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# Fabrication of magnetic porous hollow silica drug carriers

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# Fabrication of magnetic porous hollow silica drug carriers using $CaCO_3/Fe_3O_4$ composite nanoparticles and cationic surfactant double templates

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Magnetic porous hollow silica nanosphere is a new class of structured nanomaterials for drug delivery. In this paper, we report a synthesis of magnetic porous hollow silica nanospheres (MPHSNs) using $CaCO_3/Fe_3O_4$ composite nanoparticles and cationic surfactant double templates. $Fe_3O_4$ nanoparticles were first mixed into $CaCO_3$ using rotating packed bed forming $CaCO_3/Fe_3O_4$ composite nanoparticles. Tetraethoxysilane was then added as precursor to form silica layer on the surface of $CaCO_3/Fe_3O_4$ composite nanoparticles, while hexadecyltrimethylammonium bromide was used as a second template to direct the formation of porous silica shells. After the calcination of the surfactants and etching away $CaCO_3$, MPHSNs were formed with the magnetite nanoparticles remaining in the cores. Transmission electron microscopy was applied for the nanostructure determination. The pore size can be measured by micromeritics analyzer. Magnetic properties of MPHSNs were measured by a superconducting quantum interface device. Zero-field-cooled and field-cooled magnetization data in the temperature range of 5–300 K show that the MPHSNs are superparamagnetism above the blocking temperature and ferromagnetism below the blocking temperature after the calcination. The MPHSNs can be used as potential nanocarriers for targeted delivery and controlled releasing. © *2008 American Institute of Physics*. [DOI: 10.1063/1.2837490]

Magnetic nanoparticles have been widely used for drug delivery, magnetic resonance imaging, hyperthermia cancer treatment, and bioseparation.[1–4] The fabrication of biocompatible and nontoxic magnetically directed nanocarriers for targeted delivery is very crucial for the practical applications in nanomedicine, especially for tumor therapy.

On the other hand, controlled releasing is another important issue for nanomedicine fabrication. Mesoporous silica, as one kind of drug carrier, attracts more attention for controlling drug release since the pore size and high pore volume make this material suitable as a potential host for a variety of chemical compounds, such as molecules with biological activity.[5–8] Proper integration of mesoporous silica with magnetic nanoparticles could generate a new class of drug carrier for targeted delivery and controlled release, such as magnetic porous hollow silica nanoparticles. Yin *et al.*[9] reported the successful fabrication of porous nanoparticles without introducing magnetic materials. Li *et al.*[10] also demonstrated porous silica for slow release but without any magnetic properties. Caruso[11] presented the fabrication of submicrometer hollow particles using colloidal particles as templates without porous feature. Recently, Wang *et al.*[12] fabricated hierarchy Ni hollow microspheres. However, the direct usage of this magnetic hollow for drug delivery will generate sever toxicity for human body.

In the past, we have successfully fabricated magnetic hollow silica nanospheres with magnetic nanoparticles embedded in the shells as drug carriers.[13,14] The magnetic hollow silica nanospheres with a characteristics of superparamagnetism are considered to be the proper carriers for drug delivery, which were designed to prevent easy aggregation and rapid biodegradation. The toxicity test confirmed that the magnetic nanoparticles embedded silica hollow nanospheres are safe for drug carriers.[14] In this paper, different from our former approaches, $Fe_3O_4/CaCO_3$ composite particles were prepared by rotating packed bed reactor first. Then, the composite particles were used as templates to fabricate hollow structure and the magnetic nanoparticles remain in hollow core after the removal of $CaCO_3$. The hexadecyltrimethylammonium bromide (CTAB) cationic surfactant was used as a second template to form porous structure in the silica shells. Therefore, the magnetic porous hollow silica nanospheres (MPHSNs) as drug carriers can be synthesized.

To synthesize $Fe_3O_4/CaCO_3$ composite particles, 3500 ml of 5.4 wt % $Ca(OH)_2$ suspension was added to the reactor with rotating speed of 750 rpm and circulated at 400/h using rotated packed bed (RPB).[7,13,14] After 10 min, 75 ml of a methanolic dispersion of $Fe_3O_4$ nanoparticles (15 mg/ml) was added to the system and then $CO_2$ gas was introduced at a rate of 100/h. Superparamagnetic $Fe_3O_4$ nanoparticles were prepared by a method based on the hydrolysis of chelate metal alkoxide complexes at elevated temperature in solutions of diethylene glycol, which was published elsewhere.[15] $CO_2$ and $Ca(OH)_2$ contacted at a converse direction and reacted in the reactor. The suspension was circulated continuously during the process. When the

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*p*H value of the suspension reached 7.4, $CO_2$ gas was stopped and the reaction was ended. The temperature of the suspension was kept below 25 °C by circulating water during the entire reaction (about 70 min), which was monitored by a thermometer. The obtained suspension was filtrated and dried at 70 °C in vacuum for 6 h to achieve $Fe_3O_4/CaCO_3$ composite nanoparticles. Then, a sol-gel method was applied to prepare MPHSNs.

A 3 g of as-prepared $Fe_3O_4/CaCO_3$ composite nanoparticles was dispersed ultrasonically into a mixture of 60 ml ethanol (A APer Acohol and Chemical Co.) and 40 ml distilled water for 30 min in a beaker and then mechanically stirred for 30 min in a three-neck flask. Then, 0.74 g of CTAB (+99%) (Johnson Matthew Company) was added to the above suspension and the obtained mixture was dispersed ultrasonically for another 20 min.[16–18] After adding 34 ml ammonia (30%) (J.T. Baker), 3.7 ml tetraethoxysilane (TEOS) (99.9%) (Johnson Matthew Company) was dropped into the reaction mixture within 10 min to reach the *p*H value of 11. The system was stirred at 500 rpm for 2 h at room temperature. The obtained suspension was aged for 6 h at room temperature and then filtrated. The cake was dried at 50 °C for 6 h and calcined at 550 °C for 5 h to remove the surfactant template. After calcination, the product was immersed in diluted acetic acid (J.T. Baker) solution (HAc:H2O=1:15) for 5 h to remove the $CaCO_3$ cores. After three washes, two times with distilled water and one time with alcohol, and drying at 75 °C for 18 h, the MPHSNs with porous structure in the shells were obtained.

A JEOL 2010 transmission electron microscope (TEM) at an accelerating voltage of 200 kV was used to examine the morphologies and sizes of the particles. EDAX energy dispersive spectroscopy (EDS) was used to determine the composition of nanoparticles. ASAP2010 surface area analyzer was applied to measure the pore size distribution of the magnetic porous hollow silica by Barrett–Joyner–Halenda (BJH) method. The magnetic properties were measured with a Quantum Design MPMS-5S superconducting quantum interference device (SQUID) magnetometer.

Figure 1(a) is TEM micrograph showing the successful synthesis of $Fe_3O_4/CaCO_3$ composite particles. The diameters of $CaCO_3$ are about 60–90 nm with magnetic nanoparticles (darker dots) embedded in the cores. The nanoparticles are a little bit aggregated because of the nature of nanoparticles. The EDS analysis is clearly evident that C, O, Ca, and Fe appear in the spectrum besides the Cu peak from TEM grid. The composite nanoparticles are composed of $CaCO_3$ and $Fe_3O_4$ nanoparticles.

The CTAB was used as a second template while forming silica shells on the composite nanoparticles. After the calcination of CTAB surfactant and the removal of $CaCO_3$ by using weak acetic acid, the magnetic nanoparticles can be clearly seen in the silica hollow cores, as shown in Fig. 2. The pore size can be evaluated by nitrogen adsorption-adsorption isotherms and BJH method, as shown in Fig. 3. The isotherms of the sample with CTAB have a sharper infection than that without adding a surfactant, representing uniform pore size formation during capillary condensation. The sharp peak, seen in Fig. 3(b), shows a quite uniform

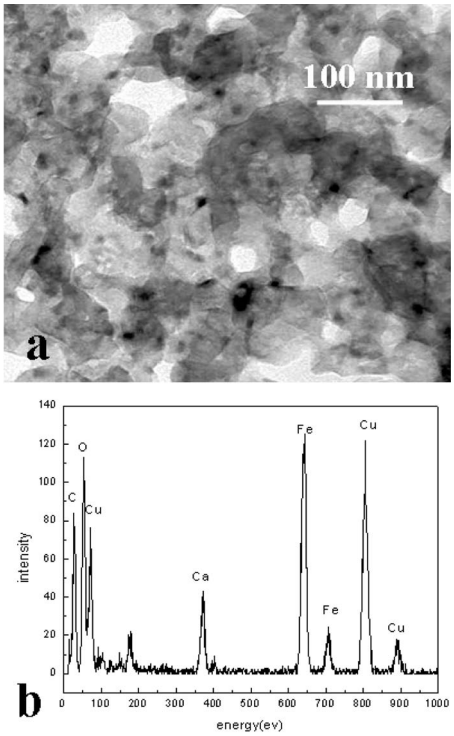


FIG. 1. $Fe_3O_4/CaCO_3$ magnetic composite nanoparticles. (a) Bright-field TEM micrograph. The $Fe_3O_4$ nanoparticles appear in darker dots embedded in the $CaCO_3$ particles. (b) The EDS spectrum of the composite particles.

pore size distribution around 3.9 nm. The nanopores also play as nanochannels connecting the outside of hollow silica and the core for drug loading.

The magnetic properties of the MPHSNs were measured by SQUID. Zero-field-cooled (ZFC) and field-cooled (FC) magnetization data measured in the temperature range of 5–300 K are shown in Fig. 4(a). In the ZFC measurement, the initial field was set to zero when cooling the sample from 300 to 5 K. A field of 100 Oe was applied and the magnetization was measured as the sample was heated from 5 to 300 K. In FC measurement, a field of 100 Oe was applied as the sample was cooled from 300 to 5 K and the magnetization was measured as the sample was heated from 5 to 300 K in the field of 100 Oe. The ZFC curve shows a maximum at 98.5 K, which is the blocking temperature ($T_B$) of the magnetic nanoparticles in the MPHSNs. Such a behavior is the characteristic of superparamagnetism and is due to the progressive blocking of the magnetic moment of the nanoparticles when decreasing the temperature. The MPHSNs exhibit superparamagnetism and ferromagnetism above

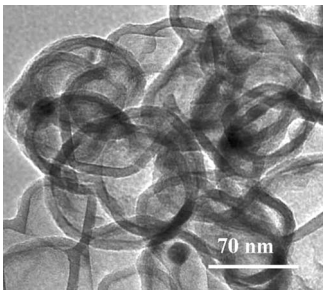


FIG. 2. TEM image of MPHSNs. The magnetic nanoparticles remain in the cores of hollow silica nanospheres.

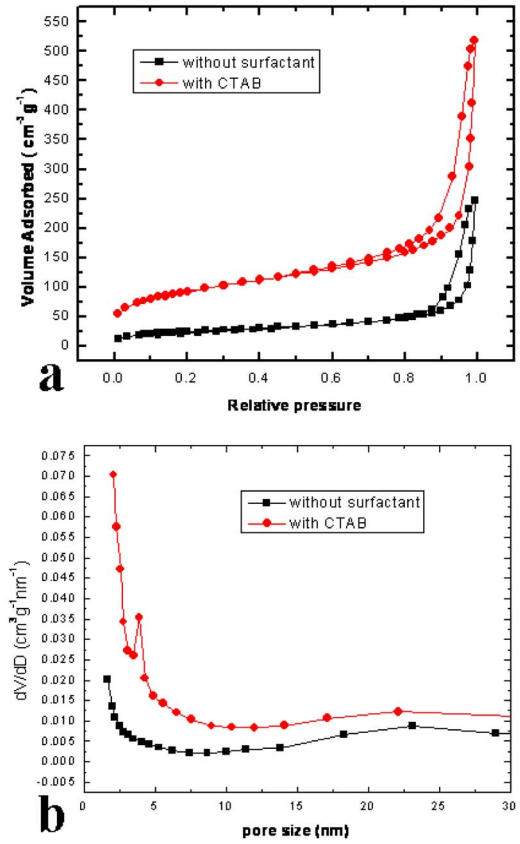


FIG. 3. (Color online) (a) Nitrogen adsorption isotherm for the MPHSNs and (b) the distribution of pore size with and without adding CTAB cationic surfactant.

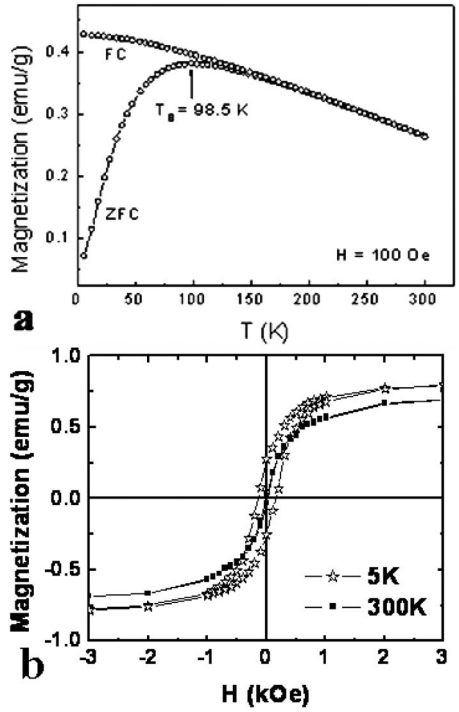


FIG. 4. The magnetic properties of MPHSNs. (a) Temperature dependence of magnetization at ZFC and FC conditions and (b) hysteresis loops at 5 and 300 K.

and below the blocking temperature, respectively. To ensure these features, the field-dependent hysteresis loops of the MPHSNs were measured at temperature both below and above the blocking temperature, as shown in Fig. 4(b). The hysteresis loop at 5 K shows a saturation magnetization of 0.81 emu/g (at the field of 10 000 Oe) and a coercivity of 145 Oe, which confirms that the MPHSNs are ferromagnetic below the blocking temperature. The absence of coercivity in the hysteresis loop at 300 K indicates a superparamagnetic behavior. The MPHSNs have superparamagnetic properties, which means they can be attracted by a magnetic field but retain no residual magnetism when the magnetic field is removed at room temperature.

In a summary, double template method has been used to fabricate MPHSNs. The composite $Fe_3O_4/CaCO_3$ nanoparticles with size of 60–90 nm were synthesized using PRB method first. Then, the composite nanoparticles were used as templates to form hollow silica nanospheres and cationic surfactant CTAB were employed as a second template to form pores while coating silica on the composite nanoparticles. The pores with the size of 3.9 nm connect the outside and inside of the hollow silica shell and the magnetic nanoparticles remaining in the core will cause less interaction and toxicity free during biocycling. The SQUID measurement of the MPHSNs demonstrates a superparamagnetic characteristic. The MPHSNs can be used as potential drug carriers for targeted delivery and controlled releasing.

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