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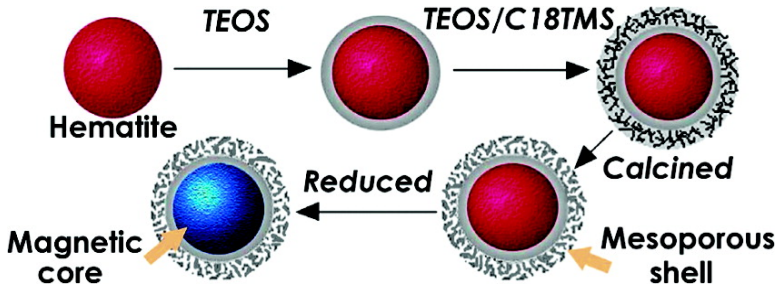

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Fabrication of Uniform Magnetic Nanocomposite Spheres with a Magnetic Core/Mesoporous Silica Shell Structure

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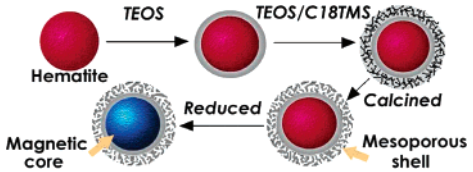
Since the discovery of M41S silica in 1992, mesoporous materials have offered a wide range of applications[1] in catalysis, separation, sensors, and dye lasers due to their high surface areas, well-defined pore structures, and tunable pore sizes.[2] In recent years, a new application of mesoporous silica as drug vehicles in drug delivery systems has also been explored[3] since silica is nontoxic and highly biocompatible. An important reason is that the wall of the pores containing free silanol groups can react with appropriate drug functional groups. However, the use of bulk mesoporous silica materials in many applications, especially in targeted drug delivery mechanisms as carrier and in the separation of certain substances from multiphase complex systems, suffers from some inherent limitations.

Magnetic separation provides a convenient method for the removal of magnetizable particles by applying an appropriate magnetic field. If one could combine the advantages of mesoporous silica and magnetic particles to fabricate a nanocomposite with high surface area and magnetic separability, a novel adsorbent material and targeted drug delivery matrix which carries the drug directly to a specific organ or location in the body under an external magnetic field could be available. Iron oxide, cobalt, or other magnetic nanoclusters have been incorporated into the pores of mesoporous silica, such as MCM-41 and SBA-15.[5] However, in those cases, the pores were obviously clogged by the introduced particles. Meanwhile, the intensity of magnetism of the loaded silica mesoporous composite was weak due to its low loading level of magnetic clusters. Very recently, Lu et al.[6] reported a new method for fabricating magnetic mesoporous silica with open pores by grafting cobalt nanoparticles on the outer surface of the SBA-15 particles. Wu et al.[7] also synthesized magnetic composite with mesoporous silica being coated on Fe_3O_4 cores. However, the shape of the resultant magnetic particles is irregular with a wide particle size distribution from hundreds of nanometers to several microns. In addition, the particle sizes reported in all of these studies mentioned above are too large to be used for drug delivery, in which a particle size range between 50 and 300 nm is strictly demanded. Above 300 nm, a significant proportion of particles will be trapped in the lungs and liver, while too small particle size will cause the magnetic forces of these tiny particles to be too weak to work for separation or drug delivery.[4] Despite of these application limitations inherent for targeted drug delivery, all of these works above really gave us some important hints to develop a mesoporous material-based magnetic carrier composite. Here, we report a novel scheme to fabricate uniform magnetic nanospheres with a magnetic core/mesoporous silica shell (MFeCMS) structure, and its drug storage and in vitro release property are demonstrated.

The synthesis strategy is designed and presented in Scheme 1. Generally, the shape and size of Fe_3O_4 particles are difficult to be controlled, which is an inherent drawback for fabricating MFeCMS nanospheres of uniform size distribution directly from Fe_3O_4. Herein

Scheme 1. Illustration of Synthesis of MFeCMS Nanospheres



a kind of uniform hematite particles was employed as the initial cores, which is facile to prepare. A thin and dense silica layer was deposited on the surface of hematite particles of desired thickness in order to protect the iron oxide core from leaching into the mother system under acidic circumstances. Then, the mesoporous silica shell was formed from simultaneous sol−gel polymerization of tetraethoxysilane (TEOS) and *n*-octadecyltrimethoxysilane (C18TMS) followed by removal of the organic group. Finally, the hematite cores of the nanospheres were reduced in a flowing gas mixture of H_2 and N_2 to produce the final MFeCMS nanospheres.

The initial hematite particles are uniform with the diameters of ca. 120 nm (Supporting Information). These uniform cores resulted in a narrow distribution of the final particle sizes. The TEM image of the silica-coated initial hematite particles (Supporting Information) shows that the silica coating is also uniform with a thickness of ca. 20 nm, which can be tuned from 10 to 50 nm by varying the TEOS concentration from 0.5×10^{-3} to 2.0×10^{-2} M. Without this dense coating, the iron oxide cores would leach into the mother system under acidic circumstances rather rapidly through the pores of the mesoporous shell. A compositional image of backscattered electrons (Figure 1a) of the hematite core/mesoporous silica shell

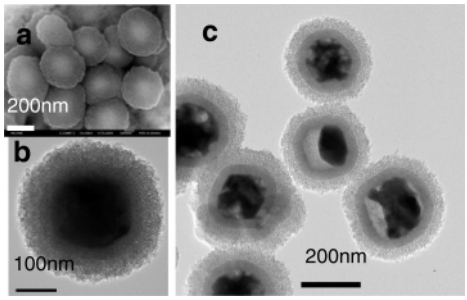


Figure 1. Backscattered electrons image (a) and TEM image (b) of HFeCMS nanospheres, and TEM image (c) of MFeCMS nanospheres.

(HFeCMS) particles shows that the particles are spherical in shape and uniform in dimension with particle diameters of ca. 270 nm. It can be seen from Figure 1a that each sphere's center is a little brighter than the shell due to the fact that the atomic number of Fe is larger than Si, which suggests the core−shell structure of the nanospheres. The TEM image of the HFeCMS nanospheres (Figure 1b and Supporting Information) shows that the yield of the core/shell spheres is 100% and the mesoporous silica shell is about 50

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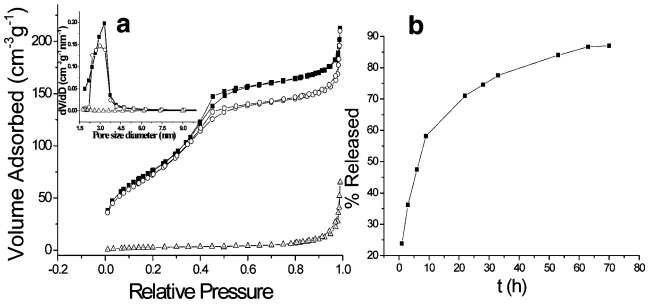

Figure 2. N_2 adsorption isotherms and corresponding pore size distribution curve (a) of HFeCMS (■), MFeCMS (○), and MFeCMS filled with ibuprofen (△); ibuprofen released from MFeCMS curve (b).

nm in thickness, which could be easily tuned by changing the concentration of the TEOS/C18TMS mixture. After removing the organic group of C18TMS, which served as the porogen during the growth process of the mesoporous layer, the pores are revealed to be randomly arranged in the mesoporous silica shell.

The nitrogen adsorption/desorption isotherm (Figure 2a) indicates a linear increase in the amount of adsorbed nitrogen at a low relative pressure ($P/P_0 = 0.4$). According to the IUPAC, it can be classified as a type of H2 hysteresis. The steep increase in nitrogen at relative pressures in the range between $P/P_0 = 0.4$ and 0.6 reflects a narrow pore size distribution, which also can be seen from the inset curve in Figure 2a. Calculated from the desorption branch of the nitrogen isotherm with the BJH method, an average pore diameter is determined to be 3.8 nm, which can be tuned by changing the molar ratio of TEOS/C18TMS.[8] The BET surface area and the BJH desorption cumulative volume of pores of HFeCMS nanospheres are 283 m^2/g and 0.349 cm^3/g, respectively, which are considerably large since all the hematite cores have been included in the calculations.

After reduction, the color of the powder changes from red to deep black, indicating the reduction of the hematite cores. The TEM image of the reduced MFeCMS nanospheres (Figure 1c) shows that most cores have shrunk while the shell remains unbroken. In the XRD pattern (Supporting Information), the main peaks respectively matching well with the standard PDF data confirm that the reduced cores are a composite of Fe_3O_4 and Fe. The composition of the reduction product can be controlled, according to the typical reduction process of hematite: α-$Fe_2O_3 \rightarrow Fe_3O_4 \rightarrow FeO \rightarrow Fe$, by altering the reduction temperature or time.[9] The H2-type hysteresis of MFeCMS (Figure 2a) is maintained, and the surface area and the pore volume are still high, which indicate that the mesoporous structure still remains after reduction.

To explore its capability as drug carrier, ibuprofen, a typical anti-inflammatory drug, was introduced into the pores of MFeCMS. The characteristic pore filling step disappears in the N_2 adsorption isotherm (Figure 2a) after ibuprofen is stored, and the pore volume decreases by 70%, which indicates most of the pores have been filled. The uptake amount of ibuprofen is ca. 12 wt %, as assessed by TG analysis. Figure 2b shows the release behavior of ibuprofen in a simulated body fluid (SBF) over a 70 h period. The release was relatively fast during the first 24 h, but decreased with time and reached a value of 87% after 70 h.

The room-temperature magnetization curve (Figure 3a) shows a large magnetic hysteresis loop, which depicts the strong magnetic response to a varying magnetic field. The saturation magnetization

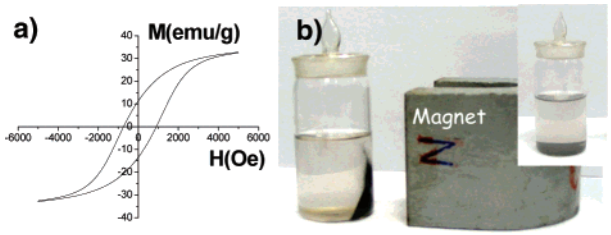

Figure 3. The magnetic properties of MFeCMS nanospheres: (a) room temperature magnetization curve, and (b) separation from solution under an external magnetic field.

value of MFeCMS nanospheres is 27.3 emu/g, which can be adjusted by controlling the synthesis parameters. The magnetic separability of such magnetic nanoparticles was tested in ethanol by placing a magnet near the glass bottle. The black particles were attracted toward the magnet within 20 s (Figure 3b), demonstrating directly that the core−shell nanospheres possess magnetic properties. This will provide an easy and efficient way to separate MFeCMS particles from a sol or a suspension system and to carry drugs to targeted locations under an external magnetic field.

In conclusion, we have successfully fabricated a novel kind of magnetic core/mesoporous silica shell nanospheres with a uniform particle diameter of ca. 270 nm. The inner magnetic Fe_3O_4/Fe core endues the nanoparticles with magnetic properties. The outer mesoporous silica shell shows high enough surface area and pore volume. Ibuprofen can be stored in the channels of the nanospheres, and most of the drug molecules incorporated can be released to the SBF in 70 h. Therefore, we expect that this material may be applicable in targeted drug delivery and multiphase separation in the future.

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Supporting Information Available: TEM images and XRD patterns of the different particles, and the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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