Polymer capsules modified with iron oxide nanoparticles as an effective platform for MRI visualization and drug delivery

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Abstract. Efficiency of existing (usually toxic) drugs can be increased substantially with the targeted effect on the site of the disease. A potential platform for the targeted drug delivery can be polymer capsules. This will help reduce side effects on the human body and start treatment at the early stages of the disease. Modification of such capsules with the magnetic nanoparticles allows their visualization using magnetic resonance imaging (MRI). In this study the use of polymer microcapsules modified with iron oxide nanoparticles are employed as contrast agents for T2-weighted magnetic resonance (MR) images, the possibility of their implementation as for drug delivery carriers are discussed. For this, two different types of polymer capsules are synthesized. The results on the spin-spin and spin-lattice relaxivities were obtained.

1. Introduction

MRI diagnostics is distributed widely in clinics due to its non-invasiveness, the absence of radiation exposure and the ability to visualize small pathological foci. Moreover, there are number of pathological processes, such as ischemic heart disease, multiple sclerosis, and brain and spinal cord cancer, which can only be visualized effectively by using contrast agents. MRI diagnostic with a contrast media increases the possibilities of imaging, e.g. inflammation regions, tumors, atherosclerotic plaques, small areas of necrosis, etc.
Contrast media accelerate the relaxation of water protons (main source of signal in MRI) in their proximity, increasing the contrast-to-noise. Iron oxide particles can be employed as efficient contrast agents for T2-weighted MRI due to the ferromagnetic properties of iron oxide. When particle size changes from micro- to nanoscale their magnetic properties change significantly. Particles become single-domain, the enhancement of superparamagnetic effects is observed [1].

The physicochemical properties of magnetic nanoparticles can be significantly influenced by two main parameters: the particle size and the particle surface coating [2]. If iron oxide nanoparticles will be modified into microcapsules, then their contrast properties can be influenced by the position of the particles relative to each other, as well as their possibility to the free movement in a magnetic field. Therefore, such modified microcapsules can serve as a universal platform for drug delivery into cells and simultaneous MRI.

In the present paper, IONPs were added to polymer microcapsules and the resulting spin-spin and spin-lattice relaxations were measured. Such polymer microcapsules can be used to improve the contrast of drug delivery for certain diseases. This can be achieved by conjugating contrast agents with various vector molecules - antibodies, aptamers, receptors, ligands, etc.

2. Materials and methods

2.1. Synthesis polymer capsules encapsulated with iron oxide nanoparticles

Two types of polymer microcapsules were synthesized as published elsewhere [3, 4]. The first step was to produce calcium carbonate (CaCO$_3$) nuclei core-particles by precipitating CaCl$_2$ and Na$_2$CO$_3$. 2 mL of a water were mixed with 615 mL of a 0.33 M CaCl$_2$ solution under constant magnetical stirring at 1000 rpm. Then, 615 mL of a 0.33 M Na$_2$CO$_3$ solution was added fast and the formation CaCO$_3$ started immediately. The second step was a polymer shell forming by the Layer-by-Layer method onto calcium carbonate cores. Six monolayers of polyelectrolytes with opposite charge were deposited on the top of the CaCO$_3$ cores, starting from poly-(allylamine hydrochloride) (PAH) and followed by poly-(sodium 4-styrenesulfonate) (PSS). This process was repeated three times. Finally, at the third step CaCO$_3$ nuclei were dissolved by a 0.2 M solution of ethylenediaminetetraacetic acid disodium salt (EDTA).

The first type of capsules (Sample 1) is modified by iron oxide nanoparticles into the cavity of the capsules, and the second type of capsules (Sample 2) is modified by iron oxide nanoparticles into the wall of the capsules. In the first case, 10 mL of IONPs (the average nanoparticle size was 15 nm) were added during the synthesis of calcium carbonate cores. In the second case 410 mL of IONPs water solution (10 mL of IONPs and 400 mL of water) were added during the formation of the capsule shell, after third monolayer.

2.2. MRI experiments

MRI characterization was performed using 9.4 T Avance III micro-imaging system (Bruker, Germany). Parameters of pulse sequences depended on relaxation rates which we had estimated before every experiment and were within the following ranges:
- for $T_2$: MSME (Multi-Slice Multi-Echo), TR = 15000 ms, TE = 5-10 ms, echo spacing = 5-10 ms, ETL = 30-40 echoes;
- for $T_2^*$: MGE (Multi-Gradient Echo), TR = 15000 ms, TE = 1.617 ms, echo spacing = 1.617 ms, ETL = 12-20 echoes;
- for $T_1$: MGE, TR = 100, 500, 1000, 2000, 4000, 8000, 15000 ms, TE = 1.617ms.

3. Results
Two different capsule samples were prepared. Transmission electron microscopy (TEM) images of polymer capsules modified with IONPs are shown in the Figure 1. As it can be seen, the diameter of all capsules was around 5 μm as determined from TEM images. Figure 1 shows a typical collapsed form of dried capsule, indicating that the template cores were successfully dissolved with EDTA. Moreover, magnetic nanoparticles are evenly distributed in the shell of polymer capsule of Sample 2 (Fig. 1B).

Figure 1. Transmission electron microscopy images of polymer capsule Sample 1 (A) and Sample 2 (B).

Concentration-dependence plots were obtained and are shown in Figure 2. Sample 2 has the greatest T$_2$-relaxivity, in which iron oxide nanoparticles was located in the capsule shell, that is, in a stationary state.
4. Discussion and Conclusions
The results reveal that $T_2$ relaxivity has a larger value than $T_1$ relaxivity, and also depends on the concentration of iron in the microcapsule (Figure 2). Therefore, polymer microcapsules modified with iron oxide nanoparticles have a more pronounced effect on the spin-spin relaxation time. This allows to employ them as contrast agents for getting $T_2$-weighted images, thus, the developed capsules can be potentially used in clinical diagnosis.

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