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Molecularly imprinting: a tool of modern chemistry for analysis and monitoring of phenolic environmental estrogens

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Abstract: Phenolic environmental estrogen (PEE) is one of the most common endocrine disrupting chemicals whose interference with the normal function of the endocrine system in animals and humans raised concern to their potential impact on wildlife and humans health. Research on PEEs calls for a high selectivity analytical methods. Molecularly imprinted polymers (MIPs) are synthetic polymers having a predetermined selectivity for a given analyte, or group of structurally related compounds, which make them ideal materials to be used in analysis of PEEs. During the past few years, a huge amount of papers have been published dealing with the use of MIPs in the analysis of PEEs. In this review, we focus on the recent applications of MIPs to analyze PEEs. We describe the preparation of MIPs and discuss different methods of polymerization. We highlight the latest applications of MIPs in the analysis of PEEs, including nanomaterial MIPs as sorbent for solid-phase extraction and MIPs as electrochemical sensors. This review provides a good platform for the analysis and monitoring of PEEs in complicated matrixes and offers suggestions for future success in the field of MIPs.

Keywords: electrochemical sensors; molecularly imprinted polymers; nanomaterial; phenolic environmental estrogens; solid-phase extraction.

Introduction

Endocrine disrupting chemicals (EDCs), also known as environmental hormone, are a group of exogenous substances that may interfere with the normal function of the endocrine system in animals and humans (Diamanti-Kandarakis et al. 2009, Vandenberg et al. 2012). A recent literature review on EDCs indicated that suspected human health risks include reproductive disorders, immune and hormonal disorders, and neurobehavioral disorders, which consequently have drawn extensive societal, scientific, and political attention (Giusti et al. 1995, Yang et al. 2006). The long-term effects of emerging contaminants on humans are still largely unknown. It has been suggested that increases in breast, testicular, and prostate cancers reported over the past 40 years are related to EDCs in the environment (Giese 2003, Murray and Oermeci 2012).

EDCs include a wide range of chemicals, among which are phenolic environmental estrogens (PEEs), a group of biologically active compounds that are synthesized from phenol (Yue et al. 2014). This review focuses on the two families of the most used PEEs – bisphenols (e.g. bisphenol A, BPA, an important intermediate in the production of epoxy resins and polycarbonate plastics) and alkylphenols (e.g. nonylphenol, extensively utilized in the production of elasticizers, abstergents, and pesticide emulsifiers) (Figure 1). As representative and ubiquitous EDCs in environment, PEEs are typical endocrine disrupters and show toxic effects on the nervous system, reproductive system, and immune system even at very low concentrations (ng l^{-1}) (Yuksel et al. 2013, Kim et al. 2014, Peng et al. 2014). Therefore, the pollution from PEEs has drawn increasing worldwide attention, and monitoring the residues of PEEs in environment is essential. Due to its low PEE concentration and complicated matrixes, materials with a high selectivity for sample pretreatment are in high demand, and thereby, molecularly imprinted polymers (MIPs) have appeared in response to this demand.

MIPs are synthetic polymers possessing specific cavities designed for target molecules (Xu et al. 2011, Chen et al. 2013, Hao et al. 2015). With tailor-made binding sites, MIPs not only recognize the size and shape of a given template but also respond to the functional groups of the molecule (Wang et al. 2009, Chen et al. 2012, Gao et al. 2016). Furthermore, in contrast to these conventional methods, MIPs have other outstanding advantages such as relative ease and low cost of preparation, high stability, physical

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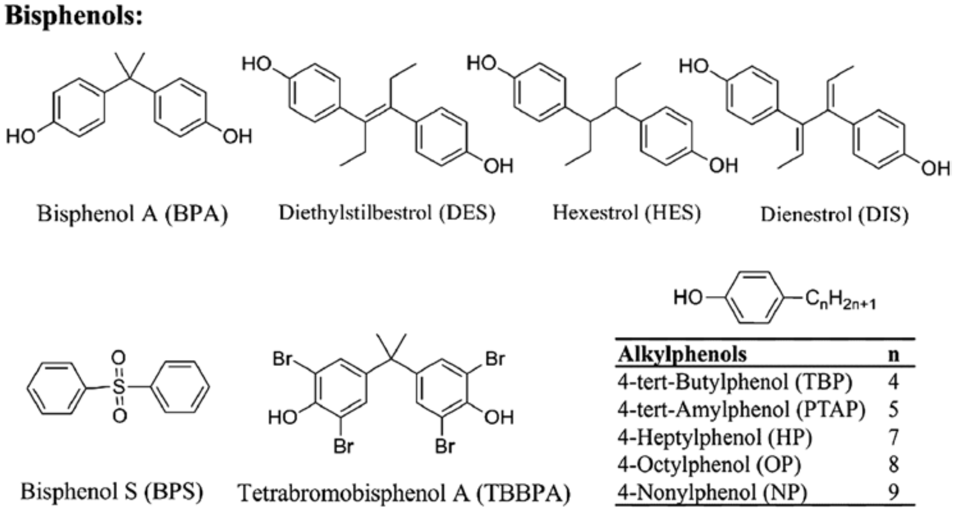

Alkylphenols	n
4-tert-Butylphenol (TBP)	4
4-tert-Amylphenol (PTAP)	5
4-Heptylphenol (HP)	7
4-Octylphenol (OP)	8
4-Nonylphenol (NP)	9

Figure 1: Structures of the main PEEs considered for this review.

robustness, and resistance to elevated temperature, and potential application to a wide range of target molecules (Zhao et al. 2012, Ma and Shi 2015, Xie et al. 2016). Successful applications of MIPs have been demonstrated in various fields including chem/biosensors (Kotova et al. 2013, Zhu et al. 2014), solid-phase extraction (SPE) (Xie et al. 2015c, Chen et al. 2016), chromatograph separation (Sellergren 2001, Michailof et al. 2008), reactive catalysis (Resmini 2012, Zhang and Riduan 2012), and membrane separations (Alizadeh and Memarbashi 2012, Sueyoshi et al. 2012). Recently, the molecular imprinting technique also has been applied for the analysis and monitoring of PEEs from the complicated matrixes.

As the developments of molecular imprinting have been described in other reviews in detail (Beltran et al. 2010, Martin-Esteban 2013), here we mainly give a comprehensive overview of applications of MIPs as a treatment method for the analysis and monitoring of PEEs from complicated matrixes, which include the main approaches to the synthesis of MIPs and formats for application (e.g. SPE and sensors). Furthermore, we discuss the applications and advantages of using the MIPs compared with the traditional methods available for the analysis of PEEs and offer suggestions for future success in the field of MIPs. To the best of our knowledge, this is the first review on molecular imprinting technology applied to PEEs.

MIP synthesis for PEEs

MIPs are materials prepared in the presence of a template that serves as a mold for the formation of a template-complementary binding site. The formation of the MIPs typically involves the copolymerization of a complex formed by the template and a functional monomer via either covalent or non-covalent interaction (hydrogen bond, ionic and/or hydrophobic interaction) with a cross-linker in the presence of a suitable porogenic solvent. After removing the molecular template, the resulting rigid three-dimensional cavity is complementary to the target analyte (Figure 2).

Selection of template

The MIPs are usually synthesized for a specific analytical use that implies the selection of a given template. As expected, the imprinting of the template itself can automatically leave a binding site that is tailored for the template. Suitable candidate templates should be chosen carefully in order to produce the highest number of well-defined binding sites. The criteria to consider when selecting a candidate template are its availability, its cost, and its chemical functionalities defining its ability to strongly interact with functional monomers (Pichon and Chapuis-Hugon 2008). In the non-covalent approach, the interactions are weak; thus, the candidate template should possess multiple functional sites for the purpose of increasing the strength of the template-functional monomer interactions. Ideally, those interactions should be strong so that the recognition mechanism after the synthesis of the MIPs could be enhanced.

Based on the non-covalent interaction in the synthesis of the PEEs-MIPs, the main considerations in the selection of template are the stability, the ability to establish hydrogen bonding, and the absence of polymerizable groups

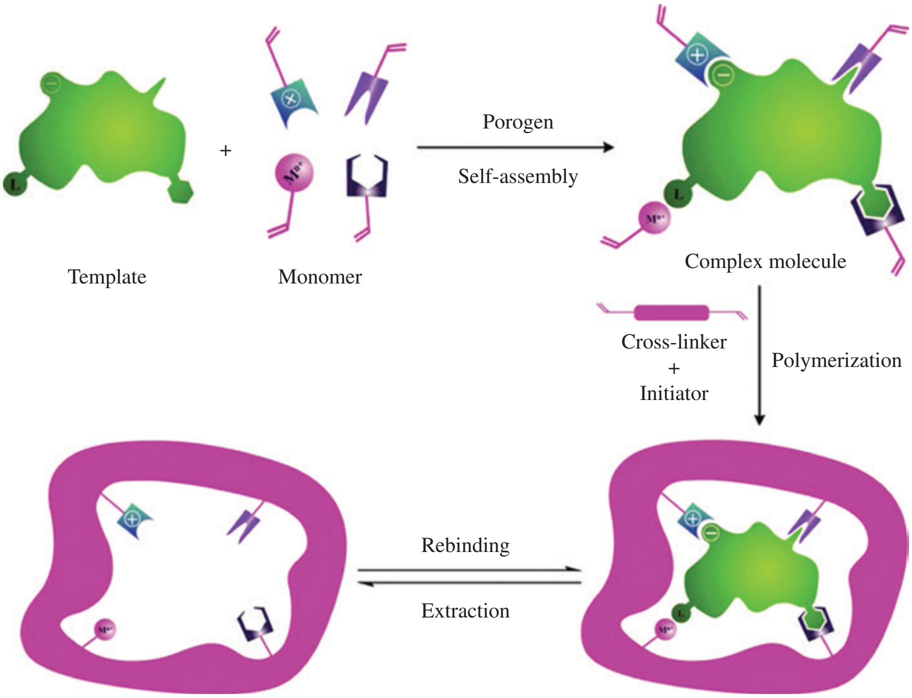

Figure 2: Schematic representation of the molecular imprinting process. This image was reproduced from Hu et al. (2013) with permission from Elsevier.

to avoid reaction with the newly free radicals (Figueiredo et al. 2016). In most cases the template is the target molecule that is to be selectively retained by the MIPs, and most of the PEEs-MIPs were synthesized using the same molecule as target and template. For example, Yang et al. (2015) prepared MIPs for selective SPE of eight bisphenols from human urine samples using BPA as template. For difficult-to-achieve template or considering the risks of template leakage during applications, a structural analog can be used as dummy template for the synthesis. This dummy template must resemble the target analyte in terms of size, shape, and functionalities. The resulting MIPs should have the ability to bind the target analyte. However, the dummy approach was not so explored in the considered studies involving MIPs and PEEs. An example is described by Li et al. that the dummy MIPs were synthesized by using tetrabromobisphenol A (TBBPA), whose structure was similar to that of BPA, as the dummy template. The resulting MIPs were evaluated and applied as a sorbent for SPE combined with high-performance liquid chromatography (HPLC) to detect BPA (Li et al. 2013).

Selection of other reagents

To make good MIPs, the selection of suitable functional monomers, cross-linkers, and porogen solvents requires careful consideration (Yu and Lai 2010, Wei et al. 2015). In most of the studies related to the synthesis of PEEs-MIPs for analytical applications, the non-covalent interaction is described (Table 1). In this case, the functional monomer is one of the most important factors, so as to allow the maximization of the template-functional monomer association determining effective molecular recognition. The studies on MIPs provide a detailed list of the functional monomers suitable for the approach (Mahony et al. 2005, Vasapollo et al. 2011), but 4-vinylpyridine (4-VP), methacrylic acid (MAA), and acrylicacid (AA) are the most common choices for synthesizing PEEs-MIPs. In addition, some novel functional monomers were successfully prepared and employed in the synthesis of MIPs selective to PEEs. Pan et al. successfully synthesized 3,4-ethylenedioxythiophene-gold nanoparticles (EDOT-Au) as functional monomers to prepared 4-Octylphenol (OP)-MIPs sensors. The resultant sensors presented high sensitivity, stability, and selectivity in the voltammetric determination of OP (Pan et al. 2015).

The choice of the cross-linker is also important to obtain selective MIPs, because the cross-linker is responsible for the stabilization of the morphology, the binding cavities, and the mechanical stability of the polymers, and the binding capacity of the polymers increases with the degree of cross-linker (Spivak 2005, Fang et al. 2011). Many reviews have highlighted the importance of providing lists of cross-linkers that are suitable for molecular

Table 1: MIPs studies on synthesis and application for PEEs.

PEEs	Analyte	Template	Functional monomer	Cross-linker	Porogen solvent	MIPs preparation technique	Analytical method	Sample	Limit of detection	References
Bisphenols	Eight bisphenols	BPA	4-VP	EGDMA	Toluene	Emulsion polymerization	SPE/HPLC	Urine	1.2–2.2 ng ml^{-1}	Yang et al. 2015
	BPA	TBBPA	4-VP	EGDMA	Toluene	Surface polymerization	SPE/HPLC	Water	3 ng ml^{-1}	Li et al. 2013
	Four bisphenols	DES	MAA	EGDMA	Acetonitrile	Surface polymerization	SPE/UPLC	Water, Milk	3.6–9.5 ng ml^{-1}	Xie et al. 2015b
	Three bisphenols	HES	AA	TRIM	Cyclohexanol, dodecanol	Bulk polymerization	HPLC	N.M.	N.M.	Tarbin and Sharman 2001
Alkylphenols	OP	OP	APTES	TEOS	Ethanol	Sol-gel	SPE/UPLC, Potentiometry	Water	0.019 ng ml^{-1}	Han et al. 2015
	NP	OP	4-VP	TEOS	Acetonitrile	Sol-gel	SPE/HPLC	Water	0.15 ng ml^{-1}	Rao et al. 2014
	OP	OP	EDOT-Au	N.M.	Acetonitrile	Electrochemical imprinting	Potentiometry	Water, Urine	0.001 μM	Pan et al. 2015
	NP	NP	AA	EGDMA	Ethanol	Surface polymerization	Fluorescence measurement	N.M.	N.M.	Han et al. 2014

APTES, (3-aminopropyl)triethoxysilane; N.M., not mentioned.

imprinting technology (Gong et al. 2008). Ethylene glycol dimethacrylate (EGDMA), divinylbenzene, and trimethylolpropane trimethacrylate (TRIM) are the most common cross-linkers for MIP preparation. When it comes to the synthesis of MIPs for the analysis of PEEs, EGDMA has been most used as a cross-linker. Tetraethoxysilane (TEOS) has also been significantly used, despite being exclusively suitable for the sol-gel process. Han et al. demonstrated that a multifunctional OP-MIP based on CdTe/CdS quantum dots (QDs), magnetic Fe_3O_4, and graphene oxide (GO) was prepared by sol-gel using TEOS as a cross-linker. The resultant MIPs presented high adsorption capacity and fast sensing rate for OP (Han et al. 2015).

The choice of porogen solvent is also one of the key factors determining effective molecular recognition (Zhang et al. 2009, Mu et al. 2011). An inappropriate selection of porogen solvent may lead to poor selectivity of the resultant MIPs. The ideal porogen solvents should have good dissolution for the template, strengthen the interaction between the template and the functional monomer, and produce large pores to obtain good flow-through property (Tan et al. 2012). MIPs are generally prepared using a moderately polar and aprotic solvent, such as toluene, chloroform, dichloromethane, and acetonitrile as porogen solvent. Therefore, strong polar interactions such as electrostatic interactions and hydrogen bonds for template can take place in these organic media (Pichon and Chapuis-Hugon 2008). Toluene and acetonitrile have been most used as porogen solvent for PEEs-MIPs prepared. A mixture of good and poor solvents with proper ratios is always adopted to tune solubility, polarity, and the ability to generate pores to a satisfactory degree. Tarbin and Sharman (2001) prepared Hexestrol (HES)-MIPs for application in the trace residue analysis area using the mixture solvents of cyclohexanol and dodecanol as porogen solvent.

Polymerization protocol

Different methods of polymerization have been used to obtain MIPs. Conventionally, MIPs are prepared by the traditional free radical polymerization. In this approach, all species, template, functional monomer, cross-linker, and radical initiator are dissolved in the porogen solvent. Prior to the polymerization, the mixture is filled with nitrogen to remove oxygen whose presence can retard polymerization (Hu et al. 2013). Among the free radical polymerization, the bulk polymerization is the most widely used procedure owing to its simplicity. Using this procedure, the polymer monolith must be crushed, ground, and sieved to obtain useful particles mainly in the 10–25 μm range. However, despite the reliability and simplicity of this method, particles with irregular shape and size are significant drawbacks associated with the bulk technique (Pichon and Haupt 2006). The resultant particles therefore invariably have a heterogeneous size distribution with poor binding-site accessibility for the target analyte.

As alternative to bulk polymerization, several other radical polymerizations have been developed to better control particles size and porosity (e.g. suspension, multistep swilling, and precipitation polymerization). The surface imprinted technique, grafting a thin imprinting layer on the surface of a supporting substrate (e.g. silica particle, polymer supports, and magnetic nanoparticles), is another useful way to improve the MIP preparation. The resultant polymers reveal high binding capacities, fast mass transfer, and rapid binding kinetics due to the easy accessibility to recognition sites and the homogeneous distribution of binding sites (Jiang et al. 2015). Recently, grafting an imprinting layer onto the surface of nanoparticles to increase the interfacial surface area has attracted a great deal of attention. Xie et al. prepared the Diethylstilbestrol (DES)-MIPs by a surface imprinting strategy using magnetic nanoparticles as supporter. The obtained MIPs exhibited not only outstanding magnetic property but also high adsorption capacity and selectivity for four EDCs (Xie et al. 2016).

In the recent years, controlled/living radical polymerization (CLRP) has shown great potential to synthesize nanostructured films with well-controlled molecular weight and composition (Fischer 2001, Chen et al. 2011). Benefiting from the negligible chain termination and slower rate, the CLRP can overcome the intrinsic limitations of the traditional free radical polymerization (Bompart and Haupt 2009, Hu et al. 2012). Due to its versatility and simplicity, reversible addition-fragmentation chain transfer (RAFT) polymerization is an ideal candidate for the CLRP method, where a wide range of functional monomers can be employed and the use of transition metal catalysts can be avoided (Moraes et al. 2013). With its controlled/living property of RAFT polymerization, the well-defined MIP layer can be easily introduced on the surface of support and thus significantly facilitates the applications in complicated samples (Li et al. 2010b, He et al. 2014). Recently, MIPs with different formats have been successfully synthesized via RAFT polymerization. Chen et al. demonstrated that the novel DES-MIPs with a homogeneous molecularly imprinted shell were successfully synthesized by surface-initiated RAFT polymerization. This material reveals high potential for the efficient enrichment of EDCs from complicated matrices (Chen et al. 2015).

Some other methods have also been introduced to prepare MIPs. In the sol-gel process, MIPs are prepared by the hydrolysis and polycondensation of silane-based functional monomers such as tetramethoxysilane or TEOS, which form highly cross-linked silica materials. Unlike the method of radical polymerizations, the sol-gel process can be performed in aqueous media under a mild thermal condition (Dai et al. 2014, Rezaei et al. 2014). The resultant MIPs are thermally stable, structurally porous, and extremely rigid, due to the high degree of cross-linking. Rao et al. (2014) prepared dummy OP-MIPs based on multi-walled carbon nanotubes (CNTs) by a sol-gel technique, which were applied to rapidly separate and detect trace 4-Nonylphenol (NP) residues in environmental water samples with high selectivity and sufficient adsorption capacity. Electrochemical imprinting is also an appealing way to prepare MIPs as it is simple, fast, and easy controlled. Pyrrole and phenylenediamine easily form polymer; therefore they are usually used as functional monomers for electrochemical imprinting. For example, Long et al. demonstrated that a novel molecularly imprinted electrochemical sensor was developed for OP determination using cobalt-nickel bimetallic nanoparticles decorated graphene as a sensitized element to modify the carbon electrode. This proposed sensor showed excellent sensitivity and selectivity toward OP in the real sample (Long et al. 2015).

Applications of MIPs in the analysis of PEEs

Due to the favorable molecular recognition capabilities and stability, MIPs become an efficient method for selective recognition, separation, determination, and purification of PEEs in complicated matrixes. As selective tools, MIPs have been already successfully used in several analytical fields such as SPE, sensors, and chromatograph. When it comes to the application of MIPs in the analysis of PEEs, it can be mainly divided into two aspects: (i) using MIPs as a kind of effective SPE sorbent for purification of PEEs and (ii) applying a MIP-based sensor to recognize and directly quantify PEEs.

Nanomaterial MIPs as sorbent for SPE

Over the years SPE has been widely employed for the isolation and preconcentration of target analyses, due to its simplicity and versatility. The widespread application of MIPs as SPE sorbents (MISPE) has attracted many researchers' attention (Hu et al. 2013, Wackerlig and Schirhagl 2016). In MISPE, the sorbent exhibits high selectivity toward the template and its structural analogs, resulting in the desired compounds being extracted from complicated matrixes while other compounds are not retained. Now, there have been numerous original papers on MISPE applications in the analysis of PEEs. Conventional MISPE sorbents present some limitations such as slow mass transfer or incomplete template removal which negatively affects the number of available sites for rebinding. New initiatives to overcome those limitations have been reported such as the combination of the imprinting technique with nanomaterials (NMs) for faster rebinding kinetics and higher binding capacity. NMs are able to play prominent roles to improve the sensitivity, increase the analytical throughput, and simplify the analytical procedures, but there still are some challenges associated with the application of NMs. First, the novel properties of NMs are a two-edged sword. The same properties that generate exciting benefits in use may also pose significant adverse health effects. Second, more efforts should be made to explore further the potential of NMs in the analysis of complex samples. Finally, the technology of synthesis is still an obstacle hindering the wide application of NMs (Liu et al. 2014).

With the development of MISPE, a technique based on magnetic particles has received increasing attention (Figure 3) (Xie et al. 2015a, Gao et al. 2016). The MISPE sorbent can not only easily isolate samples using an external magnet to replace the centrifugation and filtration steps in a convenient and economical way, but also display higher adsorption ability and excellent recognition selectivity. Co-precipitation is the easiest way to synthesize Fe_3O_4 magnetic nanoparticles by adding a base to aqueous Fe^{2+}/Fe^{3+} salt solutions under nitrogen atmosphere and vigorous stirring. Then, the magnetic nanoparticles are usually protected by a coating (e.g. silica, surfactant, metal, polymer and carbon) to prevent oxidation by oxygen. Among these coatings, silica coating is especially interesting because it is easy to prepare (e.g. using the sol-gel process) and is favorable for further functionalization. Hiratsuka et al. (2013) demonstrated that magnetic MIPs for BPA and its structural analogs, which have both magnetic and molecular recognition properties, had been developed for magnetic MISPE of BPA in river water samples.

Carbon NMs comprise a number of allotropes. Among them, CNTs and graphene have been widely used in preparation of MIPs due to their large surface area, excellent electrical and optical properties, and good chemical/physical stability (Prasad and Singh 2015, Zhai et al. 2015). CNTs can be prepared by various methods, such as chemical vapor deposition (CVD), arc discharge, and high-pressure carbon monoxide disproportionation. Some of them are also used for graphene (e.g. CVD and arc discharge). Moreover, graphene can be exfoliated to GO by harsh oxidation and sonication, followed by reduction of the GO to the parent graphene state. Notably, GO is highly soluble in water and possesses a large number of functional groups (e.g. carboxyl and hydroxyl) (Liu et al. 2014). Zhang et al. prepared novel magnetic CNTs-MIPs for the selective extraction of BPA. Combined with HPLC detection, the MIPs were successfully applied as adsorption materials for magnetic extraction and determination of BPA in environmental water samples (Figure 4) (Zhang et al. 2014). Han et al. (2015) prepared magnetic GO-based MIPs for selectivity recognition and separation of DES, which possessed excellent adsorption capacity and outstanding selectivity for DES.

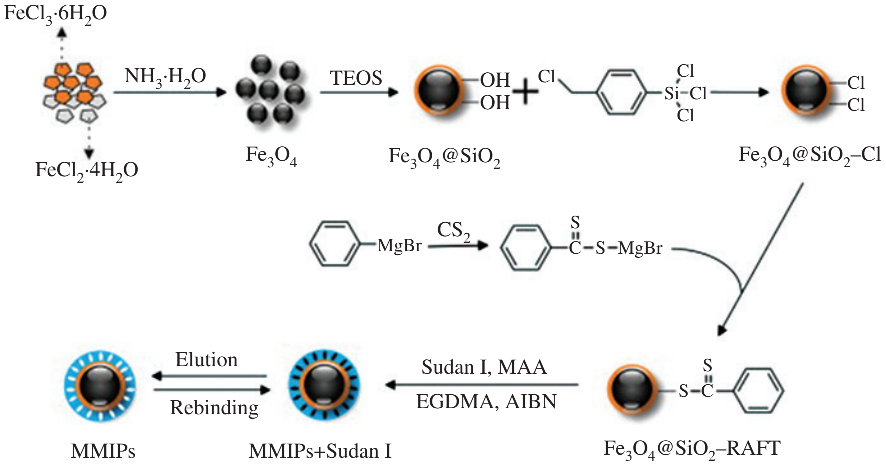

Figure 3: The synthetic strategy for MIPs based on magnetic particles. This figure was reprinted from Xie et al. (2015) with permission from Elsevier.

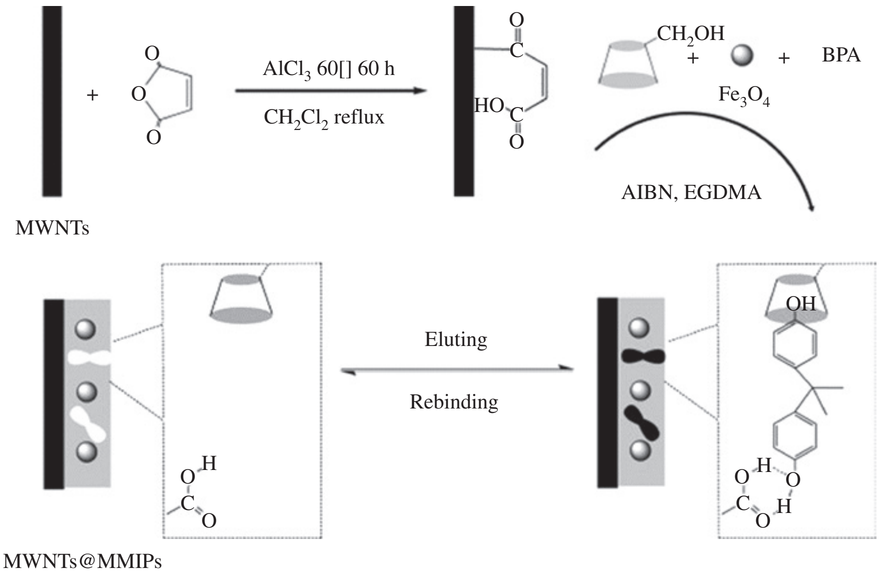

Figure 4: The protocol for synthesis of MIPs based on multiwalled CNTs. This figure was reproduced from Zhang et al. (2014) with permission from Elsevier.

MIPs as electrochemical sensors

Electrochemical sensors are widely employed for their high sensitivity and simplicity, which consists of an electrochemical transducer (chemically modified electrode) coated with a chemical or biochemical film as conducting material (Lawal 2016). PEEs are a class of electrochemically active molecules due to phenolic groups, but the direct determination is difficult because of the weak response of PEEs in conventional electrochemical sensors. Hence, further efforts have been tried to increase the surface area of the electrode to enhance oxidation signals. MIPs have been used as recognition elements in the design of sensors due to their higher thermal stability, selectivity, and reusability, which show advantages such as low cost of manufacture, extended lifetime, easy storage, and the capacity of being applied in critical conditions. However, in most cases electrochemical sensors are still not sufficient for practical applications in routine analysis to compete with reported separation methods, and commercial exploitation of molecular imprinting is still in its infancy. Furthermore, MIPs cannot yet provide a total replacement for biological molecules in terms of capacity, selectivity, and homogeneity of binding affinity (Tiwari and Prasad 2015).

Numerous MIP sensors have been developed for the detection of PEEs. The association of the MIPs with the transducer can be achieved in different ways: *in situ* electropolymerization, surface coating, chemical coupling of the MIPs, physical entrapment of MIP particles into gel or membrane, etc. (Suryanarayanan et al. 2010). As an example, Zhang et al. developed a $[Ru(bpy)_3]^{2+}$-mediated photoelectrochemical sensor for BPA detection using a MIPs-modified SnO_2 electrode. The MIP membrane was assembled on the electrode by a convenient electropolymerization method. This sensor is highly sensitive, selective, and of low cost, and can be theoretically extended to the analysis of organic molecules that can be photoelectrochemically oxidized by Ru^{3+} (Figure 5) (Zhang et al. 2015).

Integration of NMs into electrochemical MIP sensors can often dramatically improve the analytical performance. The NMs can enlarge the surface area of the electrode, accelerate electron transfer, adsorb the target pollutants, immobilize bio-active molecules, and serve as electrochemical probes (Li et al. 2010a). Generally, CNTs are applied in electrochemical MIP sensing of PEEs. Chen

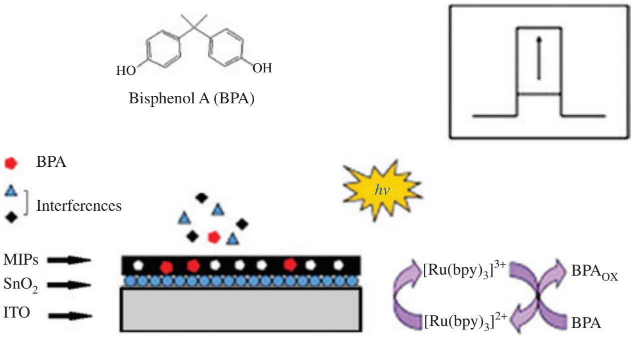

Figure 5: Schematic diagram of MIPs based on photoelectrochemical sensor. This figure was reprinted from Zhang et al. (2015) with permission from Elsevier.

et al. reported a novel electrochemical sensor for BPA through the combination of the MIPs with the multi-walled CNT paste electrode. The imprinted sensor for BPA exhibited good selectivity, stability, and reproducibility and was successfully used for the determination of BPA in real water samples (Chen et al. 2014). Graphene has also been employed in electrochemical MIP sensing of PEEs. Zhang et al. synthesized magnetic-GO MIP composite, which was used as a new electrode matrix for BPA measurement. The electrochemical sensor shows good sensitivity, selectivity, and reproducibility and proved to be an accurate and reliable method due to the determination of BPA in real samples with satisfactory results (Zhang et al. 2013).

Other applications

Besides the applications mentioned above, MIPs have also been applied in some other techniques to facilitate the analysis of PEEs. In QDs, combining the high selectivity of molecular imprinting technology and excellent fluorescent characteristics of QDs could develop a new method for target analyte recognition (Huang et al. 2015). The QDs-encapsulated molecularly imprinted mesoporous silica nanoparticle was widely used for the recognition of PEEs (Kim et al. 2012). MIPs-solid-phase microextraction has also been widely applied to the analysis of PEEs (Tan et al. 2009), which integrates sampling, extraction, concentration, and injection into one single step, and is simple, time efficient, and solvent free. The stir bars coated with MIP films could selectively extract PEEs from complicated matrixes (Zhan et al. 2012). Compared with the ordinary stir bars, MIP-coated stir bars showed better selectivity and higher enrichment capability.

Conclusion and future outlook

PEEs are a class of typical EDCs. The harm to the environment, human, and ecology has drawn extensive societal, scientific, and political attention. Due to their low concentration and complicated matrixes, methods with a high selectivity are in high demand. More recently MIPs, featuring high specificity, good stability, ease of preparation, and low cost, have become an alternative to the existing methods for the analysis of PEEs.

This review is the first comprehensive report focusing on the applications of molecular imprinting technology for the analysis and monitoring of PEEs from complicated matrixes. In this review, we discussed the choices of template, functional monomer, cross-linker, and porogen solvent during the synthesis of PEEs-MIPs. Different methods of polymerization have been used to obtain MIPs. We introduced the common methods in the preparation of PEEs-MIPs, including traditional free radical polymerization, RAFT polymerization, sol-gel process, and electrochemical imprinting. When it comes to the application of MIPs in the analysis of PEEs, our focus is mainly on the following two aspects: (i) combination of imprinting technique with NMs for faster rebinding kinetics and higher binding capacity, including magnetic particles, CNTs, and graphene, and (ii) applying highly sensitive, selective, and low cost MIP sensors for the detection of PEEs.

To conclude, from our point of view, all these works have increased the expectation for a future application of MIPs on the analysis of PEEs. New methodologies and application of NM for the preparation of MIPs have been studied so that the limitations such as low mass transfer, template leakage, and reduced water compatibility could be overcome. Although there is still a long way to go and many challenges lie ahead, we remain positive about the future potential of MIPs as selective adsorbents for the analysis and monitoring of PEEs as well as a wide variety of other applications.

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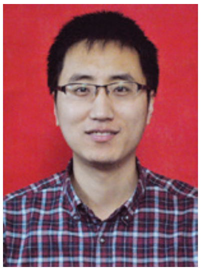

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