

Research Article

Preparation of Gd Complex-Immobilized Silica Particles and Their Application to MRI

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A preparation method for Gd-ethylenediaminetetraacetic acid disodium salt dihydrate (EDTA) complex-immobilized silica particles (Gd-EDTA/SiO₂) is proposed. Preparation of spherical silica particles was performed by a sol-gel method at 35°C using 0.2 M tetraethylorthosilicate, 25 M H₂O, and 0.01 M NaOH in ethanol, which produced silica particles with an average size of 80.4 ± 14.9 nm. Immobilization of Gd-EDTA on the silica particles was conducted at 35°C by introducing amino groups on the silica particles with (3-aminopropyl)trimethoxysilane at pH 3 (NH₂/SiO₂) and then making Gd-EDTA act on the NH₂/SiO₂ particles at pH 5. The as-prepared Gd-EDTA/SiO₂ particle colloid solution was concentrated up to a Gd concentration of 0.347 mM by centrifugation. The sphere structure of Gd-EDTA/SiO₂ particles was undamaged, and the colloid solution was still colloidally stable, even after the concentrating process. The concentrated Gd-EDTA/SiO₂ colloid solution revealed good MRI properties. A relaxivity value for T₁-weighted imaging was as high as 5.15 mM⁻¹ s⁻¹, that was comparable to that for a commercial Gd complex contrast agent.

1. Introduction

Gadolinium complexes (GdC) function as contrast agents for magnetic resonance imaging (MRI) [1–8], and solutions dissolving the GdC homogeneously at molecular level are available commercially. The GdC molecules flow fast in living bodies. This means that they are quickly discharged from the living bodies, which results in a difficulty in taking high-contrast images for a long period with the use of the solution-type commercial agents.

Not the GdC solution but colloid solution of GdC immobilized with particles is promising as a new contrast agent that can be expected to stay in living bodies for a long period, because the particles are dragged from fluid to a direction opposite to the fluid due to their projected area larger than molecules, which controls flow of the particles in liquid. Consequently, the immobilization will increase

residence time of GdC, which makes it possible to take clear MRI images for a long term. Particles used for the immobilization are required to unaggregate in living bodies, because aggregation of the particles prevents smooth flow of body fluid. Since silica particles prepared by a sol-gel method are colloidally stable [9–11], GdC-immobilized silica particles may function as the MRI contrast agent that shows long residence time and nonaggregation in living bodies.

Lux et al. produced particles composed of Gd oxide core and silica-related compound shell for bioimaging [12]. Our group also proposed a method for fabricating silica-coated Gd compound nanoparticles, which was a combination process of a homogeneous precipitation method and a sol-gel method [13]. Their particles contain the Gd compound particles as core. Besides the core-shell particles, various methods for immobilizing GdCs on silica surfaces of silica

particles or silica-coated particles have been proposed by several researchers [14–18]. An alternative method for the GdC_s immobilizing is proposed in the present work. First, silica particles fabricated with the sol-gel method were surface-modified with amino groups by using a silane coupling reagent with amino group (NH_2/SiO_2). Then, ethylenediaminetetraacetic acid (EDTA), a representative ligand for metal ion, was introduced on the particle surface through a reaction between the amino groups on particle surface and carboxyl groups of the EDTA (EDTA/SiO_2). Finally, Gd^{3+} ions were immobilized on the particle surface through formation of Gd complexes ($\text{Gd-EDTA}/\text{SiO}_2$). The present work also studied on MRI properties of the colloid solution of Gd-EDTA/ SiO_2 particles.

2. Experimental

2.1. Chemicals. A starting reagent for producing silica particles was tetraethylorthosilicate (TEOS) (95%). Solvent and catalyst for the sol-gel reaction of TEOS were ethanol (99.5%) and sodium hydroxide (NaOH) solution (5 M), respectively. (3-Aminopropyl)trimethoxysilane (APMS) (Sigma-Aldrich, 97%) was used for surface modification of silica particles. EDTA disodium salt dihydrate (Sigma-Aldrich, 99.0–101.0%) and dimethylformamide (DMF) (>99.5%) were used as a ligand for Gd^{3+} and a solvent of EDTA in introduction of EDTA on particles, respectively. A source of Gd^{3+} for forming Gd-EDTA complex was gadolinium nitrate hexahydrate ($\text{Gd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$) (99.5%). 2,4,6-Trinitrobenzenesulfonic acid sodium salt dehydrate (TNBS) (Wako Pure Chemical, 98%) was used for confirming presence of amino groups in colloid solutions. Particle colloid solutions produced in the present work were compared to Magnevist (Bayer Co., Ltd., 0.5 M Gd), which is one of the representative of MRI contrast agents. All the chemicals except for APMS, EDTA, and TNBS 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

2.2.1. Silica Particles. Silica particles were prepared by the sol-gel method at 0.2 M TEOS, 25 M water, and 0.01 M NaOH in a glass reactor at 35°C using ethanol as a solvent. Ethanol solution of the TEOS was added to a mixture of water, ethanol, and NaOH aqueous solution. The reaction time was 24 h. A colloidal suspension of the silica particles was obtained, as shown in Figure 1(a). Assuming completion of reaction, the suspension had a silica concentration of 12.0 g/L. The particles were washed by repeating centrifugation, removal of supernatant, addition of water, and sonication over three times. Final volume of the suspension was adjusted to the volume of initial solution with the addition of water. Figure 1(b) shows a TEM image of the silica particles. These silica particles had an average size of 80.4 ± 14.9 nm.

2.2.2. Immobilization of Gd-EDTA on Silica Particles. Amino groups were first introduced on silica particle surface by using APMS, since alkoxide groups of APMS were expected to react

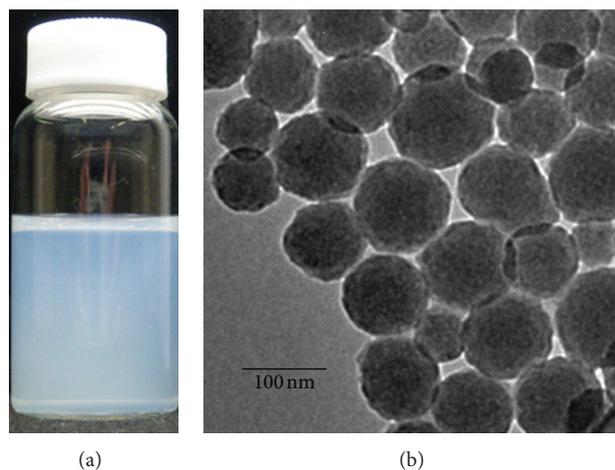


FIGURE 1: Photograph of colloid solution of silica particles and their TEM image.

with OH groups on silica surface of the silica particles. APMS was added to the silica particle colloid solution at 35°C. An initial APMS concentration was 0.03 M, and the reaction time was 24 h. The obtained NH_2/SiO_2 particle colloid solution was washed by repeating a process composed of centrifuge, removal of supernatant with decantation, addition of DMF, and shake with a vortex mixer three times. The colloid solution was concentrated with 2-fold by reducing the amount of DMF at the last process.

EDTA was next immobilized on NH_2/SiO_2 particle surface through formation of amide bonds [15, 19, 20], since carboxyl groups of EDTA was expected to react with amino groups on the NH_2/SiO_2 particles. EDTA/DMF mixture was added to the NH_2/SiO_2 particle colloid solution in a volume ratio of 1:1 at 35°C. The reaction time was 24 h, and an initial EDTA concentration was 0.03 M. The obtained EDTA/ SiO_2 particle colloid solution was washed by repeating a process composed of centrifuge, removal of supernatant with decantation, addition of water, and shake with a vortex mixer three times.

Then, $\text{Gd}(\text{NO}_3)_3$ aqueous solution was added to the EDTA/ SiO_2 colloid solution, for forming Gd complex on particle surface or for producing Gd-EDTA/ SiO_2 particles. An initial $\text{Gd}(\text{NO}_3)_3$ concentration was 0.5 mM, and the reaction temperature and time were 35°C and 6 h, respectively. The obtained Gd-EDTA/ SiO_2 particle colloid solution was washed by repeating a process composed of centrifuge, removal of supernatant with decantation, addition of the water, and shake with a vortex mixer three times. The as-prepared Gd-EDTA/ SiO_2 particle colloid solution was concentrated with 10-fold by reducing the amount of water added at the last washing process (concentrated Gd-EDTA/ SiO_2 particle colloid solution).

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 and standard deviation of particle size distribution. The presence of amino groups in solutions was confirmed by performing UV-Vis spectroscopy using TNBS. A reaction between TNBS and amino group provides yellowish coloration of solution, which is attributed to absorption with an absorption peak wavelength of 347 nm. The TNBS aqueous solution was added to the as-prepared NH_2/SiO_2 particle colloid solution, so as to make an initial TNBS concentration 0.2 mM. UV-Vis absorption spectra were measured with a Shimadzu UV-3101PC spectrometer. Introduction of amino groups and immobilization of Gd-EDTA on particle surface were qualitatively confirmed by ζ -potential measurements, though the measurements possess limited quantitative usefulness in surface analysis. To measure ζ -potential of particles, electrophoretic light scattering (ELS) was performed with a Brookhaven ZetaPlus zeta potential analyzer. HCl aqueous solution or NaOH aqueous solution was added to solution to vary pH of solution for the ELS measurement. 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. For investigation on MRI properties, T_1 - (longitudinal relaxation time-) weighted images of samples and T_1 values were obtained with a Bruker AVANCE III 400WB magnetic resonance imaging system at a static magnetic field of 9.4 T. Echo time and repetition time were 8.5 and 1500 ms, respectively. The colloid solutions for the imaging were concentrated by centrifugation, removal of supernatant, addition of the water, and sonication.

3. Results and Discussion

3.1. Morphology of Particles

3.1.1. NH_2/SiO_2 Nanoparticles. Figure 2 shows photographs of NH_2/SiO_2 nanoparticle colloid solutions prepared at various pHs in surface modification with amino groups. Though the solutions were opaque, neither precipitation nor flocculation was observed in the solutions similarly to the silica particle colloid solution, which indicated that the procedure of surface modification with amino groups did not affect colloidal stability of the particle colloid solutions.

The supernatants of the NH_2/SiO_2 nanoparticle colloid solutions were obtained by centrifuging and decanting the colloid solutions. Figure 3 shows photographs of the supernatants. The supernatants were yellowish, which indicated that free APMS molecules or APMS molecules that were not introduced on particles were left in the supernatants. Figure 4 shows UV-Vis spectra of the supernatants. Each spectrum revealed an absorption peak at 347 nm that was attributed to chemical bond between amino group and TNBS. The absorption peak intensity increased with an increase in

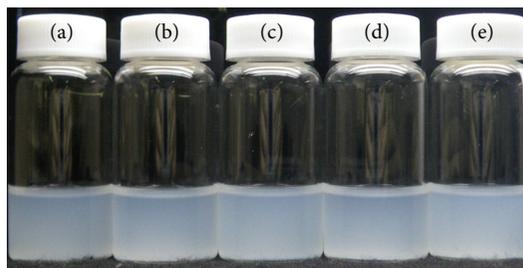


FIGURE 2: Photographs of colloid solutions of NH_2/SiO_2 particles surface modification with amino groups at pHs of (a) 3, (b) 5, (c) 7, (d) 9, and (e) 11.

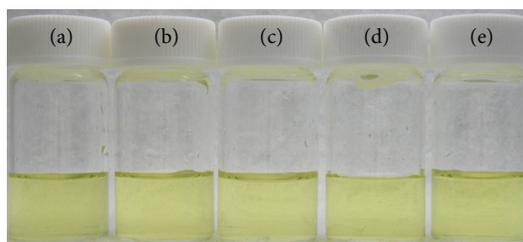


FIGURE 3: Photographs of supernatants of mixtures of NH_2/SiO_2 particle colloid solutions and TNBS aqueous solutions. The pHs in surface modification with amino groups were (a) 3, (b) 5, (c) 7, (d) 9, and (e) 11.

pH, as shown in inset of Figure 4. This result meant that a large amount of APMS added were not introduced on the particle surface and remained in the supernatant at the high pHs. Surface modification with amino groups was efficient at the low pHs. A concentration of the free APMS, which should have been in the supernatant of NH_2/SiO_2 particle colloid solution, was calculated as 22.2 mM in the final as-prepared NH_2/SiO_2 particle colloid solution at pH = 3 from the absorbance of 1.30 as shown in Figure 4. A concentration of the introduced APMS was estimated at 7.8 mM in the final NH_2/SiO_2 solution by subtracting the free APMS concentration from the initial APMS concentration of 30 mM, which meant that 6.50×10^{-4} mole APMS was on 1 g silica particles.

Figure 5 shows ζ -potentials as a function of pH for silica particles and NH_2/SiO_2 particles. ζ -potentials of the silica particles were negative in a range of pH examined, though an absolute value of the ζ -potential was lowered with decreasing pH. The ζ -potential did not become positive even at the low pHs. Such tendency of ζ -potential for pH was typical for silica particles, as reported by other research groups [21, 22]. The ζ -potential approached to zero at pH below 3.0, which resulted in an isoelectric point of 2-3. The isoelectric point of the NH_2/SiO_2 particles was 8.5, which meant that the isoelectric point of silica particles shifted to high pH with the surface modification with amino groups. This pH shift was presumably derived from amino group on surface of the particles. Consequently, this result supported that the particle surface was successfully modified with APMS.

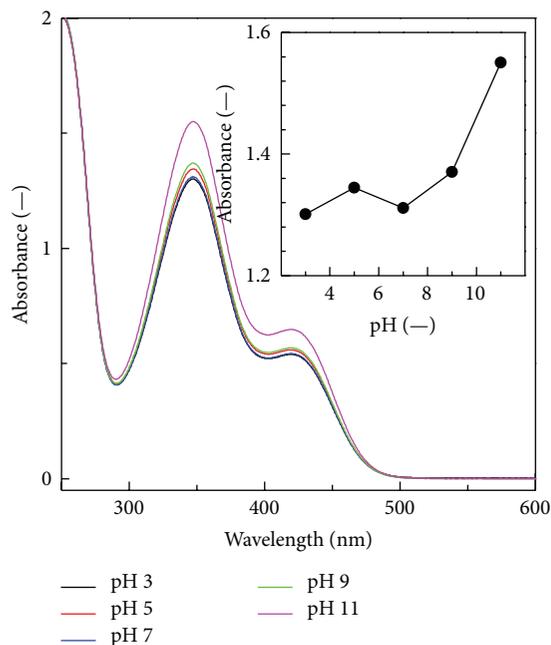


FIGURE 4: UV-Vis absorption spectra of supernatants of mixtures of NH_2/SiO_2 particle colloid solutions and TNBS aqueous solutions. The surface modification with amino groups was performed at pHs of 3, 5, 7, 9, and 11. Inset shows absorbance at 347 nm as a function of pH of mixture of silica particle colloid solution and APMS.

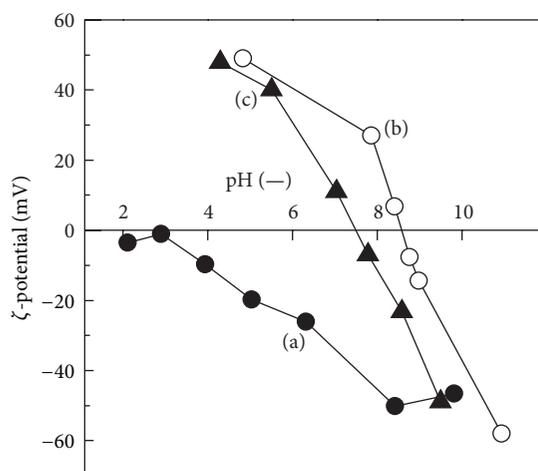


FIGURE 5: ζ -potentials of (a) silica particles, (b) NH_2/SiO_2 particles, and (c) Gd-EDTA/ SiO_2 particles versus pH.

3.1.2. Gd-EDTA/ SiO_2 Nanoparticles. Figure 6(a) shows a photograph of as-prepared Gd-EDTA/ SiO_2 nanoparticle colloid solution. Though the solution was opaque, neither precipitation nor flocculation was observed in the solutions similarly to the silica particle colloid solution, which indicated that the procedure of Gd-EDTA immobilization did not have an effect on colloidal stability of the particle colloid solution. Figure 6(b) shows a photograph of concentrated Gd-EDTA/ SiO_2 nanoparticle colloid solution. Neither precipitates nor flocculates were produced either, which

indicated that the particle colloid solution was still stable colloiddally even after the washing procedure.

Figure 5(c) shows ζ -potential of Gd-EDTA/ SiO_2 nanoparticles as a function of pH. The isoelectric point of the Gd-EDTA/ SiO_2 particles was 7.5, which meant that the isoelectric point of NH_2/SiO_2 particles shifted to low pH with the EDTA immobilization. Introduction of carboxyl groups derived from EDTA on particle surface would make the particle surface negative, because carboxyl groups have negative charge. Accordingly, this pH shift took place due to the introduction, which implied that the Gd-EDTA was immobilized on the particle surface.

ICP measurement revealed that Gd was contained in the concentrated colloid solution, which supported the implication for the successful Gd-EDTA immobilization. The Gd concentration in the concentrated colloid solution was estimated at 0.347 mM. This concentration corresponded to 0.0347 mM Gd in the as-prepared colloid solution prior to the concentrating, which meant that 1.44×10^{-6} mole Gd-EDTA was on 1 g silica particles. A Gd-EDTA-immobilization efficiency, which was defined as a ratio of (Gd concentration in the concentrated colloid solution)/(initial Gd concentration in the as-prepared colloid solution), was estimated at 6.9%, since the initial Gd concentration in the as-prepared colloid solution was 0.5 mM.

Figure 6(c) shows a TEM image of the Gd-EDTA/ SiO_2 particles. The particles did not aggregate but were dispersed. This observation supported the high colloidal stability of the particle colloid solution revealed in Figure 6(b). The particles had an average size of 79.9 ± 13.1 nm.

3.2. MRI Property. Figure 7 shows T_1 -weighted images of the colloid solutions of Gd-EDTA/ SiO_2 particles with various Gd concentrations. For T_1 -weighted images, strong magnetic resonance gives positive images with light contrast. All the solutions examined were clearly imaged against a black background, and the light contrast of image increased with increasing the Gd concentration.

Figure 8 shows a plot of relaxation rate ($1/T_1$) of the Gd-EDTA/ SiO_2 particle colloid solution as a function of the Gd concentration. The relaxation rate increased linearly with raising the Gd concentration. A value of relaxivity (r_1) is defined as a slope of relaxation rate with respect to Gd concentration. Since active magnetic dipolar coupling occurs between protons of water molecules (solvent) and paramagnetic contrast agent, that is, active exchange of the protons with the contrast agent shortens T_1 [23, 24], the r_1 value is commonly used as a guideline on the performance of positive contrast agents. The r_1 value for the Gd-EDTA/ SiO_2 particle colloid solution, which was calculated by linear fitting, was $5.15 \text{ mM}^{-1} \cdot \text{s}^{-1}$. Values of r_1 for a colloid solution of silica-coated Gd compound nanoparticles and Magnevist were 3.11 and $4.23 \text{ mM}^{-1} \cdot \text{s}^{-1}$, respectively, according to measurements in our previous work [13]. The r_1 value of the Gd-EDTA/ SiO_2 particle colloid solution was higher than and comparable to those of silica-coated Gd compound nanoparticles and Magnevist, respectively. Since the Gd-EDTA molecules on particle surface lay close to the water protons compared

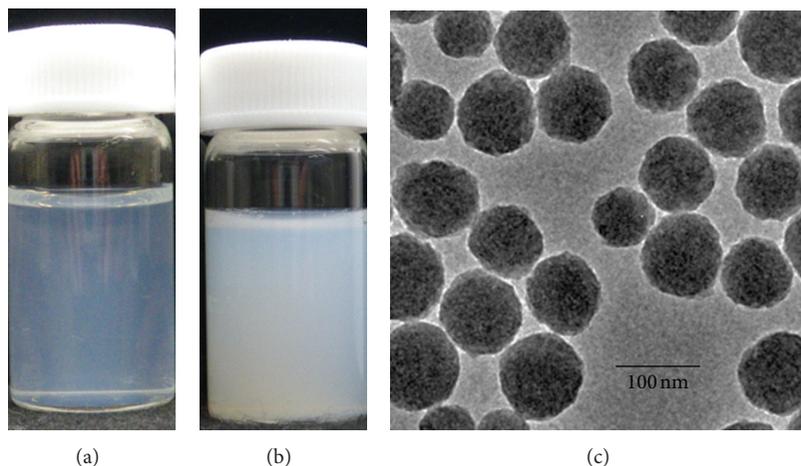


FIGURE 6: Photographs of (a) as-prepared and (b) concentrated Gd-EDTA/SiO₂ particle colloid solutions and (c) TEM image of Gd-EDTA/SiO₂ particles.

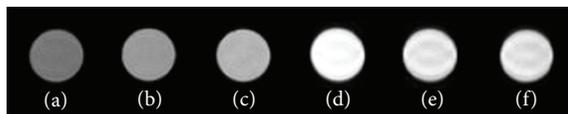


FIGURE 7: T₁-weighted images of Gd-EDTA/SiO₂ particle colloid solutions with Gd concentrations of (a) 0, (b) 0.03, (c) 0.1, (d) 0.2, (e) 0.3, and (f) 0.347 mM.

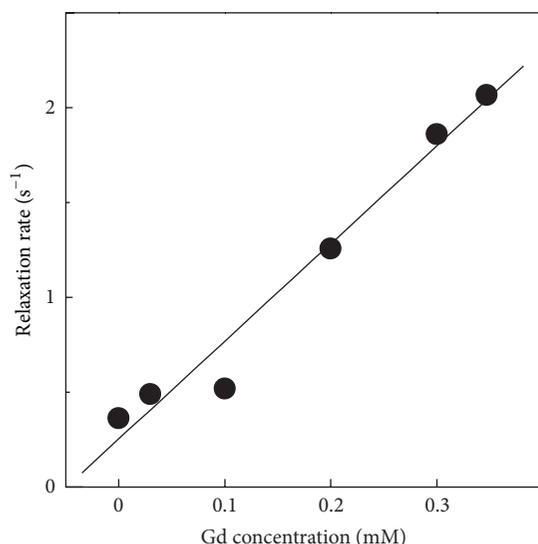


FIGURE 8: Relaxation rate ($1/T_1$) of Gd-EDTA/SiO₂ particle colloid solutions as a function of Gd concentration.

to the Gd compound inside the silica-coated particles, interaction between water protons and Gd in the Gd-EDTA/SiO₂ particles was as significant as Magnevist.

Toxicity of silica particles [25, 26], Gd ions [27, 28], and chelates such as EDTA [29, 30] has been pointed out by several researchers. Since such materials were used for producing the Gd-EDTA/SiO₂ particles, it is quite required to

take into account of their toxicities. Further study on toxicity of the Gd-EDTA/SiO₂ particles and their colloid solutions is now on progress toward practical use of the colloid solutions as MRI contrast agents.

4. Conclusions

A method for producing Gd-EDTA/SiO₂ particles was proposed. The colloid solution of spherical silica particles with the size of 80.4 ± 14.9 nm was prepared at 35°C by means of a sol-gel method using ethanol solution containing 0.2 M TEOS, 25 M H₂O, and 0.01 M NaOH. Amino groups were introduced at pH 3 on the silica particles by using (3-aminopropyl)trimethoxysilane, and then Gd-EDTA was immobilized at pH 5 on the NH₂/SiO₂ particles. The Gd-EDTA/SiO₂ particles were mechanically and colloidally stable, even after concentrating the Gd-EDTA/SiO₂ particle colloid solution up to the Gd concentration of 0.347 mM with centrifugation. The concentrated Gd-EDTA/SiO₂ particle colloid solution showed high-contrast T₁-weighting magnetic resonance images. The relaxivity value was $5.15 \text{ mM}^{-1} \cdot \text{s}^{-1}$, that was comparable to that for Magnevist, the commercial Gd complex contrast agent. These results obtained in the present work indicated that the Gd-EDTA/SiO₂ particle colloid solution had an ability of MRI contrast agent.

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