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Preparation of silica-coated gadolinium compound particle colloid solution and its application in imaging

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Abstract. A preparation method for gadolinium compound (GdC) nanoparticles coated with silica (GdC/SiO_2) is proposed. GdC nanoparticles were prepared with a homogeneous precipitation method at 80°C using 1.0×10^{-3} M $Gd(NO_3)_3$, 0.5 M urea and 0-3.0×10^{-4} M ethylenediaminetetraaceticacid disodium salt dihydrate (ETDA) in water. As a result of preparation at various EDTA concentrations, GdC nanoparticles with a size as small as 40.5±6.2 nm, which were colloidally stable, were prepared at an EDTA concentration of 2.0×10^{-4} M. Silica-coating of the GdC nanoparticles was performed by a Stöber method at 35°C using 1.0-10.0×10^{-3} M tetraethylorthosilicate (TEOS), 11 M H_2O and 1.5×10^{-3} M NaOH in ethanol in the presence of 1.0×10^{-3} M GdC nanoparticles. Performance of preparation at various TEOS concentrations resulted in production of GdC/SiO_2 particles with an average size of 106.1±11.2 nm at a TEOS concentration of 5.0×10^{-3} M. The gadolinium (Gd) concentration of 1.0×10^{-3} M in the as-prepared GdC/SiO_2 particle colloid solution was increased up to a Gd concentration of 0.2 M by concentrating with centrifugation. The core-shell structure of GdC/SiO_2 particles was undamaged, and the colloid solution was still colloidally stable, even after the concentrating process. The concentrated GdC/SiO_2 colloid solution showed images of X-ray and magnetic resonance with contrast as high as commercial Gd complex contrast agents.

Keywords: core-shell; gadolinium; homogeneous precipitation method; Stöber method; X-ray imaging; MRI

1. Introduction

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Materials with multiple properties such as fluorescence, paramagnetism and X-ray absorption can be used for simultaneous imaging by multiple imaging means (Santra *et al.* 2005, Rieter *et al.* 2007). This enables us to perform complete medical diagnosis simply. Gadolinium compounds (GdC) function as contrast agents for magnetic resonance imaging (MRI) in medical diagnosis (Ratzinger *et al.* 2010, Liu *et al.* 2011, Yim *et al.* 2011, Purysko *et al.* 2011, Bagher-Ebadian *et al.* 2011, Besheer *et al.* 2011, Xu *et al.* 2011, Kojima *et al.* 2011, Tamada *et al.* 2011). They absorb X-ray strongly because of Gd with a large atomic number (Bonvento *et al.* 2006, Carrascosa *et al.* 2007, Newport *et al.* 2008, Cheung *et al.* 2010, Pietsch *et al.* 2011). Accordingly, they will function as both of an MRI contrast agent and an X-ray contrast agent.

Gadolinium (Gd)-based contrast agents that are commercially available are Gd complexes dissolved homogeneously in solvents at molecular level. The Gd complex molecules flow fast in living bodies. This means that it is not long before they are discharged from the living bodies, which results in a difficulty in taking high contrast images for a long period using the solution-type commercial agents. Not the GdC solution but colloid solution of GdC particles is promising as a new contrast agent that can stay in living bodies, because staying time in the living bodies (duration) is longer in the case of particles than solution, which leads higher effectiveness in imaging in a unit time.

Toxicity of the GdCs has to be considered for practical use, though the GdCs are safer than conventional iodine-based X-ray contrast agents (Newport *et al.* 2008). During the use of the contrast agents of Gd complexes, free Gd ions may be released from the complexes through their dissociation, which provoke adverse reactions in some patients (Gauden and Phal 2010, Marshall and Kasap 2012). Coating of GdC nanoparticles (core) with materials inert to living bodies (shell) is a promising means of reducing the adverse reactions, because a physical barrier of the shell materials may prevent the core from making contact with the living bodies. Silica is a candidate as the shell materials, since it is inert to living bodies. Various methods for coating nanoparticles with silica, which are based on a sol-gel reaction, have been proposed by several researchers (Ji *et al.* 2009; Guo *et al.* 2010, Bardi *et al.* 2010, Wang *et al.* 2010, Wang *et al.* 2011). We have also studied on silica-coating of various materials for the past several years (Park *et al.* 2006, Kobayashi *et al.* 2007, Kobayashi *et al.* 2008, Kobayashi *et al.* 2010a, Kobayashi *et al.* 2010b, Kobayashi *et al.* 2010c, Kobayashi *et al.* 2011, Ayame *et al.* 2011, Morimoto *et al.* 2011).

A method for preparing core-shell particles composed of core of GdC and shell of silica is proposed in the present work. A homogeneous precipitation method was used for preparing a colloid solution of GdC nanoparticles, and then silica-coating of the GdC nanoparticles were performed with a modified Stöber method (GdC/SiO_2 particles). The present work also studied on X-ray imaging and MRI properties of the GdC/SiO_2 particle colloid solution.

2. Experimental

2.1 Chemicals

Gadolinium nitrate hexahydrate ($Gd(NO_3)_3 \cdot 6H_2O$) (99.5 %) and urea (99.0 %) were used as a raw chemical for GdC nanoparticles and a precipitation-inducer in preparation of GdC nanoparticles, respectively. Stabilizer used in the preparation of GdC nanoparticles was ethylenediaminetetraaceticacid disodium salt dihydrate (EDTA) (99.0-101.0%). Tetraethylorthosilicate (TEOS) (95 %) and ethanol (99.5%) were used as a raw chemical for silica shell and a solvent for silica-coating, respectively. Sodium hydroxide (NaOH) solution (5 M) was used as a catalyst for a sol-gel reaction of TEOS. Commercial MRI contrast agents used for a comparison to the GdC/SiO_2 particles in imaging examinations were ProHance (Eisai Co., Ltd., 0.5 M Gd) and Magnevist (Bayer Co., Ltd., 0.5 M Gd). All the chemicals except for the commercial contrast agents were purchased from Kanto Chemical Co., Inc., and used as received. Water that was ion-exchanged and distilled with Shimadzu SWAC-500 was used in all the preparations.

2.2 Preparation of materials

Colloid solutions of GdC nanoparticles were prepared in water by a homogeneous precipitation method similar to a work of Matijević and Hsu (1987). In each reaction, EDTA, urea aqueous solution and $Gd(NO_3)_3$ aqueous solution were successively added to water. The preparation was carried out at initial concentrations of 0-3.0×10^{-4} M EDTA, 0.5 M urea and 1.0×10^{-3} M $Gd(NO_3)_3$ in a flask reactor under stirring at 80^oC for 3 h. The GdC particles in the colloidal solutions were washed by repeating centrifugation, removal of supernatant, addition of the water and sonication over three times. For a following silica-coating step, the solvent was replaced with water/ethanol solution by adding the water/ethanol solution in the last washing step.

Silica-coating of the GdC particles was performed in ethanol by a modified Stöber method. In each reaction, TEOS and 0.1 M NaOH aqueous solution were successively added to the GdC particle colloid solution at room temperature. The reaction time was 24 h. Initial concentrations of H_2O, NaOH, and TEOS were 11, 1.5×10^{-3} and 1.0×10^{-3}-10.0×10^{-3} M, respectively. Colloidal suspensions of GdC/SiO_2 particles were washed by repeating centrifugation, removal of supernatant, addition of the water and sonication over three times.

2.3 Characterization

Morphology of the particles was investigated by transmittance electron microscopy (TEM). TEM was performed with a JEOL JEM-2000FX II microscope operating at 200 kV. Samples for TEM were prepared by dropping and evaporating the nanoparticle suspensions on a collodion-coated copper grid. Dozens of particle diameters in TEM images were measured to determine volume-averaged particle size, d_v, and standard deviation of particle size distribution, σ, defined by the following equations.

$$d_v = (\sum_i n_i d_i^{\,3} / \sum_i n_i)^{1/3} \quad (1)$$

$$\sigma = (\sum_i (d_i - d_v)^2 / \sum_i n_i)^{1/2} \quad (2)$$

where n_i is the number of particles with a size of d_i. Gd concentrations in particle colloid solutions were measured by inductively coupled plasma (ICP) emission spectroscopy. ICP measurement was performed with a Shimadzu ICPS-7510 atom emission spectrometer. Emission was detected at a wavelength of 342.247 nm. Samples for ICP were prepared by dissolving the particles with aqua regia and then diluting the obtained solution with water.

X-ray images of samples such as the GdC/SiO_2 particle colloid solutions were obtained with a Shimadzu SMX-100CT-SV3 microfocus X-ray CT system. For estimation of MR signal intensity, T_1 (longitudinal relaxation time) -weighted images and T_1 values of samples were obtained with a

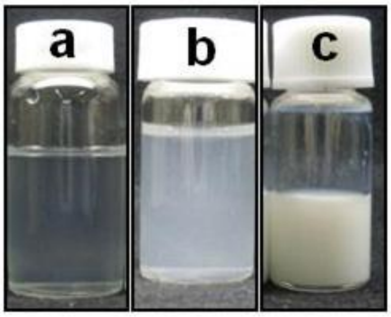

Fig. 1 Photographs of various colloid solutions. The sample (a) was the GdC particle colloid solution prepared by the homogeneous precipitation method at 2.0×10^{-4} M EDTA. The sample (b) was the GdC/SiO_2 particle colloid solution prepared by silica-coating the sample (a) at 5.0×10^{-3} M TEOS. The sample (c) was the sample (b) concentrated by centrifuge, in which the calculated Gd concentration was 0.2 M

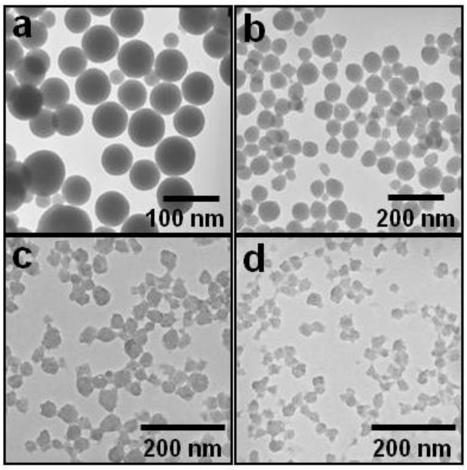

Fig. 2 TEM images of GdC particles prepared by the homogeneous precipitation method at EDTA concentrations of (a) 0, (b) 1.0×10^{-4}, (c) 2.0×10^{-4}, and (d) 3.0×10^{-4} M

Bruker AVANCE III 400WB magnetic resonance imaging system. The static magnetic field, the echo time and the repetition time were 9.4 T, 8.5 ms and 1500 ms, respectively. The colloid solutions for the imagings were prepared by concentrating with centrifugation, removal of supernatant, addition of the water and sonication. This concentrating process resulted in production of the colloid solution with a Gd concentration of 0.01-0.2 M (concentrated GdC/SiO_2 particle colloid solution).

3. Results and discussion

3.1 Morphology of particles

Fig. 1(a) shows a photograph of GdC particle colloid solution. The solution was faintly opaque,

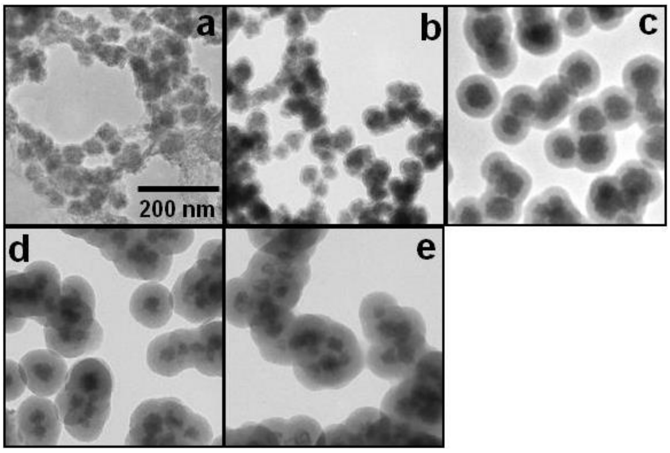

Fig. 3 TEM images of GdC/SiO_2 particles prepared by silica-coating the GdC particles at TEOS concentrations of (a) 1.0×10^{-3}, (b) 2.5×10^{-3}, (c) 5.0×10^{-3}, (d) 7.5×10^{-3}, (e) 1.0×10^{-2} M. The GdC particles used as core were the same as the sample (c) in Fig. 2

which indicated that particles scattering light with visible wavelength, *i.e.*, nano-sized particles, were produced. Fig. 2 shows TEM images of GdC particles prepared at various EDTA concentrations. With no addition of EDTA (at an EDTA concentration of 0 M) (Fig. 2(a)), spherical GdC particles with a size of 221.2±49.3 nm were produced. With additions of EDTA (Figs. 2 (b)-(d)), GdC particles were also obtained. Their particle sizes were small compared with that for no EDTA addition, and the GdC particle size decreased with an increase in the EDTA concentration; The GdC particle sizes for the EDTA concentrations of 0, 1.0×10^{-4}, 2.0×10^{-4}, and 3.0×10^{-4} M were 221.2±49.3, 60.2±8.4, 40.5±6.2, and 29.7±6.1 nm, respectively. The EDTA coordinates to Gd^{3+} ion to form complex. Collision among GdC nuclei and particles was probably controlled by physical barriers composed of the coordinating EDTA, which prevented the GdC particles from growing. Consequently, the small particles were produced with the additions of EDTA. Fig. 1(b) shows a photograph of GdC/SiO_2 particle colloid solution. The solution was opaque, compared to the GdC particle colloid solution. This observation implied that intensity of the light scattering increased with an increase in particle size due to the silica-coating. Fig. 3 shows TEM images of GdC/SiO_2 particles prepared at various TEOS concentrations. Darker and lighter parts of particles were determined to be GdC particles and silica, respectively, due to a difference in the electron density between them. At concentrations as low as 1.0×10^{-3} and 2.5×10^{-3} M, though the GdC particles were coated with silica, the silica-coated particles formed their aggregates. Ionic strength of TEOS solution increases by generation of SiO^- through hydrolysis of TEOS. An increase in the ionic strength compresses double layer on solid materials such as colloidal particles (Singh and Song 2007; Yilmaz *et al.* 2007; Li and Xu 2008), which promotes collision of particles and following particle aggregation. Since silica shell thicknesses were small at the low TEOS concentrations, the silica shells could not control the particle aggregation. An increase in TEOS concentration to 5.0×10^{-3} M resulted in quasi-perfect silica-coating of the GdC particles, though aggregation of the silica-coated particles was still observed. The particle size was 106.1±11.2 nm. At concentrations as high as 7.5×10^{-3} and 10.0×10^{-3} M, the particles contained multiple GdC particles, and their shapes were distorted. The increase in the ionic strength of the solution due to hydrolysis of TEOS led to coalescence of the silica-coated particles in the course of silica-coating. Shape of the particle

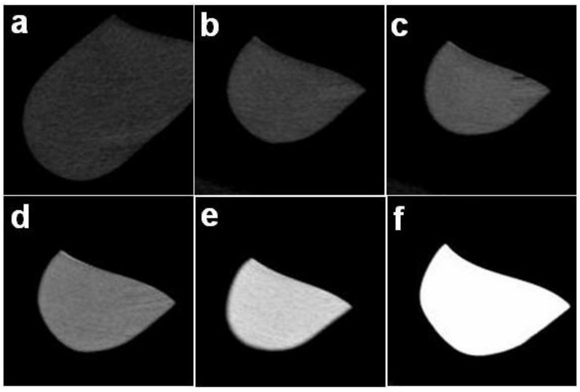

Fig. 4 X-ray images of the ProHance solutions with Gd concentrations of (a) 0.0078, (b) 0.015, (c) 0.0315, (d) 0.063, (e) 0.126, and (f) 0.25 M. These solutions were prepared by diluting the as-received ProHance, and put in glass test tubes. The Gd concentrations were estimated by calculation using the initial Gd concentration of 0.5 M in the as-received ProHance

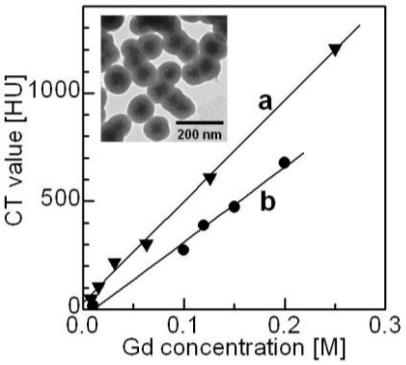

Fig. 5 CT values of (a) the ProHance solutions and (b) the GdC/SiO_2 colloid solution versus Gd concentration. The inset shows the TEM image of GdC/SiO_2 particles in concentrated colloid solution with the Gd concentration of 0.20 M. The Gd concentrations were calculated using initial Gd concentrations

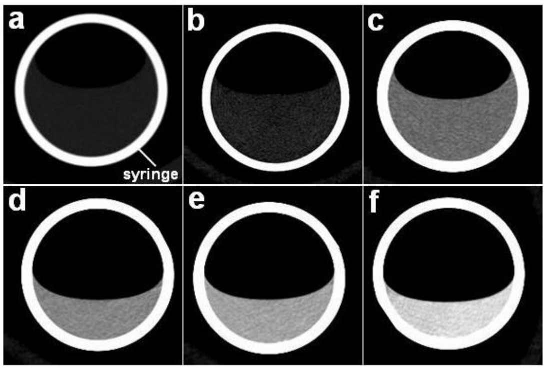

Fig. 6 X-ray images of (a) water and the GdC/SiO_2 particles colloid solution with Gd concentrations of (b) 0.01, (c) 0.1, (d) 0.12, (e) 0.15, and (f) 0.20 M. The colloid solution was put in a plastic syringe. The Gd concentrations were estimated by calculation using the initial Gd concentrations

agglomerates seemed to determine the final distorted shape of the silica-coated particles. Since a Gd concentration of the as-prepared GdC/SiO_2 particle colloid solution was low, it was hard to take clear images using the as-prepared colloid solution. Therefore, it was concentrated by centrifugation. Fig. 1(c) shows the photograph of the concentrated GdC/SiO_2 particle colloid solution. The concentrated colloid solution was colloidally stable.

3.2 X-ray imaging

Fig. 4 shows X-ray images taken by using the commercial contrast agent solutions with different Gd concentrations. Lighter parts stand for objects that absorb X-ray more strongly. The commercial solutions were clearly observed against a black background, and the parts of the commercial solutions lightened with an increase in the Gd concentration. Fig. 5(a) shows CT value of the commercial solution as a function of the Gd concentration. The CT value increased in proportion to the Gd concentration, in which a slope was 4860.3 HU/M.

The inset of Fig. 5 shows a TEM image of GdC/SiO_2 particles in the concentrated colloid solution. The particles had a size of 106.8±10.3 nm, which was close to that prior to the concentrating process (Fig. 3(c)). This observation indicated that the core-shell structure was undamaged even after the concentrating process, *i.e.*, that the GdC/SiO_2 particles were mechanically stable. Fig. 6 shows X-ray images of the concentrated GdC/SiO_2 particle colloid solutions with different Gd concentrations. For reference, an image of water is also shown. Circles with light contrast indicate syringes used for containing samples. The water was faintly imaged. Clear images, of which lightness increased as the Gd concentration increased, were also obtained. Fig. 5(b) shows CT value of the particle colloid solution as a function of the Gd concentration. A proportional increase in the CT value for the Gd concentration was also revealed, and the CT value achieved 676.8 HU at 0.2 M. A slope was 3221.8 HU/M, which was ca. 66% of that for the commercial solutions. This indicated that the CT values of the GdC/SiO_2 particle colloid solutions were low compared to those of the commercial solutions. The Gd concentrations for the GdC/SiO_2 particle colloid solutions were estimated from their initial Gd concentrations, which assumed that yields of GdCs were 100%. A few gadolinium were probably lost during preparation of the GdC/SiO_2 particle colloid solutions, and consequently the lower CT values were recorded for the particle colloid solutions. However, since the CT values were almost comparable, the GdC/SiO_2 particle colloid solutions will function as X-ray contrast agents.

3.3 MRI

Fig. 7 shows T_1-weighted images taken using colloid solutions of GdC particles and GdC/SiO_2 particles with various Gd concentrations. For comparison, the figure includes images of the commercial contrast agent solutions and the GdC particle colloid solutions concentrated with the way similar to the preparation of the concentrated GdC/SiO_2 particle colloid solution. The Gd concentrations in commercial solutions were estimated from the initial Gd concentration in the as-received solution. The Gd concentrations in particle colloid solutions were obtained from ICP measurements. Light images are taken for T_1-weighting. All the solutions examined were clearly imaged against a black background, and the parts of the solutions tended to lighten with an increase in the Gd concentration.

Fig. 8 shows plots of $1/T_1$ values as a function of the Gd concentration. All the $1/T_1$ values examined increased with an increase in the Gd concentration. Straight lines of the $1/T_1$ values versus the Gd concentration were drawn by linear fitting, in which R-squared values of the fittings were 0.974 for the GdC particle colloid solution, 0.994 for the GdC/SiO_2 particle colloid solution, and 0.999 for the Magnevist solution. A slope of $1/T_1$ value with respect to Gd concentration, which is called the relaxivity (r_1), stands for the efficiency of magnetic dipolar coupling occurring between protons of water molecules (solvent) and paramagnetic contrast agent such as Gd (Bagher-Ebadian *et al.* 2011), i.e., the efficiency of the exchange of the protons with the contrast agent (Liu *et al.* 2011). The relaxivity (r_1) is commonly used as a guideline on the performance of positive contrast agents. Values of r_1 for the GdC particle colloid solution, the GdC/SiO_2 particle colloid solution and the commercial solution, which were calculated by linear fitting, were 2.12, 3.11 and 4.23 mM^{-1} s^{-1}, respectively. The r_1 value of the GdC/SiO_2 particle colloid solution was

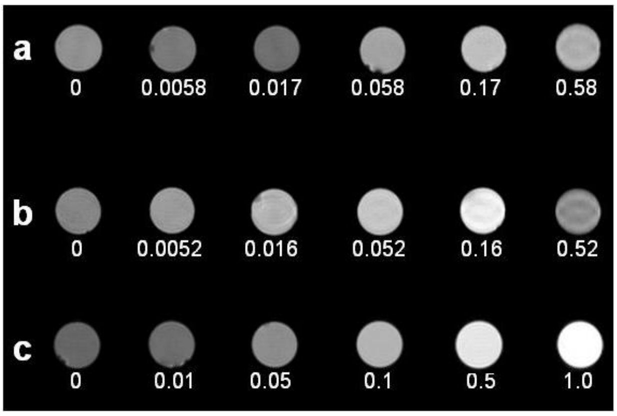

Fig. 7 T_1-weighted images of (a) GdC particle colloid solutions, (b) GdC/SiO_2 particle colloid solutions, and (c) the Magnevist solutions for various Gd concentrations. The numbers stand for Gd concentrations (mM). The Gd concentrations in Gd particle colloid solutions and GdC/SiO_2 particle colloid solutions were obtained from ICP measurements, and the Gd concentrations in the Magnevist solutions were estimated from the initial Gd concentration in the as received Magnevist

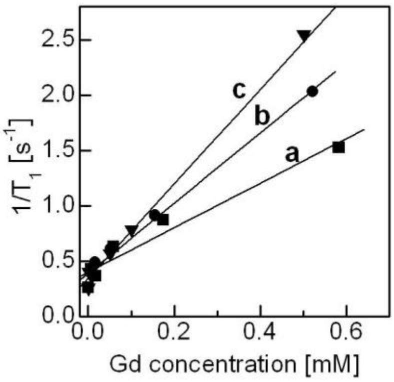

Fig. 8 Values of $1/T_1$ of (a) GdC particle colloid solution, (b) GdC/SiO_2 particle colloid solution, and (c) Magnevist solution versus Gd concentration. The Gd concentrations in Magnevist solutions were estimated from the initial Gd concentration in the as-received Magnevist, and the Gd concentrations in GdC particle colloid solutions and GdC/SiO_2 particle colloid solutions were obtained from ICP measurements

higher than that of the GdC particle colloid solution, which indicated that interaction between water protons and Gd was significant in the GdC/SiO_2 particles compared with the GdC particles. Since silica prepared by a sol-gel method has many silanol groups with protons, the GdC could stay by protons within and near the silica shell for the longer time due to its reduced diffusion coefficient. Consequently, the higher r_1 value was recorded for the GdC/SiO_2 particle colloid solution, though its mechanism is still unclear. The r_1 value of the GdC/SiO_2 particle colloid solution was faintly lower than that of the commercial solution. Since the commercial contrast agent is not a colloidal solution but a transparent solution, Gd complex should be solved in the solution in molecular level. This provides that many Gd complex molecules can contact easily with protons in the solution. In contrast, since the GdC/SiO_2 particles contain many gadolinium atoms inside the GdC core particles, such gadolinium atoms cannot contact with protons outside the particles. Consequently, the r_1 value lower than the commercial solution was obtained for the GdC/SiO_2 particle colloid solution.

4. Conclusions

A method for producing GdC/SiO_2 core-shell particles was proposed. The colloid solution of GdC nanoparticles with a size of 40.5±6.2 nm were prepared by means of the homogeneous precipitation method using 1.0×10^{-3} M $Gd(NO_3)_3$, 0.5 M urea and 2.0×10^{-4} M M EDTA. The silica-coating of the GdC nanoparticles was performed with a modified Stöber method using ethanol solution containing 1.0×10^{-3} M GdC nanoparticles, 5.0×10^{-3} M M TEOS, 11 M H_2O and 1.5×10^{-3}

M NaOH, which produced the GdC/SiO_2 particles with the size of 106.1±11.2 nm. The GdC/SiO_2 colloid solution that was concentrated with centrifugation showed high-contrast images for X-ray and magnetic resonance, which had images comparable to those for commercial Gd complex contrast agents. These results obtained in the present work indicated the the GdC/SiO_2 particle colloid solution had dual abilities of contrast agents of X-ray imaging and MRI.

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