Manganese Oxide Doped Gadolinium Oxide Nanoparticles for both T1 and T2 MRI Contrast Agent

BADRUL ALAM BONY[1], Ja Young Park[2], Krishna Kattel[3], Wenlong Xu[3], Woo Choul Heo[3], Tirusew Tegafaw Mengesha[3], and Gang Ho Lee[3]
[1]*Chemistry, Kyungpook National University, Daegu, Korea, Republic of,* [2]*Kyungpook National University, Kazakhstan,* [3]*Kyungpook National University*

Introduction

Keeping target on increasing relaxivity and having good contrast of MRI, we have developed ultra-small gadolinium oxide nanoparticles, which are surface-doped with manganese oxide abbreviated as Gd_2O_3@MnO. In this work, the surface doped gadolinium oxide nanoparticles with an average *d* of 1 to 2 nm, which can be dispersed homogeneously. They were further coated with hydrophilic biocompatible lactobionic acid. It shows high relaxivity than normal ultrasmall gadolinium oxide nanoparticle. In-vitro tests of the sample solution indicated clear dose-dependent contrast enhancements in both T_1 and T_2 map images, showing that the nanoparticles may be used as both T_1 and T_2 MRI contrast agents.

Material and Methods

In order to synthesize lactobionic acid coated ultra-small Gd_2O_3@MnO nanoparticles, ultra-small Gd_2O_3 nanoparticles were first synthesized and then surface-doped with MnO. Finally, lactobionic acid was coated on the ultra-small Gd_2O_3@MnO nanoparticles. $GdCl_3{\cdot}xH_2O$ (5 mmol) was added to triethylene glycol (40 mL) and the mixture heated to reflux at 250 °C for 24 h with magnetic stirring . After cooling to 100 °C, $MnCl_2{\cdot}4H_2O$ (5 mmol) was added to the reaction solution. The reaction solution was heated to reflux at 250 °C for a further 24 h with magnetic stirring. After cooling to 150°C, lactobionic acid (5 mmol) was added to the reaction solution, which was magnetically stirred at that temperature for another 24 h. After cooling to room temperature, unreacted Gd(III), Cl^- ions, and solvent were removed from the reaction solution by washing three times. After washing, the remaining solution was centrifuged (4000 rpm, 1h). The precipitated nanoparticles were then collected. Half of the yielded nanoparticles were redispersed in distilled water for relaxivity and MR image measurements, and the remainder was dried in air to obtain a powder sample for the other characterizations. All chemicals were purchased from Aldrich.

Results and Discussion

Figure 1a shows a high-voltage electron-microscope (HVEM) image of the lactobionic acid coated ultra-small Gd_2O_3@MnO nanoparticles. Particle diameters of the ultra- small Gd_2O_3@MnO nanoparticles are monodisperse and estimated to be 1.2 nm. Figure 1b shows a scanning tunneling electron-microscope (STEM) image, showing particle diameters of 2.3 nm. The difference between HVEM and STEM micrographs roughly corresponds to the surface coating by lactobionic acid (thickness 1 nm). Dynamic light scattering (DLS) pattern is measured, which shows that the average hydrodynamic diameter of lactobionic acid coated ultra-small Gd_2O_3@MnO nanoparticles. Surface coating by lactobionic acid was confirmed from the FTIR absorption spectrum of a powder sample (Figure 2). Magnetizations in both $M-H$ and $M-T$ curves were mass-corrected to obtain the net magnetizations by using the TGA result. The $M-H$ curves at 5K and 300K show that both coercivity and remanence are zero (i.e. no hysteresis). $M-T$ curve shows that ultra-small Gd_2O_3@MnO nanoparticles are paramagnetic down to 3K. Thus, it is expected that ultra-small Gd_2O_3@MnO nanoparticles can efficiently induce longitudinal relaxation of water protons. In fact, a high r_1 value was observed. In vitro, T_1 and T_2 map images were measured (Figure 4a and 4b, respectively). They show clear dose-dependent contrast enhancements, which are due to the increased relaxation of water protons with increased dose. This shows the potential of lactobionic acid coated ultra-small Gd_2O_3@MnO nanoparticles as both T_1 and T_2 MRI contrast agents. The longitudinal (T_1) and transverse (T_2) relaxation times were also measured at various Gd(III) ion concentrations. To further investigate the T_1 MRI contrasting capability, we tested the sample solution in vivo by taking 3T T_1 MR images of a mouse. The MR images shows the contrast enhancement in all parts can be seen 90 min after injection of the sample solution. These in-vivo T_1 MR images show a high contrast enhancement in kidneys, likely due to excretion of nanoparticles from the organs through the kidneys, which is an important requirement for MRI contrast agents, because the nanoparticles should eventually be excreted by the kidneys.

Conclusion

We synthesized ultra-small Gd_2O_3 nanoparticles, which were surface-doped by MnO by first synthesizing the ultrasmall Gd_2O_3 nanoparticles and then doping them with MnO. The Mn/Gd mmol ratio in the ultra-small Gd_2O_3@MnO nanoparticles was approximately 0.11:1. They were further coated with hydrophilic biocompatible lactobionic acid. The surface-doped nanoparticles ranged was from 1 to 2 nm in diameter. The r_1 and r_2 values were estimated to be 12.8 ms^{-1} and 26.6 ms^{-1}, respectively. Compared to the ultra-small Gd_2O_3 nanoparticles, r_1 was nearly the same, whereas r_2 was nearly double due to the MnO surface doping. In-vitro tests of the sample solution showed clear dose-dependent contrast enhancements in both T_1 and T_2 map images. The performance of the sample solution as a T_1 MRI contrast agent was proved in vivo with T_1 MR images of a mouse. The sample solution certainly provides better T_2 MR images than the undoped ultra-small Gd_2O_3 nanoparticles.

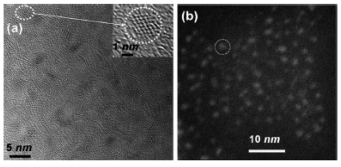

Figure 1. (a) HVEM and (b) STEM micrographs of lactobionic acid coated ultra-small Gd_2O_3@MnO

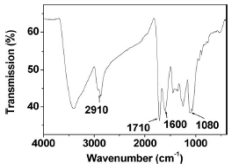

Figure 2. FTIR absorption spectrum of lactobionic acid coated ultra-small Gd_2O_3@MnO nanoparticles

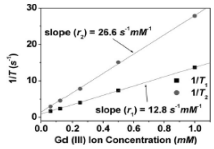

Figure 3. Plots of inverse relaxation times vs. Gd(III) ion concentration of the sample solution

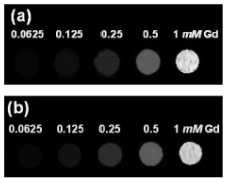

Figure 4. (a) In vitro T_1 and (b) T_2 map images showing contrast enhancements in both T_1 and T_2 map images with increasing dose

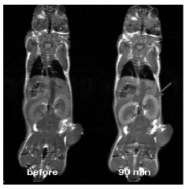

Figure 5. 3T in-vivo T_1 MR images of a mouse before (left) and 90 min after (right) injection, showing a clear contrast enhancement in the kidneys (shown by arrows)

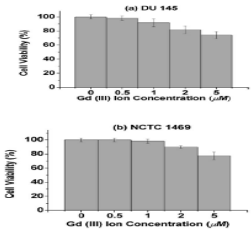

Figure 6. Cytotoxicity tests of the sample solution by using (a) DU 145 and (b) NCTC 1469 cell lines