

Synthesis of CuO doped Gd₂O₃ nanoparticles as T₁ MRI contrast agent

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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 nanoparticles can show better contrast with enhancing relaxivity. For this purpose, we have developed ultra-small gadolinium oxide nanoparticles, which are surface-doped with copper oxide abbreviated as Gd₂O₃@CuO. In this work, the surface doped gadolinium oxide nanoparticles with an average *d* of 2 to 3 nm, which can be dispersed homogeneously. They were further coated with biocompatible D-glucuronic acid. It shows high relaxivity than normal ultra-small gadolinium oxide nanoparticles. In-vitro tests of the sample solution, indicated clear dose-dependent contrast enhancements in both T₁ and T₂ map images, showing that the nanoparticles may be used as both T₁ and T₂ contrast agents.

Material and Methods

In order to synthesize D-glucuronic acid coated ultra-small Gd₂O₃@CuO nanoparticles, ultra-small Gd₂O₃@CuO nanoparticles were first synthesized and then, D-glucuronic acid was used to coat the ultra-small nanoparticles. 2.5 mmol gadolinium chloride hydrate (GdCl₃·xH₂O) and 2.5 mmol copper chloride dihydrate (CuCl₂·2H₂O) were added into 40 ml triethylene glycol and the mixture was stirred till dissolved well. Then 5 mmol NaOH was added and heated to reflux at 80 °C for 2 h with magnetic stirring. After 2 h, 5 ml H₂O₂ 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 Gd³⁺, Cu²⁺, Cl⁻ ions from the reaction solution. After washing, the remaining solution was centrifuged (4000 rpm, 1h) and the precipitated nanoparticles were then collected. Half of the yielded nanoparticles were used for measuring TEM, 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 1 shows a high resolution transmission electron microscope (HRTEM) image of the D-glucuronic acid coated ultra-small Gd₂O₃@CuO nanoparticles. The diameter of the ultra-small Gd₂O₃@CuO nanoparticles is 2.5 nm. In figure 2, the XRD pattern proves the presence of CuO and Gd₂O₃ nanoparticles. Surface coating by D-glucuronic acid was confirmed from the FTIR absorption spectrum of powder sample (Figure 3). Gd₂O₃@CuO nanoparticles can efficiently induce longitudinal relaxation of water protons. In fact, a high *r*₁ value was observed (Figure 4). Moreover, In vitro, T₁ and T₂ map images were measured (Figure 5a and 5b, 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 D-glucuronic acid coated ultra-small Gd₂O₃@CuO nanoparticles as both T₁ and T₂ MRI contrast agents. The longitudinal (T₁) and transverse (T₂) relaxation times were also measured at various Gd(III) ion concentrations. To further investigate the T₁ MRI contrasting capability, we have submitted the sample solution for in vivo.

Conclusion

The synthesized ultra-small Gd₂O₃ nanoparticles, which were surface-doped by CuO. The Cu/Gd mmol ratio in the ultra-small Gd₂O₃@CuO nanoparticles was approximately 1:1. They were further coated with hydrophilic biocompatible D-glucuronic acid. The surface-doped nanoparticles were approximately from 2 to 3 nm in diameter. The *r*₁ and *r*₂ values were estimated to be 13.8 mM⁻¹s⁻¹ and 14.5 mM⁻¹s⁻¹ respectively. Compared to the ultra-small Gd₂O₃ nanoparticles, *r*₂ was nearly the same, whereas *r*₁ was nearly double due to the CuO surface doping. Because, paramagnetic CuO can enhance the longitudinal relaxivity while it was introduced with another paramagnetic Gd₂O₃. In-vitro tests of the sample solution showed clear dose-dependent contrast enhancements in both T₁ and T₂ map images. The sample solution certainly provides higher *r*₁ value than the undoped ultra-small Gd₂O₃ nanoparticles.

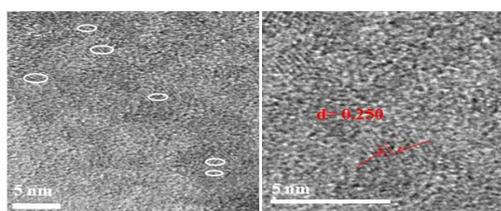


Figure 1. HRTEM images of D-glucuronic acid coated ultra-small Gd₂O₃@CuO

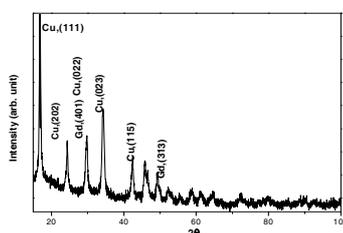


Figure 2. XRD of Gd₂O₃@CuO

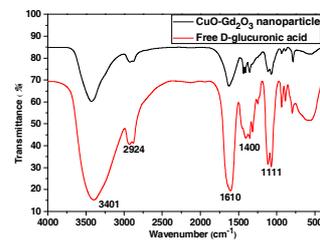


Figure 3. FTIR of Gd₂O₃@CuO

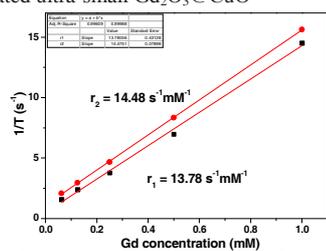


Figure 4. *R*₁ and *R*₂ relaxivity of Gd₂O₃ doped CuO

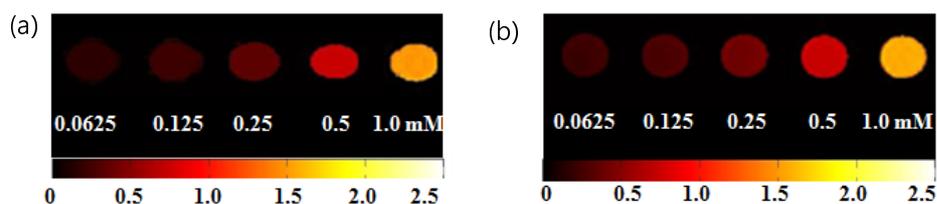


Figure 5. (a) In vitro T₁ and (b) T₂ map images showing contrast enhancements in both T₁ and T₂ map images with increasing dose