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Full Length Article

Novel smart chiral magnetic microspheres for enantioselective adsorption of tryptophan enantiomers

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ABSTRACT

Multifunctional microspheres simultaneously possessing chirality, magnetism and thermosensitivity show great potentials in direct enantiomeric separation. Herein we report a novel type of smart chiral magnetic microspheres with core/shell/shell structures (Fe_3O_4@SiO_2@PNCD) and its application in enantioselective adsorption of tryptophan (Trp) enantiomers. The prepared Fe_3O_4@SiO_2@PNCD are composed of a Fe_3O_4 nanoparticle core, an acidic-resistant SiO_2 middle shell and a thermosensitive microgel functional shell (PNCD). The PNCD plays an important role in the enantioselective adsorption of Trp enantiomers. The β-cyclodextrin (β-CD) molecules on the PNCD act as smart receptors or chiral selectors, and can selectively recognize and bind *L*-Trp enantiomers into their cavities by forming host-guest inclusion complexes. The poly(*N*-isopropylacrylamide) (PNIPAM) chains on the PNCD serve as microenvironmental adjustors for the association constants of β-CD/*L*-Trp complexes. The fabricated Fe_3O_4@SiO_2@PNCD demonstrate fascinating temperature-responsive chiral recognition and adsorption selectivity toward Trp enantiomers. Most importantly, the desorption of Trp enantiomers and the regeneration of the Fe_3O_4@SiO_2@PNCD can be easily achieved *via* simply changing the operation temperature. Moreover, the regenerated Fe_3O_4@SiO_2@PNCD can be readily recovered from the amino acids enantiomeric solution under an external magnetic field for reuse. The present study provides a novel strategy for the direct enantioselective adsorption and separation of various enantiomeric compounds.

1. Introduction

Amino acids (AAs) are basic molecular units of peptides and proteins, which play critical roles in life science and many other related fields [1–3]. Except for glycine, AAs exist as two different stereoisomers (*D*-form and *L*-form) arising from the chiral center on their α carbon, and the both two isomers often exhibit significantly disparate biological and physiological activities [2,3]. For example, *L*-tryptophan (*L*-Trp) is an essential and important constituent of proteins and a precursor of the neurotransmitter serotonin. The level of *L*-Trp in plasma is closely related to the extent of hepatic disease [4,5]. Moreover, *L*-Trp is indispensable in the growth and metabolism of human beings and animals, and the unbalance or deficiency of *L*-Trp in body may cause several chronic diseases [6,7]. *D*-tryptophan (*D*-Trp), as a nonprotein AA, does not participate the metabolism pathways of a living system, but it is an important intermediate to generate synthetic peptide antibiotics and immunosuppressive agents in pharmaceutical industry [8]. Therefore, it is of vital importance to have effective chiral recognition and enantiomeric separation of AAs enantiomers. Chromatographic and electromigration techniques are the most conventional methods for the chiral recognition and enantiomeric separation of AAs enantiomers [9–12]. However, those approaches usually require expensive instruments and laborious sample pretreatments as well as complicated derivatization procedures [13,14], thus which has limited their wide applications to some extent. By contrast, direct enantioselective adsorption by multifunctional materials seems to be effective for the chiral recognition and enantiomeric separation of AAs enantiomers [13–25].

Core-shell structured magnetic microspheres consisting of a magnetite core (typical Fe_3O_4 nanoparticles (NPs)) and an inorganic/organic functional shell have attracted widespread attention during the past several decades because of their unique properties, such as superparamagnetism, good stability, biological safety, and chemically modifiable surface. These dramatic features make them hold great promise in many fields, such as catalysts, tar-

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geted drug delivery, enzyme immobilization, biological or chemical separations, environmental remediations, and so on [26–37]. Core-shell structured chiral magnetic microspheres that simultaneously possess chirality and magnetism, as a newly emerging type of multifunctional materials, have recently aroused considerable interest and undergone extensive investigations due to their fascinating application potentials in enantioselective adsorption and separations of various chiral compounds [13–22,38]. A variety of chiral selectors, such as cellulose derivatives [13,38], macrocyclic antibiotic [14], β-cyclodextrin (β-CD) [15–19], proteins [20,21], chiral crown ethers [36], helical polymers [39,40] and hemoglobin [41], have been utilized for the surface modification of silica or zirconia-coated Fe_3O_4 NPs, thus resulting in the core-shell structured chiral magnetic micropsheres. These chiral magnetic microspheres have been proved to be effective for the enantioselective adsorption and separation of various AAs and other chiral compounds [13–22,38]. However, the desorption of AAs enantiomers and the regeneration of chiral magnetic microspheres require usage of organic solvents or high-concentration salt solution *via* repeated ultrasonication treatment [13,14,17,20,21,38]. Therefore, those operational processes seem to be complex and environmentally-unfriendly.

Poly(*N*-isopropylacrylamide) (PNIPAM) is an well-known thermosensitive polymer able to undergo volume phase transition across the lower critical solution temperature (LCST) of about 32 °C. At a temperature below the LCST, PNIPAM is hydrophilic and exhibits a swollen state and above the LCST, it precipitates out of the aqueous solution thus becoming hydrophobic [42,43]. β-CD, a cyclic oligosaccharide consisting of seven *D*-glucose units, possess a hydrophobic internal cavity and a hydrophilic exterior. The unique structure of β-CD molecules enables them with the ability to selectively bind various chiral molecules into their cavities by forming host-guest inclusion complexes through a variety of intermolecular interactions, such as hydrophobic interaction, van der Waals force, electrostatic affinity and hydrogen bonding, thus demonstrating excellent chiral recognition and high enantioselectivity toward numerous chiral molecules [1,9]. As an effective chiral selector, *b*-CD has been widely used for the chiral recognition and enantiomeric separation of various kinds of AAs enantiomers [9,15–19,25]. Furthermore, incorporation of *b*-CD molecules into PNIPAM polymer chains allows the fabrication of an intelligent polymer system (PNIPAM-*b*-CD), and the fabricated PNIPAM-*b*-CD simultaneously possesses chirality and thermosensitivity. Importantly, the thermosensitive phase transition of PNIPAM chains responding to a temperature change can dramatically affect the association constants of *b*-CD and the included guest molecules in the PNIPAM-*b*-CD [44,45]. Inspired by this fact, we recently developed a novel type of smart chiral magnetic microspheres (Fe_3O_4@PNG-CD) through combining surface-initiated atom transfer free radical polymerization (SI-ATRP) and ring-opening reaction [46]. The prepared Fe_3O_4@PNG-CD exhibit excellent enantioselective adsorption abilities toward Trp enantiomers, and can be used for the direct enantioselective adsorption and separation of AAs enantiomers. Most importantly, the desorption of Trp enantiomers and the regeneration of Fe_3O_4@PNG-CD can be easily achieved *via* simply changing the operation temperature [46]. Therefore, the problems of operation complexity and environmental unfriendliness associated with the conventional chiral magnetic microspheres when used for the direct enantioselective adsorption and separation of AAs enantiomers can be well addressed. However, the preparation of Fe_3O_4@PNG-CD involves a multistep reaction process and requires usage of highly toxic chemicals (such as 2-bromoisobutyrylbromide, *p*-toluenesulfonyl chloride and 2,2′-bipyridine). Moreover, the synthesized Fe_3O_4@PNG-CD are strongly susceptible to acids due to an absence of a protective functional layer between the magnetic core and the organic functional layer [46]. All those disadvantages of Fe_3O_4@PNG-CD are undesirable for their wide applications.

To improve the chemical stability of Fe_3O_4@PNG-CD and expand their practical applications, we developed another novel type of smart chiral magnetic microspheres (Fe_3O_4@SiO_2@PNCD) through a simple and environmentally-friendly seeded emulsion polymerization method in this work. The prepared Fe_3O_4@SiO_2@PNCD have core/shell/shell structures and are composed of a Fe_3O_4 NP core, an acidic-resistant SiO_2 middle shell and a thermosensitive microgel functional shell outside the SiO_2 layer. The Fe_3O_4 NP core affords the Fe_3O_4@SiO_2@PNCD with a convenient magnetic separability from the AAs racematic solutions under an external magnetic field. The SiO_2 middle shell can effectively shield the magnetic Fe_3O_4 NP core against possible erosion by some acids, which is extremely important for their practical applications in acidic surroundings. The organic functional shell is constructed from a PNIPAM-based thermosensitive microgel with a large amount of pendent *b*-CD molecules (poly(NIPAM-*co*-MAH-β-CD), PNCD), which play an important role in the chiral recognition and enantioselective adsorption of AAs enantiomers. The *b*-CD molecules on the PNCD act as smart receptors or chiral selectors, and can selectively recognize and bind numerous AAs enantiomers into their cavities by forming host-guest inclusion complexes. The PNIPAM chains on the PNCD serve as microenvironmental adjustors for the association constants of β-CD/AAs complexes.

The direct enantioselective adsorption of AAs enantiomers by the Fe_3O_4@SiO_2@PNCD smart chiral magnetic microspheres is demonstrated in Scheme 1. At a temperature T_1, lower than the volume phase transition temperature (VPTT) of PNCD, the association constant of β-CD and the recognized enantiomer molecules is large since the PNIPAM chains on the PNCD are swollen and hydrophilic [44,45]. As a result, one of the two enantiomers (such as *L*-form) is trapped into the cavities of β-CD due to the chiral recognition of β-CD molecules toward the *L*-enantiomers, while the other one is remained in the AAs enantiomeric solution (Scheme 1A). As the β-CD/*L*-enantiomer complexes reach equilibrium on the Fe_3O_4@SiO_2@PNCD, the enantiomers loaded Fe_3O_4@SiO_2@PNCD (such as *L*-form) can be conveniently separated from the other enantiomers (*D*-form) under an external magnetic field (Scheme 1B). When the operation temperature is raised to T_2, higher than the VPTT of PNCD, the PNCD is triggered to shrink. As a result, the bound *L*-enantiomers are desorbed from the Fe_3O_4@SiO_2@PNCD due to the reduction of association constant for collecting the separated enantiomers [44,45], and the regeneration of Fe_3O_4@SiO_2@PNCD is achieved (Scheme 1C). After that, the regenerated Fe_3O_4@SiO_2@PNCD can be further collected for recycle through applying an external magnetic field (Scheme 1D).

2. Experimental

2.1. Chemicals

N-Isopropylacrylamide (NIPAM) was bought from Tokyo Chemicals (Tokyo, Japan) and used after recrystallization with a mixture of hexane/acetone (v/v, 50/50). Maleic anhydride modified β-CD monomer (MAH-β-CD) was synthesized according to a previous report [47]. Poly (4-styrenesulfonic acid-*co*-maleic acid, SS: MA = 3:1) sodium salt (PSSMA, MW = 20,000), γ-methacryloxypropyltrimethoxysilane (MPS), sodium acetate trihydrate (NaAc), *DL*-Trp, *D*-Trp, *L*-Trp and *L*-phenylalanine (*L*-Phe) were purchased from Aladdin Chemicals (Beijing, China). Ferric chloride hexahydrate ($FeCl_3 \times 6H_2O$), tetraethyl orthosilicate (TEOS), potassium persulfate (KPS) and *N*,*N*′-methylenebisacrylamide (MBA) were obtained from Kelong Chemicals (Chengdu, China). All other chemicals were used as