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A norepinephrine coated magnetic molecularly imprinted polymer for simultaneous multiple chiral recognition

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ABSTRACT

A newly designed molecularly imprinted polymer (MIP) material was developed and successfully used as recognition element for enantioselective recognition by microchip electrophoresis. In this work, molecularly imprinted polymers were facilely prepared employing Fe_3O_4 nanoparticles (NPs) as the supporting substrate and norepinephrine as the functional monomer in the presence of template molecule in a weak alkaline solution. After extracting the embedded template molecules, the produced imprinted Fe_3O_4@polynorepinephrine (MIP–Fe_3O_4@PNE) NPs have cavities complementary to three dimensional shape of template molecules favoring high binding capacity and magnetism property for easy manipulation. The MIP–Fe_3O_4@PNE NPs prepared with L-tryptophan, L-valine, L-threonine, Gly-L-Phe, S-(−)-ofloxacin or S-(−)-binaphthol as template molecules were packed in the polydimethylsiloxane microchannel via magnetic field as novel stationary phase to successful enantioseparation of corresponding target analysts. The MIP–Fe_3O_4@PNE NPs-based microchip electrophoresis system exhibited strong recognition ability, excellent high-performance, admirable reproducibility and stability, which provided a powerful protocol for separation enantiomers within a short analytical time and opened up an avenue for multiplex chiral compound assay in various systems.

1. Introduction

Molecular imprinting technology has become a well-known means for a versatile and facile method for the preparation of tailor-made materials possessing predetermined recognition for target molecules (templates). The complex compounds are formed in situ by co-polymerizing functional monomer and cross-linking agent in the presence of template molecules. Subsequent removal of the template leaves binding sites, which are complementary in sites, shape, size, and function of the template with affinities and specificities comparable to those of natural receptors [1]. The resultant materials provide the desirable properties for highly selective molecular recognition, such as durability, specificity, stability at extreme conditions, ease of mass production and low cost [2], and thus have been widely applied in separation science [3–5], biotechnology [6–8], chemsensing [9–12], analytical chemistry [13,14], catalysis [15,16] and drug delivery [17–19]. One of the most extensive applications of molecularly imprinted polymers (MIPs) is as chiral stationary phase for the separation of enantiomers in high-performance liquid chromatography (HPLC) [20] and capillary electrochromatography (CEC) [21].

Traditionally, MIP has mainly been prepared by bulk polymerization, precipitation polymerization, suspension polymerization and multistep swelling polymerization methods [22]. Common protocols for molecular imprinting technology are based on one of three distinct approaches: the covalent approach, the non-covalent approach and semi-covalent approach [23]. The covalent approach, introduced by Wulff and Vesper, involved the formation of reversible covalent bonds between the functional monomer and template molecules before polymerization [24]. The high stability of interaction between the functional monomer and template molecules produced a rather homogenous population of binding sites, which were maximized the elimination of non-specific sites. However, this approach was rather restrictive since it was full of challenges to design an appropriate template–monomer complex in which covalent bond formation and cleavage are readily reversible under mild conditions. The other was the non-covalent approach, which was implemented by Mosbach and co-workers [25], and based on the formation of relatively weak non-covalent interactions (such as hydrogen bondings and ionic interactions) between template molecules and functional monomers before polymerization. This approach was by far the most used for the preparation of complex, due to its experimental simplicity and

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the commercial availability of different monomers able to interact with almost any kind of template. Unfortunately, it was not free of some drawbacks derived from the fact that the template–monomer interactions are governed by an equilibrium process [23]. The excess of functional monomers needed to achieve appreciable levels of template–functional monomer complexation leads to random incorporation of interactive functional groups outside the imprinted cavities, giving rise to nonspecific interactions [26]. Efforts to combine the attractive features of covalent and noncovalent imprinting procedures have led to the development of hybrid technologies, known as the semi-covalent approach [27]. The strategy employed covalent template–monomer complexes in the imprinting step but entirely noncovalent interactions for binding. So serve as a contrast to these approaches, molecularly imprinted technique has become a powerful tool for the preparation of polymeric materials with special recognition capacity, and recently, combining surface imprinting with nanomaterials became an effective solution to solve the above-mentioned problems and to achieve excellent performances [28]. Many nanomaterials have been used as supports in surface imprinting process, such as graphene [2], quantum dots [29], Fe_3O_4 [30], TiO_2/WO_3 [31], and so on. Among them, Fe_3O_4 particles, due to high performance in function-specific biological applications, smooth surfaces, narrow size distributions, large surface areas (for maximal template molecules binding), high magnetic saturation to provide maximum signal, and good dispersion in liquid media, have gained wide attraction. Once Fe_3O_4 particles are encapsulated inside MIPs, the resulting polymer material will be easily collected and isolated by an external magnetic field without additional centrifugation or filtration. Magnetic MIPs have become a hotspot based on the significant advantages of magnetic separation over conventional methods [32,33]. Generally, preparation of magnetic MIPs involves the steps of surface modification of magnetic nanoparticles with tetraethoxysilane, oleic acid, ethylene glycol or poly(vinyl alcohol) by a sol–gel process or free radical polymerization to favor surface polymerization and MIPs layer coating. However, the preparation procedure is very complicated since treatment of the support matrix is required. Thus, the development of simple and general protocol to synthesize magnetic MIPs is still highly desired.

Inspired by the high content of 3,4-dihydroxy-L-phenylalanine and lysine found in the specialized mussel adhesive protein Mefp-5 (Mytilus edulis foot protein-5), which is predominantly located at the interface between the adhesive pad and substrate in byssal attachments [34], a material-independent surface functionalization strategy involving self-polymerization of dopamine to form chemically active adherent films on virtually any material surfaces including noble metals, oxides, polymers, semiconductors, and ceramics has been developed [35,36]. By further combining the merits of surface-imprinted nanotechnology, the preparation of imprinted nanoparticles using dopamine as monomer at the surface of superparamagnetic nanospheres has been reported [37–41]. Despite the advantage of its material-independent functionalization ability, the uncontrollable surface roughness after polydopamine (PDA) coating has been an obstacle for potential applications. In an effort to further increase the versatility of this strategy, oxidative polymerization of norepinephrine, a derivative of dopamine, under alkaline conditions has been studied [42,43]. Norepinephrine not only shares the material-independent coating-forming properties of dopamine [44,45], but also can support secondary derivatization of surfaces like dopamine [46–49]. However, unlike PDA coatings, coatings derived from norepinephrine have the strong ability to activate surface-initiated, ring-opening polymerization due to the presence of the alkyl hydroxyl group in norepinephrine [43]. Due to chemical structural characteristics of norepinephrine, the hydroxy group that is linked to the aliphatic carbon atom beside the catechol enhances the hydrophilicity

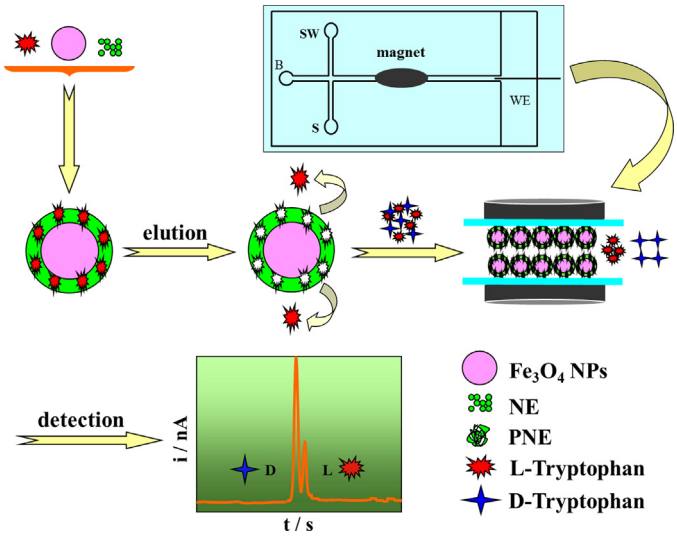

Fig. 1. Schematic illustration of the synthetic chemistry for MIP–Fe_3O_4@PNE NPs preparation and the enantioseparation on MIP–Fe_3O_4@PNE NPs-packed microchannel.

of the functionalized surfaces, thus producing a well-controlled, ultrasmooth coating on the nanometer scale [42]. Besides the polydopamine and poly(norepinephrine) coatings, the mussel-inspired surface chemistry has been widely implemented for various purposes. However, the use of Fe_3O_4@PNE NPs-based stationary phase for enantioseparation of enantiomers in microchip electrophoresis has not been reported as far as we know.

Inspired by above breakthrough, we firstly combined the merits of magnetic surface imprinted nanotechnology and the self-polymerization of functional monomer norepinephrine to prepare MIP–Fe_3O_4@PNE NPs as a novel stationary phase of microchip electrophoresis for rapid and multiple enantioseparation. As shown in Fig. 1, by simply mechanically stirring Fe_3O_4 NPs in a weak alkaline solution of norepinephrine containing template molecules, a thin adherent PNE film imprinted with template molecule was spontaneously obtained on the surface of Fe_3O_4 NPs to produce the MIP–Fe_3O_4@PNE NPs composite materials. After extracting the embedded template molecules, leaving behind cavities complementary to the three dimensional shape of template molecules, it had high rebinding capacity and specific recognition ability toward template molecule. Then, the prepared MIP–Fe_3O_4@PNE NPs were coated into PDMS microchannels in the presence of extra magnets and then evaluated the recognition properties of the novel stationary phase by microchip electrophoresis. By using L-tryptophan, L-valine, L-threonine, Gly-L-Phe, S-(−)-ofloxacin or S-(−)-binaphthol as template molecules, D- and L-tryptophan, D- and L-valine, D- and L-threonine, Gly-D-Phe and Gly-L-Phe, R-(+)- and S-(−)-ofloxacin, or R-(+)- and S-(−)-binaphthol were successfully separated on the corresponding MIP–Fe_3O_4@PNE NPs-packed microchips. More importantly, using the mixture of singly MIP–Fe_3O_4@PNE NPs with corresponding template molecule imprinting as stationary phase, simultaneous enantioseparations of different kinds of chiral samples can also be achieved in a single run, further demonstrating the capability of the designed microchip electrophoresis system for high-speed chiral separations and multiplex analysis.

2. Materials and methods

Chemicals and characterization were presented in supplementary material.