



Green Method for Synthesis of Magnetic Hollow Silica Spheres

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Abstract

The magnetic hollow silica spheres (MHSS) with uniform cavity size and shell thickness were prepared by a simple and “green” method using functionalized SiO₂ spheres as templates. Magnetic particles (Fe₃O₄) were deposited on the SiO₂ surface by varying the molar ratio of [Fe²⁺]/[Fe³⁺] and the molar concentration of iron salts. The obtained magnetic hollow silica spheres exhibited a super-paramagnetic behavior at room temperature. Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and X-ray powder scattering (XRD) were applied to characterize the MHSS. Besides, their unit cell parameters are calculated according to results indexing to XRD, the MHSS sample prepared at 0.10 M iron salts and 2:1 molar ratio of [Fe²⁺]/[Fe³⁺] has a largest cell angle () of unit cell. Due to large hollow cavity space and super-paramagnetic characteristics, the inner amino-functionalized MHSS could be labeled with radioisotope ⁹⁹Tcm to study the MHSS’s magnetic targeting distribution in vivo. These results indicate that the MHSS has potential in the magnetic targeted drug delivery system which reduces the damage to normal cells and improves the therapeutic effect of cancer.

Keywords: silica spheres, Magnetic particles, SEM, TEM, XRD, green method.

1. Introduction

Hollow magnetic silica spheres (MHSS) have received great attention in many fields including catalysts [1] [2], microwave absorbing material [3], drug carriers [4] [5] [6] and the immobility of biomolecules [7] [8] [9], due to their unique properties such as low toxicity, biocompatibility, high specific surface area and huge interior space, which could provide greater drug loading volume and better adsorption ability compared to conventional mesoporous silica materials. To date, a variety of methods (such as layer-by-layer coating technology [1] [10], spray pyrolysis [11], precipitation [12]) have been invented and employed to fabricate hollow spheres. Zhu et al. prepared the rattle-like Fe₃O₄@SiO₂ hollow mesoporous spheres using the carbon spheres absorbed with iron precursor as the templates [13]. Frank Caruso et al. fabricated MHSS by coating anionic

polystyrene latices with Fe₃O₄ nanoparticle layers alternately adsorbed with polyelectrolyte from aqueous solution [14]. Shi’s group prepared for the MHSS through sol-gel reactions followed by hydrothermal treatment and H₂ reduction [15]. However, the synthetic procedures are rather complex, and the hollow spheres surface are difficult to be functionalized. Normally, two strategies have been established to obtain functional hollow mesoporous spheres. One is that the inner and outer walls of the hollow microspheres are functionalized. For example, Darya Radziuk reported the synthesis of silver nanoparticles for remote opening of polyelectrolyte microcapsules [16]. The other is that functional microspheres are placed in the cavity of the hollow microspheres. Caruso’s group [17] demonstrated that a new concept for the immobilization of enzymes using

inner functionalized hollow microspheres, which displayed improved enantioselectivity in a given reaction. In addition, hollow mesoporous spheres were prepared by polyelectrolyte almost have semi-permeable, so the small-molecule solvent, vitamin B12, dye or ions can penetrate through which is conducive to small-molecule drug sustained release. In this paper, we reported an efficient route to prepare MHSS using the sulfonated SiO₂ spheres as the hard templates by a simple and “green” method using co-

precipitation route. The schematic procedure for the preparation of magnetic hollow spheres is shown in Figure 1. Thiol groups of the hollow silica spheres are oxidized as sulfonic acid groups by hydrogen peroxide, and then silica/Fe₃O₄ hollow spheres are prepared using sulfonic acid-functionalized hollow silica spheres as templates. The inner aminofunctionalized MHSS were labeled with radioisotope ⁹⁹Tc^m to study the MHSS's magnetic targeting distribution in vivo.

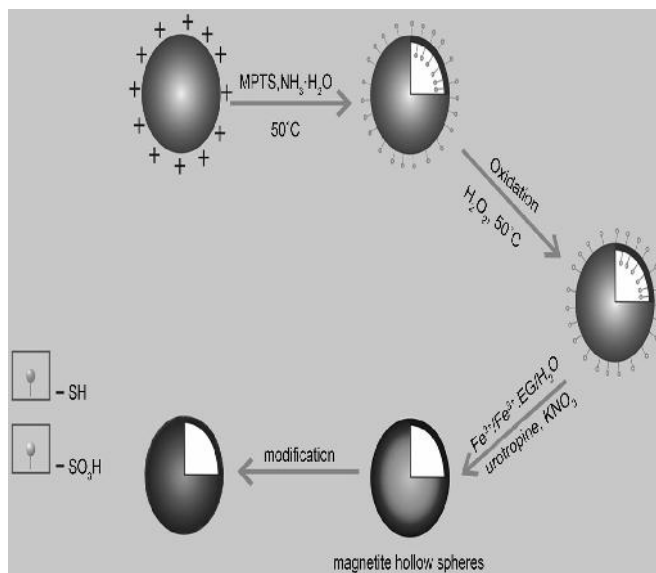


Figure 1. Schematic procedure for the preparation of magnetic hollow spheres.

2. Experimental Section

2.1. Materials

All reagents used were analytical grade and available commercially. Styrene, FeCl₃·6H₂O, FeCl₂·7H₂O, KNO₃, hydrogen peroxide (30 wt%), and aqueous ammonia solution (28 wt%) were purchased from Shanghai Lingfeng Chemical Reagent Co., Ltd., (China). 2,2'-Azobis(2-methylpropi-onamidine) dihydrochloride (AAPH), polyvinylpyrrolidone (PVP, Mw = 30000), 3-aminopropyl triethoxy-silane (APTES), Hexamethylenetetramine (HMT), and 3-mercaptopropyltriethoxysilane (MPTS) purchased from Sigma-Aldrich Co. The aforementioned chemicals were used as received.

2.2. Preparation of Thiol-Functionalized Hollow Silica Spheres (THSS)

3.0 g of styrene, 1.5 g of PVP and 0.39 g of AAPH were dissolved in 100 mL of deionized water, and then the mixture was maintained at 70°C in nitrogen atmosphere. After stirring for 24 h, the polystyrene emulsion was filtered by micro-pore film filter

and placed at room temperature for 2 days. Then, 40 mL of ethanol, 5 mL of aqueous ammonia and 1.0 g of 3 mercapto propyl triethoxy silane (MPTS) were added into polystyrene emulsion, this solution under vigorous stirring was heated up to the temperature of 50°C for 4 h. Then the product was separated by centrifugal hydroextractor, following washed with deionized water three to four times and ethanol two times. The thiol-functionalized hollow silica spheres (THSS) were prepared.

2.3. Preparation of Sulfonated Hollow Silica Spheres (SHSS)

The as prepared THSS (0.8 g) were dissolved into 30 wt% 32 mL hydrogen peroxide, and kept the oxidation reaction at 50°C for 12 h under a constant stirring at 300 rpm.

The obtained sulfonated hollow silica spheres were separated again by centrifugation, following washed with deionized water three to four times and ethanol two times. Finally, the SHSS were re-dispersed into deionized water.

2.4. Preparation of MHSS and Amino-Functionalized MHSS

First, 0.3 g of freeze-dried sulfonated SiO₂ template spheres were dispersed in a solution composed of 50 mL ethanediol and 50 mL deionized water. Next, 2.0 g of Hexamethylenetetramine (HMT) and 0.2 g of potassium nitrate (KNO₃) were added with stirring for 30 min, then 20 mL 0.05 M iron salts (Fe³⁺, Fe²⁺) was added to the reaction mixture under vigorous stirring and subsequently heated at 80 °C for 5 h. The obtained magnetic hollow spheres were purified by centrifugation and dried under vacuum at ambient temperature. With all of the other parameters being kept constant, the iron salts concentration, and the molar ratio of [Fe²⁺]/[Fe³⁺] were varied to evaluate their effects on the morphologies of MHSS. Table 1 summarized the nomenclatures we used for products adopting iron salts concentrations and different molar ratio of [Fe²⁺]/[Fe³⁺].

The dried MHSS were re-suspended in the dried toluene (50 ml), followed by the addition of 3-aminopropyl triethoxysilane (APTES, 1 ml); the mixture was then heated to reflux for 12 h. The amino-functionalized magnetic MHSS were separated by a magnet and washed with ethanol and water, and then dried for 12 h.

2.5. Preparation of ^{99m}Tc Labeled MHSS and Biodistribution

The ^{99m}TcO₄⁻ was reduced using stannous chloride, typically, 8 mg of SnCl₂, 0.1 ml of 0.5 mol/L sodium gluconate solution, 0.4 ml of PBS (pH = 5.7), and 5 mg of unlabeled compound (MHSS-a) (amino-functionalized-MHSS) were mixed in the vial to form homogeneous solution, which were subjected to ultrasonic treatment for 15 min. Then 1 ml of 5 mCi/ml ^{99m}TcO₄⁻ eluate was added, the mixture was heated to 70 °C for 2 h, the labeled compound (MHSS-^{99m}Tc) were separated by magnetic field and washed with deionized water, and the radiochemical purity of the labeled compound was checked with Capintec CRC-15R external dose calibrator.

To further investigate the biodistribution of nanoparticles, 0.5 mCi/1 ml ^{99m}Tc labeled MHSS solution were injected into the female mice via caudal vein. After a certain time in magnetically targeted therapy, the animals were sacrificed with an overdose of sodium pentobarbital, and the main organs (the blood, heart, lung, liver, spleen, pancreas, stomach, small intestine, large intestine, brain, muscle and bone) were detached and weighed. The main organs were rinsed with buffer and remaining cell-associated radioactivity was measured with a γ -counter respectively.

2.6. Characterization

A Hitachi S-4800 field emission scanning electron microscope (SEM) and a Philips-Tecnaï-12 transmission electron microscope (TEM) were used to characterize the morphology of the products. The infrared spectra were recorded by a Nicolet Impact 410 FT-IR using KBr disks. X-Ray Powder Diffraction (XRD) was used to characterize the crystalline phases of the materials. A vibrating-sample magnetometer (VSM JDM-13) was used to characterize the magnetic properties

3. Results and Discussion

3.1. The Structure and Morphology of THSS

As shown in Figure 2(a), Figure 2(b), it can be seen that the THSS spheres have clear cavity, and uniform size. The particle sizes of the samples are approximately 100 nm diameters, and the shell thickness is about 15 nm and the core diameter is about 75 nm.

The SEM image recorded in Figure 2(c) clearly exhibited a uniform spheres structure. with diameters and the sizes are close to the TEM results. FTIR measurements can be used to deduce the surface properties of materials. Figure 2(d) illustrates the FTIR spectra of THSS samples. The peak at 2555 cm⁻¹ is attributed to the stretching vibrations of S-H, the peaks at 698 cm⁻¹ and 753 cm⁻¹ are attributed to the stretching vibration of the monoreplacement in the phenyl ring group of samples, and the peak at 1035 cm⁻¹ is attributed to the vibration of Si-O-Si. Similarly, two peaks at 1641 cm⁻¹ and 3435 cm⁻¹ are assigned to the O-H bond. These findings indicate that the mercapto group is presented in THSS.

Nano SiO₂ can be successfully coated on the surface of polystyrene because of the mutual interaction between positive charged polystyrene and negative charged MPTS, which may be hydrolyzed into SiO₂ carried thiol group under catalysis by ammonia.

Therefore, the formation process of hollow silica spheres was related to ammonia, which not only served as a reactant to form SiO₂, but also as an alkali media to "dissolve" PS template spheres with ethanol [18] [19]. This method is a simple and "green" method to remove any templates of polystyrene cores in synthesis process which need not any additional dissolution, calcination, and etching process.

3.2. The Structure and Morphology of SHSS

The TEM images of as-synthesized SHSS are illustrated in Figure 3(a) and Figure 3(b). The TEM observation indicates that as synthesized SHSS exhibiting hollow structure.

The average size is around 100 nm, with the hollow diameter of 75 nm and the silica shell of 15 nm. Some

shells of SiO₂ were linked among the particles (Figure 3(b)).

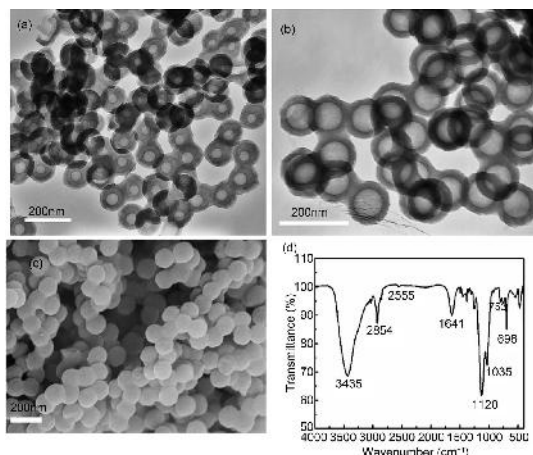


Figure 2. (a)-(b) TEM images, (c) SEM images and (d) FTIR spectra of THSS samples

because SiO₂ formed by MPTS hydrolysis were the reunion of Si-O-Si. The morphology of the obtained SHSS recorded in Figure 3(c) exhibits uniform spherical shape with the size of 100 nm. Figure 3(d) displays FTIR spectroscopy of as-synthesized SHSS structure, in which the structural change of hollow silica spheres can be observed. The absorption peaks around 698 and 753 cm⁻¹ are attributed to the phenyl group, and the peak at 1035 cm⁻¹ is assigned to the vibration of Si-O-Si. The pair peaks at 1641 cm⁻¹ and 3435 cm⁻¹ are assigned to the O-H bond. In addition, the peak at 2555 cm⁻¹ has vanished in comparison to Figure 2(d), but appearance of a new peak at 1450 cm⁻¹ can be attributed to the absorption peaks of sulfonic group, indicating mercapto group (S-H) has been oxidized to sulfonic groups.

3.3. The Structure and Morphology of MHSS by Varying the Molar Ratio of [Fe²⁺]/[Fe³⁺]

Figure 4 shows the TEM images of MHSS prepared by different ratio of Fe²⁺ to Fe³⁺.

The TEM image of MHSS-a (Figure 4(a)) demonstrates that the well dispersed MHSS has a uniform spherical hollow structure with a diameter around 105 nm and wall thickness of approximately 6 - 6.5 nm. It is obvious that black Fe₃O₄ completely coated on silica layer when the ratio of [Fe²⁺]/[Fe³⁺] is 2:1 and the iron concentration is 0.10 M, because both the ratio of Fe²⁺ to Fe³⁺ and the total iron concentration are two key factors influences the size of magnetic particles on the surface of MHSS.

Generally speaking, under the perfect condition, coprecipitation occurs when the mole ratio of [Fe²⁺] to [Fe³⁺] is 1:2. But actually, the Fe²⁺ is easily oxidized when exposed in air, so the mole ratio of [Fe²⁺] to [Fe³⁺] is kept constant at 2:1 to avoid formation of

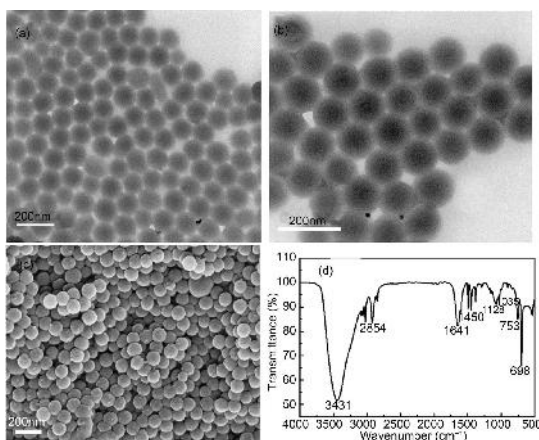


Figure 3. (a)-(b) TEM images, (c) SEM images and (d) FTIR spectra of SHSS samples.

On the other hand, deposition speed of Fe³⁺ ions are faster than that of Fe²⁺ ions, due to their different $\log K$ between Fe³⁺ ion and Fe²⁺. The $\log K$, Fe(OH)₃ = 3.98 × 10⁻³⁸, and $\log K$, Fe(OH)₂ = 7.94 × 10⁻¹⁶, so the precipitate of Fe³⁺ and Fe²⁺ occur at pH 3 - 4 and pH 8 - 9 based on the calculations from their $\log K$ respectively. When coprecipitation of Fe³⁺ with Fe²⁺ ions occurs at 2:1 ratio of [Fe²⁺] to [Fe³⁺], the precipitate of Fe³⁺ preferentially occurs, then coprecipitation of Fe²⁺ with Fe³⁺ promoted the Fe₃O₄ crystal deposition on SHSS surface. But when the mole ratio of [Fe²⁺] to [Fe³⁺] is 2:2, shortfall amount of Fe²⁺ ions are not enough to support whole Fe³⁺ ions approaches to Fe₃O₄ crystal deposition, due to Fe²⁺ liable to be oxidized by trace amount oxygen in the air. Thus, the excess Fe³⁺ ions can accelerate the electrostatic adsorption between new-formed Fe₃O₄ crystals, resulting in formation of MHSS-b with severe aggregation on SHSS surface, as shown in Figure 4(b).

Whether an absence of Fe³⁺ ions is favorable to Fe₃O₄ crystal deposition on SHSS surface, there is unsatisfied answer shown in Figure 4(c). It is because at 2:0 ratio of [Fe²⁺] to [Fe³⁺], the Fe³⁺ ions employed for Fe₃O₄ crystal deposition can only be obtained by oxidization of Fe²⁺ with trace hydrogen peroxide residued in synthesis process. Therefore few obtained Fe³⁺ ions can be applied to participate Fe₃O₄ crystal deposition on SHSS surface, which leads to generation of MHSS-c with the small amount of magnetic particles covered on SHSS surface (Figure 4(a)) [21].

Second, the influence of the total iron concentration must be considered, when the mole ratio of [Fe²⁺] to [Fe³⁺] is controlled at 2:1, and the total iron concentration is 0.05 M, the image of MHSS-d recorded in Figure 4(d) still shows hollow silica/magnetic composite spheres, it can be seen Fe₃O₄ layer of 2 - 3 nm thickness are coated on SHSS surface, which is much thinner than the Fe₃O₄ coating layer prepared at the total iron concentration of 0.10 M. It demonstrates that total iron concentration can influence the thickness of Fe₃O₄ coating layer on the SHSS surface, appropriate iron concentration can improve Fe₃O₄ crystal deposition on the SHSS surface, less iron concentration can only form thin Fe₃O₄ coating layer.

To further confirm the crystalline structure, XRD measurement was used to analyze the sample of varying the concentration of iron salts and different ratio of [Fe²⁺]/[Fe³⁺].

The diffraction peaks of the particles synthesized in this study were measured to be $2\theta = 29.70, 35.06, 42.71, 56.60, 62.20$, corresponding to (2 2 0), (3 1 1), (4 0 0), (5 1 1) and (4 4 0) crystal planes of the Fe₃O₄ respectively (Figure 5). It can be found that well-resolved diffraction peaks appeared on the pattern, and the pattern can be indexed to Fe₃O₄ (JCPDS#79-0418) according to the reflection peak positions and relative intensities, which confirms the magnetite structure of this sample.

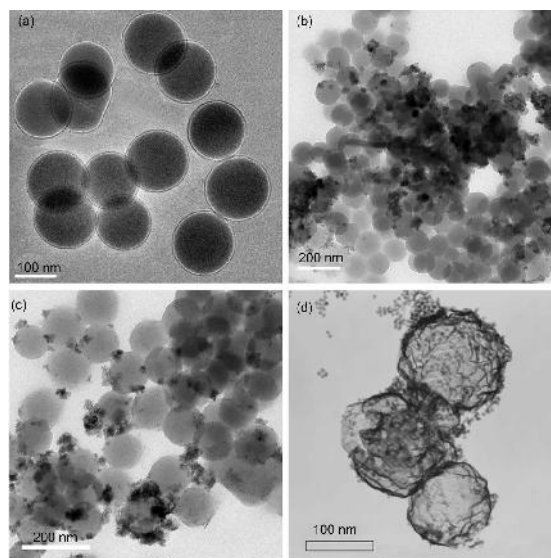


Figure 4. TEM of magnetite nanoparticles prepared at various iron salts concentrations and the molar ratio of [Fe²⁺]/[Fe³⁺]: (a) 0.10 M, 2:1, MHSS-a; (b) 0.05 M, 2:2, MHSS-b; (c) 0.05 M, 2:0, MHSS-c; and (d) 0.05 M, 2:1, MHSS-d.

4. Conclusion

In this paper, an efficient functionalized SiO₂ sphere templating route has been developed to prepare magnetic hollow silica spheres (MHSS) with uniform 70 nm cavity diameter size and 15 nm shell thickness respectively. The unit cell parameters of them have been calculated according to the results of indexing to the XRD pattern, they all belong to monoclinic symmetry. The MHSS-a has a largest cell angle () of unit cell, so having a perfect spherical morphology with the highest saturation magnetization at 34.38 emu/g. The magnetic properties and morphologies of MHSS were affected by the [Fe²⁺]/[Fe³⁺] molar ratio and the iron salts concentration. As in vivo application, the 99Tcm labelled MHSS were injected into the mice to study the biodistribution of magnetic nanoparticles in different organs, and the results revealed that MHSS were found to accumulate in the spleen, lung and liver, showing obvious magnetic targeting effects in the mouse. The findings demonstrate that magnetic hollow silica spheres have great potential in the magnetic targeted drug delivery system

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