *et al.* reported another novel system for harvesting cell sheets which relies on a PNIPAAm-based MIP hydrogel layer with thermo-responsive affinity toward specific biomolecules. The imprinting process was performed by redox-initiated polymerization at 37 °C in phosphate buffer solution using a cell-adhesive peptide Arg-Gly-Asp-Ser (RGDS) as the target biomolecule, NIPAAm as the thermo-responsive backbone monomer, and *N*-[3-(dimethylamino)propyl]methacrylamide (DMAPMA), acrylamide (AAm), and methylene bisacrylamide

Table 6 Summary of T-MIPs

Template	Thermo-responsive element	Method	Application	Ref.
<i>p</i> -Nitrophenyl phosphate	NIPAAm	Bulk	'On/off' switchable catalysis	242
SD	NIPAAm	SI-RAFT	PC application	243
TC	NIPAAm	Surface imprinted	As a potential effective photocatalyst for selectively remove TC existing in aquatic environments	244
Theophylline	NIPAAm	Electropolymerization	Sensor	245
Adenine	NIPAAm	Bulk		246
Cu(II)	NIPAAm	Free radical	As adsorbent	247
Lysozyme	NIPAAm	Surface imprinted	Monolithic column as an artificial antibody for the on-line selective separation of the protein	248
Lysozyme	NIPAAm	Surface imprinted	Chemical carriers, drug delivery system, and sensors	180
Cefalexin	NIPAAm	Surface imprinted	As sorbents to selectively recognise and release CFX molecules	249
SDZ	NIPAAm	Surface imprinted	As a sorbent material in SPE	250
L-Pyrogutamic acid	NIPAAm	Living-radical polymerization	Controlled drug release and separation field	251
Myoglobin	NIPAAm	Free radical polymerization	Biotechnology, assays, and sensors	252
Lysozyme	NIPAAm	Frozen polymerization	Separation in proteomics	253
Lysozyme	NIPAAm	Precipitation polymerization	Recognition and controlled release of proteins	254
BSA	NIPAAm	Free radical polymerization	Adsorb the BSA from the protein mixture	255
RGDS	NIPAAm	Redox polymerization	A novel system for harvesting cell sheets	256
Lysozyme	NIPAAm	Photo-initiated free radical copolymerization	Development of novel sensors or materials for controlled release applications	257
DBTS	Ligand–gel interactions between DBTS and chitosan hydrogel		Application in analytical and industrial separations	258
Dopamine hydrochloride	<i>N,N</i> -Methylene-bis-acrylamide	Free radical polymerization	As a sorbent material in SPE	259
S-Naproxen	PAMPS		A new generation of MIPs with on/off-switchable functions	260
2,4-D	NIPAAm	SI-RAFT	A new, general, and efficient approach to obtaining both pure water-compatible and stimuli responsive MIPs	261

Abbreviations: NIPAAm, *N*-isopropylacrylamide; SD, sulfadiazine; TC, tetracycline; PC, photocatalysis; SDZ, sulfadiazine; SI-RAFT, surface-initiated reversible addition-fragmentation chain transfer; CFX, cefalexin; AMPS, 2-acrylamido-2-methyl-propanesulfonic acid; RGDS, Arg-Gly-Asp-Ser; DBTS, dibenzothiophene sulfone; PAAm, poly(acrylamide); PAMPS, poly(2-acrylamide-2-methyl propanesulfonic acid).

(MBAAm) as positively charged and hydrogen-bonding monomers and crosslinker, respectively. This study is the first demonstration of molecular imprinting as a methodology to biofunctionalize thermo-responsive cell culture substrates to harvest cell sheets for potential biomedical applications.²⁵⁶

Unlike the above reported PNIPAAm-based MIPs, which demonstrated thermo-sensitive properties simply because of the hydrophilicity/hydrophobicity of PNIPAAm responding to changes in temperature, new thermo-responsive MIPs have been developed recently. For example, Aburto *et al.*²⁵⁸ synthesized a dibenzothiophene sulfone (DBTS)-imprinted chitosan hydrogel (IH_{DBTS}) by cross-linking chitosan with glutaraldehyde in the presence of DBTS as the template. The IH_{DBTS} was found to be stimuli-responsive with temperature and showed a LCST between the swollen and the collapsed phases at 50 °C due to the stronger ligand–gel interactions where DBTS served as a ligand.²⁵⁸ Suede *et al.*²⁵⁹ prepared a temperature sensitive dopamine-imprinted polymer in 80% aqueous methanol solution by copolymerization of methacrylic acid and acrylamide at 60 °C with *N,N*-methylene-bis-acrylamide as the cross-linker and dopamine hydrochloride as the template molecule. The thermo-responsive MIPs exhibited a swelling–deswelling transition in 80% aqueous methanol solution at about 35 °C and the recognition ability and adsorption capacity of

dopamine by the MIPs were maximal.²⁵⁹ Li *et al.* reported zipper-like on/off-switchable MIPs composed of template-imprinted polymeric networks that incorporated zipper-like interactions between poly(acrylamide) (PAAm) and poly(2-acrylamide-2-methyl propanesulfonic acid) (PAMPS).²⁶⁰ Under low temperature conditions, the polymer showed marginal recognition ability towards the imprint species due to the inter-polymer interaction between PAAm and PAMPS, which inhibited access to the imprinted networks. In contrast, at relatively high temperatures (such as 40 °C), the polymer demonstrated a significant molecular recognition ability towards the imprint species resulting from the dissociation of the interpolymer complexes of PAAm and PAMPS, which enabled access to the imprint networks. MIPs having positive on/off-switchable functions would have substantial potential for applications.²⁶⁰

In comparison with the previously reported method with thermo-responsive monomers in the molecular imprinting systems, a new efficient approach to obtain SR-MIPs has been developed by introduction of PNIPAAm brushes into the MIP microspheres *via* RAFT polymerization. Zhang *et al.* reported both pure water-compatible and stimuli-responsive MIPs by the facile grafting of poly(NIPAAm) brushes onto the preformed MIP particles *via* surface-initiated reversible RAFT polymerization. 2,4-D, 4-VP, EGDMA, and a mixture of methanol and water

(4:1, v/v) were utilized as the template, functional monomer, crosslinker, and porogenic solvent, respectively. The introduction of PNIPAAm brushes into the MIP microspheres significantly improved their surface hydrophilicity and stimuli-responsive properties, leading to their pure water-compatible and thermo responsive binding properties. The present methodology represents a general and promising method to develop advanced MIP materials with water-compatible and/or stimuli-responsive binding properties for a wide range of templates.²⁶¹

3.3.3. Photo-responsive technology. Light, a remote stimulus and a kind of “clean energy”, is of particular importance and attractive in terms of its broad use in molecular devices and smart materials, because it provides a wide range of adjustable parameters, such as wavelength, duration, and intensity.²⁶² The interest in creating photo-responsive MIPs (P-MIPs) has led to the incorporation of a photo-reactive moiety in a polymeric network, which can convert photo-irradiation to a chemical signal through photoreactions such as isomerization and dimerization.²⁶³ Fig. 12A shows photo-reactive moieties (azobenzene and spiropyran) that have been investigated most often in the development of P-MIPs. Photoisomerization processes are often fast, reversible and repeatable, which make the photo-reactive moieties such as azobenzene and spiropyran attractive, and are used in diverse forms to functionalize MIPs in a broad range of applications. Azobenzenes have two isomeric states, the more thermally stable *trans* configuration, and the less stable *cis* form. Under UV irradiation, azobenzenes can be isomerized from the *trans* form to the *cis* form and return to the original form by visible light irradiation or heating.

As we know, the photo-responsive functional monomer generally contains three parts: the photo-responsive group, the recognition group and the polymerizable group. To date, a series of photo-responsive functional monomers have been designed, as listed in Fig. 12B, and accordingly, diverse P-MIPs have been prepared by various methods, as summarized in Table 7. However, there are hardly any commercial photo-responsive functional monomers available, and it is a challenging task to realize their commercialization.

Minoura and his co-workers^{264,265} described the first report of P-MIP membranes containing azobenzene chromophores. MIP membranes were synthesized by using dansylamide (DA) as a template and a polymerizable derivative of azobenzene, compound **67**, as the functional monomer, whilst EGDMA and tetraethylene glycoldiacrylate as crosslinkers. By UV irradiation, PhAAAn underwent *trans*-to-*cis* isomerization, and *cis*-to-*trans* isomerization occurred upon visible light irradiation. However, the binding activity and selectivity of P-MIP membranes were not high, since the hydrogen bonds between the functional monomer and the target molecule were not very strong. Gong' group²⁶⁶ developed P-MIPs for the selective extraction of guanine from complex samples. P-MIPs were fabricated using guanine as the template, water-soluble 5-[(4-(methacryloyloxy)-phenyl)diazetyl]isophthalic acid (MAPDIA) as the functional monomer, and water-soluble triethanolamine trimethacrylate as the cross-linker, which displayed good selectivity toward guanine with a dissociation constant of $(2.70 \pm 0.16) \times 10^{-5} \text{ mol L}^{-1}$ in

aqueous media.²⁶⁶ As we know, the azo-containing P-MIPs have great potential in many applications such as selective extraction, separation and drug delivery. However, the obtained MIPs have limited physical forms (*i.e.*, bulk polymer membranes, bulk monoliths, and bulk hydrogels), which significantly confines their applications. In 2011, Zhang's group²⁶⁷ firstly described the successful preparation of azo-containing MIP microspheres (number average diameter = 1.33 μm , polydispersity index = 1.15) *via* precipitation polymerization by using an acetonitrile-soluble azo-functional monomer compound **72**. To obtain uniform P-MIPs, MIPs can also be prepared by the surface imprinting technique on the surface of uniform silica nanoparticles.²⁶⁸ Zhong's group developed a functionalized azobenzene-based polymer on the surface of silica nanoparticles. The functionalized monomer possessed an azobenzene chromophore for photoisomerization, a carboxyl group and a hydroxyl group for substrate interaction, and a polymerizable double bond.²⁶⁹ Compared to the system reported by Zhang's group,²⁶⁷ these imprinted MIP-silica microspheres showed better selectivity.

The sol-gel process, which is another convenient and versatile method for preparing MIPs besides the above mentioned free radical polymerization methods, has already been developed to prepare P-MIPs. Zhong *et al.*²⁷⁰ synthesized a photo-responsive functional monomer bearing a siloxane polymerisable group and azobenzene moieties. P-MIPs were prepared using 2,4-D as a template molecule by a sol-gel route, which were able to release and selectively bind 2,4-D upon irradiation at 360 and 440 nm, respectively.²⁷⁰

The spiropyran group is also used as a photo switching moiety. The unique photo-switchable properties of spiropyran are attributed to the cleavage of the C–O bond which leads to a planar sp^2 hybridized spiro carbon, making the molecule appear colourful. Under visible light irradiation or thermal stimuli, the ring-reclosure can be achieved and the molecule changes back to its colourless state. In addition, the force-induced covalent-bond activation can break the C–O bond to change spiropyran to merocyanine.²⁷¹ Bakker and his co-workers²⁷² introduced photoswitchable MIP microspheres containing spiropyran as the photoactivatable unit by the precipitation polymerization approach. Instead of using only one photochromic functional monomer, methacrylic acid was also used to form selective binding sites. The approach eliminated the need to design and synthesize photochromic monomers with functional groups that are capable of binding with the template.²⁷² However, smart materials incorporating spiropyran have a common problem, which is the loss of reversibility induced by photodegradation, photobleaching, or photooxidation when the photoswitching cycle is repeated several times. So, further improvements are necessary in order to increase long term stability.

3.3.4. pH-Responsive technology. Polymers containing a carboxylic acid or an amino functional group sensitive to changes in pH are called pH-responsive polymers. Such a polymeric network, containing ionizable groups, can accept or donate protons at a specific pH, causing a change in the

Fig. 12 (A) Isomerization of azobenzene and spiropyran. (B) Chemical structural formulae for photo-responsive functional monomers. Full chemical names: (**67**) *p*-phenylazoacrylanilide (PhAAAn); (**68**) 4-[(4-methacryloyloxy)phenylazo] benzenesulfonic acid (MAPASA); (**69**) 4-[(4-methacryloyloxy)-phenylazo]benzoic acid (MPABA); (**70**) di(ureidoethylenemethacrylate)azobenzene; (**71**) 4-{4-[2,6-bis(*n*-butylamino)pyridine-4-yl]-phenylazo}-phenyl methacrylate (FM); (**72**) 4-[(4-methacryloyloxy)-phenylazo]pyridine (MAzoPy); (**73**) 4-hydroxy-4-[3-(trimethoxysilyl)propoxy]azobenzene; (**74**) 4-hydroxyl-40-[(triisopropoxysilyl)propoxy]azobenzene (TPPSP-AZO-OH); (**75**) azobenzene-based monomer with a carboxyl group and a hydroxyl group; (**76**) 4-[(4-(3-(trimethoxysilyl)propoxy)phenyl)diazanyl]phenyl 2-(2,4-dichlorophenoxy)acetate; (**77**) spiropyran methacrylate (SPMA).

hydrodynamic volume of the polymer chains, which undergo a volume phase transition from a compact state to a swelling state.²⁷⁹ There are two types of pH-sensitive polyelectrolytes, *i.e.*, weak polyacids and weak polybases, as listed in Table 8.

In 2003, a new type of MIP that responds to pH emerged. Tao *et al.*²⁸⁰ firstly reported a novel pH-responsive MIP using amylose as the host matrix and acrylic acid as the functional monomer. As a result, they found that the rebinding ability

Table 7 Summary of P-MIPs

Template	Photo-reactive group	Polymerization method	Reaction	Irradiation wavelength	Ref.
DA	PhAAAn	Bulk	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	365 nm 440 nm	264
Dansylamide	PhAAAn	Bulk	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	353 nm 440 nm	265
Caffeine	MPABA	Bulk	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	365 nm 440 nm	273
Paracetamol	MAPASA	Bulk	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	353 nm 440 nm	274
Bis(TBA)- <i>N</i> -Z-L-glutamate	Di(ureidoethylenemethacrylate)azobenzene	Bulk	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	365 nm 440 nm	275
TM	FM	Bulk	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	365 nm 440 nm	276
Guanine	MAPDIA	Bulk	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	365 nm 440 nm	266
2,4-D	4-[(4-Methacryloyloxy)-phenylazo]pyridine	Precipitation polymerization	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	365 nm 440 nm	267
BPA	4-[(4-Methacryloyloxy)phenylazo]benzenesulfonic acid	Surface imprinting	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	365 nm 440 nm	268
Ibuprofen	Azobenzene-based monomer with a carboxyl group and a hydroxyl group	Surface imprinting	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	365 nm 440 nm	269
2,4-D	Azo-containing functional monomer	Surface imprinting	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	365 nm 440 nm	277
2,4-D	4-[(4-(3-(Trimethoxysilyl)propoxy)phenyl) diazenyl]phenyl 2-(2,4-dichlorophenoxy)acetate	Sol-gel	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	360 nm 440 nm	270
Ibuprofen	BPPO-AZO-TPPSP	Sol-gel	<i>trans</i> → <i>cis</i> <i>cis</i> → <i>trans</i>	365 nm 440 nm	278
Terbutylazine	Spiropyran methacrylate	Precipitation polymerization	Closed to open Open to closed	UV light Visible light	271

Abbreviations: DA, dansylamide; PhAAAn, *p*-phenylazoacrylanilide; MPABA, 4-[(4-methacryloyloxy)phenylazo]benzoic acid; MAPASA, 4-[(4-methacryloyloxy)phenylazo] benzenesulfonic acid; TM, 5-(3,5-dioctyloxyphenyl)-10,15,20-tri-4-carboxyphenyl-porphyrin; FM, 4-[4-[2,6-bis(*n*-butylamino)pyridine-4-yl]-phenylazo]-phenyl methacrylate; MAPDIA, 5-[(4-(methacryloyloxy)phenyl)diazene]isophthalic acid; BPPO-AZO-TPPSP, 2(*S*)-(4-isobutylphenyl)propyloxy-40-[(triisopropoxysilyl) propyloxy]azobenzene.

Table 8 Summary of pH-responsive MIPs

Template	pH-Responsive group	Polymerization method	Application	Ref.
BPA	Acrylic acid	Bulk	As the host matrix	280
Sulfasalazine	MAA	Precipitation	Drug delivery and release drug dosage form	286
DXP	DEAEMA	Precipitation	As a coating for implantable glucose sensors	281
(<i>S</i>)-Omeprazole	HEMA	Suspension	Enantioselective controlled delivery of racemic drug	287
Insulin	PMAA	Bulk	Insulin delivery system	288
Cyanuric acid	Bis-silylated triazine precursor	Sol-gel		282
BPA	MAA	Hydrogel inverse opals	Inverse opals hydrogels	283
Dox	4-Vpy	Bulk	Drug delivery system	289
HVA	Hemin, 4-Vpy	Precipitation	A novel catalytic system	284
PPT	PMMP	Bulk	Separation and enrichment of PPT	285
BPA	PAA	Phase inversion		181
Diclofenac	MAA	Bulk	Drug delivery system for diclofenac	290

Abbreviations: MAA, methacrylic acid; PAA, poly(acrylic acid); DXP, dexamethasone-21 phosphate disodium; DEAEMA, 2-(diethylamino) ethyl methacrylate; HEMA, poly(hydroxyethyl methacrylate); PMAA, polymethylacrylic acid; 4-Vpy, 4-vinyl pyridine; Dox, doxorubicin; HVA, homovanillic acid; PPT, podophyllotoxin; PMMP, 1-phenyl-3-methyl-4-methacryloyl-5-pyrazolone.

toward BPA was reversible in response to the acidity of the solution. Gong *et al.*²⁸¹ reported a pH-sensitive MIP nanospheres/hydrogel composite as a coating for implantable glucose sensors. The molecularly imprinted pH-sensitive nanospheres prepared by precipitation polymerization using dexamethasone-21 phosphate disodium (DXP) as the template molecule exhibited a faster DXP release rate at a lower pH value within the pH range tested (6.0–7.4). Fertier *et al.*²⁸² reported a pH-responsive imprinted bridged silsesquioxane obtained from a bis-silylated triazine derivative by the sol-gel hydrolysis condensation of the

precursor in the presence of cyanuric acid H-bonded through the three DAD (donor-acceptor-donor) faces. Mangeney's group²⁸³ proposed a strategy for the development of BPA optical sensors by the combination of molecularly imprinted hydrogels and photonic crystals. The hydrogel was made of a molecularly imprinted poly(methacrylic acid) reticulated using EGDMA as the cross-linker and BPA as the template molecule, and demonstrated excellent pH sensing performances. Zhao *et al.*²⁸⁴ presented a catalytic system based on an imprinted tetrapolymer of 4-vinylpyridine, hemin, acrylamide, and *N*-isopropylacrylamide

cross-linked by EGDMA with homovanillic acid as the template molecule, namely pH-sensitive and water-soluble nanospheric imprinted hydrogels, which was used as an enzyme mimic of horseradish peroxidase.

In addition to the widely used acidic or alkaline functional groups, a new pH-responsive functional monomer has been synthesized recently. Ding *et al.*²⁸⁵ explored a novel pH-responsive intelligent membrane with a predetermined affinity to podophyllotoxin (PPT) using an acyl pyrazolone compound 1-phenyl-3-methyl-4-methacryloyl-5-pyrazolone (PMMP) as the functional monomer. It was found that at pH values below 8.4, the molecularly imprinted composite membrane (MICM₂) led to a faster transport to PPT than 4'-demethylpodophyllotoxin (DMEP), achieving the maximal permeating selectivity at pH 2.5 with a PPT/DMEP selectivity factor of 2.82. However, at pH values above 8.4, MICM₂ preferentially permeated more DMEP than PPT, attributed to the tautomerization of β -diketone and enol of PMMP structure in response to the change in the pH value. This peculiar pH-control property would make it possible to use MICM₂ as a potential medicine control release material or separation material.²⁸⁵

3.3.5. Other responsive technologies. Besides the above four main kinds of SR-MIPs, there are salt ion and biomolecule responsive MIPs, *etc.* In 2010, Kempe *et al.*²⁹¹ found that salt ions had an influence on template binding to two models of MIPs, targeted towards penicillin G and propranolol, respectively, in water-acetonitrile mixtures. The results showed that in 100% aqueous solution, 3 M salt solutions augmented the binding of both templates, which followed the Hofmeister series with kosmotropic ions promoting the largest increase. This suggested that the hydration of kosmotropic ions reduced the water activity in water-poor media, providing a stabilizing effect on water-sensitive MIP-template interactions.²⁹¹ Recently, biomolecule-responsive hydrogels which undergo changes in the volume in accordance with the concentration of a target biomolecule, such as glucose and protein, have become increasingly important as smart biomaterials for drug delivery systems and molecular diagnostics, because they can sense the target biomolecule and undergo structural changes.²⁹² In 2012, Miyata²⁹³ prepared tumor-marker-imprinted hydrogels that shrank in the presence of a target-tumor marker glycoprotein by using various cross-linkers such as low-molecular-weight and high-molecular-weight cross-linkers. This design not only provided a basis for the development of useful biomolecule-responsive hydrogels as smart biomaterials but also provided more insight into key factors of molecular imprinting.²⁹³

3.3.6. Dual/multi responsive technology. Multi-stimuli responsive MIPs that are responsive to two or more stimuli have emerged, although they face great challenges in their synthesis. Moreover, multifaceted responsiveness can greatly enhance the versatility of these materials as they allow tuning of their properties in multiple ways rather than in a single way. Dual responsive polymers mainly include magnetic/thermo, magnetic/photo, thermo/photo, thermo/pH, and thermo/salt dual responsive MIPs (DR-MIPs), as can be seen in Table 9. For example, Yan *et al.*²⁹⁴ prepared temperature responsive magnetic MIPs (t-MMIPs) by adopting MAA and NIPAAm as the

Table 9 Summary of dual/multiresponsive MIPs

Type of polymer	Template	Responsive element	Method	Application	Ref.
Thermo/magnetic	2,4,5-Trichlorophenol	NIPAAm, Fe ₃ O ₄	Free radical	Selective separation and enrichment fields	294
Thermo/magnetic	SMZ	NIPAAm, γ -Fe ₂ O ₃	Free radical	Separation, drug release, protein recognition and so on	295
Thermo/magnetic	BSA	NIPAAm, Fe ₃ O ₄	Surface grafting	Chromatographic separation, solid-phase extraction, drug delivery, medical diagnostics and biosensors	296
Photo/magnetic	Caffeine	Fe ₃ O ₄ , MPABA	Suspension	Trace caffeine analysis in complicated samples	297
Thermo/photo	2,4-D	Azo, NIPAAm	ATRP	Separation, extraction, assays, drug delivery and bioanalytical analysis	298
pH/thermo	OB	p-VPBA, NIPAAm	Free radical	Chemical sensing and bio-separation	299
pH/thermo	OB	NIPAAm, boronic acid	Precipitation	Nanosensor for biological systems	300
pH/thermo	HRP	NIPAAm, p-VPBA	Surface imprinting	Solid-phase extraction, sensors, and especially protein delivery agents	301
Thermo/salt	BSA	NIPAAm, NaCl	Free radical		302
Thermo/salt/bio-molecule	Lysozyme or cytochrome c	NIPAAm, NaCl, bio-molecule	Free radical	Non-proteinaceous receptor	303
Photo/thermo/pH	Propranolol	Azo monomer, NIPAAm, DMAEMA	RAFT	Drug delivery and bioanalytical chemistry	183
Ionic strength/temperature/pH	BSA	Ca ²⁺ , NIPAAm, carboxyl groups of alginate	PPG and GIG method	Calcium alginate core-shell hydrogel microspheres	304

Abbreviations: SMZ, sulfamethazine; MPABA, 4-[(4-methacryloyloxy)phenylazo]benzoic acid; ATRP, atom transfer radical precipitation polymerization; azo, azobenzene; OB, ovalbumin; p-VPBA, 4-vinylphenylboronic acid; HRP, horseradish peroxidase; DMAEMA, 2-(dimethylamino)ethyl methacrylate; PPG, prepolymerization-gelating; GIG, gelating-*in situ* grafting.

functional monomer and temperature responsive monomer, respectively. The t-MMIPs were then applied to selectively recognize and release 2,4,6-trichlorophenol (TCP) molecules at 60 °C and 20 °C, respectively. The maximum binding amounts at 60 °C were 197.8 mg g⁻¹ and 122.6 mg g⁻¹ for t-MMIPs and their corresponding NIPs (t-MNIPs), respectively. At 20 °C, about 32.3–42.7% of TCP adsorbed by t-MMIPs was released, whereas 25.3–39.9% of TCP was released by t-MNIPs. t-MMIPs had demonstrated great potential for applications in selective separation and enrichment fields.²⁹⁴ In the same year, the same group²⁹⁵ developed other thermal-responsive magnetic MIPs (TMMIPs) as potential effective adsorbents for selectively removing sulfamethazine (SMZ) present in aquatic environments. The unique aspect of TMMIPs was that they combined molecular recognition, magnetic separation and thermo-responsiveness.²⁹⁵ Zhang *et al.*²⁹⁶ prepared a novel BSA surface-imprinted thermo-sensitive magnetic composite microsphere by the surface grafting copolymerization method in the presence of a temperature-sensitive monomer NIPAAm, a functional monomer MAA and a cross-linking agent *N,N*-methylenebisacrylamide (MBA). The thin imprinted shell presented favorable recognition performance to BSA, and the adsorption capacity and imprinting factor could reach 71.85 mg g⁻¹ and 1.70, respectively. Moreover, the adsorption and desorption of MIPs to BSA could be controlled by external temperature benefiting from thermosensitivity. This property enabled its potential application in rapid separation and purification of BSA.²⁹⁶

Chen *et al.*²⁹⁷ demonstrated the construction and characteristics of photonic and magnetic dual responsive MIPs (DR-MIPs) prepared by suspension polymerization. The resultant DR-MIPs of Fe₃O₄@MIPs exhibited specific affinity for caffeine by photoisomerization induced reversible uptake and release of caffeine upon alternate UV and visible light irradiation. The magnetic properties of DR-MIPs enabled fast and simple separation while the photonic responsive properties offered simple template elution with the assistance of UV-Vis irradiation, which proved potentially applicable for trace caffeine analysis in complicated samples.²⁹⁷

Zhang *et al.*²⁹⁸ obtained azobenzene (azo)-containing MIP microspheres with both photo- and thermo-responsive template binding properties in pure aqueous media. The introduction of NIPAAm brushes into the azo-containing MIP microspheres significantly improved their surface hydrophilicity and imparted thermo-responsive properties to them, leading to their pure water-compatible and thermo-responsive template binding properties. In addition, the binding affinity of the imprinted sites in the grafted azo-containing MIP microspheres was found to be photo-responsive toward the template in pure water, which proved to be highly repeatable under photoswitching conditions.²⁹⁸

Li *et al.*²⁹⁹ synthesized a pH and temperature dual-responsive macroporous protein imprinted cryogel by a facile “one-pot” method using NIPAAm and 4-vinylphenylboronic acid (*p*-VPBA) as the main functional monomers. With regulation of temperature and pH, the resulting MIP cryogels

exhibited excellent selectivity, satisfactory kinetics, and good regeneration for ovalbumin, which will open new opportunities for the selective purification and extraction of other template glycoproteins.²⁹⁹ In the same year, the same group³⁰⁰ synthesized monodisperse MIP nanospheres with smart shells based on covalently immobilized template and surface imprinting. The combination of the boronic acid group with thermo-sensitive imprinted layers led to a dual-responsive system capable of recognizing the target glycoprotein in response to changes in pH and temperature, which has great potential applications in chemical sensing and bio-separation.³⁰⁰ Besides, Tang *et al.*³⁰¹ described a molecularly imprinted fluorescence nanosensor for monitoring glycoproteins based on boronate affinity and thermo-sensitivity. The properties and performance of the prepared nanosensor for glycoproteins were regulated by controlling the pH value and temperature. Moreover, the nanosensor was successfully applied to the detection of horseradish peroxidase (HRP) in biological fluids.³⁰¹

Zhao *et al.*³⁰² presented a type of thermo-sensitive and salt-sensitive molecularly imprinted hydrogel for BSA by self-assembly of a basic functional monomer (DMAPMA) with BSA, which polymerized in the presence of NIPAAm. The resultant polymer showed sensitive responses to both temperature and ionic strength and a clear conformational memory of the template protein. Salt ions played an important role in the recognition process in aqueous solutions, which can screen the electrostatic interactions between the charged polymer chains and protein molecules. When the salt concentration increased, repulsive electrostatic interactions between the polymer chains were gradually screened. When NaCl was added to adjust the volume of MIPs, nonspecific adsorption was also inhibited. The presented approach is an attractive and broadly applicable method to develop solid polymer electrolyte membranes or electrode devices, sensors, and especially protein delivery agents with controlled-release.³⁰²

Compared to DR-MIPs, multi responsive MIPs are relatively less reported and there are only a limited number of articles. For example, Chen *et al.*³⁰³ obtained multiple-responsive protein imprinted polymers that can respond to temperature, salt concentration, and the corresponding template protein with significant specific volume shrinking using lysozyme or cytochrome *c* as a template, NIPAAm as a major monomer, MAA and AAm as functional co-monomers, and *N,N*-methylenebisacrylamide (MBAAm) as a crosslinker. The results implied that the combination of molecular imprinting and a stimuli-responsive polymer may be a useful method to obtain protein-responsive polymers that can undergo specific shrinking and binding in the presence of the template protein. Zhang *et al.*¹⁸³ described an approach to obtain narrowly dispersed pure water-compatible and multiple stimuli (*i.e.*, light, thermo and pH)-responsive MIP microspheres by grafting of dually responsive hydrophilic polymer brushes onto the preformed photo-responsive MIP particles. The strategy greatly reduced the complicated optimization for MIP formulations and allowed the efficient synthesis of intelligent MIPs with triple stimuli-responsive template binding properties, which made MIPs

highly useful for applications such as environmentally tunable drug delivery/release systems. Ying *et al.*³⁰⁴ prepared poly vinyl acetate grafted calcium alginate hydrogel microspheres with BSA as a molecular template. The rebinding and swelling properties of microspheres showed responsiveness toward ionic strength, temperature, and pH. The highest separation factor was 1.85 and imprinting efficiency was 1.75 when the Ca^{2+} ionic strength was 1.25 and 0.34 mol kg^{-1} , respectively. And the separation factor was found to be decreased as temperature increased from 29 to 45 °C, while the imprinting efficiency reached a peak value at about 37 °C. Separation factors of BSA imprinted microspheres at different pH values were also recorded and two peaks were found, which were considered to be caused by the similar swollen states due to ionic and covalent crosslinking structures of the modified microspheres.

To date, more and more researchers have focused on preparing SR-MIPs, and great advances have been made in the field of separation, sensors, drug delivery and biomedical applications. However, there are still some challenges and opportunities as follows. Firstly, responsive functional monomers are still limited for preparation of SR-MIPs, and more kinds of functional monomers should be developed to meet the requirements of various kinds of applications. Secondly, dual/multiple SR-MIPs are still scarce, and more attention should be paid to the combination of response elements involving core-shell structures or monomer copolymerization methods in the future development of SR-MIPs.

4. Applications of MIPs

As especially highlighted above, various smart technologies and strategies of MIT have attained rapid development, along with the continuous use and improvement of traditional polymerization procedures, which have greatly stimulated the rapid advancement of molecular imprinting, and therefore diversified novel MIPs with superior performances have been prepared. Consequently, more exciting and universal applications have been realized. For example, by introducing surface imprinting technology combined with hollow porous polymer synthesis technology into precipitation polymerization, MIPs with high adsorption capacity, imprinting efficiency, good morphology, uniform size and ideal surface properties are produced, which are particularly suitable as sorbents or stationary phases for sample pretreatment or chromatography. By introducing the composite imprinting material strategy into sol-gel processes such as preparation of nanomaterials and nanoimprinting, MIPs with excellent interface characteristics, electrical and optical properties are prepared, which are more suitable for chemical/biological sensing. Hence, attractive and competitive MIPs have found a wide range of applications, as diagrammatically shown in Fig. 13. As seen, MIPs are widely used in sample pretreatment and chromatographic separation (SPE, monolithic column chromatography, *etc.*) and sensing (electrochemical sensing, fluorescence sensing, *etc.*) of active

molecules, pharmaceuticals, environmental pollutants and so on. Representative applications of MIPs in purification/separation and sensing of real samples will be comprehensively summarized and discussed in this section as follows.

4.1. Sample pretreatment and chromatographic separation

4.1.1. Sample pretreatment. Especially for trace/ultratrace level analytes, samples should be enriched or transformed into optimal forms prior to the final instrument analysis. Choosing the appropriate sample pretreatment techniques plays an important role in qualitative and quantitative determination. Liquid liquid extraction (LLE) is the most widely used pretreatment technique while it has the disadvantages of large organic solvent consumption and low enrichment efficiency. In order to overcome those drawbacks, a series of extraction techniques have been developed, such as liquid phase microextraction (LPME), solid phase extraction (SPE), solid phase microextraction (SPME) and stir bar sorption extraction (SBSE). Although these extraction techniques have been applied to extract a wide variety of compounds ranging from high polarity to moderate polarity, they still lack selectivity and suffer from matrix interferences. Fortunately, MIPs have outstanding recognition performances towards target template molecules, and therefore they can be utilized as selective sorbent materials in the customized pretreatment techniques. In recent years, the applications of MIPs in pretreatment techniques have attracted particular attention and have become a favorite topic. In the following paragraphs, based on the technology development of MIT mentioned in the above Sections 2 “Fundamentals of MIPs” and 3 “Smart MIT for MIPs”, we will discuss the present progress in using MIPs in SPE, SPME, and SBSE, and summarize their applications in real samples.

4.1.1.1. Solid phase extraction (SPE). Ever since Sellergren proposed the potential of MIPs as SPE sorbents for the selective extraction of pentamidine from urine samples in 1994,³⁰⁵ numerous studies of the applications of MIPs in SPE have been reported. Among the various pretreatment techniques, SPE is most widely used for MIPs, called MISPE. MISPE sorbents are available in several forms, such as cartridges, disks, the SPE pipette tip, 96-well SPE microtiter plates and online precolumns. Taking the cartridge as an example, the prepared MIP sorbents are firstly packed into an empty SPE cartridge. Fig. 14A(a) shows the packing procedure of the MISPE cartridge. Then, the MISPE cartridge is conditioned and activated with sample-like solvents, and the samples containing target analytes which may be an aqueous or organic phase, are loaded on it. Subsequently, the analytes are eluted with solvents and collected after removing the unabsorbed molecules from the MIP sorbent. Fig. 14A(b) shows the general procedure of MISPE. The major impact factors of MISPE are the preparation of MIPs, sample loading, washing solvents and eluting solvents.³⁰⁶

In order to meet the requirements of high extraction recovery of MISPE, MIPs as sorbents should have good adsorption capacity, high selectivity and stability. Thus, studies of MISPE focus on the preparation of MIPs and several kinds of

Fig. 13 Structural diagram of the applications of MIPs in pretreatment techniques, chromatography and sensor. Abbreviations: SPE, solid phase extraction; DSPE, dispersive SPE; MSPD, matrix solid phase dispersion; SPME, solid phase microextraction; SBSE, stir bar sorption extraction; HPLC, high performance liquid chromatography; CEC, capillary electrochromatography; CLC, capillary liquid chromatography.

Fig. 14 Schematic diagrams of two modes of off-line MISPE. (A) The traditional procedure of off-line MISPE. (a) The prepared MIPs were packed into an empty SPE tube. Firstly, a frit was packed into the bottom of the SPE tube to support the sorbents. Then, amount of MIPs were packed into the above tube and filled homogeneously. Finally, another frit were packed on the MIPs sorbents and pressed with proper pressure. (b) The obtained MISPE tube was activated with sample-like solvents and liquid samples were loaded on it. After the impurities were washed from the MIPs sorbents, the target analytes were eluted with suitable solvents and collected. (B) The procedure of MIPs synthesized within the pores of commercial polyethylene frit, adapted from ref. 386. (a) The PE frit was connected to a commercial needle and immersed in the polymerization reagent. Then the polymerization was carried out by UV irradiation. (b) After polymerization, the template was removed from the imprinted PE frit. (c) The above imprinted PE frit without template was placed inside the SPE tube. Finally, the prepared frit MIPs SPE tube was used to off-line SPE which also includes the processes of condition, loading, washing and elution.

conventional preparative procedures have been commonly used, such as bulk polymerization,^{307–310} precipitation polymerization,^{311–313} suspension polymerization,^{314–317} and emulsion polymerization.³¹⁸ With the development of MIT, many more novel technologies and strategies have also been proposed for the preparation of MIPs with better performances, such as surface imprinting.^{319–321} Mechanisms and preparation processes of MIPs are provided in Sections 2 “Fundamentals of MIPs” and 3 “Smart MIT for MIPs”.

Samples loaded on the MISPE cartridge are mostly aqueous solutions rather than organic extracts. However, for the MIPs that are synthesized in organic solvents, when the aqueous samples are loaded, the remaining water on the cartridge from samples may influence the binding ability of the MIPs, resulting in poor recognition abilities for the target analytes. To solve these likely problems, more suitable, stable and easily reproduced MIPs should be synthesized to make them work well in polar solutions. Otherwise, extra processes are necessary, such as air drying of the MISPE cartridge.³²²

The washing step is also an important factor in the MISPE procedure. The purpose is to let the analytes retain by the selective binding forces while other interferents should be washed off.³²³ The analytes need to be bound strongly on the MIP sorbents so that washing solvents cannot elute them at all. Thus, the washing solvents should not disturb the selective interactions between MIPs and the analytes. Based on the above point, some kinds of solvents are widely used, such as dichloromethane, acetonitrile, methanol, acetone, and water.^{324–328}

Eluting the target analytes from MIP sorbents using a specific solvent is the last step of MISPE. The eluting solvent should be strong enough to release the analytes from the binding sites. In order to obtain high enrichment factors, small eluent volume is needed or an evaporation step is used to concentrate the analytes.³²⁹ However, the problem of template leakage may exist during the elution procedure, especially in trace and ultra-trace analysis. Recently, a series of strategies have been employed to reduce the bleeding of MIPs and enable them work well, such as the dummy imprinting strategy,³³⁰ and post treatment of MIPs with microwave assisted extraction,³³¹ accelerated solvent extraction³³² and supercritical fluid extraction.³³³

Hence, the optimized MISPE method should be based on the properties of MIPs, the interaction between MIPs and analytes, and the appropriate solvents used in the extraction procedure. Owing to the high selectivity of MIPs for the template molecule and its structural analogues, MISPE methods have already been applied in environmental,^{334–337} food^{338–340} and biological fields,^{341,342} *etc.* Besides, some companies have already developed commercial SPE cartridges packed with the specific MIPs for the determination of target analytes in different samples.³⁴³ Among these applications of MISPE, various modes of MISPE have been developed which can be classified as off-line MISPE,^{344–346} on-line MISPE,^{347–349} dispersive SPE (DSPE)³⁵⁰ and matrix solid phase dispersion (MSPD).^{351–353}

Off-line MISPE. So far, most MISPE methods have been performed in off-line mode, which is similar to the off-line SPE

technique with conventional sorbents. The main reasons are that operation and instrumentation are easy and simple, and many kinds of solvents and additives can be used for elution without considering their influences on analytical instruments. MISPE is often combined with high performance liquid chromatography (HPLC),³⁵⁴ gas chromatography (GC),³⁵⁵ capillary electrophoresis (CE),³⁵⁶ UV-Vis spectrometry³⁵⁷ and inductively coupled plasma optical emission spectroscopy (ICP-OES)³⁵⁸ for the determination of various analytes in environmental (river water, lake water, wastewater, seawater, groundwater, soil extracts, *etc.*), food, medicinal plants and biological samples (serum, urine, blood, plasma, *etc.*), as listed in Table 10. In this section, we will discuss the development of MIPs for SPE and the different kinds of MISPE methods, including some typical examples of single preparation methods and dual/multi combination methods.

Bulk polymerization is the preferred method to synthesize MIPs as sorbents for off-line MISPE, which has rapidly developed and has been widely used in many fields. To simplify the selection of functional monomers, Noguer *et al.*³⁵⁹ designed MIPs by computational screening of the library of functional monomers and synthesized them by bulk polymerization. Coupled with HPLC-UV, the method was applied to the determination of methidathion in olive oil, and the LOD and LOQ were 0.02 and 0.1 mg L⁻¹, respectively.³⁵⁹ In theory, the imprinted sites of MIPs that used a single molecule as a template can bind with the template specifically, but cannot show high affinity for the cogeneric compounds. In order to improve the MIP selectivity of the template, Qin *et al.*³⁶⁰ used two types of sulfonamides (SAs) as mixed templates to synthesize MIPs by bulk polymerization. The dual-template MIPs possessed more binding sites and stronger recognition ability, and consequently they were used in off-line SPE coupling with HPLC-DAD for the quantitative analysis of seven kinds of SAs in fish farming water, with high recoveries of 84.16–101.19% and the relative standard deviation (RSD) of 1.98–7.10%.³⁶⁰ Stimuli-responsive MIPs can undergo large conformational changes in response to light stimuli, and as a kind of “clean energy”, light can be manipulated precisely and rapidly. For instance, Li *et al.*³⁶¹ synthesized novel photoresponsive MIPs using a new water-soluble azobenzene derivative as a functional monomer, and the MIPs could efficiently extract guanine from beer (extracting 98.36%) and then release it into aqueous media under photocontrol.³⁶¹

Although bulk polymerization is the most popular and general method to prepare MIPs due to its attractive properties, the obtained block MIPs should be crushed, ground and sieved before being used and they are usually irregular in size and shape and have low polymer yield. In order to prepare MIPs with suitable physical characteristics (*i.e.*, size, shape, porosity, pore volume and surface area) and better imprinting performances, a number of classical polymerization procedures and smart technologies have been developed, such as multi-step swelling, suspension polymerization and precipitation polymerization procedures, and surface imprinting technology. Fu *et al.*³⁶² prepared MIP materials as SPE sorbents by a multi-step

Table 10 Applications of off-line molecularly imprinted solid phase extraction (MISPE)

Analyte	Template	Functional monomer	Crosslinker	Initiator	Porogen	Preparation method	Sample	Analytical method	LOD (ng mL ⁻¹)	Linear range (ng mL ⁻¹)	RSD (%)	Ref.
Tramadol	Tramadol	MAA	EGDMA	AIBN	Chloroform	Bulk polymerization	Human plasma, urine	MISPE-HPLC	1.2; 3.0	2.0–350	<3.8	307
mBP	mBP	4-VP	EGDMA	AIBN	Chloroform	Bulk polymerization	Bottle water	MISPE-HPLC	16.5	0.05–10.0 mg L ⁻¹	<11.1	308
QCA, MQCA	QCA	DEEMA	EGDMA	AIBN	THF	Bulk polymerization	Animal muscles	MISPE-HPLC	0.1–0.3 µg kg ⁻¹	0.1–10	<4.5	310
2-CP	2-CP-4-AAP	MAA	EGDMA	AIBN	ACN	Bulk polymerization	Water	MISPE-HPLC	0.05 ng L ⁻¹	10–100	1.2–5.5	336
Histamine	Histamine	Different kinds	TRIM	1,1'-Azobis(cyclohexanecarbonitrile)	DMF	Bulk polymerization	Wine	MISPE-HPLC-DAD	0.09 mg L ⁻¹	0.5–10 mg L ⁻¹	<5	338
FNT	FNT	MAA	EGDMA	AIBN	Toluene	Bulk polymerization	Tomato	MISPE-HPLC-DAD	0.050 µg g ⁻¹	0.13–2.0 µg g ⁻¹	<8.1	340
Dichlorvos	Dichlorvos	MAA, BMIM ⁺ PF ₆ ⁻	TRIM	AIBN	ACN/toluene = 3 : 1, v/v	RTIL-mediated bulk polymerization	Food	MISPE-HPLC	94.8 ng L ⁻¹	0.5–500	4.41	57
Pyrethroids	Cypermethrin	MAA	EGDMA	AIBN	ACN/acetone = 9 : 1, v/v	Bulk polymerization	Aquaculture seawater	MISPE-GC-ECD	16.6–37.0 ng L ⁻¹ ;	0.01–0.5 mg L ⁻¹	2.4–7.8	344
Bovine albumin	Bovine albumin	2-VP	EGDMA	AIBN	MeOH	Bulk polymerization	Blood serum, urine, whey and milk	MISPE-UV-Vis	0.67 mg L ⁻¹	20–200 mg L ⁻¹	<5	357
Tilmicosin	Tylosin	MAA	EGDMA	AIBN	Chloroform	Bulk polymerization	Feeds	MIP-SPE-HPLC	0.35 mg kg ⁻¹	1.0–100 mg L ⁻¹	<7.6	388
Kirenol	Kirenol	AM	EGDMA	AIBN	THF	Bulk polymerization	Chinese medicine	MISPE-HPLC-UV	0.75 µg mL ⁻¹	—	2.8	389
Artemisinin	Artemisinin	Styrene	EGDMA	AIBN	ACN	Bulk polymerization	Chinese medicine	MISPE-HPLC-UV	—	—	<4.14	390
ML	ML	MAA	EGDMA	AIBN	Chloroform	Bulk polymerization	Food supplement, freeze-dried meat samples	MISPE-HPLC	0.866; 0.897	6.86 × 10 ⁻⁷ –8.3 × 10 ⁻⁴ M; 1.56 × 10 ⁻⁶ –8.9 × 10 ⁻⁴ M	<9.4	391
(E)-Resveratrol	(E)-Resveratrol	4-VP	EGDMA	AIBN	ACN/ethanol = 5 : 1, v/v	Bulk polymerization	Wine, fruit juice	MISPE-HPLC-UV	1.5; 7.0	0.5–5 µg mL ⁻¹	<6	392
Digoxin	Digoxin	MAA	EDMA	AIBN	ACN	Bulk polymerization	Human urine	MISPE-sweep-MEKC	1–20 mg L ⁻¹	0.3 mg L ⁻¹	<7.3	393
CV	CV	MAA	EGDMA	AIBN	MeOH	Bulk polymerization	Seawater, seafood	MISPE-HPLC-DAD	0.1; 0.05 µg kg ⁻¹	0–200	2.74–4.62	394
Quinoxaline 1,4-dioxides	MEQ	MAA	EGDMA	AIBN	MeOH	Bulk polymerization	Feeds	MISPE-HPLC	—	—	<10	395
NAM	NAM	MAA	EGDMA	AIBN	Chloroform	Bulk polymerization	Pork liver	MISPE-HPLC	—	—	8	396
GTX2,3	Caffeine	MAA	EGDMA	AIBN	PVA	Suspension polymerization	Cultured dinoflagellate	MISPE-HPLC-FLD	—	—	2.75	314
Sudan dyes	Phenylamine and naphthol	MAA	EGDMA	AIBN	Chloroform	Suspension polymerization	Catsup	MISPE-HPLC-UV	0.002–0.007	0.01–2.5 µg g ⁻¹	<3.4	315
Ofloxacin	Pazufloxacin	MAA	EGDMA	AIBN	Chloroform	Suspension polymerization	Human urine	MISPE-HPLC	0.03	0.07–60	2.9–4.5	316

Table 10 (continued)

Analyte	Template	Functional monomer	Crosslinker	Initiator	Porogen	Preparation method	Sample	Analytical method	LOD (ng mL ⁻¹)	Linear range (ng mL ⁻¹)	RSD (%)	Ref.
Benzocaine	Benzocaine	MAA	EGDMA	AIBN	Chloroform	Suspension polymerization	Human serum and fish tissue	MISPE-HPLC-UV	—	—	1.26	317
OFL, LOM	2-Hydroxy-3-naphthoic and 1-methylpiperazine	MAA	EGDMA	AIBN	Chloroform	Suspension polymerization	Chicken muscle	MISPE-HPLC	0.005 µg g ⁻¹	0.025–2.0 µg g ⁻¹	<4.7	330
Dicofol	α-Chloro-DDT	MAA	EGDMA	AIBN	Chloroform	Suspension polymerization	Aquatic products	MISPE-GC-ECD	0.1 ng g ⁻¹	0.4–100 ng g ⁻¹	<5.6	363
Plant hormones	3-Hydroxy-2-naphthoic acid and 1-methylpiperazine	MAA	EDMA	AIBN	Chloroform	Suspension polymerization	Banana	MISPE-HPLC-UV	3.0–3.8 µg kg ⁻¹	0.04–4.00	<4.6	397
CTL	CTL	MAA	EGDMA	AIBN	Chloroform	Precipitation polymerization	Human serum and urine	MISPE-HPLC	0.2; 0.4	1–100; 2–100	2.5; 1.5	311
Andrographolide	Andrographolide	AM	EDMA	AIBN	ACN/toluene = 3 : 1, v/v	Precipitation polymerization	Chinese medicine	MISPE-HPLC	0.27–0.48	50–1600	3.1–4.3	312
Parabens	BuP	4-VP	EGDMA	AIBN	Chloroform	Precipitation polymerization	River water	MISPE-IC/MS	1 ng L ⁻¹	—	—	334
PEs	DINP (dummy template)	AM	Divinylbenzene	AIBN	toluene/ACN = 2 : 13, v/v	Precipitation polymerization	Plastic bottled beverage	DMI-SPE-GC	0.85–1.38	5.0–750.0	<5.49	398
2-Methoxyestradiol	Estradiol	MMA and GMA	EGDMA	AIBN	ACN	Precipitation polymerization	Rat plasma	MISPE-HPLC	0.02 µg mL ⁻¹	0.06–20 µg mL ⁻¹	<11.9	399
E2	E2	4-VP	EGDMA	AIBN	Mineral oil/toluene = 2 : 3, v/v	Precipitation polymerization	Dairy, meat samples	MISPE-HPLC-UV	—	1–500 nM kg ⁻¹	<8.38	400
SUHs	PS	MAA	TRIM	AIBN	Dichloromethane	Precipitation polymerization and bulk polymerization	Rice grain	MISPE-HPLC	10.1–50.0 ng L ⁻¹	0.40–20.0	—	401
S-(–)-Amlodipine	S-(–)-Amlodipine	MAA	EGDMA	AIBN	Toluene	Multistep swelling and polymerization	Plasma	MISPE-HPLC	—	0.25–8.00 µg mL ⁻¹	<9.1	362
Emodin	Emodin	MAA	EGDMA	AIBN	Ethanol	Surface imprinted polymerization	Kiwi fruit root	MIPs/MWNTs-SPE-HPLC	—	—	<4.0	319
Estrogen	E ₂	APTES	TEOS	—	Chloroform	Surface imprinted	Polluted water	MISPE-HPLC	12.0 ng L ⁻¹	0.05–300 mg L ⁻¹	<5	320
Olaquinox	Olaquinox	APTES	TEOS	—	DDW	Surface imprinted	Chick feed	MISPE-HPLC	68.0 ng L ⁻¹	—	9.8	342
BPA	BPA	APTES	TEOS	—	MeOH	Surface imprinted	Shampoo, bath lotion, cosmetic cream	MISPE-HPLC-FLD	0.001 µM	0.003–0.5 µM	<9	370
BPA	DDBP	4-VP	EGDMA	AIBN	Toluene	Surface imprinted	Tap, drinking, rain, lechate of one-off tableware	DMP-SPE-HPLC-UV	0.0152	0.076–0.912	<11	371
TCs	OTC	MAA	KH570	TEOS	ACN	Surface imprinted	Milk	MIP-HCM-SPE-HPLC	1.4–7.6	0.075–1.0 mg L ⁻¹	1.5–5.0	402
Dicofol	α-Chloro-DDT (dummy template)	AM	DVB	AIBN	Toluene/ACN = 2 : 13, v/v	Surface imprinted	Cabbage, tomato, carrot samples	IL-MIPs-SPE-GC-ECD	0.02 ng g ⁻¹	0.4–40.0 ng g ⁻¹	<7.6	403
Sudan IV	Sudan IV	APTES	TEOS	—	Chloroform	Surface imprinted	Chilli powder, duck egg	MISPE-HPLC	25.2 ng L ⁻¹	—	2.86	404

Table 10 (continued)

Analyte	Template	Functional monomer	Crosslinker	Initiator	Porogen	Preparation method	Sample	Analytical method	LOD (ng mL ⁻¹)	Linear range (ng mL ⁻¹)	RSD (%)	Ref.
TBPA	DPA	APTES	TEOS	—	MeOH	Surface imprinted	Tap, river, lake water	MISPE-RRLC-2	2	8.4–800	3.6	405
PBBs	TMB	γ -MPTMS	TMOS	—	DMF	Surface imprinted	Water, fish	MISPE-GC-ECD	2.0–8.0 ng L ⁻¹	0.01–5.0	<7.89	406
FQs	PAZ	APTS/MAA	EGDMA	AIBN	Chloroform	Surface imprinted	Tilapia samples	MISPE-HPLC	0.0063–0.0075 μ g g ⁻¹	0.05–25 μ g g ⁻¹	<4.9	407

Abbreviations: MAA, methacrylic acid; EGDMA, ethylene glycol dimethacrylate; AIBN, 2,2'-azobisisobutyronitrile; mBP, monobutyl phthalate; 4-VP, 4-vinylpyridine; QCA, quinoxaline-2-carboxylic acid; MQCA, methyl-3-quinoxaline-2-carboxylic acid; DEEMA, diethylaminoethylmethacrylate; THF, tetrahydrofuran; 2-CP, 2-chlorophenol; 4-AAP, 4-amino-anti-pyrene; ACN, acetonitrile; TRIM, trimethylolpropane trimethacrylate; DMF, *N,N*-dimethylformamide; ENT, fenitrothion; BMIM + PF₆⁻, 1-butyl-3-methylimidazolium hexafluorophosphate; RTIL, room temperature ionic liquid; ML, melamine; EDMA, ethylene dimethacrylate; CV, crystal violet; MeOH, methanol; MEQ, mequinol; GTX 2,3, gonyautoxins 2,3; PVA, polyvinyl alcohol; OFL, ofloxacin; 17 β -estradiol; SUHs, sulphonylurea herbicides; PS, pyrazosulphuron ethyl; APTES, γ -aminopropyltriethoxysilane; TEOS, tetraethoxysilane; DDW, double deionised water; BPA, bisphenol A; DDBP, 4,4'-dihydroxybiphenyl; TCs, tetracyclines antibiotics; OTC, oxytetracycline; KH570, methacryloxypropyltrimethoxysilane; DVB-80, divinylbenzene-80; TBBPA, tetrabromobisphenol A; DPA, diphenolic acid; PBBs, polybrominated biphenyls; TMB, 3,3',5,5'-tetramethylbenzidine; γ -MPTMS, γ -mercaptopropyltrimethoxysilane; FQs, fluoroquinolones; PAZ, pazufloxacin; APTS, 3-aminopropyltriethoxysilanes.

swelling polymerization procedure to specifically extract *S*-(–)-amlodipine from plasma in an aqueous system. Spherical polymer beads with uniform size and good monodispersity were obtained and the MIPs showed good recognition ability for the template molecule. The linear range of MISPE-HPLC was 0.25–8.00 μ g mL⁻¹ ($r = 0.9948$) and the recovery was 98.3% with RSD less than 9.1%.³⁶² The multi-step swelling polymerization method can be used to prepare monodispersed and uniformly sized MIPs, but two or more steps are required. To prepare molecularly imprinted microspheres using a simple procedure, by aqueous suspension polymerization, Yan *et al.* adopted the dummy template strategy to synthesize dicofol MIPs. The obtained MIP microspheres were monodisperse, spherical, and of uniform size, and the surface was porous and rough which was suitable for rebinding or releasing the target molecules from their surface. Using the dummy imprinting for preparing MIPs can eliminate template leakage. Good linearity of the proposed MISPE-GC-ECD method was achieved to determine the dicofol residue in fish and prawn products in a range of 0.4–100 ng g⁻¹ ($r^2 = 0.9995$) and recoveries at three spiked levels ranged from 85.8 to 101.2% for six aquatic products.³⁶³ Besides, precipitation polymerization is also a good choice to obtain surfactant/stabilizer-free imprinted polymer microspheres which are normally produced in a single preparation step with excellently controlled particle size and distribution.³⁶⁴ To obtain more hydrophilic groups of MIPs which can be used in polar solvents, Luo *et al.*³⁶⁵ used anion compounds as hydrophilic functional monomers to synthesize water-compatible MIPs by precipitation polymerization. Compared with strong anion exchange SPE (SAX-SPE) and mixture anion exchange SPE (MAX-SPE) which were also used to determine water-soluble acid dyes in soft drinks and wastewater, only the proposed MISPE could remove almost all of the matrix interferences and exhibit higher selectivity, recovery and enrichment ability.³⁶⁵

Although MIPs prepared by bulk polymerization, precipitation polymerization and multi-step swelling polymerization methods exhibit high selectivity and adsorption ability, the imprinted materials are usually thick, as a result the template molecule is difficult to elute.³⁶⁶ In order to overcome this drawback, surface imprinting technology has been proposed and developed, which has also been combined with other imprinting strategies. Many kinds of surface imprinted polymers have been synthesized based on silica nanoparticles, carbon nanotubes (CNTs) and magnetic nanoparticles (Fe₃O₄), and several excellent reviews have described the recent development.^{367–369} Taking silica material for example, Hu's group prepared highly selective MIPs for bisphenol A (BPA) on the silica nanoparticle support or at the surface of silica micro-particles by surface imprinting technology coupled with the dummy template strategy.^{370,371} The materials contained more recognition sites and most of the recognition sites were situated at the surface, which resulted in the rapid rebinding and easy removal of the target molecule. Both MIPs were used as SPE sorbents coupled with HPLC to determine BPA in chemical cleansing and cosmetic samples and real water samples.^{370,371}

Tian *et al.* established molecular imprinted ionic liquid-modified silica as an SPE sorbent for the extraction of tanshinones from the *Salvia miltiorrhiza* Bunge extract and functional drinks.³⁷² Carbon nanotubes have unique mechanical, thermal and chemical properties and an extremely large surface area, which are suitable as support matrices³⁷³ or shell materials to prepare MIPs.^{374,375} MCNTs@MIPs possess more imprinted cavities within the polymer network due to the high surface-to-volume ratio of MCNTs.³⁷⁶ Magnetic nanoparticles can not only act as support materials independently but also combine with silica nanoparticles (SiO_2),^{377–380} CNTs^{374,375} and attapulgite (ATP).¹⁹⁰ For magnetic SPE, magnetic MIP (MMIP) sorbents can be collected by an external magnetic field without additional centrifugation or filtration, which provides a relatively rapid and convenient method to extract the target analytes and separate/reuse the MMIPs.³⁸¹ Shi *et al.* used the dummy template strategy by surface imprinting polymerization to prepare MIPs for resveratrol (RH) with a super paramagnetic core-shell $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-MPS}$ as a support. The MMIPs were employed as SPE sorbents coupled with HPLC for the analysis of RH in real wine samples. The recoveries of spiked samples ranged from 79.3 to 90.6% with an LOD of 4.42 ng mL^{-1} .³⁸² Thermo-responsive monomers can control the adsorption and release of templates and can increase the mass transfer rate by changing temperature, and therefore by using the thermo-responsive monomer [*N*-isopropylacrylamide (NIPAm)], Shi *et al.* synthesized thermo-responsive magnetic MIPs (TMMIPs) *via* surface imprinting technology for selective recognition of curcuminoids in complex natural products.³⁸³ The obtained TMMIPs combined the advantages of surface imprinting technology, thermo-responsive technology and magnetic nanoparticles.

Apart from the classical SPE cartridge, MIPs are also used for SPE disks, the SPE pipette tip or other homemade devices. Compared with the classical SPE cartridge, a microdisk is used as a device for SPE to miniaturize the analytical system and reduce the consumption of organic solvents and samples. Queiroz *et al.* prepared parabens MIPs by the sol-gel process for microdisc SPE coupled with LC-UV to determine parabens in human milk samples.³⁸⁴ The MIPs exhibited high affinity and selectivity and a fast mass transfer rate. According to the optimum conditions, only 300 μL acetonitrile was used in the desorption process and the linear range of the MISPE-LC-UV method was from the LOQ values ($10\text{--}20 \text{ ng mL}^{-1}$) to 150 ng mL^{-1} ($r > 0.992$).³⁸⁴ Pipette tip SPE (PT-SPE) is another miniaturized form of SPE which uses a small amount of sorbent. Yan *et al.* synthesized ionic liquid MIPs (IL-MIPs) by precipitation polymerization and applied them as selective sorbents of miniaturized pipette tip SPE for the separation and extraction of dicofol from celery samples. The PT-SPE procedure used less IL-MIPs (2.0 mg) and consumed less washing solvent (0.8 mL $\text{ACN}/\text{H}_2\text{O} = 1:1$, v/v) and elution solvent (1.0 mL acetone–10% acetic acid).³⁸⁵ Furthermore, Barahona *et al.* developed a new form of MISPE, in which a small amount of MIPs was synthesized within the pores of commercial polyethylene (PE) frits by surface imprinting technology, as schematically illustrated in Fig. 14B.³⁸⁶ Similar to the MISPE cartridge, the prepared

frit-MIPs were loaded in a glass SPE column by the process of conditioning, loading, washing and elution. The modified PE frits showed excellent selectivity to thiabendazole in toluene media.³⁸⁶ Moreover, Yang *et al.* proposed a molecularly imprinted membrane (MIM) (containing an artificial nanocavity) as a solid phase receptor on the surface of glass slides. The MIM based double-receptor sandwich method was used for the extraction of adenosine triphosphate, and then fluorescence detection was performed for the analysis of adenosine triphosphate in a medicine injection, a medicine tablet and three human urine samples.³⁸⁷

On-line MISPE. Traditional off-line MISPE is usually time-consuming, solvent contaminative and poorly reproducible compared with on-line MISPE. Ever since Masqué *et al.* proposed the potential of on-line MISPE,⁴⁰⁸ two kinds of commonly used on-line MISPE methods have emerged, *i.e.*, packing pre-column and monolithic column. There are several advantages of on-line MISPE, such as reduction of the loss of analytes and the risk of contamination, shortened pretreatment time, decreased consumption of solvents, and improved reproducibility, which enhance detection sensitivity and increase the potential of automation.⁴⁰⁹ The important influencing factor of on-line-MISPE is the performance of MIPs which should provide fast mass transfer and good permeability. Thus, several typical studies have been proposed and have focused on the synthesis of MIPs with improved properties as follows.

In packing pre-column on-line-MISPE, MIPs are usually packed in a stainless steel column to extract the target analytes and the elute flows into the analytical column to detect by a switch valve. The basic schematic diagram is shown in Fig. 15A. In order to eliminate the interferences in water samples and increase the loading volume, Haginaka *et al.* prepared a restricted access media-MIP (RAM-MIP) for flufenamic acid by multi-step swelling polymerization followed by a hydrophilic surface modification technique.⁴¹⁰ The outer surfaces of RAM-MIPs were covered with a hydrophilic polymer which could decrease the non-specific interactions and give better selectivity factors than the corresponding MIPs. The RAM-MIP pre-column coupled with LC-MS/MS was applied for selective on-line extraction and determination of non-steroidal anti-inflammatory drugs (mefenamic acid, indomethacin, etodolac and ketoprofen) in river water samples.⁴¹⁰ To achieve faster diffusion of the analyte, Fang *et al.* synthesized a novel molecular imprinted silica gel microsphere by the surface molecular imprinting technique combined with a sol-gel process.⁴¹¹ The MIPs exhibited high selectivity and adsorption capacity and offered a fast kinetics for the adsorption and desorption of chrysoidine. The packed MIP pre-column was applied for on-line SPE coupled with HPLC to pretreat and determine chrysoidine in oil bean curd, yellow croaker and paprika with satisfactory recoveries (89.3–97.6%).⁴¹¹ To shorten the preparation time, Zhang *et al.* used attapulgite as a matrix and β -naphthol as the template to synthesize MIPs by ultrasonic irradiation which needed shorter preparation time (only 30 min) than the traditional heating method and showed better specific

Fig. 15 Schematic illustration of two modes of on-line MISPE. (A) An MIP packed column was used for on-line SPE analysis by a switch valve coupled with HPLC. The conditions, sample, washing and elution solvents were introduced into the SPE column by vacuum pumps. And the elution solvent was injected into the analytical column by a switch valve and analyzed by HPLC. (B) The polymerization of in-column MIPs for on-line SPE coupled with CE, adapted from ref. 415. Firstly, an irradiation window was made by burning the inlet end of separation capillary and the inner wall of the capillary was silylated to attach MIPs. Then, the capillary was filled with polymerization reagent and both ends were sealed with two rubbers. A LED lamp was placed in front of the window and irradiated. After the unpolymerized solution was flushed out with nitrogen gas, the capillary was sealed again for further polymerization by an LED lamp. Finally, the template was removed and MIP coated capillary was achieved and applied in on-line SPE coupled with CE.

recognition selectivity and faster mass transfer kinetic properties for estrogens.⁴¹²

Apart from the above types of online SPE columns, monolithic column has specific advantages of high reproducibility, versatile surface chemistry, rapid mass transport and easy preparation. Compared with the traditional *in situ* synthetic technique of MIPs, hybrid organic–inorganic materials have significant advantages, such as good thermal stability, high hardness, excellent biocompatibility and good flexibility.⁴¹³ Lv *et al.* prepared a novel molecularly imprinted organic–inorganic hybrid composite monolithic column (MIP-HCMC) based on monolithic synthesis in combination with hybrid composite and sol–gel technology.⁴¹⁴ MIP-HCMC was used as a pre-column in on-line SPE coupled with HPLC for the determination of fluoroquinolone residues in milk, and satisfactory purification and enrichment effects were obtained under the optimized conditions. The LODs and LOQs were 1.69 and 5.63 $\mu\text{g kg}^{-1}$ for ofloxacin, 1.63 and 5.43 $\mu\text{g kg}^{-1}$ for lomefloxacin, 3.74 and 12.5 $\mu\text{g kg}^{-1}$ for ciprofloxacin, 1.37 and 4.56 $\mu\text{g kg}^{-1}$ for enrofloxacin, respectively.⁴¹⁴

Most of the MISPE techniques usually couple with HPLC or GC for the determination of target analytes. Moreover, capillary electrophoresis (CE) is also an important and widely used separation tool owing to its advantages of high resolution, fast

separation and small sample/reagent consumption. Recently, a simple in-column MISPE concentrator *via* directly coating a short layer of MIP materials at the inlet end of the inner wall of the separation capillary has been developed for CE.⁴¹⁵ Lee *et al.* proposed miniaturized light emitting diode induced polymerization (LEDIP) technology for ease of operation and online fabrication of MISPE sorbents. The schematic illustration of the preparation of an in-column MISPE sorbent using an LEDIP system is shown in Fig. 15B. Under the optimum synthesis conditions, a thin and porous MIP layer was coated on the pretreated separation capillary, which allowed the fast desorption of analytes and offered online preparation of the samples for CE with high separation efficiency. The MIP polymer layer could still be retained inside the capillary after exceeding 100 cycles of the MISPE process and the MISPE concentrator could be regenerated online by the LEDIP system with a reproducibility of 14.5% (RSD, $n = 3$). The adsorption equilibrium of methyltestosterone was reached after 15 min and the desorption equilibrium time was only 20 s which meant a low band broadening effect. This technique was successfully applied to analyze urine samples, and most of these background components in the urine samples were not present in the electropherogram and the baseline for spiked urine samples was nearly as clean as standard solutions.⁴¹⁵

DSPE. Dispersive SPE (DSPE) is based on the SPE methodology, but for the procedure of DSPE, the sorbent is directly added into the sample matrix without packing in a column and conditioning.⁴¹⁶ After extraction, the MIP sorbents should be separated from the samples by centrifugation or filtration. Compared to MISPE, MI-DSPE needs a small amount of MIPs and can also eliminate matrix interferences.

For example, Hu *et al.* prepared ractopamine imprinted polymers by bulk polymerization and used them as DSPE sorbents for analysis of trace β -agonists in pig tissues.⁴¹⁷ 20 mg of MIPs was used for the DSPE procedure which was carried out by shaking and centrifugation, and then the MIPs containing target analytes were desorbed using a methanol/acetic acid mixture. After the nitrogen drying step, re-dissolved solution (methanol) was injected into the HPLC system for analysis.⁴¹⁷ To overcome the disadvantage of traditional MIPs, such as incomplete template removal, slow mass transfer and small binding capacity, Zhang *et al.* developed a new programmed heating method to imprint sulfonylurea herbicides at the surface of silica nanoparticles.⁴¹⁸ A uniform imprinted polymer layer with controllable thickness was formed after the programmed heating and used as a DSPE sorbent which showed large adsorbing capacity and high selectivity for sulfonylurea analogues. The MI-DSPE coupled with HPLC method achieved good linearity for four sulfonylurea herbicides in the range of 0.04–1.00 $\mu\text{mol L}^{-1}$ with correlation coefficients of 0.9917–0.9990. The LODs and LOQs were in the range of 0.004–0.013 $\mu\text{mol L}^{-1}$ and 0.013–0.04 $\mu\text{mol L}^{-1}$, respectively. The developed method was also applied to the simultaneous analysis of sulfonylurea herbicides in soil, rice, soybean and corn samples.⁴¹⁸

MSPD. Classical pretreatment techniques, such as LLE, SPE, cloud point extraction (CPE) and dispersive liquid liquid microextraction (DLLME), cannot be directly applied for semi-solid and solid samples, which should be pretreated with liquid solutions to meet the demand of those extraction methods. Moreover, matrix interferences of semi-solid and solid samples are usually present and difficult to eliminate. Matrix solid phase dispersion (MSPD) is one of the most promising techniques to reduce these matrix interferences and carry out the process of disruption, extraction and clean-up of semi-solid, solid or high viscous samples in a single step.⁴¹⁹ In MSPD, a sample matrix is directly mechanically blended with suitable sorbents which are packed in a column and subsequently washed and eluted with solvents. This technique can save the pretreatment time and the consumption of organic solvent, which has been increasingly applied for food and biological samples.^{420–423} However, the common sorbents of MSPD, such as C₁₈, C₈, silica and florisil, lack selectivity towards target analytes and easily subjected to interference by non-target substances with similar characteristics.^{424,425}

To solve the above problem, Chen's group prepared atrazine MIPs by bulk polymerization and used them as MSPD sorbents coupled with micellar electrokinetic chromatography (MI-MSPD-MEKC) to extract and determine four triazines.⁴²⁶ The prepared atrazine MIPs showed a rough surface, large dimensional pores and satisfactory mechanical strength, which could selectively adsorb atrazine and its analogs and significantly eliminate the matrix interferences. The developed MI-MSPD-MEKC method was successfully applied for the simultaneous determination of four triazines in soil, strawberry and tomato samples.⁴²⁶ To solve the problem of template leakage, Yan *et al.* adopted the dummy template strategy to synthesize MIPs by bulk polymerization, and used them for MSPD coupled with HPLC for simultaneous extraction of four auxins from orange samples.⁴²⁷ The advantages and potential of surface imprinting technology have received much attention, Wang *et al.* synthesized surface imprinted hybrid organic-inorganic silica nanoparticles and used as sorbents of MSPD for the specific recognition of methyl parathion in pear and green vegetable samples. The obtained MIPs have high affinity and more surface exposed binding sites and are used for the transfer of template molecules.⁴²⁸

Multi-pretreatment techniques. Until now, a number of various pretreatment techniques have been developed to enrich, clean up and extract target analytes from different samples. However, one single pretreatment technique often cannot meet the requirements of trace and ultra-trace analysis, especially in complicated matrices. Recently, multi-pretreatment techniques have been proposed based on MIPs and applied for biological and food samples,^{429–431} such as MISPE-DLLME^{432–434} and MI-MSPD-DLLME.⁴³⁵

DLLME based on a ternary component solvent system has several advantages such as short extraction and equilibrium time, less organic solvent consumption, high recovery and an enhanced enrichment factor.⁴³⁶ However, due to the lack of good selectivity, DLLME is not suitable for extraction of target

analytes from complex samples. Recently, Mudiam's group used MISPE-DLLME as the pretreatment technique to determine *t,t*-muconic acid (*t,t*-MA) in urine samples⁴³² and 3-phenoxybenzoic (3-PBA) acid in rat liver and blood samples.⁴³³ In MISPE-DLLME, the elution solution obtained from the MISPE procedure was used as the disperser solvent of DLLME and mixed with an extraction solvent. The mixture was rapidly injected into the aqueous solution to form a cloudy solution containing fine droplets of extraction solvent. After centrifugation, the sediment solution with or without subsequent treatment was injected into a related instrument for analysis. To meet the requirement of GC-MS for quantitative determination of polar analytes (3-PBA), MISPE-DLLME with injector port silylation was used to enhance the sensitivity and reduce the derivatization time.⁴³³ Besides, Yan *et al.* synthesized MIPs by aqueous suspension polymerization using the dummy template strategy for the MSPD procedure, and then MI-MSPD combined with DLLME was used for the simultaneous determination of four Sudan dyes in egg yolk samples.⁴³⁵ The solid sample was directly blended with MIP microspheres, and the elution solution of MSPD was used as a disperser of DLLME for purification and enrichment of the analytes before HPLC analysis.⁴³⁵

4.1.1.2. Solid phase microextraction (SPME). SPME was first proposed by Pawliszyn and coworkers in the early 1990s⁴³⁷ and has been widely used for sample preparation in the analytical laboratories due to its simplicity, solvent free and time-saving process. Some reviews have reported the advancement of SPME and its applications.^{438–441} Fiber SPME is the most widely used method and a series of materials have been used as fiber coatings, such as polydimethylsiloxane (PDMS), carboxen (CAR), divinylbenzene (DVB), carbowax (CW), polyacrylate (PA) and polypyrrole.^{442–445} However, only a few types of materials are commercially available which show poor selectivity for polar compounds or complex matrix samples during the extraction process.⁴⁴⁶ Therefore, it is urgently imperative to develop SPME fiber coatings with high selectivity, sensitivity and reproducibility. Owing to the special characteristics of MIPs, such as high specificity, good chemical stability and easy preparation, they are very suitable for SPME, and the SPME based on MIPs is named MISPME. Similar to SPME, in MISPME, the target analytes attain partition equilibrium between the sample and the MIP stationary phase. Then the analytes were thermally desorbed directly into the injection port of GC or eluted with suitable solvents for HPLC. The procedure of MISPME is shown in Fig. 16C. Since the introduction of the MISPME method by Koster's group,⁴⁴⁷ its various patterns have been developed and coupled with analytical instruments to determine diverse compounds in environmental, biological and food samples. Based on MIPs and SPME support materials, MISPME has different modes, such as MIP coated fibers, MIP monolithic fibers and in-tube MISPME.

MIP coated fibers. MIP coated fiber is the most commonly used mode of MISPME and has been developed rapidly in many fields. MIPs were synthesized on the surface of SPME fibers which commonly include glass capillary,⁴⁴⁸ silica fiber⁴⁴⁹ and

Fig. 16 Schematic diagrams of two modes of MISPME. (A) The polymerization procedure of one pattern of MIPs coated SPME fiber, adapted from ref. 455. Firstly, windows at one side of two different bore silica capillaries were prepared by burning the polyimide protecting layer. After cleaning and silylation of the small bore capillary, it was inserted into the larger bore capillary to form a sleeve as mold. Then, the polymerization solution was introduced in the interspace between two capillaries and both of the two capillaries ends were sealed with rubbers. The polymerization was triggered by UV light or heat. Finally, the larger bore capillary was etched away and MIPs coating with controlled thickness was formed on the surface of the window of inserted capillary. (B) The polymerization procedure of one pattern of MIP monolithic SPME fiber, adapted from ref. 468. At first, window at one side of silica capillary was prepared by burning the polyimide coating. With the help of a syringe, the capillary was filled with polymerization solution and both ends of the capillary were sealed with rubbers. The polymerization was triggered by UV light or heat. At last, the silica wall of capillary was etched away and MIP monolithic fiber was obtained after removing the template. (C) The procedure of MISPME. The prepared MIP coated fibers or MIP monolithic fibers with the aid of the SPME holder were used to complete the SPME procedure. Then, the MISPME fibers containing target analytes were desorbed by GC or HPLC.

stainless steel fiber (SSF).⁴⁵⁰ For instance, Buszewski's group prepared two novel MIP coated SPME fibers by the improved electrochemical polymerization method using SSF as mold and applied them to the determination of antibiotic drugs in biological samples (synthetic body fluids, human plasma and human whole blood samples).^{451,452} Both these MISPME coatings showed good selectivity, satisfactory extraction efficiency and high reproducibility without any influence of interferences commonly existing in biological samples.^{451,452} To control the thickness of the SPME fiber, Hu *et al.* used a surface reversible addition-fragmentation chain transfer polymerization method coupled with grafting on the silica fiber to achieve ultra-thin MIP coated SPME fibers with about 0.55 μm thickness, for the determination of Sudan dyes in complicated samples (chili tomato sauce and chili pepper samples). The MIP coating was highly dense and homogeneous with porous structure which could provide powerful capabilities of sufficient template elution, fast adsorption and desorption of analytes.⁴⁵³ To overcome the limitation of MISPME fiber in its application to aqueous media, Li *et al.* used a sol-gel technique to prepare water-compatible MIPs for SPME coupled with GC, and applied them to the determination of trace organophosphorous (OPPs) in vegetable (cucumber, green pepper, Chinese cabbage, eggplant and lettuce) samples. The MIP fiber showed excellent thermal and chemical stability and relatively high selectivity in real aqueous samples instead of hydrophobic organic solvents.⁴⁵⁴ Except the commonly used fibers, Tan *et al.* developed a novel MIP coated SPME fiber by using a capillary inserted into a large bore capillary to form a

sleeve as mold. The schematic diagram of the preparation of the MIP coated SPME fibers is shown in Fig. 16A.⁴⁵⁵ Two new capillaries with different bores were cut to appropriate length with the same size of windows. The smaller bore capillary was inserted into the larger bore capillary to form a sleeve. The prepolymer solution was introduced into the interspace between the two capillaries, followed by polymerization under UV photoirradiation. After polymerization, the larger bore capillary was etched away with hydrofluoric acid, and MIP coating with controlled thickness on the surface of the inserted capillary was obtained. The MI-SPME fibers coupled with HPLC were successfully applied to selectively extract BPA from tap water, human urine and milk samples.⁴⁵⁵

In most cases, only one MIP coated SPME fiber could be obtained in a synthesis process, because the fibers placed in one tube easily adhere together.⁴⁵⁶ Therefore, improving the preparation yield and efficiency became a serious problem to be urgently solved. Recently, Zhang *et al.* synthesized MIPs coated on the modified SSF in a capillary and five capillaries were put into the same reaction solution to obtain good repeatability. The MIP fibers were applied to extract ofloxacin from milk, with the recovery of 89.7–103.4%.⁴⁵⁷ Hu *et al.* developed a simple strategy to prepare MIPs coated on SSF on a large scale. More than 20 MIP coated fibers could be obtained in one glass tube by the improved multiple bulk co-polymerization method. The obtained Sudan I MIP coated SPME fibers coupled with HPLC were applied for fast and selective determination of Sudan dyes in hot chilli powder and poultry feed samples.⁴⁵⁸ As we know,

automation is a very important tool in the practical application of sample pretreatment, which can reduce analysis time, increase sample throughput and eliminate the human errors.⁴⁵⁹ Lan *et al.* developed a new automated magnetic MIP (MMIP) coated SPME fiber for quantitative enrichment of estrogens in milk powder.²⁰² MMIPs were synthesized using core-shell $\text{Fe}_3\text{O}_4@\text{SiO}_2$ nanoparticles as a magnetic support and 24 electromagnetic SSFs were placed parallelly for simultaneous extraction. Compared with traditional MISPME, the proposed procedure is time-saving and organic solvent-free.²⁰²

MIP monolithic fibers. Molecularly imprinted monoliths (MIMs), which combine the advantages of molecular imprinting and monolithic columns, were firstly proposed by Matsui *et al.* in 1993.⁴⁶⁰ Since then, MIMs have been an effective tool for separation and extraction of target analytes and have developed rapidly.^{461–463} To date, a number of studies have used MIMs as sorbents of SPME coupled with GC or HPLC and then successfully applied them in food and biological samples. In MIM-SPME, the preparation of imprinted fibers was completely different from the above-mentioned procedures and quite simple. It is based on the direct synthesis of MIMs using different kinds of capillaries as mold, which are etched away after polymerization.⁴⁶⁴

For instance, Wu *et al.* prepared an ephedrine imprinted monolith by *in situ* polymerization with silica capillary as a mold coupled with CE for selective determination of ephedrine (E) and pseudoephedrine (PE) in biological samples. The obtained MIP fibers were used for at least 50 extraction cycles without significant decrease in their extraction ability.⁴⁶⁵ Through controlling the surface of the MIP monolithic fiber, Gan *et al.* synthesized MIP monolithic SPME fibers using two kinds of molds, polytetrafluoroethylene (PTFE) capillary and silica capillary. These two kinds of fibers were used to extract four sulfadimidines from milk and Pearl river water samples. The results indicated that the PTFE-MI-SPME monolithic fiber showed highest selectivity toward sulfadimidine in complex samples.⁴⁶⁶ Chen *et al.* synthesized a pirimicarb imprinted polymer monolith in a micropipette tip and applied it to the polymer monolith microextraction (PMME) which is a type of SPME using a polymer monolith as a sorbent.⁴⁶⁷ The MIP monolith could be connected with syringes of different sizes simply without any other treatment to perform the PMME process. The monolith showed high specific recognition for pirimicarb in tomato and pear samples coupled with HPLC determination.⁴⁶⁷ In order to cope with the difficulty in the selective recognition of MIPs in aqueous media, Martín-Esteban *et al.* prepared MIP monoliths and used them in supported liquid membrane (SLM) protected MISPME.⁴⁶⁸ The preparation procedure of the MIP monolithic fiber is depicted in Fig. 16B. For the extraction procedure, the monolithic MIP fibers were located inside a polypropylene hollow capillary and protected by an organic solvent immobilized as a thin SLM in the pores of the capillary wall. The proposed pretreatment technique was optimized and used for the determination of thia-bendazole (TBZ) in spiked orange juices combined with HPLC.

The detection limit of $4 \mu\text{g L}^{-1}$ was low enough to permit the satisfactory analysis of TBZ in real samples according to the European regulation.⁴⁶⁸

In-tube MISPME. In-tube SPME is developed from the fiber-based SPME technique, and it uses a capillary column as an extraction device including open tubular, packed capillary and monolithic capillary techniques.⁴³⁸ The main advantages of in-tube SPME are overcoming the mechanical stability problems of fiber-based SPME and being suitable for automation.⁴⁶⁹ In-tube MISPME was first proposed by Mullett *et al.* in 2001, and the MIPs prepared by bulk polymerization were packed into a capillary column which was used as a simple automatic device coupled with HPLC to determine propranolol in biological fluids.⁴⁷⁰ From then on, numerous studies have been carried out in order to improve the mechanical resistance and extraction efficiency.

Recently, in-tube SPME based on MIPs has been developed as a valuable technique for sample pretreatment, which has relatively low backpressure, large adsorption capacity, high extraction efficiency and short extraction time.⁴⁷¹ Zhang *et al.* synthesized a MIP monolithic column in a fused silica capillary column by *in situ* polymerization combined with the dummy template strategy. The prepared column was used for in-tube MISPME coupled to CE and for the electrochemical detection of 8-hydroxy-2'-deoxyguanosine in human urine.⁴⁷² To improve the extraction capacity, Hu *et al.* established a novel fiber-in-tube SPME method by longitudinally packing multiple molecularly imprinted fibers into a polyetheretherketone (PEEK) tube as the online extraction unit.⁴⁷³ The MIP coated silica fibers were manually inserted into the hollow PEEK tube one by one with longitudinal arrangement. The method was applied to the analysis of fluoroquinolones in pork liver and chicken samples with RSDs less than 7.2%. To extend the method, two different MIP fibers, ofloxacin and sulfamethazien MIPs, were inserted into the PEEK tube in order to achieve the simultaneous extraction of these two antibiotic drugs. The results showed that the hydride packing strategy could simultaneously enrich multiple target analytes in complicated samples.⁴⁷³

4.1.1.3. Stir bar sorption extraction (SBSE). SBSE, which was firstly developed by Baltussen *et al.* in 1999, is derived from SPME and has a similar extraction mechanism to that of SPME.⁴⁷⁴ SBSE possesses some advantages, such as a high enrichment factor, good reproducibility, high adsorption capacity and solvent-free, and has been applied in environmental, food and biological samples. The SBSE device comprises a magnetic stir bar covered with a polymeric coating, and the extraction process is based on the partitioning equilibrium of target analytes between the stationary phase and the samples.⁴⁷⁵ Several variables affect the extraction efficiency of SBSE, such as extraction time and temperature, sample pH, the stir rate and sample volume. The coating of SBSE is an essential factor in enhancing the retention of analytes.⁴⁷⁶ However, at present, only a PDMS coated stir bar is commercially available, restricting the applications to the extraction of polar compounds. Recently, with the advance of MIPs, the combination of molecular

imprinting with SBSE (MISBSE) has provided novel sample pretreatment methods with high selectivity and easy operation.

Initially, the MIP-SBSE device used a commercial PDMS coated stir bar as a substrate during the synthesis process.⁴⁷⁷ After that, many modified methods have been developed. For instance, Turiel *et al.* prepared a TBZ MIP coated magnetic stir bar by two different procedures based on physical or chemical coating.⁴⁷⁸ Li's group prepared a series of MIP coated stir bars by glass capillary filled with a magnetic core as a substrate.^{479–483} MIPs were linked to the stir bar by chemical bonding through silylation of the substrate surface followed by multiple co-polymerization reactions. The MIP coated stir bars have been successfully applied to the determination of triazine herbicides, β_2 -agonists, triazole fungicides, sulfa drugs, trimethoprim and sulfonamides in environmental, biological and food samples.^{479–483} To improve the extraction capacity, Hu *et al.* prepared a stir bar coated with dummy MIPs (DMIPs) for BPA by the sol-gel technique.⁴⁸⁴ The scanning electron micrographs of the DMIP coated bar showed that the DMIP coating was homogeneous with a thickness of $57 \pm 2.5 \mu\text{m}$. During the extraction process of BPA, DMIP coated stir bars exhibited high specific affinity and good anti-interference ability and avoided the problem of template leakage.⁴⁸⁴ Functionalized magnetic nanoparticles have been widely used because of their higher hydrophilicity, stability and surface area compared with traditional MIPs. Zhou *et al.*⁴⁸⁵ prepared a vanillin molecularly imprinted stir bar based on Fe_3O_4 @polyaniline nanoparticles using the magnetic field-induced self-assembly process. The magnetic complexes were adsorbed on the surface of the magnetic stir bar under magnetic induction, and the coating of MIPs was generated by one-step co-polymerization. The MIP stir bar coupled with HPLC-UV was applied to the determination of vanilla-flavor enhancers (vanillin, ethyl maltol and methyl vanillin) in infant milk powders, with the wide linear ranges of $0.01\text{--}100 \mu\text{g mL}^{-1}$, $0.02\text{--}100 \mu\text{g mL}^{-1}$ and $0.03\text{--}100 \mu\text{g mL}^{-1}$, respectively, and LODs of $2.5\text{--}10.0 \text{ ng mL}^{-1}$.⁴⁸⁵

Although the stir bar is easier to be interfaced into a GC injector for online desorption than HPLC, excitingly, Hu *et al.* developed a MIP coated stir bar coupled with HPLC for online desorption and analysis of nine triazines in rice samples, based on a special homemade interface.⁴⁸⁶ A heatable quad-port interface was designed and divided into two parts, the upper part and the lower part, to easily load and remove the stir bars. The upper part of the interface for solvent outflow possessed one outlet port, while the lower part possessed three axisymmetric inlet ports that were converged at the root of the device. The heatable interface was connected with a precision syringe pump for online liquid desorption of SBSE and introduction of the desorbed analytes into HPLC. Compared with two off-line desorption methods, ultrasonic-assisted desorption (UAD) and static thermal desorption (STD), the proposed method showed higher sensitivity and reproducibility.⁴⁸⁶

From the above discussion, we can see that MIPs have been successfully applied to several kinds of pretreatment techniques, such as SPE (off-line MISPE, on-line MISPE, DSPE, MSPD), SPME (MIP coated fibers, MIP monolithic fibers, in-tube MISPME),

and SBSE. But only one or two kinds of techniques based on MIPs are used commercially and there are still many key problems associated with MIP development to be solved before commercialization. The application of MIPs to real sample analysis also suffers from some problems, such as the incompatibility of MIPs to the aqueous samples, low sample-loading capacity of MIPs in complex matrices, low automation and miniaturization of pretreatment techniques based on MIPs, and so on. Thus, further development of MIPs is urgently required.

4.1.2. Chromatographic separation. Besides their wide range of applications in pretreatment techniques, MIPs are also used as stationary phases in chromatography techniques, such as HPLC,⁴⁸⁷ capillary electrochromatography (CEC),⁴⁸⁸ capillary LC (CLC)⁴⁸⁹ and thin layer chromatography (TLC),⁴⁹⁰ as packing materials and monolithic column materials, due to their high affinity and selectivity to the target analytes.

4.1.2.1. Packing materials for chromatography. As packing materials, MIPs are packed into a chromatography column by a slurry packing method and used as the stationary phases of chromatography for the separation of template analytes. The commonly used bulk polymerization technology can afford MIPs with irregular size and shape, which has an impact on the chromatographic performance.⁴⁹¹ For instance, Ansell *et al.* synthesized (–)-ephedrine-MIPs by bulk polymerization and used them as stationary phases in supercritical fluid chromatography (SFC) for the separation of ($\pm$)-ephedrine enantiomers. Compared to MIPs packed into the HPLC column, better resolution and separation at high sample loading were achieved in SFC using an amine modifier. The MIP stationary phases were stable under the conditions employed and the chromatography was reproducible.⁴⁹² To prepare monodispersed MIPs, Kitahara *et al.* synthesized MIPs by the templating polymerization method using cholesterol-immobilized silica gel which was packed into an HPLC column for selective recognition of cholesterol. The recognition ability of the MIP column was evaluated using cholesterol, cholesterol esters and fatty acid methyl esters by comparison with the NIP column, which showed a high affinity with $K_{\text{MIP}}'/K_{\text{NIP}}'$ imprinting factors of >5.7 .⁴⁹³ To obtain small sized molecularly imprinted microspheres, Lai *et al.* synthesized MIPs ($3\text{--}5 \mu\text{m}$) by precipitation polymerization and used them as HPLC and SPE packing materials for the analysis of an anti-AIDS drug emtricitabine (FTC). Chromatographic evaluation and characterization illustrated that the MIP column exhibited good recognition and affinity to FTC with the imprinting factor of 2.26.⁴⁹⁴ In addition, fast chromatography is now regarded as a convenient method for the concentration and preliminary purification of organic products, which has the advantages of high loading capacity, ease of automation and suitability for large-scale separation.⁴⁹⁵ Meng *et al.* successfully used flash column chromatography packed with MIPs synthesized by dispersion polymerization for the extraction of shikimic acid from Chinese star anise.⁴⁹⁶ The MIPs showed good affinity ($21.94 \mu\text{mol g}^{-1}$) and specificity ($I = 4.2$) toward shikimic acid. And the MIP flash column could be reused for 4 rounds with acceptable loss of capacity (15%). Compared with

HPLC, these results showed that flash chromatography packed with MIPs is a more rapid, simple, feasible and economical method to obtain highly purified active ingredients from plants on a large scale.⁴⁹⁶

4.1.2.2. Monolithic column materials for chromatography.

Compared with packed columns, the monolithic column is considered as a well-established stationary phase for chromatographic analysis which is generally formed *in situ* from the reactant solution without the need for frits and with easy preparation.⁴⁹⁷ In recent years, monolithic molecular imprinting has attracted significant interest and represents a novel method for the preparation of stationary phases, which combines the advantages of monolithic column and imprinting technology. Monolithic MIPs are prepared in a simple process directly within stainless steel columns or capillary columns, avoiding the tedious procedure of grinding, sieving and column packing. Up to now, monolithic MIPs have been widely applied as stationary phases in HPLC, CEC and CLC owing to their ease of preparation, high reproducibility, large surface area, low backpressure and fast mass transport.

Zhang *et al.* synthesized macroporous molecularly imprinted monolithic polymer columns for protein recognition by HPLC.⁴⁹⁸ The cytochrome *c* (cyc)-MIP monolithic polyacrylamide materials were directly prepared by one-step *in situ* free radical-initiated polymerization within an HPLC column tube (4.6 mm × 25 cm). The monolithic MIP column was successfully applied to the separation of cyc from the competitive protein of lysozyme (lys), and showed obvious affinity and specific recognition capacity towards the template protein.⁴⁹⁸ Xu *et al.* prepared a monolithic and surface initiated MIPs column for HPLC by the combination of surface imprinting and *in situ* synthesis methods. In this method, the MIP-column was synthesized *in situ* and the MIP was coated on the surface of silica beads. For the preparation of the MIP column, the initiator coupled with silica beads (40–60 μm) was packed into a stainless steel HPLC column. The MIP column exhibited excellent retention capability and a large imprinting factor for the template.⁴⁹⁹ For the CEC applications, Xie *et al.* prepared (*S*)-ornidazole ((*S*)-ONZ) MIP monoliths by a simple single-step thermal copolymerization for the fast chiral separation of antiparasitic drugs by pressurized CEC (pCEC).⁵⁰⁰ The influences of polymerization mixture composition on the chiral recognition of ONZ, the reproducibility of the monolithic column and the pCEC conditions on chiral separation were investigated. The monolithic stationary phase showed optimal porous properties and good selectivity towards ONZ, and the enantiomers were rapidly separated within 9 min.⁵⁰⁰ For the preparation of monolithic MIP stationary phases, organic polymer based monolithic MIPs were used, which have the advantages of excellent pH stability and easy availability of various monomers. However, when the MIP monolith is exposed to different organic solvents, it can shrink or swell which may be the cause for the decreased recognition of the template molecule.⁵⁰¹ The organic–inorganic hybrid technique combines an organic polymer with a silica gel process, avoiding the shortcomings of organic and inorganic matrix monoliths.

Wang *et al.* prepared a molecularly imprinted capillary monolithic column by the organic–inorganic hybrid method combined with the multi-template imprinting strategy.⁵⁰² The prepared imprinting capillary monolithic column was evaluated with CEC for the recognition of ractopamine. In addition, the effects of electroosmotic flow (EOF) and selectivity were also studied.⁵⁰² Owing to the advantages of simple column preparation, no bubble formation and stable EOF application, open-tubular CEC (OT-CEC)-based MIP columns are potential tools for the specific recognition of enantiomers among the various forms used in CEC.⁵⁰³ Moon *et al.* used an OT-CEC column with a monolithic MIP layer for simultaneous separation and characterization of phospholipid (PL) molecular structures by electrospray ionization-tandem mass spectrometry (ESI-MS/MS).⁵⁰⁴ The MIP layer OT-CEC column was prepared by thermally initiated polymerization and a simple nanospray interface utilizing a sheath flow was developed to connect OT-CEC with ESI-MS/MS. The developed method was applied to human urinary lipid extracts for separation and structural identification of 18 molecules which showed potential to separate PLs by their acyl chain length and polar head groups at high speed.⁵⁰⁴ In recent years, molecular crowding has emerged as a new concept to obtain MIPs with greater capacity and selectivity, which originated from the peculiar molecular environments in biological cells, such as proteins and nucleic acids.⁵⁰⁵ Huang *et al.* also applied the molecular crowding theory to prepare imprinted monolithic columns for CEC. Poly(methyl methacrylate) (PMMA) was used as a molecular crowding agent and the PMMA-based MIP capillary was able to separate zopiclone enantiomers. Compared with the MIPs prepared without the addition of the crowding-inducing agent, the employment of PMMA endowed the MIPs with superior retention properties and excellent selectivity for d-ZOP. The resolution of enantiomer separation on this monolithic column was 2.09 and the greatest column efficiency achieved was up to 74 000 plates per m.⁵⁰⁶ CLC using capillary columns instead of the regular columns with bigger inner diameters for HPLC was also developed. Hearn *et al.* developed a method for the preparation of MIPs as porous layers in an open tubular (MIPs-PLOT) capillary column for use in the chiral separation of ketoprofen racemate by CLC.⁵⁰⁷ The preparation of an MIP-PLOT capillary column was based on in-capillary ultraviolet initiated polymerization using light emitting diodes (LEDs) in conjunction with the continuous delivery of the prepolymerization reagents into the polymerization zone of the capillary using an automated capillary delivery device. The proposed MIP-PLOT stationary phases used non-chiral polymer precursors to create enantioselective nano-cavities through the molecular self-assembly process and provided a new approach for the separation of chiral compounds in complex or racemic analyte mixtures having chemical and biological origin.⁵⁰⁷

From what has been summarized above, we can see that MIPs have commonly been used as stationary phases in chromatography in two modes, packing MIPs into pre-columns and monolithic columns. Both of them have been widely used in HPLC, CEC, CLC and TLC for the separation of analytes in

environmental, food, biological and medical fields. However, a tedious treatment process is required for packing MIPs into the column. Although monolithic column technology can simplify the procedure, there is much room for improvement, such as developing novel synthesis methods of MIPs to decrease the backpressure in order to combine with low pressure analytical instruments, to shorten analysis time, and to increase the reproducibility, reusability and regenerative ability.

4.2. Chemical and biological sensing

The employment of MIPs as specific sensing materials in sensors, namely MIP-based sensors, which were first proposed by Mosbach to monitor the specific binding of vitamin K₁ to a “surface-imprinted” silicon surface by using optical surface ellipsometry,⁵⁰⁸ has made considerable progress due to their high selectivity and stability, simplicity, cost-effectiveness, and versatility in the fields such as clinical diagnostics, environmental control, food analysis and drug screening.^{509–512} The characteristic feature of MIP-based sensors is that the MIPs have both recognition and transduction properties, that is, the MIPs as recognition elements can specifically bind target analytes and as transduction elements can generate output signals for detection. The characteristic feature and basic construction of MIP-based sensors are schematically illustrated in Fig. 17A. As seen from the figure, typically, the output detection signals can be classified into 3 types, electrochemical, optical and piezoelectric types according to the transduction mechanism. And the transducers used are electrodes, optical transponders and piezoelectric crystals, respectively. In general, for analytical determination, it is necessary to consider the main parameters of MIP-based sensors such as response time, the linear dynamic range, detectability, sensitivity, selectivity and reproducibility.

4.2.1. Electrochemical sensing. Since the first report published by Hedborg,⁵¹³ in which thin MIP membranes were applied as sensing layers in field-effect capacitors against L-phenylalanine anilide and a lowering of the capacitance was

obtained upon specific binding of the template molecules, molecularly imprinted electrochemical sensors (MIECSs) have received more and more attention because of their high sensitivity, high selectivity, low cost and the possibility of easy miniaturization and automation. So, it is not surprising that some groups have summarized the development of MIECSs.^{514,515} For MIECSs, generally, the MIPs are in the form of particles or films modified on electrodes, which are prepared by electropolymerizing electro-monomers like pyrrole, aniline, *o*-phenylenediamine (*o*-PD), *p*-aminobenzenethiol (*p*-ATP) and 3,4-ethylenedioxythiophene (EDOT),⁵¹⁶ and miscellaneous systems like self-assembled monolayers (SAMs), sol-gels and pre-formed polymers. According to the response signal, electrochemical sensors can mainly be classified into the following four types: electric-current (amperometry and voltammetry), potentiometry (ion selective electrodes and field-effect transistors), capacitance/impedance and conductivity. And their recognition ability is commonly based on ground and sieved polymers that are coated on the surface of transducers as monoliths or membranes, and the electrochemical transducer signals are derived from analytes themselves, electrochemical probes, competitive measurements, or the binding of analytes to MIPs, and therefore the quantitative detection of analytes is realized. Fig. 17B schematically illustrates the basic mechanisms and main types of MIECSs.

4.2.1.1. Electric current. An MIP-based electric-current sensor was first constructed by Mosbach to detect morphine taking advantage of competitive binding between an electroinactive competitor codeine and morphine.⁵¹⁷ Since then, this technique has been well known and widely used, which includes two types, namely amperometry and voltammetry. In MIP amperometry sensors, electroactive species can be detected directly, which requires a linear relationship to be established between the concentration of electroactive species and the current measured at constant potential.⁵¹⁸

For example, Kubota *et al.*⁵¹⁹ prepared an amperometric sensor employing a hemin-MIP particles modified glassy carbon

Fig. 17 (A) Schematic representation of the characteristic feature and basic construction of MIP-based sensors. (B) Schematic diagram of the main types and basic mechanisms of molecularly imprinted electrochemical sensors (MIECS).

Fig. 18 Schematic illustration of non-electroactive molecular detection. (A) Preparation principle of the thiolation-3-indoleacetic acid (IAA)-based MIECS by electro-polymerizing pyrrole to form the poly-pyrrole (PPY) membrane on a glass carbon electrode (GCE) through non-electroactive competitor thiolation-IAA (IAA-S) recognition. (1) IAA was eluted from the MIPs film; (2) cavities were occupied by IAA-S; (3) the competition reaction between IAA in samples and IAA-S; (4) Ag NPs were labeled on IAA-S and (5) copper deposition on the Ag NP surface to form Cu@Ag NPs labeled IAA-S. Reproduced with permission from ref. 522. Copyright © 2014 Published by Elsevier B.V. (B) Electrochemical MIPs (e-MIPs) were prepared in an easy and conventional way by copolymerization of functional monomer vinylferrocene (VFc) presenting electroactive properties with a cross-linker ethylene glycol dimethacrylate (EDMA) with the addition of electroactive material VFc as a signal probe. Reproduced with permission from ref. 521. Copyright © The Royal Society of Chemistry 2014. All rights reserved.

electrode (GCE) surface for 4-aminophenol (4-Aph) detection, based on the cycles of reduction and oxidation between hemin-MIP and 4-Aph. This sensor was more selective and stable compared to peroxidase-based biosensors. Under optimized operational conditions, a linear response was obtained in the range of $10.0\text{--}90.0\ \mu\text{mol L}^{-1}$ with a sensitivity of $5.5\ \text{nA L } \mu\text{mol}^{-1}$ and an LOD ($S/N = 3$) of $3.0\ \mu\text{mol L}^{-1}$. However, for non-electroactive molecules, competitive measurements can be employed by the electroactive competitor recognition for the detection of targets, or by the addition of electroactive materials such as potassium ferricyanide⁵²⁰ and vinylferrocene⁵²¹ as signal probes to electrolyte systems. Fig. 18 schematically shows the sensing procedures and principles for the detection of non-electroactive molecules. For example, Li *et al.*⁵²² proposed a new strategy for improving the sensitivity of MIECS on the GCE surface by electro-polymerizing pyrrole to form the poly-pyrrole (PPY) membrane in the presence of a template thiolation-3-indoleacetic acid (IAA) for the detection of IAA. Fig. 18A illustrates the preparation process and the detection mechanism. Firstly, IAA was eluted from the MIP film, after incubation, cavities were occupied by thiolated-IAA (IAA-S), then Ag NPs were labeled on IAA-S for catalytically reducing and

depositing copper onto its surface (Cu@Ag NPs labeled IAA-S), and therefore, IAA could be determined indirectly by the competition reaction between IAA and labeled IAA-S. The change in the signal decreased when IAA-S was replaced by IAA in the samples. So, a good linearity for IAA was attained in the range of $9 \times 10^{-10}\text{--}6 \times 10^{-7}\ \text{mol L}^{-1}$ with a low LOD of $2.31 \times 10^{-10}\ \text{mol L}^{-1}$. Besides, using electroactive materials as signal probes is another good method. Brisset *et al.*⁵²¹ introduced a redox tracer vinylferrocene (VFc) as an electrochemical sensing element inside the binding cavities of cross-linked MIP particles, and immobilized it on a carbon paste electrode (CPE), to develop a versatile electrochemical MIP (e-MIP) sensing receptor for the detection of benzo[a]pyrene (BaP) by measuring the redox tracer signal, as illustrated in Fig. 18B. The two cyclopentadienyl rings in vinylferrocene could generate aromatic stacking interactions with BaP, which promoted the recognition of BaP by e-MIPs. Different volumetric proportions of solvents (toluene in acetonitrile) were studied to produce various MIPs (*e.g.*, a 30% ratio gave e-MIP30 particles) in the binding test, and among them, e-MIP30 exhibited the highest affinity for BaP, and the current intensity at $0.46\ \text{V}$ vs. BaP was linear in the concentration ranges of 0.08 to $3.97\ \mu\text{M}$ with the LOD of $0.09\ \mu\text{M}$. This simple

determination of BaP by measuring the redox tracer signal was applied to other substances. Overall, amperometry is the most convenient approach among electrochemical technologies, which has been widely used for commercial products.

On the other hand, voltammetry is the most often used approach due to its intrinsic oxidation and reduction potential properties. The commonly used voltammetry testing types include linear sweep voltammetry (LSV),⁵²³ cyclic voltammetry (CV),⁵²⁴ differential pulse voltammetry (DPV),⁵²⁵ square wave voltammetry (SWV)⁵²⁶ and anodic stripping voltammetry (ASV). Table 11 summarizes the related techniques and their analytical performances for drugs, organic molecules and biomacromolecules.^{523,526–545} For LSV and CV, their potentials linearly change with time. While the potential sweep of DPV and SWV comprises constant increments in either rectangular pulse or square oscillations, which can offer better sensitivity and signal-to-noise ratios than LSV and CV, since programmed current sampling is applied.⁵¹⁸ For instance, Luo *et al.*⁵²⁵ prepared MIPs on the surface of a vinyl group functionalized graphene sheet (GR/NVC) to form the GR/MIP composite, which was used to fabricate MIECS for the detection of 4-nitrophenol (4-NP). Under optimized conditions, the DPV current response of the GR/MIP sensor showed a shorter response time within 120 s and a much higher current response revealed that the peak current was linearly proportional to the concentration of 4-NP over a wide response range from 0.01 to 100 μM and 200 to 1000 μM with a lower LOD of 5 nM. This LOD value is lower than that obtained using a polycarbazole (PCZ)/nitrogen-doped graphene chemosensor for determination of 4-NP with an LOD of 0.062 μM ($S/N = 3$).⁵⁴⁶ Meanwhile, CV can be used for the signal detection of single-stranded oligodeoxyribonucleotide (ss-ODN) imprinting achieved successfully by Tiwari and Turner.⁵⁴⁵ They used ss-ODN as the template and *o*-phenylenediamine (*o*-PD) as the functional monomer on indium-tin oxide (ITO) to prepare a sequence-specific MIP-based ss-ODN biosensor. The Δi current response to Δi of ss-ODN concentration was linear in the range of 0.01–300 fM with a sensitivity of 0.62 $\mu\text{A fM}^{-1}$ within a response time of 14 s. This suggests that this ss-ODN biosensor shows good performance including higher sensitivity, a wide analytical range and fast response time, which could greatly benefit the improved commercial genetic sensors. Although a number of MIP-based electro-current sensors and methods have been proposed and developed, it is still difficult to find electroactive analogues for the detection of non-electroactive molecules, which has restricted their applications, and more efforts need to be made.

4.2.1.2. Potentiometry. Potentiometry was applied to molecular imprints for the first time by Mosbach *et al.* in 1990 for enantiometric separation,⁵⁴⁷ in which a flow stream potential across the column electrode was continuously recorded and correlated with the concentration of phenylalanine anilide, and moreover, the potentiometric signal was found to be exponentially linear with concentration. This made substrate-specific electrode preparation using MIT possible, and prompted

greatly the application of potentiometry. Two main devices fall into this category: ion selective electrodes (ISEs) and field-effect transistors (FETs).

In general, recognition featured MIP films play an important role in an ion-selective membrane and have been widely used for the recognition of numerous ionic species. However, for uncharged non-electroactive/neutral molecular species, it remains an open challenge. Qin *et al.*⁵⁴⁸ developed a novel strategy for the selective and sensitive detection of neutral species chlorpyrifos (CPF), by using a polymeric membrane ISE based on uniform-sized MIPs as the sensing elements for molecular recognition and the charged indicator ion with a structure similar to that of the analyte for the transduction of potential signal, as schematically displayed in Fig. 19A. As seen, when the electrode was placed in the sample solution, the MIPs in the polymeric membrane containing binding cavities as receptors could selectively extract CPF through hydrogen bonding and hydrophobic interactions. Thus, this process reduced the potential response to the indicator ions. Accordingly, this MIP-based polymeric membrane ISE had excellent response in the sample solution, and the quantitative concentration of CPF was in the range of 2 to 50 nM with the LOD of 0.96 nM. Therefore, the present strategy would pave the way for measuring non-ionic species at trace levels. However, to date, very few nano-imprinted materials have been exploited for polymeric membrane potentiometric sensors.⁵⁴⁹ Meanwhile, as is well known, surface imprinting, *i.e.*, in which most of the imprinted sites were situated at the surface or in the proximity of the surface in the imprinted materials, shows a higher affinity and sensitivity to the target analyte and a more homogeneous distribution of recognition sites. By adopting surface imprinting technology, biomarker detection can be greatly improved using MIP based potential sensors. For instance, Wang *et al.*⁵⁵⁰ applied surface molecular imprinting using hydroxyl functionalized alkanethiol molecules as SAMs on an Au-coated silicon chip through the sulfur–metal bond (Au–S) as sensing elements into a potentiometric sensor for the detection of carcino-embryonic antigen (CEA), amylase and poliovirus, as displayed in Fig. 19B. The potential of the Au–S bond would change when the charged biological molecule binds to the imprinting cavity, which could be measured potentiometrically. Therefore, the detection of protein cancer biomarkers could be highly sensitive and specific with the saturation concentration of 75 ng mL^{-1} for CEA, 100 ng mL^{-1} for amylase and 3100×10^8 virus particles per mL for poliovirus, respectively. This approach has the potential to generate a general assay methodology for biomolecules.

As for FETs, potentiometric systems are mainly applied to the development of ion-sensitive field effect transistors (ISFETs) and extended-gate field effect transistors (EGFETs). In 2001, Willner *et al.* proposed ISFETs based on molecularly imprinted TiO_2 thin films assembled on SiO_2 and Al_2O_3 gate interfaces for the selective analysis of 4-chlorophenoxyacetic acid⁵⁵¹ or 2,4-dichlorophenoxyacetic acid and different chiral carboxylic acids.⁵⁵² Soon in 2002, they reported the imprinted membranes assembled on the gate surface of ISFETs as

Table 11 The commonly used voltammetry testing for MIP-based electrochemical sensors

Analyte category	Templates	Recognition elements (function monomers)	Electrode	Detection technique	Linear range	LOD (S/N = 3)	Ref.
Drugs	Quinoxaline-2-carboxylic acid (QCA)	<i>o</i> -PD	Film/GCE	SWV	1.0×10^{-8} – 5.0×10^{-4} mol L ⁻¹	2.1 nmol L ⁻¹	526
	Trimethoprim (TMP)	Py	Film/GCE	CV	1.0×10^{-6} – 1.0×10^{-4} M	1.3×10^{-7} M	527
	Methcathinone and cathinone	Py	Film/SPE	DPV	—	3.3, 8.9 pg mL ⁻¹	528
	Chlortetracycline (CTC)	<i>o</i> -PD	Film/GCE	DPV	10.0–500.0 μM	13.25 μg mL ⁻¹	529
	Cefotaxime (CEF)	<i>o</i> -PD	Film/GCE	CV	3.9×10^{-9} – 8.9×10^{-6} mol L ⁻¹	1.0×10^{-10} mol L ⁻¹	530
	Folic acid (FA)	<i>o</i> -PD	Film/Au	CV, DPV	1.0–200 μM	0.9 μM	531
	Warfarin	<i>o</i> -PD	Film/GCE	CV	0.031–0.616 ng mL ⁻¹	0.024 ng mL ⁻¹	532
	Dopamine (DA)	<i>p</i> -Aminobenzenethiol (<i>p</i> -ATP)	Film/Au	DPV	0.02–0.54 μmol L ⁻¹	7.8 nmol L ⁻¹	533
	Oxytetracycline (OTC)	Prussian blue	Film/Pt	DPV	1.0 μM	230 fM	534
	Sildenafil	<i>p</i> -Phenylenediamine(<i>p</i> -PD)	Film/GCE	CV, DPV	—	6.2 nmol L ⁻¹	535
	Isocarboxiphos (ICP)	<i>o</i> -PD	Film/GCE	CV, DPV	7.5×10^{-8} – 5×10^{-5} M	2.01×10^{-8} M	536
	Chrysoidine	Py	Film/GCE	CV, DPV	5.0×10^{-8} – 5.0×10^{-6} M	1.7×10^{-8} M	523
	Benzophenone	<i>o</i> -PD	Film/GCE	CV, LSV	0.05–5 mM	10 nM	537
	Diphenylamine (DPA)	3,4-Ethylenedioxythiophene (EDOT)	Film/Au	DPV	4.95–115 μM	3.9 μM	538
	Triazophos	1,2-Hydroxyphenol	Film/GCE	CV	0.2–10 μM	93 nM	539
Organic molecules	Methyl parathion (MP)	Phenol	Film/Au	CV	0.1–10 μg mL ⁻¹	0.01 μg mL ⁻¹	540
	Pyroglutamic acid (PGA)	5-Methyl-2-thiophene carboxylic acid (5-MTCA)	Film/PGE	DPASV, CV	2.8–170.0 ng mL ⁻¹	0.77 ng mL ⁻¹	541
	Ascorbic acid (AA)	<i>o</i> -PD- <i>co</i> - <i>o</i> -aminophenol	Film/GCE	DPV	0.1–10 mM	36.4 μM	542
	BSA	1,2-Diphenylethylamine, 3-aminophenylboronic acid	Film/GCE	DPV	10 pg mL ⁻¹ –10 μg mL ⁻¹	7.5 pg mL ⁻¹	543
	DNA hybridization	Aniline	Film/GCE	DPV	—	—	544
	p53 gene point mutation	Aniline	Film/ITO	CV	0.01–300 fM	3.25×10^{-13} mol L ⁻¹	545
Biomacromolecules							
Glass carbon electrode (GCE); screen-printed electrode (SPE); pencil graphite electrode (PGE); indium-tin oxide (ITO) coated glass; <i>o</i> -phenylenediamine (<i>o</i> -PD); pyrrole (py).

Fig. 19 (A) Representation of the potentiometric detection of neutral species using a uniform-sized MIP as the sensing element on a polymeric membrane ion selective electrode (ISE) surface and charged indicator ion for the transduction of potential signal. Reproduced with permission from ref. 548. Copyright 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) Formation of biomolecule-templated thiol self-assembled monolayers (SAMs) on a gold substrate, and the subsequent removal of the template molecules to create the recognition sites in the SAMs matrix. Reproduced with permission from ref. 550. Copyright © 2010 Elsevier B.V. All rights reserved.

transducers for the selective sensing of saccharide.⁵⁵³ After that, MIP-based ISFETs and EGFETs gradually increased. For example, Kugimiya *et al.*⁵⁵⁴ used a phosphate-selective polymer as a molecular recognition material and ISFET as a transducer for phosphate detection. The phosphate concentrations in the solution would decrease because of the specific binding of phosphate to the phosphate-selective polymer, and this change could be measured by ISFET. So, an effective sensing system for measuring phosphate was obtained in the presence of other interferential analyte anions (NO_3^- , NO_2^- , F^- , Cl^- and Br^-) each with concentration of 20 μM . Besides, this method was suitable for the long-term measurement of phosphate concentrations in storage dams, sewage treatment plants, rivers and lakes with good stability and could be performed at low cost and on a large scale. Moreover, EGFETs have gained more and more attention, because expensive instruments and reagents are not necessary, and minute changes in potential at the gate surface could be converted into detectable electrical signals. Noworyta *et al.*⁵⁵⁵ developed a novel chemical sensor for selective determination of the inosine by depositing inosine-templated MIP films on an EGFET signal transducing unit, in which thin inosine MIPs and EGFET served as recognition and signal transduction units providing high sensitivity of the integrated chemosensor device, respectively. Therefore, the linear dynamic concentration range was 0.5–50 μM with the high detectability of 0.62 μM . Besides, higher selectivity for inosine was also achieved using this molecularly engineered sensing element. This MIP film-coated EGFET chemosensor showed advantageous flexibility during measurements through gate voltage adjustments, which offered a promising strategy

for devising and developing MIP-based FETs. Apparently, the development of MIP-based potentiometric sensors will open up the possibility for their various envisioned applications.

4.2.1.3. Capacitance/impedance. Capacitive sensors, also named impedance sensors, based on MIPs, were proposed by Wolfbeis *et al.*,⁵⁵⁶ in 1999 who reported that ultrathin membranes with perfect insulating layers were important for this sensor. Gradually, capacitive sensors have evoked much attention because they possess the merits of high sensitivity, additional reagents/label free and real-time monitoring based on the theory of the electrical double-layer.⁵⁵⁷ Generally, ultrathin and electrically insulating polymer film plays an important role in a good capacitive sensor. Alkanethiol is usually used to fill the defects of the membrane after electropolymerization to enhance the insulating properties, but this process and response time are rather long.⁵⁵⁸ Yao *et al.*⁵⁵⁹ constructed a MIP-based capacitive sensor specific for tegafur, in which the sensitive membrane was employed at a lower potential scan rate instead of treating with alkanethiol after electropolymerization to acquire good insulating properties. So, it showed more satisfactory performances, *e.g.*, no significant effects were observed upon addition of these interferents that have similar structures to tegafur. After that, Najafi *et al.*⁵⁶⁰ made use of electropolymerized MIPs to construct a new capacitive sensor for the direct detection of thiopental in human serum by electropolymerization of phenol on a gold electrode. This new material had some unique advantages like high sensitivity, label-free and real-time monitoring. The developed sensor showed a good linearity between 2 and 20 μM with a low

detection limit of 0.6 μM by capacitive measurements. Besides, the sensor fabrication procedure was simple, and it could be expected to apply in other assays. More work should be performed to attain the MIP-based reception layer with low thickness and a high uniformity membrane, which is the advantage of the molecular imprinting capacitive sensors and highly desirable.

4.2.1.4. Conductivity. MIP-based conductometric sensors were firstly reported by Parhometz *et al.*⁵⁶¹ for the sensing of herbicide atrazine in 1995 and Mosbach *et al.*⁵⁶² for a charged analyte benzyltriphenylphosphonium ions in 1996. As seen above, the development of MIP-based conductometric sensors relies on the preparation of MIPs as membranes. For example, Dickert *et al.*⁵⁶³ used multi-walled CNTs (MWCNTs) loaded on polyurethane as a conductive filler to synthesize a sensitive layer, and then combined the layer with MIPs to design a conductometric sensor. This nanotube–polyurethane composite showed a better conductivity than the TiO_2 composite because of the thickness of the resulting polymer. The capric acid imprinted aminopropyl-triethoxysilane (APTES) precursor layer could interact with the acidic components because of the amino groups in it, and showed a conductance of about 2.7 μS . This conductometric sensor was highly sensitive over a wide concentration range of capric acid in fresh oil, and the amino group in the silica layer is a promising candidate through the experimental verification for detecting the age of used lubricating oil. These conductance measurements are used for environmental monitoring as they are relatively easy to perform. Soares *et al.*⁵⁶⁴ used thiourea as a functional monomer to integrate optimized MIP receptors within a flexible membrane to measure soluble phosphate in environmental water samples. The MIPs were able to produce a reversible change in conductance in the presence of phosphate produced in membrane form, which could be used to quantify various concentrations of phosphate in wastewater samples. The linear range between 0.66 and 8 mg P L^{-1} was obtained with an LOD of 0.16 mg P L^{-1} . And the selectivity for phosphate upon the addition of 1 mM phosphate solution (31 mg P L^{-1}) produced a much greater response than that generated by equimolar (1 mM) solutions of either nitrate (62 mg L^{-1}) or sulphate (96.1 mg L^{-1}). This membrane containing thiourea based MIP receptor incorporated within a conductometric sensor would be promising for direct quantification of phosphate in environmental monitoring applications. It also provided a strategy and a method involving MIP-based conductometric sensors. However, the MIP-based conductometric sensors are not widely used because of the additive effects of the interferents, and the discrimination between the analytes and the interferents is not very obvious.

4.2.1.5. Sensitivity enhancing methods. As discussed in Section 3.1.2 “Nanoimprinting technology”, the introduction of surface chemistry and nanotechnology into the fabrication of MIPs-based sensors has greatly enhanced the analytical sensitivity and decreased detection limits. Various nanomaterials such as nanoparticles, magnetic nanoparticles, nanowires,

nanotubes, nano-channels, QDs, and graphene, *etc.* have been explored either as modifiers of electrodes or as new electrode materials with interesting applications. For example, CNT-based electrochemical sensors generally have higher sensitivities, lower LOD, and faster electron transfer kinetics than traditional carbon electrodes because of the unique advantages of CNTs such as enhanced electronic properties, large edge plane/basal plane ratios, and rapid electrode kinetics.⁵⁶⁵ So, the analytical performances and applications of micro- and nanostructured MIPs, providing a comprehensive understanding of the nano-MIPs, were summarized.^{566,567} Mao *et al.*⁵⁶⁸ synthesized nanocomposites of graphene sheets/Congo red-MIPs (GSCR-MIPs) through free radical polymerization (FRP), using GSCR nanocomposites, a functional monomer MAA, and a cross-linker EGDMA in the presence of the DA template, induced by AIBN. Fig. 20A shows the preparation procedure. Then, the resultant GSCR-MIP nanocomposites were applied as molecular recognition elements to construct DA electrochemical sensors. The prepared MIPs possessed large surface area because polymerization occurred at the surface of GS with unique mechanical properties and extremely large area. So, the selective detection of DA presented a good linearity within 1.0×10^{-7} – 8.3×10^{-4} M, which revealed a lower LOD and wider linear response compared to some previously reported DA imprinted electrochemical sensors. Huang *et al.*⁵⁶⁹ developed an amperometric sensor on Au NPs that could increase the surface area of the GCE and enhance the current signal in the presence of BPA as a template. The nanoimprinting technology offered an attractive route to enhance the sensitivity of the imprinted sensor. Therefore, the linear response range of the sensor was between 8.0×10^{-6} and 6.0×10^{-2} mol L^{-1} with a LOD of 1.38×10^{-7} mol L^{-1} . Besides, the RSD of currents was 5.0% in five replicates for a 5.0×10^{-4} mol L^{-1} BPA solution using the same sensor. This showed that the Au NP-modified electrode significantly enhanced the current response of the sensor, presenting a broad linear range and quantitatively repeatable analytical performance. Liu *et al.*⁵⁷⁰ developed an imprinted film-based CdS QD doped chitosan electrochemical sensor for urea recognition, as illustrated in Fig. 20B. CdS QD doped nanoparticles with favorable electron transfer and magnified surface area on the imprinted film could enhance greatly the sensitivity of this CdS QD-MIP electrochemical sensor. Therefore, wide linear ranges from 5.0×10^{-12} to 4.0×10^{-10} M and 5.0×10^{-10} to 7.0×10^{-8} M were obtained with a low LOD of 1.0×10^{-12} M. This showed that the doping of CdS QDs in the fabrication of a urea MIP film could improve the analytical performance of the MIP-based sensor in terms of response time and detection sensitivity. New structures of composite nanomaterials are expected to further improve the analytical performances of this type of sensor. Overall, nanoimprinting technology and the composite imprinting material strategy hold great potential for enhancing the sensitivity of MIP-based electrochemical sensors, as well as more new methods should also be explored.

4.2.2. Fluorescence sensing. Previously, several MIP-based fluorescence detection methods were based on either fluorescent labeled dansyl-L-phenylalanine reported in 1995,⁵⁷¹ or the

Fig. 20 (A) Illustration of the synthesis route of graphene sheets/Congo red-MIPs (GSCR MIPs) hybrids. The template DA, functional monomer MAA, cross-linker EGDMA and initiator AIBN were added to GSCR nanocomposites organic mixture solvent, and then the product was obtained after eluting DA. Reproduced with permission from ref. 568. Copyright © 2010 Elsevier B.V. All rights reserved. (B) Schematic illustration of the CdS QDs-MIPs electrochemical sensor fabrication. First, the electrodeposition solution was prepared. Then, the pretreated Au electrode was immersed in the electrodeposition solution. Finally, the CdS QDs-MIPs/Au was obtained after the removal of the template molecule. Reproduced with permission from ref. 570. Copyright © 2011 Elsevier Inc. All rights reserved.

formation of fluorescent complexes reported in 1996,⁵⁷² or the creation of template-selective sites reported in 1998.⁵⁷³ Since then, fluorescence detection has attracted a great deal of interest because of its advantages of high sensitivity and convenience, offering an attractive approach for various chemically, environmentally, and biologically significant species.⁵⁷⁴ MIP-based fluorescent sensors combine the advantages of the high selectivity of MIP recognition and the high sensitivity of fluorescence detection. Based on the native characteristics of the targets (fluorescent substances or non-fluorescent substances), MIP-based fluorescence sensing can usually be classified into two categories, direct and indirect fluorescence detection.

As for direct fluorescence detection, the analyte is intrinsically active fluorescent, which is required to have one chromophore or fluorophore at least and can give rise to detection signals for qualitative and quantitative analysis according to fluorescence intensity changes of the MIPs. For example, Moreno-Bondi *et al.*⁵⁷⁵ synthesized a linear multifunctional copolymer poly(methacrylic acid-co-2-methacrylamidoethyl-methacrylate) (P(MAA-co-MAAEMA)) to develop nano-patterned rhodamine 123 (R123)-MIP film arrays by electron beam lithography (EBL), which allows direct writing on silicon substrates. The linearity of the polymeric mixture array with high sensitivity and selectivity towards R123 showed a positive-tone behavior in the dose range of 0.1–8 Mcm⁻². This study produced new opportunities in the implementation of nanostructured MIP film-based arrays for multiple target detection. Other related fluorescent analytes have also been reported by direct fluorescent detection using MIP-based fluorescent sensors like fluoroquinolone.⁵⁷⁶ However, very few analytes allow direct fluorescence detection.

As for indirect detection of non-fluorescent analytes, there are usually three methods adopted as follows. The first method involves using a labeled template or an analogue derivative in a displacement or competitive assay^{577,578} for the fabrication of MIP-based fluorescence sensors. For example, Sellergren *et al.*⁵⁷⁹ developed an automated molecularly imprinted sorbent based assay (MIA) based on a fluorescent competitive assay for the rapid and sensitive determination of penicillin-type β -lactam antibiotics (BLAs) in biological samples. Generally, the analyte and a constant amount of labeled fluorescent analogue were packed in a reactor in the assay, and then the fluorescence of the labeled derivative was measured which was eluted from the sorbent by using a desorbing solution. This sensor showed a dynamic range from 0.68 to 7.21 μ M (20–80% binding inhibition) with an LOD of 0.19 μ M for penicillin G in a mixed solution of acetonitrile and HEPES buffer (0.1 M at pH 7.5) (4:6, v/v). Besides, the MIP reactor could be reused for more than 150 cycles without significant loss of recognition. Satisfactory results could be obtained through comparative analysis.

The second method involves synthesizing substances using a fluorophore as a functional monomer, by monitoring the change in the fluorescence spectrum of the combination of the analytes with the fluorescent functional monomer. For example, a pyrene derivative,⁵⁸⁰ 1,8-naphthalimide dye⁵⁸¹ and Hyp-En-Dans⁵⁸² as functional monomers have been reported, and some typical examples are listed in Table 12, which summarizes commonly used fluorescent functional monomers in MIP-based fluorescent sensors.^{581–591} Dong *et al.*⁵⁹¹ used dansyl-modified β -cyclodextrin (β -CD-en-DNS) as the functional

Table 12 MIP-based fluorescence sensors with fluorescent functional monomers

Analyte	Monomer	Ref.
Caffeine	1,8-Naphthalimide dye	581
Target proteins	O-Acryloyl L-hydroxyproline conjugated with dansyl ethylenediamine (Hyp-En-Dans)	582
Cholesterol	Dansyl-modified β -cyclodextrin	591
Urea	Naphthalimide-based	583
Creatinine	4-Methylamino-N-allylnaphthal-imide (4-MAANI)	584
Atrazine	Vinyl-substituted zinc(II) protoporphyrin (ZnPP)	585
Fungicide fenaminosulf	Neutral red	586
BPA	Dansyl methacrylate	587
Tetracycline (Tc)	AnHEMA	588
Cholic acid	F ₁ and F ₂	589
Cbz-L-Phe or Z-L-Phe	Nitrobenzoxadiazole (NBD) fluorophore	590

AnHEMA: (2-hydroxyethyl anthracene-9-carboxylate) methacrylate. F₁: 4-dimethylamino-N-allylnaphthalimide; F₂: 4-piperazinyl-N-allylnaphthalimide.

monomer and the dansyl group as the reporter to form a complex with cholesterol by inclusion interactions to develop a cholesterol-imprinted polymer fluorescent chemosensor. The binding of cholesterol with β -CD forced the dansyl group out of the CD cavity in the process of pre-polymerization, which led to the re-encapsulation of the dansyl groups after removing cholesterol, as a result the fluorescence intensity of the dansyl group could change and thereby signal the binding event. A good linear relationship between the negative logarithm of cholesterol concentration ($-\log C_{\text{cholesterol}}$) and fluorescent intensity was obtained from 5×10^{-7} to 1×10^{-4} mol L⁻¹. This study would have broad application potential in the fabrication of molecular imprinting based sensors for organic compound determination in aqueous solutions.

The third method involves embedding a fluorescent signal element into MIPs and detecting analytes by fluorescence spectroscopy. Among the optical materials investigated for sensors, organic fluorescent compounds⁵⁹² and quantum dots (QDs)^{593,594} are the most widely used fluorescent signal sources. For example, Cai *et al.*⁵⁹⁵ developed perfluorooctanesulfonate (PFOS, C₈F₁₇SO₃⁻) MIPs, named the PFOS-imprinted dye-(NH₂)-SiO₂ NP fluorescent sensor, using fluorescein isothiocyanate (FITC) as a fluorescent signal element. The formation of PFOS-amine complexes could suppress the fluorescence emission of the fluorescent dye through the charge-transfer quenching mechanism from the dye to PFOS, resulting in fluorescence quenching. And the quenching efficiency of PFOS followed an increasing trend with increasing ion strength. Then, the linear relationship covered the concentration range of 5.57–48.54 $\mu\text{g L}^{-1}$ and a high detectability was obtained up to 5.57 $\mu\text{g L}^{-1}$ for PFOS with ionic strength at 0.2 M. The highest $K_{\text{SV,MIP}}$ to $K_{\text{SV,NIP}}$ ratio for PFOS, 7.82, indicated an excellent imprinting effect responsible for the high selectivity of the sensor toward PFOS.

Besides the most widely used organic fluorescent compounds as fluorescent signal elements, QDs are also widely used for the MIP-based fluorescent sensors. Chen's group¹⁵³ developed a fluorescent sensing system for 2,4,6-trinitrotoluene (TNT) on the basis of electron transfer-induced fluorescence quenching *via* preparing MIPs with trinitrophenol (TNP) as a dummy template molecule capped with CdTe QDs (DMIP@QDs) through a sol-gel process. Fig. 21A illustrates the preparation

process of DMIP@QDs and the sensing mechanism for TNT. As seen from the figure, DMIP@QD particles were prepared by means of the hydrolysis reaction of APTES and TEOS using aqueous ammonia solution as the catalyst in the presence of TNP. In the presence of TNT, a Meisenheimer complex could be formed between TNT and the primary amino groups of APTES on the surface of the QDs, and therefore the energy of the QDs would be transferred to the Meisenheimer complex, named fluorescence resonance energy transfer (FRET), resulting in the fluorescence quenching of the QDs. Therefore, TNT could be detected fluorescently. The fluorescence-quenching fractions of the sensor presented a satisfactory linearity with TNT concentrations in the range of 0.8–30 μM with an LOD of 0.28 μM . A high binding affinity to TNT over its competing molecules presented satisfactory results. This simple, rapid and reliable DMIP@QDs sensing strategy was expected to open up attractive prospects for TNT detection. However, the sensitivity of the MIPs@QD sensor is often poor because QDs are embedded into highly cross-linked MIPs. Therefore, more efforts still need to be made to improve further the sensitivity of MIPs@QDs-based systems while retaining their high selectivity. For instance, reducing the imprinting shell thickness is an effective method, considering the relationship between the quenching efficiency and the MIP shell thickness, an ultrathin shell will be the ideal goal of MIP@QD sensors for higher sensitivity. Also, providing mesoporous structures in the MIPs is another effective method. Accordingly, Chen's group¹⁷⁴ developed a novel imprinting fluorescent probe for specific recognition and sensitive detection of phycocyanin (PC) through the electron-transfer-induced fluorescence quenching mechanism between QDs and mesoporous structured microspheres (SiO₂@QDs@ms-MIPs). The use of mesoporous silica structured MIP materials as selective recognition units and QDs as fluorescence detection units improved greatly sensitivity, response time, binding capacity and selectivity because of a large pore volume and the nanosized pore wall thickness of the mesoporous structure and the strong fluorescent signal of QDs. As a result, the linearity within 0.02–0.8 μM and a high detectability of 5.9 nM were obtained. Furthermore, excellent recognition specificity for PC over its analogues was also displayed with a high imprinting factor of 4.72. This proposed method provided promising prospects to develop convenient,

Fig. 21 (A) Schematic illustration of the preparation of a dummy template molecule capped with CdTe QDs (DMIP@QDs) and the sensing mechanism for TNT. Reproduced with permission from ref. 153. Copyright © 2013 Elsevier B.V. All rights reserved. (B) Schematic illustration of the preparation process and possible detection principle of the ratiometric fluorescent sensor SiO₂@NBD@MIPs for the detection of phycocyanin (PC) using nitrobenzoxadiazole (NBD) as fluorescent signal source based on FRET between NBD and PC. Reproduced with permission from ref. 597. Copyright © 2016 Elsevier B.V. All rights reserved.

rapid, sensitive fluorescent detection of trace proteins from complex matrices.

More excitingly, ratiometric fluorescence detection can achieve higher sensitivity of the molecularly imprinted sensors.⁵⁹⁶ Chen *et al.*⁵⁹⁷ developed a SiO₂@NBD@MIPs ratiometric fluorescent sensor for the sensitive detection of PC using nitrobenzoxadiazole (NBD) as a fluorescent signal source based on FRET between APTES–NBD conjugates at 535 nm and PC at 657 nm. As seen from Fig. 21B, SiO₂ nanoparticles as core materials, APTES as a functional monomer, PC as the template molecule and TEOS as the cross linker were anchored onto the surface of the SiO₂ core through a condensation reaction to form SiO₂@NBD@MIPs, which showed the emission spectrum of only NBD in the absence of PC. However, the hydrogen bond between the carboxyl group of PC and the amino group of APTES would quench the NBD fluorescence and increase the PC fluorescence emission through FRET, so, the ratiometric fluorescence detection of PC based on FRET would be realized. The ratio of the intensities at 657 nm and at 535 nm (I_{657}/I_{535})

increased steadily with PC concentration increasing and the linear range was 1–250 nM with the LOD of 0.14 nM. And the SiO₂@NBD@MIP sensor could be applied to seawater and lake water samples successfully with precisions below 4.7%. This proposed ratiometric fluorescence could effectively reduce the background interference and fluctuation of diverse conditions, and greatly improve the detection sensitivity. In addition, mesoporous structures were used in MIP-based ratiometric fluorescence sensors for highly sensitive detection of TNT. Xu and Lu¹⁷⁵ proposed a mesoporous structured MIPs@QD ratiometric fluorescence sensor, QD@SiO₂@mSiO₂, by combining with the ratiometric fluorescence technique and mesoporous silica materials for dual signal amplification. Most of the recognition sites were located on the surface of the silica matrix for this mesoporous imprinted silica shell, so TNT had more chance to enter the recognition sites and to quench the fluorescence of QDs. The fluorescence intensity decreased with the amount of TNT ranging from 50 nM to 600 nM with an LOD of 15 nM. This QD@SiO₂@mSiO₂ sensor integrated the high

selectivity of MIPs and the high sensitivity of ratiometric fluorescent sensors and mesoporous silica, which demonstrated great potential for the analysis of other substances.

Meanwhile, photoluminescent nanoclusters (NCs) such as gold nanoclusters (Au NCs) have also attracted increasing attention and have gradually become ideal fluorescent signal candidates. Compared with widely used fluorescent elements especially QDs, Au NCs exhibit stronger and more durable fluorescence signals attributed to better resistance to photobleaching and blinking. Chen's group⁵⁹⁸ proposed a flexible fluorescence sensing strategy based on MIP-coated Au NCs for the recognition and detection of BPA. The fluorescence-quenching fractions of the sensor offered a satisfactory linearity with BPA concentrations over the range of 0–13.1 μM , and the LOD could reach 0.10 μM . Due to the rapid development of versatile MIPs and the gradual concern for Au NCs, their synergistic effects could provide new opportunities to develop such composite materials for potential utilization.

To sum up, MIPs are used for only separation in the first approach and detection in the second method, which is not ideal for sensor applications. However, MIP-based label-free fluorescent micro/nanomotor sensors are attractive for diverse practical applications,^{599,600} which will push forward the development of intelligent micro/nanoscale systems and strategies for MIP-based fluorescent sensors. In the meantime, both of the above fluorescent signal materials have inherent limitations for the third method, since organic fluorescent dyes typically undergo rapid photobleaching, whereas QDs are less chemically stable, potentially toxic, and show fluorescence intermittence.⁶⁰¹ So, it is necessary to find new substitutes for current luminescent materials and integrate the ratiometric fluorescence technique into this method to improve sensitivity greatly. In addition, fluorescent optical fibers associated with MIPs serving as coating/layers over the fibers will also be useful because of their rapid on-site monitoring and portability.

4.2.3. Chemiluminescence sensing. Using MIPs as recognition elements in the chemiluminescence (CL) sensor initially originated from the study in 2000 by Lin *et al.*, in that dansyl-L-phenylalanine (dns-L-Phe) was recognized using the $\text{HSO}_5^-/\text{Co}^{2+}$ solution to flow MIPs giving out CL emission,⁶⁰² gradually, the MIP based CL sensors have gained great significance, since both selectivity and sensitivity of the CL analysis have been improved effectively.⁶⁰³ The basic setup is illustrated in Fig. 22A. As seen from the figure, pump 1 is connected to the sample solution and a luminescent substance like luminol, and pump 2 is connected to the oxidation or reduction solutions; these two pumps drive the mixed solutions to flow through the MIPs-packed flow cell with the aid of a switch valve, and then signals are detected and transformed by a computer, and meanwhile waste solutions are collected. Various CL systems combining MIPs used as sensitive recognition elements have been developed, including luminol- H_2O_2 ,^{604,605} sodium thiosulfate–potassium permanganate,⁶⁰⁶ luminol- $\text{K}_3\text{Fe}(\text{CN})_6$,⁶⁰⁷ the alkaline luminol- KIO_4 ,⁶⁰⁸ KMnO_4 - HCl - $\text{C}_2\text{H}_5\text{OH}$,⁶⁰⁹ $\text{Ru}(\text{bpy})_3\text{Cl}_2$ -tripropylamine (TPA)⁶¹⁰ and so on.

A novel CL system with core-shell MIPs as recognition components has been developed quickly, taking advantage of

the excellent adsorption ability and rapid binding kinetics of core-shell MIPs.⁶⁰⁴ In particular, magnetic MIPs have much more recognition sites located on the surface of the MIPs and are magnetically susceptible, and therefore have excellent adsorption ability and are easily separated. Luo *et al.*⁶¹¹ developed a novel flow injection CL (FI-CL) sensor using $\text{Fe}_3\text{O}_4@\text{SiO}_2$ magnetic MIPs (MMIPs) as recognition elements for the determination of sulfadiazine (SDZ) which could be selectively adsorbed on the MMIPs on-line reacting with the alkaline luminol- H_2O_2 to produce a strong CL signal in the analysis process. Fig. 22B illustrates the determination process containing four steps, adsorption of SDZ, removal of other substances, CL detection and cleaning the MMIP column. So, the sensor could be used to analyze SDZ with high sensitivity and selectivity. It provided a wide linear range from 0.4 μM to 0.1 mM with the LOD of 0.15 μM for SDZ and the RSD for 0.1 μM SDZ was 2.56% ($n = 11$). In addition, the introduction of FI-CL could greatly improve detection efficiency because of its simple operation and high sensitivity. Yu *et al.*⁶⁰⁹ established a new method taking advantage of the quenching effect of the phenolphthalein-imprinted polymer on the potassium permanganate- HCl -anhydrous alcohol CL system to determine phenolphthalein by a highly selective FI-CL. This flow path used a Y-shaped column instead of the traditional flow injection cell, through which three reactants could be injected simultaneously. Therefore, a wide linear range from 0.01 to 1 $\mu\text{g mL}^{-1}$ with a low LOD of 8.9 ng mL^{-1} was attained.

However, anti-interference ability of the above CL sensor is not high enough to determine analytes in samples. Accordingly, the combination of electrochemiluminescence (ECL) and MIPs has received much attention due to their high sensitivity, specific recognition and easy miniaturization.⁶¹² Xie *et al.*⁶¹³ reported the core-shell imprinted nanoparticle/chitosan composite film for the selective recognition of thifensulfuron-methyl (TFM) on the bare GCE surface to establish an enhanced ECL sensor, the ECL intensity of which could be strikingly enhanced by the adsorbed TFM molecules in the composite film. So, a wide linear range from 5.0×10^{-10} to 1.0×10^{-7} M with a lower LOD of 0.32 nM for TFM was detected, and it could become a promising technique for sulfonylurea herbicide detection. An MIP-antibody sandwich ECL immunoassay method has also been reported. Gan *et al.*⁶¹⁰ developed a single antibody sandwich ECL immunosensor for ultratrace detection of protein hemoglobin (Hb) using MMIPs as alternatives to the first antibody as capture probes and antibodies labeled with Ru-silica ($\text{Ru}(\text{bpy})_3^{2+}$ -doped silica) doped Au ($\text{Ru}@\text{SiO}_2@\text{Au}$) nanocomposites as labels. These MMIPs as capture probes would aid mass production, reduce cost and avoid the loss of bioactivity associated with the use of conventional antibodies; in addition, it could be easily immobilized and washed off. Based on the enrichment of MMIPs and further amplification of $\text{Ru}@\text{SiO}_2@\text{Au}$ nanocomposites, ultrasensitive detection of Hb concentration in the range from 0.1 to 4×10^4 pg mL^{-1} with an LOD of 0.023 pg mL^{-1} was achieved, with the logarithm of ΔECL intensity changing linearly. This approach could offer significant potential for protein detection in a clinical laboratory setting.

Fig. 22 (A) Schematic diagram of the basic setup for flow sensing system: (a) and (b) are sample solutions and luminescent substance solution, respectively, (c) is oxidation or reduction solutions, P1 and P2 are peristaltic pumps. (B) Schematic diagram of the procedure for the MMIPs flow cell and determination of sulfadiazine (SDZ). (1) SDZ was adsorbed; (2) interferent was removed; (3) chemiluminescence reaction products were added to detect; (4) cleaning the MMIPs flow cell. Reproduced with permission from ref. 611. Copyright © 2006 Elsevier B.V. All rights reserved.

4.2.4. Colorimetric/UV-Vis sensing. In the past, MIAs with radioactive stains,⁶¹⁴ and the colorimetric staining method⁶¹⁵ were used to analyze morphine. However, excitingly, when MIPs combine with colloidal-crystals, sensors named molecularly imprinted photonic hydrogels (MIPHs) or molecularly imprinted photonic polymers (MIPPs), can be fabricated. They can determine analytes or respond to chemical and environmental stimuli by a visually perceptible change in color.

Recently, Chen's group⁶¹⁶ has constructed a novel MIPH film colorimetric sensor using cholesterol as a template molecule, which was prepared by a noncovalent self-assembly approach *via* combining MIT with photonic crystals, as illustrated in Fig. 23A(a). As seen, silica particles were prepared by vertical deposition on glass substrates, and silica colloidal crystal moulding was formed to construct a close-packed face-centered cube, and then three-dimensional (3D) highly-ordered, interconnected macroporous structure MIPH was constructed by removing silica particles and imprinted molecules. Fig. 24A(b) shows the microstructure of MIPH film, which could generate a readable optical signal directly self-reporting within less than 2 min upon binding cholesterol, and the blue shift effect of the Bragg diffraction peak of the MIPHs could be gradually enlarged with the increase in the amount of cholesterol. Therefore, the detection level could approach 10^{-13} g mL⁻¹. Similarly, another kind of MIPH has been developed using vanillin as a template, and the rapid response increased with vanillin concentration increasing from 10^{-12} to 10^{-3} mol L⁻¹ within 60 s.⁶¹⁷ Later, water-compatible MIPHs have also been designed and synthesized in a water-methanol system to enhance the recognition ability in an aqueous environment.

Meng *et al.*⁶¹⁸ developed a novel label-free colorimetric chemo-sensor for handy and fast screening of ketamine based on MIPHs. The MIPHs could specifically recognize ketamine rather than other drug molecules owing to their high selective recognition ability, and the standard error for 5 cycles in $100 \mu\text{g mL}^{-1}$ ketamine buffer was within 5%, indicating a good reproducibility. The sensing ability of ketamine-MIPHs in real biological samples such as urine and saliva also showed the diffraction shifts of MIPHs and non-imprinted photonic hydrogels (NIPHs) to ketamine with a series of concentrations in urinous buffers and salivary buffers. It was obvious that the MIPHs gradually presented a maximum Bragg shift of 78 nm, while almost no response for NIPHs. The resultant MIPHs were also successfully applied in the detection of ketamine in real urine samples obtained from the drug abuser, which clearly indicated that MIPHs had a remarkable practical performance.

As for MIPPs, some research results have also been reported. Wu *et al.*⁶¹⁹ determined atrazine based on MIPPs, which were constructed by a three-step approach as schematically represented in Fig. 23B, including preparation, polymerization and removal steps. The intensity of the optical diffraction of MAA-based MIPPs decreased monotonically as the atrazine rebinding process progressed, which was accompanied by distinct color changes almost covering the whole visible-light wavelength range from blue to red light, and therefore atrazine could be discriminated by the naked eye. Besides, the selectivity experiments showed that the MIPP film had high specificity for atrazine against other herbicides. A larger adsorption capacity of $13.64 \mu\text{mol g}^{-1}$ for MIPPs was obtained than that of non-imprinted photonic polymers (NIPPs) ($4.13 \mu\text{mol g}^{-1}$).

Fig. 23 (A) (a) Schematic illustration of the preparation of molecularly imprinted photonic hydrogels (MIPHs) film using cholesterol as a template molecule. (1) Silica colloidal crystals on glass substrate; (2) infiltration of complex solution into colloidal crystals template followed by photo-polymerization; (3) MIPHs film after the removal of silica microspheres and template molecules; (4) imprinted cavities with complementary shape and binding sites to the template molecule; (5) a complex of a monomer and a template molecule. (b) The SEM of the fabricated MIPHs film. Reproduced with permission from ref. 616. Copyright © The Royal Society of Chemistry 2011. (B) Schematic representation of a three-step approach for the construction of the molecularly imprinted photonic polymers (MIPPs), including the preparation of a colloidal-crystal template, the polymerization of the pre-ordered complex of atrazine with functional monomers in the interspacers of the colloidal crystal, and the removal of the used templates, colloid particles and atrazine molecules. Reproduced with permission from ref. 619. Copyright © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Moreover, the MIPP film also showed good physical stability and chemical inertness and the standard error of the recoverability over five cycles was within 5%, indicating good reproducibility. Similarly, a 3D, highly-ordered and interconnected macroporous array of poly(methacrylic acid) (PMAA) containing a defect-embedded imprinted photonic polymer for BPA was also developed.⁶²⁰ The defect layer could enhance the sensitivity of the photonic crystal material, and it opened new possibilities towards the development of smart optical sensing devices. These MIPPs containing defect layers had great potential for real-time sensing applications due to the narrow linewidths of their optical features.

In the meantime, the synthesis of MIP membranes based on the formation of colored complexes is a good method to develop colorimetric test systems. Sergeyeva *et al.*⁶²¹ designed and synthesized new MIP membranes based on the formation of colored complexes of creatinine with picrates, capable of selective creatinine recognition. The MIP membranes were created on the surface of microfiltration polyvinylidene fluoride (PVDF) membranes using photo-initiated grafting polymerization, and then they were applied to easy-to-use colorimetric test systems for reliable detection of creatinine in analyzed samples. The PVDF microfiltration membranes with MIP modification had distributed pores in the volume of the membrane, special recognition and superior chemical stability. And the linear dynamic range of this developed colorimetric test-system for creatinine was from 0.25 to 2.5 mM with the LOD of 0.25 mM. Besides, the composite creatinine-imprinted MIP membranes demonstrated high selectivity when only negligible

binding of the structural analogues of creatinine was observed. Compared to traditional colorimetric methods, the developed MIP membrane based colorimetric test-systems are more selective and less expensive.

4.2.5. Surface plasmon resonance (SPR)/infrared spectroscopy (IR) sensing. Surface plasmon resonance (SPR) is an optical phenomenon at a conductive interface for detection of small quantities of analytes, which depends on the changes in the dielectric permittivity of the sensor surface. In 1998, the MIP-based SPR sensor was first developed by Lai *et al.* for sorbent assay of theophylline, caffeine and xanthine.⁶²² In view of recent studies, this sensor is of great interest because these small and portable instruments provide high potential for the on-site detection. Generally, SPR spectroscopy measures the optical dielectric constants of thin films deposited onto noble metal-coated substrates like Au NPs or Ag NPs, which are extremely sensitive to the refractive index changes occurring within a few hundred nanometers from the sensor surface. Moreover, the SPR sensors incorporated with MIPs have been widely used to monitor protein,⁶²³ environmental contaminants,⁶²⁴ drugs⁶²⁵ and food.⁶²⁶

In general, the combination of SPR with electrochemistry or applying the surface-initiated ATRP for grafting polymeric films on the Au chips is a powerful analytical technique.⁶²⁷ For example, Advincula *et al.*⁶²⁸ used the MIP film which was prepared by *in situ* electrochemical polymerization of a carboxyl functionalized-terthiophene monomer on the Au substrate carrying the optical surface mode as the working electrode, for the SPR sensing of theophylline, as seen from Fig. 24A(a) and (b).

Fig. 24 (A) Schematic illustration of sensing of theophylline by SPR utilizing ultrathin electrochemical MIP (E-MIP) films of the carboxyl functionalized-terthiophene monomer. (a) Theophylline was imprinted, (b) cavity was formed, and (c) SPR setup for sensing of the theophylline. Reproduced with permission from ref. 628. Copyright © 2010 American Chemical Society. (B) Schematic illustration for fabricating MIP-ir-Au NPs and selective detection of BPA using a small portable Raman spectrometer. A silica monomer–template complex was anchored on the surface of Au NPs directly to form MIP-Au NPs, and then by a simple thermal reaction to generate MIP-ir-Au NPs. Reproduced with permission from ref. 634. Copyright © 2013 Elsevier B.V. All rights reserved.

π -Conjugated poly(terthiophene) films possess electropolymerizability and doping (swelling) properties which could improve the sensitivity and selectivity of the chemical sensor, and lead to highly efficient and faster template removal (c). This complexing ability of a single monomer to the template *via* the orthogonal –COOH functional group facilitated crosslinking through the terthiophene pendant group. Thus, improved sensitivity, high selectivity and robust chemical sensing were attained, with good linearity in the range of 10–50 μM for theophylline ($R = 0.994$) with a low LOD of 3.36 μM , and the working lifetime could retain about 85% of its original response after 45 days of storage under dry and ambient conditions. Besides, the electrochemical MIP (E-MIP) film did not show any observable response upon exposure to the structural analogues of bromine and caffeine (500 μM) albeit with 10 times greater concentration than theophylline. This method was expected to be a promising approach for the fabrication of ultrathin sensor films and for application

in SPR. Zhou *et al.*⁶²⁷ prepared a uniform controllable thin film on a gold chip by molecular imprinting surface-initiated ATRP coupled to immobilization for the detection of ametryn. MIP film directly grafted on the SPR sensing chip by this surfaced-initiated method resulted in a great improvement in the sensitivity and selectivity of the SPR sensing analysis. The linear response was in the range of 0.1–10 μM ($R = 0.9985$), with the LOD of 0.003 μM for soybean and 0.006 μM for white rice. This combination of SPR sensing with MIP film would provide great potential for highly selective and highly sensitive analysis of triazine herbicides in complicated samples.

However, for small molecules, this type of combination becomes harder to measure since the effective change in the dielectric constant at the Au–sample interface is small. Nevertheless, Wei *et al.*⁶²⁹ combined a 3D binding matrix MIP film (molecularly imprinted film, MIF) containing a water-compatible porous structure with the SPR chip to develop a SPR sensor for

the detection of small molecules such as testosterone in urine. This high porosity MIP providing a high capacity and accessibility for testosterone compared with conventional MIP resulted in high sensitivity for rapid detection of targets. So, the LOD of testosterone in artificial urine was obtained down to 10^{-6} ng mL $^{-1}$, and it showed high stability and reproducibility over 8 months of storage at room temperature. This method would be a great candidate for rapid and simple detection of small molecules in aqueous solution such as hormones, stimulants and others. Future efforts should be focused on various molecularly imprinted nanoparticles prepared over thin films and incorporated into SPR to increase the amount of recognition sites, thereby further improving binding capacity and detection sensitivity.

MIP-based sensors are also used in infrared spectroscopy (IR), in which the target analyte adsorbed by a molecularly imprinted layer on a stable substrate was measured using specific IR bands. Sreenivasan *et al.*⁶³⁰ used the surface of polystyrene modified by coating a thin layer of polyaniline by oxidizing aniline with creatinine as an imprint molecule, on which the adsorbed creatinine was detected using the Fourier transform attenuated total internal reflection infrared spectroscopy (FT-ATR-IR) technique. The comparison of the adsorption extent of creatinine between MIPs and NIPs as a function of time indicated that the enhanced adsorption by the imprinted surface was indeed due to the creation of affinity sites. This study offered the possibility of using MIPs in combination with FT-IR spectroscopy for the detection of other analytes. Since IR bands are specific to functional groups, the approach reported here could be used for the sensing of multiple components, which of course warrants extensive optimization.

4.2.6. Surface-enhanced Raman scattering (SERS) sensing.

The surface-enhanced Raman scattering (SERS) spectroscopy technique has been employed for the measurement of vibrational characteristic signatures of the adsorbed compounds in imprinted layers, which is generally explained in terms of a combination of an electromagnetic (EM) mechanism describing the surface electron movement in the substrate and a chemical mechanism (CM) related to charge transfer between the substrate and the analyte molecule.⁶³¹ In 2003, Wulff *et al.*⁶³² proposed the combination of SERS and MIT for the release and uptake of *N*-benzyloxycarbonyl-(L)-aspartic acid in aqueous solution, however, the stability of MIP layers was not high without an additional lubricant like cysteamine. Therefore, a major problem with the MIP-based SERS sensor is the combination of the MIP particles or layers with the SERS-active metal surface.

Fortunately, the combination of single MIP particles with SERS for signal amplification and optical readout in this type of sensor has been successfully realized. Molecular recognition sites in monolayers on a silica, Au or Ag surface for SERS are relatively common, but Au and Ag are mostly used. In 2010, Haupt *et al.*⁶³³ developed a chemical nano-sensor with a sub-micrometer core-shell composite in which the polymeric core, the thin outer MIP shell and gold colloids are located between the core and the shell to detect the (S)-propranolol target.

The clusters of Au colloids acted as antennae and allowed for near-field optical enhancement upon detection of the bound target molecules. The well-known procedure of measurements on aggregated Au colloids was chosen to obtain a reference for the SERS measurements of (S)-propranolol. Compared with measurements on plain MIPs particles, the detection limit of 10^{-7} M and three orders of magnitude higher sensitivity were obtained. Measurements of potential interfering substances showed that the propranolol could still be detected at a similar intensity as in the absence of the interfering substances. This was the first study of the detection of a target molecule by SERS in a single molecularly imprinted composite particle. Subsequently, Long and Li *et al.*⁶³⁴ explored an MIP-based SERS sensor through fabricating the surface-imprinted core-shell Au NPs as a specific functional SERS substrate for the detection of BPA. Fig. 24B shows the schematic illustration of the fabrication of MIP-ir-Au NPs and selective detection of BPA using a small portable Raman spectrometer. As observed, a silica monomer-template complex and the MIP layer anchored on the surface of Au NPs directly were prepared to form MIPs-Au NPs; after thermal reaction, the template was removed and MIP-ir-Au NPs were generated. MIP-ir-Au NPs exhibited a rapid and selective binding for BPA, and a good linear relationship between SERS intensity and BPA concentration was obtained in the range from 0.5 to 22.8 mg L $^{-1}$. Hence, the MIP-based SERS sensor demonstrated a significant potential utility for BPA detection in real samples.

Related SERS studies on the Ag surface have also been reported. Chang and Li *et al.*⁶³⁵ developed a Ag@MIP substrate SERS-based sensor for the determination of 4-mercaptobenzoic acid (4-MBA). The sensor provided a high detectability for 4-MBA as low as 10^{-15} M. However, this MIP-based SERS mechanism is currently not well understood from classical SERS enhancement theory. More work is needed to be performed to explore related mechanisms and push forward the development of MIP-based SERS sensors. To make this MIP-based SERS sensor applicable, Lu *et al.*⁶³⁶ constructed an innovative “two-step” MIP-based SERS biosensor, combining silver dendrites presenting significantly enhanced Raman cross sections as SERS-active substrates for signal collection, with MIPs for the separation and detection of melamine in milk. There, MIPs used as sorbents in SPE achieved effective clean-up of whole milk samples and SERS applied for detection of melamine provided a good linearity between the height of the melamine SERS band (at 703 cm $^{-1}$) and melamine concentration in the range from 0.005 to 0.05 mM with the LOD of 0.012 mM. This innovative biosensor showed great promise in the food industry owing to its high throughput and trace level detection of food chemicals. In addition, micromolecular glycoproteins have also been recognized by this Ag NP substrate through a boronate-affinity sandwich assay.⁶³⁷ Although these MIP-based SERS sensing methods have resulted in the effective detection of analytes in real samples to some extent, the sensitivity and stability should still be significantly improved.

4.2.7. Other sensors. Besides the above-mentioned chemo/biosensors, other MIP-based sensors have been devised and

constructed by utilizing weight signal (mass-sensitive) such as piezoelectric (PZ) transduction sensors. In 1999, Karube *et al.*⁶³⁸ first proposed a selective PZ odor sensor using MIPs, that is, PZ quartz crystals coated with 2-methylisoborneol (MIB) imprinted polymers gave responses for MIB detection. Since then, PZ transduction has gradually become one of the most economical and reliable methods for the determination of biologically and clinically important compounds due to its good LODs, low cost and easy miniaturization.⁶³⁹ Sensors used in PZ transduction combined with MIPs can be classified into 3 types, namely surface acoustic wave (SAW), bulk acoustic wave (BAW) and quartz crystal microbalance (QCM) based MIP sensors. As for their related devices, one of the electrodes wetted by the sample solution serves as the substrate for the adsorption/absorption and chemical/electrochemical reaction, which affects the electrode mass, and the change in the resonant frequency by the change in electrode mass is determined. Taking QCM as an example under flow injection analysis (FIA) conditions, its device operation is schematically illustrated in Fig. 25A.

As we know, SAW is a kind of elastic wave traveling on the surface of the piezoelectric material with a certain characteristic natural resonance frequency. In an SAW resonator, for volatile organic compound (VOC) imprinting, the VOCs can act not only as templates but also as solvents. And the parameters controlling the kinetics and thermodynamics of imprinting recognition have been reported by Fourati *et al.*⁶⁴⁰ On the other hand, it is well known that the most favorable transducer for determining absorption processes is the BAW device, because combining MIPs with the BAW sensor enables the sensor to possess high selectivity and good stability by a simple method.⁶⁴¹

However, both of them have rarely been reported. Researchers should put great efforts into the SAW and BAW sensors based on MIPs.

QCM devices are considered to be highly suitable sensing platforms by combining with MIT for the development of effective MIP-based sensors due to their dynamic monitoring of mass changes at the ng level using an oscillating crystal electrode.⁶⁴² The sensors have been used to detect various molecules such as proteins,^{643,644} DNA/RNA,⁶⁴⁵ drugs^{646,647} and nerve agents.⁶⁴⁸ The sensors are usually fabricated by immobilizing the MIP layer onto the surface of QCM, however, the growth of a nanosized MIP film on the QCM surface commonly utilizes either *in situ* self-assembly approaches or a direct physical adsorption. Alkanethiol-based SAMs around a specific template on Au surfaces providing the main chemical recognition element directly interfaced with QCM transduction can allow *in situ* monitoring like the frequency shift and the motional resistance response and can have a wide range of applications in QCM sensors.⁶⁴⁹ For example, Advincula *et al.*⁶⁵⁰ prepared a simple and robust 2D molecularly imprinted monolayer coated Au QCM sensor for the nitroaromatic compound 2,4-dinitrotoluene (DNT), in which shorter chain butanethiol SAMs were utilized. Fig. 25B illustrates the fabrication process of the sensor. As seen from the figure, the imprinted SAM film was prepared by the co-adsorption of DNT and butanethiol onto a clean Au surface of the quartz crystal *via* solution immersion. The interface with the piezoelectric transducer surface could enable the determination of the binding kinetics. Therefore, the highly selective sensor realized sensitive detection with a LOD of 5.4 ppm for DNT. This self-assembly imprinting based QCM technique should have potential applications for more nitroaromatic compounds if the right alkythiol is chosen.

Allyl-based SAMs have also been employed for QCM because of the rough surface. Diltemiz *et al.*⁶⁴⁵ combined QCM with a thymine imprinted polymer for nucleobase detection using the surface UV-light irradiation polymerization method to form allyl-based SAMs that have a rough surface compared to the thiol-modified monolayer, which provided an effective method for DNA/RNA sequence detection. The sensor system for detection of DNA/RNA had been greatly improved because of polymer coated sensors and the DNA/RNA sequences with single-base differences were detected and collected. So, the frequency changes of the thymine molecules bound to the imprinted polymer on the quartz crystal were directly proportional to the concentration of the biomolecules ranging from 10 to 100 μM . And it could be used to detect thymine selectively in the liquid phase with the selectivity coefficients of 1.25 (11 800/9400) for poly(dT), 2.50 (11 800/4700) for uracil and 5.36 (11 800/2200) for poly(U), respectively. This approach offered a specific, cheap and easy process for the preparation of sensors coated with MIPs on the QCM electrodes based on the biomimicking approach of DNA. These SAMs as the excellent choice to optimize MIP-based QCM film systems have great potential to become commercialization products, and numerous efforts would be needed to be made. Moreover, in the case of electrochemical QCM (E-QCM), its sensitivity, viscosity and

Fig. 25 (A) Schematic illustration of QCM device operation. (B) Fabrication of a 2D DNT/QCM sensor using molecularly imprinted SAMs. Reproduced with permission from ref. 650. Copyright © 2011 American Chemical Society.

Fig. 26 Development history and the fusion process of MIT and applications of MIPs in sample pretreatment, chromatographic separation and sensing. The horizontal axis presents a time axis of MIT development and fusion from the 1930s to present, which is inserted as four main points for 1930s, 1990s, 2000s and 2015, and since its discovery in 1930s, molecular imprinting has developed slowly until 1990s, and then it has blossomed and reached prosperity in 2000s, and nowadays it is universal with diverse imprinted materials created. During 1930–1990s, two kinds of polymerization procedures such as free radical polymerization and the sol–gel process have been developed for MIP preparation. Since 1990s, besides the classic polymerization procedures continuously used and improved, various smart technologies and strategies of MIT have been proposed and attained rapid development, for example, surface imprinting is firstly proposed in 1995, dummy imprinting is proposed in 1997, magnetic/thermo-responsive imprinting in 1998, and solid-phase synthesis in 2013. In the longitudinal direction, the profile is schematically shown from MIT's diverse technology and strategy development to MIPs' versatile applications in sample pretreatment, chromatography and sensing. For the pretreatment techniques and chromatography separation aiming at high selectivity, the MIPs used as sorbents and stationary phases should have ideal morphology, uniform size and excellent surface properties by adopting appropriate preparative technologies and strategies. For the sensors aiming at high selectivity, high sensitivity and simplicity, the MIPs utilized as recognition and sensing materials should have excellent interface properties by employing appropriate preparative technologies and strategies.

conductivities should be greatly improved for combining with molecular imprinting.

In summary, the development of MIP-based chemical and biological sensors has aroused increasing interest because of the growing demand in food analysis, pollutant monitoring, drug detection and clinical diagnostics in recent years. However, for both high selectivity and high sensitivity, a perfect interface between the recognition element and the transducer is extremely necessary and important. Accordingly, devising and preparing MIP particles or films may be crucial for the progress of MIP-based sensors. New inorganic materials, stimuli-responsive hydrogel materials, directly electropolymerized thin film matrices and nanomaterials have been employed to synthesize MIP particles or films. Therefore, computational and combinatorial tools for the synthetic MIPs are urgently required. In addition, imprinting sensing towards enzyme, DNA, cells, bacteria, viruses and even towards organism and gas will continue to be a great challenge and opportunity.

Furthermore, high throughput MIP-based array sensors consisting of multisensory units with multiplexing capabilities also have promising and challenging prospects for multi-component analysis at the same time. At last, the applicability of imprinting sensors in complicated samples also needs continuous exploration.

5. Conclusions and perspectives

In this review, the current status of molecular imprinting is summarized with focus on literature studies published in the most recent years, concerning various improved typical and/or new preparative technologies and strategies of MIT, and representative applications of various MIPs. The fundamentals of MIPs including essential elements, preparation procedures and characterization methods are briefly outlined, emphasizing on the novel and/or improved procedures, such as bulk, emulsion, suspension and precipitation polymerization, and the sol-gel

process for synthesizing MIPs with performance improvement. Smart MIT for MIPs is particularly highlighted, involving ingenious MIT (surface imprinting, nanoimprinting, solid-phase synthesis technology, *etc.*), special strategies of MIT (multi-functional monomer imprinting, dummy imprinting, segment impinging, *etc.*), and stimuli-responsive MIT (magnetic responsive, thermo-responsive, dual/multi responsive technology, *etc.*), which greatly facilitates the preparation of attractive and competitive well-designed MIPs. Versatile applications of the as-prepared MIPs are comprehensively reviewed, containing sample pretreatment (MISPE, MISPME, MISBSE) and chromatographic separation (packing materials, monolith materials), and chemical/biological sensing (electrochemical, fluorescent, SERS sensors, *etc.*). So, the development history and fusion process of diverse technologies and strategies of MIT, and the wide range of applications of MIPs are thoroughly surveyed, as schematically illustrated in Fig. 26. As seen from the figure, the review is more technology-oriented covering the traditional preparation procedures/methods with improvement and emerging smart preparation technologies and strategies, and focuses on the utility of MIPs in multiple fields such as MIP-based sample pretreatment/chromatographic separation and sensing. The advancement gained very recently is emphatically discussed and also the original seminal work reported much earlier is briefly mentioned. By continuously improving morphology, size, rigidity and surface properties *via* adopting appropriate preparative technologies and strategies such as LCRP precipitation polymerization and multi-template suspension polymerization, appropriately formatted MIPs with high selectivity have become ideal pretreatment/chromatographic materials for highly effective enrichment, purification and separation of target analytes in complicated matrices. By effectively improving and controlling interface properties *via* employing appropriate preparative technologies and strategies such as the surface imprinting sol-gel process and nanoimprinting emulsion polymerization, appropriately patterned MIPs have been increasingly used as recognition and sensing materials to construct ideal sensors for highly selective, high sensitive and simple sensing detection. Consequently, the recent substantial advances of MIT have contributed significantly to the diversified preparation of MIPs and their extensive use in purification/separation and chemo/biosensing.

Still, MIT faces a number of challenges and opportunities, such as low binding capacity, template leakage, incompatibility with aqueous media, and difficult macromolecular imprinting. The possible solution strategies and future perspectives are proposed, as follows: fusion of MIT and other technologies, exploration of special strategies of MIT, and development of SR-MIPs, and applicability of MIPs for sample preparation and chemo/biosensing. We have reasons to believe that the full attention and persistent action will promote the development of molecular imprinting, and then create diversified MIPs for further applications.

5.1. Fusion of MIT and various technologies

Fusion of MIT and various technologies should be continuously strengthened to push forward MIT. In recent years, MIT has

constantly borrowed, referred and combined other technologies for improving itself. And various polymer synthesis technologies have already been introduced into MIT, such as radical polymerization and the sol-gel process, and grafting. As a multi-disciplinary technology, MIT involves polymer chemistry, materials science, analytical chemistry, environmental science, and biological/drug research, *etc.* Meanwhile, MIT should develop rapidly along with the advances in polymer technology, nanotechnology, click chemistry technology, microfluidic technology, stimuli-responsive technology, biotechnology and optical technology, and so on. Through reasonable combination of MIT and other technologies, the optimal efficacy of MIPs can be obtained. Therefore, the borrowing and integration of related technologies will bring significant breakthroughs and accelerate molecular imprinting development, and therefore it is possible to attain various better performing MIPs, which will be active in multiple aspects. Several examples are provided below.

Nanoimprinting can increase considerably the amount of effective recognition sites and therefore remarkably improve imprinting capacities. Nanomaterials of varying size and dimensions are still of tremendous potential. Developing nano-sized imprinted materials with good biocompatibility will provide great potential for living cell imaging and nano-device system development. In addition, it will be greatly promising to combine nanogels with other ingenious MITs to produce high-powered MIPs. By introducing photonic crystals into MIT, label-free colorimetric sensors can be constructed, relying on the blue shift effect of the Bragg diffraction peak. Taking advantage of highly sensitive fluorescence, MIP based fluorescent sensors/probes with high selectivity and sensitivity can be obtained. By introducing magnetic materials and catalytic micromotors into MIP preparation, attractive magnetic imprinted micromotor microsensors will be fabricated, which will not only contribute to the research connotations of concerned-target imprinting, but also provide attractive routes to the multi-functionalization/integration and intellectualization of micro/nano-sized devices. Moreover, the utilization of combinatorial chemistry will greatly simplify the optimization process and improve preparation efficiency. Overall, just as collisions generate sparks, the ingenious fusion of MIT and various technologies enriches creativity and leads to the development of MIT.

5.2. Special strategies of MIT

The introduction of special imprinting strategies such as multi-template, multi-functional monomer, dummy template, segment template and composite material imprinting can effectively overcome the challenges of MIT and smoothly realize various applications including multi-analyte detection, hazardous source monitoring, macromolecular imprinting and so on. Multi-template imprinting displays excellent advantages and it is highly desirable; however, related reports are still very limited. The imprinting procedure and efficiency must be considered for multiple template molecules/ions to obtain good results. It is encouraging to figure out the imprinting mechanism and then provide the best performances for multiple analytes,

followed by high throughput analysis/removal to satisfy detection/monitoring/remediation requirements. Multi-functional monomer imprinting, based on multipoint interactions, can improve the selectivity of MIPs/IIPs by virtue of synergy of two or more functional monomers. Macromolecular imprinting and stimuli-responsive imprinting especially benefit from the multi-functional monomer strategy. Moreover, devising and synthesizing new specific functional monomers are also effective methods to enhance the selectivity of MIPs, and to imprint various analytes. Theoretical calculations (computer simulations) have become important tools to attain ideal monomers. The development of monomers greatly broadens the application range of MIT.

Dummy imprinting can avoid the risk of template leakage, and provide an attractive alternative for expensive/insecure, or easily degradable/low soluble target analytes (original template molecules). The structurally analogous target analytes are used as template molecules. Segment imprinting, utilizing a partial structure of the target molecule as a pseudo-template to prepare MIPs, can also solve the problem of template leakage. Besides using expensive/highly toxic original template molecules, segment imprinting is particularly popular for biological macromolecules with quite large structures. Both dummy imprinting and segment imprinting can offer similar selectivity to the target molecule imprinting and can extend the application range of MIPs. However, it is not easy to select appropriate dummy and segment template molecules. More work should be carried out to search for desirable molecules. Composite material imprinting can combine and amplify the advantages of both composite materials and MIPs. Core-shell structure is commonly prepared, since it not only can provide higher imprinting capacity and faster mass transfer, but also can easily combine various functional groups and properties. Researchers should strive to seek diverse composite materials and select their ingenious combination with MIPs. Core-shell structured composite material imprinting has drawn great interest with promising applications.

Consequently, the special strategies of MIT will expand imprinting targets from small molecules and ions to proteins, and even to living cells and organisms. Exploration of related mechanisms will facilitate solving some bottleneck issues and broaden the application fields of MIPs.

5.3. Stimuli-responsive MIPs

SR-MIPs have attracted increasing attention owing to their unique characteristics of high selectivity intelligently regulated/modulated by simple stimuli response, which can effectively cope with some problems of MIT such as recognition in aqueous media by temperature-/pH-responsive SR-MIPs. However, there are still substantial challenges and opportunities. We attempt to propose some important explorations as follows:

(1) Design and synthesis of new responsive functional monomers: more types of diverse functional monomers should be developed, which can provide a wide range of options. With the smart design and synthesis of new functional monomers according to different response modes, the selectivity of

SR-MIPs will be significantly improved, and a variety of analytes will be imprinted.

(2) Exploration of new stimuli responsive systems: researchers should develop new SR-MIPs responsive to rarely reported stimuli such as ultrasound, electric field, chemical/biological species and enzymes, which is an important potential research direction. More endeavours will be made to create new SR-MIPs with new responsive elements, which will greatly enrich the research connotations of SR-MIPs and broaden the application fields of MIT.

(3) Development of dual/multi-responsive SR-MIPs: in view of increasing requirements for functionalized materials, developing dual/multi SR-MIPs with good biocompatibility has become an important research direction. More attention should be paid to the reasonable and ingenious combination of dual/multiple response elements to offer optimal performances, involving core-shell or monomer copolymerization structures in SR-MIP development.

(4) Applications of SR-MIPs: with the development of SR-MIPs, more efforts should be concentrated on the application aspects. Excitingly, the persistent problem perplexing MIT, namely recognition and detection of target analytes in the aqueous environment, can be readily solved by means of SR-MIPs. How to effectively utilize the advantages of SR-MIPs for sample pretreatment and sensing, as well as for drug delivery, environmental protection, life science and other fields, has become the research emphasis. Considering the strong recognition ability in aqueous environments and eco-friendliness of SR-MIPs, significant efforts are still urgently required to further explore and develop the versatile functions of SR-MIPs, thereby promoting their practical applications.

5.4. Applications of MIPs

As described above, MIPs with appealing features have been most frequently utilized as affinity-based separation media for sample pretreatment and chromatography, meanwhile, they have also been widely used as sensing elements for sensors. Until now, MIPs have been extensively applied in environmental, food, biological and medical fields. Although MIPs enjoy significant benefits and diverse applications, a number of challenges and opportunities still remain.

In terms of the applications of MIPs in sample pretreatment and chromatography, there are still several problems to be resolved and improved. First, traditional enrichment and separation technologies always need large scale equipment and large quantities of sorbents resulting in consuming massive resources. For instance, extensively used off-line SPE is usually accomplished with the aid of an SPE system, where an SPE column should be packed with sorbents (the dosage of the sorbent should be between several milligrams and grams) and a large volume of organic solvents. Based on the characteristics of MIPs and the requirements of environmental friendly techniques, miniaturized pretreatment techniques have been developed which can minimize the consumption of organic solvents and materials, and decrease environmental effects, *e.g.*, manufacturing mini SPE columns or separation columns

(like capillary columns packed with MIPs), and using molecularly imprinted membranes to displace the SPE column. Second, some kinds of online pretreatment techniques have been proposed in order to simplify the operational procedures, increase the reproducibility and shorten pretreatment time, such as online MISPE, but most of them have difficulty in achieving online treatment, especially for MISPME and MISBSE. So, finding suitable methods to implement online enrichment or separation using MIPs has become a potential challenging task, such as improving the synthesis method of MIPs to obtain appropriate patterns (like monolithic MIPs) and developing a new device interface to connect with the subsequent detector to separate and detect analytes online or automatically. Third, although many kinds of SPE columns or chromatographic columns have been commercially popular (like C_{18} , C_8 column), MIPs as sorbents of SPE or stationary phases of chromatographic columns have seldom been used commercially. The possible reasons are that the morphology and rigidity of MIPs cannot sustain the packing pressure, MIPs cannot be used under aqueous conditions, and low adsorption or sample loading capacity and poor selectivity of MIPs cannot adapt to complex matrix samples. Based on that, smart strategies of synthesis methods of MIPs should be continuously explored. Fourth, in the synthesis of MIPs, only a small amount of product is obtained, and the synthesis of identical materials next time is difficult even under the same conditions. Thus, batch synthesis of MIPs is needed, and some studies of synthesis of MISPME on a large scale have been reported recently in order to improve the preparation yield and efficiency. Fifth, to develop more simple, rapid and economical chromatography than the conventional HPLC or GC with the help of MIPs is also feasible, like the reported flash chromatography which is repacked with MIPs, affording highly purified active ingredients from plants on a large scale.

In terms of the applications of MIPs in chemical and biological sensing, several problems still remain unresolved. First, the sensitivity and mechanism of imprinted sensors are focused. On one hand, a perfect interface between the recognition element and the transducer is extremely imperative for high sensitivity and selectivity. On the other hand, taking sensitivity for example, for MIP-based electrochemical sensors, the sensitivity enhancing methods mainly include surface chemistry and nanotechnology/nanomaterials, and click chemistry. As is well known, the problem of low sensitivity is common in MIP-based fluorescent systems, and much work still needs to be done to improve the sensitivity while retaining the high selectivity. Very possibly, reducing the MIP-shell thickness, providing (meso)porous structures, and adopting ratiometric fluorescence measurements are three effective methods to improve sensitivity. As for colorimetric/UV-Vis sensors, it is highly desirable that the signal change (structure color change) of MIPs in response to trace template molecules should be large enough so that it can be observed by the naked eye or ultraviolet spectrometers. New MIP-based SERS sensors, first introduced in 2010, have shown excellent analytical performances; however, so far, only a few studies have been

reported. Probably, it is difficult to balance the SERS substrate and the MIP layer. In addition, the imprinting sensing mechanism is still not well understood from classical SERS enhancement theory. So, greater efforts are required to explore related mechanisms and push forward the development of SERS sensors. Researchers should continuously develop new sensing elements, smartly combine them with MIT, and therefore strengthen their sensing applications. In-depth exploration of mechanisms will efficiently solve some bottleneck issues and expand the application range of MIT. Second, films may be crucial in the progress of MIP sensors, and new inorganic materials, stimuli-responsive hydrogel materials, directly electropolymerized thin film matrices, and nanomaterials have been utilized for synthesizing MIP films. Computational or combinatorial tools are urgently adopted for preparing MIPs. Moreover, MIP-based intelligent micro/nano-sized devices have promising prospects and more related endeavors and explorations should be continuously made to push forward their development. Third, the imprinting sensing of macromolecules such as proteins, DNA, cells, bacteria, viruses and even organisms will continue to be a great challenge, and various smart MITs should be employed such as dual/multiple functional monomer imprinting and segment imprinting along with the intelligent introduction of sensing elements.

Besides the above-mentioned purification/separation and sensing applications, MIPs are increasingly used in various fields. The above two applications and enzyme mimics catalysis are generally regarded as the top three uses. The application area of MIT and MIPs needs to be further broadened. They are found to be useful for drug delivery, immunoassay, artificial antibodies, catalysis, adsorption, membrane separation and so on, and therefore they can be hopefully used for industrial scale applications in bioengineering, clinical medicine, natural medicine, the food industry and environmental monitoring. Meanwhile, MIT has important theoretical significance and practical value in the investigation of enzyme structures and in the understanding of the working mechanism of receptor-antibody. On the other hand, gaseous small-molecule imprinting is rarely attempted, possibly because of the too small size of molecules, the gaseous state at room temperature and out-of-control operation. With the in-depth study and increasingly extensive application of MIT, gas as a target object and recognition in the gaseous phase will become the important research direction of MIT.

Obviously, the high throughput applications of MIPs in complex matrices are especially desirable. MIPs are widely applicable in real samples; however, high volume production and large scale applications of MIPs have been rarely reported. Although some MIPs are found to be commercially available for pretreatment/chromatography, the commercial exploitation of MIT is still in its infancy by conventional procedures with its own set of pros and cons, and hence, an efficient means of preparing MIPs should be urgently developed. A huge gap between general lab-scale use and industrial-scale applications mainly lies in the preparation factors of MIPs, such as different operation conditions, relatively low preparation amounts and

high costs, immaturity of preparation techniques, and eco-friendly requirements. Several proposed methods can bridge this gap by using the existing mature preparation technologies to attain high scale production of MIPs, but often sacrificing selectivity; by developing various smart MITs for up-scaling MIP production; and by borrowing, coupling and integrating various technologies for MIP preparation such as combinatorial chemistry, theoretical calculations and experimental design. Therefore, long-term significant efforts should be made to introduce various technologies and strategies into MIT for MIP preparation in order to rapidly obtain abundant MIPs for industrial and commercial applications.

List of abbreviations and acronyms

1-MA-3MI-Br	1-(α -Methyl acrylate)-3-methylimidazolium bromide	DBTS	Dibenzothiophene sulfone
2,4,6-TCP	2,4,6-Trichlorophenol	DBTTC	Dibenzyltrithiocarbonate
2,4-D	2,4-Dichlorophenoxyacetic acid	DDBP	4,4'-Dihydroxybisphenyl
2,4-DCP	2,4-Dichlorophenol	DLLME	Dispersive liquid liquid microextraction
3-PBA	3-Phenoxybenzoic	DMET	2,4-Diamino-6-(methacryloyloxy)ethyl-1,3,5-triazine
4-APh	4-Aminophenol	DMF	<i>N,N</i> -Dimethylformamide
4-MBA	4-Mercaptobenzoic acid	DMIPs	Dummy MIPs
4-NP	4-Nitrophenol	DMT	2,4-Diamino-6-methyl-1,3,5-triazine
4-SSA	4-Styrenesulfonic acid	DMZ	Dimetridazole
4-VP	4-Vinylpyridine	DNP	2,4-Dinitrophenol
AAm	Acrylamide	DNT	Dinitrotoluene
ACN	Acetonitrile	DPV	Differential pulse voltammetry
AFM	Atomic force microscopy	DR-MIPs	Dual responsive MIPs
AFP	Alpha-fetoprotein	DSPE	Dispersive SPE
AIBN	2,2'-Azobisisobutyronitrile	DVB	Divinylbenzene
AML	<i>rac</i> -Amlodipine	d-ZOP	d-Zopiclone
AMP	Adenosine monophosphate	E	Ephedrine
ASV	Anodic stripping voltammetry	EBL	Electron beam lithography
ATP	Adenosine triphosphate	ECS	Electromagnetic controlled system
ATRP	Atom transfer radical polymerization	EGDMA	Ethylene glycol dimethacrylate
AuNCs	Gold nanoclusters	EGFETs	Extended-gate field effect transistors
BaP	Benzo[<i>a</i>]pyrene	EGMRA	Ethylene glycol maleic rosinat acrylate
BET	Brunauer–Emmett–Teller	E-MIP	Electrochemical MIP
BHb	Bovine hemoglobin	EOF	Electroosmotic flow
BLAs	Penicillin-type β -lactam antibiotics	ERY	Erythromycin
BP	Benzophenone	FETs	Field-effect transistors
BPA	Bisphenol A	FITC	Fluorescein isothiocyanate
BSA	Bovine serum albumin	FQ	Fluoroquinolon
CAR	Carboxen	FRP	Free radical polymerization
CBZ	Carbamazepine	GC	Glassy carbon
CE	Capillary electrophoresis	GS	Graphene sheets
CEA	Carcinoembryonic antigen	GSCR-MIPs	Graphene sheets/congo red-MIPs
CL	Chemiluminescence	Hb	Hemoglobin
CLC	Capillary liquid chromatography	HQ	Hydroquinone
CPE	Cloud point extraction	HSA	Human serum albumin
CPF	Chlorpyrifos	IAA	Thiolation-3-indoleacetic acid
CS	Chitosan	ICP-OES	Inductively coupled plasma optical emission spectroscopy
CV	Cyclic voltammetry	IIPs	Ion-imprinted polymers
CW	Carbowax	IPTS	3-Isocyanatopropyltriethoxysilane
DA	Dopamine	IR	Infrared spectrum
		ISEs	Ion selective electrodes
		ISFETs	Ion-sensitive field effect transistor
		ITO	Indium-tin oxide
		LCRP	Living/controlled radical polymerization
		LCST	Lower critical solution temperature
		LEDs	Light emitting diodes
		LLE	Liquid liquid extraction
		LSV	Linear sweep voltammetry
		Lys	Lysozyme
		MAA	Methacrylic acid
		MBA	<i>N,N'</i> -Methylene bisacrylamide
		MBP	4,4'-Methylenebisphenol
		MDA	4,4-Methylene diphenylamine
		MEKC	Micellar electrokinetic chromatography

MIECS	Molecularly imprinted electrochemical sensors	SLM	Supported liquid membrane
MIM	Molecular imprinting membrane	SMIPs	Spherical MIPs
MIMs	Molecularly imprinted monoliths	SPE	Solid phase extraction
MIP-G	MIPs grafted graphene	SPME	Solid phase microextraction
MIPIs	Molecularly imprinted photonic hydrogels	SPR	Surface plasmon resonance
MIP-NPs	MIP nanoparticles	SR-MIPs	Stimuli-responsive MIPs
MIPs	Molecularly imprinted polymers	SSF	Stainless steel
MIT	Molecular imprinting technology	ss-ODN	Single-stranded oligodeoxyribonucleotide
M-MIPs	Magnetic molecularly imprinted polymers	STD	Static thermal desorption
MNPs	Magnetic nanoparticles	SWV	Square wave voltammetry
MNZ	Metronidazole	<i>t,t</i> -MA	<i>t,t</i> -Muconic acid
MRGA	Maleic rosin glycol acrylate	TBBPA	3,3',5,5'-Tetrabromobisphenyls
MSM	Metsulfuron-methyl	TBZ	Thiabendazole
MSPD	Matrix solid phase dispersion	TEM	Transmission electron microscope
MWNTs	Multi-walled carbon nanotubes	TEMED	<i>N,N,N',N'</i> -Tetramethylethylenediamine
NCs	Nanoclusters	TEOS	Tetraethoxysilane
NIPAAm	<i>N</i> -Isopropylacrylamide	TFM	Thifensulfuron-methyl
N-MIPs	Nanostructured MIPs	THF	Tetrahydrofuran
NMR	Nuclear magnetic resonance	THO	Theophylline
NSAIDS	Non-steroidal anti-inflammatory drugs	TiO ₂	Titanium dioxide
OCBZ	Oxcarbazepine	TMIPs	Temperature-responsive MIPs
OFX	Ofloxacin	TMIPs	Thermo-responsive MIPs
OPPs	Organophosphorous	TMOS	Tetramethoxysilane
PA	Polyacrylate	TNP	Trinitrophenol
PAHs	Polycyclic aromatic hydrocarbons	TNT	2,4,6-Trinitrotoluene
PANI	Polyaniline	TRIM	Trimethylolpropane trimethacrylate
PC	Photocatalysis	UAD	Ultrasonic-assisted desorption
PDMS	Polydimethylsiloxane	USF	Uranyl-salophen-fluorescein
PE	Polyethylene	VSM	Vibrating sample magnetometer
PEEK	Polyetheretherketone	XPS	X-ray photoelectron spectroscopy
PEG	Polyethylene glycol	ZOP	Zopiclone
PET	Polyethylene terephthalate	α -Chloro-DDT	1,1-Bis(4-chlorophenyl)-1,2,2,2-tetrachloroethane
PFOS	Perfluorooctanesulfonate	β -CDs	β -Cyclodextrins
PhAAAn	<i>p</i> -Phenylazoacrylanilide	γ -MAPS	γ -Methacryloxypropyltrimethoxysilane
PMAA	Poly(methacrylic acid)		
P-MIPs	Photo-responsive MIPs		
PMMA	Poly(methyl methacrylate)		
PMME	Polymer monolith microextraction		
PNIPAAm	Poly(<i>N</i> -isopropylacrylamide)		
PS	Polystyrene		
PVDF	Polyvinylidene fluoride		
QDs	Quantum dots		
R123	Rhodamine 123		
RAFT	Reversible addition-fragmentation chain transfer		
RAM-MIP	Restricted access media-MIP		
RGDS	Arg-Gly-Asp-Ser		
RH	Resveratrol		
RTILs	Room temperature ionic liquids		
SAM	Self-assembled monolayers		
SAs	Sulfonamides		
SBSE	Stir bar sorption extraction		
SDS	Sodium dodecyl sulfate		
SDZ	Sulfadiazine		
SEM	Scanning electron microscope		
SERS	Surface enhanced Raman scattering		

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