Toward Designer Magnetite/Polystyrene Colloidal Composite Microspheres with Controllable Nanostructures and Desirable Surface Functionalities

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ABSTRACT: An effective method was developed for synthesizing magnetite/polymer colloidal composite microspheres with controllable variations in size and shape of the nanostructures and desirable interfacial chemical functionalities, using surfactant-free seeded emulsion polymerization with magnetite (Fe₃O₄) colloidal nanocrystal clusters (CNCs) as the seed, styrene (St) as the monomer, and potassium persulfate (KPS) as the initiator. The sub-micrometer-sized citrate-acid-stabilized Fe₃O₄ CNCs were first obtained via ethylene glycol (EG)-mediated solvothermal synthesis, followed by 3-(trimethoxysilyl)propyl methacrylate (MPS) modification to immobilize the active vinyl groups onto the surfaces, and then the hydrophobic St monomers were polymerized at the interfaces to form the polymer shells by seeded emulsion radical polymerization. The morphology of the composite microspheres could be controlled from raspberry- and flower-like shapes, to eccentric structures by simply adjusting the feeding weight ratio of the seed to the monomer (Fe₃O₄/St) and varying the amount of cross-linker divinyl benzene (DVB). The morphological transition was rationalized by considering the viscosity of monomer-swollen polymer matrix and interfacial tension between the seeds and polymer matrix. Functional groups, such as carboxyl, hydroxyl, and epoxy, can be facilely introduced onto the composite microspheres through copolymerization of St with other functional monomers. The resultant microspheres displayed a high saturation magnetization (46 emu/g), well-defined core−shell nanostructures, and surface chemical functionalities, as well as a sustained colloidal stability, promising for further biomedical applications.

1. INTRODUCTION

Magnetic nanomaterials have been extensively investigated due to the wide range of practical and potential applications in the nano/microbiomedical fields including magnetic separation of biomolecules, magnetic resonance imaging (MRI) contrast enhancement, magnetic-field induced hyperthermia therapies, and MRI tomography assisted and magnetically guided targeted drug delivery.1−8 The magnetic properties of the nanomaterials allow convenient mechanical sorting, trafficking, and micromanipulation in biological systems simply by using an external magnetic field, while they can also be viewed and followed with MRI tomographic methods. In practice, the high saturation magnetization of the magnetic composite nanomaterials is critically important for achieving high performance in contrast in bioimaging applications and, in some other cases, for convenient and efficient enrichment and separation under external magnetic fields.9−12 As an important member of the magnetic composite nanomaterials, core/shell structured composite microspheres have been extensively explored to realize the combination of respective properties of each component, and the polymer shells of the magnetic microspheres are also of vital importance for the composites to function in the biological conditions that require low toxicity, biocompatibility, and specific biointeractive functionalities.13−15 It is therefore crucial to control the size and shape of the magnetic seeds, followed by controlling the morphological features of polymer shell of the magnetic composite microspheres, for achieving optimized chemical and biological properties.16−20 Toward this goal, new synthetic methodologies have been sought for facile and convenient syntheses of such composite microspheres in controllable ways.

Recently, several synthetic approaches, such as template-based self-assembly21,22 phase separation and controlled surface nucleation,23,24 emulsion polymerization,25,26 and distillation-precipitation polymerization,10,27 were developed to fabricate structure-tunable magnetic composite microspheres and to tailor their properties of polymer shells accordingly. Among these methods, emulsion polymerization was developed as a facile and straightforward way to prepare magnetic composite microspheres with readily controllable morpholo-
gies. For example, Lu and co-workers25 reported simple and reproducible preparation of Fe3O4@PSt-co-DVB colloidal composites via emulsion copolymerization. The structural stability and surface morphology of the composites could be readily modulated by adjusting different ratios of styrene and DVB. Xu et al.28 realized facile preparation of Fe3O4@PSt microspheres with magnetic seeds encapsulated symmetrically or asymmetrically inside the polymer microspheres by varying the type of initiators, through emulsifier-free emulsion polymerization in the presence of aqueous magnetic fluid. Besides, Yin and co-workers15 reported fabrication of a range of spherical and nonspherical magnetite–polystyrene composite colloids with anisotropic structures. Although a great deal of progresses has been made, these reported results typically produced composite microspheres with unsatisfied uniformity in size and relatively low saturation magnetization. In addition, many synthetic procedures required the coating of a transition silica layer to enhance the stability and hydrophilic property of the magnetic seeds for subsequent growth of polymer shells. Consequently, the procedures involved time-consuming multisteps, and the existence of the silica inner-shell unavoidably resulted in a decrease in the saturation magnetization due to the lowered magnetic fraction. Furthermore, the microspheres thus produced lacked specific surface functionalities needed for further promising applications in various fields.29

Herein, a facile and direct method is presented to prepare uniform Fe3O4@polymer composite microspheres with controllable morphologies and high saturation magnetizations through a surfactant-free seeded emulsion polymerization. The citrate-acid-stabilized Fe3O4 CNCs were directly modified with vinyl groups via silane coupling reaction, thereby eliminating the transition silica layer used in the previous reports. More importantly, the morphology of the resultant microspheres could be varied from raspberry- and flower-like shapes to eccentric structures by, quite predictably, altering the feeding ratios of the monomers to the magnetic seeds. In addition, it was observed that concentric core–shell structures were produced when DVB was added as the cross-linker to the reaction mixtures. The structurally tunable composite microspheres thus produced were observed to be uniform in size and water-dispersible, and to possess high magnetic susceptibility. Furthermore, selective functionalities including carboxyl, hydroxyl, and epoxy groups were successfully grafted onto the microspheres through the additions of the corresponding functional monomers into the reaction mixtures by copolymerization. Such uniform microspheres with controllable morphology, high magnetization, and surface accessible functionalities would undoubtedly serve as building blocks of more sophisticated nano/microstructures or as useful tools in the studies of catalysis and biomedical fields.

2. EXPERIMENTAL SECTION

2.1. Chemicals. Iron(III) chloride hexahydrate (FeCl3·6H2O), sodium acetate (NaOAc), ethylene glycol (EG), styrene (St), acrylate acid (AA), glycidyl methacrylate (GMA), and anhydrous ethanol were purchased from Shanghai Chemical Reagents Company, China. Styrene was distilled under reduced pressure before use. 2-Hydroxyethyl methacrylate (HEMA), divinyl benzene (DVB), and 3-(trimethoxysilyl)propyl methacrylate (MPS) were purchased from Sigma-Aldrich. Trisodium citrate (Na3Cit), aqueous ammonia solution (25%), and potassium persulfate (KPS) were purchased from Shanghai Aijian Reagent Company and recrystallized from water before use. Deionized water was used in the experiments.

2.2. Synthesis of Magnetic Colloidal Nanocrystal Clusters (Fe3O4 CNCs). The Fe3O4 CNCs were prepared through a modified solvothermal reaction as reported.30,31 Generally, 2.2 g of FeCl3·6H2O, 2.6 g of NaOAc, and 0.47 g of Na3Cit were dissolved in 40 mL of EG to form a homogeneous solution under ultrasonication. Then, the yellow mixture was transferred into a 50 mL three-necked flask and stirred vigorously at 160 °C for 1 h. The homogenous yellow solution changed gradually to dark brownish dispersion as the reaction proceeded. Then, the dispersion was instantly transferred into a Teflon-lined stainless-steel autoclave (50 mL capacity) and held in oven at 200 °C for 15 h. The performed dark brownish precipitates in solution were isolated by magnet and washed several times with ethanol and deionized water to remove the residues from the products. The purified products were kept in ethanol for further use.

2.3. Modification of Vinyl Group onto Fe3O4 CNCs. The obtained Fe3O4 CNCs were mixed with 32 g of ethanol, 9 g of deionized water, and 1 g of MPS to form a brownish dispersion. Then the dispersion was transferred into a 100 mL three-necked flask. After injection of 2 mL of aqueous ammonia solution, the dispersion was stirred vigorously at 70 °C for 24 h to introduce vinyl groups onto the surface of Fe3O4 CNCs. After reaction, the product was a much lighter brown color, and was washed with ethanol and deionized water several times, and isolated by an applied magnet. The purified product was dried in vacuum for further use.

2.4. Synthesis of Raspberry-, Flower-Like and Eccentric Fe3O4@PSt Composite Microspheres. The coating PSt on Fe3O4 CNCs was realized through seeded emulsion polymerization. In a typical synthesis, 20 mg of vinyl-modified Fe3O4 CNCs as seeds was dispersed in 25 mL of deionized water to form a homogeneous medium under ultrasonication. After being transferred into a 50 mL three-necked flask, the dispersion was injected slowly with 0.1 mL of styrene, stirred vigorously, and bubbled gently with N2 for 30 min. Upon the temperature being heated to 75 °C, 0.3 mL of KPS solution (10 mg/mL) was added into the above dispersion. The reaction was allowed to proceed for 10 h. The obtained product was washed with deionized water and ethanol several times, and separated by an applied magnet. The feeding amount of St monomer was increased from 0.1, 0.2, 0.3, to 0.6 mL, respectively, in order to investigate the morphology evolution of Fe3O4@PSt composite microspheres from raspberry-, flower-like structures to eccentric microspheres.

2.5. Synthesis of Concentric Fe3O4@PSt Composite Microspheres. Preparation of concentric spherical Fe3O4@PSt composite particles followed a similar procedure, except that a certain amount of cross-linker of DVB was added together with St monomer in the initial stage. The feeding amount of DVB was changed from 1%, 3%, 5%, to 8%, respectively, in order to investigate the intergity of P(St-co-DVB) shell.

2.6. Synthesis of Cross-Linked Fe3O4@Copolymer Composite Microspheres. The preparation of concentric spherical Fe3O4@PSt composite microspheres followed a similar procedure, except that a 20% amount (as the whole monomers) of AA, or GMA, or HEMA together with an 8% (as the whole monomers) amount of cross-linker DVB were added after the emulsion polymerization proceeded for 1 h.

2.7. Characterization. High-resolution transmission electron microscopy (HRTEM) images were taken on a JEM-2010 (JEOL, Japan) transmission electron microscope at an accelerating voltage of 200 kV. The samples for HRTEM measurements were obtained by placing one drop of the samples on copper grids coated with carbon. Samples were obtained after being purified with the aid of magnet. Scanning electron microscopy (SEM) measurements were performed using a TS-5136MM (TESCAN, Czech) scanning electron microscope at an accelerating voltage of 20 kV. Samples dispersed at an appropriate concentration were cast onto a thin glass sheet at room temperature and sputter-coated with gold particles. Fourier transform infrared (FT-IR) spectra were recorded on a Magna-550 (Nicolet) spectrometer. The samples were dried and mixed with KBr to be compressed to a plate for measurement. Magnetic characterization was carried out with a vibrating sample magnetometer on a model 6000 physical property measurement system (Quantum Design) at 300 K.
3. RESULTS AND DISCUSSION

3.1. Preparation and Vinyl Modification of Fe₃O₄ CNCs. The Fe₃O₄@PSt composite microspheres with various structures were produced through surfactant-free seeded emulsion polymerization, using vinyl group modified Fe₃O₄ CNCs as seeds. First, the Fe₃O₄ CNCs were prepared via EG mediated solvothermal process with acetate sodium as alkaline resources and trisodium citrate as electrostatic stabilizers (Figure 1a). The Fe₃O₄ CNCs were spherical in shape and nearly uniform with an average size of 183 nm. From the enlarged image, it could be found that each CNC was composed of many primary crystals. Figure 1b demonstrated the uniformity of Fe₃O₄ CNCs and revealed the rough surface property formed by close stacking of small nanocrystals. Due to the existence of citrate acid as stabilizer, the Fe₃O₄ CNCs with a negative charge of \(-35.4\) mV could be well dispersed in water and maintained as stable for several hours without obvious visible sedimentation due to the electrostatic repulsion effect.

In order to introduce C\(=\)C double bond, Fe₃O₄ particles were modified with MPS in ethanol–water mixture solvent. The hydrolysis and condensation reaction occurred between the hydroxyl groups of Fe₃O₄ and Si–OH of MPS, catalyzed by ammonia. Thus, the C\(=\)C double bond from surface-capped MPS molecules would copolymerize with growing polystyrene radicals and thus further promoted anchoring of the polymer chains on the magnetite CNC surface. It was worth pointing out here that, since the stabilizer citrate acid containing carboxylate groups owned a similar infrared absorbance with MPS, MPS-modified Fe₃O₄ could not be distinguished from bare Fe₃O₄ in FT-IR spectrum. However, if unmodified Fe₃O₄ CNCs were utilized, the Fe₃O₄ CNCs became unstable and aggregated upon initiation, indicating the Fe₃O₄ CNCs and the polymer were immiscible during the polymerization. Consequently, vinyl functionalization was necessity for the fabrication of Fe₃O₄@PSt composite microspheres.

3.2. Preparation of Fe₃O₄@PSt Composite Microspheres. 3.2.1. Effect of Monomer/Seed Ratio. Using MPS-modified Fe₃O₄ CNCs as seeds, Fe₃O₄@PSt composite microspheres with tunable structures could be facially prepared via surfactant-free seeded emulsion polymerization. Surfactant was not used because the sulfate residues from the initiator KPS could stabilize the growing polymer beads. Figure 2 showed typical TEM images of Fe₃O₄@PSt composite microspheres with increased St/Fe₃O₄ ratio. At a low level of St/Fe₃O₄ ratio (5:1, Figure 2a), we found that many small nodules were randomly distributed around the magnetic core. Close inspection on the enlarged view of one microsphere (Figure 2a inset) showed that the Fe₃O₄ CNC was compactly surrounded by small polymer particles. Additionally, the external surface profile in Figure 3a also revealed such microspheres with rough surface characteristics formed by stacking of small polymer particles. The reason for the formation of such raspberry-like structures was the big interfacial tension between the hydrophobic PSt particles and relatively hydrophilic Fe₃O₄ CNCs stabilized by citrate acid. More specifically, small polymer nodules formed around the seed’s surface tended to be contracted, due to the interfacial tension driven phase separation process and thereby depositing onto the surface of the seed rather than spreading around and covering the whole seed. With more weight ratio of St/Fe₃O₄ (10:1, Figures 2b and 3b), polymer particles around the Fe₃O₄ CNCs grew in size and subsequently fused each other to form larger polymer particles, resulting in flower-like shapes with enlarged “petals”. Such coalescence phenomenon was driven by the growth of initial small polymer nodules and decrease of surface energy. Further increasing the feed ratio to 15:1 (Figures 2c and 3c), it could be found that as-formed larger polymer particles surrounding the seeds tended to coalesce into a continuous layer, fully covering the seed. Finally, when the feed ratio was increased to 30:1 (Figures 2d and 3d), as expected, a continuous, smooth, and intact polymer shell formed around the Fe₃O₄ seeds. It is worthwhile to point out
here that the magnetic core was eccentrically located inside the polymer shell (Figure 3d), probably ascribed to the phase separation effect between the hydrophobic PSt layer and relatively hydrophilic Fe3O4 CNCs.

3.2.2. Effect of Reaction Time on the Morphology of the Composite Microspheres. In order to further indentify the mechanism, the morphology evolution of Fe3O4@PSt microspheres with different weight ratio of St/Fe3O4 as a function of time was investigated. Reaction intermediates at specific time intervals were retrieved and characterized by TEM measurement. At relatively lower St/Fe3O4 ratio of 15:1, primary PSt particles nucleated upon initiation and attached onto the Fe3O4 CNC outer surface through copolymerization of St with the surface vinyl group at initial stage of polymerization. Due to the difference of interfacial tension between newly formed polymer particles and hydrophilic seeds, the phase separation took place...
during polymerization. Because of the relatively low content of monomer St in the polymerization system, the viscosity of the monomer-swollen PST particles was high, avoiding the fusion of the polymer particles to each other and enhancing the formation of polymer nodules. In other words, the phase separation and the high viscosity of the polymer particles resulted in many small PST nodules that formed around the Fe₃O₄ cores, and the morphology of the composite microspheres was a raspberry-like structure initially (Figure 4a ii). As the polymerization proceeded, the swollen monomers in the polymer particles were initiated continuously, and the small polymer nodules grew in size with time, meanwhile merging with nearby ones, leading to flower-like composite microspheres (Figure 4a iii–vi). Then, further extension of the reaction time to 12 h did not obviously influence the final morphology. Actually, in this reaction system, the amount of swollen monomers was not sufficient to decrease the viscosity of the polymer matrix and then make polymer nodules fully fuse with a nearby one, which was mainly responsible for the formation the above morphology. Accordingly, the scheme representing the formation of Fe₃O₄@PSt flower-like structures was illustrated in Figure 4b. On the basis of the discussion, it was seemingly rational to predict that further increase of monomer content would lead to decrease the viscosity of the monomer-swollen polymer particles and then formation of a continuous polymer layer, changing flower-like structures to core–shell ones.

In fact, the structure formation pathway at St/Fe₃O₄ ratio of 30:1 was quite similar as we predicted (Figure 5a i–iii). Within a short time period of polymerization (25 min), the continuous polymer layers formed and completely covered the seeds, resulting in core–shell structures rather than many small PST nodules as occurred in St/Fe₃O₄ ratio of 15:1. With abundant existence of monomer St, the monomer-swollen polymer particles owned low viscosity in the initial stage of polymerization, thereby effectively promoting fusion of the as-formed polymer particles. In other words, the coalescence of polymer particles was kinetically and thermodynamically favored due to the lower viscosity of the polymer particles. Noticeably, phase separation served as a driving force to push the magnetic core to the surface of the polymer shells. Further elongation of the reaction only increased the shell thickness of the microspheres, retaining the anisotropic structure (Figure 5a iv–vi). Similarly, the schematic illustration of the formation of Fe₃O₄@PSt eccentric structures was given in Figure 5b. As a result, the initial nucleation process, determined by the amount of monomers, was responsible for the morphological transition, as well as the structures of the final microspheres.

Additionally, the versatility of the synthetic method was systematically tested by changing the core size and the stabilizer. As exhibited in Figures S2 and S3, with increasing weight ratio of St to Fe₃O₄, morphology of the microspheres could evolve from the flower-like shapes to eccentric structures with the inner core sized in 98 or 311 nm, which meant the morphological transition was independent with the core size. Furthermore, using poly(γ-glutamic acid) (PGA) stabilized Fe₃O₄ CNCs as seeds, the morphological transition could also be clearly and similarly observed (Figure S4). Consequently, it could possibly be concluded that hydrophilic ligand-stabilized Fe₃O₄ CNCs with various sizes could be used for structure-tunable preparation of Fe₃O₄/PSt composite microspheres. Importantly, the microspheres could be obtained in relatively large scale with nearly 1.0 g amount of product (Figure S5), which was beneficial for further large-scale production and practical application.

Colloidal stability measurement demonstrated that as-prepared Fe₃O₄@PSt composite microspheres could be well-dispersed in PBS solution and maintained for more than 2 h without visible sedimentation (Figure S6). Such sustained aqueous stability was attributed to the surface remaining initiator residues of SO₄²⁻.

3.3. Preparation of Fe₃O₄@P(St-co-DVB) Composite Microspheres. Addition of certain amounts of cross-linker DVB also made a significant impact on the structures of prepared microspheres. Cross-linked Fe₃O₄@PSt microspheres showed much more intact and smooth polymer layers with increased feeding amount of DVB (Figure 6a–d). Compared with the monomer St, DVB with two reactive double bonds was more active, and it accelerated the nucleation of the primary particles at the beginning of polymerization. The large amount of primary particles were evenly deposited onto the Fe₃O₄ seed and copolymerized with surface-capped vinyl groups on magnetic cores. Due to the preliminary particle enriched DVB on the surface of Fe₃O₄ seed, hydrophobicity of the seed particles was increased dramatically, and the difference of interfacial tension between the polymer-covered seed and the hydrophobic polymer was decreased accordingly. Afterward, PST chains could be easily deposited onto the polymer-covered Fe₃O₄ cores with enhanced compatibility and formed a relatively smooth layer of polymer. Moreover, the relatively high viscosity of the cross-linked polymer shell restricted the movement of the magnetic core to form eccentric structures and resulted in concentric core–shell structures.

On the basis of the above discussions, the resultant morphology of microspheres was highly dependent on the weight ratio of monomers to magnetic seeds, as well as the feeding amount of cross-linker DVB (Scheme 1). Specifically, the weight ratio of St to Fe₃O₄ greatly influenced the initial polymerization conditions, the viscosity of the monomer-swollen polymer particles and surface tension driven phase separation process, the product could be controlled from raspberry- and flower-like shapes to spherical core–shell microspheres. Furthermore, the existence of cross-linker DVB also dramatically increased the viscosity of the copolymer and affected the final morphology of the polymer shell.
increased amount of DVB, the roughness of polymer shells was decreased gradually, showing more intact and smooth shell layers.

3.4. Preparation of Fe₃O₄@polymer Composite Microspheres with Specific Surface Functionalities. In this section, selective functional groups were introduced into the surface of composite microspheres through copolymerization of St with functional monomers. A series of functional monomers, such as AA, GMA and HEMA, were used in the reaction. The morphologies of composite microsphere with or without addition of cross-linker DVB were compared. Without addition of DVB and at St to AA ratio of 4:1, Fe₃O₄@Poly(St-co-AA) showed flower-like structures (Figure 7a). Addition of DVB resulted in core–shell structures as discussed above (Figure 7d). Fe₃O₄@Poly(St-co-HEMA) and Fe₃O₄@Poly(St-co-GMA) composite microspheres possessed core–shell structures (Figure 7b,e) with or without the addition of DVB. Although DVB did not greatly change the morphology of Fe₃O₄@P(St-co-GMA) composite microspheres, it affected the location of the magnetic core inside the composite microspheres (Figure 7c,f). The morphological difference in these three non-cross-linked composite microspheres was probably due to the reactivity difference of functional monomers.

The FTIR spectra of Fe₃O₄@copolymer further demonstrated the existence of the various functionalities (Figure 8 a). Compared with the spectrum of Fe₃O₄@PSt particles, all Fe₃O₄ particles with a copolymer shell showed an obviously strengthened peak at 1720 cm⁻¹, ascribed to the carboxylate groups (−COO−) of the AA, HEMA, and GMA. Magnetization curves revealed the magnetic properties of Fe₃O₄CNCS and Fe₃O₄@copolymer microspheres at 300 K. Fe₃O₄ CNCs owned a high saturation magnetization as much as 77 emu/g. After polymer coating, the composite microspheres still retained excellent magnetization. The saturation magnetization values of Fe₃O₄@P(St-co-HEMA) and Fe₃O₄@P(St-co-GMA) were 30 and 28 emu/g, respectively. As for Fe₃O₄@P(St-co-AA), the magnetization reached to 46 emu/g. Furthermore, all samples took superparamagnetic behavior at 300 K, rendering them promising candidates for further magnetic-field-guided enrichment and purification.

4. CONCLUSION

In conclusion, uniform Fe₃O₄@polymer composite microspheres were synthesized through surfactant-free seeded emulsion polymerization. The preparation procedure was conducted as the following steps: At first, the Fe₃O₄ CNCs seeds were prepared through a solvothermal process and were subsequently modified with MPS to introduce vinyl functionality to the surfaces. Afterward, surfactant-free emulsion polymerization of styrene was initiated by KPS, and the corresponding polymer particles were allowed to grow in size as the reactions proceeded. The morphologies of the resultant composite microspheres were controllable by varying the feeding ratios of monomer to magnetite and the concentrations of cross-linker DVB. In addition, at certain concentrations of the cross-linker DVB, well-defined concentric structures with continuous and smooth polymer shell were obtained. The observed morphological characteristics and the transitions from one to another proved a synergistic effect of the viscosity of the monomer-swollen polymer particles and the phase separation processes that were driven by the interfacial tensions. This method allows the magnetic composite microspheres to be...
functionialized with carboxylic, hydroxyl, and epoxy groups by copolymerization with AA, GMA, and HEMA, respectively. In addition, these composite microspheres displayed an excellent aqueous dispersity and very high saturation magnetizations. The microspheres with high magnetization, specific surface functionalities, and well-controlled micro/nanomorphologies will undoubtedly play a significant role in catalysis and biorelated fields.

**ASSOCIATED CONTENT**

1. **Supporting Information**

**HRTEM and TEM images and colloidal stability of Fe₃O₄@PSt composite microspheres.** This material is available free of charge via the Internet at http://pubs.acs.org.

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