

Synthesis of magnetic nanoparticles on the polyelectrolyte microcapsules shells

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INTRODUCTION

Nowadays a great number of scientific works is dedicated to microencapsulation. This technique is of special interest for medicine, particularly for treatment of cancer diseases which demands rather toxic and expensive medical substances. The microencapsulation method allows to deliver drugs to the desired place in organism and control their concentration, which means reducing their amount injected into organism, preventing their influence on healthy tissues and, as a result, increasing the drug effectiveness.

Shells of microcapsules can contain nanoparticles or organic dyes, allowing to target, visualize and open the capsules at the desired place and moment. Specifically, magnetic nanoparticles, being inserted in the shells, allow to use them for high-sensitive disease diagnostics and targeted delivery of biologically active and medical substances to organism [1]. The other potential applications are investigated, for example, the gene therapy based on magnetic heating-initiated hyperthermic effect [2]. The ability of magnetic nanoparticles to warm up under alternating electromagnetic field can be applied for controlled release of encapsulated substance [3].

In the present work, magnetite Fe₃O₄ nanoparticles were synthesized and deposited on polyelectrolyte microcapsules in two ways. After electrostatic adsorption of magnetic nanoparticles by the surface of polyelectrolyte capsules, the latter became magnetic field responsive, which allows to move them to the necessary point using a magnet and apply for the targeted drug delivery to organism. The composition, structure and size of nanoparticles were determined by means of transmission electron microscopy, dynamic light scattering and electron diffraction.

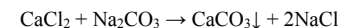
MATERIALS AND METHODS

Materials

In this study the following materials were used: sodium polystyrene sulfonate (PSS) (molecular weight 70 000), polyallylamine hydrochloride (PAH) (molecular weight 70000), disodium ethylenediaminetetraacetate (EDTA), calcium chloride dehydrate (CaCl₂·2H₂O), sodium carbonate (Na₂CO₃), sodium chloride (NaCl), iron (II) chloride tetrahydrate (FeCl₂·4H₂O), iron (III) chloride hexahydrate (FeCl₃·6H₂O), sodium hydroxide (NaOH), citric acid (C₆H₈O₇) from Sigma Aldrich (Germany); ammonium hydroxide from Fluka (the United States). Citrate buffer solution (pH~5) for stabilization of magnetite nanoparticles was prepared by mixing sodium hydroxide and citric acid solutions. Water used in the experiments was purified by the Milli-Q Plus 185 (Millipore, USA) purification system.

Fabrication of polyelectrolyte microcapsules with magnetite nanoparticles in the shell

Calcium carbonate cores of micron size were prepared by mixing calcium chloride and sodium carbonate solutions at room temperature [4], [5]. According to the reaction:

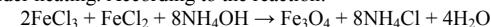


spherical water-insoluble colloid calcium carbonate particles with average diameter of 4.0±0.5 μm were obtained.

The capsule shells were formed during alternate electrostatic adsorption of oppositely charged macromolecules of the polyelectrolytes by the surface of CaCO₃ particles [6]. Eight layers of polyelectrolytes (positively charged PAH and negatively charged PSS, both in NaCl solution) were alternately deposited on the cores. The first layer was PAH, since the surface of CaCO₃ cores had a negative charge [7]; the outer surface of the shell was negative as well, since the last layer consisted of PSS. As a result, spherical microcapsules with diameters of ~4 μm were produced. Since CaCO₃ cores have uneven, spiky surface, the fabricated polyelectrolyte shells attain porous, spongy structure with pore diameter of ~20-70 nm [4].

An EDTA salt solution was added to the suspension of colloid particles coated with polyelectrolyte shells in order to remove the CaCO₃ cores. As a result, the cores were dissolved and calcium was removed from the capsules due to the formation of a stable complex of Ca with EDTA [4]. Thus, the hollow polyelectrolyte shells were obtained.

To prepare magnetite nanoparticles the commonly known technique was used at first: chemical coprecipitation of Fe³⁺ and Fe²⁺ ions in molar ratio 2:1 by a base (ammonium hydroxide NH₄OH) in aqueous solution under heating. According to the reaction:



the suspension of magnetite nanoparticles was obtained.

In order to prevent aggregation of nanoparticles citrate buffer solution was added to the suspension which resulted in stabilization of nanoparticles by negatively charged citric ions.

Suspension of magnetic nanoparticles was added to the precipitate of microcapsules of eight PAH/PSS layers on CaCO₃ cores. After adsorption of the particles by surface and pores of polyelectrolyte shells, the cores were dissolved by adding an EDTA salt solution (pH~6.5). Thus, hollow polyelectrolyte microcapsules with magnetite nanoparticles in the shells were obtained.

Then, a novel method of producing Fe₃O₄ nanoparticles was proposed: Fe³⁺ and Fe²⁺ ions in molar ratio 2:1 were coprecipitated directly on polyelectrolyte microcapsules on CaCO₃ cores under heating, i.e. magnetite nanoparticles were synthesized in aqueous suspension of microcapsules. In this case, the nucleation seeds of magnetite nanoparticles are adsorbed right after their formation onto the surface and pores of capsules and are therefore stabilized, so the stabilization by citric ions is not needed.

Methods of Investigation

During the fabrication of polyelectrolyte shells the state of microcapsules was periodically checked for aggregation of capsules and crystallization of cores. Light microscope Nikon Eclipse E200 was used for visual observation. The images of microcapsules with magnetite nanoparticles in the shells were obtained by means of transmission electron microscopes Philips EM300 and Philips CM12. Magnetite nanoparticles, produced apart from microcapsules and stabilized by citric ions, were investigated using dynamic light scattering analysis in order to determine their sizes and size distribution. The composition and structure of nanocrystals synthesized directly on the surface of microcapsules were investigated using electron diffraction method.

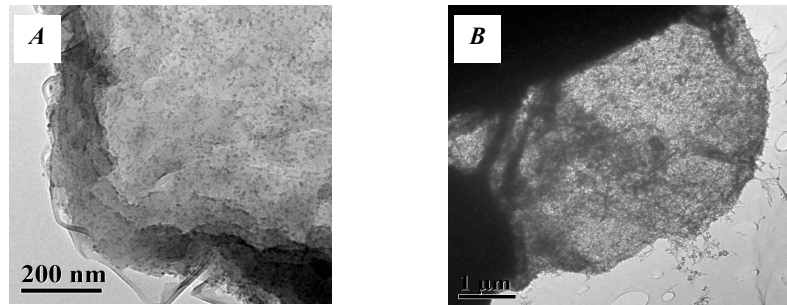


Figure 1: TEM images of polyelectrolyte microcapsules with magnetite nanoparticles synthesized apart from capsules (A) and in the suspension of capsules (B).

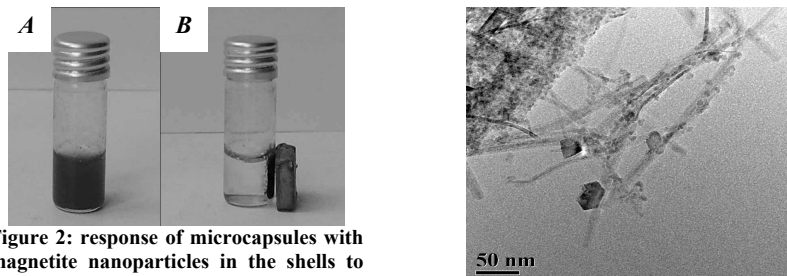


Figure 2: response of microcapsules with magnetite nanoparticles in the shells to the presence of magnetic field: (A) microcapsules are suspended in water, and (B) microcapsules are attracted to a magnet.

Figure 3: High-resolution TEM image of magnetite nanoparticles synthesized in the suspension of microcapsules.

RESULTS AND DISCUSSION

Dynamic Light Scattering Analysis

By means of dynamic light scattering, the size distribution of magnetite nanoparticles, produced apart from microcapsules and stabilized by citric ions, was determined. The size of nanoparticles ranges from 7 to 50 nm, the size of the majority (~85%) – from 9 to 20 nm.

Transmission Electron Microscopy (TEM)

TEM images of microcapsules with magnetite nanoparticles are presented in Fig.1. The images show that nanoparticles cover the capsules evenly but the particles synthesized apart from the capsules (Fig.1 A) cover the shell in lower concentration than the particles synthesized in the suspension of capsules (Fig.1 B). As a result, the latter microcapsules are more magnetic field responsive which allows to move capsules easily to the necessary point using a magnet [Fig.2]. The higher concentration of magnetite synthesized in the suspension of capsules may be caused by the

fact that these nanoparticles are formed directly on the surface of shells and inside the pores. Moreover, in this case citric ions from buffer solution are absent, in contrast to the synthesis of particles apart from capsules, where citric ions could prevent nanoparticles from being adsorbed by the negatively charged shell surface, due to the same charge and relatively large size of these ions.

High-resolution TEM image of magnetite nanoparticles synthesized in the suspension of capsules [Fig.3] reveals that the particles are a mixture of nanospheres (~5-10 nm in diameter), nanorods (10-15 nm in diameter and 100-150 nm in length) growing out of the shells and nanowhiskers (reaching 250 nm in length) growing close to the shells. Moreover, separate magnetite polycrystals (20-40 nm in diameter) are seen. Such elongated form of magnetite nanoparticles may be caused by conditions of their formation, i.e. porous, «spongy» structure of the polyelectrolyte shells.

Electron Diffraction Studies

Elongated nanocrystals were also investigated by means of electron diffraction method in order to identify their composition. The experimental electron diffraction patterns confirmed that the majority of nanocrystals are magnetite Fe_3O_4 .

CONCLUSIONS

A novel technique of synthesizing nanoparticles in the suspension of microcapsules was applied for producing polyelectrolyte capsules modified by magnetite nanoparticles which can be moved to the necessary point using a magnet. This technique could be used for targeted drug delivery to organism. Such technique reduces the three-stage experiment (synthesis of microcapsules, synthesis of nanoparticles, deposition of nanoparticles on the capsules) to two stages (synthesis and deposition of nanoparticles are combined) and doesn't demand stabilization of magnetite particles by citrate buffer. Microcapsules with magnetic nanoparticles fabricated in this way are more magnetic field responsive than microcapsules with nanoparticles synthesized and stabilized apart from the capsules.

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