Review

Molecularly Imprinted Polymers with Stimuli-Responsive Affinity: Progress and Perspectives

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Abstract: Intelligent stimuli-responsive molecularly imprinted polymers (SR-MIPs) have attracted considerable research interest in recent years due to the potential applications in drug delivery, biotechnology and separation sciences. This review comprehensively summarizes various SR-MIPs, including the design and applications of thermo-responsive MIPs, pH-responsive MIPs, photo-responsive MIPs, biomolecule-responsive MIPs and ion-responsive MIPs. Besides the development of current SR-MIPs, the advantages as well as the disadvantages of current SR-MIPs were also displayed from different angles, especially preparation methods and application fields. We believe this review will be helpful to guide the design, development and application of SR-MIPs.

1. Introduction

Inspired by the mechanism of enzyme catalysis and antibody formation, researchers have been committed to exploring similar synthetic approaches with the purpose of obtaining tailored binding materials by chemical means [1]. To date, molecular imprinting has proven to be the most efficient and versatile technique for incorporating specific molecular recognition sites into polymers leading to polymeric artificial receptors [2–8]. The essential molecular imprinting process involves the self-assembly of a template molecule and a functional monomer via either non-covalent interactions (such as hydrogen bonding, van der Waals forces, ionic interactions, hydrophobic interactions or metal coordination interactions, *etc*.) or via reversible covalent bonds, the resulting complexes subsequently being copolymerized with a suitable cross-linker [9]. After removal of the templates from the obtained cross-linked polymer network, binding cavities complementary in shape, size and functionality to the template are formed [10] (Figure 1). The resultant molecularly imprinted polymers (MIPs) have found use in a wide range of applications encompassing the fields of separation processes (chromatography, capillary electrophoresis, solid phase extraction, and membrane separation), immunoassays [11], antibody mimics [12], artificial enzymes [13], sensors [14], catalysis [15], organic synthesis, drug delivery [16] and drug development [17]. This versatility stems from their favorable properties, e.g., mechanical, thermal, chemical stability, ease of preparation, low cost, and especially high affinity.
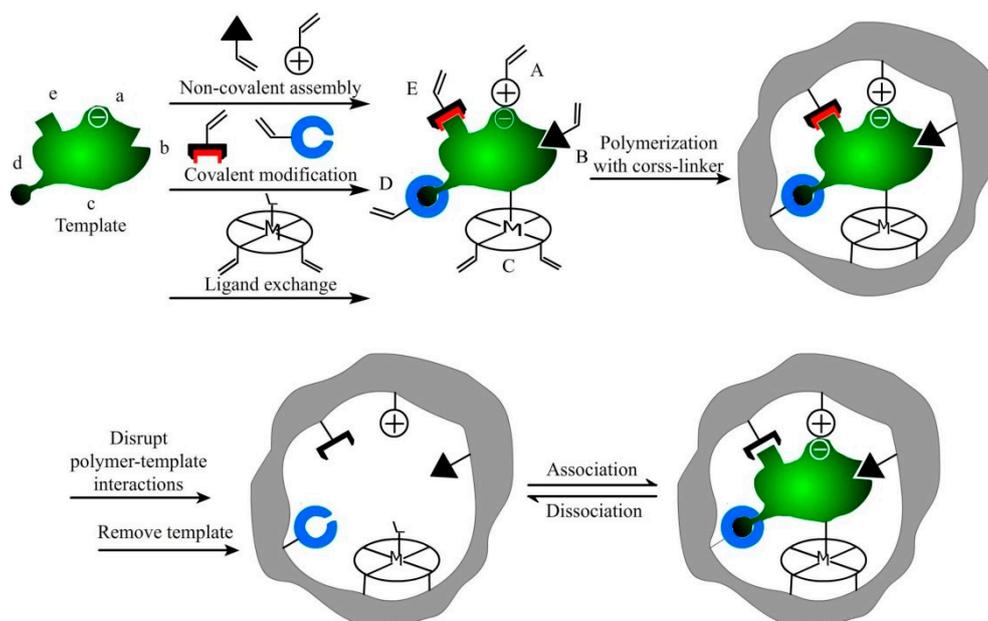
Figure 1. Highly schematic representation of the molecular imprinting process. Reprinted with permission from Reference 3. Copyright 2014, Wiley.

In spite of the tremendous progress that has been made in the molecular imprinting field, many challenges (e.g., applications in biology) remain to be addressed, especially in the design of advanced

MIP materials mimicking the biological receptors [18,19]. It is known that one of the most fascinating characteristics of the natural receptors is their high responsiveness towards external stimuli (e.g., the temperature, pH, *etc.*). Therefore, in order to find the perfect consistency between the synthetic receptor and the natural one, stimuli-responsive (also called "stimuli-sensitive" or "smart") MIPs have attracted considerable research interest in recent years [20–23].

The effective and general methodology to design stimuli-responsive MIPs is the combination of stimuli-responsive materials and the molecular imprinting technique, which endow the MIPs with the ability to respond to external stimuli while modulating their affinity for the target molecules and providing a switchable capacity of the binding or releasing processes. Currently, a variety of intelligent MIPs have been prepared which respond to specific stimuli such as changes in temperature [24], pH [25], incident light [26], ionic strength [27], or even the presence of a specific molecule [6,28]. Puoci *et al.* have reviewed work in the field until 2008 with special focus on a series of stimuli-responsive MIPs and their applications in drug delivery systems (DDS) [29]. The article gave a systematic classification of stimuli-responsive MIPs in DDS. Moreover, the development of stimuli-responsive MIPs, such as their applications and methodologies, has grown rapidly in recent years [6,30–32]. Therefore, in this review, we provide an overview of different responsive MIPs developed until now (Table 1), especially their synthetic methods, material formats and applications, furthermore, considering the challenges presently encountered and some feasible resolutions. By means of the points raised in this article, we would like to provide some assistance for further development of preparation methodologies and the expansion of some potential applications in the field of stimuli-responsive MIPs.

Table 1. Overview of different responsive MIPs.

Stimulus	Template	Monomer and cross-linker	Form of MIPs	Reference
Thermo-responsive	Lysozyme	NIPAAm, AA, DMAPMA, MBAAm	Particle	[24]
		NIPAm, MAA, AAm, MBAA	Core-shell	[33,34]
		NIPAm, VBIDA, AAm, MBAA	Bulk	[35]
	2,4-D	NIPAAm, 4-VP, EGDMA	Particle	[36]
	RGDS Peptide	NIPAAm, AAm, DMAPMA, MBAA	Hydrogel layers	[37]
	Propranolol	NIPAAm, MPABA, EGDMA	Particle with brush	[38]
	Curcuminoids	NIPAAm, 4-VP, EGDMA	Core-shell	[39]
	Sulfamethazine	NIPAm, AAm, EGDMA	Core-shell	[40]
	CFX	NIPAm, MAA, EGDMA	Core-shell	[41]
	2,4,5-Trichlorophenol	NIPAm, MAA, EGDMA	Core-shell	[42]
	4-Amino pyridine	NIPAm, MAA, EGDMA	Hydrogel	[43]
	Cu(II) ion	NIPAm, VBEDA, MBAA	Hydrogel	[44]
	DBTS	Chitosan, Glutaraldehyde	hydrogel	[45]
	Cisplatin	HEMA, MAA, MBAA	Hydrogels	[46]
	BSA	TBA, AAm, MA, MBAA	Hydrogels	[47]
		AMPS, NIPAm, AAm	Hydrogel	[48]
		DMAPMA, NiPAm, MBAA	Bulk	[49]
	Ca^{2+} or Pb^{2+}	NIPAm, MAA, MBAA	Gel	[50]
	Atrial natriuretic peptide	NIPAm, MAA, MBAA	Particle	[51]
	Cyt c or Lys	NIPAm, MAA, AAm, MBAA	Bulk	[52]
	Adenine	NIPAm, MAA, EGDMA	Bulk	[53]
	p-Nitrophenyl phosphate	NPP, DVB	Bulk	[54]
	BHb	NIPAm, MBA	Core-shell	[55]
	Sulfadiazine	NIPAm, EGDMA	Core-shell	[56]
	Dopamine	MAA, AAM, MBAA	Particle	[57]

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Table 1. *Cont.*

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Stimulus	Template	Monomer and cross-linker	Form of MIPs	Reference
pH-responsive	Propranolol	NIPAm, DMAEMA, EGDMA	Particle with brush	[58]
	DXP	HEMA, DMAEMA, EGDMA	Particle	[59]
	(*S*)-omeprazole	HEMA, PCL-T, EGDMA	Particle	[60]
	Bisphenol-A	AAc, acryloylamylose, MBAA	Powders	[61]
		PES, MBAA	Particle	[62]
		MAA, EGDMA	Layer	[63]
	HVA	NIPAM, 4-VP, hemin, AAm, EGDMA	Particle	[64]
	Diclofenac	MAA, MAAm, 4-VP, EGDMA	Bulk	[65]
	Insulin	MAA, PEG, MBA	Bulk	[66]
Photo-responsive	Caffeine	MPABA, TRIM	Bulk	[67]
	Bis(TBA)-*N*-Z-L-Glutamate	Di(ureidoethylenemethacrylate)azobenzene, EGDMA	Bulk	[68]
	Caffeine or theophylline	MPABA, 4-(dimethylamino)pyridine, triethylamine, TRIM	bulk	[69]
	Paracetamol	MAPASA, MBAA	Bulk	[70]
	1,3,5-Benzenetriol	MAPASA, TTT	Bulk	[71]
	Porphyrin	Azobenzene, DVB, Styrene	Bulk	[26]
	Propranolol	NIPAAm, MPABA, EGDMA	Particle with brush	[38]
	2,4-D	DCPA-AZO-TESP, TEOS	Core-shell	[72]
		MAzoPy, EGDMA	Particle	[73,74]
		4-((4-(3-(trimethoxysilyl) propoxy) phenyl) diazenyl) phenyl 2-(2,4-dichlorophenoxy)acetate, TEOS	Bulk	[75]
	4-HA	PES/PES-N$_2$-NH$_2$	Microfiber	[76]
	Ibuprofen	Azobenzene, EGDMA	Core-shell	[77]
		BPPO-AZO-TPPSP, TEOS	Bulk	[78]
	Guanine	MAPDIA, TEAMA	Bulk	[79]
	PAF	MANFAB	Bulk	[80]
	BPA	MAPASA, EGDMA	Core-shell	[81]
	DA	PhAAAn, TEGDA, EGDMA	Membrane	[82,83]
Biomolecule-responsive	Cyt C or Lys	NIPAm, MAA, AAm, MBAA	Bulk	[52]
	Hydrocortisone	HEMA, EGDMA	Bulk	[84]
	AFP	NSA, AAm, MBAA	Particle	[49]
		acryloyl-lectin, AAm, MBAA	Hydrogel	[85]
	Thrombin	AM, MBAA	Hydrogel	[86]
	DL-Norephedrine Hydrochloride or DL-Adrenaline hydrochloride	NIPAm, AAc, MBAA	Hydrogel	[87]
Ion-responsive	BSA	DMAPMA, NiPAm, MBAA	Bulk	[88]
	Proton	NIPAm, AAc, MBAA	Particle	[89]

2. Thermo-Responsive Molecularly Imprinted Polymers

The biochemical processes of natural receptors, such as enzyme-catalysis, exhibit extremely sensitive dependence on temperature [24,90]. To simulate the temperature-dependent recognition and catalytic capacity, several thermo-responsive MIPs have been developed in parallel with a plethora of non-imprinted thermo-responsive polymers [24,38,40]. These polymers can exhibit either a lower critical solution temperature (LCST), below which they are a hydrophilic state, or an upper critical solution temperature, above which they are hydrophilic. The most widely studied synthetic thermo-responsive polymer is poly (*N*-isopropylacrylamide) (PNIPAm), which undergoes a reversible phase transition at 32 °C (also called as Lower Critical Solution Temperature, LCST) in water, changing from hydrophilicity below the temperature to hydrophobicity above it [43,91]. The phase transition from soluble stretching polymer chain to insoluble coil-globule state is attributed to the decreasing enthalpic contribution of

water hydrogen-bonded to the polymer chain in comparison to the enthalpic gain of the system with increasing temperature. Correspondingly, the phase transition from swollen state to collapsed state occurs in water when a moderate cross-linked PNIPAm network is used around the LCST [88,92]. This feature endows the MIPs containing PNIPAm blocks the fascinating property of regulatory binding capacity accompanied by the size changes of binding sites derived from temperature variation.

To date, PNIPAm has been the most employed synthetic polymer to prepare thermo-responsive MIPs, due to its LCST which is close to the temperature of the human body [93]. One of the earliest thermo-responsive MIPs was reported by Watanabe *et al*. [87]. The MIPs based on PNIPAm hydrogels were prepared via redox polymerization of NIPAm, AAc, MBA, and template such as DL-norephedrine hydrochloride or DL-adrenaline hydrochloride in 1,4-dioxane. The imprinted and non-imprinted gels showed a volume change in aqueous solution as a function of temperature but still retained the molecular recognition ability in the shrunken states. When the guest molecule was present in a saturated solution, the polymers exhibited another phase ("molecular recognition phase"), whose volume was responsive to the concentration of the guest molecule. Further on, Tanaka's group reported a similar imprinted polymer gel based on PNIPAm that swelled and shrank reversibly in response to temperature changes. The addition of a small amount of functional monomer such as methacrylamidopropyltrimethylammonium chloride (MAPTAC) resulted in gels able to capture target molecules such as pyranine-3 or pyranine-4 via a multiple-point electrostatic interaction [94]. From the relationship between swelling ratio and affinity of the gel as a function of temperature (Figure 2), it is seen that the recognition of the resulting polymeric gels towards the target molecule can be changed reversibly by more than one order of magnitude, accompanied by reversible swelling and shrinking of polymeric network in response to temperature. In their shrunken state, the imprinted sites of the gels exhibit higher affinity presumably due to the ability of the templates to ion-pair with three (pyranine-3, charge: 3−) or four (pyranine-4, charge: 4−) MAPTAC monomers in the gel. While in the swollen state, the affinity of the imprinted sites decreases dramatically because MAPTAC monomers are well separated from one another, which means the target molecules can only be captured by MAPTAC with a single contact.
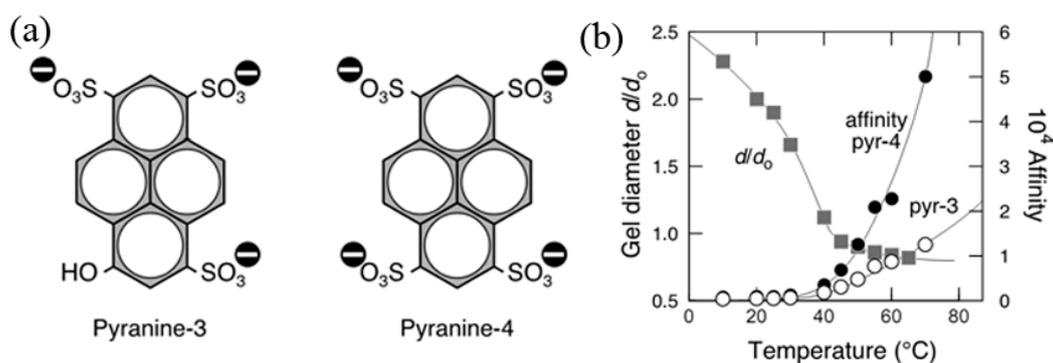
Figure 2. (**a**) The chemical structures of pyranine-3 and pyranine-4; (**b**) The affinity of the gels to pyranine-3 and pyranine-4 as a function of temperature. Reprinted with permission from Reference 94. Copyright 1999, Science.

This reversible molecular adsorption by using multiple-point interaction based on PNIPAm gels definitely provides a pioneering idea to prepare thermo-responsive MIPs, and the MIPs with reversible

recognition towards various target molecules such as ions, small organic molecules, and even proteins were realized by using the same approach. Alvarez-Lorenzo *et al*. have reported a PNIPAm based temperature-sensitive polymeric gel to adsorb and release divalent ions reversibly by two-point interaction [50]. The imprinted gels prepared with calcium methacrylate (CaMAA2) or lead methacrylate (PbMAA2) showed higher affinity for target molecules as compared to randomly polymerized gels containing methacrylic acid (MAA) or lithium methacrylate (LiMAA) as functional monomers. Due to the reversible volume phase transition caused by temperature, the affinity decreased in the swollen state but recovered upon shrinking.

A slightly different procedure was also employed to prepare temperature-responsive imprinted polymers for capturing divalent cations or anions without using a template [95]. Besides the co-monomers mentioned above, the polymeric network was added with a cleavable cross-linker, such as *N,N*-cystaminebis(acrylamide) (BAC), whose disulfur bridges in the pendant cystamine groups can be cleaved and oxidized to form a pair of sulfonic functions, or 2,3-dihydroxy-*N,N,N',N'*-tetramethyl *N'',N'''*-bis(3-((2-methylacryloyl)aminopropyl)-1,4-butanediammonium) dibromide, whose C–C with vicinal diol can be cleaved and leading to a pair of adjacent tertiary amines. Since the pair of sulfonic functions or adjacent tertiary amines located face to face with each other, the hydrogels prepared in this case were capable of specifically recognizing divalent cations or molecules containing two anionic functions, respectively.

Moreover, they showed significant volume phase transition and reversible recognition properties on varying the temperature. Liu *et al*. proposed thermo-responsive imprinted polymer gels capable of recognizing L-pyroglutamic acid (PGA) and 4-aminopyridine (APY) molecules [43] through multiple–pointelectrostatic interactions. The gels were synthesized starting from *N*-isopropylacrylamide and methacrylic acid as temperature-responsive and functional monomers, respectively. In their subsequent investigations, reversible recognition and release of target molecule are both realized by a change in temperature. Since the imprinted polymer hydrogels have good thermal responsivity, selectivity and reusability, they are potentially applicable in the separation field and in drug controlled release systems.

Recently, "on/off"-switchable catalysis by a smart enzyme-like thermo-responsive imprinted polymer was reported by Li *et al*. [54]. This unique imprinted polymer was also based on PNIPAm while being imprinted with *p*-nitrophenyl phosphate, a transition state analogue for the hydrolysis of the substrate *p*-nitrophenyl acetate. At a relatively low temperature (such as 20 °C), the polymer networks were hydrophilic, enabling the substrate to access the catalytic sites resulting in enhanced catalytic efficiency in the hydrolysis of *p*-nitrophenyl acetate. On the contrary, at higher temperatures (such as 40 °C), this polymer demonstrated a dramatically increased hydrophobicity, rendering the imprinted sites less accessible and hence resulting in poor catalysis. Thus, the polarity switch inherent in the use of a thermo-responsive PNIPAm endowed the polymer with a switchable catalytic activity.

In consideration with the application of MIPs in the biological field, some biomacromolecules, e.g., proteins have also been used as a template to design thermo-responsive MIPs [24,30,38,48]. A thermo-sensitive macroporous PNIPAm hydrogel showing selective recognition for lysozyme was developed by an imprinting procedure based on metal coordinate interaction [35]. In contrast to a traditional functional monomer, a metal chelate monomer (*N*-(4-vinyl)-benzyl iminodiacetic acid)

forming coordination complex with the template protein in the presence of Cu^{2+} was used. Finally, this imprinted hydrogel was used to purify the protein template from an artificial mixture of proteins and areal sample, in both cases resulting in a high selectivity. Another example of lysozyme imprinting based on a PNIPAm nanogel was proposed by Pan *et al.* [24]. AA and DMAPMA, containing a negatively charged carboxyl group and a positively charged tertiary amine group, respectively, were used as co-monomers and MBAAm as a crosslinker. Protein-imprinted spherical nanogel particles were readily prepared via aqueous precipitation polymerization. Compared to the non-imprinted counterparts, the lysozyme-imprinted nanogels possessed higher rebinding capacity, more rapid rebinding kinetics, and a much higher specificity toward lysozyme. Importantly, both the rebinding and release characteristics of lysozyme-imprinted nanogels showed dramatic temperature-dependence, with clear on-off transition around 33 °C. Hua *et al.* reported on a temperature-sensitive protein-imprinted hydrogel based on PNIPAm by using *N*-(3-(Dimethylamino)propyl)-methacrylamide (DMPMA) as functional monomer and bovine serum albumin (BSA) as a template through electrostatic interaction [88]. After removal of the template proteins by treatment with 500 mM aqueous NaCl solution, the polymer affinity to recognize the target protein was greatly influenced by external stimuli, such as temperature and ionic strength. The authors found that the optimal binding conditions (maximal affinity toward the template) were very close to the original imprinting state, proving that the origin of the specificity relied on the spatial integrity of the recognition site formed in the imprinting process. The changes in gel volume result in a decreased affinity of the MIPs.

Considering the similarity with NIPAm, TBAm [47] and MBAAm [57] were also used as thermo-responsive co-monomers in MIPs to achieve responsive molecular recognition. TBAm has proven to be a temperature sensitive monomer that allowed for swelling and shrinking of the hydrogels in response to temperature [96]. According to this, Demirel *et al.* prepared poly(*N-tert*-butylacrylamide-*co*-acrylamide/maleic acid) imprinted hydrogels for recognizing BSA with a thermo-responsive performance [47]. Adsorption studies also showed that other stimuli, such as pH and initial BSA concentration, also influenced the BSA adsorption capacity of the MIP hydrogels. In the same manner, temperature sensitive binding capacity of dopamine-imprinted MBA cross-linked polymers was observed in 80% aqueous methanol solution around 35 °C by Suedee *et al.* [57]. Subsequently, the resulting MIP was tested for its application as a sorbent material of solid-phase extraction (SPE), utilizable in the selective extraction of dopamine from urine samples mixing with other adrenergic compounds (epinephrine, isoproterenol, salbutamol and serotonin).

The above literature showed that the introduction of thermo-responsive co-monomers into the networks of MIPs was a general and efficient approach to fabricate thermo-responsive MIPs. Nevertheless, it is accompanied by a number of disadvantages. One obvious problem is the greater complexity of the self-assembly system between template and functional monomers caused by the addition of NIPAm. This, together with the decreased proportion of functional monomers, should lead to a lower affinity compared to conventional imprinted polymers without PNIPAm blocks. The problem is ubiquitous and similar to the development of water-compatible MIPs, whose affinity would be largely affected by the addition of hydrophilic co-monomers. Another problem is the contradiction between the affinity and the responsiveness of this kind of MIPs. One of the most attractive features of MIPs is their robustness with respect to reusability and compatibility with a range of solvents and

test conditions. These properties depend strongly on the degree of cross-linking in the MIP. On the other hand, the volume inversion of PNIPAm based MIPs will be greatly limited in a case of a robust polymeric network, subsequently leading to a poor responsiveness to temperature. Overall, using this method, complicated and time-consuming optimizations are necessary for preparing a well-performing thermo-responsive MIP.

Recently, Pan *et al.* reported a novel approach to prepare both thermo-responsive and water-compatible MIP microspheres by the facile surface-grafting of PNIPAm brushes via RAFT polymerization [36] (Figure 3). The reported method demonstrated an efficient approach to avoid the disadvantages of PNIPAm based MIPs mentioned above by grafting a high-density layer of linear PNIPAm on the surface of preformed MIP microspheres. Distinctively, the hydrophilic/hydrophobic conversion on the surface of MIPs microspheres caused by the thermo-responsive PNIPAm brushes leads to a thermo-responsive binding property. Moreover, unlike those described above, the approach only requires the facile PNIPAm-grafting on the preformed MIP microspheres and no PNIPAm blocks in the imprinted network, thus avoiding many complicated and time-consuming optimizations for MIPs formulations and making the preparation more flexible. This represents a novel and promising way to develop advanced MIP materials not only with thermo-responsive binding property, but also with other stimuli-responsive properties such as when replacing the thermally responsive polymer with a pH or light sensitive polymer, *etc*.
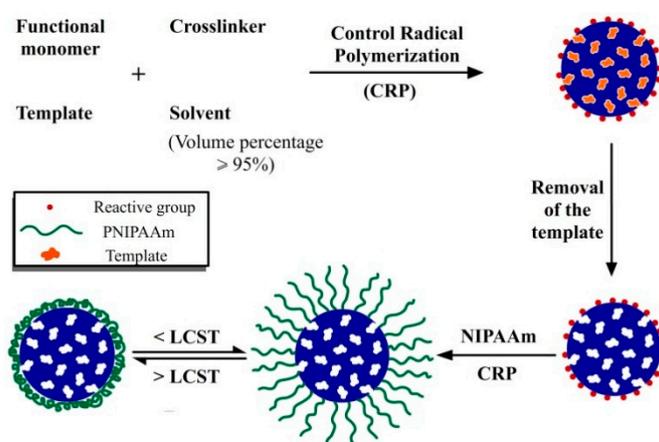
Figure 3. Protocol for the preparation of water-compatible and stimuli-responsive MIP microspheres with surface-grafted functional polymer brushes. Reprinted with permission from Reference 36. Copyright 2010, Elsevier.

Furthermore, by the combined use of PNIPAm brushes on the surface and PNIPAm blocks into the imprinted network, Qin *et al.* prepared a molecularly imprinted bead with double thermo-sensitive gates for selective recognition and release of proteins [33]. The MIP beads were prepared by two-step surface-initiated iniferter polymerization on mesoporous chloromethylated polystyrene (MCP) beads, which formed double layers, an internal thermo-sensitive lysozyme imprinted layer, and an external linear PNIPAm brush layer. The two layers showed different volume phase transition temperature. At 43 °C, the outer linear PNIPAm layer and the inner imprinting layer were all collapsed, resulting in a hydrophobic shell and distorted recognition sites in the core, respectively. This led to nonspecific

protein binding on the MIP bead surface. When the temperature changed to 38 °C, the MIP bead expanded to form a hydrophilic PNIPAm shell and a spatial integrity of the internal recognition site in the core, so a suppression of nonspecific protein binding was observed accompanied by improved specific protein binding. At even lower temperatures around 23 °C, the internal recognition site showed a more swollen state and a weak binding capacity to the template protein. The results further indicate that fabricating the thermo-sensitive surface layer or the interior imprinted sites for the MIPs can both create thermo-responsive binding capacity in spite of their different manner and different effect. Besides, if we regulate the performance (e.g., an identical volume phase transition temperature) of the surface and interior of MIPs to an optimal level, fantastic thermo-responsive MIPs could be obtained.
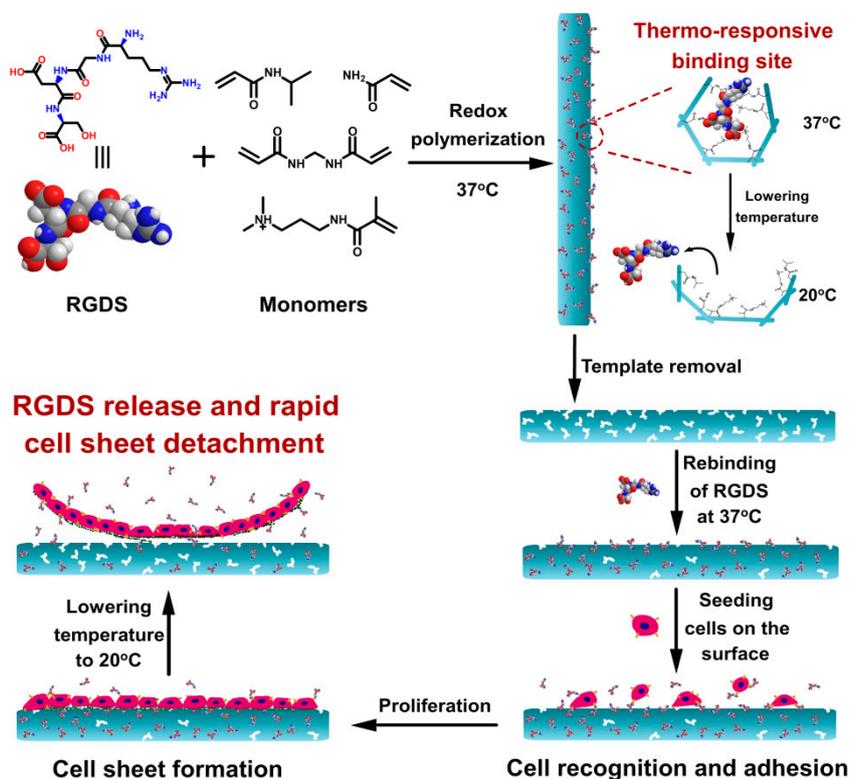
Figure 4. Strategy to introduce the RGDS peptide to a thermo-responsive cell culture substrate by means of molecular imprinting and the schematic illustration for the cell adhesion and the harvesting of a cell sheet. Reprinted with permission from Refence 37. Copyright 2013, Wiley.

To enhance cell adhesion during culture and facilitate the rapid harvest of cell sheets, Pan *et al*. reported a novel system for harvesting cell sheets which relies on a PNIPAm-based MIP hydrogel layer with thermo-responsive affinity toward specific biomolecules by redox-initiated polymerization (Figure 4) [37]. Molecular imprinting methodology was employed to introduce the cell-adhesive peptide RGDS onto a thermo-responsive cell culture substrate, which was innovatively used as a highly efficient novel system for harvesting cell sheets. With the reversible thermo-responsive "specific recognition sites", the imprinted hydrogel could recognize and bind RGDS molecules at a temperature common for cell culture (37 °C), and then rapidly release RGDS when the temperature was lowered. Compared with simple physical absorption and covalent immobilization approaches, the thermo-responsive "specific

binding" in the imprinted hydrogel promotes cell adhesion during cell culture and facilitates cell detachment during cell sheet harvest.

3. pH-Responsive Molecularly Imprinted Polymers

Weak polyelectrolytes, such as poly(carboxylic acid) [97], poly(phosphoric acid) [98] and polyamine [99], contain ionizable groups and are able to accept or donate protons at a specific pH. These pH-sensitive polymers exhibit a conformational change upon variation of the pH which translates into swelling/shrinking behavior when present as gels. Such hydrogels are the most common candidates for pH-responsive systems. In addition, dendrimers such as polyethyleneimine (PEI) modified with methacryl groups was can also reversibly be opened and closed in response to pH [100]. Therefore, MIPs based on pH-responsive polyelectrolytes should demonstrate pH-dependent recognition and such systems have therefore been considered as promising materials for controlled drug delivery [59,60,101].

In molecular imprinting, functional monomers like acrylic acid (AAc), methacrylic acid (MAA), maleic acid (MA), and *N,N*-dimethylaminoethyl methacrylate (DMAEMA) are often used in order to provide interactions between the polymer and template molecules through hydrogen bond or charge complementarity. Hence, MIPs with the recognition relying on hydrogen bonding or electrostatic interactions always exhibit a pH-responsive binding capacity caused by the pH-induced change of the interaction between templates and the imprinting sites.

Based on this principle, a spherical MIP has been reported by Puoci *et al.* as a pH-sensitive sustained drug release system for sulfasalzine using MAA as the functional monomer and EGDMA as the cross-linker, respectively. In addition to displaying a more sustained release period compared to then on-imprinted polymers, the imprinted polymers also showed a different release rate at different pH values. When the MIPs were placed in a media with the pH change from 1 to 6.8, a sudden release of sulfasalzine was observed. This can be explained by the carboxylic groups situated at imprinted sites being ionized at pH values higher than their average pK_a. In this state, they do not interact with the template (sulfasalazine) through hydrogen bonding. To expand the application of spherical MIPs for biological samples, the author further prepared a *p*-acetaminophenol (AMP) imprinted polymer with a hydrophilic external layer, which led to a drastic reduction of protein absorption, hence referred to as a restricted access material [102]. When tested as controlled release device in gastrointestinal simulating fluids, the new polymers showed a pH-responsive release, which further confirmed the release mechanism based on the ionization of carboxylic acid groups. The same effect has been observed in some drug delivery systems based on MIPs.

Other acidic monomers such as maleic acid (MA) have also been used to obtain pH-responsive MIP [47]. Since it is analogous to MMA and was mentioned in the last section, it will not be presented here reduplicatively. In contrast to the previous systems, Wang *et al.* described another pH-sensitive MIP nanospheres/hydrogel composite for controlled releasing of dexamethasone-21 phosphate disodium (DXP) [59]. The MIP nanospheres based on a basic functional monomer, DMAEMA, exhibited a faster DXP release rate in a pH range of 6.0–7.4, which is an inspiration for suppressing inflammation because inflammation induces an acidic microenvironment. The pH-responsive release process mainly resulted from the variable ionic interaction (electrostatic interaction) between DXP and DMAEMA in response to pH value. Incorporating the MIP nanospheres into a preformed

poly (2-hydroxyethyl methacrylate (HAMA)-*N*-vinyl-2-pyrrolidinone (NVP)-2-methacryloyloxyethyl phosphorylcholine (MPC)) hydrogels formed a pH-sensitive MIP nanospheres/hydrogel composite, which can be designed as a coating on implantable biosensors for potentially suppressing the inflammation. Recently, the metal coordinate bond strategy was also used to fabricate MIH with pH-responsive property and controlled release capacity in aqueous phase. Zhang *et al*. prepared a smart MIH by using 2-hydroxyethylmethacrylate (HEMA) and MBA as backbone and cross-linker respectively in the presence of Dox-Cu^{2+}-4-VP complex [25]. The MIH showed a pH-responsive release property, not more than 10% of loaded drug was released from Dox-MIH at pH 7.2 in seven days. In contrast, near to 60% of loaded drug was released at pH 5.0 during the same period. These results indicated that Dox-MIH with pH-responsive behavior possessed great promise as a sustained-release delivery system of anticancer drugs.

Another approach to realizing pH-responsive binding or releasing property is to exploit the swelling/shrinking behavior of the imprinted hydrogels upon variation of pH values. For instance, Kanekiyo *et al*. designed a novel pH-responsive MIPs by using acrylic acid (AA) as an ionizable comonomer and acryloylamylose as a functional monomer [61], respectively, and the latter can form a helical inclusion-complex with template molecule (BPA) through hydrophobic interaction in aqueous solution [103] (Figure 5). The ionizable unites (carboxyl group) of the amylase-based MIPs displayed a reversible structural change of the imprinted binding sites upon varying the pH of the solution, ultimately leading to pH dependent binding of the template.
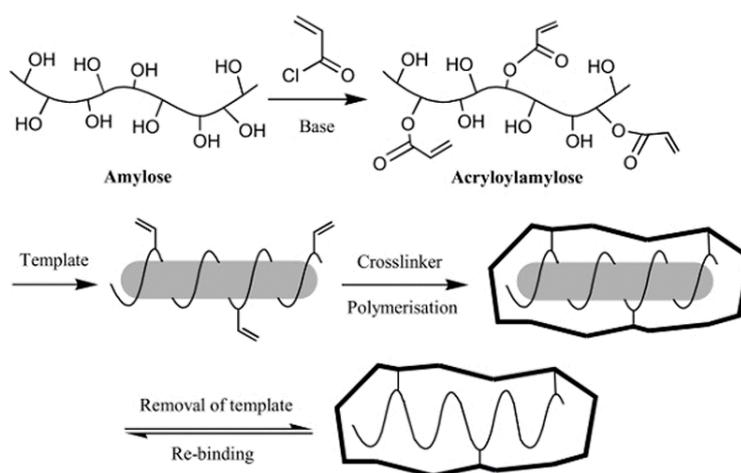
Figure 5. Outline of molecular imprinting using amylose. Reprinted with permission from Reference 103. Copyright 2002, Royal Society of Chemistry.

Similarly, Oral *et al*. reported pH-responsive and recognitive polymeric networks based on PEG star polymers to distinguish D-glucose from similar sugars by using methylacryl acid (MAA) as the ionizable comonomer [104]. In addition, equilibrium swelling and rebinding properties of BSA imprinted hybrid hydrogel microspheres based on calcium alginate and phosphate were also evaluated in different pH values and even ionic concentrations [105]. Recently, this type of pH-responsive imprinted hydrogels was applied as horseradish peroxidase mimetic enzymes. The novel enzyme-like catalytic system was based on an imprinted tetrapolymer of 4-vinylpyridine (4-VP), chloro (3,7,12,17-tetramethyl-8,13-divinylporphyrin-2,18-dipropanoato(2-))iron(III) (hemin, used as the

catalytic center), AM, and NIPAm cross-linked by EGDMA with homovanillic acid as the template molecule. Under optimal pH conditions (close to the pI of the polymer), the imprinted gel shrunk to the smallest size with an excellent hydrophobic microenvironment in the imprinted nanostructures, which significantly increased the catalytic efficiency (Figure 6). This remarkably sensitive catalysis in response to pH conditions shows us an effective way to modulate the microenvironment around the catalytic centers for mimetic enzyme [64].
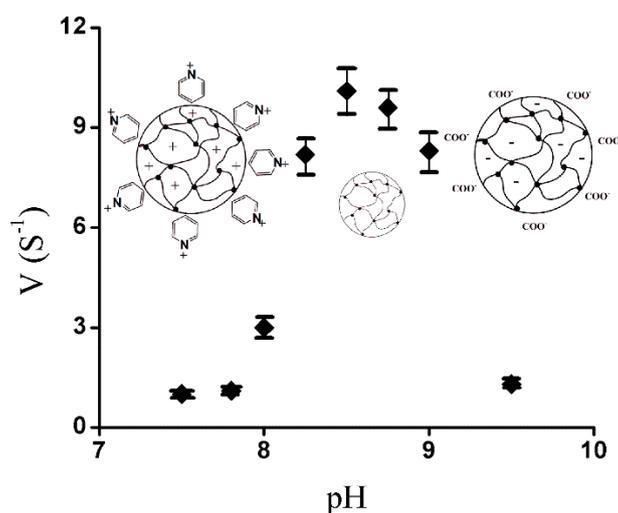
Figure 6. pH effect on the catalytic rate of the imprinted hydrogels in Tris-HCl buffer. Reprinted with permission from Reference 64. Copyright 2010, Wiley.

Post-modification of performed MIPs with pH-responsive polymers can also allow obtaining a pH-dependence binding capacity. Zhao *et al.* reported a pH-responsive MIP particles fabricated by pore-filling poly (acrylic acid) (PAA) gels into BPA-imprinted polyether sulfone particles [62]. The pH-dependence swelling and shrinking of the PAA gels in the MIPs particles gave rise to reversible control of the rebinding ability toward BPA due to the volume exclusion effect. Despite of a decrease in the adsorbed BPA amount (or rate) after filling the PAA gels, the methodology demonstrated a novel strategy to create pH-responsive MIPs as smart chemicals and as drug-delivery systems.

Soon afterwards, Suedee *et al.* fabricated a pH-responsive controlled-release drug device based on a synthesized composite latex, which was consisted of a pH stimuli-responsive poly (hydroxyethyl methacrylate) (HEMA) and polycaprolactone-triol (PCL-T) blend, and a MIP with preloaded drug, (*S*)-omeprazole. The pH-responsive releasing of (*S*)-oeprazole was due to the PHEMA polymer in the composite latex, which was mainly functioned as a barrier to provide sustained release of the required pH-dependent drug. Moreover, the results demonstrate that drug delivery systems containing (*S*)-omeprazole imprinted nanoparticles displayed maximum efficacy while minimizing dose frequency [60].

4. Photo-Responsive Molecularly Imprinted Polymers

Photo irradiation is one of the most frequently adopted external stimuli for stimuli-responsive polymeric materials. Those photo-sensitive materials commonly contain photosensitive chromophores, such as azobenzene [106], stilbene [107], spiropyran and spitooxazines [108] and fugides [109].

Amongst the numerous photosensitive chromophores, the UV-visible photo-induced *trans-cis* isomerization of azobenzene and its derivatives is probably the most extensively studied for its chemical stability, large change in dipole [110], and high quantum yield [111]. The azobenzene chromophore exhibits two isomeric states, the thermodynamically more stable *trans*-isomer and the meta-stable *cis*-isomer. The *trans*-form is converted into the *cis*-isomer by UV light irradiation or heat, and the *cis*-isomer can return to the *trans*-form photo-chemically under visible light irradiation or thermally in the dark (Figure 7). Since the *trans-cis* photoisomerization of azobenzene brings about large changes in molecular geometry and dipole moment to the chromophore [112], when the azobenzene chromophore was incorporated into imprinted receptor sites, the photo-induced changes in orientation and space should result in a significant alteration of receptor geometry and, consequently, affect the binding capacity of the host-guest.
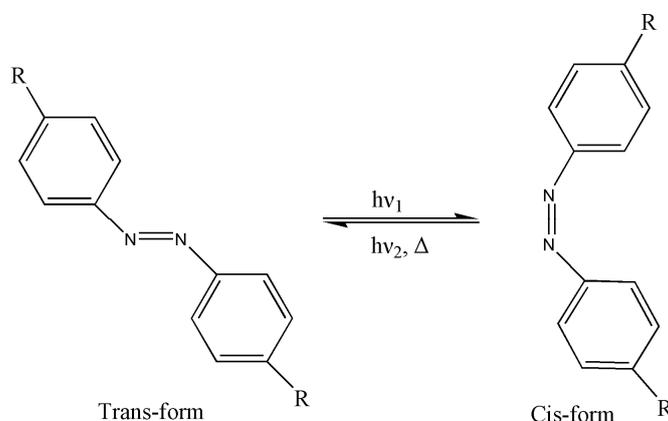
**Figure 7.** Schematic figure of the *trans-cis* isomerization of azobenzen.

The first successful precedent for designing photo-responsive MIP membrane was demonstrated by Minoura *et al.* using a derivative of azobenzene, *p*-phenylazoacrylanilide (PhAAAn). The mixtures of EGDMA and tetraethylene glycol diacrylate (TEGDA) were used as the cross-linkers due to the formation of mechanically stable, but flexible, polymer membranes. Since photo-isomerization of a chromophore had a great influence on the binding site, the resulted MIP membranes exhibited a reversible absorption/release of the template dansylamide (DA), and a better selectivity towards its analogue, dansyl-L-leucine (DL) and *N,N*-dimethylnaphthylamine (DMN). However, the binding capacity and the selectivity of the MIP membranes were not high, which may be attributed to the weaker interactions between the azobenzene functional monomers and target molecules [82].

For the purpose of a more powerful interaction between template and functional monomer, Gong *et al.* employed an novel azobenzene-based functional monomer, 4-((4-methacryloyloxy)phenylazo)benzoic acid (MPABA), which contained a carboxyl group on the para-position of benzene ring [67]. The authors made a detailed study on the influence of cross-linker/monomer ratio, and found that lower cross-linker/monomer ratios (e.g., 1:1 and 3:1) displayed no photo-isomerization properties, which was attributed to the higher chance for azobenzene monomers to aggregate and pack with each other, leading to the reduction of free volume necessary for the reorientation of azobenzene chromophores during their isomerization. The optimized bulk MIP material possessed the ability of reversible release and caffeine

uptake more than four times greater upon irradiation at 365 and 440 nm, respectively, which demonstrates its potential applications in smart separations and drug delivery systems.

Various interactions have been employed in photo-responsive molecular recognition systems. By the same group, a water-soluble azobenzene-containing functional monomer 4-((4-methacryloyloxy)phenylazo) benzenesulfonic acid (MAPASA) was developed for the fabrication of a photo-responsive molecularly imprinted hydrogel material through electrostatic interaction [70]. The photo-responsive MIP hydrogels were designed by cross-linking with various bisacrylamide and bismethacrylamide. The results showed that the photo-isomerization was greatly related to the spacer length of the both ends of the cross-linkers, that is the rate of photo-isomerization gradually increased with spacer length. However, the template binding capacity of the imprinted receptors dropped with the increasing flexibility of the hydrogels. In an optimal condition, the MIP hydrogels showed excellent specific binding capacity and repeatable photo-regulating release/uptake properties in biocompatible aqueous media. In addition, the relative low cross-linking degree and good optical transparency in aqueous media awarded the MIPs hydrogels faster photo-responsive rate, moreover, the use of water-soluble functional monomer and cross-linkers demonstrated their wider applications in the biological field. Li *et al*. also used a water-soluble azobenzene derivative containing two carboxylic acid groups (–COOH), 5-((4-(methacry-loyloxy)phenyl) diazenyl)isophthalic acid (MAPDIA) as the functional monomer, and developed a photo-responsive MIP for guanine using a new water-soluble triethanolaminetrimethacrylate (TEAMA) as the cross-linker [79]. The MIP can release and take up guanine with irradiation at 365 and 440 nm, respectively. In addition, the MIP was successfully applied to the photo-controlled solid-phase extraction of guanine from complex real samples (beer) with good recovery. Subsequent photo-controlled release of guanine in aqueous media allowed for convenient quantitative analysis with high efficiency.

Recently, Gong also demonstrated a new photo-responsive molecular recognition system for 2,3,4,5,7,8,9,10-octafluorophenazine (PAF) uptake through fluorine–fluorine interaction [80]. The new kind of photo-responsive functional monomer containing fluorine-substituted azobenzene chromophore, named (4-methacryloyloxy)nonafluoroazobenzene (MANFAB), was designed and synthesized for the MIPs. The reversible release and uptake of PAF from toluene can be photo-regulated by alternate irradiation at 315 and 440 nm, indicating a possibility for photo-responsive molecular recognition directed by fluorine–fluorine interaction. In addition, Takeuchi *et al*. synthesized a novel photo-responsive functional monomer bearing diaminopyridine and azobenzene moieties, which was applied to the preparation of photo-regulated MIPs for recognizing porphyrin derivatives carboxylic acids through hydrogen bonding [26]. Gomy *et al*. designed a photo-responsive cross-linker with bisurea binding functionalities serving as well as a functional monomer towards dicarboxylate moieties (Figure 8) [68]. Despite of the rigid polymer, the photo-isomerization properties of the azobenzene chromophore are retained. This new approach to form imprinted sites can be used for non-covalent MIPs preparation with potential improved performance, so that more functionality can be introduced without suffering affinity performance losses due to reduced cross-linking.
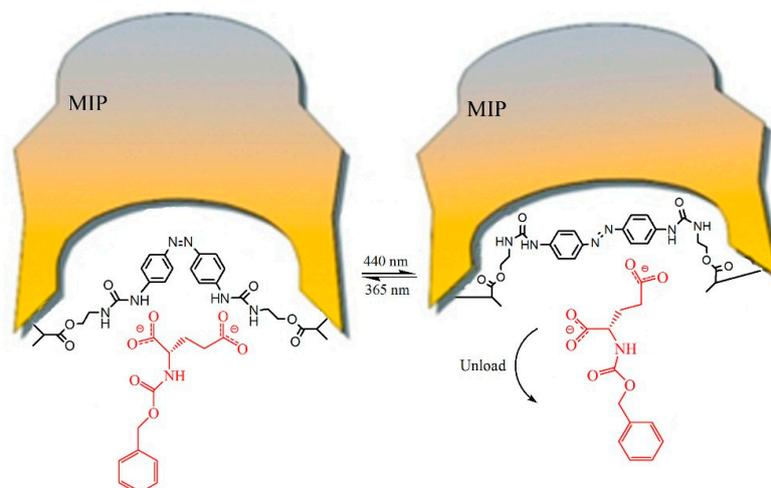
Figure 8. Photoisomerization of the MIPs matrix allowed switching the substrate affinity by altering the geometry and spatial arrangement of the receptor binding sites. Reprinted with permission from Reference 68. Copyright 2007, ACS.

For photo-responsive materials, the efficient area of irradiation on the materials is one of the most crucial factors for rapid and high-efficiency photo-isomerization. Therefore, besides the materials with a great transparency [70] or prepared as a membrane with large exposed area, micro/nano-particle materials are also appropriate candidates for photo-responsive MIPs because of their large specific surface area. However, photo-responsive bulk MIPs always need a time-consuming grinding and sieving procedure to particles, as well leading to great loss of binding sites [113]. Precipitation polymerization has proven very versatile for preparing MIPs micro-/sub-microspheres for its easy operation and lack of need for any surfactant or stabilizer. Recently, Fang *et al.* described a successful preparation of azobenzene (azo)-containing MIP microspheres with photo-responsive template binding properties via precipitation polymerization [74]. The photo-responsive MIP microspheres with a number-average diameter of 1.33 μm and a narrow polydispersity exhibited obvious molecular recognition effects towards 2,4-dichlorophenoxyacetic acid (2,4-D), such as fast template rebinding kinetics and appreciable selectivity over structural analogue. More importantly, the photo-regulation process of the MIP microspheres had also proven to be highly repeatable under photo-switching conditions, leading to obvious photo-responsive binding properties towards the template molecule. Very recently, molecularly imprinted organic–inorganic hybrid azobenzene nanoparticles were synthesized by semi-covalent approach for radiation induced selective recognition of 2,4-D [75]. The hybrid MIP particles were prepared by polymerizing TEOS with a silane containing azobenzene and template molecule via a hydrolysis-condensation mechanism. Removal of the template molecules, the MIP materials were able to release and uptake 2,4-D upon irradiation at 360 and 440 nm, respectively. Moreover, the concentration of 2,4-D can be quantified by monitoring the *trans*-to-*cis* photo-isomerization rate constant.

In a word, the successful preparation of photo-responsive MIPs through various interactions and in different physical formats demonstrate their tremendous potential applications in a range of fields, such as smart separation, extraction, and assays, intelligent chemical carriers, and catalysis *etc*. However, there are still several disadvantages for the current photo-responsive MIPs. To date, azobenzene chromophore is the most adopted and efficient photo-isomerization group in the molecular imprinting

field. Considering the high toxicity of azobenzene, the existence of azobenzene groups in imprinting polymeric network will tremendously limit their applications *in vivo*, such as drug delivery systems. Furthermore, the current photo-responsive MIPs are confined to the photo-regulatory of imprinted sites, so that the ratios of photo-isomerization show great diversity due to their physical properties, such as the size, photo-permeability and the degree of cross-linking. Similarly to some thermo- and pH-responsive MIPs, we may fabricate a photo-responsive polymer layer onto the surface of preformed and optimized MIPs, and realize a photo-regulatory derived from the surface of MIPs. Since a successful precedent has been done for reversible photo-regulation of enzyme activity by using a photo-responsive azobenzene polymer chain pendant [114], the suggested approach could be a promising way to overcome the disadvantages of current photo-responsive MIPs, such as the limited ratios of photo-isomerization and complexity of imprinting systems.

5. Biomolecule-Responsive Molecularly Imprinted Polymers

The physiological reactions are closely related to a variety of biomolecules. For example, the releasing of insulin from secretory cells is regulated by complex cell signal based on the changes of physiological sugar concentration. To mimic those natural feedback systems, a few studies on the preparation of stimuli-sensitive materials that directly respond to a specific molecule have been reported.

Biomolecule-sensitive MIPs were firstly reported by Watanabe *et al.*, which was mentioned in the section of thermo-responsive MIPs. The imprinted polymers based on PNIPAm exhibited a temperature-dependence volume change and a molecular recognition phase, whose volume was responsive to the concentration of the guest molecule [87]. Other biomolecule-responsive MIPs were investigated by Sreenivasan *et al.* for the release of testosterone in response to the concentration of hydrocortisone, which was used as the template molecule and able to replace the stronghold of testosterone in the imprinted sites leading to a hydrocortisone-responsive releasing way [84]. To date, the most classic example for biomolecule-responsive MIPs is the dynamic biomolecule recognition of glycoprotein-imprinted gel using lectin and antibody molecules as ligands for a target tumor marker glycoprotein [49]. The bioconjugated imprinted gels can recognize saccharide and peptide chains in tumor specific marker glycoprotein (α-fetoprotein (AFP)), which lead to a shrinking behavior of imprinted gels. Furthermore, the same group designed a DNA-responsive gels by the same biomolecular imprinting approach [85]. The DNA-responsive shrinking of the imprinted gel was caused by the formation of the DNA duplex that acted as reversible cross-linking points. The swelling ratio of DNA-imprinted gels was strongly dependent on the sequence of DNA in a buffer solution. Since the DNA-imprinted gels can sense single-nucleotide polymorphisms and induce their structural changes, they may prove useful for many potential applications such as smart devices in sensing systems and for molecular diagnostics and drug delivery. Besides these commonly used methods, some novel strategies have been reported to prepare responsive MIP. Bai *et al.* prepared a new type of aptamer-based hydrogel with specific response to target proteins [86]. The volume shrinking of the superaptamer hydrogels is visible to the naked eye in response to femtomolar concentrations of protein (Figure 9). These materials open up new avenues for the design of improved materials for molecule-specific responsive polymers that can ultimately be used for biosensors, drug delivery, and responsive micro-devices.
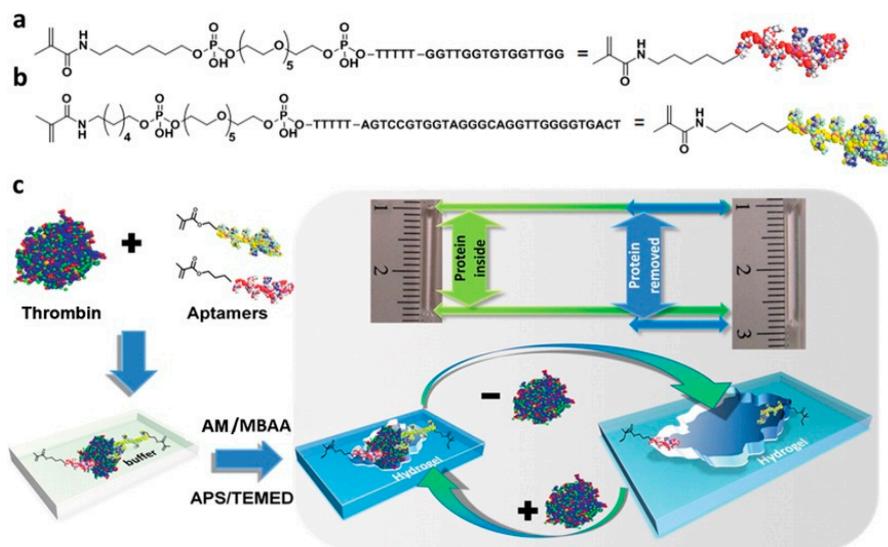
Figure 9. Outline of the biomolecular imprinting scheme used to create superaptamer thrombin-responsive hydrogels. Reprinted with permission from Reference 86. Copyright 2013, ACS.

6. Ion-Responsive Molecularly Imprinted Polymers

Currently, ion-responsive molecularly imprinted polymers are rarely reported. As mentioned above, the PNIPAm-based hydrogels undergo volume changes in response to the ionic strength, leading to ion-responsive binding properties. Intriguingly, Chu *et al.* reported a molecular-recognition microcapsule for ion-responsive controlled release, which may bring us some inspirations for the preparation of ion-responsive MIPs [115]. The reported ion-responsive microcapsule is composed of a core-shell porous membrane and linear grafted poly (*N*-isopropylacrylamide-*co*-benzo-18-crown[6]-acrylamide) (PNIPAm-*co*-PBCAm) chains in the pores acting as molecular-recognition gates. Benzo-18-crown[6] acrylamide (BCAm) is a crown ether receptor, which allows ionic molecular recognition. When specific guest molecule such as Ba^{2+} is captured by the crown ether host, the grafted polymer swells and closes the pores. To the contrary, when Ba^{2+} is removed from the crown ether host, the grafted polymer shrinks and then the pores open. The changes lead to a release of solute from the prepared microcapsules significantly sensitive to the existence of Ba^{2+} ions. Significantly, the prepared poly (NIPAm-*co*-BCAm)-grafted microcapsules showed us an excellent approach to design ion-responsive MIPs by a surface grafting of MIPs with similar functional polymers. Taking advantage of the ion-imprinting strategy, Yu Hoshino *et al.* developed proton-imprinted nanoparticles using NIPAm and AAc as comonomer by pseudo-precipitation polymerization (Figure 10). The pK_a variation range was up to 2.2 which is significantly larger than that of the nonimprinted NPs. More importantly, the apparent pK_a value of the proton-imprinted particles reversibly shifted up and down without significant changes in the pK_a variation range during repeated shrinking (heating, 75 °C) and swelling (cooling, 30 °C) cycles. The principles employed in the preparation of proton-imprinted nanoparticles can be used to other stimuli-responsive materials and will be an integral step in the creation of active proton transporters that enable effective ion transport, gas separation, and catalytic reactions [89].
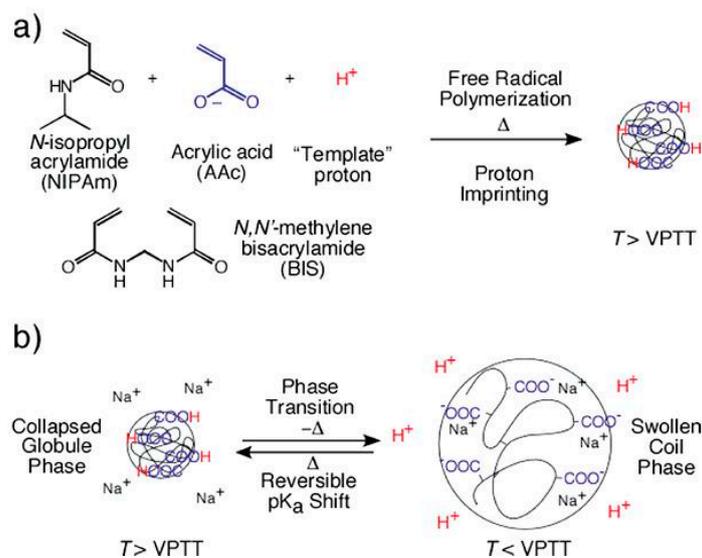
Figure 10. (**a**) Preparation of proton-imprinted NPs; (**b**) Reversible pK_a shift of carboxylic acids in NPs triggered by the phase transition of NPs. Reprinted with permission from Reference 89. Copyright 2014, Wiley.

7. Conclusions

In this review, we give a short introduction to the development in stimuli-responsive MIPs, and it is obvious that stimuli-responsive MIPs will have important applications in separation, extraction, sensors, synthesized chemistry and biomedicine, *etc*. Up to now, various versatile approaches were developed to realize regulatory affinity in an imprinted network, but the approaches commonly displayed either advantages or disadvantages from different angles. Therefore, balancing the two aspects of the complex system is one of the most significant factors for outstanding responsive MIPs. In addition, new synthetic techniques, such as controlled radical polymerizations (CRPs), exhibit very fine control over polymer synthesis so that defined molecular weight, architecture, (co) monomer content and block distribution could be established in the imprinted network when the techniques were adopted for preparing responsive MIPs. This will lead to improved affinity as well as a well-defined responsibility, like a switch, due to homogeneous responsive blocks in the polymeric network in comparison with other radical polymerization. Furthermore, a variety of responsive blocks can be combined in one system step by step, affording truly multi-responsive MIPs for more extensive applications.

At present, despite the potential uses of responsive MIPs in biomedicine, the real applications in clinical trials are very rare. For example, temperature-responsive MIPs have drawn the greatest attention as temperature-induced phase transitions are perhaps the best understood in both theoretical and practical terms. However, the difficulties to achieve local temperature changes *in vivo* have limited their biomedical application. This is also the same problem for photo-responsive MIPs. However, MIPs that can respond to a specific biomolecule or ion are obviously of greater medical relevance. For example, sugar-responsive MIPs with insulin-binding affinity based on phenylboronic acid (a saccharide molecular receptor) [116,117] will be a promising drug carrier candidate for diabetes therapy. Another problem is the biocompatibility of responsive MIPs. Although the suitable hydrophilic/hydrophobic equilibrium of the MIPs can be regulated elaborately, the toxicity of current material compositions,

such as *N*-alkylacrylamide and azobenzene monomers, should be seriously considered. Excitingly, biopolymer such as natural thermo- and pH-responsive polypeptides and biocompatible PEO and PPO block co-polymers such as pluronics, poloxamers and tetronics are available substituted candidates *in vivo*. Therefore, the development of responsive MIPs with biocompatible properties is a challenge that can be expected to yield a new generation of drug delivery devices, bioseparation devices, biosensors and tissue engineering materials for biomedical applications.

Supplementary Information

Supplementary materials can be accessed at: http://www.mdpi.com/2073-4360/7/9/1478/s1.

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Author Contributions

The manuscript was completed through contributions of all authors. Jianmin Pan, Guoqing Pan and Börje Sellergren initiated the topic and designed the entire content of this paper. Wei Chen and Yue Ma contributed to the writing of the paper. Zihui Meng, Jianmin Pan, Guoqing Pan and Börje Sellergren then disscussed and revised the paper. All authors have given approval to the final version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

AA, Acrylic acid; AAm, Acrylic amide; AFP, α-Fetoprotein; BPA, Bisphenol A; BSA, Bovine serum albumin; CFX, Cefalexin; Cyt C, Cytochrome C; DA, Dansylamide; DBTS, Dibenzothophene sulfone; DEDTC, *N,N*-diethyldithiocarbamate; DMAEMA, 2-(Dimethylamino)ethyl methacrylate; DMAPMA, *N*-(3-(dimethylamino)propyl)methacrylamide; DMF, Dimethyl formamide; DMSO, Dimethylsulfoxide; Dox, Doxorubicin; DVB, Divinylbenzene; EGDMA, Ethylene glycol dimethacrylate; HEMA, 2-Hydroxyethyl methacrylate; LCST, Low-critical solution temperature; Lys, Lysozyme; MAA, Methacrylic acid; MBAA, *N,N*-methylenebisacrylamide; MIPs, Molecularly imprinted polymers; MIH, Molecularly imprinted hydrogel; M-MIPs, Magnetic responsive MIPs; MPABA, 4-((4-Methacryloyloxy) phenylazo)benzoic acid; MAPASA, 4-((4-Methacryloyloxy)phenylazo) benzenesulfonic acid; MRS, Molecular recognition sites; QDs, Quantum dots; PCL-T, Polycaprolactone-triol; PCS, Photocatalytic sites; PEG, Poly(ethylene glycol); PES, Polyethersulfone; PhAAAn, *p*-phenylazoacrylanilide; NIPAAm, *N*-isopropylacrylamide; RAFT, Reversible addition-fragmentation chain transfer; RGDS, Arg-Gly-Asp-Se peptide; SRP, Stimuli

responsive polymers; tBAm, *N-tert*-butylacrylamide; TRIM, Trimethylolpropane trimethacrylate; TTT, Tetramethacryloyl triethylene tetramine; VBIDA, *N*-(4-vinyl)-benzyl iminodiacetic; 4-HA, 4-Hydroxybenzoic acid; 4-VP, 4-Vinylpyridine.

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