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In situ synthesis and characterization of magnetic nanoparticles in shells of biodegradable polyelectrolyte microcapsules

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ABSTRACT

Hollow microcapsules with the shell composed of biodegradable polyelectrolytes modified with the maghemite nanoparticles were fabricated by *in situ* synthesis. The nanoparticles were synthesized from the iron salt and the base directly on the capsule shells prepared by "layer by layer" technique. An average diameter of the capsule was about 6.7 μm while the average thickness of the capsule shell was 0.9 μm. XRD, HRTEM, Raman and Mössbauer spectroscopy data revealed that the iron oxide nanoparticles have the crystal structure of maghemite γ-Fe_2O_3. The nanoparticles were highly monodisperse with medium size of 7.5 nm. The Mössbauer spectroscopy data revealed that the nanoparticles have marked superparamagnetic behavior which was retained up to room temperature due to slow spin relaxation. Because of that, the microcapsules can be handled by an external magnetic field. Both these properties are important for target drug delivery. Based on the Mössbauer spectroscopy data, the spin blocking temperatures T_B of about 90 K was found for the particles with size $D \leq 5$ nm and $T_B \approx 250$ K for particles with $D \geq 6$ nm. The anisotropy constants K were determined using the superparamagnetic approximation and in the low temperature approximation of collective magnetic excitation.

1. Introduction

Magnetic nanostructures are considered as promising materials in high-density magnetic storage devices, magnetic heads, and sensors [1,2]. Recently, more attention was paid to the application of magnetic nanostructures in biology and medicine and focused mainly on the targeted drug delivery [3], hyperthermia treatment [4], magnetic resonance imaging (as contrast media) [5], separation of biochemical products [6] and gene manipulation and immunoassays [7]. For the application of magnetic nanoparticles in these areas, they should be non-toxic, chemically stable and biocompatible with cells, tissues and the whole body. Iron oxides (especially magnetite-Fe_3O_4, maghemite γ-Fe_2O_3 and hematite α-Fe_2O_3) were widely studied [8,9] and are gradually implemented in various fields of biomedicine. The polyelectrolyte capsules prepared by a layer-by-layer technique are promising drug delivery systems [10,11]. But a simpler way for targeting of polyelectrolyte capsules is the magnetic modification, which is possible by the incorporation of magnetic nanoparticles into capsules.

One of the main methods for the adaptation of polyelectrolyte capsules for targeted drug delivery by magnetic field is the electrostatic adsorption of previously synthesized magnetic nanoparticles on the surface of oppositely charged layer of the capsule shell [12–14]. In addition to this physical approach there are some chemical approaches for the magnetic modification of polyelectrolyte capsules. Magnetic nanoparticles were synthesized inside the capsules due to the possibility of keeping the component concentrations in a closed volume [15]. But the presence of nanoparticles inside the capsule reduces the effective volume of the cavity for functional compound encapsulation.

Only a few works are devoted to the magnetic modification of polyelectrolyte shells by chemical techniques. In Ref. [16], spherical shells composed of polyallylamine and magnetite nanoparticles were obtained by formation of the capsule internal layers from polyallylamine/citrate–ion complex. Then the anions were replaced with hydroxide ions and capsules were placed in a solution of two- and trivalent iron salts for magnetite preparation followed by removing the external polyelectrolyte layers in a highly alkaline medium. In Ref. [17], the *in situ* synthesis of magnetite Fe_3O_4 nanoparticles on polyelectrolyte shells was performed using a palladium catalyst adsorbed on polycation layers. Magnetite was obtained by nitrate ion reduction with the aid of dimethylboranamine in the presence of trivalent iron ions in an aqueous suspension of capsules at 60 °C.

Previously, we proposed alternative technique for the magnetic modification of polyelectrolyte capsules [18]. Synthesis of magnetite nanoparticles by chemical condensation of Fe^{3+} and Fe^{2+} ions in a suspension of capsules from polyallylamine and polystyrene sulfonate has led to the preparation of magnetic capsules. The process was performed under heating of the reaction mixture at 80 °C. However, dealing with

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biochemical materials, in particular for the encapsulation of proteins, such heating is undesirable.

In this work, we have modified polyelectrolyte capsules by this method using biopolymer polylysine and dextran sulfate and heating the reagents to a temperature suitable for biomaterials. After formation of the nanocomposite capsules the comprehensive study of their structural and magnetic properties was performed. The particular efforts in this work were devoted to distinguish between magnetite Fe_3O_4 and maghemite γ-Fe_2O_3 nanoparticles and to the study the size effect on the magnetic behavior of these materials.

Usually, the X-ray diffraction (XRD) and high resolution transmission electron microscopy (HRTEM) are mainly used for the characterization of magnetic nanocapsules. Meanwhile magnetite Fe_3O_4 and maghemite γ-Fe_2O_3 have the similar spinel-type crystal structure and their identification by structural methods is hardly possible especially if the system contains a mixture of various iron oxide compounds. In our study different and complementary techniques were used for the evaluation of particle structural, physicochemical, and magnetic properties. Along with XRD and TEM, we applied the Mössbauer spectroscopy and Raman spectroscopy for the particle characterization.

2. Sample preparation and characterization techniques

2.1. Materials

Poly-L-lysine hydrobromide (PLL, Mw 40–60 kDa), sodium chloride, calcium chloride, sodium carbonate, trisodium salt of ethylenediamine tetraacetic acid (EDTA) and iron(II) chloride tetrahydrate were purchased from Sigma-Aldrich (Germany), and iron(III) chloride hexahydrate was purchased from Acros Organics (US). Dextran sulfate sodium salt from *Leuconostoc* spp. (DS, Mw ~500 kDa) and ammonium hydroxide were purchased from Fluka, Sweden and US, accordingly.

2.2. Preparation of hollow capsules

We used the particles of calcium carbonate $CaCO_3$ as cores for microcapsules. The spherical $CaCO_3$ microparticles were prepared by colloidal crystallization from supersaturated solution as previously described in Ref [19]. The rapid mixing of equal volumes of 0.33 M $CaCl_2$ and Na_2CO_3 solutions with further intensive agitation of reaction mixture on a magnetic stirrer during 30 s and suspension exposure for 10–15 min at room temperature without stirring led to the formation of the $CaCO_3$ microspherulites with a typical size of 5–6 μm (Fig. 1(a) and (b)).

Polyelectrolyte capsules were fabricated by layer-by-layer deposition technique [20]. PLL and DS were alternately adsorbed on the surface of core particles from solutions with polymer concentration of 2 mg/mL and NaCl concentration of 11.7 mg/mL (see Fig. 2).

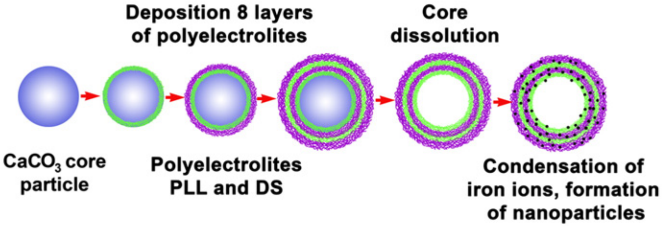

Fig. 2. Scheme of capsule fabrication.

After the adsorption of each polymer layer the capsules were washed three times with deionized water to remove the excess of a polyelectrolyte. The capsule shell with the composition of $(PLL/DS)_4$ was formed by eight cycles of polyelectrolyte adsorption. To obtain hollow capsules, the $CaCO_3$ core was decomposed by EDTA. Scheme of capsule fabrication is shown in Fig. 2.

2.3. Synthesis of magnetic nanoparticles

The *in situ* synthesis of magnetic nanoparticles in a suspension of polyelectrolyte capsules was performed using the Elmore method of magnetite fabrication [21] (chemical condensation of Fe^{3+} and Fe^{2+} ions with molar ratio 2:1 on capsule shells by adding a base):

$$2FeCl_3 + FeCl_2 + 8NH_4OH \rightarrow Fe_3O_4\downarrow + 8NH_4Cl + 4H_2O.$$

Here (↓) means precipitation. In our work 0.15 M iron(III) and iron(II) chloride solutions and suspension of hollow capsules were mixed and heated up to 37 °C in the reaction vessel. Then the vessel was put into a water bath at 37 °C which was placed on a magnetic stirrer. Total mass of iron ions was 0.25%, the number of capsules was approximately 10^8/ml. At intensive stirring 0.75 mL of 25% ammonium hydroxide solution was added to the suspension and the obtained mixture was stirred for 6 min. After that the capsules with iron oxide nanoparticles formed in the shells were washed three times with deionized water under separating the capsules from the supernatant by centrifugation (2000 rpm for 1 min). For further investigation, the nanocomposite capsules were centrifuged and the residue was lyophilized.

2.4. Characterization techniques

The microstructure, phase composition, magnetic and electronic properties of the samples were studied by scanning (SEM) and transmission (TEM) electron microscopy including high resolution TEM (HRTEM), X-ray powder diffraction, Raman spectroscopy, and Mössbauer spectroscopy.

X-ray diffraction studies were performed on a “Belok” station installed on the synchrotron source from a bending magnet of the storage ring in

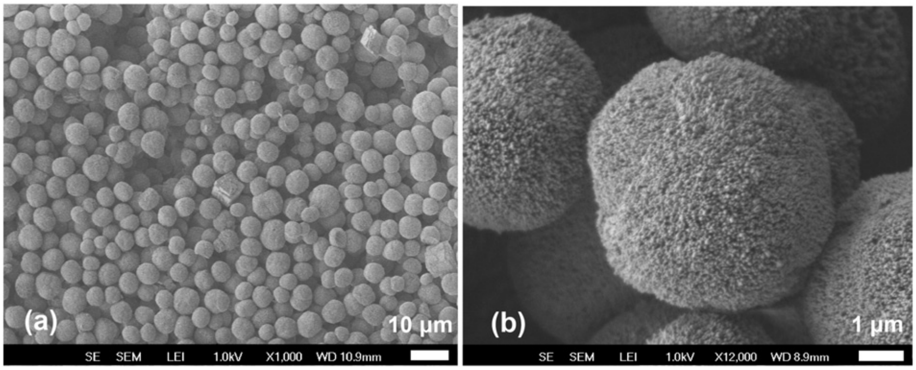

Fig. 1. SEM images of spherical microparticles of the $CaCO_3$ spherulites used as the cores for microcapsules: (a) low magnification image demonstrating the uniform size of the particles and (b) higher magnification image of the particle surface.