

# Fabrication and fluorescence properties of multilayered core–shell particles composed of quantum dot, gadolinium compound, and silica

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**Abstract** A preparation method for multilayered quantum dot/silica/gadolinium compound/silica (QD/Si/Gd/Si) core–shell particles is proposed. Silica (Si)-coated quantum dot (QD/Si) core–shell particles were prepared by a Stöber method at room temperature in water/ethanol solution with TEOS and NaOH in the presence of QD nanoparticles. Succeeding gadolinium compound (Gd)-coating of the QD/Si core–shell particles was performed by a homogeneous precipitation method using  $\text{Gd}(\text{NO}_3)_3$ , urea, and polyvinylpyrrolidone in the presence of the QD/Si particles, which resulted in production of multilayered QD/silica/gadolinium compound (QD/Si/Gd) core–shell particles. For Si-coating of the QD/Si/Gd particles, the Stöber method was performed at room temperature in water/ethanol solution with TEOS and NaOH in the presence of the QD/Si/Gd particles. Consequently, Si-coated QD/Si/Gd, i.e., multilayered QD/Si/Gd/Si, core–shell particles were obtained. The QD/Si/Gd/Si particles revealed strong fluorescence, which was almost comparable to the QD particles with no shells. These particles are expected to be harmless

to living bodies, and have dual functions of magnetic resonance imaging and fluorescence.

## Introduction

Imaging by using magnetic resonance (MR) is focused as an advanced technique for medical diagnosis [1–3]. Tissues in living bodies can be imaged with high contrast using gadolinium compounds (Gd) in MR imaging (MRI) because of their paramagnetism. Some gadolinium complexes are commercially available as MRI contrast agents. The MRI contrast agents are liquid solutions dissolving the gadolinium complexes. The gadolinium complexes face a problem for difficulty in obtaining clear images for a long period because of their short residence time in living bodies. Formation of Gd nanoparticles can solve the problem. Nanoparticles have a projected area larger than molecules, so that flow of nanoparticles will be more controlled, i.e., their residence time will be prolonged.

The gadolinium complexes have another problem. They may release free gadolinium ions through dissociation of the complexes, and then the gadolinium ions may provoke adverse reactions in some patients [4, 5], so that the gadolinium complexes cannot be administered to such people. Among various methods for reducing adverse reactions derived from gadolinium complexes, coating of Gd nanoparticles (core) with materials inert to living bodies (shell) is a good candidate, because the shell materials prevent the Gd from contacting living bodies. Studies on coating of nanoparticles with silica (Si), which is inert to living bodies, have been extensively conducted [6–14]. They are techniques based on a sol–gel reaction of silicon alkoxide. We have also proposed methods for Si-coating of various materials [15–31].

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Fluorescence imaging has been also performed in the field of medical diagnosis [32–34]. Cadmium compound (Cd) semiconductors have been widely used as a fluorescent marker, i.e., an imaging agent for the medical examination, because of their size-tunable photoluminescence, high brightness, and exceptional photostability [34, 35]. Colloid solutions of Cd nanoparticles are commercially available as the fluorescent marker by the name of “quantum dots (QD).” It is well known that Cd is harmful to living bodies. Its harm may also be reduced with the Si-coating.

Materials composed of components that have different properties should have multiple functions. Composite particles with magnetism and fluorescence have been of great interest in applications such as cell labeling [36–39], biosensing [40], and diagnostic medical devices [41, 42]. Based on the viewpoint for multi-functionalization of materials, particles containing QD and Gd will act as both the fluorescent marker and the MRI contrast agent.

This study proposes a method for preparing multilayered core–shell particles composed of core of QD, the first shell of silica, the second shell of Gd, and the third shell of Si. QD nanoparticles were Si-coated with a modified Stöber method (QD/Si particles), the QD/Si particles were coated with Gd using a homogeneous precipitation method (QD/Si/Gd particles), and then the QD/Si/Gd particles were Si-coated with a modified Stöber method (QD/Si/Gd/Si particles). In this study, their fluorescence property was also studied toward materials with dual functions.

## Materials and methods

### Materials

Quantum dot nanoparticles used were Qdot<sup>®</sup> (Invitrogen Co.) with a catalog number of Q21371MP. The QD nanoparticles are CdSe<sub>x</sub>Te<sub>1-x</sub> nanoparticles coated with ZnS and successively surface-modified with carboxyl groups, and their concentration is  $8 \times 10^{-6}$  M. Figure 1a shows a transmission electron microscope (TEM) image of the QD nanoparticles. The QD nanoparticles had an average size of  $10.3 \pm 2.2$  nm. Tetraethylorthosilicate (TEOS) (95%), sodium hydroxide (NaOH) solution (5 M), and ethanol (99.5%) were used as a Si source, a catalyst and a solvent in Si-coating by a sol–gel reaction of TEOS, respectively. Gadolinium nitrate hexahydrate (Gd(NO<sub>3</sub>)<sub>3</sub>·6H<sub>2</sub>O) (99.5%) and urea (99.0%) were used as chemicals for Gd compound shell and a precipitation-inducer for Gd-coating, respectively. Stabilizers used in the Gd-coating were *n*-hexadecyltrimethylammoniumbromide (CTAB) (96%), polyvinylpyrrolidinone (PVP) (*M<sub>w</sub>*: 40,000), and sodium *n*-dodecyl sulfate (SDS). Except for the QD nanoparticles, all the other chemicals were purchased from Kanto Chemical

Co., Inc., and were used as received. Water that was ion-exchanged and distilled with Shimadzu SWAC-500 was used in all the preparations.

### Synthesis of particles

#### *QD/Si particles*

According to our previous study [28], QD/Si particles were prepared in a 10-mL glass vessel under vigorous stirring with a modified Stöber method. The Stöber method is based on hydrolysis and condensation of TEOS in the presence of ammonia as a catalyst in ethanol [43–45]. Since, amines such as ammonia are harmful to the human body [46, 47], NaOH was used as a catalyst for the hydrolysis and condensation of TEOS instead of ammonia in the modified Stöber method. To the colloid of QD nanoparticles were added water/ethanol solution and successively TEOS/ethanol solution. Then, the Si-coating was initiated by rapidly injecting 0.1 M NaOH aqueous solution into the QD/TEOS colloid solution. The Si-coating was performed for 24 h at room temperature. A total volume of the solution was 5 mL, and initial concentrations of QDs, H<sub>2</sub>O, NaOH, and TEOS were  $6.4 \times 10^{-9}$ , 5,  $4 \times 10^{-4}$ , and  $5 \times 10^{-4}$  M, respectively. Figure 1b shows a TEM image of the QD/Si particles. The QD/Si particles had an average size of  $20.1 \pm 2.4$  nm.

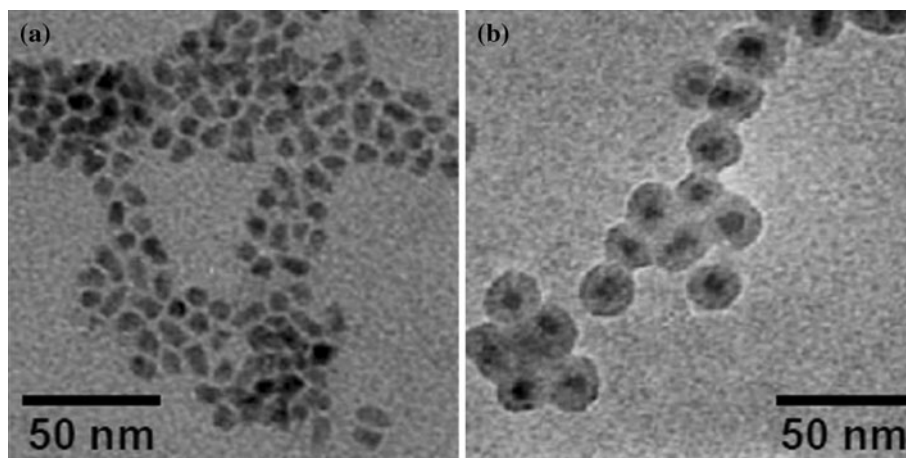
#### *QD/Si/Gd particles*

Gd-coating of the QD/Si particles was performed by a NaOH-addition method and a homogeneous precipitation method in the presence of the QD/Si particles, in a 10-mL glass vessel under active stirring.

In the NaOH-addition method, the Gd-coating was performed in 1:1 (v/v) water/ethanol solution. To water were added the as-prepared QD/Si particle colloid solution and ethanol. After 15 min, to the mixture successively added were the Gd(NO<sub>3</sub>)<sub>3</sub> aqueous solution and 0.1 M NaOH aqueous solution (for adjusting initial pH to ca. 10.5). The reaction was carried out at room temperature for 24 h. A total volume of the solution was 5 mL, and initial concentrations of QD and Gd(NO<sub>3</sub>)<sub>3</sub> were  $3.2 \times 10^{-9}$  and  $3 \times 10^{-4}$  M, respectively.

In the homogeneous precipitation, the Gd-coating was performed in 1:1 (v/v) water/ethanol solution at initial concentrations of  $3.2 \times 10^{-9}$  M QD, 1 g/L stabilizer, 0.5 M urea, and  $3 \times 10^{-5}$ – $3 \times 10^{-3}$  M Gd(NO<sub>3</sub>)<sub>3</sub>. To water successively added were the as-prepared QD/Si particle colloid solution, ethanol, and stabilizer aqueous solution. After 15 min, to the mixture successively added were urea aqueous solution, nitric acid (for adjusting pH to 5), and aqueous Gd(NO<sub>3</sub>)<sub>3</sub>. The mixture was stirred at 300 rpm and 60 °C for 6 h.

**Fig. 1** TEM images of (a) QD nanoparticles and (b) QD/Si nanoparticles



Colloidal suspensions of QD/Si/Gd particles were washed by repeating centrifugation, removal of supernatant, addition of the water, and sonication over three times.

#### *QD/Si/Gd/Si particles*

Si-coating of the QD/Si/Gd particles was performed by the modified Stöber method in a 10-mL glass vessel under vigorous stirring. In each reaction, TEOS and 0.1 M aqueous NaOH solution were successively added to the QD/Si/Gd particle colloid solution at room temperature. The reaction time was 24 h. A total volume of the solution was 5 mL, and initial concentrations of QD, H<sub>2</sub>O, NaOH, and TEOS were  $3.2 \times 10^{-9}$ , 5,  $1 \times 10^{-3}$ , and  $5 \times 10^{-4}$ – $5 \times 10^{-3}$  M, respectively. Colloidal suspensions of QD/Si/Gd/Si particles were washed by repeating centrifugation, removal of supernatant, addition of the water, and sonication over three times.

#### Characterization

Morphology of the particles was investigated by 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. Several hundred particle diameters in TEM images were measured to determine volume-averaged particle size,  $d_v$ , and standard deviation of particle size distribution,  $\sigma$ , 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  $d_i$ .

Fluorescence intensity of each particle was measured with an optical system with confocal microscope, which was also used in our previous studies [48, 49]. The optical system for observation of fluorescence of particles consisted primarily of an epi-fluorescent microscope (IX-71, Olympus) with a 60× oil immersion objective lens (UPLSAPO; Olympus), a Nipkow disc-type confocal unit (CSU10, Yokogawa, Tokyo, Japan) and an electron multiplier type charge-coupled device camera (Ixon DV887, Andor, Belfast, Northern Ireland). One  $\mu$ L of sample was pipetted on to a glass slide ( $25 \times 60$  mm; Matsunami glass) and covered with a glass cover slip ( $24 \times 32$  mm; Matsunami glass). Particles were illuminated with a blue laser (488 nm, 50 mW, Spectra-Physics, CA, USA), and the laser-excited fluorescence was filtered with a 760–840 nm band-pass filter. The fluorescent images of particles were acquired by accumulating 100 images taken at an exposure time of 0.2 s and converted into AVI files. QDs possessing the same fluorescent wavelength are uniform in size, and its fluorescence is composed of fluorescent and non-fluorescent states called on- and off-states, respectively. This fluorescent property results in blinking of QDs. The mean time of the off-state during 20 s of observation was about 4 s and the calculated value of the standard error of the mean was very low. Therefore, based on an off-state time of 4 s, we selected ten single-particle QD. Their fluorescent intensity of  $4 \times 4$  pixels ( $1.12 \mu\text{m}^2$ ) during 20 s were averaged and calculated as gray value by Image J software (<http://rsb.info.nih.gov/ij/>).

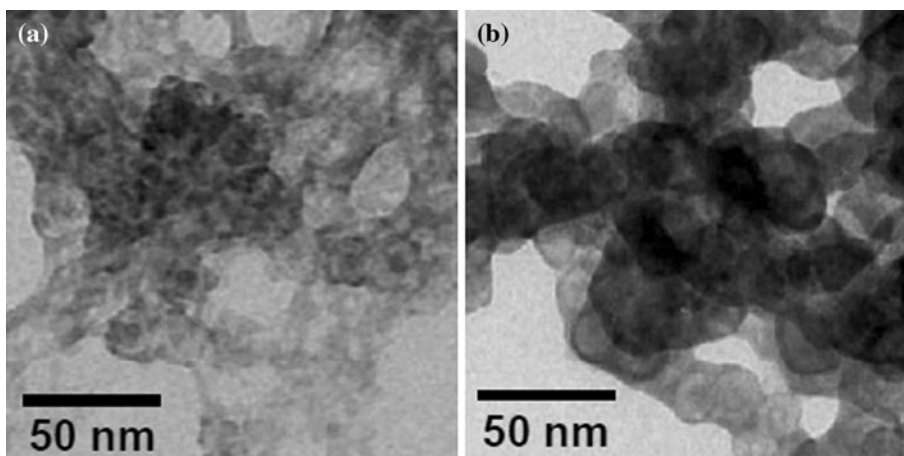
## Results and discussion

### QD/Si/Gd particles

#### *Gd-coating with NaOH-addition method and homogeneous precipitation method*

Figure 2a shows TEM images of particles prepared with the NaOH-addition method. No Gd-coated core-shell

**Fig. 2** TEM images of QD/Si nanoparticles after Gd-coating by (a) NaOH-addition method and (b) homogeneous precipitation method. Initial concentrations of QD and  $\text{Gd}(\text{NO}_3)_3$  were  $3.2 \times 10^{-9}$  and  $3 \times 10^{-4}$  M, respectively. Urea concentration in the homogeneous precipitation method was 0.5 M



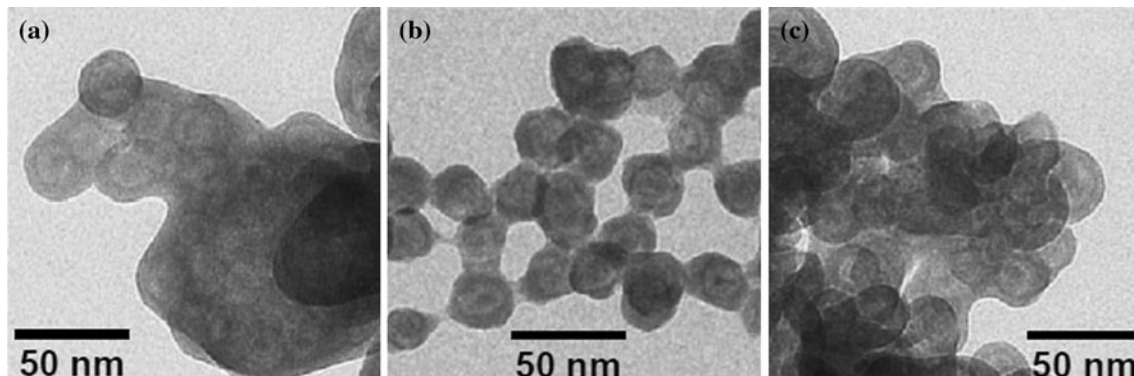
particles were produced. Instead, gel network of Gd formed, and the network appeared to incorporate the QD/Si particles. A local increase in pH of the colloid solution took place with the NaOH addition, which resulted in generation of large amount of Gd nuclei. The NaOH addition also provided a local increase in ionic strength of the solution close by the drops of NaOH aqueous solution. Since, an increase in the ionic strength compresses double layer on solid materials such as colloidal particles [50–52], the double layer repulsions both among the Gd nuclei and between the nuclei and the QD/Si particles were probably reduced with the NaOH addition. Thus, the aggregation of the Gd nuclei and the successive formation of their gel network took place simultaneously with the aggregation of the nuclei and the QD/Si particles. During the gel network formation, the QD/Si particles present in the colloid solution were probably incorporated with the network.

Figure 2b shows TEM images of particles prepared with the homogeneous precipitation method. The QD/Si particles were coated with Gd shell, though aggregation of the QD/Si/Gd particles was observed. Since, heating decomposed urea slowly, pH of the solution increased slowly and homogeneously, and then Gd nuclei was generated. The

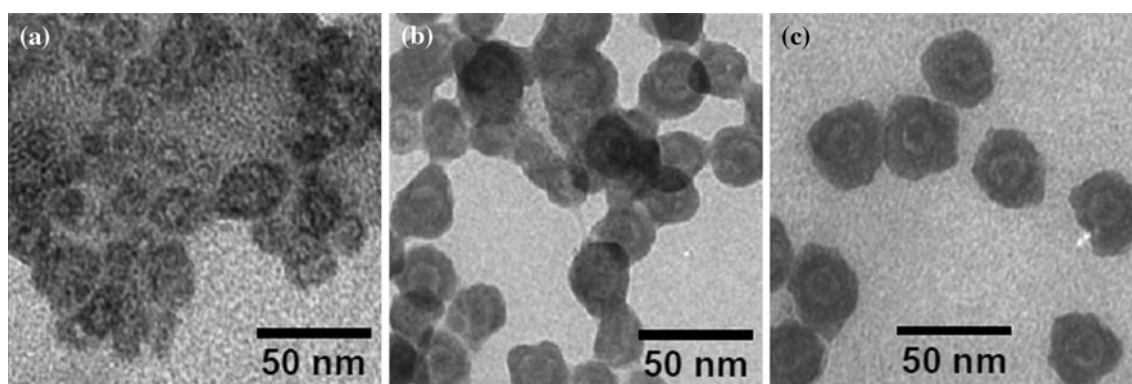
slow decomposition of urea resulted in not a fast but a slow increase in ionic strength of the solution. The slow increase in ionic strength controlled aggregation and growth of the Gd nuclei. Consequently, the Gd nuclei were deposited on the QD/Si particle surface. Accordingly, it was found that the homogeneous precipitation method was suitable to Gd-coating of the QD/Si particles, compared to the NaOH-addition method. Therefore, the homogeneous precipitation method was used for all subsequent experiments.

#### *Effect of stabilizer*

Figure 3 shows TEM images of QD/Si/Gd particles prepared with the homogeneous precipitation method using various stabilizers. In the cases of CTAB and SDS, though the QD/Si particles were coated with Gd shell, aggregation of the QD/Si/Gd particles was observed, which was similar to the case with no stabilizer (Fig. 2b). Because both CTAB and SDS are ionic surfactants, the addition of them may increase the ionic strength of solution. The increase in the ionic strength probably accelerated the aggregation of particles. The addition of PVP appeared to control the aggregation, i.e., quasi-perfect multilayered QD/Si/Gd



**Fig. 3** TEM images of QD/Si/Gd nanoparticles prepared with homogeneous precipitation method using stabilizers of (a) CTAB, (b) PVP, and (c) SDS. Initial concentrations of QD,  $\text{Gd}(\text{NO}_3)_3$ , urea and stabilizer were  $3.2 \times 10^{-9}$ ,  $3 \times 10^{-4}$ , 0.5 M, and 1 g/L, respectively



**Fig. 4** TEM images of QD/Si/Gd nanoparticles prepared with homogeneous precipitation method at  $\text{Gd}(\text{NO}_3)_3$  concentrations of (a)  $3 \times 10^{-5}$ , (b)  $3 \times 10^{-4}$ , and (c)  $3 \times 10^{-3}$  M. Initial concentrations of QD, urea, and PVP were  $3.2 \times 10^{-9}$ , 0.5 M, and 1 g/L, respectively

core-shell particles were produced with the PVP addition. Since, PVP is a polymer dispersant, the PVP addition probably did not provide remarkable change of ionic strength. Consequently, the particle aggregation became unpronounced. Therefore, the PVP was used for all subsequent experiments.

#### *Effect of $\text{Gd}(\text{NO}_3)_3$ concentration*

Figure 4 shows TEM images of QD/Si/Gd particles prepared with the homogeneous precipitation method at various  $\text{Gd}(\text{NO}_3)_3$  concentrations. At a gadolinium concentration of  $3 \times 10^{-5}$  M, the QD/Si particles were Gd-coated, though the QD/Si/Gd particles were incorporated in gel network of Gd. An increase in the  $\text{Gd}(\text{NO}_3)_3$  concentration to  $3 \times 10^{-4}$  M, quasi-perfect multilayered QD/Si/Gd particles were obtained, though the QD/Si/Gd particles appeared to aggregate. For a  $\text{Gd}(\text{NO}_3)_3$  concentration as high as  $3 \times 10^{-3}$  M, the particle aggregation was almost prevented, and consequently the QD/Si/Gd particles became highly dispersed. The particle size was  $42.5 \pm 6.2$  nm. Values of pHs of the particle colloid solutions at the  $\text{Gd}(\text{NO}_3)_3$  concentrations of  $3 \times 10^{-5}$ ,  $3 \times 10^{-4}$ , and  $3 \times 10^{-3}$  M were 8.1, 7.9, and 6.0, respectively. Because the QD/Si/Gd particle surface was covered with the Gd, properties of the QD/Si/Gd particle surface should be similar to those of the Gd particle surface. According to our previous study [53], Gd particles prepared with the homogeneous precipitation method had  $\zeta$ -potentials of ca. 21, 24, and 37 mV at pHs of 8.1, 7.9, and 6.0, respectively. Accordingly, with the increase in the  $\text{Gd}(\text{NO}_3)_3$  concentration,  $\zeta$ -potential of QD/Si/Gd particles may have increased. Possibly, the increased  $\zeta$ -potential at the high  $\text{Gd}(\text{NO}_3)_3$  concentration provided large electric repulsion among the QD/Si/Gd particles, compared to the low  $\text{Gd}(\text{NO}_3)_3$  concentration. Thus, the high-dispersed QD/Si/Gd particles were produced at the high  $\text{Gd}(\text{NO}_3)_3$  concentration.

#### QD/Si/Gd/Si particles

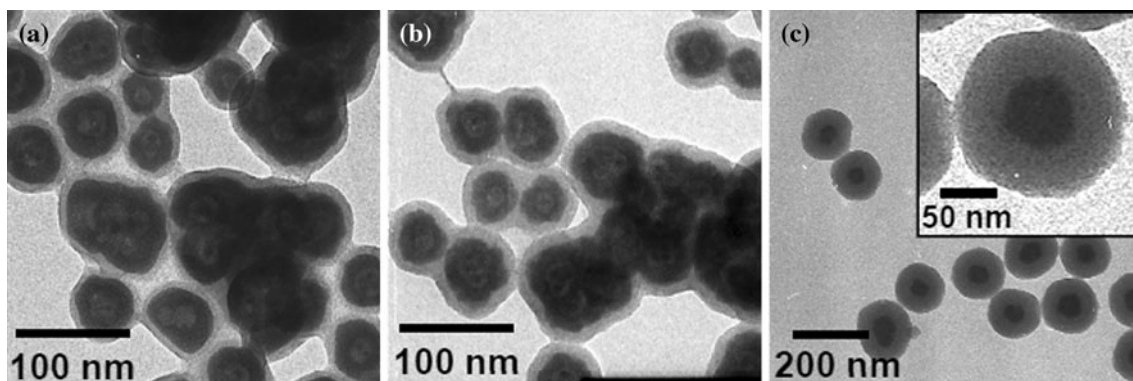
Figure 5 shows TEM images of QD/Si/Gd/Si particles prepared at various TEOS concentrations. The QD/Si/Gd particles were coated with Si shell in all the TEOS concentrations examined. The particle sizes at  $5 \times 10^{-4}$ ,  $1 \times 10^{-3}$ , and  $5 \times 10^{-3}$  M were  $68.1 \pm 7.9$ ,  $72.4 \pm 8.7$ ,  $157.3 \pm 27.7$  nm, respectively. However, at the concentrations of  $5 \times 10^{-4}$  and  $1 \times 10^{-3}$  M, the QD/Si/Gd/Si particles aggregated and connected with other QD/Si/Gd/Si particles. Because Si particles have good stability as colloids, core particles should be colloidally stabilized by Si-coating. The Si shells were, however, so thin due to the low TEOS concentrations that the shells did not stabilize the QD/Si/Gd/Si particles colloidally. The increase in TEOS concentration to  $5 \times 10^{-3}$  M increased the Si shell thickness. The increase in thickness controlled the particle aggregation, and consequently high-dispersed QD/Si/Gd/Si particles were quasi-perfectly produced.

#### Fluorescence properties

Figure 6 shows fluorescence images of various particles on the glass plates. Bright spots show the fluorescence of QD contained in QD/Si/Gd/Si core-shell particles examined. Table 1 gives fluorescence intensities of various particles. As the layer number increased, fluorescence intensity of single particle tended to decrease. Excitation and emission of QD are probably prevented by optical absorption and scatter caused by Gd layer as  $\text{SiO}_2$  layer does not affect fluorescent intensity of QD. Nevertheless, the QD/Si/Gd/Si particles revealed fluorescence with intensity as large as 67.5% of that of the QD particle with no shells.

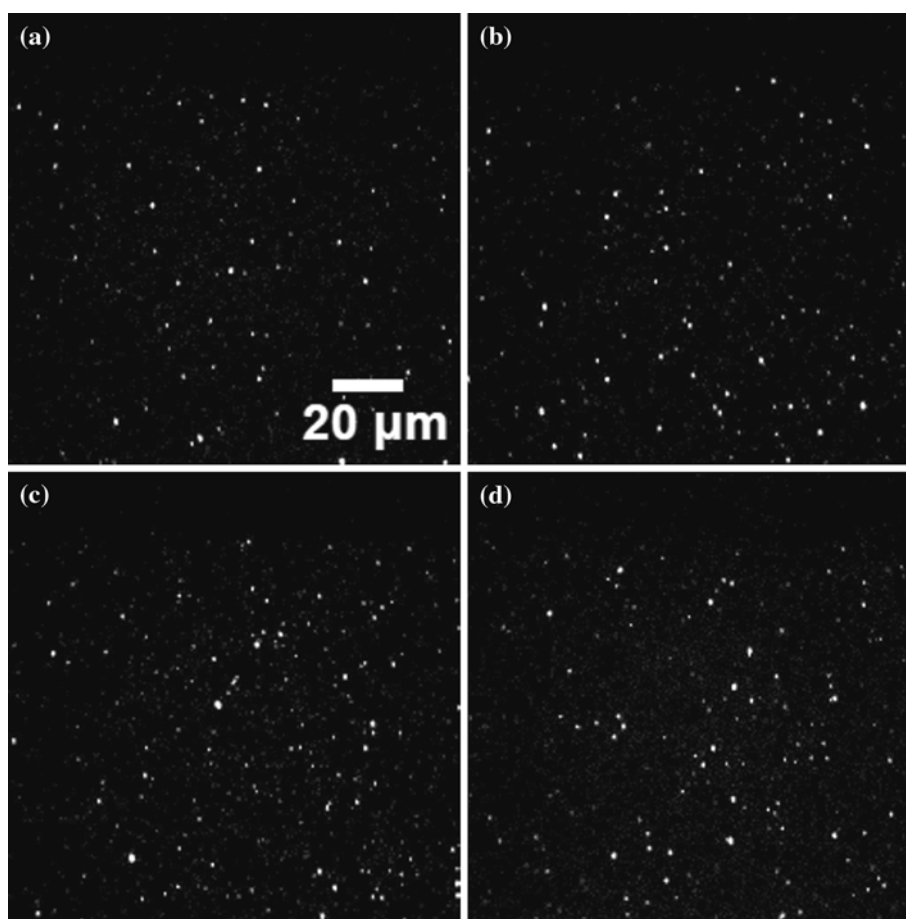
#### Toward harmless fluorescence marker with MRI ability

Our previous study revealed that silica-coated Au nanoparticles revealed high contrast X-ray imaging [31]. A



**Fig. 5** TEM images of QD/Si/Gd/Si nanoparticles prepared at TEOS concentrations of (a)  $5 \times 10^{-4}$ , (b)  $1 \times 10^{-3}$ , and (c)  $5 \times 10^{-3}$  M. Initial concentrations of QD,  $\text{Gd}(\text{NO}_3)_3$ , urea, and PVP were  $3.2 \times 10^{-9}$ ,  $3 \times 10^{-3}$ , 0.5 M, and 1 g/L, respectively

**Fig. 6** Fluorescence images of (a) QD, (b) QD/Si, (c) QD/Si/Gd, and (d) QD/Si/Gd/Si particles



preliminary experiment confirmed that the silica-coated Au nanoparticles were nontoxic for mice. Therefore, the obtained multilayered core-shell particles will be harmless, because they have the outer silica shell. Our another previous study demonstrated that multilayered Si/Gd/Si core-shell particles showed MRI ability [54]. This result implies that the multi-layered core-shell particles

obtained in this study will be functioned as an MRI contrast agent. This study indicated that the multi-layered core-shell particles emitted strong fluorescence. Consequently, it was summarized that the multi-layered core-shell particles were harmless to living bodies, and had dual functions of fluorescence marking and high contrast MRI.

**Table 1** Relative fluorescent intensities of various particles

	QD	QD/Si	QD/Si/Gd	QD/Si/Gd/Si
Fluores. intensity	100	95.2	63.5	67.5

QD Fig. 1a, QD/Si Fig. 1b, QD/Si/Gd Fig. 4c, and QD/Si/Gd/Si Fig. 5a

## Conclusions

This study proposed a method for producing multilayered QD/Si/Gd/Si core-shell particles. QD nanoparticles Si-coated with a modified Stöber method using TEOS and NaOH were coated with Gd shells by means of a homogeneous precipitation method. Si-coating of QD/Si/Gd core-shell particles was achieved by a sol-gel reaction of TEOS initiated by NaOH with the aid of stabilizer PVP. Fluorescence intensity of the multilayered QD/Si/Gd/Si particles was as large as 67.5% of that for the QD nanoparticles. Taking the results obtained in our previous studies and in this study, the multilayered QD/Si/Gd/Si core-shell particles can be used in the field of medical diagnosis as a harmless fluorescence marker with MRI ability.

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