Biopolymer coated Gd_2O_3 nanoparticles for MRI contrast agent

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Introduction

Magnetic resonance imaging (MRI) is widely used in modern clinical medicine as a diagnostic tool, and provides noninvasive and three-dimensional visualization of biological phenomena in living organisms with high spatial and temporal resolution. Therefore, considerable attention has been paid to magnetic nanoparticles as MRI contrast agents with efficient targeting ability and cellular internalization ability, which make it possible to offer higher contrast and information-rich images for detection of disease. The surface modified Gd_2O_3 nanoparticles as an active ingredient has a higher relaxation rate compared to currently commercialized MRI contrast agent. The performance of nanoparticles for biomedical applications is highly dependent on the nature and quality of surface coating materials. In particular, the development of functionalized nanoparticles for magnetic resonance imaging (MRI) requires the grafting of hydrophilic and biocompatible polymers, this polymer enhances the steric repulsion and therefore the stability of the colloids.

Materials and Methods

Biocompatible polyethylene glycol diacid (PEG) coated ultrasmall gadolinium oxide nanoparticles were synthesized in one-pot. Two separate solutions were prepared: (i) a precursor solution made of 5 mmol of $GdCl_3.xH_2O$ in 25 mL of triethylene glycol and (ii) a NaOH solution made of 15 mmol of NaOH in 10 mL of triethylene glycol. The precursor solution was heated to 100 ^oC with magnetic stirring until the precursors were completely dissolved. The NaOH solution was then poured into the precursor solution. The solution became cloudy for a while just after the addition of NaOH and then black. The mixed solution was magnetically stirred at 180 ^oC for 4 hours in air. The solution temperature was then lowered to 80 ^oC and 5 mmol of PEG was added to the solution, the solution temperature was again raised to 180 ^oC and stirred for additional 4 hours. The solution was then cooled to room temperature and transferred to a 1 L beaker containing 500 mL of triply distilled water. The supernatant was decanted and the remaining sample solution was washed with triply distilled water. This procedure was repeated three times.
BSA coated Gd_2O_3 nanoparticles were synthesized by using the EDC/NHS coupling method. 5 mmol of EDC and 5 mmol of NHS were added to 20 mL of PBS (pH = 6) at room temperature and under atmospheric condition. Here, the pH = 6 of the PBS was obtained by slowly dropping 1mM HCl to the original PBS with pH = 7.2. After magnetic stirring for 15 minutes, PEG-diacid coated Gd_2O_3 nanoparticles were added to the solution and then, the solution was magnetically stirred for 2 hours. Then, 1.5 g of BSA was added to the above solution with magnetic stirring for additional 2 hours to obtain BSA coated Gd_2O_3 nanoparticles. The solution was then transferred to a 1 L beaker containing 500 mL of triply distilled water. The top transparent solution was decanted and the remaining sample solution was washed with triply distilled water. This procedure was repeated three times. The first half volume of the sample solution was used to prepare a MRI sample solution. The remaining half volume was subjected to a powder form by drying it in air for various characterizations. All chemicals purchased from Aldrich.

Result and Discussion

The changes in surface chemistry of Gd_2O_3 nanoparticles after coating with BSA were characterized by FT-IR spectra. Figure 1 shows FT-IR spectra of PEG, BSA and BSA coated Gd_2O_3 nanoparticles. HRTEM micrographs revealed nanoparticles with an average diameter 3 nm (Figure 2). The longitudinal (T_1) and transverse (T_2) relaxation times were measured at various Gd^{3+} ion concentration and, r_1 and r_2 values were calculated from the respective slopes as shown in Figures 3 and 4. MRI contrasting capability of the nanoparticles was tested by measuring R_1 and R_2 map images and a clear dose dependent contrast enhancement on R_2 map images was observed (Figures. 5 and 6).

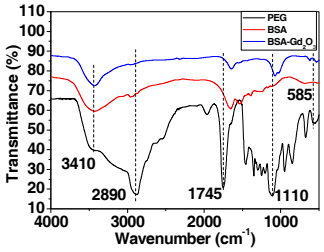

Figure 1. FTIR of PEG, BSA, and BSA coated Gd_2O_3 nanoparticles

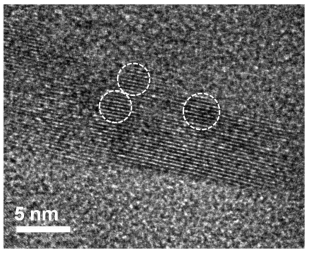

Figure 2. HRTEM images of BSA coated Gd_2O_3 nanoparticles.

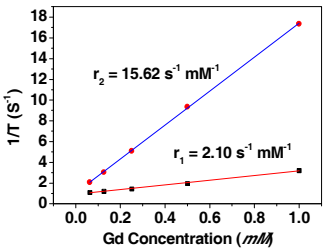

Figure. 3. Plot of $1/T_1$ and $1/T_2$ inverse relaxation times of sample solution of BSA coated Gd_2O_3nanoparticles

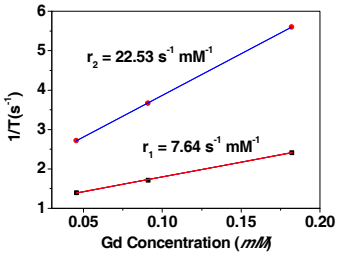

Figure 4. Plot of $1/T_1$ and $1/T_2$ inverse relaxation times of sample solution of cleaved BSA coated Gd_2O_3 nanoparticles.

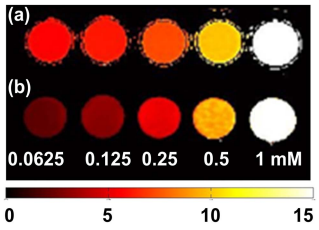

Figure 5. (a) In vitro T_1 and (b) T_2 map images showing contrast enhancements in both T_1 and T_2 map images with increasing dose of BSA coated Gd_2O_3

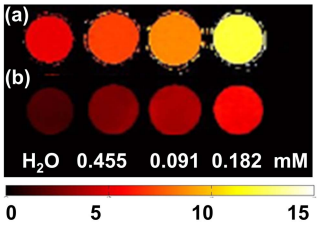

Figure 6. (a) In vitro T_1 and (b) T_2 map images showing contrast enhancements in both T_1 and T_2 map images with increasing dose of cleaved BSA coated Gd_2O_3