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Synthesis of Fe_3O_4@poly(methacrylic acid) core–shell submicrospheres via RAFT precipitation polymerization

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ABSTRACT

Submicron-sized superparamagnetic magnetite colloid nanocrystal clusters (MCNCs) composed of many interconnected tiny Fe_3O_4 nanoparticles provide a new avenue for constructing highly magnetic polymer submicrospheres for biotechnological and medical applications. Herein, a facile and efficient method is described for the synthesis of Fe_3O_4@poly(methacrylic acid) (PMAA) core–shell submicrospheres using the MCNCs modified with polymerizable vinyl groups as the submicronic cores. The controlled encapsulation of the MCNCs with PMAA shells was achieved via precipitation polymerization mediated by a reversible addition–fragmentation chain transfer (RAFT) agent. A variety of factors influencing the formation of PMAA layers were examined, such as the loading amounts of the magnetic seeds and monomers, polymerization time, and the MCNCs' surface chemistry. Compared with previous approaches, much higher seed dosage could be employed in the polymerization system without leading to significant particle conglutination. The shell thickness was readily tailored via varying two synthesis parameters, that is, monomer dosage and reaction time. The resulting hybrid particles showed high saturation magnetization and pH responsiveness. Also, this method was successfully extended to coating other hydrophilic polymer shells over the MCNCs and hence may be a general way for the synthesis of magnetic polymer submicrospheres.

1. Introduction

Magnetic polymer particles, especially those containing magnetite Fe_3O_4 and maghemite γ-Fe_2O_3 nanoparticles inside, have attracted considerable research interest due to their broad potential applications in different areas, such as target drug delivery, enhanced magnetic resonance imaging (MRI), separation or purification of bioentities, immunoassay tests, immobilization of enzymes, and catalysis [1–3]. Among these magnetic polymer particles, submicron-sized ones are particularly suitable for in vitro applications like bioseparation and immunoassay, due to their faster magnetic separation than the nanoparticles and also larger specific surface area for ligand coupling together with weaker sedimentation than the micron-sized controls [4–7]. Such magnetic polymer submicrospheres are usually prepared via a variety of heterogeneous polymerization techniques like emulsion and miniemulsion polymerization in the presence of surface-modified iron oxide nanoparticles of ~10 nm in size [8,9]. However, these approaches still have been challenged by producing composite particles with high and uniform magnetic content and narrow particle size distribution, which are necessary for rapid and homogeneous separation in an applied magnetic field. Emphasizing these problems, Elaissari and co-workers [10,11] and Gu and co-workers [12–14], respectively, developed clever strategies based on seeded emulsion polymerization in the presence of preformed magnetic emulsions composed of submicrometer organic ferrofluid droplets dispersed in water. However, the fabrication of uniform and highly magnetic emulsions seems not to be an easy task [15,16].

On the other hand, a convenient method for the preparation of monodisperse or narrowly dispersed magnetite colloid nanocrystal clusters (MCNCs) has recently been developed by one-pot solvothermal reduction of $FeCl_3$ with ethylene glycol [17–21]. The MCNCs are spherical in shape and the uniform diameters can be tunable in a wide submicrometer range (100–800 nm). Each MCNC is composed of many interconnected primary Fe_3O_4 nanocrystals of ~10 nm in size and minor amount of organic components, which render the resulting clusters superparamagnetism and also high magnetization. Therefore, these MCNCs provide a new avenue for constructing functional composite submicrospheres with high magnetic content and hence have attracted considerable attention [22–33].

Using the readily obtained MCNCs instead of the above mentioned "soft" magnetic emulsion as the "hard" seeds has become an alternative approach for the synthesis of uniform and highly

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magnetic polymer submicrospheres. Li et al. [34] reported on coating of MCNCs with poly(divinylbenzene-*co*-methacrylic acid) by suspension polymerization. However, excessively large amount of the monomers had to be used for achieving a thin polymer shell (ca. 10 nm). Xu et al. [35] demonstrated an effective method for synthesizing magnetic polymer submicrospheres with controllable size and shape and desirable interfacial chemical functionalities by surfactant-free seeded emulsion polymerization with MCNCs as the seeds. A distillation–precipitation polymerization (DPP) method [36], conducted while the solvent boiling and with no need for any surfactant and stabilizer, has proved to be an facile way for the surface functionalization of inorganic nano- and microsized particles with a variety of polymers [37]. Recently, this method has been employed to coat MCNCs with hydrophilic polymer layers [38–40]. Ma et al. [39] encapsulated 3-methacryloxypropyltrimethoxysilane (MPS) modified MCNCs with a crosslinked poly(methacrylic acid) (PMAA) shell via DPP. Liu et al. [40] succeeded in direct coating of carboxyl-capped MCNCs with crosslinked PMAA and other hydrophilic polymers. However, all these the methods based on free radical polymerization mechanism for encapsulation of the MCNCs with polymer shells shows a disadvantage, that is, relatively low concentration of the MCNCs seeds can be used in the polymerization mixture in order to restrain possible aggregation of the final core–shell particles, hence decreasing the preparation efficiency. The aggregation may be attributed to the poor controllability of the conventional radical polymerization, that is, the slow initiation and fast chain propagation and termination reactions. Once the polymerization is initiated, the superabundant oligomer radicals captured rapidly by the seeds greatly favors the coalescence of neighboring particles through recombination of two radicals located on different particles.

Herein, we propose to employ controlled/living radical polymerization (CRP) approaches for coating polymer shells on the MCNCs. The CRP mechanism may greatly reduce the radical amount on the particle surface, which would be beneficial to the inhabitation of particle coalescence and hence allow elevated MCNC concentration in the polymerization system. For proof of the concept, we studied the encapsulation of the MCNCs with crosslinked PMAA via reversible addition–fragmentation chain transfer (RAFT) precipitation polymerization (denoted as RAFT–PP) of MAA together with *N,N′*-methylenebisacrylamide (MBA) as a crosslinking monomer in the presence of vinyl-modified MCNCs as the seeds. This method can employ several times higher seed concentration in the polymerization mixture than that achieved previously by the DPP approach without significant particle aggregation. Also, the thickness of the polymer shell can be tuned more flexibly by varying either the monomer dosage or the reaction time. The resulting hybrid particles exhibited high saturation magnetization and pH responsiveness. Furthermore, this method was successfully extended to coating different hydrophilic polymer shell layers over the MCNCs based on other monomers, such as acrylic acid (AA), 2-hydroxyethyl methacrylate (HEMA), acrylamide (AAM), and *N*-isopropylacrylamide (NIPAAm).

2. Experimental section

2.1. Materials

Sodium acetate, trisodium citrate dehydrate and ethylene glycol were purchased from Guangfu Chemical Reagents Company (Tianjin, China). $FeCl_3$ was acquired from Alfa Aesar. Hydroxybenzotriazole (HOBT) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) were obtained from GL Biochem (Shanghai, China). Allylamine of technical grade was kindly supplied by Tancheng Chemical Company (Shandong, China). 2,2′-Azobisisobutyronitrile (AIBN, Tianjin Chemical Reagents Company, Tianjin, China) was recrystallized from methanol. Acetonitrile (Tianjin Chemical Reagents Company, Tianjin, China) was dried over calcium hydride and then distillated. MAA and AA (Tianjin Chemical Reagents Company, Tianjin, China) were purified by vacuum distillation. HEMA (Tianjin Institute of Chemical Reagents, Tianjin, China) was purified by washing with aqueous NaOH solution, dried over $MgSO_4$, and distilling under reduced pressure. NIPAAm (Acros) was purified by recrystallization from 60/40 hexane/toluene mixture. MBA and acrylamide (AAm) of electrophoresis grade were purchased from Sangon (Shanghai, China). RAFT agent 2-(1-carboxy-1-methyl-ethylsulfanylthiocarbonylsulfanyl)-2-methyl-propionic acid (CMP) was synthesized according to literature [41] as a yellow crystalline solid; mp 172–178 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): 1.59 (s, 12H) and 12.88 (s, 2H).

2.2. Synthesis and surface modification of MCNCs

The MCNCs were prepared by the solvothermal method reported previously by Liu et al. [19]. Briefly, the mixture of $FeCl_3$ (3.9 g), trisodium citrate dihydrate (1.8 g), and sodium acetate (7.2 g) sufficiently dissolved in ethylene glycol (120 mL) was sealed in a Teflon-lined stainless-steel autoclave, heated to 200 °C and maintained for 10 h and then let cool to room temperature. The black product was thoroughly washed sequentially with ethanol and deionized water and finally dried under vacuum at 50 °C. For further surface modification with vinyl groups on the surface, MCNCs (1.0 g), allylamine (2 mmol), HOBT (2 mmol), and EDC (2 mmol) were mixed in cold ethanol (40 mL) and then stirred at room temperature for 8 h. The modified MCNCs were extensively washed with ethanol and then dried under vacuum at 50 °C.

2.3. Coating of MCNCs with crosslinked polymers via RAFT–PP

The RAFT–PP was performed in a 10 mL glass reaction tube immersed in a thermostatic bath. Typically, to the reaction tube, vinyl-modified MCNCs (25 mg), MAA (36 mg), MBA (9 mg), CMP (2.3 mg), and AIBN (0.7 mg) were mixed with acetonitrile (5 mL). After purged with nitrogen for 10 min, the reaction system was sealed, immersed in the thermostatic bath at 60 °C, and tumbled end over end at 200 rpm for 18 h. The resulting composite particles were collected by magnetic separation, thoroughly washed with ethanol, and finally dried under vacuum. The polymer graft percentage of the composite particles after polymerization was calculated according to the following formula:

$$\text{Polymer graft percentage} = (W_1 - W_0)/W_0 \times 100\%,$$

where W_0 and W_1 denote the mass of seed particles and the resultant composite particles, respectively.

2.4. Characterization of magnetic particles

Transmission electronic microscopy (TEM) images were taken on a JEOL TEM operated at 100 kV. High-resolution images were obtained using a Technai G2 20-S-TWIN TEM operated at 200 kV. Samples were dispersed in ethanol at an appropriate concentration, cast onto a carbon coated copper grids, and then dried under vacuum. Powder X-ray diffraction (XRD) patterns were recorded on a D/max 2500 V X-ray diffractometer using Cu Kα radiation at 40 kV and 100 mA. Hydrodynamic diameters (D_h) and zeta potentials of the particles were measured by dynamic light scattering (DLS) with a Malvern ZEN3600 Zetasizer Nano instrument using a He–Ne laser at a wavelength of 632.8 nm. Fourier-transformation infrared (FT-IR) spectra were determined on a Bio-Rad FTS 135