One-Pot Aqueous Synthesis of Gadolinium Doped CdTe Quantum Dots with Dual Imaging Modalities

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Abstract

A facile one-pot strategy has been developed for the aqueous synthesis of Gd doped CdTe (Gd:CdTe) QDs as fluorescence and magnetic resonance imaging dual-modal agent. The prepared Gd:CdTe QDs showed narrow size distribution and the average size was less than 5 nm. The amount of Gd³⁺ dopant in Gd:CdTe QDs significantly affected the optical properties of obtained QDs. The highest PL QY for the prepared Gd:CdTe QDs was up to 42.5 %. The QDs showed the weak toxicity and significant enhancement in MRI signal. The specific relaxivity value (*r1*) was determined to be 4.22 mM⁻¹s⁻¹. These properties make the prepared Gd:CdTe QDs be an effective dual-modal imaging agent and have great potential applications in biomedical field.

Keywords: Aqueous Synthesis, Gd doped CdTe, Quantum dots, Fluorescence, MR imaging

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1. Introduction

Colloidal semiconductor nanocrystals (NCs), also known as quantum dots (QDs), have reached great achievements in applications of biological labeling and sensing,[1-3] light-emitting diode displays,[4, 5] optoelectronic devices,[6, 7] and photovoltaic devices [8, 9]. Especially, QDs have attracted great interest in fluorescence imaging (FI) technique because of their supreme characteristics compared to conventional fluorophores, including size-tunable and spectrally narrow light emission along with efficient light absorption throughout a wide spectrum and improved brightness with outstanding resistance to photobleaching and degradation [10-14].

The disadvantages of low tissue penetration depths and the interference of auto-fluorescence greatly limit the application of FI technique.[15, 16] While the application of QDs with high quantum yield (QY) in FI technique not only makes it possible for *in vivo* imaging at molecular level for disease diagnosis, [17-19] but also provides a suitable engineering platform for combining the strengths of other non-invasive imaging techniques, facilitating the correlation of images with different resolution and tissue/molecular specificity. Among non-invasive imaging techniques, magnetic resonance imaging (MRI) with excellent tissue penetration depth and high spatial resolution is widely used for anatomical imaging of soft body tissues but the sensitivity is low [20, 21]. Therefore, magnetic QDs that simultaneously contain the response ability of FI and MRI have been intensively studied in order to gather the merits of these two imaging modalities and increase the accuracy of imaging

results.[22, 23]

The designs of magnetic QDs usually adopt two different strategies.[23] One is based on integrating QDs and superparamagnetic nanocrystals or other MRI contrast agents to form hybrids. The other is based on inducing magnetic ions into QDs. Compared with QDs/MRI agents based hybrids, magnetic ions doped QDs have a smaller particle size, which is not only suitable for cellular imaging, but also facilitates the clearance of the agents from the body.[22, 24-26] Furthermore, magnetic ions doped QDs can be prepared by a one-step strategy,[27-29] which affords advantages of simplicity and low cost. Therefore, intensive efforts have been drawn into the development of magnetic ions doped QDs as MRI-FI nanoprobe. Since Schwartz et al. reported the synthesis of Co^{2+} and Ni^{2+} doped ZnO nanocrystals in 2003,[30] more and more magnetic ions doped QDs have been prepared as dual-modal agents in the last two decades, such as Ni-doped CdTeSe/CdS,[31] Fe-doped CdTeS,[32] Gd-doped CdSe,[27] Mn-doped CdSe,[33], Mn-doped CdS/ZnS [34], Gd-doped ZnO[29], Gd-doped ZnAgInS₃[35] and Gd-doped CuInS/ZnS[36]. However, most of these magnetic QDs were prepared in organic phase and further surface modifications were necessary to make them water –soluble, which are time-consuming and always lead to the decrease of quantum yields. So aqueous routes for synthesizing magnetic QDs are highly desired in terms of the practical applications. Zhang et al reported the preparation of Gd-doped CdTe QDs by using NaBH_4 and $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ to reduce Na_2TeO_3 and the quantum yield of obtained QDs reached 37 %.[37]

1 In this work, we report another facile one-pot strategy for aqueous synthesis of Gd
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3 doped CdTe (Gd:CdTe) QDs by using NaTeH as Te source and 3-mercaptopropionic
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5 acid as capping ligand. One of the advantages of the proposed method is that the toxic
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7 $N_2H_4 \cdot H_2O$ is avoided. We systematically investigated the effects of the amount of
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9 gadolinium ion and reaction time on the properties of obtained Gd:CdTe QDs. The
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11 highest quantum yield of prepared Gd:CdTe QDs was up to 42.5 %. They also
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13 exhibited ultrasmall particle size with narrow distribution and little cellular toxicity
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15 and can serve as an effective FI-MRI dual-model imaging agent.
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23 **2. Experimental**

24 *2.1 Materials*

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26 3-Mercaptopropionic acid (MPA, 98%) and $NaBH_4$ ($\geq 97\%$) were purchased from
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28 Aladdin. $CdCl_2$ (99.9%), $GdCl_3$ (99.99%) and tellurium powder (99.9%) were
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30 obtained from Alfa Aesar. Other chemicals were obtained from the local suppliers. All
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32 chemicals were used without further purification unless otherwise stated. Milli-Q
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34 water with a resistivity of 18.2 M Ω /cm was used throughout.
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42 *2.2. Cells and animals*

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44 Caco-2 cells were purchased from Shanghai Cellular Institute of China Scientific
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46 Academy. The cells were cultured in DMEM medium, supplemented with 10% FBS
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48 (BioInd, Israel), 100 units mL^{-1} penicillin G, and 100 $\mu g mL^{-1}$ streptomycin (GIBCO,
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50 USA). In all experiments, the cells were maintained in 100-mm culture dishes
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52 (Corning, USA) at 37 °C in a humidified atmosphere of 5 % CO_2 and 95 % air
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54 (FORMA Series 2 Water Jacket, Thermo Scientific, USA).
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Balb/c nude mice (6-8 weeks old) were obtained from the experimental animal center of our university. Animal care and experiments were performed in compliance with the relevant laws and the experimental protocols were approved by the Ethical Committee for Animal Experiments of East China Normal University.

2.3 Synthesis of Gd:CdTe QDs

The synthesis of Gd:CdTe QDs was similar to the synthesis procedure of CdTe QDs [38] with some modification. First, NaHTe was prepared by adding 40 mg NaBH₄ to a flask containing 46 mg tellurium powder and 2 mL Milli-Q water under nitrogen atmosphere. The reaction was kept on for several hours until all tellurium powder was dissolved.

2.5 mL of CdCl₂ solution (40 mmol / L), 21.0 μL of MPA and GdCl₃ solution were added into a three-necked flask containing 100 mL Milli-Q water, followed by adjusting pH to 8.0-9.0 by addition of 1.0 M NaOH solution. The mixture was deaerated by N₂ bubbling for 30 min. Then NaTeH solution (0.060 mmol) was quickly injected into the mixture under vigorous stirring, followed by refluxing the mixture under a nitrogen atmosphere. Aliquots of reaction solutions were removed at regular intervals for UV-vis absorption and PL characterization. In order to investigate the effect of amount of Gd³⁺ on the properties of doped CdTe QDs, three samples were prepared by using the molar ratios of Gd:Cd = 0.02:1, Gd:Cd = 0.04:1 and Gd:Cd = 0.1:1. The obtained Gd:CdTe QDs samples were named as Gd:CdTe (2 %) QDs, Gd:CdTe (4 %) QDs and Gd:CdTe (10 %) QDs, respectively. For purification, 2-propanol was added to Gd:CdTe QDs solution and the precipitates were collected

by centrifugation.

2.4 Characterization

UV-visible absorption spectra and PL spectra were recorded using 1.0 cm UV-quartz cuvettes at room temperature under ambient conditions on a TU-1901 UV-visible spectrophotometer and a Perkin Elmer LS55 fluorescence spectrometer, respectively. Transmission electron microscopy (TEM) measurements were carried out on a JEM-2100 transmission electron microscope (Japan). Powder X-ray diffraction (XRD) measurements were performed on a D8 Discover X-ray diffractometer (Bruker, Germany). The PL QY of the samples was determined by using Rhodamine 6G (with ethylalcohol absolute as the solvent, QY=95%[39]) as the reference according to the protocol described in previous literatures [40-42].

2.5 MTT assay

The cytotoxicity of Gd:CdTe QDs was evaluated by the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) viability assay. Caco-2 cells were cultured at 1×10^5 cells on 96-well plates for 24 hours, and then incubated with the different concentrations of the QDs for 24 hours. After that, the cells were cultured with MTT reagents for 4 h. The products were dissolved with DMSO on the plate, and the absorbance at 490 nm was measured with a micro-plate reader (Multiskan MK3, Thermo Scientific, USA).

2.6 Fluorescence imaging in vitro

$300 \mu\text{g mL}^{-1}$ of Gd:CdTe QDs were incubated with Caco-2 cells for 1 h at 37 °C

and with 5% CO₂. The cells were washed by using PBS buffer solution for three times and used for fluorescence imaging.

2.7 MRI measurements

MR imaging of Gd:CdTe QDs solutions were performed by using a 3 T MRI Scanner (SIEMENS MAGNETOM Trio I-class, Germany). T1 images were measured with a slice thickness of 2 mm, the acquisition number of 1, 60 × 60 mm field of view (FOV), 256 × 256 matrices and an echo time (TE) of 12 ms.

For *in vivo* MR imaging, the mouse was first anesthetized by intraperitoneal injection of a ketamine (100 mg/kg;) and xylazine (10 mg/kg). Then Gd:CdTe QDs solution was given by an intravenous injection in the tail vein. The mouse was placed in an animal coil and MR imaging was performed by using the 3 T MRI Scanner.

3. Results and Discussion

3.1 Influence of Gd³⁺ ion and reaction time on the optical properties of Gd:CdTe QDs

The amount of Gd³⁺ in Gd:CdTe QDS has significant effect on the physical properties of doped CdTe QDs. So We first investigated the influence of the amount of Gd³⁺ and reaction time on the optical properties of Gd:CdTe QDs by fixing the molar ratio of Cd/Te/MPA to be 1.0:0.5:2.4. Fig. 1 shows the temporal evolution of absorption and normalized PL spectra of Gd:CdTe QDs prepared with different molar ratios of Gd/Cd. For all three samples, the first absorption peak and the emission peak wavelengths red-shifted with the increase in the reaction time, accompanying with the

1 broadening of peaks. This is mainly due to the growth of nanocrystals and the
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3 inhomogeneity in particle size. After 21 h reaction, the emission peak wavelengths
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5 were 604 nm, 602 and 612 nm for the Gd:CdTe (2 %), Gd:CdTe (4 %) and Gd:CdTe
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7 (10 %) QDs, respectively. The corresponding full widths at half maximum (FWHM)
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9 were 62.2 nm, 61.6 nm and 67.4 nm, respectively. Additionally, serious aggregation of
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11 Gd:CdTe (10 %) QDs was found if the reaction time was longer than 21 hours.
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17 Fig. 2 shows the temporal evolution of the PL emission peaks and quantum yields
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19 of Gd:CdTe QDs prepared with different molar ratios of Cd/Gd. It is clear that the
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21 amount of Gd^{3+} in the reaction mixture affects the quantum yields of the obtained
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23 QDs much more than their emission wavelengths. With the increase of the content of
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25 Gd^{3+} , the emission wavelength slightly increased under the same reaction time,
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27 whereas the corresponding QY significantly decreased. Because the surface defects of
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29 the doped QDs were increased due to the doping of Gd^{3+} whose ionic radius is less
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31 than that of Cd^{2+} . This leads to the quenching of the fluorescence of the doped CdTe
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33 QDs. The highest PL QY was up to 42.5 % obtained from the Gd:CdTe (4%) QDs
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35 after reaction for 12 hours.
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47 *3.2 Characterization of morphologies and crystal structure*

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49 The Gd:CdTe QDs prepared with different molar ratios of Gd/Cd were
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51 characterized by TEM. Fig. 2 shows the representative morphology images and
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53 particle size distributions of Gd:CdTe QDs prepared with different molar ratios. The
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1 reaction time was 8 hours. It can be seen that all the Gd:CdTe QDs were
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3 quasi-spherical shapes with uniform distribution of particle size. The average sizes for
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5 the Gd:CdTe (2 %), Gd:CdTe (4 %) and Gd:CdTe (10 %) QDs are 3.4, 3.8 and 4.0 nm,
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8 respectively. This result indicates that the increase in the amount of Gd^{3+} leads to
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10 larger particles in the tested concentration range. The compositions of the three of
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12 Gd:CdTe QDs samples were qualitatively measured by using energy dispersive
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14 spectroscopy (EDS), as shown in Fig. 3. The obtained EDS patterns conform the
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16 presence of the Gd element in the Gd:CdTe QDs samples. The molar ratios of Gd/Cd
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18 of the Gd:CdTe (2 %), Gd:CdTe (4 %) and Gd:CdTe (10 %) QDs samples measured
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20 by ICP-AES are 0.018, 0.034 and 0.092, respectively. These results illustrate that
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22 Gd^{3+} has been successfully introduced into the CdTe QDs and its amount increases
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24 with the increase in the molar ratio of Gd/Cd in the reaction solution.
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42 The crystal structures of the Gd:CdTe (2 %), Gd:CdTe (4 %) and Gd:CdTe (10 %)
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44 QDs were investigated by using XRD spectroscopy. The results are presented in Fig. 5.
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46 The XRD pattern of CdTe cubic (JCPDS No. 65-1046) is also given as a reference. It
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48 can be seen that the characteristic reflection peaks of the three samples are nearly
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50 located at the same positions as those of CdTe cubic. No other impurity peaks were
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52 found, which indicates that the introduction of Gd^{3+} into CdTe QDs did not change the
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54 crystal structure of CdTe. However, the diffraction peaks of Gd:CdTe QDs were
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1 slightly shifted toward the higher angles with the increase in the amount of Gd^{3+}
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3 dopant, which further confirms that the Gd^{3+} ions have been embedded into the crystal
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5 lattice of CdTe QDs.
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11 12 13 14 15 *3.3 Cytotoxicity and fluorescence cell imaging in vitro* 16

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18 Due to the aim of biomedical application, it is necessary to evaluate the
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20 biocompatibility of Gd:CdTe QDs. The MTT viability assay was employed to
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22 measure the cytotoxicity of the Gd:CdTe QDs on Caco-2 cell line. The cell viability
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24 results after incubating the cell with different concentrations of the Gd:CdTe (4 %)
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26 QDs are depicted in Fig. 6. As can be seen, the cell viability and proliferation were
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28 not hindered by the presence of the Gd:CdTe (4 %) QDs at the concentration up to
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30 250 $\mu g mL^{-1}$. The cell viability was still about 65 % at the highest dose of 400 μg
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32 mL^{-1} . This result reveals that the Gd:CdTe QDs have good biocompatibility in the
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34 tested concentration range.
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44 The fluorescence images were acquired by using a fluorescence microscope. As
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46 shown in Fig. 7A, the Caco-2 cells exhibited bright fluorescence after incubation with
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48 the Gd:CdTe (4%) QDs for 4 hours, but no emission can be observed from the cells
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50 incubated without the QDs (Fig. 7C). Fig. 7B and 7D give the corresponding optical
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52 images of the Caco-2 cells. These results indicate that Gd:CdTe QDs could be used as
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54 effective fluorescence imaging agent.
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57 **Fig.6 is here**
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3.4 Applications for MR imaging

The paramagnetism of Gd^{3+} ion can accelerate longitudinal (T_1) relaxation of water protons and produce bright contrast in regions where they localize. So we evaluated the capability of prepared Gd:CdTe QDs as T_1 contrast agents for MR imaging by using a 3 T MRI scanner. T_1 -weighted MR images of the Gd:CdTe QDs solutions with different concentrations are shown in Fig. 8A. It is clear that the MR signal was greatly enhanced with the increasing of Gd^{3+} ion concentrations. The specific relaxivity values (r_1) determined from a plot of the relaxation rate ($1/T_1$) versus the Gd^{3+} ion concentration was $4.22 \text{ mM}^{-1}\text{s}^{-1}$ (Fig. 8B), which is comparable to that of Omniscan, one of the most frequently used commercial T_1 -MRI contrast agents.[23]

We further applied the prepared Gd:CdTe QDs for *in vivo* MR imaging. Fig. 8c shows the MR images of balb/c nude mouse before and after the injection of the Gd:CdTe QDs solution. The kidneys, liver and spleen were chosen to analysis the contrast signals. The T_1 contrast effect of the kidneys, liver and spleen were all enhanced after Gd:CdTe QDs administration. The intensity of the kidneys, liver and spleen increased to 159 %, 162 %, and 138 % in T_1 -weighted images obtained after the post-injection of 1 h, respectively (Figure 8d). These results clearly demonstrate the Gd:CdTe QDs can serve as an effective T_1 -MRI contrast agent.

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4. Conclusions

1 In summary, we have developed a facile and green one-pot strategy for the
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3 synthesis of Gd doped CdTe QDs with FI-MRI dual modalities. The effect of the Gd³⁺
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5 dopant on the optical properties of obtained QDs was investigated in detail. The
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7 average size of prepared Gd:CdTe QDs is less than 5 nm and the highest PL QY is up
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9 to 42.5 %. The result of MTT assay reveals the weak toxicity of Gd:CdTe QDs. We
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11 successfully demonstrated the capability of Gd:CdTe QDs as a fluorescence imaging
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13 agent. Furthermore, Gd:CdTe QDs showed contrast enhancement in MR imaging due
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15 to their effect on the T1 relaxation times. These properties allow Gd:CdTe QDs to
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17 function as effective dual-modal imaging agent and find a broad range of applications
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19 in biomedical field.
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33 Scientist.
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Figure Legends

Fig. 1. Temporal evolution of absorption (A, C and E) and normalized PL emission spectra (B, D and F) for the samples prepared with different ratio of Gd/Cd. The reaction time was (a) 1 h, (b) 2 h, (c) 4 h, (d) 6 h, (e) 8 h, (f) 12 h, (g) 19 h and (h) 21 h. The PL spectra of (a) to (f) were recorded with an excitation wavelength of 365 nm and (g) to (h) were recorded with an excitation wavelength of 480 nm. The Cd/Te/MPA molar ratio was 1.0:0.5:2.4.

Fig. 2. Temporal evolution of the PL emission peaks (A) and quantum yields (B) of Gd:CdTe QDs prepared with different ratios of Gd / Cd.

Fig. 3. TEM and HRTEM images of (A) Gd:CdTe (2 %), (B) Gd:CdTe (4 %) and (C) Gd:CdTe (10 %) QDs. (D), (E) and (F) are corresponding size distributions of the obtained Gd:CdTe QDs. The Cd/Te/MPA molar ratio was 1.0:0.5:2.4.

Fig. 4. EDX patterns of (A) Gd:CdTe (2 %), (B) Gd:CdTe (4 %) and (C) Gd:CdTe (10 %) QDs. The Cd/Te/MPA molar ratio was 1.0:0.5:2.4.

Fig. 5. XRD patterns of (a) Gd:CdTe (2 %), (b) Gd:CdTe (4 %) and (c) Gd:CdTe (10 %) QDs.

Fig. 6. Cell viability of Caco-2 cells incubated with various concentrations of Gd:CdTe (4 %) QDs for 24 h.

Fig. 7. (A) The fluorescence image and (B) optical image of the Caco-2 cells after incubation with the Gd:CdTe (4%) QDs. (C) The fluorescence image and (D) optical image of the Caco-2 cells after incubation without the Gd:CdTe (4%) QDs.

Fig. 8. (A) T1-weighted MR images of Gd:CdTe (4%) QDs solution at different Gd concentrations. (B) The linear relationship between T1 relaxation rates ($1/T_1$) and Gd^{3+} ion concentrations for Gd:CdTe (4%) QDs. (C) Dynamic contrast enhanced T1-weighted images of mouse taken at three time points (preinjection, 30 min and 1 h postinjection). (D) Signal intensities in kidneys, liver and spleen at the three time points.

Figure 1a

Figure 1b

Figure1c

Figure 1d

Figure 1e

Figure 1f

Figure 2a

Figure 2b

Figure 3

Figure 4a

Figure 4b

Figure 4c

Figure 5

Figure 6

Figure 7

Figure 8a

Figure 8b

Figure 8c

Figure 8d

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