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The preparation of glutathione-capped CdTe quantum dots and their use in imaging of cells

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ABSTRACT

In this paper, different sizes of glutathione-capped CdTe (GSH/CdTe) quantum dots (QDs) have been prepared directly in aqueous solution. The QDs have tunable fluorescence in the range of 510–670 nm, and they also have high photoluminescence quantum yield (PLQY) without any postpreparative treatment. Furthermore, the QDs have strong resistance to photobleaching, and they also have to be considered as cytocompatible. In addition, for the first time, folic acid was covalently conjugated to the GSH/CdTe QDs for imaging of cancer cells, demonstrating their potentially broad application as biolabels.

1. Introduction

Among various nanomaterials developed, quantum dots (QDs) represent one of the most successful new biological probes. Compared to conventional organic fluorophores, QDs have advantageous properties, including tunable emission, photostability, and high brightness [1,2]. These unique properties make QDs highly desirable for certain biological applications and bring new possibilities for biological imaging [3,4]. Originally, QDs widely used in biolabeling are synthesized in an organic phase using high temperature and high-boiling-point solvents such as trioctylphosphine oxide (TOPO) or trioctylphosphine (TOP) [5,6]. Generally, these nanocrystals are capped with hydrophobic ligands. In order to obtain biofunctional QDs, it is necessary to transfer them into aqueous solution and render them water soluble. The transformation process is often complicated and involves multiple steps. Furthermore, transfer of these dots to an aqueous phase results in a reduction in the overall luminescence efficiency of the QDs [7,8].

The aqueous-based preparation of thiol-capped QDs was pioneered by Weller and co-workers [9]. Up to now, water-based synthesis with thiols as capping ligands has been developed as an interesting alternative [10–13]. Compared to the conventional organometallic approaches, preparation in aqueous solution is cost-efficient and convenient, but low quantum yield (QY) of 1–10% were typically obtained [10]. Of all the QDs reported to date, only the two materials, CdTe and HgTe exhibit optical properties superior to their organometallic analogues when prepared in water [10,14]. Here, in our study, we choose glutathione as ligands to synthesize high quality CdTe QDs in aqueous solution. Without any postpreparation treatment, the GSH/CdTe QDs achieved QY as high as 42%, better than, QDs derived from other water-soluble ligands [10]. Furthermore, the fluorescence of the as-prepared QDs was tunable in a large scale (510–670 nm). In addition, the QDs showed excellent photostability and cell viability studies suggested that the QDs are biocompatible.

Today, the challenges of biological imaging demand further development of new probes that have better sensitivity, longer stability, good biocompatibility, and minimum invasiveness. Special challenges are faced to conjugate QDs with biomolecules in aqueous environments and to recognize specific biological structure. GSH/CdTe QDs are just an attractive candidate for biological applications. Through surface amido or carboxyl functional groups, GSH/CdTe QDs can be conjugated with various biomolecules. In our paper, for the first time, the QDs were successfully conjugated with folic acid for cell imaging, demonstrating their potentially broad application as biolabels.

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2. Experiment

2.1. Materials

Tellurium powder (300 mesh, 99%), sodium hydrogen boride (99%), and cadmium acetate dihydrate (98.5%), were purchased from China Medicine Group Shanghai Chemical Reagent Corporation. Glutathione (GSH), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), N-hydroxysuccinimide(NHS), folic acid, and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were obtained from Sigma–Aldrich. All other reagents were analytical reagent grade. Ultrapure water used in the experiment was purified with Mill-Q (18.2 MΩ cm^{-1}) water system.

2.2. Instrumentation and methods

Fluorimetric spectra were collected with an Edinburgh FLS920 spectrofluorimeter (Edinburgh Instruments Ltd., England) equipped with a xenon lamp and a quartz cuvette (1.0 cm optical path) as the container. Absorption spectra were recorded on an UV-1700 spectrophotometer (Shimadzu Corp., Kyoto, Japan). Transmission electron microscopy (TEM) images were collected on a Hitachi Model H-800 instrument. Fluorescent images were acquired on a confocal laser scanning microscope (LEICA TCS SPE, Germany) using a 405 nm laser excitation source. The phase purity of the as-synthesized products was measured by X-ray powder diffraction (XRD) using a Bruker D8 Advance X-ray diffractometer. Centrifugation was done on the instrument of Sigma 3K 15 Centrifuge. In the MTT assay, absorbance was measured in a TRITURUS microplate reader.

2.3. Preparation of water-soluble GSH/CdTe QDs and its purification

2.3.1. Preparation of NaHTe

In a two-necked flask (25 mL), 30.0 mg tellurium powder and 10 mL water were deaerated with argon for 10 min. Then slightly excessive $NaBH_4$ was added and the resulting suspension was stirred under argon until $NaBH_4$ was completely dissolved. After that, the resulting suspension was heated to 35 °C under vigorous stirring and argon bubbling. During 15 min, the colored suspension changed its characteristic color from violet to colorless. Fresh NaHTe was obtained and was cooled to room temperature.

2.3.2. Preparation and purification of GSH/CdTe QDs

The CdTe QDs were prepared using the reaction between Cd^{2+} and NaHTe solution following the method described previously [15]. In a three-necked flask (250 mL) equipped with a reflux condenser, cadmium acetate dihydrate (0.5 mmol) was dissolved in 100 mL water. After glutathione (GSH, 0.6 mmol) was added, the solution was adjusted to pH 11.5 with aqueous NaOH (1.0 M) and stirred under argon at room temperature for 30 min. Then 0.1 mmol NaHTe solution was injected under argon and the mixture was refluxed. The color of the precursors mixture turned from colorless to orange, supporting the growth of the nanocrystals. After refluxing for particular time, aliquots of the reaction solution were taken out for further characterization. The as-prepared QDs were precipitated with an equivalent amount of 2-propanol, followed by resuspension in a minimal amount of ultrapure water. Excess salts were removed by repeating this procedure three times, and the purified QDs were dried overnight at room temperature in vacuum.

2.3.3. Measurements of fluorescence quantum yield of GSH/CdTe QDs

The spectrometer arrangement was calibrated with a dilute Rhodamine B aqueous solution (QY ~ 31%) [16–18]. Then the absorption spectra of both Rhodamine B and CdTe solutions were measured. In some place the absorption spectra of both samples were crossed. The optical density in this cross punt should be in the region of 0.05–0.15, and not higher than 0.2. This cross point was used in the next step for the excitation of PL spectra of both Rhodamine B and CdTe solutions. Then the integral intensities of both spectra were compared to calculate the QY of CdTe solution.

2.4. Cytotoxicity of GSH/CdTe QDs

To investigate cytotoxicity of the GSH/CdTe QDs, MTT assay were carried out when the QDs existed. HL-7702 and HepG2 cells were seeded on a 96-well microtiter plates to a total volume of 100 μL/well. Plates were maintained at 37 °C in a 5% CO_2 incubator for 24 h. Purified GSH/CdTe 510 QDs or 670 QDs of different concentrations were loaded into each well, with six duplicates for each QDs concentration. No QDs were added to the control cells. After 24 h of incubation, the supernatant was removed, and the cells were washed with PBS three times. To evaluate cell viability, 100 μL MTT solution (0.5 mg/mL in PBS) was added to each well and incubated the mixture at 37 °C for 4 h. After incubation, the remaining MTT solution was removed, and 100 μL of dimethyl-sulfoxide (DMSO) was added to each well to dissolve the formazan crystals. The optical absorbance was measured at 490 nm on a microplate reader.

2.5. Cell imaging

2.5.1. Preparation of folic acid-conjugated CdTe QDs

10 mg of GSH/CdTe 510 QDs or 670 QDs powders was dissolved in 10 mL of phosphate buffer solution (PBS) (pH 7.4), 10 mg of NHS and 20 mg of EDC were added to the QDs solution, and stirred for 30 min to activate the carboxyl groups on GSH/QDs. Then 1.2 mg of folic acid was dissolved in PBS buffer, and added to the activated QDs solution. The mixture was incubated at room temperature in the dark with gentle agitation. After reaction overnight, free folic acid was removed by an ultracentrifuge filter with a molecular weight cutoff (MWCO) of 30,000 g mol^{-1}, the folic acid-conjugated QDs were obtained and stored in the dark at 2–8 °C for further studies.

2.5.2. Cell imaging

The human hepatoma cell line (HepG2), human normal liver cell line (HL-7702) and human ovarian cancer cell line (HO-8910PM) were obtained from the Shangdong Academy of Medical Sciences. Cells were cultured in RPMI 1640 (Hyclone, 1% antibiotics penicillin/streptomycin, 100 U/ml) plus 10% fetal bovine serum (FBS, Gibco) and maintained at 37 °C in 5% CO_2. The HepG2 cells were collected and grown on glass coverslips for 24 h. Folic acid-conjugated CdTe QDs were added and the cells were incubated for 2 h at 37 °C and 4% CO_2. Then the coverslips were removed, washed with PBS, fixed to a chamber filled with PBS mounted on a glass slide, and imaged on a confocal laser scanning microscope (LEICA TCS SPE, Germany) using a 405 nm laser excitation source. The protocols under the same conditions were used for HL-7702 cells and HO-8910PM cells.

3. Results and discussion

3.1. Synthesis and characterization of GSH/CdTe QDs

In our paper, the synthesis of CdTe QDs was based on the reaction of cadmium acetate and sodium hydrogen telluride with

Table 1
Overview of the properties of the CdTe QDs capped with different stabilizers.

Stabilizer	Thioglycolic acid	Thioglycol	L-cysteine	Glutathione
Crystal structure	Zinc blende	Zinc blende	Zinc blende	Zinc blende
Diameter, nm	1.4–2.2	1.4–2.0	1.4–2.3	1.4–3.3
Stability[a]	Stable	Moderate	Moderate	Stable
Typical PLQY	10%	5%	10%	42%
Emission wavelength (nm)	510–550	510–530	510–560	510–670

[a] "Stable" means here that colloidal solutions of CdTe QDs are stable for months and even years being stored under air in the dark at room temperature. "Moderate" means that colloidal solutions coagulate occasionally during the storage, however, they are generally stable for months as well.

glutathione as the stabilizer. The detailed experimental methods are described in Section 2. Once the temperature reaches the boiling point of aqueous reaction media, around 100 °C, QDs are formed and start to grow immediately. After 15 min of refluxing, the smallest green emitting CdTe QDs showed fluorescence emission peak at 510 nm, with QY of 25% were obtained. With further heating, the emission peak continued to shift towards longer wavelengths. By adjusting the reaction time in an aqueous solution under general heat (100 °C) in less than 90 min, different sized CdTe QDs were prepared. Obviously, these reaction conditions were very mild, facile and environmentally friendly, when compared to current organometallic methods, which require high reaction temperatures (330 °C) and the use of hazardous reagents (such as TOPO and TOP). Furthermore, the GSH/CdTe QDs possess excellent optical properties. First, they have a high quantum yield over a broad spectral range of 510–670 nm (see Supporting Information, Fig. S1), the best quantum yield was above 42%, which is higher than CdTe QDs capped with other thiol compounds [10]. This indicate the high quality of the QDs. Second, they have sharp emission features, and the full width at half-maximum (FWHM) was about 30 nm. The narrow emission band widths indicate the growth of crystallites with few electronic defect sites. Finally, they have a large emission wavelength, an emission wavelength range from 510 to 670 nm, much wider than other water-soluble ligands modified CdTe QDs. As comparison, CdTe QDs were prepared in aqueous solution by using thioglycolic acid, thioglycol or L-cysteine as stabilizers. Some characteristics of the series of thiol-stabilized CdTe QDs with different sizes are summarized in Table 1 [10].

For other thiol ligands capped CdTe QDs prepared directly in aqueous solution were reported to have low QY of 1–10%. Up to now, several post-preparative strategies have been developed to improve their QY, such as photochemical etching under a 450 W xenon lamp under aerobic conditions [12], long-term illumination under room light of low-pressure mercury-rare gas discharge lamps [14], and size-selective precipitation [19].

In contrast, our GSH/CdTe QDs achieved high QY without any post-preparative treatment. According to the recent study [15,20], GSH was not as stable as other thiol compounds, such as thioglycolic acid (TGA), and would decompose to give S^{2-} ions over a prolonged reaction time. Sulfur ions would occupy Te positions on the surface of the CdTe core. Due to the lattice mismatch between CdTe and CdS, CdS would passivate the CdTe core, this may be one main reason for the resulting high QY for these QDs. Another reason for the increased fluorescence QY is the formation of a thick wide-band-gap shell of Cd^{2+}–GSH complexes analogous to the CdS shell around the CdTe core, as reported elsewhere [20]. Photoluminescence (PL) spectra of different-sized GSH-coated CdTe QDs are shown in panel a of Fig. 1. The corresponding images irradiated under an ultraviolet lamp are shown in Fig. 1c, from which we can see the strong PL emission from green to red of the as-prepared

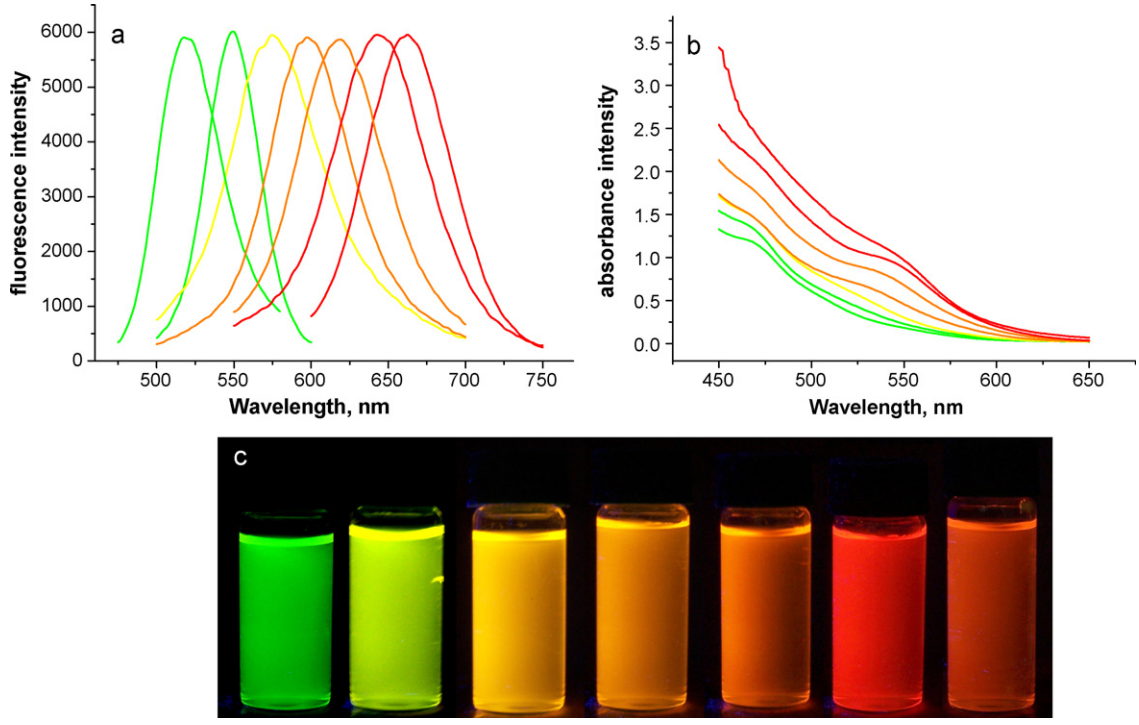

Fig. 1. (a) Fluorescence spectra and (b) absorption spectra of GSH/CdTe QDs with different colors. (c) Image of different-sized GSH-coated CdTe nanocrystals illuminated under an ultraviolet lamp.

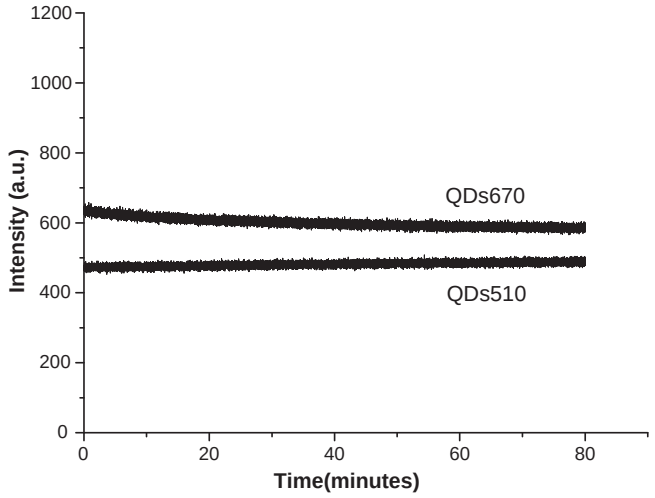

Fig. 2. Time-resolved photobleaching curves for GSH/CdTe 510 QDs and 670 QDs, respectively.

CdTe QDs without any postpreparative treatment. As to the PL enhancement of other thiol ligands modified QDs with longterm illumination, the current investigations revealed that sulfide ions released from the thiol ligands, resulting in the deposition of a CdS shell coating on CdTe QDs, producing water-soluble and highly fluorescent CdTe/CdS core–shell nanocrystals [11].

Absorption spectra of different-sized GSH-coated CdTe QDs are shown in panel b of Fig. 1, from which it can be seen that GSH/CdTe QDs have a wider range of absorption and show a peak corresponding to 1s–1s electronic transitions in the absorption spectra. The first absorption peak positions of the QDs were at 475, 480, 500, 520, 530, 540, 550, and 555 nm, respectively. According to the first excitonic absorption band and an empirical fitting function from a previous report [21], the average size of crude CdTe particles range from 1.4 to 3.3 nm.

Early in 1998, Nie and co-worker [3] studied the photobleaching resistance of the mercaptoacetic acid modified CdSe QDs and the dye rhodamine 6G. They found that the as-prepared CdSe QDs emission is nearly 100 times as stable as rhodamine 6G against photobleaching. However, the fluorescent intensity of the CdSe QDs was reduced obviously in 60 min photobleaching process. Here, in our paper, we have studied the photostability of GSH capped QDs510 and QDs670, respectively. Their fluorescence spectra were shown in Supporting Information, Figure S2. The time-resolved photobleaching curves for QDs510 and QDs670 were shown in Fig. 2. A novel finding was that, in 80 min, the fluorescent intensity of QDs510 increased slightly, on the contrary, the fluorescent intensity of QDs670 was reduced slightly. But, all in all, both QDs510 and QDs670 have strong resistance to photobleaching. It was hypothesized that the highly stable CdTe/CdS core–shell structure was responsible for the exceptional optical properties. For the difference between the behavior of QDs510 and QDs670 in the 80 min, we presume that, compare to QDs670, there are more unsaturated Te atoms which were recently identified as hole traps on the surface of QDs510. The irradiation promotes oxidation of unsaturated Te atoms leads to an improvement of the CdS shell around the CdTe core via substitution of oxidized surface Te sites by sulfur from the stabilizer molecules [10]. A slight enhancement of the fluorescent intensity can be observed.

GSH capped QDs510 and QDs670 were provided for transmission electron microscopy (TEM), the fluorescence emission peaks of which were noted at 510 and 670 nm, respectively. Under TEM (Fig. 3), the CdTe QDs appear as approximately spherical particles. The small spherical particles were found to have an average diameter of 1.4 ± 0.30 nm for QDs510 and 3.3 ± 0.30 nm for QDs670, respectively, which were comparable with the calculated result from the empirical fitting function previously. In addition, due to the small dimensions of CdTe QDs and they aggregated readily during drying on a Cu grid [22], the size distribution of the CdTe QDs was further confirmed by the confocal fluorescence images. As can be seen from Fig. 4, the images of QDs showed that the as-prepared nanocrystals have good monodispersity and high photoluminescence.

The powder XRD profile of QDs670 shows broad peaks typical for nanocrystals (Fig. 5). The lattice parameters derived from XRD measurements fit to the cubic zinc blende structure of bulk CdTe crystal. The XRD peak positions were located between positions for a pure cubic CdTe crystal and a pure cubic CdS crystal. This result indicated a decomposition of the Cd^{2+}–GSH layer and incorporation of sulfur into the nanocrystals [23]. Lastly, GSH/CdTe QDs are very stable in various biological buffers in ambient conditions, and did not precipitate after several weeks of incubation in various biological buffer solutions, such as tris(hydroxymethyl)aminomethane (Tris), phosphate buffered saline (PBS), and *N*-(2-hydroxylethyl)piperazine-*N*′-(2-ethanesulfonic acid) (HEPES). Even after the GSH/CdTe QDs were stored for more than one year at 4 °C, they still remained stable, the fluorescence spectra and QY did not change.

The results of fluorescence spectra, absorption spectra, photostability, TEM, confocal fluorescence images, and XRD analysis showed that the GSH/CdTe QDs possessed a good crystalline structure and high fluorescence. All the result demonstrated that GSH are superior to other thiols as a capping ligand for CdTe QDs. Our results contribute to the understanding of the role of surface lig-

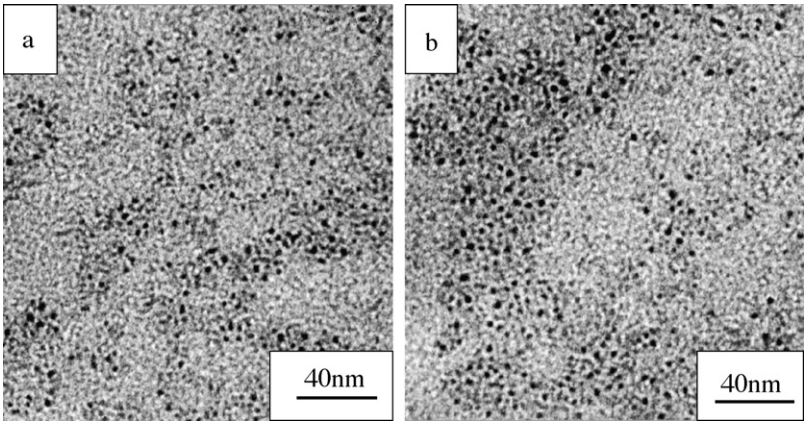

Fig. 3. TEM images of (a) GSH/CdTe 510 QDs and (b) GSH/CdTe 670 QDs, respectively.

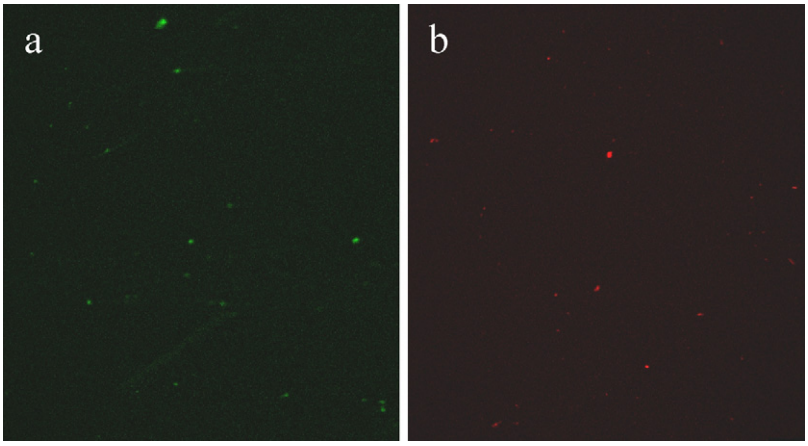

Fig. 4. Confocal fluorescence images of (a) GSH/CdTe 510 QDs and (b) GSH/CdTe 670 QDs, respectively.

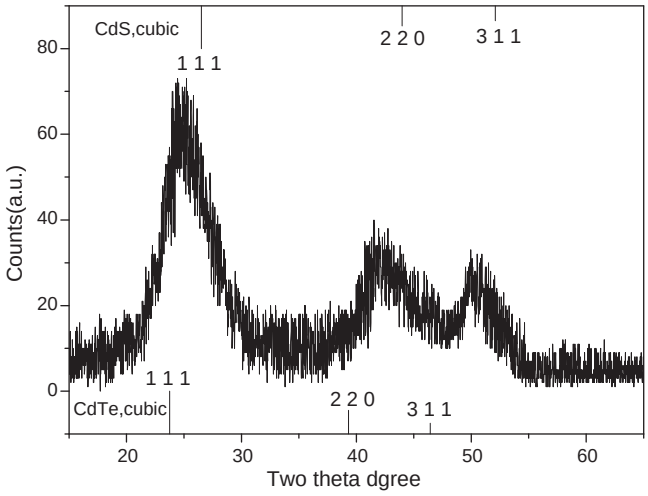

Fig. 5. XRD pattern of GSH/CdTe 670 QDs.

ands, which is critical to the design of stable, high-quantum-yield QDs.

3.2. Cytotoxicity evaluation

HL-7702 and HepG2 cell lines were treated with different concentrations of purified GSH/CdTe QDs510 and GSH/CdTe QDs670 for 24 h to determine the effect of concentration of the nanoparticles. The experiment results revealed that QDs670 was potentially less toxic compared to QDs510. At all the concentrations of the QDs tested, the cell survival rates of HL-7702 cells incubated with QDs510 were much lower than that of QDs670 (Fig. 6a). For QDs510, when the concentration was increased to 50 μg/mL, the cell viability remained only 81%. In contrast, QDs670 maintained greater than 90% cell viability even at particle loadings as high as 100 μg/mL. No significant cell death was seen in cells after incubation with either of these QDs. According to these experimental observations, QDs670 and QDs510 appear to show almost no toxic effect and low toxicity on the cells, respectively. The first reason is that, compared with other thiol ligands, GSH is a nontoxic reagent in aqueous QDs synthesis. Recent study has suggested that the cytotoxicity could be mainly attributed to the surface ligands rather than the QDs themselves [24,25]. The second reason was the fact that CdTe core of QDs670 was well-capped by CdS to minimize any toxic free Cd^{2+} release. Derfus and co-workers [26] suggested the CdSe nanoparticles elicit cytotoxicity at least partially through release of free cadmium ion. Last, the much lower cytotoxicity of QDs670 was attributed to the effective prevention of QDs dissolution by the GSH coating. For QDs510, due to their short refluxing time, free Cd^{2+} content exist in the particles was much higher than that of QDs670. Furthermore, QDs510 were not well-passivated by a GSH shell. Similar experiment results were obtained in HepG2 cell lines (Fig. 6b). As GSH is found mainly in the cell cytosol and other aqueous phases of the living system, it is highly biocompatible in using GSH stabilized QDs as biological probes.

3.3. Confocal fluorescence imaging of cancer cells

Recently, GSH-capped CdTe QDs were also found to be more biocompatible than other water-soluble QDs [15,20,27]. As we know,

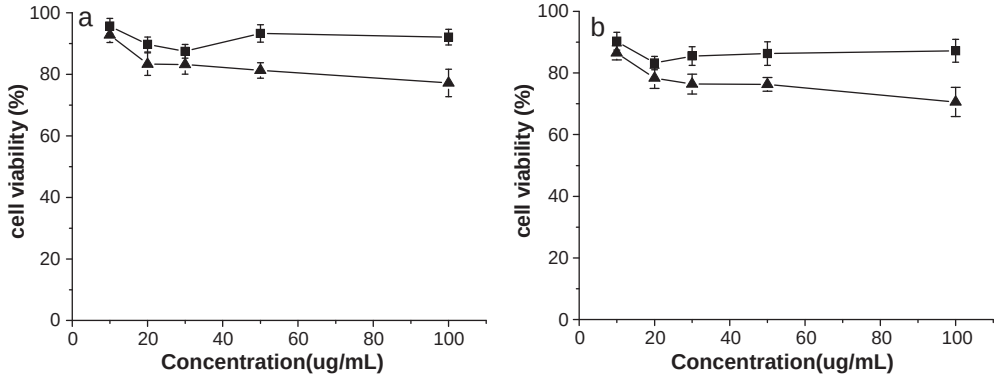

Fig. 6. In vitro cell viability of (a) HL-7702 and (b) HepG2 in the presence of the specified concentrations of (▲) QDs510 and (■) QDs670.

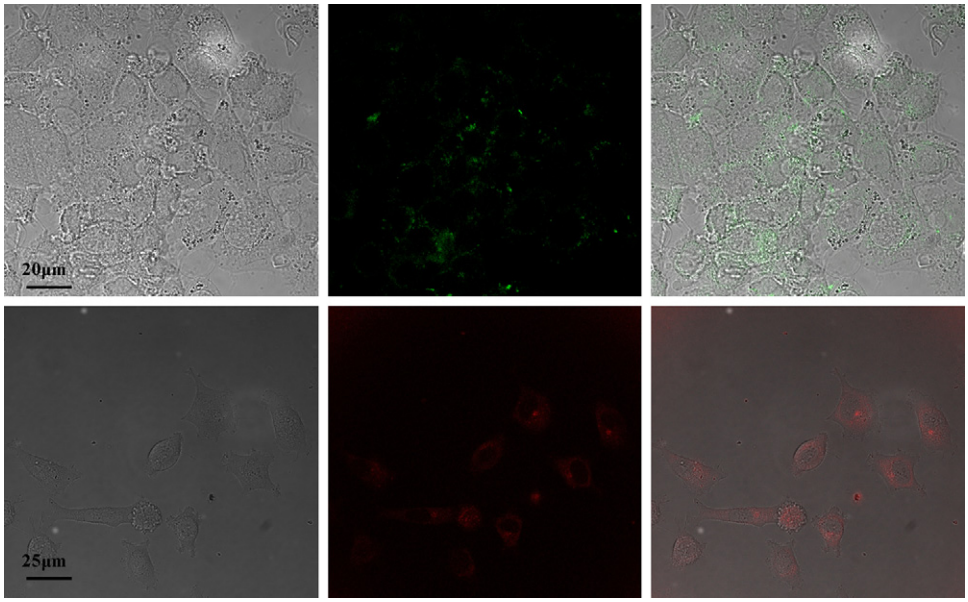

Fig. 7. Bright field, confocal, and superimposed images of human hepatoma cell line (HepG2, top row) with CdTe QDs510 attached and human ovarian cancer cell line (HO-8910PM, bottom row) with CdTe QDs670 attached. The QDs were surface modified with folic acid.

glutathione is a thiol-containing oligopeptide found in most organisms, the two carboxylate or amine groups on the glutathione could be easily conjugated with various biomolecules [28]. For biological applications, QDs must be water soluble and buffer-stable [1,2,29]. Undoubtly, the GSH/CdTe QDs would be of great interest as fluorescent labels for bioimaging applications. To investigate the potential use of the QDs in imaging of cancer cells, folic acid was covalently conjugated to the CdTe QDs. The folate receptor is known to be overexpressed by a variety of neoplastic tissues, including ovarian, breast, colorectal and other human tumors [30,31]. It is a potential molecular target for tumor selective diagnostic imaging. In physiological conditions, folic acid coated CdTe 510 QDs were incubated with human hepatoma cell line (HepG2) and human normal liver cell line (HL-7702), while folic acid coated CdTe 670 QDs were incubated with human ovarian cancer cell line (HO-8910PM). HepG2 and HO-8910PM cell lines are known to express abnormally high levels of folate receptors on the cell surface. After different incubation time periods, the cells were washed with PBS three times, and imaged in bright field using a laser confocal scanning microscopy (Fig. 7). The images also showed the attachment of the QDs510 (green fluorescence) or QDs670 (red fluorescence) onto the surface of the cells. While the binding of the QDs to the surface of the cells is rapid and extensive fluorescence can be detected within an hour. For human normal liver cell line (HL-7702), no green fluorescence are clearly observed from the surface of the cells (see Supporting Information, Fig. S3), proving that specific binding takes place through the folic acid receptor, and the QDs based nanoprobe are useful for live HepG2 and HO-8910PM cell imaging.

4. Conclusion

In summary, a biomolecule (glutathione) was used to synthesize high-quality, photostable and biocompatible CdTe QDs. The GSH-coated QDs have up to 42% QY and their size-dependent emission ranged from 510 to 670 nm. Compared with the current synthetic methods for preparing luminescent nanocrystals, our approach is mild, environmentally friendly, and inexpensive. Importantly, for the first time, we have demonstrated that folic acid-labeled QDs can specifically target folic acid receptor on the surface of human hepatoma and human ovarian cancer cell. We anticipate that biocompatible GSH/QDs with properties superior to organic fluorophores and other ligands modified QDs will have potential applications in biological tagging and cell imaging.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.talanta.2010.11.064.

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