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Fabrication of functional block copolymer grafted superparamagnetic nanoparticles for targeted and controlled drug delivery

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ABSTRACT

The functional block copolymer (poly(hydroyethyl acrylate-b-N-isopropylacrylamide), P(HEA-b-NIPAm)) grafted Fe_3O_4 nanoparticles (Fe_3O_4@P(HEA-b-NIPAm)) with temperature-responsive poly(N-isopropylacrylamide) (PNIPAm) as the skin layer were designed via the consecutive surface-initiated atom transfer radical polymerization (SI-ATRP) from the surfaces of the superparamagnetic Fe_3O_4 nanoparticles. The targeted functional and temperature-sensitive nanoparticles were characterized by the FT-IR, XPS, TEM, VSM, and DLS techniques. It is expected that the multi-functional nanoparticles could be used for the targeted and controlled drug delivery.

1. Introduction

In the last decades, more and more investigations with several types of iron oxides have been carried out in the field of nanosized magnetic particles (mostly maghemite, γ-Fe_2O_3 or magnetite, Fe_3O_4 single domains of about 5–20 nm in diameter), among which magnetite is the most promising candidate since its biocompatibility has already been proved [1]. Although these magnetic nanoparticles have been successfully used as magnetic resonance imaging (MRI) contrast agents and in hyperthermic treatment for cancer cells [2–4], their application in targeted and controlled drug delivery has been limited because that the pristine iron oxide magnetic nanoparticles cannot be loaded with drugs. Therefore, the incorporation of magnetic nanoparticles with polymers has been developed to increase their biocompatibility and ability to realize the controlled delivery for pharmaceuticals.

Several methods, such as physical adsorption of polymers [5], dispersion or emulsion polymerization in the presence of the magnetite nanoparticles [6–8], and the so-called "grafting to" and "grafting from" methods [9–11], have been developed to prepare polymer-coatings on the magnetite nanoparticles. Among these methods, the "grafting from" approach via the surface-initiated atom transfer radical polymerization (SI-ATRP) has been proved to be the most potential method because that it does not require stringent experimental conditions and allows the direct polymerization of the functional monomers without involving the tedious protection and deprotection procedures in a controlled fashion, yielding polymers with narrowly dispersed molecular weights [12–14]. By far, there is little work on the block copolymers grafted magnetic nanoparticles via the SI-ATRP approach.

Aimed at the targeted and controlled release of drugs, the crosslinked thermo-responsive polymer shells have been coated onto the magnetic nanoparticles via the SI-ATRP technique [15,16]. In the present work, the block copolymer (poly(hydroyethyl acrylate-b-N-isopropylacrylamide), P(HEA-b-NIPAm)) has been grafted from the surfaces of the superparamagnetic Fe_3O_4 nanoparticles with the poly(N-isopropylacrylamide) (PNIPAm) skin layer via the consecutive SI-ATRP of hydroyethyl acrylate (HEA) and N-isopropylacrylamide (NIPAm) after the Fe_3O_4 nanoparticles were surface-modified with α-bromoisobutyric acid (BIBA) (Scheme 1). The products, functional superparamagnetic Fe_3O_4@P(HEA-b-NIPAm) nanoparticles, were characterized with Fourier transform infrared (FT-IR), X-ray photoelectron spectrometer (XPS), transmission electron microscope (TEM), vibrating sample magnetometer (VSM), and dynamic light scattering (DLS) techniques.

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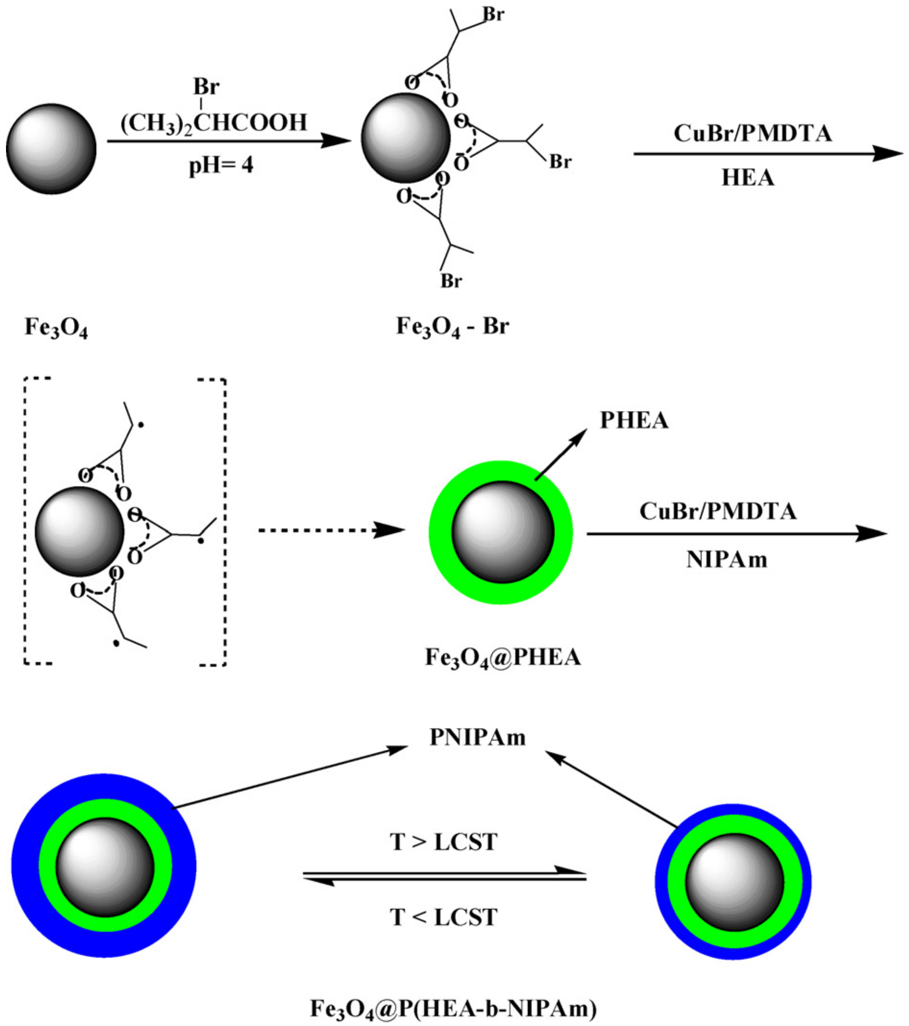

Scheme 1. Schematic illustration of the route to the functional superparamagnetic nanoparticles Fe_3O_4@P(HEA-b-NIPAm).

2. Experimental

2.1. Materials

Ferric chloride hexa-hydrate ($FeCl_3{\cdot}6H_2O$), ferrous chloride tetra-hydrate ($FeCl_2{\cdot}4H_2O$), ammonia solution ($NH_3{\cdot}H_2O$, 25% of ammonia), α-bromoisobutyric acid (BIBA), and isopropyl alcohol were analytical grade reagents received from Tianjin Chemical Co. (Tianjin, China) and used without further purification. Hydroethyl acrylate (HEA) is analytical reagent grade from Beijing Eastern Yakeli Chemical Engineering S & T Ltd., Co., Beijing, China. N-isopropylacrylamide (NIPAm) and N,N,N′,N′,N″-pentamethyldiethylenetriamine (PMDTA) were purchased from Aldrich. Cu(I)Br (Tianjin Chemical Co., Tianjin, China) was purified by stirring in glacial acetic acid, filtered, washed with ethanol and dried.

2.2. Initiator-modified Fe_3O_4 nanoparticles

The co-precipitation method was used to prepare the Fe_3O_4 nanoparticles [17]: $FeCl_3{\cdot}6H_2O$ (13.0 g) and $FeCl_2{\cdot}4H_2O$ (4.8 g) in a 1:2 molar ratio were dissolved in distilled water (200 mL) under nitrogen atmosphere with vigorous stirring. As the solution was heated to 70 °C, $NH_3{\cdot}H_2O$ (28 wt%, 25 mL) was added dropwise to the solution under vigorous stirring and the reaction was allowed to proceed for 5 h at 70 °C, and then the temperature was increased to 85 °C to vapor the residual NH_3.

Then 100 mL aqueous solution of α-bromoisobutyric acid (BIBA) (0.048 mol (8 g)) was dropped into the dispersion of the Fe_3O_4 nanoparticles and the pH value of the dispersion was controlled to be about 4.0 in the procedure. After the mixture was stirred for 24 h, the ultimate initiator-modified Fe_3O_4 nanoparticles (Fe_3O_4–Br) were washed with distilled water to neutral to discard the excessive α-bromoisobutyric acid by the magnetic separation procedure.

2.3. Consecutive SI-ATRP

The initiator-modified Fe_3O_4 nanoparticles (Fe_3O_4–Br), 3.0 mmol CuBr, 6.0 mmol PMDTA and 15.0 mL HEA were dispersed ultrasonically into 80 mL water. The dispersion was heated at 60 °C for 48 h. The products, Fe_3O_4@PHEA, were washed with ethanol/water and dried under vacuum.

The Fe_3O_4@PHEA nanoparticles, 3.0 mmol CuBr, 6.0 mmol PMDTA and 100.0 mmol NIPAm were dispersed ultrasonically into 80 mL isopropyl alcohol. The mixture was heated at 60 °C for 60 h. The products, Fe_3O_4@P(HEA-b-NIPAm), were washed with ethanol/water and dried under vacuum.

2.4. Characterizations

Bruker IFS 66 v/s infrared spectrometer (Bruker, Karlsruhe, Germany) was used for the Fourier transform infrared (FTIR) spectroscopy analysis in the range of 400–4000 cm^{-1} with the res-