Ultrasmall gadolinium manganese oxide nanoparticles as MRI contrast agent

Badrul Alam Bony[1], Wenlong Xu[1], Tirusew Tegafaw Mengesha[1], Chorong Kim[1], Sung June Kim[1], Md. Wasi Ahmad[1], and Gang Ho Lee[1]
[1]*Chemistry, Kyungpook National University, Daegu, Korea*

Introduction

Magnetic resonance imaging (MRI) is a powerful and noninvasive diagnostic technique of the human anatomy on the basis of superior spatial resolution and contrast. A large number of MRI techniques are performed employing gadolinium complexes and gadolinium nanoparticles. However, doped or alloy nanoparticles can show better contrast with enhancing relaxivity. For this purpose, we have developed ultra-small gadolinium manganese oxide nanoparticles, which are abbreviated as $GdMnO_3$. The average size of prepared nanoparticles is of 2 to 3 nm, which can be dispersed homogeneously. They were coated with biocompatible and water soluble D-glucuronic acid. It shows high relaxivity than normal ultra-small gadolinium oxide nanoparticles. Morever, in vivo and 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 can be used as both T_1 and T_2 contrast agents.

Material and Methods

In order to synthesize D-glucuronic acid coated ultra-small $GdMnO_3$ nanoparticles, ultra-small $GdMnO_3$ nanoparticles were first synthesized and then, D-glucuronic acid was used to coat the ultra-small nanoparticles. 2.5 mmol gadolinium chloride hydrate ($GdCl_3.xH_2O$) and 2.5 mmol manganese chloride dihydrate ($MnCl_2.4H_2O$) were added into 40 ml triethylene glycol and the mixture was stirred till dissolved well. Then 15 mmol NaOH was added and heated to reflux at 80 °C for 2 h with magnetic stirring. After 2 h, 5 ml H_2O_2 was added and continued heating at 80 °C for another 2h. To coat the nanoparticles, 5 mmol D-glucuronic acid was added to the reaction solution. The reaction solution was heated to reflux at 80 °C for a further 6 h with magnetic stirring. After cooling to room temperature, it was washed three times using ethanol to remove unreacted Gd^{3+}, Mn^{3+}, Cl^- ions from the reaction solution. After washing for three times, the nanoparticles were then collected. Half of the yielded nanoparticles were used for measuring TEM, relaxivity, cytotoxicity 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 1 shows a high resolution transmission electron microscope (HRTEM) image of the D-glucuronic acid coated ultra-small $GdMnO_3$ nanoparticles. The size of the ultrasmall $GdMnO_3$ nanoparticles is around 3.0 nm. In figure 2, the XRD pattern proves the formation of $GdMnO_3$ nanoparticles. Surface coating by D-glucuronic acid is confirmed from the FTIR absorption spectrum of powder sample (Figure 3). $GdMnO_3$ nanoparticles can efficiently induce longitudinal relaxation of water protons. In fact, a high r_1 and r_2 value were observed (Figure 4). Moreover, In vitro, T_1 and T_2 map images were measured (Figure 5). They show clear dose-dependent contrast enhancements, which are due to the increased relaxation of water protons with increased dose. Invivo image of liver and kidney were showed in Figure 7 & 8 which show the potential of D-glucuronic acid coated ultra-small $GdMnO_3$ nanoparticles as T_1 MRI contrast agents. The longitudinal (T_1) and transverse (T_2) relaxation times were also measured at various Gd (III) ion concentrations.

Conclusion

In summary, biocompatible and water soluble D-glucuronic acid coated ultrasmall $GdMnO_3$ nanoparticles were synthesized through a straight forward one step route. The size of the synthesized nanoparticles is around 3 nm, which is ultrasmall. We addressed the possibility of ultrasmall $GdMnO_3$ nanoparticles as a new MRI contrast agent by measuring their water proton relaxivities. Due to excellent relaxometric properties of Gd^{3+} and Mn^{3+} ion, they can provide the enhanced contrast for MR imaging. The ultrasmall $GdMnO_3$ nanoparticles exhibit r_1 = 13.40 $mM^{-1}s^{-1}$ and r_2 = 70.31 $mM^{-1}s^{-1}$ considering Gd^{3+} concentration, demonstrating that the nanoparticles can act as efficient T_1 contrast agent and T_1 MR images reflects the relaxivity value by providing bright images. It also exhibited clear dose-dependent contrast enhancement in its R_1 and map R_2 images Furthermore, because of using Mn^{3+} nanoparticles, the toxicity of ultrasmall $GdMnO_3$ nanoparticles is also decreased than individual Gd_2O_3 nanoparticles and specifically, the synthesized ultrasmall $GdMnO_3$ nanoparticles are non-toxic up to 500 µM.

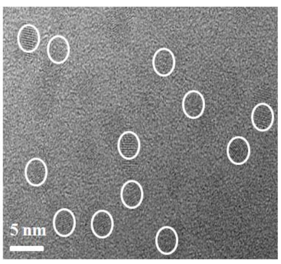

Figure 1. HRTEM images of ultrasmall $GdMnO_3$

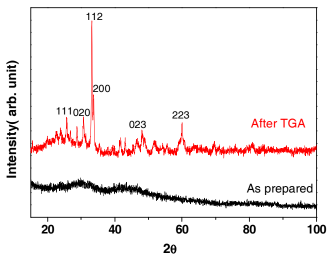

Figure 2. XRD of $GdMnO_3$

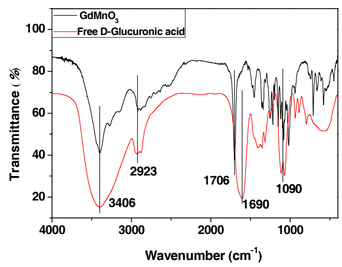

Figure 3. FTIR of $GdMnO_3$

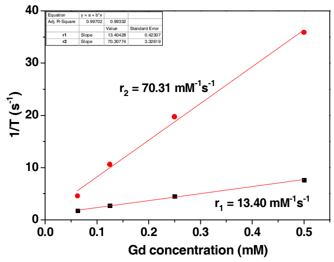

Figure 4. R_1 and R_2 relaxivity of $GdMnO_3$

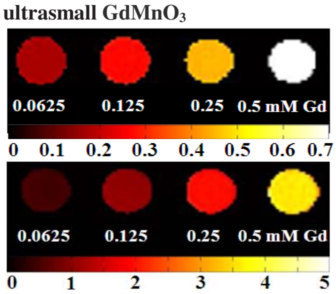

Figure 5. In vitro T_1 (upper) and T_2 (below) map images.

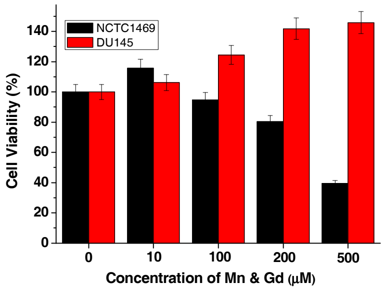

Figure 7. Cytotoxicity test

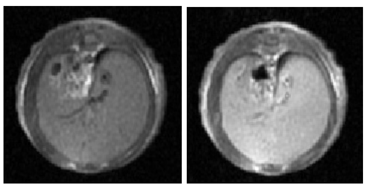

Figure 7. Invivo image of liver. (Before and after injection)

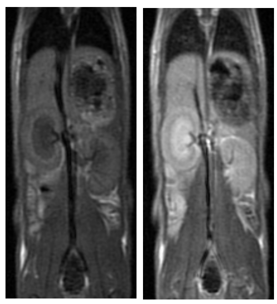

Figure 8. Invivo image of Kidney. (Before and after injection)