

Stimuli-responsive molecularly imprinted polymers:
versatile functional materialsCite this: *J. Mater. Chem. C*, 2013, **1**,
4406Shoufang Xu,^{a,c,d} Hongzhi Lu,^a Xiuwen Zheng^a and Lingxin Chen^{*b}

Stimuli-responsive molecularly imprinted polymers (SR-MIPs) have received widespread attention with the rapid development of stimuli responsive polymers and molecularly imprinted polymers, and significant progress has been achieved in recent years in the field of SR-MIPs. To date, magnetic responsive MIPs, temperature responsive MIPs, pH responsive MIPs, photo-responsive MIPs, and dual or multi stimuli responsive MIPs have been prepared, and display broad application perspectives in many fields such as drug delivery, biotechnology, separation sciences, and chemo/biosensors. In the present feature article, those SR-MIPs are summarized comprehensively, and particular attention is paid to the mechanism of SR-MIPs, their preparation methods, and the application aspects. Finally, some significant attempts to further develop SR-MIPs are also proposed.

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1 Introduction

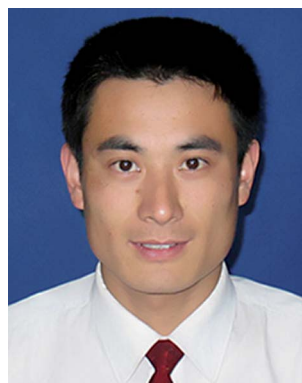
Molecularly imprinted polymers (MIPs), with origins in the molecular imprinting technique proposed by Polyakov in 1931,¹ are synthesized by the copolymerization of functional monomers and cross-linkers in the presence of template molecules.

After removal of the template molecules, recognition cavities complementary to the template molecules in shape, size and chemical functionality are formed in the highly cross-linked polymer matrix, which have a predetermined selectivity for a given analyte, or a group of structurally similar compounds.^{2–4} The molecular imprinting process is represented in Scheme 1.² In recent years, great achievements based on MIPs have been made in many fields, such as purification and separation,^{5–10} chiral recognition,^{11–14} chemo/biosensing,^{15–17} and catalysis and degradation,^{18,19} due to the desired selectivity, physical robustness, thermal stability, as well as low cost and easy preparation of the MIPs.

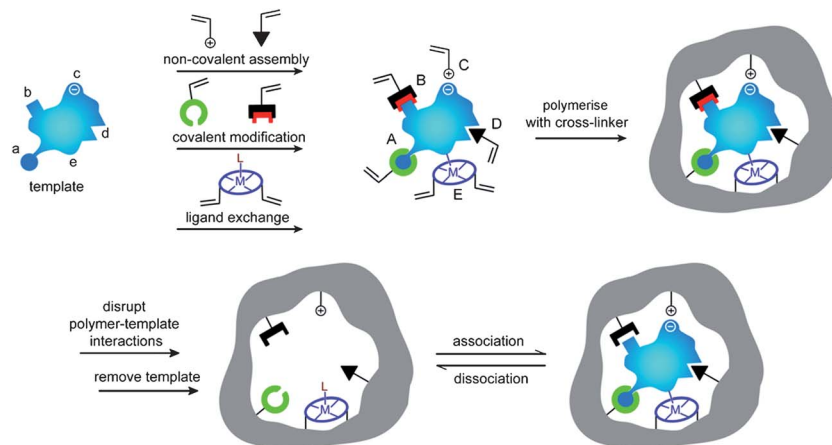
Stimuli responsive polymers (SRP), also known as environmental responsive polymers or smart polymers, are a class of special materials that are able to respond to specific external

^aSchool of Chemistry & Chemical Engineering, Linyi University, Linyi 276005, China^bKey Laboratory of Coastal Zone Environmental Processes and Ecological Remediation, Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences, Yantai 264003, China. E-mail: lxchen@yic.ac.cn; Fax: +86-535 2109130; Tel: +86-535 2109130^cUniversity of Chinese Academy of Sciences, Beijing 100049, China^dKey Laboratory of Resources & Environmental Analytical Chemistry in University of Shandong, Linyi University, Linyi 276005, China

Shoufang Xu received her Ph.D. degree from the Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences in 2012. She received the Special Prize of Presidential Scholarship of Chinese Academy of Sciences in 2012, and the Scholarship Award for Excellent Doctoral Student granted by the Ministry of Education in 2011. She is currently a lecturer at the School of Chemistry & Chemical Engineering, Linyi University. Her research interests focus on the preparation of molecularly imprinted polymers (MIPs) and the application of MIPs in the separation and analysis of typical organic pollutants.



Hongzhi Lu received his Masters degree from Shandong Normal University in 2007. He is currently a lecturer at the School of Chemistry & Chemical Engineering, Linyi University. His research interests focus on the synthesis and application of functional polymers.



Scheme 1 Schematic representation of the molecular imprinting process. Reversible binding between the template and polymerizable functionalities may involve one or more of the following interactions: (A) reversible covalent bond(s), (B) covalently attached polymerizable binding groups that are activated for non-covalent interaction by template cleavage, (C) electrostatic interactions, (D) hydrophobic or van der Waals interactions, or (E) coordination with a metal center; each form with the complementary functional groups or structural elements of the template, (a)–(e), respectively. Subsequent polymerization in the presence of cross-linker(s), a cross-linking reaction or other process results in the formation of an insoluble matrix (which itself can contribute to recognition through steric, van der Waals, and even electrostatic interactions), in which the template sites reside. The template is then removed from the polymer through disruption of the polymer–template interactions and extracted from the matrix. The template, or analogues thereof, may then be selectively rebound by the polymer in the sites vacated by template, that is, the “imprints”. While the representation here is specific to vinyl polymerization, the same basic scheme can equally be applied to sol–gel systems, polycondensation, etc. (Adapted with permission from ref. 2.)

stimuli with a considerable change in their properties, such as molecular chain structure, solubility, surface structure, swelling or dissociation behavior.^{20–24} These stimuli can be temperature,²² pH,²⁵ ionic and/or solvent composition of the media,²⁶ electric field,²⁷ magnetic field,²⁸ ultrasound,^{29,30} and photonic irradiation.^{31,32} Because of their intriguing properties, interest in the potential applications of SRP for drug delivery, biotechnology, separation sciences, and chemosensors is growing rapidly. This, in turn, calls for the development of more new materials with improved properties, or the capability of producing new responses to designated stimuli.

By combining SRP with MIPs, a kind of novel functional material, stimuli responsive MIPs (SR-MIPs) have been developed. These SR-MIPs combine the advantages of SRP and MIPs: not only can they respond to external stimuli,^{33,34} but they also have molecular recognition ability for template molecules.^{4,11–14,33,34} The recognition of the template will be specific when the MIPs maintain a 3D structure similar to that of the imprinting state, whereas the memory of the template will be lost when external stimuli cause the loss of the imprinting state due to shrinkage or swelling of the MIPs. So, the release and adsorption of template molecules can be achieved through



Xiuwen Zheng received his Ph.D. degree from the University of Science & Technology of China in 2004. Since then he has been working at the School of Chemistry & Chemical Engineering, Linyi University. He is now a professor and director of the School of Chemistry & Chemical Engineering. His research interests focus on the development of novel carbon-based nanocomposites for biosensors, biomedical imaging and drug delivery.



Lingxin Chen received his Ph.D. from the Dalian Institute of Chemical Physics, Chinese Academy of Sciences in 2003. After two years of postdoctoral experience at the Department of Chemistry, Tsinghua University, he worked first as a BK21 researcher and then as a research professor at the Department of Applied Chemistry, Hanyang University, Korea, in 2006. He is currently a professor at the Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences. His research interests include the study of novel properties of materials such as functionalization nanoparticles for developing nanoscale biochemical analysis methods, and molecular imprinting based sample pre-treatment–chromatography combined technology.

external stimuli, such as changes in temperature, pH or light, *etc.* SR-MIPs have received widespread attention since their conception due to their superior properties. A series of SR-MIPs, such as magnetic responsive MIPs, temperature responsive MIPs, pH responsive MIPs, photonic responsive MIPs, and dual or multi stimuli responsive SR-MIPs have been developed and displayed broad application prospects in drug delivery, biotechnology, separation sciences, biosensors and so on, as shown in Scheme 2. To the best of our knowledge, very few review works about SR-MIPs have been reported, and most of them place more emphasis on their drug delivery systems.^{33–36} In the present feature article, we summarize those SR-MIPs comprehensively, from the mechanism to the preparation methods, and then consider their various applications. We hope that SR-MIPs can be understood by more people, and people who are engaged in this field will be helped by this review.

2 Single signal responsive MIPs

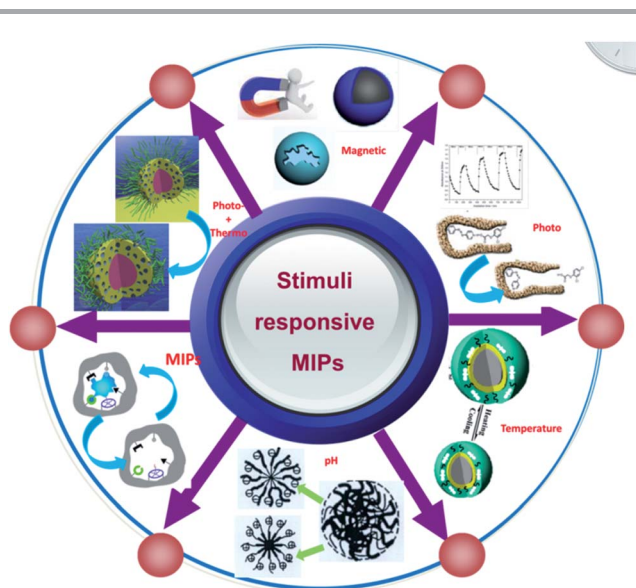
To date, single signal responsive MIPs, such as magnetic responsive MIPs, photonic responsive MIPs, temperature responsive MIPs and pH responsive MIPs, have aroused extensive interest and have become a research hotspot in the field of SR-MIPs. Therefore single signal responsive MIPs are first reviewed.

2.1 Magnetic responsive MIPs (M-MIPs)

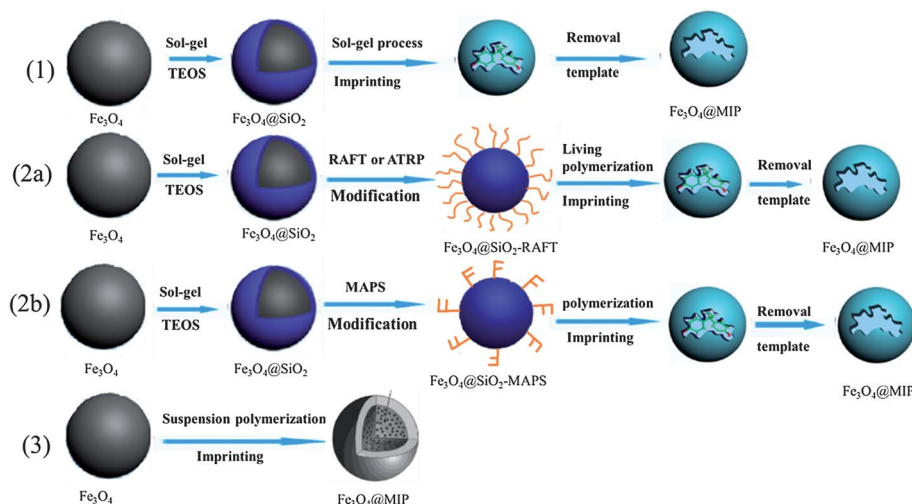
Magnetic responsive polymers, which show directional movement under an external magnetic field, are prepared by encapsulating magnetic material, such as Fe_3O_4 nanoparticles, into polymers. As a novel functional material, especially as a solid

phase carrier for magnetic separation technology, magnetic responsive polymers have broad application prospects in the fields of biomedicine, cell labelling, cell separation and bio-engineering, which can be attributed to their property of facilitating rapid separation. With the development of surface imprinting techniques, magnetic Fe_3O_4 nanoparticles have also been employed as a solid support for surface imprinting. Surface imprinting is a very appealing way to prepare MIPs with cavities at the material surface or close to the surface, resulting in not only a higher binding capacity, but also faster mass transfer and binding kinetics.^{37,38} Compared to other solid supports used for surface imprinting, such as silica gel, nanoporous alumina membranes and chitosan, the magnetic Fe_3O_4 nanoparticles surface imprinted polymers, also called magnetic responsive MIPs (M-MIPs), have the remarkable advantage of magnetic separation in addition to surface imprinting.

The general preparation of M-MIPs involves three consecutive steps: (1) preparation of Fe_3O_4 magnetic nanoparticles by a coprecipitation method³⁹ or a solvothermal reduction method,⁴⁰ (2) surface modification of the Fe_3O_4 magnetic nanoparticles to favor surface polymerization, and (3) synthesis of M-MIPs through a sol-gel process or free radical polymerization. To date, three main methods have been developed for preparing M-MIPs, as illustrated in Scheme 3: (1) $\text{Fe}_3\text{O}_4@\text{SiO}_2$ nanoparticles are prepared, and then $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{MIPs}$ are prepared by a sol-gel process using silyl reagents.⁴¹ (2) $\text{Fe}_3\text{O}_4@\text{SiO}_2$ nanoparticles are prepared, and then vinyl double bond or reversible addition-fragmentation chain transfer (RAFT) agents are introduced, and M-MIPs are finally prepared by precipitation polymerization dependent on a free radical polymerization mechanism.^{42–46} Submicron magnetic particles of magnetite colloid nanocrystal clusters, also known as Fe_3O_4 nanoparticles prepared by a solvothermal reduction method, display significant advantages over traditional Fe_3O_4 nanoparticles prepared by the coprecipitation method, and are always employed in this kind of method to prepare M-MIPs. (3) Oleic acid modified Fe_3O_4 is prepared, and then M-MIPs are prepared by suspension polymerization dependent on a free radical polymerization mechanism.^{47–49} These three preparation methods each enjoy their own advantages. The distinct advantages of sol-gel processes are the ease of fabrication at room temperature without the problem of thermal or chemical decomposition, and the use of eco-friendly reaction solvents, ultrapure water or ethanol, which is quite different from the general solvents used for free radical polymerization, such as chloroform, acetonitrile and toluene. An ultrathin MIPs shell with controllable shell thickness can be obtained using the second method, which is favorable for faster mass transfer, and higher binding capacity can always be achieved. However, the time consuming and laborious surface modification of Fe_3O_4 nanoparticles restrict its application. Compared to the two former methods which usually involve complicated preparation processes and long time scales, suspension polymerization is the simplest method for preparing M-MIPs. However, the large particle size and low imprinting capacity of this method are problematic. Another disadvantage is the poor compatibility of the reaction solvent (water) under optimal molecular



Scheme 2 Scheme of stimuli responsive MIPs. SR-MIPs are divided into two types: single responsive MIPs and dual/multi responsive MIPs. The former group mainly includes magnetic responsive MIPs, photonic responsive MIPs, temperature responsive MIPs, and pH responsive MIPs. (Adapted with permission from ref. 2, 43, 65, 87 and 106.)



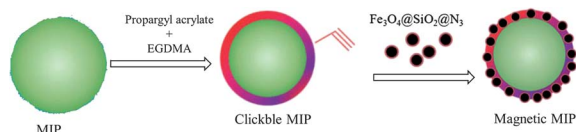
Scheme 3 Scheme of M-MIP preparation methods. (1) $\text{Fe}_3\text{O}_4@\text{SiO}_2$ is first prepared, and then molecular imprinting is carried out on the surface of $\text{Fe}_3\text{O}_4@\text{SiO}_2$ by a sol-gel process. (2) $\text{Fe}_3\text{O}_4@\text{MIPs}$ are prepared by a free radical polymerization mechanism using a living precipitate polymerization method (2a), or a traditional precipitate polymerization method (2b); one Fe_3O_4 particle is embedded into each MIPs particle. (3) $\text{Fe}_3\text{O}_4@\text{MIPs}$ are prepared by suspension polymerization; in this type of method, several Fe_3O_4 particles are embedded into each MIPs particle. (Adapted with permission from ref. 43.)

imprinting conditions, especially when non-covalent intermolecular interactions (e.g. hydrogen bonds) are considered.

Besides these commonly used methods, some novel strategies have been reported to prepare M-MIPs. The common feature of the methods described above is that magnetic Fe_3O_4 nanoparticles are embedded into cross-linked MIPs, as a core material or otherwise. The drawback of this approach is that the magnetic susceptibility of the embedded Fe_3O_4 may decrease if the surrounding polymer layer exceeds a certain amount. Recently, Ye *et al.* presented a more general and modular approach to prepare M-MIPs based on click reactions.^{50,51} In this method, unlike in the structures introduced above, the Fe_3O_4 nanoparticles are on the surface of MIPs materials. The process for this approach is displayed in Scheme 4. Firstly, MIPs nanoparticles and Fe_3O_4 nanoparticles are synthesized and modified to introduce clickable alkyne groups with alkyne and azide groups onto their surface, and then the two types of modular building blocks, MIPs nanoparticles and Fe_3O_4 nanoparticles, are conjugated to give composite materials which offer both molecular binding selectivity and efficient magnetic separation by using simple click chemistry. The saturation magnetization of the $\text{MIP}@\text{Fe}_3\text{O}_4$ material prepared by click reactions was found to be $29 \text{ A m}^2 \text{ kg}^{-1}$, which was higher than

that of Fe_3O_4 embedded MIPs. For example, the saturation magnetization of $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-MIP}$ beads was $0.41 \text{ A m}^2 \text{ kg}^{-1}$,⁴³ and the saturation magnetization of $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-dye-MIP}$ beads was $3.67 \text{ A m}^2 \text{ kg}^{-1}$.⁴⁴

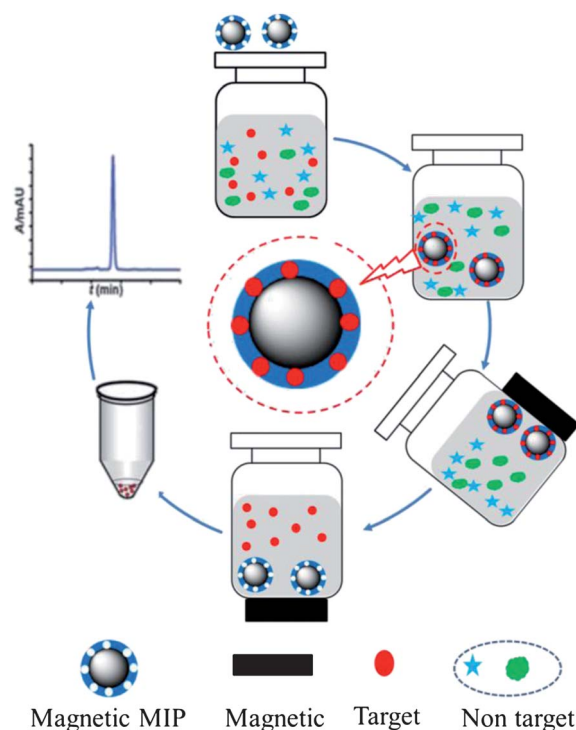
As mentioned above, surface imprinting is an ideal method to improve the binding capacity and binding kinetics compared to bulk polymerization. In order to further improve the binding capacity and binding kinetics of MIPs, a novel surface molecular imprinting technique was reported based on spherically molecularly imprinted monolayers prepared from 3-mercaptopropionic acid self-assembled onto core-shell $\text{Fe}_3\text{O}_4@\text{Au}$ nanoparticles with pre-adsorbed templates of parathion-methyl, which is widely used in agricultural production.⁵² The whole imprinting process can be summarized in three steps: (1) coating of gold on the surface of Fe_3O_4 nanoparticles by the reduction of HAuCl_4 ; (2) binding of the template molecule onto the gold shell by van der Waals forces; (3) obtaining the spherical, molecularly imprinted monolayer through the self-assembly of a monolayer of 3-mercaptopropionic acid on the surface of the $\text{Fe}_3\text{O}_4@\text{Au}$ NPs through covalent Au-S bonds. Herein, Fe_3O_4 can make the imprinting process faster and more effective because of its magnetic effect on washing after each self-assembly process. The spherically molecularly imprinted monolayer can also provide more recognition sites for the templates on account of the high surface area of the spheroidal structure, and has faster association/dissociation kinetics. The imprinted sensor showed very fast uptake kinetics: no less than 92% binding was obtained within a short shaking period of 3 min, and adsorption equilibrium was reached after 12 min. The response of the spherically molecularly imprinted monolayer was linearly proportional to the concentration of parathion-methyl over the range of 2.0×10^{-7} to $1.0 \times 10^{-4} \text{ M}$, with a lower detection limit of $1.0 \times 10^{-7} \text{ M}$. The above discussion on the different preparation methods of M-MIPs is briefly summarized and compared in Table 1.



Scheme 4 Scheme of the preparation of magnetic MIPs based on click reactions. First, the MIP is prepared by precipitation polymerization, and then alkyne groups are introduced onto the surface of the MIPs. When Fe_3O_4 particles modified with azide groups are added, the Fe_3O_4 particles are conjugated to the surface of the MIPs by click chemistry. (Adapted with permission from ref. 50.)

M-MIPs can not only show a controllable rebinding process, but also allow the centrifugation and filtration steps to be replaced by magnetic separation in a convenient and economical way. The application of these M-MIPs as sorbents allows not only preconcentration but also selective extraction of the target analytes from complex samples, which is important, particularly when impurities can interfere with quantification.^{53–56} The magnetic separation procedure based on M-MIPs is displayed in Scheme 5. The whole process involves extraction, magnetic separation, elution, concentration and analysis steps. A review article about the application of M-MIPs to the extraction of compounds from complex matrices, such as environmental, food, biological and plant samples, has been published,⁵⁷ so no more details are provided about it in the present work.

Besides being used as sorbents for sample pretreatment, M-MIPs are also used in photocatalytic degradation or chemosensing. Shen *et al.*⁵⁸ firstly prepared M-MIPs directly in an aqueous system in the presence of Fe_3O_4 magnetic nanoparticles using *o*-phenylenediamine as the functional monomer, and thus constructed a film with molecular recognition sites (MRS) and photocatalytic sites (PCS), as illustrated in Scheme 6. During the photo-degradation, the MIPs firstly selectively recognize the target molecules, and then the target molecules migrate to the photocatalytic domains, resulting in the decomposition of the binding target pollutants. The use of M-MIPs effectively solves the problem of nano-sized MIP-photocatalysts being difficult to separate and reuse. Chen *et al.*⁵⁹ developed a kind of surface glycoprotein imprinting over magnetic $\text{Fe}_3\text{O}_4/\text{Au}$ multifunctional nanofibers, which were consecutively modified with aniline, 3-aminophenylboronic acid and acrylic acid to introduce boronic acids and polymerizable double bonds. With horseradish peroxidase as a glycoprotein template, thin protein-imprinted films were fabricated *via* radical induced graft copolymerization. The results showed that the magnetic multifunctional $\text{Fe}_3\text{O}_4/\text{Au}$ nanofibers could not only direct the selective occurrence of imprinting polymerization, but also drive glycoprotein templates into the polymer through reversible covalent complex formation. The MIPs were used in an electrochemical sensor for detecting



Scheme 5 Scheme of a magnetic separation procedure based on magnetic responsive MIPs. The whole process involves extraction, separation, elution, concentration and analysis.

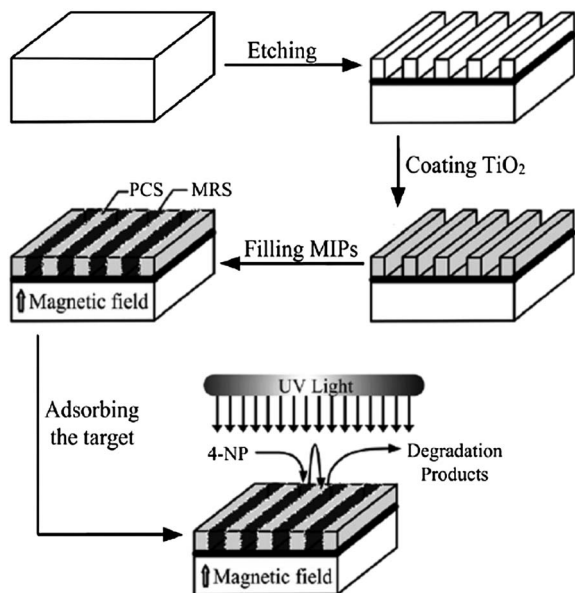
the template protein, and good linearity in the low concentration range of 0.01 to 0.30 mg mL^{-1} and a low detection limit of 0.005 mg mL^{-1} were obtained.

2.2 Photo-responsive MIPs (P-MIPs)

Photo-irradiation is one of the most frequently adopted external stimuli for SRP as it is convenient to apply and easy to control. Photo-responsive polymers are a class of intelligent polymer materials, which can rapidly respond to external changes of light by a physical or chemical change. Generally, group isomerization or dissociation occurs due to the light stimulus or

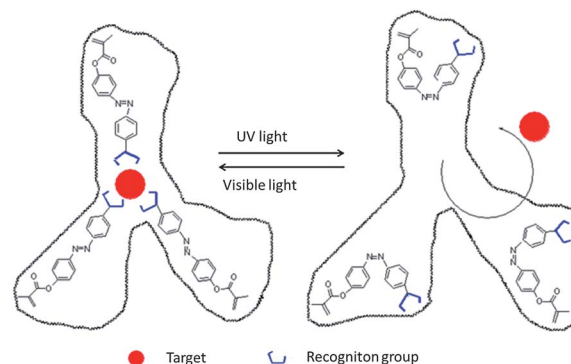
Table 1 Comparisons of different preparation methods of M-MIPs

Method of imprinting	Mechanism	Modification of Fe_3O_4	Advantages	Disadvantages
Sol-gel process	Sol-gel process	Silanization	Ease of fabrication at room temperature; eco-friendly reaction solvent	Lack of polymerization method and the functional monomer
Living polymerization	Free radical polymerization	Chain transfer reagent or iniferter	Controllable shell thickness; regular spherical particles; monodispersity	Laborious surface modification of Fe_3O_4 nanoparticles
Precipitation polymerization	Free radical polymerization	Vinyl modification	Controllable shell thickness; regular spherical particles	Laborious surface modification of Fe_3O_4 nanoparticles
Suspension polymerization	Free radical polymerization	Oleic acid modification	Simple process with one step polymerization	Big particle size; low imprinting capacity
Click reaction	Free radical polymerization	Azide groups modification	High saturation magnetization	Laborious process
Self-assembly		Au deposition	Higher binding capacity; fast binding kinetics; ease of surface modification by Au-S bond	High cost



Scheme 6 The route for the preparation of a double-domain film and its application in the removal of a target contaminant. (i) Glass is etched by HF in order to construct ruptured stripes about 2×70 mm in size; (ii) the glass is spin-coated with a TiO_2 layer using a Czocharski method; (iii) the prepared MIPs (0.1 g) are filled into the canals with the help of a magnetic field; (iv) the MRS and PCS domains selectively adsorb and decompose the highly toxic target pollutants, respectively. (Adapted with permission from ref. 58.)

light irradiation. The preparation of photo-responsive polymers involves the introduction of a photosensitive group, such as azobenzene or triphenylmethane, into the main chain of the polymer. The UV-vis photoinduced *trans-cis* isomerization of azobenzene and its derivatives is probably the most extensively studied example.^{60,61} The azobenzene chromophore has two isomeric states, the more thermodynamically stable *trans*-isomer and the less stable *cis*-isomer. When irradiated with light of an appropriate wavelength, azobenzene and a range of its derivatives undergo photoisomerization. Typically, *trans-cis* isomerization of the azobenzene chromophore can occur when exposed to UV light, while the *cis* azobenzene chromophore transforms into the *trans* conformation after irradiation by visible light. Similarly, the preparation of P-MIPs involves replacing the commonly used functional monomers, such as MAA, AAm and VP, by photo-responsive functional monomers, which always contain azobenzene. The *trans-cis* photoisomerization of the azobenzene functional monomer brings about large changes in the geometry and dipole moment of the chromophore, and such photoinduced configuration change brings about a significant alteration in the receptor geometry, and hence the strength of the host-guest interaction. As can be seen from Scheme 7, the internal cavities of the P-MIPs no longer match with the template molecules in shape, size and chemical functionality when irradiated by UV light, which would result in the release of the template. When irradiated by visible light, the recognition site would return to its original state, which can selectively adsorb template again. Thus, photo-regulated release and uptake of substrates can be achieved by

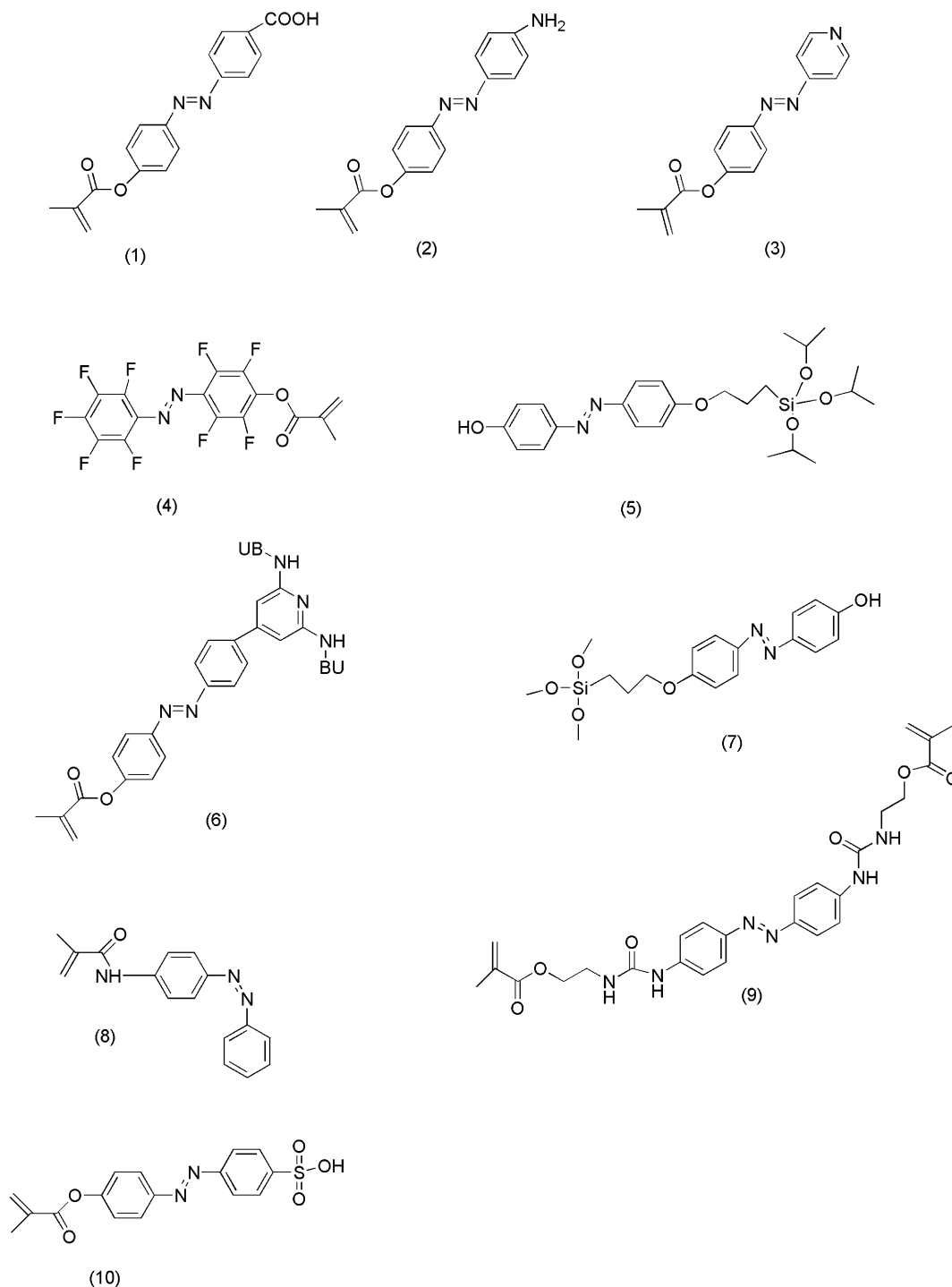


Scheme 7 Schematic for the reversible photo-regulated substrate release and uptake process in molecularly imprinted photo-responsive materials.

the incorporation of reversibly photo-switchable chromophores into the imprinted binding sites.

The photoinduced *trans-cis* isomerization of an azobenzene containing functional monomer can be characterized by UV-vis spectroscopy.⁶² The azobenzene containing functional monomer exhibits one strong absorption band at around 335 nm, and another weak one around 439 nm, which are typical for azobenzene compounds and can be ascribed to the $\pi-\pi^*$ and $n-\pi^*$ electron transitions of the $\text{N}=\text{N}$ bond, respectively. Upon irradiation by UV light, the intensity of the $\pi-\pi^*$ transition decreased rapidly, while that of the $n-\pi^*$ transition showed a slight increase, which could be attributed to the *trans-cis* isomerization of the azobenzene chromophore. Upon irradiating the *cis*-azobenzene containing functional monomer by visible light, the intensity of the $\pi-\pi^*$ transition increased rapidly, while the intensity of the $n-\pi^*$ transition decreased slowly.

From the discussion above, we can see that the photo-responsive functional monomer is the key feature for preparation of P-MIPs. However, as far as we know, there are hardly any commercial products available, and the photo-responsive functional monomers must be synthesized directly. Generally, a photo-responsive functional monomer is comprised of three groups. One is the photo-responsive group, the second is the recognition group, such as a carboxyl group or amino group, and the third is the polymerizable group, such as a vinyl double bond or silicon hydroxyl. To date, the most commonly investigated photo-responsive functional monomers contain azobenzene, and a series of azobenzene-containing functional monomers have been designed, as listed in Scheme 8.⁶²⁻⁷² It is well-known that MAA, AAm and 4-VP are the most commonly used functional monomers for molecular imprinting. Azobenzene-containing functional monomers similar to MAA, AAm and 4-VP have been synthesized by simply incorporating azobenzene into those molecules. 4-[(4-Methacryloyloxy)phenylazo]benzoic acid (MPABA), synthesized by Gong *et al.*,⁶² is the MAA-like azobenzene-containing functional monomer, and is the most used azobenzene-containing functional monomer. Rate constants for the *trans-cis* and *cis-trans* isomerization of MPABA were found to be 7.59×10^{-4} and $14.68 \times 10^{-4} \text{ s}^{-1}$, respectively. However, MPABA can be only dissolved in highly polar solvents, such as DMF and DMSO, which restricts its biomedical



Scheme 8 Chemical structural formulae for azobenzene-containing functional monomers. Full chemical names: (1) 4-[(4-methacryloyloxy)phenylazo]benzoic acid (MPABA) (adapted from ref. 62); (2) 4-amino-4-methacrylatylazobenzene (AMAAB) (adapted from ref. 71); (3) 4-[(4-methacryloyloxy)phenylazo]pyridine (adapted from ref. 65); (4) 4-methacryloyloxy-4,4,4,4-tetrafluoroazobenzene (MANFAB) (adapted from ref. 66); (5) 4-hydroxy-4-[(triisopropoxysilyl)propoxy]azobenzene (adapted from ref. 67); (6) 4-{4-[2,6-bis(*n*-butylamino)pyridine-4-yl]-phenylazo}-phenyl methacrylate (adapted from ref. 70); (7) 4-hydroxy-4-[(trimethylsilyl)propoxy]azobenzene (adapted from ref. 68); (8) *p*-phenylazoacrylonitrile (PhAAAn) (adapted from ref. 63); (9) di(ureidoethylenemethacrylate)azobenzene (adapted from ref. 69); (10) 4-[(4-methacryloyloxy)phenylazo] benzenesulfonic acid (MAPASA) (adapted from ref. 64).

applications (*e.g.* drug delivery systems) because of its low water compatibility. Water-soluble azobenzene-containing functional monomers are urgently needed. In order to meet this requirement, a kind of water-soluble azobenzene-containing functional

monomer called MAPASA, with benzenesulfonic acid as the recognition element, has been developed for the fabrication of P-MIPs that can function in biocompatible aqueous media, also by Gong's group.⁶⁴ Low polarity solvents, such as acetonitrile and

toluene, are the most commonly used solvents for molecular imprinting processes by non-covalent methods. Meanwhile, acetonitrile is the most frequently used solvent for precipitation polymerization, which can produce regular spherical molecularly imprinted particles. A methacrylate azobenzene functional monomer with a pyridine group (4-((4-methacryloyloxy)-phenyl-azo)pyridine) with good solubility in acetonitrile, which allows the implementation of molecular imprinting *via* precipitation polymerization, was designed and synthesized.⁶⁵ A photo-responsive fluorine-substituted functional monomer has been synthesized for the imprinting of perfluorocarbon compounds dependent on fluorine–fluorine interactions, which is assumed to be strong enough to perform intermolecular recognition in the same way as the hydrogen bond.⁶⁶ To adapt to the imprinting by sol–gel process, a silicane reagent was introduced to the azobenzene-containing functional monomer.^{67,68} Additionally, a new azo monomer di(ureidoethylenemethacrylate) azobenzene has been developed and successfully prepared by Schmitzer and Gomy for P-MIP preparation as both the functional monomer and the cross-linker.⁶⁹

With the development of the molecular imprinting technique, various methods have been developed and used to prepare P-MIPs. Bulk polymerization is the most popular and general method to prepare MIPs due to its attractive properties, such as rapidity and simplicity of preparation, and purity in the produced MIPs. Unquestionably, bulk polymerization has also been used to prepare P-MIPs. For example, Minoura and coworkers⁶³ described the first preparation of P-MIPs membranes with photo-regulated template binding properties using *p*-phenylazoacrylanilide as the functional monomer by bulk polymerization. Then Gong *et al.*⁶² reported the fabrication of P-MIPs by bulk polymerization for the photo-regulated release and uptake of caffeine using MPABA as the functional monomer. Rate constants for the *trans*–*cis* and *cis*–*trans* isomerization of the azobenzene chromophores within the P-MIP material were found to be 3.33×10^{-4} and $10.37 \times 10^{-4} \text{ s}^{-1}$, respectively, which are 2.3- and 1.4-fold smaller than the corresponding photoisomerization processes of the MPABA monomer in solution. This phenomenon is common in P-MIPs, and the slower isomerization rate is likely to be caused by the rigid environment of the polymer matrix, which hinders chromophore reorientation. The favorable binding constant of the P-MIP receptors for caffeine was $5.48 \times 10^4 \text{ M}^{-1}$ in DMF. The density of the caffeine-specific receptor sites in the P-MIP material was $0.95 \mu\text{mol g}^{-1}$. Upon irradiation at 365 nm, 58.3% of receptor-bound caffeine was released from the MIP material. Subsequent irradiation at 440 nm caused 96.4% of the released caffeine to be rebound by the MIP material. In this work they also found that, although the photo-regulated substrate release and uptake processes were generally repeatable, a gradual reduction in the extent of substrate release and rebinding was observed. This may be caused by the slow deformation of MIPs receptors during the course of repeated photo-switching.

On the other hand, the monolithic polymers obtained by bulk polymerization have to be crushed, ground and sieved to an appropriate size, which results in particles with irregular shapes and sizes, and some high affinity binding sites are

destroyed and changed into low affinity sites. These rather limited physical formats (*i.e.*, bulk polymer membranes, bulk monoliths) have significantly restricted their application. Therefore, precipitation polymerization, enjoying some advantages for synthesizing spherical particles, such as not requiring a surfactant, containing a single preparative step and allowing excellent control over the particle size, is needed to produce high quality, uniform and spherical P-MIPs. For example, Gong's group prepared P-MIPs for the photo-regulated release and uptake of pharmaceuticals in aqueous media using the water-soluble azo-functional monomer MAPASA by precipitation polymerization.⁶⁴ Zhang *et al.*⁶⁵ prepared P-MIP microspheres by precipitation polymerization in acetonitrile using an acetonitrile-soluble azo-functional monomer with a pyridine group. The binding association constant K_a and apparent maximum number N_{max} values of the high-affinity sites for the azo-containing MIP microspheres were evaluated from the Scatchard plot and found to be $2.3 \times 10^4 \text{ M}^{-1}$ and 10.0 mmol g^{-1} , respectively, which were higher than the corresponding values for bulk polymers.⁶⁵ Such spherical azo-containing MIP particles should be of tremendous potential in many applications, such as smart separation, extraction and assays, intelligent chemical carriers, and efficient drug delivery systems.

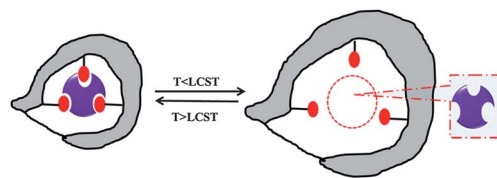
In addition to the above-mentioned free radical polymerization methods, the sol–gel process is another effective way to prepare polymers. As a convenient and versatile method, the sol–gel process has already been developed by a number of researchers and has been utilized to prepare MIPs. Generally, sol–gel based materials are prepared through acid-catalyzed or base-catalyzed hydrolysis of silanes, which is followed by polycondensation of the silanols into a polysiloxane network. The amorphous sol–gel molecularly imprinted materials have some advantages. For example, template removal from sol–gel materials can be more thorough under much stronger removal conditions, such as hydrolysis in strong acid and strong base, or even combustion. Also, the control of porosity, thickness and surface area of sol–gel materials is more convenient. Considering all the merits of sol–gel process, azobenzene-containing silicane functional monomers have been designed and used to prepare photo-responsive molecularly imprinted sol–gel organic–inorganic hybrids by Gong and coworkers,⁶⁷ and Zhong's group.⁶⁸ According to Gong's report,⁶⁷ the binding strength of the organic–inorganic hybrid sol–gel imprinted receptor sites for ibuprofen was found to be $2.28 \times 10^3 \text{ M}^{-1}$, and the density of receptor sites in the imprinted hybrid material was $4.0 \mu\text{mol g}^{-1}$. The new organic–inorganic hybrid material showed specific affinity to ibuprofen, and reversible uptake and release of ibuprofen upon alternate irradiation at 365 and 440 nm, respectively.

P-MIP particles have tremendous potential applications in many fields; however, more emphasis is put on designing new photo-responsive functional monomers, preparing and characterizing P-MIPs, while little attention has been paid to applied research. The applications of photo-responsive MIPs are limited, which can be attributed to the following two reasons: (i) the photoinduced *trans*–*cis* isomerization of azobenzene functional monomers in highly cross-linked MIPs is slow, which

cannot meet the requirements of rapid analysis, so the application of photo-responsive MIPs in environmental analysis is restricted; (ii) visible light has a limited ability to penetrate human tissue, which restricts its applications in drug delivery systems. So far, only a few teams have reported applications of P-MIPs. A typical example is that of Gong and coworkers, who developed a reliable method to detect the content of melamine in dairy products with the advantages of the simple pre-treatment of samples, a quick detection step, good sensitivity and no need for expensive instruments.⁷³ They fabricated novel hydrophilic MIPs using MAPASA as the functional monomer, which contains a water-soluble photo-regulated unit and a hydrogen bond donor, tetramethacryloyl triethylene tetramine as the cross-linker, and 1,3,5-benzenetriol as the mimic template. They found that the rate of the *trans-cis* photoisomerization of the azobenzene chromophores within the imprinted receptor sites was affected by the concentration of melamine in the solution. Thus, melamine in dairy products could be quantified. The assay could be finished within 40 min, and melamine concentration in milk and milk powder at 0.1 ppm or even lower could be detected. This work demonstrated new potential applications for P-MIPs in chemosensing, food safety and environmental analysis.

2.3 Thermo-responsive MIPs (T-MIPs)

Thermosensitive polymers can change the dimensions of their structures depending on temperature. Usually thermosensitive polymers have both a hydrophobic group and a hydrophilic group. At low temperatures, the hydrogen bond interactions formed between hydrophilic portions in the polymer chains and water molecules predominate, which is responsible for the water solubility. When the temperature is increased higher than the low-critical solution temperature (LCST), the hydrogen bonds are destroyed and hydrophobic interactions increase, which results in the aggregation of polymer chains and contraction of the gel network. Nowadays, poly(*N*-isopropylacrylamide) (PNIPAAm) is the most studied temperature-responsive polymer, because its LCST is around 32 °C in aqueous solution, close to body temperature, and it has been widely used as a smart drug delivery system due to its unique phase separation upon external temperature change.^{74,75} It dissolves in water below the LCST and precipitates from the aqueous solution above the LCST due to the disruption of the hydrogen bonding with water and the increasing hydrophobic interactions among the isopropyl groups. Combining the properties of a thermosensitive polymer with molecular imprinting techniques may provide a promising strategy for ensuring the system can respond more rapidly to an external temperature change. From Scheme 9, we can see that the template can be easily removed from the MIPs by reducing the environment temperature, which would enhance mass transfer and rebinding percentage. Recently, thermo-responsive MIPs (T-MIPs) using NIPAAm as a functional monomer have been prepared for many target species, such as proteins,^{76–78} organic molecules (4-amino pyridine),⁷⁹ metal ions (Cu(II) ions),⁸⁰ peptide,⁸¹ cisplatin⁸² and adenine.⁸³



Scheme 9 Schematic of temperature responsive MIPs. The polymers swell when the temperature is lower than the LCST, resulting in the release of the template. The contracted polymers can rebind the template when temperature is higher than the LCST.

The characteristics of protein imprinting determine that proteins are the ideal templates for T-MIPs. The crucial difference between the techniques for imprinting small molecules and large metastable biologicals is in the choice of monomers and solvents for the MIPs synthesis. Small molecules are relatively stable in organic solvents, whereas biomolecules such as proteins need to be imprinted under conditions close to their natural environments to ensure conformational integrity. Therefore, to imprint biologicals, much effort has been invested in studying water-based polymer systems, namely hydrogels. The other difficulty in protein imprinting is that the large structures of biological macromolecules might also result in restricted mobility within highly cross-linked polymer networks, and thus poor rebinding efficiency. Water soluble NIPAAm, with its temperature responsive properties, is suitable for protein imprinting, and this kind of stimuli-sensitive recognition is very similar to the recognition of proteins in natural systems. To date, several works focusing on the design of T-MIPs for protein imprinting have been reported. For example, Qin *et al.*⁷⁶ prepared a thermosensitive imprinted macroporous hydrogel showing selectivity for lysozyme based on metal coordinate interactions using NIPAAm as a co-functional monomer, which demonstrated its high selectivity when used to purify the template lysozyme from a mixture of proteins and a real sample. The adsorption capacity of the T-MIP first increased and then decreased as the temperature changed over the range 28–43 °C, while the imprinting cavity also underwent a volume change, and the adsorption capacity reached a maximum at 28 °C. The theoretical maximum adsorption capacity for the specific interaction of T-MIPs was determined to be 233.64 mg g^{−1} dry gel. This result demonstrated that the thermosensitive lysozyme imprinted hydrogel exhibited relatively high selectivity and adsorption capacity.

A T-MIP coated CdTe quantum dots (QDs) material, combining the merits of molecular imprinting technology, possessing the thermosensitive behaviour of NIPAAm and the fluorescent property of the QDs, was developed by Zhang's group recently for protein affinity.⁸⁴ The NIPAAm was introduced as the temperature-sensitive element, which allowed for swelling and shrinking in response to temperature changes to realize the recognition and release of template bovine hemoglobin. Experimental results demonstrated that a conspicuous temperature dependent on–off fluorescence intensity could be observed, which indicated the change in recognition ability of the T-MIP coated QDs with the change in temperature from 28 to 44 °C. Moreover, compared with other proteins, such as

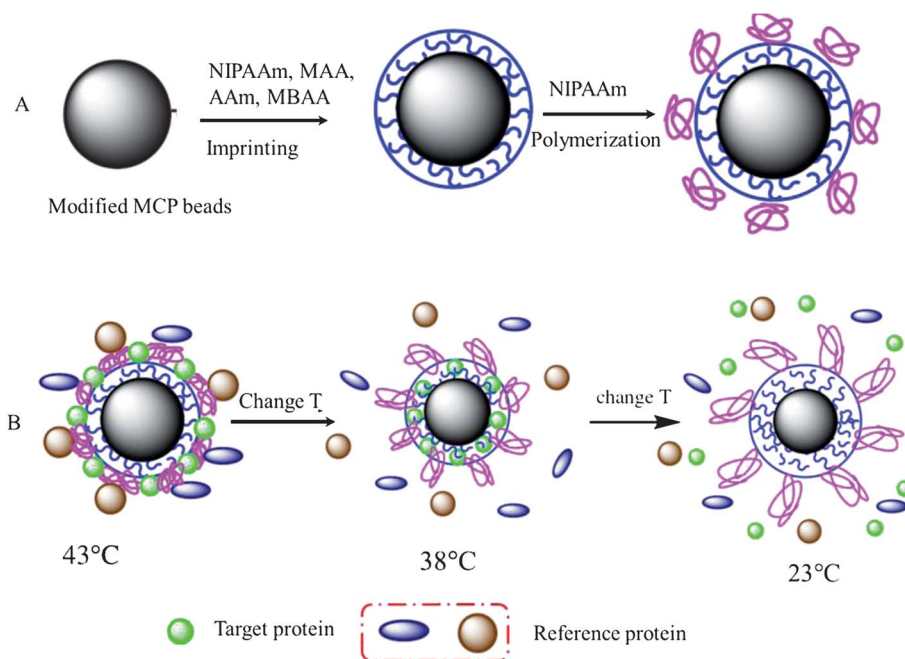
bovine serum albumin, lysozyme and ovalbumin, the template bovine hemoglobin caused unique fluorescence changes in the T-MIP coated QDs. This phenomenon confirmed that the T-MIP coated QDs with conformational memory could respond to the template protein with a volume transition, but the other proteins could not produce this response.

Qin *et al.*⁸⁵ also reported a new approach for preparing protein imprinted beads with double thermo-responsive gates: an external PNIPAAm layer, which acted as a thermosensitive “gate”, and an internal thermosensitive lysozyme imprinted layer, which acted as a selective “gate”. The coated MIP beads had good selectivity for the template protein (lysozyme) and sensitive temperature stimulus-responsive behavior, both of which were superior to those of MIP beads having a layer of the thermosensitive lysozyme-imprinted polymer only, as illustrated in Scheme 10. Using the coated MIP beads, reference proteins and the template lysozyme could be released separately at 38 °C and at 23 °C. Apart from these static format thermosensitive protein imprinted polymers, thermosensitive lysozyme imprinted monolithic columns for proteins also have been prepared by Zhang's group.⁸⁶ The dynamic binding capacity for lysozyme on the T-MIP monolith was 5.92 mg g⁻¹, while the value for the non-imprinted polymer (NIP) monolith was only 1.21 mg g⁻¹, and the imprinting factor for lysozyme reached 3.48 at 20 °C.⁸⁶

Besides those bulk T-MIPs, core-shell structured T-MIPs were also prepared for the photodegradation of sulfadiazine by Xu and coworkers.⁸⁷ Firstly, SiO₂/ZnO/ZnS NPs or SiO₂/ZnO/ZnS/Ag₂S NPs were synthesized and modified with a RAFT agent. Then T-MIPs were prepared *via* surface-initiated RAFT

polymerization of NIPAAm and ethylene glycol dimethacrylate (EGDMA), rendering the material solution accessible and temperature sensitive. These sulfadiazine imprinted polymers composed of a PNIPAAm matrix exhibited a reversible temperature induced swelling/shrinking transition, and their photocatalytic activity could accordingly be modulated by the temperature-dependent binding behavior. The photodegradation of sulfadiazine at lower temperature (15 °C) showed a significantly stronger catalytic effect than at 45 °C, *i.e.*, the degradation percentages of sulfadiazine with the SiO₂/ZnO/ZnS/MIPs at 15 °C and 45 °C were 59.23% and 21.55%, respectively. These results can be attributed to the higher binding ability of the polymers at a lower temperature, *i.e.*, the equilibrium adsorption capacities for sulfadiazine of the SiO₂/ZnO/ZnS/MIPs at 15 °C and 45 °C were 3.98 and 2.45 mg g⁻¹, respectively.

In addition to the widely studied NIPAAm systems, new non-NIPAAm temperature responsive systems have been developed recently. For example, a dibenzothiophene sulfone imprinted chitosan hydrogel was synthesized by the cross-linking of chitosan with glutaraldehyde, which was found to be temperature responsive with an LCST at 50 °C.⁸⁸ Suede *et al.*⁸⁹ prepared a dopamine imprinted polymer in 80% aqueous methanol solution using MAA and AAm as functional monomers and *N,N*-methylene-bis-acrylamide as the cross-linker. They found that the obtained MIPs exhibited a swelling–deswelling transition in 80% aqueous methanol solution at about 35 °C, and the capacity of the T-MIPs to recognize the template molecule in aqueous methanol solution changed with temperature, with the highest selectivity found to be at 35 °C.



Scheme 10 Strategy for the preparation of protein imprinted beads with double thermo-responsive gates by surface-initiated living radical polymerization. (A) Mesoporous chloromethylated polystyrene beads (MCP beads) modified with a dithiocarbamate iniferter are used as supports for the grafting of lysozyme-imprinted polymers (MIP beads), and then coated with poly(*N*-isopropylacrylamide) (coated MIP beads) by two-step polymerization. (B) Schematic illustration of the coated MIPs beads with thermosensitive swelling/collapse phase transitions for the selective adsorption of proteins. (Adapted with permission from ref. 85.)

As discussed above, this kind of T-MIP is prepared by using thermosensitive monomers as the functional monomers in the molecular imprinting process. The other type of T-MIP is prepared by grafting a PNIPAAm brush onto the surface of the MIP, as illustrated in Scheme 11. MIPs are first prepared using traditional functional monomers, such as MAA and AAm, by living polymerization, and then PNIPAAm brushes are grafted from the surface of the MIPs. Upon increasing the temperature higher than the LCST, polymer brushes would aggregate on the surface of the MIPs, which would hinder the conveyance of the template. Thus temperature controlled release and adsorption of the template molecules can be achieved. For example, Zhang *et al.*⁹⁰ prepared pure water-compatible T-MIPs for 2,4-dichlorophenoxyacetic acid by the facile grafting of PNIPAAm brushes onto preformed MIP particles *via* surface-initiated RAFT polymerization. The introduced PNIPAAm brushes significantly improved the surface hydrophilicity at ambient temperature, and imparted thermo-responsive properties to the MIPs, leading to their pure water-compatible and thermo-responsive binding properties. The MIP particles grafted with PNIPAAm brushes showed enhanced dispersion stability in water at ambient temperature. The static water contact angles were 66.7° and 124.8° for the grafted and un-grafted MIPs, respectively. The results clearly showed that the grafted MIP film exhibited significantly higher hydrophilicity than the un-grafted one. The specific template binding of the grafted MIPs dramatically decreased at elevated temperature (45 °C) in pure aqueous solution in comparison with that observed at ambient temperature, which was due to the collapsing of the polymer brushes at the higher temperature, resulting in the blocking of the binding sites.

2.4 pH responsive MIPs (pH-MIPs)

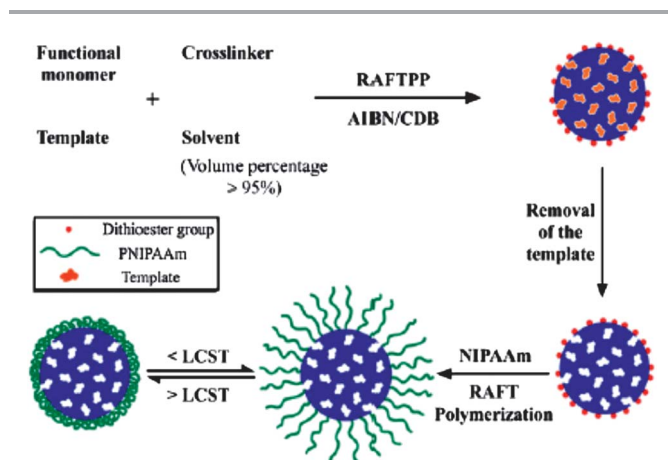
pH-sensitive gels contain a large number of groups, such as carboxyl, sulfonic acid, amino groups, *etc.*, which are prone to ionization (accepting or donating a proton) with changes of

environmental pH, or ionic strength. At the same time, the hydrogen bonds between the macromolecular chains would be destroyed, causing a decrease in the cross-linking points in the gel network, and thereby resulting in a discontinuous change in the gel volume.^{91,92} Depending on the type of ionizable groups, pH-sensitive hydrogels may be divided into two types: cationic and anionic. The pH sensitivity of cationic hydrogels mainly derives from the protonation of basic groups in the polymer chain, such as amino groups and pyridine groups. At low pH, the basic groups are protonated, giving rise to internal charge repulsions between neighbouring protonated basic groups. Charge repulsion leads to an expansion in the overall dimensions of the polymer containing these groups. At higher pH values, the groups become less ionized, and thus the charge repulsion is reduced and the polymer-polymer interactions increase, leading to a reduction in the overall hydrodynamic diameter of the polymer. The most commonly used anionic pH-responsive functional groups are carboxyl groups. At low pH, carboxyl groups are protonated and hydrophobic interactions dominate, leading to volume shrinkage. At high pH, carboxyl groups dissociate into carboxylate ions, resulting in a high charge density in the polymer and causing it to swell. Other pH-sensitive functional groups, such as imidazole, dibutylamine, tertiary amine and methacrylate groups have also been investigated. These groups are also cationic groups and are acid-swella-ble.

By incorporating those pH-sensitive functional groups into MIPs, pH responsive MIPs (pH-MIPs) can be prepared. MAA, AAm and 4-VP are the most commonly used functional monomers for molecular imprinting, however, so far, the concept of pH sensitivity has not been definitely discussed for MIPs based on MAA, AAm and 4-VP, and their pH sensitive properties have not been studied in detail. A reasonable explanation might well be that the highly cross-linked structure of MIPs restricts the pH response. In order to obtain rigid recognition sites, a large amount of cross-linker is required in the synthesis of MIPs. Commonly the molar ratio of template to functional monomer to cross-linker is 1 : 4 : 20. Thus, molecularly imprinted hydrogels (MIH) with a low degree of cross-linking have increasingly been designed and prepared in order to achieve a pH response. In a typical experiment, the amount of cross-linker is lower than the amount of functional monomer for the MIH, which is significantly different from general MIPs.

The concept of pH-MIPs was first proposed by Tao *et al.*⁹³ They presented a novel strategy to prepare pH responsive MIPs by using amylose as the host matrix, acrylic acid (AA) as the co-functional monomer, and bisphenol A (BPA) as the template. They found that changing the acidity of the solution could reversibly control the rebinding ability towards BPA. The rebinding ability of the polymers gradually decreased with the increasing pH of the solution. The binding amount was 2.5 $\mu\text{M g}^{-1}$ at pH 4.5, while the value was 1.0 $\mu\text{M g}^{-1}$ at pH 8.5. The presented methodology is a promising way to develop environmentally friendly separation materials, human-body-friendly drug delivery systems, *etc.* in the near future.

Wang *et al.*⁹⁴ prepared a pH-MIP nanosphere/hydrogel composite exhibiting the controlled release of dexamethasone-21-phosphate disodium (DXP) as a potential coating for



Scheme 11 Scheme of the preparation of MIPs with thermo-sensitive brushes. First, the MIP is prepared by RAFT precipitation polymerization (RAFTPP), a living polymerization method. Then the PNIPAAm brush is grafted onto the surface of the MIPs by RAFT living polymerization. The PNIPAAm brush is thermosensitive, and would aggregate on the surface of the MIPs when the temperature is higher than the LCST. (Adapted with permission from ref. 90.)

implantable biosensors to improve their biocompatibility. The pH-MIPs were first prepared using 2-hydroxyethyl methacrylate (HEMA) and 2-(diethylamino)ethyl methacrylate (DEAEMA, an acid-swallowable functional monomer) as functional monomers, EGDMA as a cross-linker and DXP as the template *via* UV-initiated precipitation polymerization. The pH-MIP nanospheres exhibited a faster DXP release rate at lower pH within the pH range tested (*i.e.*, 6.0–7.4), which was desirable for suppressing inflammation because inflammation induces an acidic microenvironment. pH-sensitive MIP nanosphere/hydrogel composites were then prepared by dispersing pH-MIPs into the optimized hydrogel monomer solution (60 mol% HEMA, 34 mol% VP, 5 mol% methacryloyloxyethyl phosphorylcholine, 0.3 mol% trimethylolpropane triacrylate, and 0.7 mol% poly(ethylene glycol)₂₅₈-diacrylate), followed by UV light irradiation polymerization. Hydrogel coatings have been applied to implantable glucose sensors to improve their biocompatibility and lifetime *in vivo*. So, this pH-MIP nanosphere/hydrogel composite designed as a coating for implantable biosensors can potentially suppress the inflammation response of the implanted biosensors efficiently, thereby effectively improving their lifetime.

Griffete *et al.*⁹⁵ prepared inverse opal films of MIPs by a colloidal crystal template method using MAA as the functional monomer, EGDMA as the cross-linker, and BPA as the template. The resulting inverse opals were found to display large responses to external stimuli (pH or BPA). The procedure for the preparation of the molecularly imprinted opal hydrogel film and their response to pH are illustrated in Scheme 12. As can be seen, the Bragg peak shifted markedly as a function of pH from $\lambda_{\text{max}} = 505$ nm at pH 2 to 687 nm at pH 9. Indeed, the pH dependence of diffraction resulted from the ionization of the carboxyl groups in the hydrogel, which lead to the immobilization of counter ions inside the gel. This resulted in an osmotic pressure, which swelled the gel against its restoring elastic constant. Thus, an increased pH increases the ionization, which is responsible for the gel swelling and the diffraction red shifting. Interestingly, they also found that the film thickness was a critical parameter for improving the sensing capacities, and the thick films generated an improved pH response.

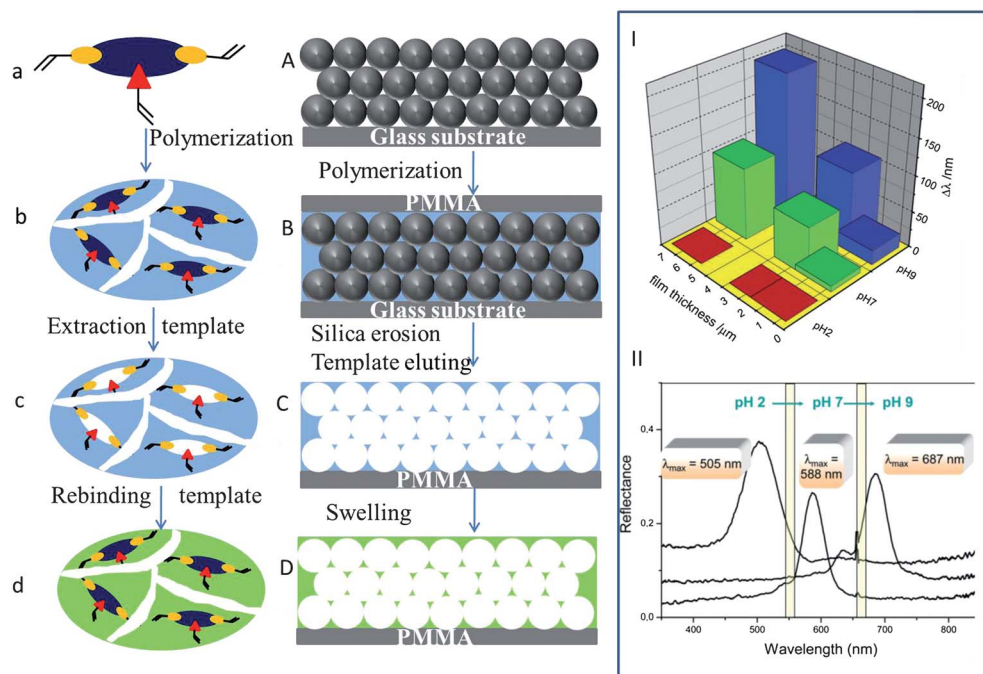
The common feature of the methods mentioned above is that a pH sensitive monomer is used as the functional monomer for preparation of pH-MIPs. Zhao *et al.*⁹⁶ proposed another way to prepare pH-sensitive MIPs. They fabricated pH-MIPs by pore-filling poly(acrylic acid) gels into BPA-imprinted polyethersulfone particles. It was confirmed that changing the acidity of the solution reversibly controlled the rebinding ability toward BPA at pH values between 3 and 6. The mechanism is illustrated in Scheme 13. The pH-sensitive PAA gel is incorporated into the cavities of the MIPs. At higher pH (pH 7.5), the swelled PAA gel hindered the entrance of the template, resulting in a lower binding capacity. In acidic solution (pH 2.5), the PAA gel shrank, and template molecules could enter into the receptors freely, increasing the rebinding capacity. The present methodology provides a simple way to prepare pH-MIPs and is applicable to the imprinting of other hydrophobic molecules.

Recently, Zhao *et al.*⁹⁷ developed a novel enzyme mimic of the horseradish peroxidase catalytic system based on an imprinted tetrapolymer of 4-VP, hemin, AAm and NIPAAm cross-linked by EGDMA with homovanillic acid as the template molecule. These intelligent gels not only catalyzed a chemical reaction, but their catalysis also showed a remarkably sensitive response to the pH conditions. It was found that the hydrogel was in a largely swollen state under both acidic and alkaline conditions, while it was in a compact state at pH 8.0. This pH-responsive variation of the gel particle size was attributed to the ionic monomers copolymerized with NIPAAm. At alkaline conditions, the carboxyl groups of hemin were deprotonated, causing a negative electrostatic repulsion within the polymer. When this repulsion overcame the attractive forces, such as hydrogen bonding or hydrophobic interactions, the gel network would swell. Similarly, under acidic conditions the pyridine residues of 4-VP in the polymer were protonated and the positive repulsion forces increased, so that the polymer gel also swelled. In the range between pH 7 and 8, the negative and positive charges were balanced, so the gel particles adopted a compact spherical state. The results of this study indicated that incorporating stimuli-sensitive monomers into a catalytic, molecularly imprinted system was an effective way to modulate the microenvironment around the catalytic centers in artificial enzymes.

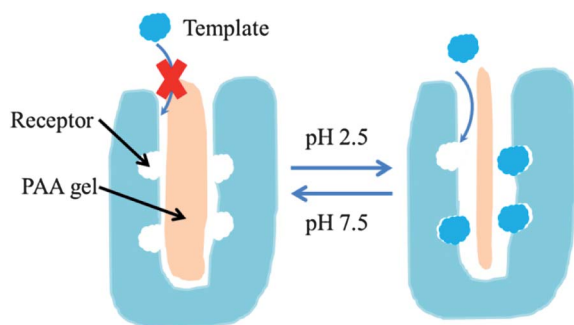
3 Dual responsive MIPs

In the field of SRP, research on dual and multiple stimuli responsive polymers is common.^{98–100} However, dual and multi stimuli responsive MIPs are relatively less explored. The preparation of dual responsive MIPs (DR-MIPs) is in its early stages, while reports into multi responsive MIPs are scarce. As far as we are aware, there are only a limited number of articles about dual responsive MIPs, mainly involving magnetic and thermo-DR-MIPs, magnetic and photo-DR-MIPs, photo- and thermo-DR-MIPs, and thermo- and salt-DR-MIPs.

With a suitable choice of functional monomers, M-MIPs can be easily transformed into DR-MIPs by replacing the traditional functional monomer by a stimuli responsive functional monomer, such as NIPAAm and azobenzene containing functional monomers. For instance, magnetic and thermo-DR-MIPs were prepared by surface imprinting technique adopting $\gamma\text{-Fe}_2\text{O}_3$ nanoparticles as a magnetic substrate and T-MIPs as a shell.¹⁰¹ The imprinted polymers were fabricated by using sulfamethazine as the template, NIPAAm as the functional monomer, acrylamide as the assistant functional monomer and EGDMA as the cross-linker. The combination of NIPAAm, magnetic nanoparticles and MIPs endows the magnetic and thermo-DR-MIPs with the properties of thermo-response, magnetic separation and molecular recognition. The prepared magnetic and thermo-DR-MIPs have great potential in antibiotics separation and release fields, which is attributed to its sensitive temperature responsiveness, good reusability, high selectivity and easy separation. Yan *et al.*¹⁰² also prepared magnetic and thermo-DR-MIPs by a surface imprinting technique. The difference in their approach is that they used CoFe_2O_4 /halloysite nanotube magnetic composites as the magnetic substrate. This kind of



Scheme 12 Schematic illustration of the procedure for the preparation of molecularly imprinted opal hydrogel films and their response to pH. Left: (a) complex of the monomer and template molecule, (b) imprinted molecules within the polymer matrix, (c) imprinted cavities with complementary shape and binding sites to the template molecule, and (d) rebinding of the template. Middle: (A) SiO_2 colloidal crystals on a glass substrate, (B) infiltration of the complex solution into the colloidal template followed by photopolymerization, (C) the photonic MIP film after the removal of SiO_2 nanoparticles and template molecules, and (D) rebinding of the template resulting in the colour change of the opal hydrogel. Right: (I) Bragg peak variation ($\Delta\lambda$) versus pH for molecularly imprinted inverse opal hydrogel films with various thicknesses. (II) Optical response of the inverse opal hydrogel films after BPA extraction upon soaking in buffer solutions at different pH values. (Adapted with permission from ref. 4 and 95.)



Scheme 13 Switching of the substrate affinity of a MIP receptor resulting from the swelling of PAA gel. pH-sensitive PAA gel swells at pH 7.5, and hinders the entrance of the template; in acidic solution (pH 2.5), the PAA gel shrank, and template molecules could enter into the receptors freely. (Adapted with permission from ref. 96).

magnetic and thermo-DR-MIP exhibited magnetic sensitivity ($M_s = 1.758 \text{ emu g}^{-1}$), magnetic stability (in the pH range 2.0–8.0), and showed outstanding recognition ability towards the imprinted species under high temperature conditions (such as 60°C). In contrast, at relatively low temperatures (such as 20°C), the captured target was released from the swelled MIPs. Our group¹⁰³ prepared magnetic and photo-DR-MIPs by suspension polymerization using MPABA as a photoresponsive functional monomer and Fe_3O_4 as magnetic substrate. The DR-MIPs were successfully applied to the preconcentration of trace

caffeine from real samples. The photonic property makes the photo-regulated uptake and release of targets or pollutants from environmental or foodstuff samples possible, and the magnetic property allows for simple and rapid separation. The whole system of enrichment, separation, and release of targets can be recycled. Thus, the system is convenient, cost-effective and environmentally friendly, and provides a new method for pollution abatement and analysis.

In addition to magnetic response elements, temperature response is another commonly employed element when preparing dual responsive MIPs because of its easy control. For example, Zhao and co-workers¹⁰⁴ reported a thermo- and salt-sensitive DR-MIP for selective protein recognition. *N*-[3-(Dimethylamino)propyl]methacrylamide (DMAPMA), which is positively charged in neutral solution and is able to self-assemble onto the template protein through electrostatic interactions, was chosen as the functional monomer, and NIPAAm was introduced as a thermosensitive assistant monomer. The polymer was easily synthesized by the copolymerization of NIPAAm, DMAPMA, MBAA, and the template protein in Tris-HCl buffer (pH 7.0). The resultant polymer showed sensitive responses to both temperature and ionic strength, that is, it exhibited a remarkable volume change at temperatures above 40°C or at sodium chloride concentrations above 1.0 M. The easy preparation, stimuli-responsiveness, high selectivity and binding capacity of the MIPs make them attractive materials for

solid-phase extraction, sensors, and especially protein delivery agents in a controlled-release system.

Thermo- and photonic DR-MIPs can be prepared by living polymerization.¹⁰⁵ First P-MIPs are prepared using azo-containing functional monomers by RAFT or ATRP polymerization, and then PNIPAAm brushes are grafted onto the P-MIPs. The introduction of PNIPAAm brushes onto the P-MIP microspheres significantly improves their surface hydrophilicity and endows them with thermo-responsive properties, leading to their pure water-compatible and thermo-responsive template binding properties. The binding affinity of the imprinted sites in the grafted P-MIP microspheres is found to be photo-responsive toward the template in pure water, and this photo-regulation process is highly repeatable under photo-switching conditions.

Through other techniques, multi stimuli responsive MIPs can achieve regulation. However, more difficulties from the technical perspective need to be solved in designing them. As far as we know, only one kind of multi stimuli responsive MIP has been fabricated, by Zhang *et al.*⁹⁰ Like the photonic and thermo-DR-MIPs, the photonic, thermo- and pH multi stimuli responsive MIPs were also prepared by grafting polymer brushes onto the P-MIPs. The difference was that the PNIPAAm brushes were replaced with copolymerized NIPAAm and DMAEMA brushes.

4 Conclusions and outlook

In this review, we have summarized the mechanism, preparation and application of various SR-MIPs. Each type of SR-MIPs has its advantages and disadvantages. For example, magnetic Fe₃O₄ nanoparticles are the most commonly used responsive element, and surface imprinting is the most commonly used preparation method for M-MIPs. The biggest advantage of M-MIPs is that they possess a well-developed and simple preparation method, and they can offer a rapid separation approach. However, the uptake and release of the template cannot be achieved by adjusting the external magnetic field. For T-MIPs, NIPAAm is the most frequently used functional monomer. Two methods can be employed to prepare T-MIPs, either by using NIPAAm as the functional monomer or co-functional monomer, or by grafting PNIPAAm brushes onto the surface of MIPs. T-MIPs are suitable for the selective separation and purification of macromolecules, and controlled drug delivery systems, which can be attributed to the fact that controlled release of the template can be achieved by adjusting the environmental temperature. The scarcity of suitable thermo-responsive functional monomers is the major problem hindering T-MIPs. By using azo-containing functional monomers to replace the traditional functional monomers such as MAA, AAm and VP, P-MIPs can be prepared. The uptake and release of the template can be controlled by adjusting the UV light or visible light. More importantly, the azo-containing functional monomer can be designed and synthesized according to the template and polymerization method. However, the slow photoinduced *trans-cis* isomerization of the azobenzene functional monomer in highly cross-linked MIPs has restricted its application in most fields.

pH stimuli response is another commonly used means for preparing smart MIPs. pH responsive MIPs are appropriate for drug delivery systems because many diseases are accompanied by changes in the pH of the physiological environment. The preparation of MIPs which can respond within a narrow pH range is an important research direction in this field. Dual/multiple stimuli responsive MIPs can achieve regulation by even more methods. However, how to combine a variety of responsive elements into one system reasonably, and minimizing the interference between the various response elements is an urgent problem.

With the development of SRP and MIPs, SR-MIPs have received more and more attention because of their excellent properties. Their response to external stimuli makes it possible to alter their volume as well as their affinity for target molecules by changing the environmental conditions. More and more teams have put their efforts into preparing SR-MIPs, and great advances have been made in the field of SR-MIPs. Using P-MIPs as example, more and more photoresponsive functional monomers have been designed, and P-MIPs with various morphologies have been prepared by different polymerization methods.

Although remarkable achievements have been attained in the field of SR-MIPs, there are still substantial challenges and opportunities. For example:

(1) Functional monomers are still scarce in the field of single signal responsive MIPs. Fe₃O₄ nanoparticles, azobenzene monomers, NIPAAm and DMADEM are the most commonly used functional monomers or response signals for M-MIPs, P-MIPs, T-MIPs and pH-MIPs, respectively. More types of diverse functional monomers should be developed, which can provide a wide range of options for researchers. For instance, diphenylethene and triphenylmethane are also photosensitive groups, and so diphenylethene and triphenylmethane could be introduced into photoresponsive functional monomers for preparing P-MIPs. Among the thermosensitive functional monomers, *N,N*-diethyl acrylamide also has an LCST in the range of 25–32 °C, which is close to body temperature; in addition, polyethylene glycol and polypropylene glycol also have an amphiphilic structure, and also display temperature-responsive properties. So, introduction of these elements for the preparation of T-MIPs can be attempted in future research.

(2) Exploring various novel stimuli responsive systems is always an important goal for the development of SR-MIPs. In the field of SRP, electric field and ultrasound are also often used as stimulus elements in addition to the commonly used pH, temperature, light and magnetic elements. However, for SR-MIPs, relatively few studies have been reported about electric field or ultrasound stimulated MIPs. Therefore, the development of new stimuli responsive MIPs showing responses to stimuli such as ultrasound, electric fields, chemical/biological species and enzymes is an important potential direction for MIPs development.

(3) Developing dual/multiple SR-MIPs with good biocompatibility has become an important research direction in this field, with increasing requirements for functional polymer materials. However, reports into dual/multiple SR-MIPs are still

scarce. Part of the attention should be shifted to dual/multiple SR-MIPs in future development. The key point in the preparation of dual/multiple SR-MIPs process is how to combine a variety of response elements into one system reasonably and ingeniously, while minimizing the interference between the various response elements. The ultimate goal is that the advantages of every response element could be expressed to their maximum limit. Among the reported dual/multiple SR-MIPs, the combination of response elements usually involves core-shell structures or monomer copolymerization methods.

Generally, stimuli-responsive components easily mutually interfere in random copolymers. Core-shell structured dual/multiple SRP are prepared by using different stimuli-responsive polymers as the core and shell sequentially. The phase transition of the core or shell is always impacted by the other; in particular, the phase transition behavior of the core would be affected by the collapse of the shell. An interpenetrating polymer network (IPN) is a network structure formed by two or more interpenetrating polymer chains. No chemical cross-linking is formed between the two polymer networks, which results in the polymer networks being relatively independent from each other. By grafting stimuli-responsive branches onto a stimuli-responsive main chain, a grafted dual/multiple SRP can be prepared. The dual response ability can be controlled by adjusting the length of the branches. Therefore, the graft copolymerization and IPN methods are effective methods to prepare dual/multiple SRPs. A variety of structured dual/multiple SR-MIPs can be prepared by incorporating those methods into the MIPs preparation process.

(4) To date, more emphasis is placed on basic research in the field of SR-MIPs, and a lot of the literature is limited to the preparation and characterization of SR-MIPs, and is lacking in applied research. With the development of SR-MIPs, more effort should be transferred to conducting research into these applications. How to effectively use the advantages of SR-MIPs in drug delivery, environmental protection and other fields has become a crucial task.

One of the most promising features of SR-MIPs used in drug delivery systems is the possibility to modulate the drug release profile in response to a specific external stimulus. It should be noted that the good biocompatibility of SR-MIPs is an essential requirement for their biomedical applications. The ultimate goal of SR-MIPs is to obtain imprinted materials capable of the selective recognition of template molecules in pure aqueous media with minimum nonspecific binding of the drug as well as other matrix components. Another problem to be solved is that, in a controlled drug delivery system, the difference in temperature and pH of the lesion site and normal tissue is relatively small, which demands that the SR-MIPs are able to respond to a small temperature/pH difference. However, most of the presented T-MIPs or pH-MIPs are usually only sensitive to a relatively large change in temperature or pH, which does not meet the actual application requirements. For photosensitive MIPs, the main limitation is that visible light has limited ability to penetrate human tissue. Therefore, long-term efforts are still urgently needed to further explore and develop the versatile functions of SR-MIPs.

Abbreviations and acronyms

AA	acrylic acid
AAM	acrylic amide
ATRP	atom transfer radical polymerization
DMAPMA	<i>N</i> -[3-(dimethylamino)propyl]methacrylamide
DMF	dimethyl formamide
DMSO	dimethylsulfoxide
DR-MIPs	dual responsive MIPs
EGDMA	ethylene glycol dimethacrylate
HEMA	2-hydroxyethyl methacrylate
LCST	low-critical solution temperature
MAA	methacrylic acid
MBAA	<i>N,N</i> -methylenebisacrylamide
MIPs	molecularly imprinted polymers
MIH	molecularly imprinted hydrogel
M-MIPs	magnetic responsive MIPs
MPABA	4-[(4-methacryloyloxy)phenylazo]benzoic acid
MRS	molecular recognition sites
PCS	photocatalytic sites
P-MIPs	photo-responsive MIPs
PNIPAAm	poly(<i>N</i> -isopropylacrylamide)
pH-MIPs	pH responsive MIPs
QDs	quantum dots
RAFT	reversible addition-fragmentation chain transfer
SRP	stimuli responsive polymers
SR-MIPs	stimuli-responsive MIPs
T-MIPs	thermo-responsive MIPs
4-VP	4-vinylpyridine

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