Synthesis and characterization of D-glucuronic acid coated dysprosium oxide nanoparticles for magnetic resonance imaging (MRI) contrast agent

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Introduction

Magnetic nanocolloids can possess higher water proton relaxivities than molecular chelated complexes because metal ions in a nanoparticle are densely populated. This capability of nanoparticles allow us to acquire high resolution Magnetic Resonance (MR) images and help to detect various diseases Thus, they can be used as sensitive MRI contrast agents. We developed a simple one-step synthesis of D-Glucuronic acid surface-modified ultra small Dy_2O_3 nanoparticles. It was well characterized by using MP-XRD, TEM, FT-IR spectrophotometer, TGA, SQUID magnetometer and Magnetic Resonance Imaging (MRI) instrument. The resulting data suggest that ligand-coated ultra-small nanoparticles will be extremely valuable for target specific biomedical applications such as MRI contrast agents.

Materials and methods

In order to synthesize D-glucuronic acid coated Dy_2O_3 nanoparticles, first of all, 5 mmol hydrated dysprosium nitrate, $Dy(NO_3)_3.XH_2O$ precursor was dissolved into 30 ml triethylene glycol solvent. When metal precursor was dissolved into the solvent completely, 15 mmol of NaOH was added into the reaction mixture and again allow dissolving for it. Then the mixture was refluxed up to 80 with magnetic stirring for 2 hours. After 2 hours, 7.5 ml hydrogen peroxide (H_2O_2, 50%) was injected slowly into the flask. Again the mixture was heated for 2 hours at 80 , refluxed and magnetically stirred. After 2 hours, the reaction mixture was allowed to cool and 5 mmol of D-glucuronic acid was added. Then the mixture was heated again at about 80 , refluxed and magnetically stirred. The reaction solution was cooled to room temperature and then, the solvent, unreacted coating ligand, unreacted Dy(III) ions etc.were removed from the reaction solution by washing them with distilled water for three times. The reaction solution was kept for a week until Dy_2O_3 nanocolloids were settled down to the bottom of the solution. The top transparent solution was decanted. Half of the Dy_2O_3 nanocolloid was dispersed in distilled water to prepare a MRI solution. The remaining half was dried in air to prepare a powder sample for characterizations.

Result and Discussion:

HRTEM images show that the diameter (d) of the Dy_2O_3 nanoparticle in its nanocolloid is nearly monodisperse and ranges from 2 to 3 nm (fig.1). The surface coating of nanoparticles by D-glucuronic acid was confirmed by recording a FT-IR absorption spectrum of a powder sample. The amount of surface coating of the Dy_2O_3 nanoparticle with the D-glucuronic acid in nanocolloid were estimated to be 52% by recording a TGA curve of a powder sample. It shows that the nanoparticles are sufficiently coated with the D-glucuronic acid. To characterize magnetic properties of the nanoparticle in the Dy_2O_3 nanocolloid, both M-H and ZFC M-T curves and were recorded. The M-H curves (fig.3) show that both coercivity and remanence are zero. This lack of hysteresis as well as no magnetic transition down to T =3 K in the ZFC M-T curve (fig.4) shows that the nanoparticles are mainly paramagnetic down to T =3 K. From the M-H curve at T =5 K and at H=T, magnetizations of the Dy_2O_3 nanoparticles were estimated to be ~ 155emu/g. The r_1 and r_2 relaxivities of 0.16 and 40.28 s^{-1} mM^{-1} were obtained from the slopes in the plots of R_1 and R_2 relaxivity as a function of Dy concentration respectively (fig.5). The R_1 and R_2 map images clearly showed dose dependent contrast changes with increasing the dose (fig.6). For the Dy_2O_3 nanocolloid to be safely applied in vivo, it should be nontoxic. We performed an *in vitro* cytotoxicity test of the nanocolloid by using the human prostate cancer (DU145) and the mouse normal hepatocyte (NCTC1469) cell lines as shown in fig.7. The Dy_2O_3 nanocolloid is not toxic for the tested concentration range up to 100 μM Dy. Furthermore, it is expected that D-glucuronic acid coated Dy_2O_3 nanoparticles will be extremely valuable for MRI contrast agent. Therefore, we are planning to perform *in vivo* MR experiment soon.

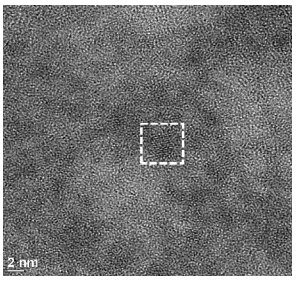

Fig. 1 HRTEM image

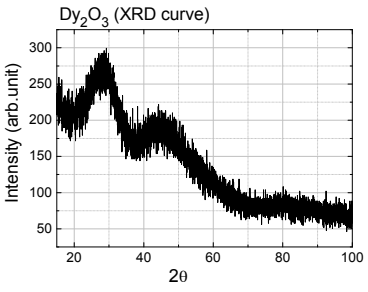

Fig. 2 XRD curve

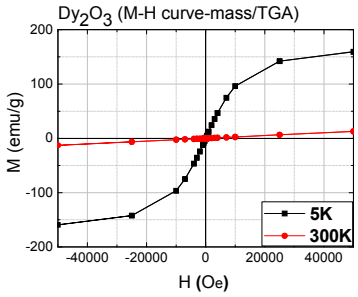

Fig. 3 M-H curve

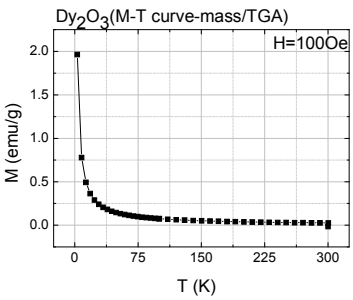

Fig. 4 M-T curve

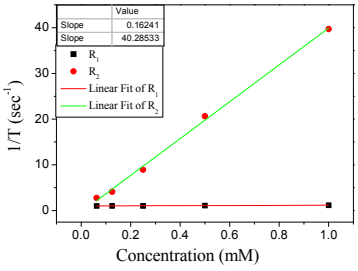

Fig. 5 Measurement of Relaxivity

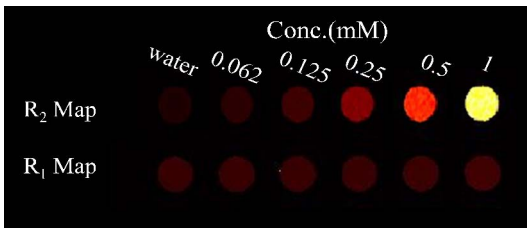

Fig. 6 Map images

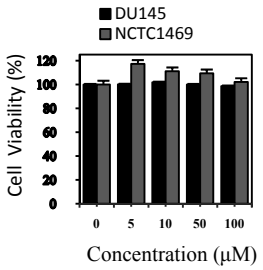

Fig. 7 *In vitro* cytotoxicity test