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Fabrication of hollow particles composed of silica containing gadolinium compound and magnetic resonance imaging using them

Yoshio Kobayashi^{1*}, Hikaru Morimoto¹, Tomohiko Nakagawa², Yohsuke Kubota², Kohsuke Gonda² and Noriaki Ohuchi^{2,3}

Abstract

A preparation method for hollow particles composed of silica shell containing gadolinium compound (GdC) is proposed. GdC nanoparticles with an average size of 40.5 ± 6.2 nm were prepared with a homogeneous precipitation method at 80°C using 1.0×10^{-3} M $\text{Gd}(\text{NO}_3)_3$ and 0.5 M urea in the presence of 2.0×10^{-4} M ethylenediaminetetraacetic acid disodium salt dihydrate. Silica-coated GdC (GdC/SiO_2) nanoparticles with an average size of 100.9 ± 9.9 nm were fabricated with a sol-gel method at 35°C using 5.0×10^{-3} M tetraethylorthosilicate, 11 M H_2O , and 1.5×10^{-3} M NaOH in ethanol in the presence of 1.0×10^{-3} M GdC nanoparticles. The GdC/SiO_2 particles were aged at 80°C in water after replacement of solvent of the as-prepared GdC/SiO_2 particle colloid solution with water, which provided diffusion of GdC into the silica shell and then formation of a hollow structure. The hollow particle colloid solution revealed good MRI properties. A relaxivity value for longitudinal relaxation time-weighted imaging was as high as $3.38 \text{ mM}^{-1} \cdot \text{s}^{-1}$ that attained 80% of that for a commercial Gd complex contrast agent.

Keywords: Hollow, Core-shell, Particle, Gadolinium, Homogeneous precipitation method, Silica, Sol-gel, MRI

Background

Gadolinium compounds (GdC) can function as a contrast agent for magnetic resonance imaging (MRI) in medical diagnosis [1-6]. Typical commercial GdC-based contrast agents are solutions dissolving homogeneously gadolinium complexes at a molecular level. The GdC molecules are not strongly dragged in fluid because of their small sizes. Consequently, they cannot stay in living bodies for a long period, which provides difficulty taking steady images. Formation of particles of GdC and an increase in their apparent size are promising solutions to the problem because of their projected area which is larger than molecules or nanoparticles. Thus, their residence time will increase, which may realize steady imaging.

Growth of tumor generated in tissue produces a number of slits with a size of several hundred nanometers on the wall of the vessel near the tumor. Polymers or nanoparticles smaller than the slit size may be able to pass through the slit. Their discharge from the tumor is controlled because lymph, which is a way for the discharge, is premature in tumor. This behavior is called an enhanced permeation and retention (EPR) effect [7-9]. Accordingly, nanoparticle formation has another advantage; nanoparticles that show MRI properties may have the ability to detect the tumor by the EPR effect.

Gadolinium complexes may release free gadolinium ions through dissociation of the ions. The release of gadolinium ions may provoke adverse reactions in some patients [6,10,11]. As one of the methods for reducing the adverse reactions derived from gadolinium complexes, coating of GdC nanoparticles (core) with materials inert to living bodies (shell) can be given because contact of the GdC with living bodies may be controlled with a physical barrier of the shell materials. From this viewpoint, we have also studied on the silica coating of

* Correspondence: ykoba@mx.ibaraki.ac.jp

¹Department of Biomolecular Functional Engineering, College of Engineering, Ibaraki University, 4-12-1 Naka-narusawa-cho, Hitachi, Ibaraki 316-8511, Japan

Full list of author information is available at the end of the article

GdC nanoparticles [12]. In a preliminary experiment, the silica-coated GdC (GdC/SiO_2) particles with a core-shell structure became hollow particles after the GdC/ SiO_2 particles were washed with a centrifuge and were aged in water. In several previous studies, hollow particles are fabricated by calcining core-shell particles composed of organic compound core and inorganic compound shell to remove the core [13-15]. The hollow particles in the preliminary experiment were obtained with no calcination. Methods for producing hollow silica particles that do not use calcination process have been proposed by several researchers [16-18]. They use liquids such as aqueous basic solutions and organic solvents that dissolve core materials. The use of such liquids may damage the silica shell or give environmental load. Care of the problems is not required to be taken for the preliminary experiment since it did not use acid, base, and organic solvent to remove the core. If the components of GdC particles are left in the silica shell after the formation of hollow particles, the hollow particles are expected to function as new MRI contrast agents because many protons contained in the silica shell may interact efficiently with the GdC components compared to the GdC particles localized only at the center of the Gd/SiO_2 particles.

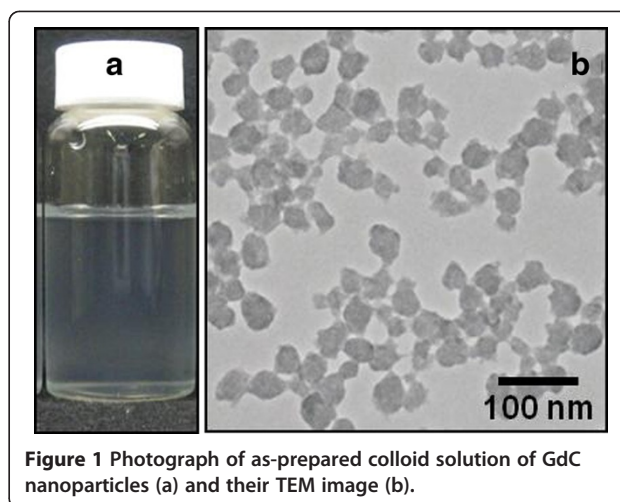
The present work proposes a method for preparing hollow particles composed of GdC and silica. A colloid solution of GdC nanoparticles was prepared with a homogeneous precipitation method, and then the GdC nanoparticles were silica-coated with a modified Stöber method. Elimination of GdC core was performed by replacing the solvent of the reactant with water and aging the aqueous colloid solution. The present work also studied on MRI properties of the hollow particle colloid solution.

Results and discussion

Morphology of particles

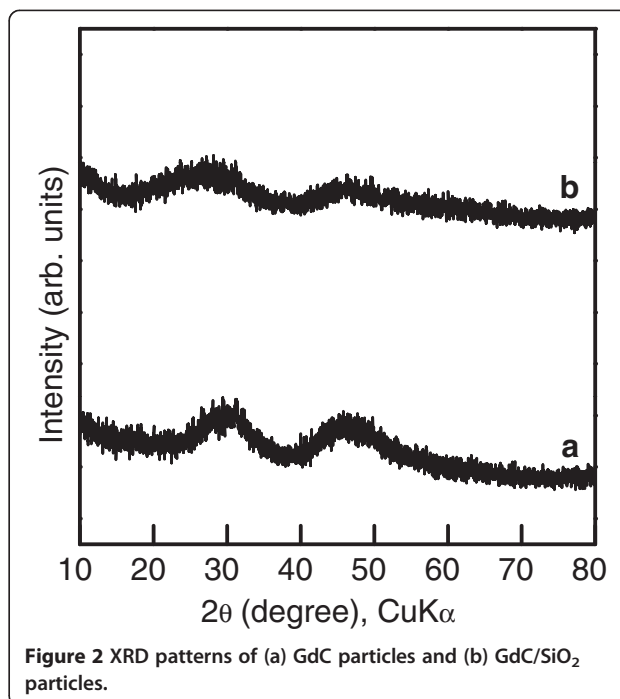
GdC nanoparticles

A photograph was taken for the colloid solution of GdC particles, as shown in Figure 1a. The colloid solution was faintly turbid but colloidally stable. Figure 1b shows a transmission electron microscopy (TEM) image of the GdC particles. Quasi-spherical particles were obtained, though they partially stuck together. Their particle size was 40.5 ± 6.2 nm. Figure 2 (pattern a) shows an X-ray diffractometry (XRD) pattern of the GdC particles. The pattern was structureless, except for broad peaks at *ca.* 30° and *ca.* 45° . Accordingly, the GdC particles were amorphous or too fine to be detected. The inductively coupled plasma (ICP) measurement showed that Gd concentration in the GdC particle colloid solution was 0.819 mM, which indicated that 81.9% of the $\text{Gd}(\text{NO}_3)_3$ used for production of GdC particles was transformed to GdC particles.



GdC/SiO₂ core-shell particles

Figure 3a shows a TEM image of the GdC/SiO_2 particles, which were as-prepared, i.e., dispersed in $\text{H}_2\text{O}/\text{ethanol}$ solution with the H_2O concentration of 11 M. The image was taken several days after preparation. Darker and lighter parts corresponded to GdC and silica, respectively, since the electron density of GdC is significantly higher. The GdC particles were successfully coated with silica shell, though the GdC/SiO_2 particles partially stuck together. No damage was seen for the GdC/SiO_2 particles even several days after preparation. Accordingly, the GdC/SiO_2 particles were chemically stable in the as-prepared solution. The particles had a size of 100.9 ± 9.9 nm, which were composed of core particles with a size



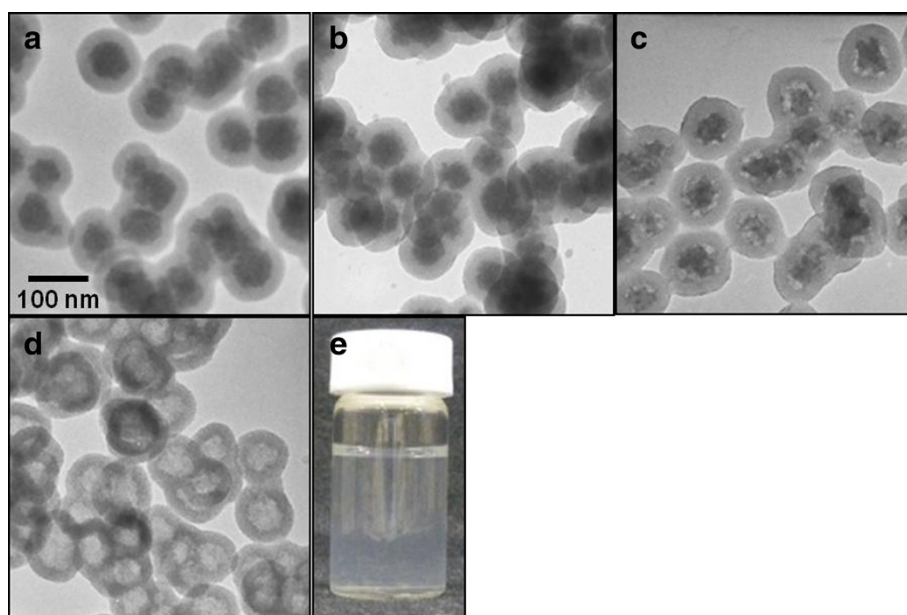


Figure 3 TEM images of various particles. (a) GdC/SiO₂ particles several days after preparation, (b) GdC/SiO₂ particles immediately after replacement of solvent to water, (c) GdC/SiO₂ particles aged at room temperature for 3 h after replacement of solvent to water, (d) GdC/SiO₂ particles aged at 80°C for 3 h after replacement of solvent to water. Image (e) shows a photograph of sample (d).

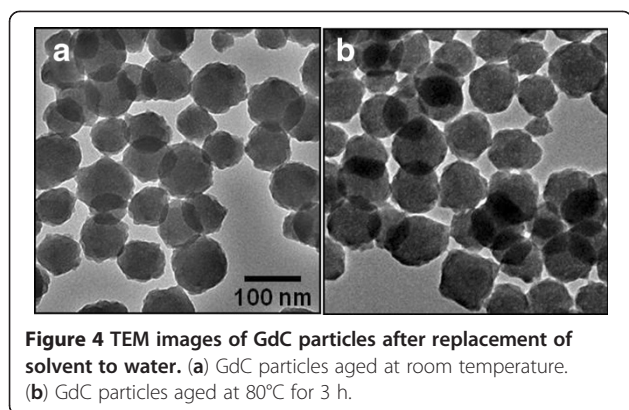
of 51.8 ± 8.2 nm and a shell with a thickness of 24.6 nm. The core size was larger than that of the GdC particles prior to the silica coating. Aggregation and particle growth were considered to take place during the silica coating. Hydrolysis of tetraethylorthosilicate (TEOS) provided an increase in ionic strength of the solution. Since an increase in the ionic strength compresses double layer on solid materials such as colloidal particles [19-21], the double-layer repulsion between the GdC particles probably became small through the hydrolysis. Thus, the GdC particles probably aggregated and grew because of the high ionic strength that would favor the particle aggregation. Figure 2 (pattern b) shows an XRD pattern of the GdC/SiO₂ particles. There was no large difference between the patterns of GdC particles and the GdC/SiO₂ particles. The GdC particles were also amorphous or too fine to be detected. Accordingly, the results of TEM observation and XRD measurement indicated that the silica coating made no chemical effect on the GdC particles. The ICP measurement revealed that an actual Gd concentration in the Gd/SiO₂ particle colloid solution was 0.698 mM, which indicated that 85.2% of Gd contained in the GdC particles was consumed for the formation of GdC/SiO₂ particles.

Hollow particles

Figure 3b,c shows TEM images of the GdC/SiO₂ particles, of which solvents were replaced with water. The GdC/SiO₂ particles immediately after the washing process (Figure 3b) appeared to be similar to those prior to the replacement (Figure 3a), which indicated that the

washing process did not damage their core-shell structure mechanically. For 3 h after the washing (Figure 3c), the surface of the GdC core appeared to be partially dissolved and then became rough. The silica shell was not damaged in spite of the surface roughening. The surface roughing was promoted by heating at 80°C, as shown in Figure 3d. Then, hollow particles were produced. The silica shell was still maintained even after the heating. Figure 3e shows a photograph of the hollow particle colloid solution. The solution was colloidally stable since no sedimentation took place. According to the ICP measurement, an actual Gd concentration in the hollow particle colloid solution was 0.426 mM. This meant that 61.0% of Gd contained in the GdC/SiO₂ particles was considered to still remain in the shell of hollow particles and 39.0% of Gd was removed from the hollow particles.

Figure 4a shows a TEM image of GdC particles after the solvent of their colloid solution was replaced with water. The replacement of solvent with water did not damage the GdC particles mechanically. After the replacement, the colloid solution of GdC particles was aged at 80°C for 3 h. Their TEM image is shown in Figure 4b. The image appeared to be similar to that prior to the aging (Figure 4a). Those results indicated that both the replacement and the aging at 80°C did not affect the structure of GdC particles. Accordingly, it could be concluded that the formation of hollow structure required the GdC particles to have contact with the silica shell. The GdC was presumed to diffuse into the silica shell, which



provided the production of new compounds such as gadolinium silicate in the shell. Consequently, the hollow particles were produced. However, a precise mechanism of the hollow particle formation is still unclear.

MRI property

Longitudinal relaxation time (T_1)-weighted images of the colloid solutions of hollow particles with various actual Gd concentrations are shown in Figure 5. 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 actual Gd concentration.

Figure 6 shows a plot of longitudinal relaxation rate ($1/T_1$) of the hollow particle colloid solution as a function of the actual Gd concentration. The relaxation rate increased linearly with increasing actual Gd concentration. A value of relaxivity (r_1) is defined as a slope of relaxation rate with respect to actual Gd concentration and is commonly used as a guideline on the performance of positive contrast agents. The r_1 value, which was calculated by linear fitting, was $3.38 \text{ mM}^{-1} \cdot \text{s}^{-1}$. This value attained 80% of that of Magnevist since an r_1 value of Magnevist, which was measured in our previous work [22], was $4.23 \text{ mM}^{-1} \cdot \text{s}^{-1}$. Our previous work also gave that a colloid solution of GdC/SiO₂ particles revealed an r_1 value of $3.11 \text{ mM}^{-1} \cdot \text{s}^{-1}$ [22], which indicated that the r_1 value of the hollow particle colloid solution was larger

than that of the GdC/SiO₂ particle colloid solution. Active exchange of the protons with the contrast agent shortens T_1 , i.e., increases r_1 [23,24]. Since the GdC present in the shell lay close to the water protons compared to the GdC inside the GdC/SiO₂ particles, the interaction between water protons and gadolinium ions was more significant than that for the GdC/SiO₂ particles. Accordingly, the formation of hollow particles with shell-containing GdC was found to improve imaging ability based on longitudinal relaxation.

Conclusions

A method for producing hollow particles with silica shell containing GdC was proposed. The GdC nanoparticles with the average size of 40.5 nm were prepared by means of the homogeneous precipitation method using aqueous solution of $1.0 \times 10^{-3} \text{ M}$ Gd(NO₃)₃, 0.5 M urea, and $2.0 \times 10^{-4} \text{ M}$ ethylenediaminetetraacetic acid disodium salt dihydrate (EDTA). The silica coating of the GdC particles was achieved with the sol-gel method using $5.0 \times 10^{-3} \text{ M}$ TEOS, 11 M H₂O, and $1.5 \times 10^{-3} \text{ M}$ NaOH in the presence of the GdC particles at the Gd concentration of $1.0 \times 10^{-3} \text{ M}$, which produced the GdC/SiO₂ particles with the average size of 100.9 nm. The replacement of the solvent of GdC/SiO₂ particle colloid solution with water and the aging of GdC/SiO₂ particles in water at 80°C transformed the GdC/SiO₂ particles to hollow particles due to the diffusion of GdC into the silica shell. The hollow particle colloid solution showed high-contrast T_1 -weighted magnetic resonance images. Its relaxivity value, which was $3.38 \text{ mM}^{-1} \cdot \text{s}^{-1}$, was recorded at the value as high as 80% of that for Magnevist, the commercial Gd complex contrast agent. These results obtained in the present work indicated that the hollow particle colloid solution had an ability of MRI contrast agent.

Methods

Chemicals

Gadolinium nitrate hexahydrate (Gd(NO₃)₃ · 6H₂O, 99.5%) and urea (99.0%) were used as a raw chemical for GdC nanoparticles and a precipitation inducer in the preparation of GdC nanoparticles, respectively. The stabilizer used in the preparation of GdC nanoparticles was EDTA (99.0% to 101.0%). A raw chemical for silica shell and a

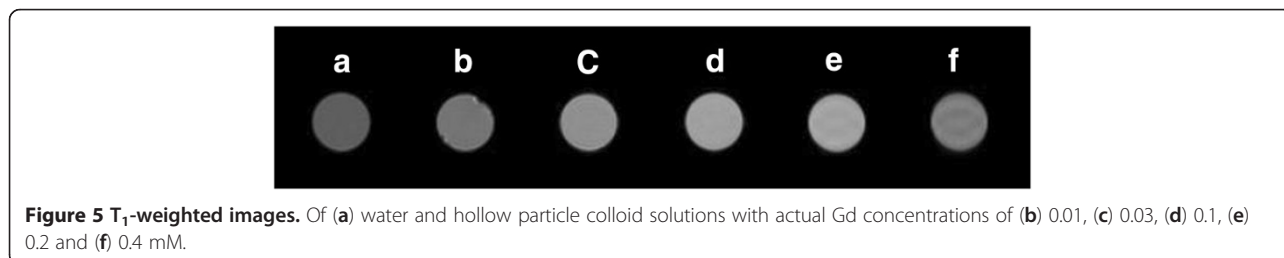
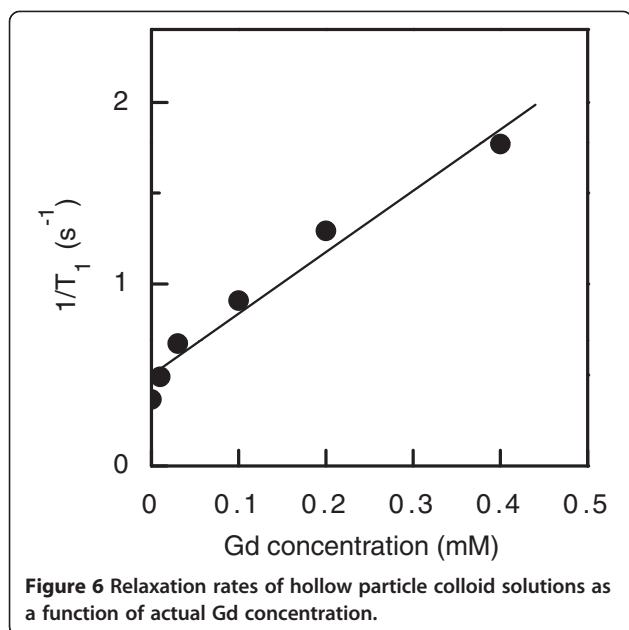


Figure 5 T_1 -weighted images. Of (a) water and hollow particle colloid solutions with actual Gd concentrations of (b) 0.01, (c) 0.03, (d) 0.1, (e) 0.2 and (f) 0.4 mM.



solvent for silica coating were TEOS (95%) and ethanol (99.5%), respectively. A sol-gel reaction of TEOS in the silica coating was catalyzed with sodium hydroxide (NaOH) solution (5 M). The commercial MRI contrast agent used for comparison to the particle colloid solutions in imaging examinations was Magnevist (0.5 M Gd, Bayer Co., Ltd., Leverkusen, Germany). All the chemicals except for the commercial contrast agents were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan) and used as received. The water that was ion-exchanged and distilled with Shimadzu SWAC-500 (Kyoto, Japan) was used in all the preparations.

Preparation of materials

GdC particles

A colloid solution of GdC nanoparticles was prepared in water containing EDTA by a homogeneous precipitation method, according to our previous work [22]. $\text{Gd}(\text{NO}_3)_3$ aqueous solution was added to aqueous solution dissolving urea and EDTA in a hermetically sealed flask reactor. The mixture was stirred at 80°C for 3 h. Initial concentrations of $\text{Gd}(\text{NO}_3)_3$, urea, and EDTA were 1.0×10^{-3} , 0.5, and 2.0×10^{-4} M, respectively. The GdC particles in the colloidal solution were washed by repeating centrifugation, removal of supernatant, addition of water, and sonication three times. The solvent was replaced with H_2O /ethanol solution by adding the H_2O /ethanol solution at the last washing process.

GdC/SiO₂ core-shell particles

GdC/SiO₂ core-shell particles were fabricated by the silica coating of the GdC particles, which was performed

in the H_2O /ethanol solution by a sol-gel method, according to our previous work [22]. TEOS and 0.1 M NaOH aqueous solution were successively added to the GdC particle colloid solution at 35°C. The reaction time was 24 h. Initial concentrations of Gd, TEOS, H_2O , and NaOH were 1.0×10^{-3} , 5.0×10^{-3} , 11, and 1.5×10^{-3} M, respectively.

Hollow particles

Hollow particles were fabricated from the Gd/SiO₂ core-shell particles. The colloidal suspensions of GdC/SiO₂ particles were washed by repeating centrifugation, removal of supernatant, addition of water, and sonication three times, which resulted in the replacement of solvent with water. Then, the washed colloid suspensions were aged in water.

Characterization

The samples were characterized by TEM and XRD. TEM was performed with a JEOL JEM-2000FX II microscope (Akishima, Japan) 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:

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

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

where n_i is the number of particles with a size of d_i . XRD measurements were carried out with a Rigaku RAD-B (Tokyo, Japan) operating at 7.5 kW Cu $K\alpha$ radiation using a wide-angle goniometer. Samples for XRD were obtained with centrifugation of the solution containing the particles, removal of the supernatant, and drying of the residue at room temperature for 24 h in vacuum.

Actual Gd concentrations in particle colloid solutions were measured by ICP emission spectroscopy. ICP measurement was performed with a Shimadzu ICPS-7510 atom emission spectrometer (Kyoto, Japan). The emission was detected at a wavelength of 342.247 nm. Samples for ICP were prepared by dissolving the particles with aqua regia completely and then diluting the obtained solution with water to adjust its concentrations to concentrations suitable for the measurements.

For the estimation of MR signal intensity, T_1 -weighted images of colloid solutions with different Gd concentrations were taken with a Bruker AVANCE III 400WB

magnetic resonance imaging system (Madison, WI, USA) at a static magnetic field of 9.4 T. Times of echo and repetition were 8.5 and 1,500 ms, respectively. The colloid solutions were prepared by diluting the as-prepared colloid solutions with water.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YK (Kobayashi) drafted the manuscript. KG and NO modified it. HM, TN, and YK (Kubota) participated in some practical work. All authors read and approved the final manuscript.

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Author details

¹Department of Biomolecular Functional Engineering, College of Engineering, Ibaraki University, 4-12-1 Naka-narusawa-cho, Hitachi, Ibaraki 316-8511, Japan. ²Department of Nano-Medical Science, Graduate School of Medicine, Tohoku University, Seiryomachi, Aoba-ku, Sendai 980-8575, Japan. ³Department of Surgical Oncology, Graduate School of Medicine, Tohoku University, Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.

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