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The cytotoxicity of cadmium based, aqueous phase – Synthesized, quantum dots and its modulation by surface coating

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ABSTRACT

In this report, we evaluated the cytotoxicity of a series of quantum dots (QDs) directly synthesized in aqueous phase, i.e., thiols-stabilized CdTe, CdTe/CdS core–shell structured and CdTe/CdS/ZnS core–shell–shell structured QDs, with a variety of cell lines including K562 and HEK293T. We have demonstrated that the CdTe QDs are highly toxic for cells due to the release of cadmium ions. Epitaxial growth of a CdS layer reduces the cytotoxicity of QDs to a small extent. However, the presence of a ZnS outlayer greatly improves the biocompatibility of QDs, with no observed cytotoxicity even at very high concentration and long-time exposure in cells. Our systematic investigation clearly shows that the cytotoxicity of QDs can be modulated through elaborate surface coatings and that the CdTe/CdS/ZnS core–shell–shell structured QDs directly synthesized in aqueous phase are highly promising biological fluorescent probes for cellular imaging.

1. Introduction

Nanomaterials have found wide applications in biomedicine and biotechnology because of their novel physicochemical properties [1,2]. Among them, quantum dots (QDs) have proven to be ideal optical probes for biological imaging [3] and attracted great attention since the pioneering work of Alivisatos and Nie [4,5]. In comparison with traditional organic fluorophores, QDs possess a number of advantages including high fluorescence intensity, broad absorption coefficients, narrow emission spectra, size-depending emission and high photostability [4–9].

During the past two decades, great efforts have been taken for the synthesis of QDs with high photoluminescence quantum yield (PLQY) [10–18]. Highly fluorescent QDs are readily synthesized through the organometallic route, for example CdSe capped with triocytlphosphine oxide (TOPO) has been reported to reach a PLQY as high as 85% [19]. Nevertheless, in order to meet the requirement of bioapplications, such hydrophobic QDs have to be transferred from the organic phase to aqueous solution [20], which is rather complicated procedure and often associated with the significant loss of both PLQY and stability [21]. An alternative approach is to directly synthesize QDs in water, which avoids phase transfer of QDs and the use of organic solvents. As a result, this approach is regarded to be much simpler, cheaper and more environmentally friendly than the organometallic one, however, the traditional direct synthesis of QDs in aqueous phase (aqQDs) often brought about low PLQY [22].

Much effort has been devoted to improve the spectral properties of aqQDs [23–26]. We recently developed a highly efficient microwave-assisted strategy, program process of microwave irradiation (PPMI) that could produce highly fluorescent water-dispersed CdTe aqQDs with high PLQY (~70%) [6,27]. More importantly, the same strategy was also successfully applied in the synthesis of both core–shell structured CdTe/CdS QDs [28] and core–shell–shell structured CdTe/CdS/ZnS QDs [29] which are water-soluble and highly fluorescent. Fig. 1 shows the schematic surface properties of these three thiol-stabilized QDs synthesized in aqueous phase.

In this contribution, we aim to evaluate the cytotoxicity of a series of aqQDs synthesized with PPMI. It is critically important to obtain QDs with low cytotoxicity in order to realize applications in cellular as well as *in-vivo* imaging [7]. The cytotoxicity of QDs

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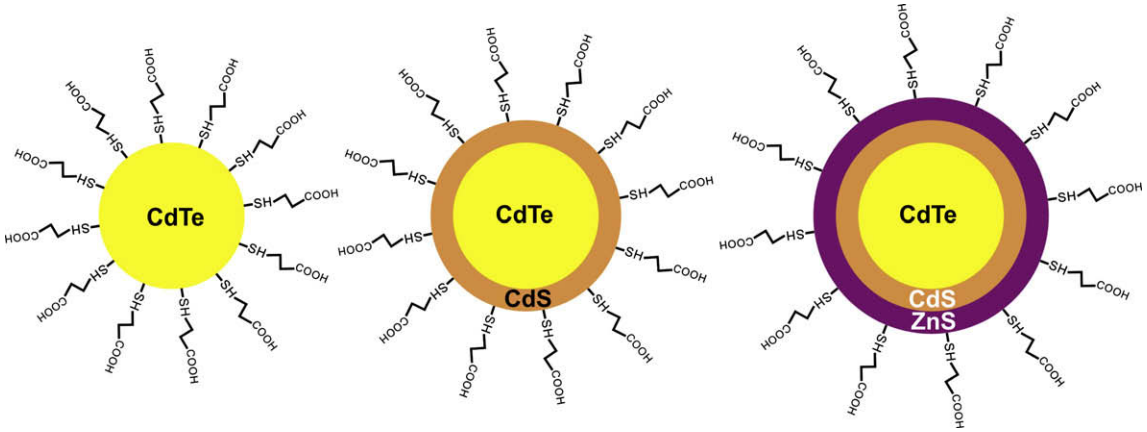

Fig. 1. The schematic surface properties of three kinds of thiol-stabilized QDs: CdTe QDs, CdTe/CdS core–shell QDs and CdTe/CdS/ZnS core–shell–shell QDs synthesized in aqueous phase. With an aim to provide easier comprehension, only twelve thiol molecules are given on the surface of the model QD.

synthesized in organic phase has been well studied previously. Derfus et al. first observed that Cd^{2+} ions could liberate from the surface of CdSe nanoparticles, which led to their cytotoxic effects [30]. In another study, Yamamoto and coworkers found that it was the capping molecule of QDs that determined the cytotoxicity of QDs [31]. More recently, Parak and coworkers carried out a more systematical investigation that employed CdSe and CdSe/ZnS with different coatings. They concluded that both the released Cd^{2+} ions and the surface chemistry of QDs were responsible for the cytotoxicity of QDs [32]. For aqQDs, there were also a few studies about the cytotoxicity of them. Maysinger et al. examined the subcellular localization and toxicity of cadmium telluride (CdTe) QDs and pharmacological means of preventing QD-induced cell death and the localization of CdTe QDs was found to depend upon QD size [33]. Parak and coworkers demonstrated that mercaptoacetic acid stabilized CdTe nanoparticles which were synthesized in aqueous solution showed the similar cytotoxicity to CdSe particles synthesized in organic solution and then transferred to aqueous solution by a ligand exchange procedure [34]. However, there exists no systematic research of cytotoxicity of QDs with different nanostructures directly prepared in aqueous phase up till now. Given the importance of surface chemistry of QDs on their cytotoxicity, it is also intriguing to know whether aqQDs behave differently when they interact with cells. With these motivations, we carried out a systematic study on the cytotoxicity of a series of water-dispersed aqQDs, that is, CdTe, CdTe/CdS, and CdTe/CdS/ZnS QDs.

2. Materials and methods

The water-dispersed CdTe QDs [6,27], CdTe/CdS core–shell QDs [28], and CdTe/CdS/ZnS core–shell–shell QDs [29] were synthesized based on our previous reports. By controlling both the reaction time and temperature, we obtained CdTe QDs (100 °C, 5 min), CdTe/CdS core–shell QDs (100 °C, 5 min), and CdTe/CdS/ZnS core–shell–shell QDs (70 °C, 10 min) with PLQYs of 40, 60 and 75%, respectively. In order to exclude the influence of residual reagents such as MPA, Cd^{2+}, Te^{2-}, and Zn^{2+} in solution, the samples were carefully purified before subsequent cellular experiments. In detail, 2-propanaol was added dropwise under stirring until the sample solution becomes slightly turbid. The turbid dispersion was kept on stirring for 15 min, and then subjected to centrifugation. The precipitate was collected while the supernatant was added another portion of 2-propanol to obtain the second precipitated fraction. This procedure was repeated three times. Afterwards, these precipitate were washed by Milli-Q water for three times to adequately remove residual reagents from samples. Finally, the CdTe, CdTe/CdS, and CdTe/CdS/ZnS QDs samples were employed for cytotoxicity studies.

Human erythroleukemia cells (K562 cell) were cultured in RPMI-1640 medium and human embryonic kidney cell line (HEK293T cell) was cultured in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% heat-inactivated fetal bovine serum (FBS) and antibiotics (100 μg/ml streptomycin and 100 U/mL penicillin) at 37 °C in the humidified atmosphere with 5% CO2. The cells (in culture medium) were dispensed in 96-well plates (90 μL in each well containing 3×10^4 or 5×10^4 cells per well). Then 10 μL of QDs dissolved in culture medium and with different concentrations (from 3 μM to 187.5 nM) were added to each well. Of note, the concentration of QDs was calculated from the absorbance maximum of QD according to the previously reported method [35]. The samples were incubated for different periods (0.5, 3, 24 and 48 h) at 37 °C under the humidified atmosphere (5% CO2) and in dark. In a first set of experiments, toxic effects of the ingested QDs on cells were investigated. Colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assays were performed to assess the metabolic activity of cells treated as described above. With different incubation time, 10 μL stock MTT (5 mg/ml) was added to each well, and cells were then incubated for 4 h at 37 °C. Cells were lysed with acidulated sodium dodecyl sulfate (SDS). Absorbance was measured at 570 nm using microplate reader (Bio-Rad 680, U.S.A.). All measurements were done in triplicate, and at least three independent experiments were carried out. In order to obtain complementary evidence, the biochemical assays of viability were confirmed via bright-field microscopy. In this study, cells were dispensed in 96-well plates and treated with QDs as described above, with a series of incubation time, 0.5, 3, 6, 9, 12, 15, 18, 24 and 48 h, at 37 °C under the humidified atmosphere (5% CO2) and kept in dark.

3. Results and discussion

3.1. Cytotoxicity of CdTe, CdTe/CdS and CdTe/CdS/ZnS QDs for the K562 cell line

Cytotoxicity was evaluated by both MTT viability assays (Figs. 2A, 3A and 4A) and morphological observation of cells with bright-field microscopy (Figs. 2B, 3B, and 4B).

3.1.1. CdTe QDs

As shown in Fig. 2A, we observed the decrease of metabolic activity of K562 cells treated with different concentrations of CdTe QDs and different exposure time. Of note, CdTe QDs of 3 μM was highly toxic for K562 cells. A short-time (30 min) exposure led to 31% decrease in cell viability. Only 34% cells were alive after 24 h and nearly all cells (92%) were dead after 48-h incubation. A significant dose-dependent decrease in cellular viability was observed, with low concentrations of QDs led to lower cytotoxicity. However, even QDs of low concentrations (e.g. 0.75 μM) led to significant death rate of cells after long-time incubation (24 or 48 h). Microscopic studies confirmed the biochemical assays of cellular viability. As shown in Fig. 2B, while no obvious morphological change of K562 cells was observed in the presence of CdTe QDs with short-time incubation, cells showed undefined nuclei after 24 h incubation. Afterwards, all cells fell to pieces when the incubation time was extended to 48 h.

From these results, we concluded that the bare CdTe QDs directly prepared in aqueous phase are severely toxic to K562 cells, just as those reported for QDs synthesized in organic phase

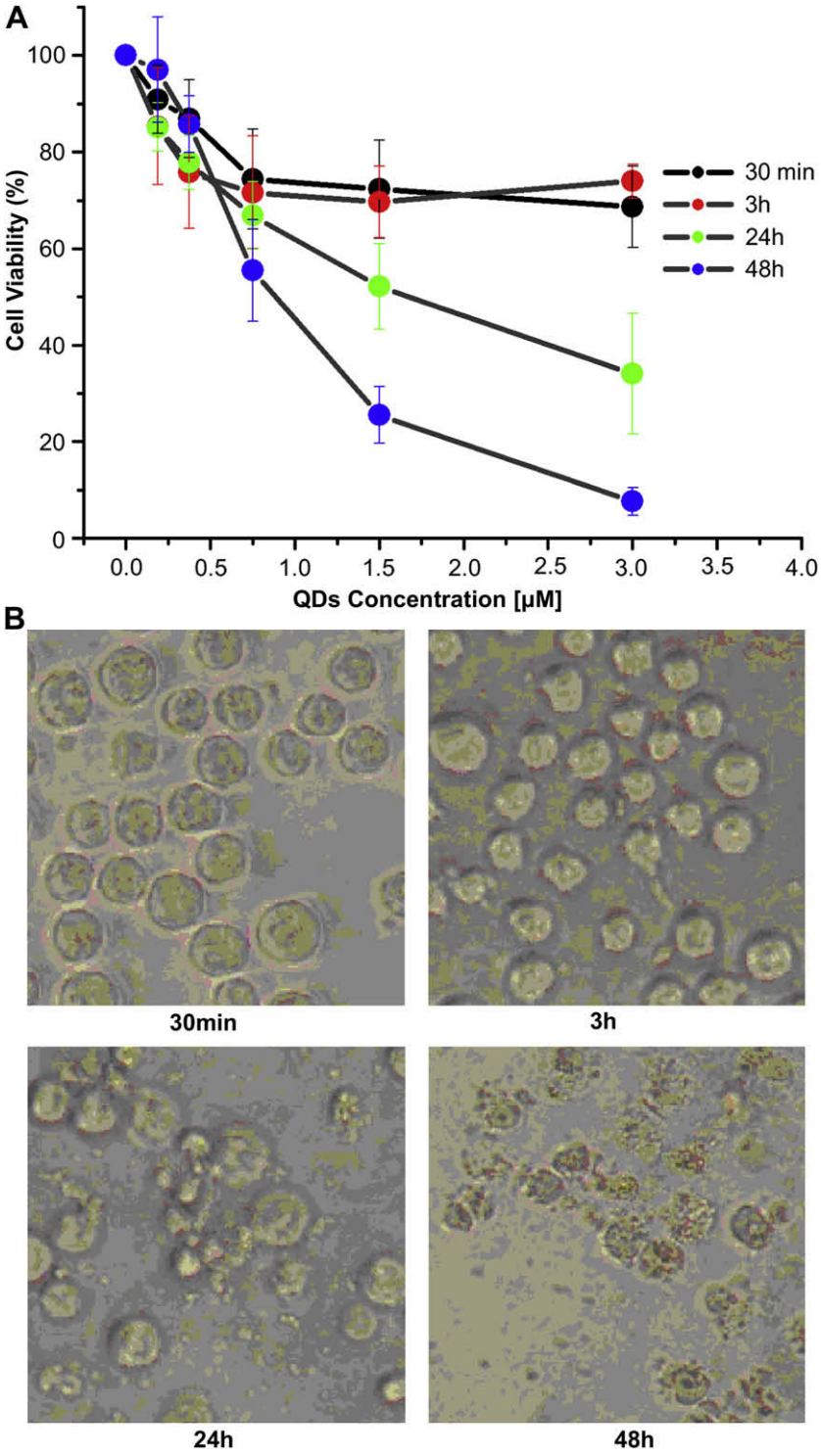

Fig. 2. Cytotoxicity of CdTe QDs with different concentrations and incubation time with K562 cells. (A) Viability of K562 cells after treated with CdTe QDs in RPMI-1640 medium at 37 °C in the humidified atmosphere with 5% CO_2. The cell viability was calculated as a percentage from the viability of the control (untreated) cells. The viability of the control cells was considered 100%. The results are means ± SD from three or four impendent experiments. (B) Morphology of K562 cells after incubated with 3 μM CdTe QDs for 0.5, 3, 24, and 48 h, respectively.

[30–34]. The released Cd^{2+} might be responsible for the observed toxicity since CdTe QDs lacked effective coatings and could be slowly degraded [30].

3.1.2. CdTe/CdS core–shell QDs

Epitaxial growth of a shell with broader band gap on the surface of QDs is an effective approach to improve its spectral properties [11]. Herein we employed PPMI-produced CdTe/CdS core–shell QDs stabilized with MPA [28] to investigate the effect of shell on the cytotoxicity of aqQDs.

As seen in Fig. 3A, the cytotoxicity of CdTe/CdS QDs was also time and dose dependent. It is interesting to note that CdTe/CdS QDs of 3 μM were almost non-toxic when they were exposed to K562 cells for 30 min, in direct contrast with CdTe QDs.

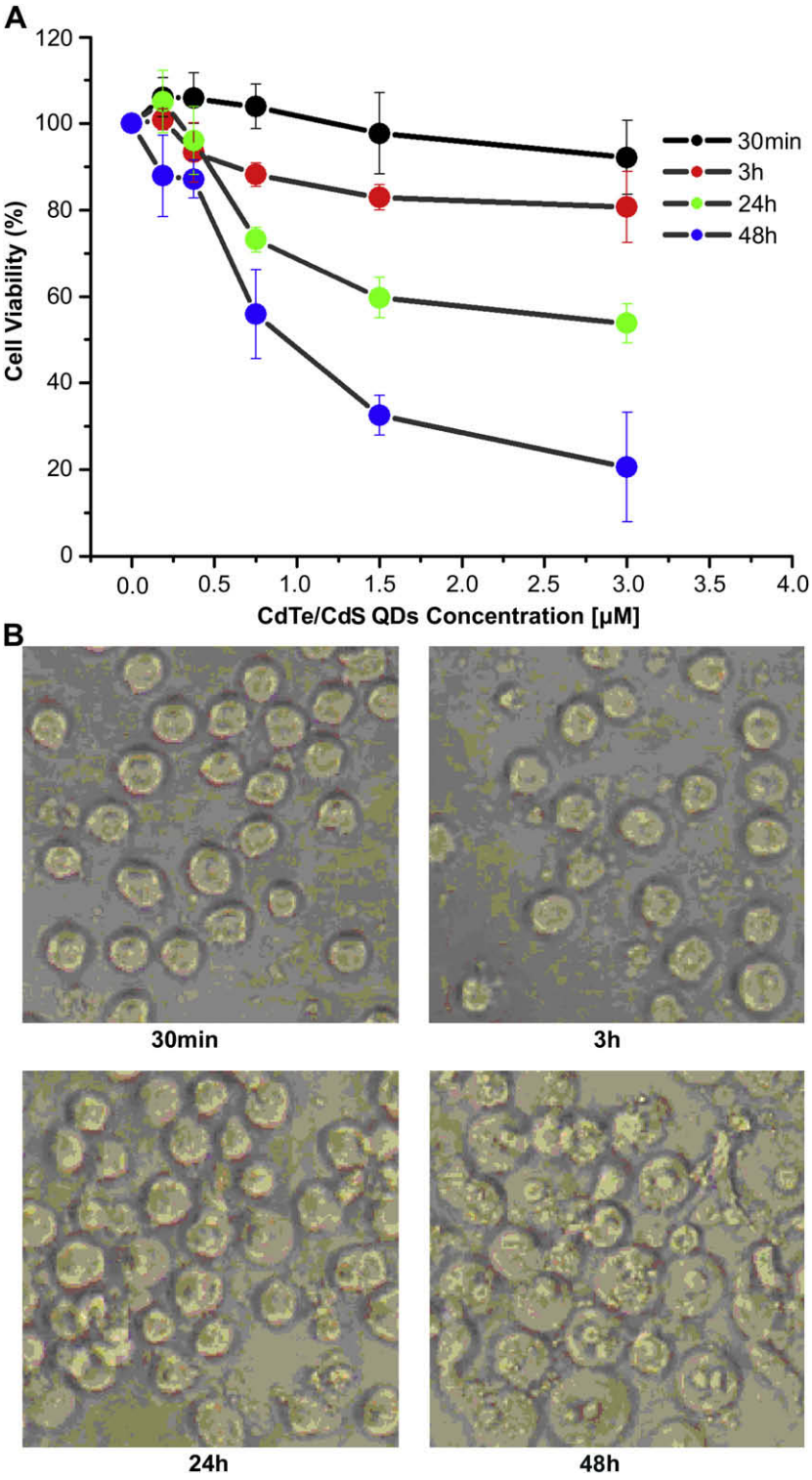

Fig. 3. Cytotoxicity of CdTe/CdS core–shell QDs with different concentrations and incubation time with K562 cells. (A) Viability of K562 cells after treated with CdTe/CdS core–shell QDs in RPMI-1640 medium at 37 °C in the humidified atmosphere with 5% CO_2. The cell viability was calculated as a percentage from the viability of the control (untreated) cells. The viability of the control cells was considered 100%. The results are means ± SD from three or four impendent experiments. (B) Morphology of K562 cells after incubated with 3 μM CdTe/CdS core–shell QDs for 0.5, 3, 24, and 48 h, respectively.

However, CdTe/CdS core–shell QDs induced marked increase in cytotoxicity with prolonged exposure. In detail, 19, 46, and 79% decrease in viability were observed when K562 cells were incubated with CdTe/CdS core–shell QDs (3 μM) for 3, 24, and 48 h, respectively. Consistently, the morphology study of K562 cells incubated with 3 μM CdTe/CdS core–shell QDs showed that cells lived better than those with CdTe QDs (Fig. 3B), but still cells were also in the swollen step, exhibiting granular cytoplasm, undefined nuclei, and evidence of bleb during the 48-h incubation.

These results demonstrated that the CdTe/CdS QDs were much less cytotoxic compared with the CdTe QDs, but still were not

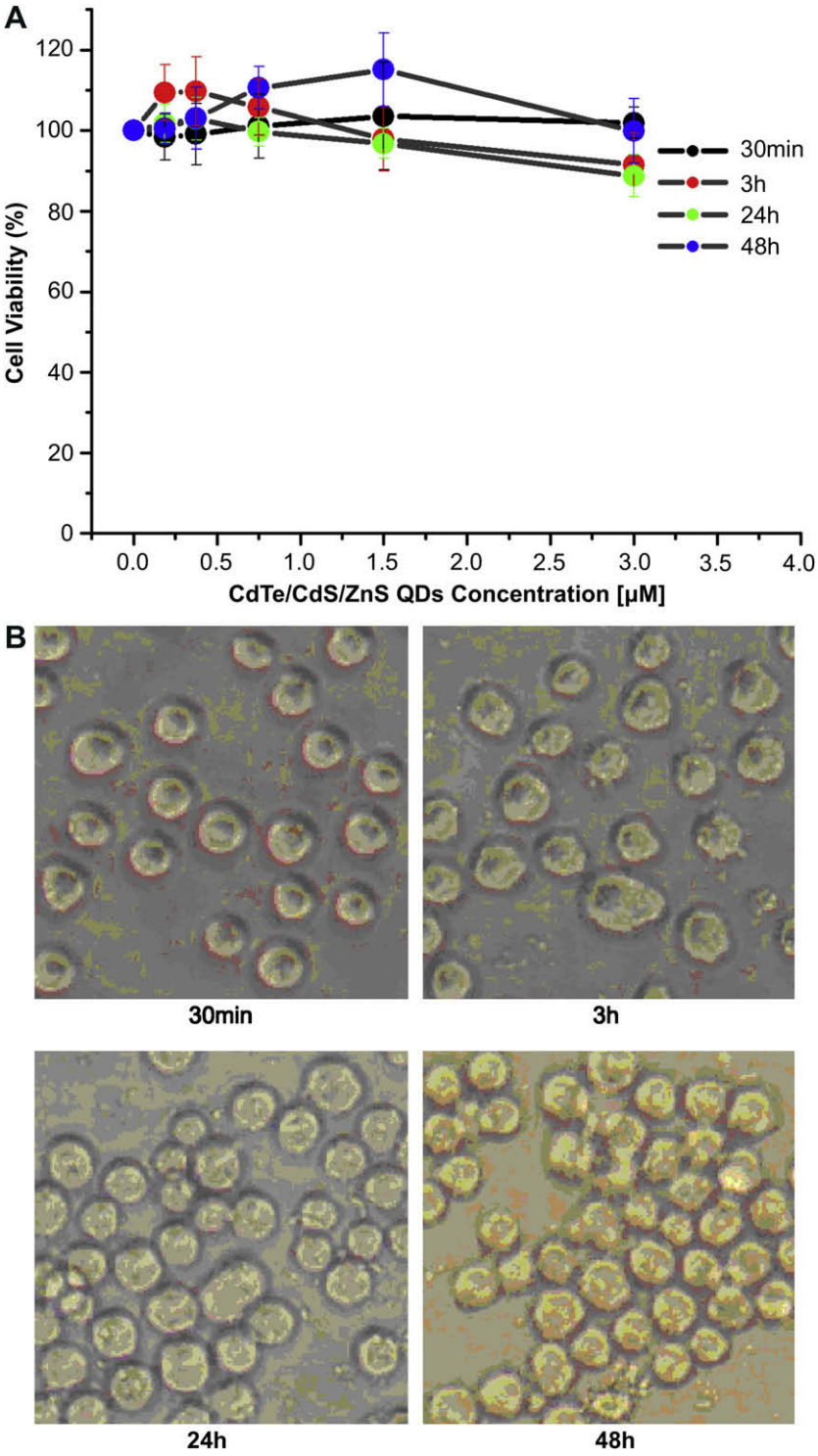

Fig. 4. Cytotoxicity of CdTe/CdS/ZnS core–shell–shell QDs with different concentrations and incubation time with K562 cells. (A) Viability of K562 cells after treated with CdTe/CdS/ZnS core–shell–shell QDs in RPMI-1640 medium at 37 °C in the humidified atmosphere with 5% CO_2. The cell viability was calculated as a percentage from the viability of the control (untreated) cells. The viability of the control cells was considered 100%. The results are means ± SD from three or four impendent experiments. (B) Morphology of K562 cells after incubated with 3 μM CdTe/CdS/ZnS core–shell–shell QDs for 0.5, 3, 24, and 48 h, respectively.

completely biocompatible. A reasonable interpretation is that the chemical bonds between cadmium ions and sulfur ions at the surface CdTe/CdS QDs are more stable than that in CdTe QDs [28], leading to less released Cd^{2+} ions. Unfortunately, the liberation of Cd^{2+} ions from the CdTe/CdS core–shell QDs surface was still inevitable during the long-time incubation [36,37], which resulted in severe cytotoxicity in the end.

3.1.3. *CdTe/CdS/ZnS core–shell–shell QDs*

ZnS is a non-toxic, chemically stable wide band gap (3.8 eV for the bulk material) semiconductor and often employed as the outer layer for QDs. Importantly, there were no free cadmium ions at the surface of such an outlayer, which should favor the use of QDs in cellular studies [30,32]. We employed highly fluorescent CdTe/CdS/ZnS core–shell–shell QDs stabilized with MPA synthesized through

PPMI [29]. Fig. 4A shows the cytotoxicity of as-prepared CdTe/CdS/ZnS core–shell–shell QDs evaluated with the MTT viability assay. We found that the QDs were non-toxic to K562 cells at 3 μM concentration and 48-h incubation. Moreover, the morphology of K562 cells incubated with 3 μM CdTe/CdS/ZnS core–shell–shell QDs for 48 h was almost the same as that of untreated cells (Fig. 4B). These results confirmed that the ZnS shell provided a highly stable and inert passivation layer for QDs. It was curious for us to know whether such CdTe/CdS/ZnS core–shell–shell QDs were toxic at very high concentrations. Interestingly, with up to 16 μM QD, the highest concentration that could be obtained, we did not find any cytotoxicity at 24 h incubation (data not shown), which highlighted the excellent biocompatibility of the CdTe/CdS/ZnS core–shell–shell QDs.

3.2. Cytotoxicity of CdTe, CdTe/CdS core–shell and CdTe/CdS/ZnS core–shell–shell QDs for HEK293T cells

The cytotoxicity of these three kinds of QDs was also evaluated in the HEK293T cell line. As shown in Fig. 5, when treated with QDs at high concentrations, the CdTe and the CdTe/CdS QDs led to the decrease of cell viability up to 65 and 50% in 24 h, respectively. With prolonged incubation of 48 h, most cells were dead for these two kinds of QDs. In contrast, in both cased only minimal change in cell viability was observed for the CdTe/CdS/ZnS QDs with 48 h incubation (Fig. 5B). Also of note, there was a small increase of cell viability for the CdTe/CdS/ZnS QDs with 24 h incubation, which might arise from the stimulation of cells in the presence of nanoparticles [38]. In short, the cytotoxicity of aqQDs for HEK293T has the same tendency as that of the K562 cell line, with slight difference in the change of cell viability.

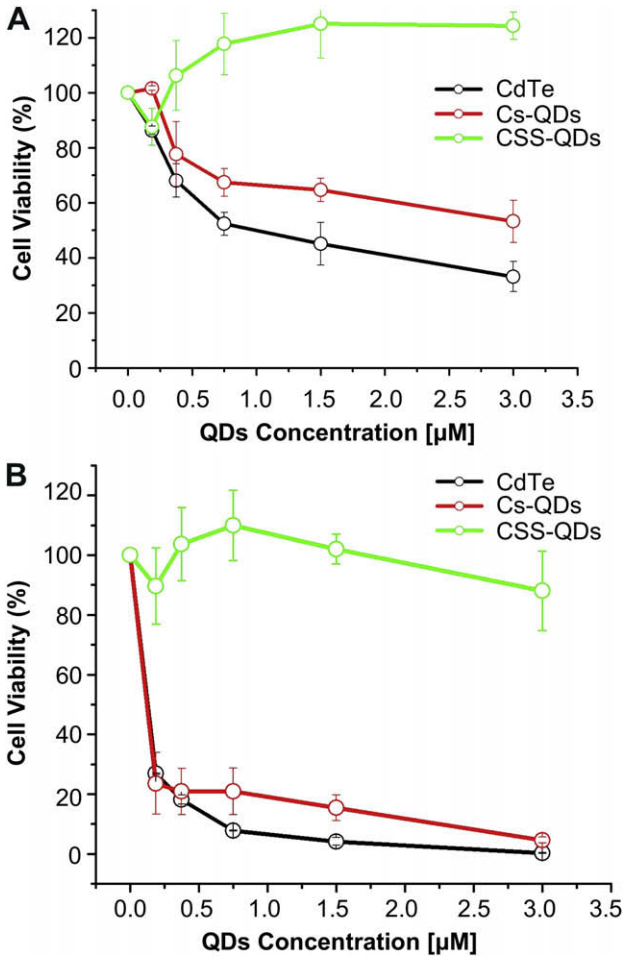

Fig. 5. Viability of HEK293T cells after treated with different concentrations of CdTe QDs, CdTe/CdS core–shell QDs and CdTe/CdS/ZnS core–shell–shell QDs at 37 °C in the humidified atmosphere with 5% CO_2 for 24 h (A) and 48 h (B), respectively. The cell viability was calculated as a percentage from the viability of the control (untreated) cells. The viability of the control cells was considered 100%. The results are means ± SD from three or four impendent experiments.

We found the CdTe/CdS/ZnS core–shell–shell QDs are highly biocompatible, possibly because the coated ZnS outlayer inhibits the release of cadmium ions efficiently. On the other hand, our QDs are directly synthesized from aqueous solution, which do not carry residual organic molecules. While this factor was often ignored, previous study clearly showed that residual organic solvents along with the evaluated nanomaterials can lead to unexpectedly high cytotoxicity [39–41]. This may also contribute to the observed extremely low cytotoxicity of our CdTe/CdS/ZnS core–shell–shell QDs. The lower cytotoxicity may bring some potential applications, for example, as a new gene delivery agent [42]. In addition, these CdTe/CdS/ZnS core–shell–shell QDs possess good aqueous dispersibility, excellent spectral properties (PLQY: 40–80%, fwhm: 30–50 nm) and high photostability [29]. With these excellent properties and biocompatibility in mind, this kind of water-dispersed CdTe/CdS/ZnS core–shell–shell QDs might be a highly promising probe for biological applications.

4. Conclusions

The cytotoxicity of a series of water-dispersed CdTe QDs, CdTe/CdS core–shell QDs, and CdTe/CdS/ZnS core–shell–shell QDs, which were directly prepared in aqueous phase, was systematically studied for the first time in this work. We found that both the CdTe QDs and the CdTe/CdS core–shell QDs were severely cytotoxic due to the liberation of cadmium ions from the surface. In contrast, the CdTe/CdS/ZnS QDs are non-toxic even at very high concentration and long-time incubation for a variety of cell lines, which is possibly due to the fact that the ZnS shell effectively protects the release of cadmium ions from the inner side. Our data clearly showed that the cytotoxicity of nanomaterials such as QDs could be effectively modulated through elaborate surface coating techniques.

Acknowledgments

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.biomaterials.2008.09.029.

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