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Molecularly Imprinted Polymer-Based Biosensors

For the early, rapid detection of pathogens, biomarkers, and toxins in clinical, environmental, or food samples.

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Digital Object Identifier 10.1109/MNANO.2017.2779718
Date of publication: 17 January 2018

EARLY DETECTION OF PATHOgens, biomarkers, or toxins in clinical, environmental, or food samples is of great interest, and it continues to be a challenge in disease diagnosis as well as in environmental and food-safety monitoring. A molecularly imprinted polymer (MIP) is a polymer capable of mimicking the function and structure of antibodies and biological receptors to recognize target molecules with high sensitivity and selectivity. As a critical component of polymeric sensors, MIP can be incorporated into a variety of signal amplification or transduction platforms to fabricate polymeric sensors. These polymeric sensors have been investigated and shown promising potential in the detection of target molecules. In this article, we summarize and discuss the recent advances of MIP-based polymeric sensors.

MIP OVERVIEW

Molecular recognition and detection are the basis for disease diagnosis and environmental and food-safety monitoring. While

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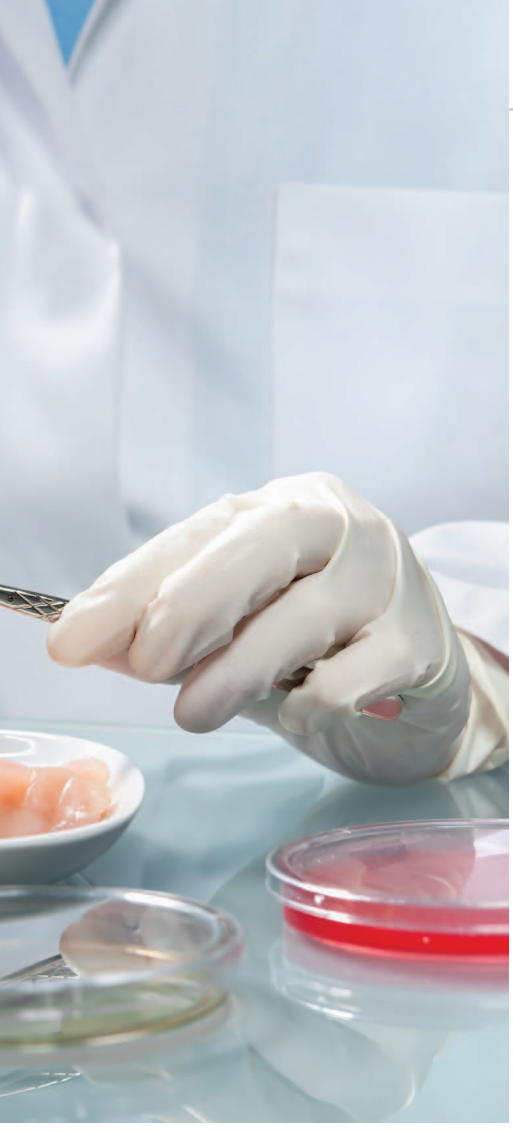

While early detection of pathogens, biomarkers, and toxins in clinical, environmental, and food samples is important to human health, it is also very challenging.

early detection of pathogens, biomarkers, and toxins in clinical, environmental, and food samples is important to human health, it is also very challenging. This is especially the case when the concentration of analyte is ultralow. Although conventional technologies using cell cultures, polymerase chain reactions, chromatography/mass spectrometry, or enzyme-linked immunosorbent assays can offer precise detection, the tests are tedious, inefficient, and expensive. They also require costly instruments, antibodies, and well-trained personnel.

Therefore, there is an increasing interest in developing portable and cost-effective sensors with high sensitivity, selectivity, and rapid response. Because of their unique chemical and physical properties and ease of modification, polymers containing a polymeric network via cross-linking monomers, or molecularly functionalized monomers, have recently been in the spotlight and demonstrated great potential in the development of sensors with high responsivity to target molecules.

An MIP is one kind of polymer that contains specific molecular recognition cavities within a polymeric network and mimics the function and morphology of antibodies and biological receptors to recognize specific molecules. The specific molecular recognition cores can be generated during the polymerization of functional monomers with cross-linkers in the presence of template molecules. After the removal of template molecules, the molecular recognition cavities are created. The MIP has several distinguished advantages that make it a promising alternative.

- It has high selectivity and sensitivity to the target molecule.
- In comparison to biological molecules, it has mechanical properties, higher physical and chemical stability, and is insensitive to temperature; therefore, it can be stored at room temperature or higher.
- The preparation time is short, and the cost is low.
- It can be easily chemically modified.

Sensors based on MIP have been widely used in a broad range of applications, including biomedical devices and environmental and food-safety monitoring [1]. The selection of functional monomers is important for the design of MIP sensors due to the direct binding between monomers and functional groups of template molecules in the formation of molecular recognition cores during the polymerization [2]. There are two binding interactions, covalent and noncovalent binding.

There have been very few studies reported regarding covalent binding thus far. After the cleavage of the covalent bonds between the template molecules and the specific groups of monomers during polymerization, the covalent bonds can rebind in the presence of target molecules. This is stable and could remarkably reduce nonspecific binding. However, the slow and insufficient dissociation of covalent binding as well as a rigid polymeric network caused by the strong covalent binding impedes further binding sites for the MIP, resulting in low overall recognition capability for the target molecules. More importantly, the slow binding and rebinding rate limits its flexibility of thermodynamic equilibrium [3]. Nevertheless, for noncovalent binding, the properties of the functional monomers directly influence the binding interactions through complementary noncovalent binding, including hydrophobic hydrogen bonds, ionic bonds, van der Waals forces, or $\pi-\pi$ interactions [3], [4].

In contrast, the template molecules are easier to be bound and removed from the monomers with noncovalent binding. Therefore, MIP with noncovalent binding is more prevalent in the literature. Generally, a polymeric sensor consists of a molecule recognition element, transducer, or signal amplifier. An MIP acts as the molecule recognition element that determines the molecular recognition event and affects the sensitivity of the entire sensor. In this article, we will focus on the MIP-based polymeric sensor with noncovalent binding between the monomer and template molecules. According to the types of functional groups used during the process of polymerization, MIP-based polymeric sensors can be categorized into several major types, as shown in Figure 1.

SELECTION OF FUNCTIONAL MONOMERS

Major considerations for the selection of functional monomers for an MIP are the interactions between monomer and template molecules and the method of sensor signal amplification or transduction. A variety of monomers are already available for the synthesis of MIP via free-radical polymerization, electropolymerization, or sol–gel process according to the chemical structure of monomers, which is determined by the sensor signal amplification or transduction [3], [5]; for the fabrication of an electrochemical sensor, the electropolymerization using cyclic voltammetry (CV) is the most common method. It is evident that the MIP can be electropolymerized and interfaced directly on the surface of the electrode, resulting in a significant signal enhancement and consistent signal readout [6]. Therefore, the functional monomers should contain the structure that is able to be electropolymerized under CV, such as phenol, pyrrole, and aniline.

MIP-BASED POLYMERIC SENSOR WITH ONE TYPE OF FUNCTIONAL MONOMER

Typically, an MIP is fabricated using one monomer via free-radical polymerization. Although some monomers, including methacrylic acid (MAA), acrylic acid (AA), *N*-isopropylacrylamide (NIPAAm), and acrylamide (AAm), are commonly used for the preparation of MIP in many other applications, few MIP-based polymeric sensors use only one type of these monomers. Among these monomers, MAA, which could

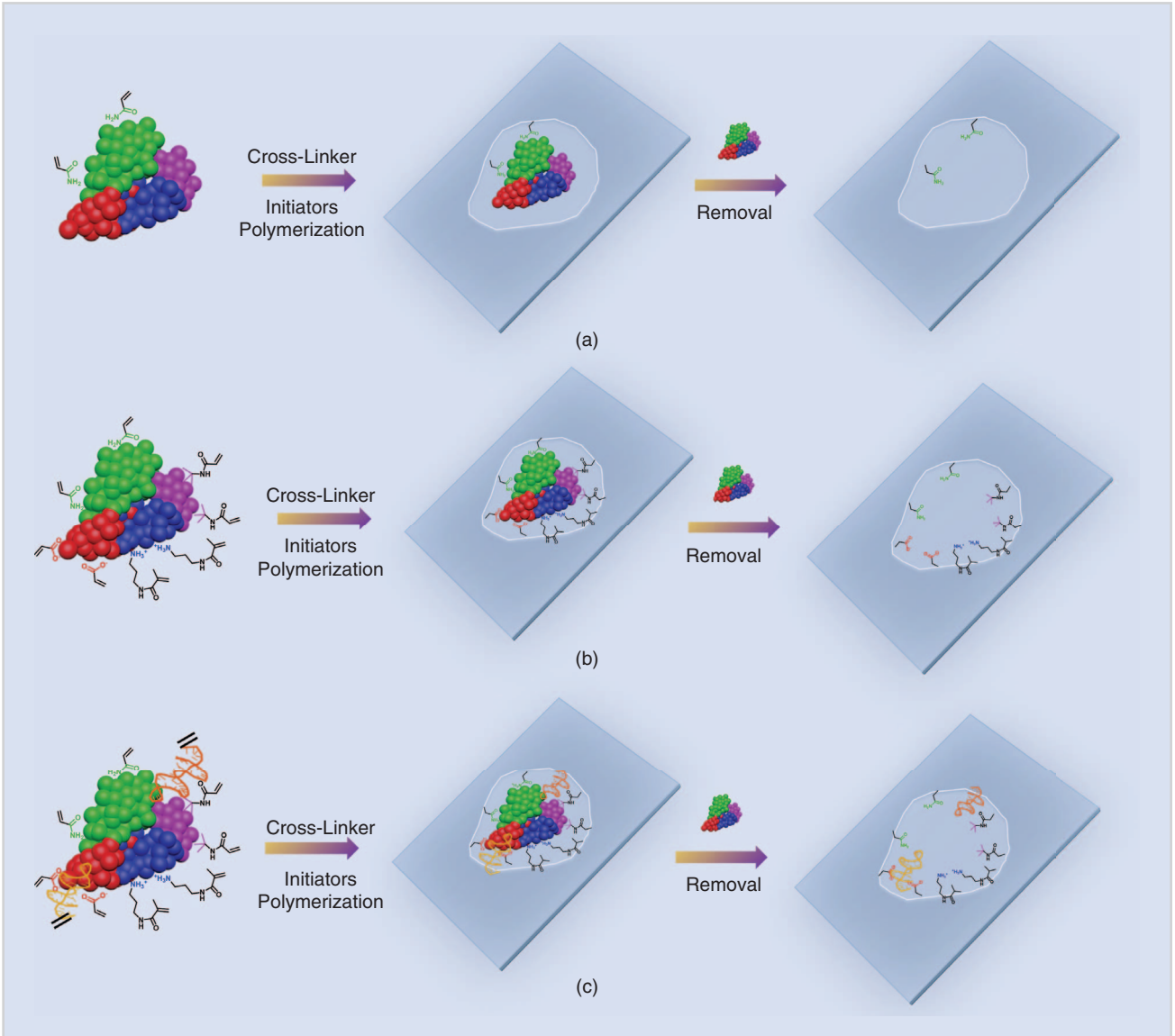

FIGURE 1 The main types of MIP-based polymeric sensors: (a) an MIP-based polymeric sensor with one functional monomer, (b) an MIP-based polymeric sensor with different functional monomers, and (c) an MIP-based polymeric sensor with different functional monomers in combination with biologically functional molecules.

form a hydrogen bond or ionic bond, is the monomer most often used to prepare MIP, e.g., Ebarvia et al. developed a piezoelectric quartz sensor for caffeine detection. MAA (monomer), ethylene glycol dimethacrylate (cross-linker), and caffeine (template) were polymerized to form an MIP and spin coated on a surface of the electrode of a 10-MHz AT-cut quartz crystal to fabricate a sensor. A hydrogen bond was generated from the hydrogen atom of the carboxyl group of MAA and the oxygen atom of the carbonyl group of caffeine. This hydrogen bond and electrostatic attraction were the predominant interactions in the MIP and in caffeine [7]. Although a good linear relationship was found in the concentration range between 1×10^{-9} mg/mL to 1×10^{-3} mg/mL and a good detection limit with 3.76×10^{-11} mg/mL, MIP with one functional monomer can only produce one or two kinds of interactions for binding, which do not sufficiently bind to molecule and usually would induce unspecified binding. This is especially true for larger macromolecules, i.e., proteins. Compared to small molecules, macromolecules contain many different charge distributions on the entire surface that require different specific bonds to increase the affinity to target molecules. Therefore, there are few reports using only one monomer to fabricate the MIP sensor via free-radical polymerization.

In contrast, there are many articles reporting electrochemical sensors made of only one functional monomer. This might be because there are many interactions formatted between different active charged groups in different functional monomers and template molecules during electropolymerization, which greatly impacts the formation of MIP film. For instance, an MIP electrochemical nanosensor developed by Cai et al. showed that arrays of carbon-nanotube tips covered with a nonconducting MIP polyphenol (PPn) can detect ~10 pg/L of ferritin and ~0.1 pg/L of human papillomavirus-derived E7 using electrochemical impedance spectroscopy. A 13-nm PPn thin film was observed, and 12 imprinted cavities were found on each nanotube tip [5]. The template proteins, which were incorporated into the MIP thin film, led to imprinted binding cavities in the thin film on the surface of the electrode after removal of the template protein. Because the MIP was constructed by the nonconducting MIP, the electrical signal indicator is accessible to the surface of the electrode via such cavities. Therefore, the sensor electrical impedance signal is reduced because of the reduced electrical leakage via the surface-imprinted cavities in the MIP. Owing to the relatively lower conductivity of the protein, increased impedance indicates the detection of the target protein [5].

The other popular sensor signal transduction method is surface-enhanced Raman scattering (SERS) caused by the MIP's easy surface modification, rapid detection, and potential for portability. Hu et al. developed a SERS sensor that is fabricated by MAA as a monomer and silver dendrite as a substrate for the detection of melamine in whole milk. The detection of melamine was as low as 5×10^{-6} M [8]. Kamra et al. reported a SERS sensor to covalently immobilize MIP nanoparticles on a Raman active substrate using a disulfide-derivatized perfluorophenylazide through a gold–sulfur bond to detect propranolol [9]. The limit of detection (LOD) is 7.7×10^{-4} M.

The reasonable design and selection of the combination of monomers plays a key role in the fabrication of an MIP sensor.

MIP-BASED POLYMERIC SENSOR WITH DIFFERENT FUNCTIONAL MONOMERS

In most cases, the MIP sensor was prepared by using more than one kind of functional monomer due to sufficient binding interactions of the monomers and the template molecules. Because there are one or two bonds between the small molecule and the MIP, one monomer is enough. However, for macromolecules, including protein and peptides, there are many functional groups on the surface. These groups allow the formation of hydrophobic hydrogen bonds, ionic bonds, or van der Waals forces when they are exposed to various monomers with corresponding binding groups; the localization of charged groups on the surface is determined by the chemical properties and outer surface structure of the target molecules, including the proteins and peptides.

During prepolymerization, a large number of charged spots on the protein surface bind to monomers of the opposite surface to generate the ionic bond. The polymeric network produced by polymerization provides an interface between the charged surface and monomers. After the polymerization and removal of template molecules, the changed groups stay at the imprinted cavities to serve as the specific binding site. The neutral monomer can be used as the backbone for the MIP matrix surrounding the imprinted cavities, which significantly decreases nonspecific binding and enhances the affinity to target molecules [10]. Therefore, most MIP sensors require different combinations of monomers to obtain the optimal sensitive and selective properties.

The reasonable design and selection of the combination of monomers plays a key role in the fabrication of an MIP sensor. Generally, a neutral monomer is selected as the backbone monomer in combination with other hydrogen bonds and negative-charged, positive-charged, and hydrophobic functional monomers for constructing the imprinted cavities. Classic monomers are presented in Figure 2. NIPAAm is usually used as the backbone monomer because of its neutral charge. The amide group of AAm and the oxygen atom of the hydroxyl group easily form a hydrogen bond. The monomer with the negative charge, such as AA, can be used to bind

Integration of biological functional molecules with MIP to further improve the performance of the MIP-based polymeric sensors has attracted increasing attention in recent years.

the positive-charged sites of target molecules, whereas the monomer with the positive charge, such as *N*-(3-aminopropyl) methacrylamide hydrochloride, can be used to bind the negative-charged sites of target molecules.

In a very important study, Hoshino et al. prepared MIP nanoparticles for the recognition of peptides and used a 27-MHz quartz crystal microbalance to demonstrate that the binding affinity and size of the MIP nanoparticles were equal to the natural antibodies [11]. In these MIP nanoparticles, NIPAAm was the backbone monomer, whereas AAm, AA, *N*-(3-aminopropyl) methacrylamide hydrochloride (APS), and *N*-*tert*-butylacrylamide (TBAM) were employed as hydrogen-bonded, negative-charged, positive-charged, and hydrophobic functional monomers, respectively [11].

Altintas et al. reported a surface plasmon resonance (SPR) biosensor based on MIP nanoparticles to detect *Escherichia coli* (*E. coli*) bacteriophages. The MIP nanoparticle was synthesized by using three monomers (NIPAAm, TBAM, and AA), followed by covalently coupling on a self-assembled monolayer-modified gold substrate [12]. This sensor provided a separation–filtration system to detect and remove waterborne viruses for water purity. Compared to the SERS sensor described previously, the LOD of this sensor is about 1,000-fold lower, which is attributed to the combination of the three different monomers.

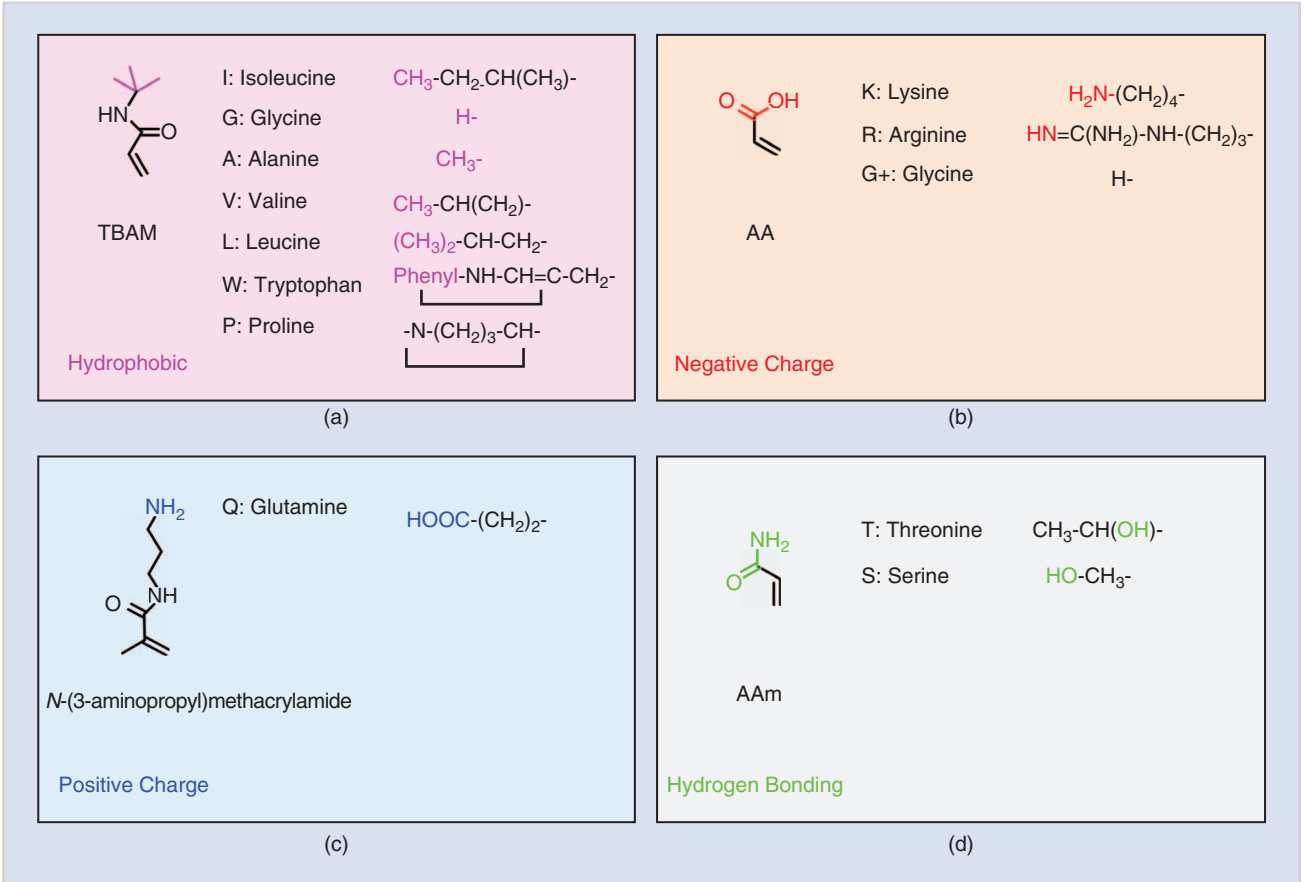

FIGURE 2 The major classes of functional monomers and their corresponding binding group of protein and formation of binding bond: (a) TBAM, a monomer with hydrophobic groups, can bind the hydrophobic groups of target molecules; (b) AA, a monomer with negative-charged groups, can bind to the positive-charged sites of target molecules; (c) *N*-(3-aminopropyl) methacrylamide hydrochloride, a monomer with positive-charged groups, can bind to the negative-charged target molecule sites; and (d) a hydrogen bond can be formed between the amide group of AAm and the oxygen atom of the hydroxyl group.

MIP-BASED POLYMERIC SENSOR WITH FUNCTIONAL MONOMERS IN COMBINATION WITH BIOLOGICALLY FUNCTIONAL MOLECULES

In addition to the optimal combination of different monomers, the integration of biological functional molecules with MIP to further improve the performance of the MIP-based polymeric sensors has attracted increasing attention in recent years (Table 1). Although target molecules and imprinted cavities through complementary noncovalent binding, including hydrophobic hydrogen bonds, ionic bonds, van der Waals forces, or $\pi-\pi$ interactions, ensure the selectivity of the sensor, monomers in combination with the biologically functional molecules that can specifically bind to template molecules, such as aptamers, antibodies, and some chemical agents, will dramatically enhance the selectivity and binding capability to the target molecules.

Hydrogels are one kind of polymer consisting of a water-swelling polymeric network via cross-linking monomers or molecularly functionalized monomers used to fabricate highly responsive sensors [13]–[17]. More importantly, hydrogel-based sensors have shown good potential for signal amplification [18], [19]. However, their quantification is inadequate [18]–[22].

Miyata et al. synthesized a vinyl-rabbit immunoglobulin G (IgG) through chemically modifying rabbit IgG by *N*-succinimidylacrylate. It was then mixed with goat antirabbit IgG, AAm, and *N*, *N*′-methylenebisacrylamide. After polymerization, an antigen-antibody hydrogel sensor was obtained, which improved reversible antigen sensitivity. The significant swelling rate was observed when the hydrogel sensor was in the presence of the concentration of the antigen in the phosphate buffer solution. The significant swelling rate is 4 mg/mL [23].

Miyata et al. reported a glycoprotein (α-fetoprotein)-imprinted hydrogel sensor that contained AAm, lectin, and an anti-α-fetoprotein antibody. The lectin and the anti-α-fetoprotein antibody of the hydrogel sensor must bind to the peptide and saccharide chains of the α-fetoprotein in the sample simultaneously for glycoprotein-imprinted cavities to cause polymeric network shrinkage due to the reversible cross-linking points formed by lectin–glycoprotein–anti-α-fetoprotein-antibody complexes [17]. However, the pricey antibody and antigen would increase the cost of the sensor, and the complex fabrication process dramatically decreases the stability of the polymeric sensor. Moreover, the accuracy could be greatly compromised in measuring volumetric changes. As previously mentioned, the MIP using one monomer usually affects the affinity to target molecules.

TABLE 1 The components and performance of MIP-based polymeric sensors.

SENSOR TYPE	SIGNAL AMPLIFICATION OR TRANSDUCTION	MONOMER	TEMPLATE MOLECULES	LOD	REFERENCE
Piezoelectric quartz	Electrode of a 10-MHz AT-cut quartz crystal	MAA	Caffeine	Caffeine: 1.5×10^{-13} M	[7]
Electrochemical	Carbon-nanotube tips array modified electrode	Phenol	Human ferritin- and human-papillomavirus-derived E7 protein	Ferritin: 2.1×10^{-17} M Human-papillomavirus-derived E7 protein: 5.3×10^{-18} M	[5]
SERS	Klarite substrates	MAA	(R,S)-propranolol	(R,S)-propranolol: 7.7×10^{-4} M	[9]
SERS	Silver dendrite SERS substrate	MAA	Melamine	Melamine: 5×10^{-6} M	[8]
Optical	Volumetric measurement	NIPAAm vinyl-Rabbit IgG	Goat antirabbit IgG	—	[23]
Optical	Volumetric measurement	AAm, vinyl lectin, and vinyl antibody	α-fetoprotein	—	[17]
SPR	Gold chip	NIPAAm, TBAM, AA	*E. coli* bacteriophage	*E. coli* bacteriophage: $\sim 3 \times 10^{-9}$ M	[12]
Optical	Length measurement	AAm, NIPAAm, aptamers	Thrombin and PDGF-$\beta\beta$	Thrombin: 10^{-15} M PDGF-$\beta\beta$: 10^{-12} M	[18]
Laser diffraction	Length measurement	AAm, NIPAAm, aptamers	Apple stem pitting virus	Apple stem pitting virus: 4.1×10^{-11} M	[19]
Electrical	Aggregation of TGA-chitosan decorated gNPs	AAm, NIPAAm, aptamers, TGA-chitosan decorated gNPs	Thrombin and anatoxin	Thrombin: 1×10^{-18} M Anatoxin: 1×10^{-14} M	[29]
Electrochemical	Gold array electrode	Pyrrole	RTA	RTA: 2.1×10^{-12} M	[30]

IgG: immunoglobulin G; gNP: gold nanoparticle; RTA: ricin toxin chain A; PDGF: platelet-derived growth factor; TGA: thioglycolic acid.

Aptamer-based polymeric sensor systems could be very attractive due to their high selectivity, thermal stability, robustness, affordability, and simplicity of use.

Aptamers, single-stranded oligonucleotides or peptide molecules with a specific sequence, are able to bind to small target molecules, proteins, or nucleic acids with high selectivity and affinity [24]–[27]. The initial oligonucleotide pool composed of thousands of different oligonucleotides or peptides and systematic evolution of ligands by exponential enrichment was used to select and separate aptamers [28]. Aptamers hold great promise for molecular recognition and binding by creating a molecularly imprinted polymer with aptamer-specific binding activity. The recognition and capture of target molecules by specific aptamers could induce shrinking responses of the hydrogel sensor mentioned previously. Therefore, aptamer-based polymeric sensor systems could be very attractive due to their high selectivity, thermal stability, robustness, affordability, and simplicity of use.

It was recently reported that the monitoring of volumetric changes of these hydrogels using aptamers allowed for the detection of biomolecules, such as thrombin [18], [19]. The hydrogel sensors developed by Bai et al. and Bai and Spivak were synthesized using AAm and a pair of acrylate aptamers for thrombin detection. They found that the prepolymerization aptamer-thrombin binding complex provides molecularly imprinted cavities with aptamer-specific binding. However, if there is only one aptamer and template molecule in hydrogel, the hydrogel shrinkage to the target molecule is smaller than that of hydrogel with a complete pair of acrylate aptamer and template molecules. Unfortunately, the accuracy could be greatly compromised for measuring volumetric changes (length) fewer than 1 mm out of 15–20 mm when using a traditional ruler with the naked eye [18], [19]. Subsequently, Bai et al. prepared a hydrogel sensor containing AAm, NIPAAm, and one aptamer for the detection of the apple stem pitting virus using a laser to improve the precision of the detection. Although the polymeric matrix of MIP was fabricated by the AAm and NIPAAm, there was only one aptamer, which proves that the volumetric shrinkage is not significant. Thus, it is difficult to measure the change with the naked eye.

Recently, we reported a new promising signal cascade strategy via an ultrasensitive polymeric sensor composed of gold nanoparticle (gNP)-decorated polymers and aptamers in virtue of gNP's sensitive electromechanical properties [29]. The gNP aggregation in a polymeric network results in the electrical conductance change upon specific aptamer-based biomolecular recognition [29]. We used this strategy to fabricate sensors for the detection of thrombin and anatoxin. It was discovered that after the introduction of aptamer, the performance of thrombin-specific sensor was increased, and the signal cascade strategy enabled the LOD of 1×10^{-18} M, which has a much higher performance compared to previous reports by others [18].

The MIP matrix fabricated by mixing functional monomers and molecules with high affinity has attracted increasing interest. Recently, a novel electrochemical sensor for the detection of ricin toxin chain A (RTA), reported by Komarova et al., was electropolymerized by Coomassie Brilliant Blue (BB)-RTA/pyrrole on the gold array electrode. It was followed by the removal of RTA using Proteinase K [30]. The LOD is 0.1 ng/ml^{-1}. The Coomassie BB was capable of stabilizing the polypyrrole film and enhancing the affinity to RTA.

DISCUSSION

Although the molecularly imprinted technology has been developed during the last few decades, there are still many challenges. Improving molecule recognition is one major challenge, especially for macromolecules, such as proteins. A reasonable and optimal selection of different functional monomers and their ratio can be an efficient approach to improve molecule binding. To further enhance molecule recognition, biological functional molecules including aptamers should be taken into consideration for combination with different functional monomers.

An appropriate sensing platform is the other way to improve the MIP polymeric sensor. Electrochemical MIP sensors have attracted considerable interest and they possess several advantages. First, compared to free radical polymerization of MIP, the control of eletropolymerization charge density allows precise control of MIP film thickness, density of crosslinking, and size. Second, the location of the MIP film can be controlled to attach onto the surface of metallic or semiconductor electrodes to form micropatterns [31]. The other predominant sensing platform is SERS, which allows the easy modification of the active SERS substrate surface. However, it has a common problem: the integration of MIPs and the metal or semiconductor electrode of the SERS active surface has to be intimate to increase the impedance or Raman signal. As a result, the sensitivity of the senor can be improved [9].

OUTLOOK

Because polymeric sensors based on one type of monomer or different monomers have limitations, the addition of biological functional molecules including aptamers or antibodies is able to dramatically generate a higher affinity for the target molecules due to the cooperation effect. To the best of our knowledge, there is no report integrating different monomers simultaneously with hydrophobic hydrogen bonds, ionic bonds, and biological functional molecules to bind the corresponding complementary

binding groups of template molecules. It is safe to say that this strategy will combine the enhancement of polymer-protein surface interface and the strong nature of biological ligand binding, resulting in a promising way to further increase the rebinding capability of polymeric sensors based on the MIP.

In addition to the combination of different monomers and biological functional molecules, the optimal choice of sensor signal amplification or transduction is critical to increase the performance of the polymeric sensor. Using the inorganic materials and organic polymer composites or conductive organic materials and organic polymer composites to enhance the conductivity of MIP is the other promising strategy to improve polymeric sensor performance, but there are few reports. This efficient strategy can also be integrated with many other sensing platforms, including electrochemical sensors or surface-enhanced Raman detection, which is currently not reported.

CONCLUSION

In this review, we have summarized and discussed the advancements and challenges of MIP-based polymeric sensors. Notably, the selection of the monomer is important for molecule recognition, and appropriate signal transducer or signal amplifier can help enhance the signal readout. Due to its high sensitivity, selectivity, short preparation, development time, and low cost, MIP-based polymeric sensors hold great potential, including the possibility of rapidly detect pathogens, biomarkers, and toxins much earlier in clinical, environmental, or food samples, even in samples with ultralow concentrations.

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