A Comparative Study of Water Dispersible Orange-Emitting Mn-Doped ZnSe/ZnS and CdTe/CdS Core/Shell Quantum Dots

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Abstract: 3-Mercaptopropionic acid (MPA)-capped Mn-doped ZnSe/ZnS and CdTe/CdS core/shell quantum dots (QDs) were prepared via a mild aqueous phase process. The synthesis conditions were adjusted to yield QDs with roughly similar nanocrystal average diameter and light emission wavelengths. X-ray powder diffraction, transmission electron microscopy and spectrofluorometry have been used to characterize the crystal structure and optical properties of the as-prepared QDs. Growth inhibition tests using E. coli bacterial cells were also carried out to assess the cytotoxicity of the dots and showed that core/shell ZnSe:Mn/ZnS@MPA QDs do not exhibit any cytotoxicity against E. coli cells up to a concentration of 14 µM while at this concentration CdTe/CdS@MPA core/shell QDs exert a severely more pronounced cytotoxicity. These results indicate that the cytotoxicity is likely associated to the presence of Cd in the chemical composition of CdTe/CdS@MPA QDs and that ZnSe:Mn/ZnS@MPA nanocrystals are safer and could be used as biological probes for cells and tissues imaging.

Keywords: Quantum Dots (QDs), Cytotoxicity, Cd-Free QDs, 3-Mercaptopropionic Acid, Core/Shell Structure, Photoluminescence.

INTRODUCTION

A growing interest in quantum dots (QDs) and their toxicity has been well sustained over the last two decades as demonstrated by Figure **1**. For example, in 2020, more than 10 000 publications have mentioned ''quantum dots'' in their title, abstract or full text. The words ''toxicity'' or ''cytotoxicity'' have been associated with more than 1000 of them. This high degree of interest arises from the unique properties of QDs such as high photoluminescence (PL) quantum yield, broad absorption with narrow PL spectra, adjustable light emission by changing QDs size and composition, low photobleaching and better resistance to chemical and photo-physical degradation when compared to conventional organic dyes. [1-3] These features make QDs highly attractive for a large panel of applications including display,[4, 5] light-emitting diodes (LEDs), [6-8] solar cells, [9-11] fluorescent sensors [12-15] and biological probes. [16-22] Furthermore, due to the particle size-dependence of their PL emission, one major advantage of QDs when used as biosensors originates from the different light colors that can be obtained from a set of QDs by a single excitation allowing therefore to detect a multiple bio-molecular targets from a single imaging trial.[18, 23, 24] However, QDs still have two major drawbacks which make difficult the wide use of these light emitting nanomaterials in the applications mentioned above. The first drawback is that the most efficient and generally used QDs are Cd-based. For example, for biological labeling, semiconductor nanocrystals such as CdSe and CdTe and their corresponding core shell structures like CdSe/ZnS, CdSe/CdS/ZnS and CdTe/ZnTe are the most studied and stable QDs.[25-27] Unfortunately, due to the inherent toxicity of Cd, especially for application dealing with human health, such materials are subjected to the Restriction of Hazardous Substances (RoHS) legislation, which entered into force in Europe in 2011.[28] The second drawback is that high quality QDs are usually prepared in organic medium via a high temperature injection approach using coordinating solvents/ligands such as tri-noctylphosphine (TOP), tri-n-octylphosphine oxide (TOPO), or oleic acid (OA) or non-coordinating solvents such as 1-octadécène (ODE).[29-31] In addition to the high cost of these reagents and their harmfulness to humans and to the environment, the resulting QDs are capped with hydrophobic ligands and are only dispersible in low or non-polar organic solvents such as toluene, chloroform or hexane. Therefore, in order to make these hydrophobic QDs compatible with biological application, a subsequent transfer of the dots from the organic medium to an aqueous solution, through surface ligand exchange, is required. However, the ligand exchange process not only leads to PL Quantum Yield (PL QY) drop but also reduces the stability of the dots after the transfer to water.[32] A single step synthesis of high quality and stable QDs in water without using expensive and harmful reagents would therefore be preferred. Over the last decade, our team developed simple aqueous synthesis of different water dispersible QDs and their corresponding core/shell structures [16, 33-35], including Cd-free metal doped QDs such as ZnSe:Mn/ZnS, ZnSe:Mn/ZnO, ZnS:Mn/ZnS and ternary alloyed ZnSeS:Mn, $AgInS_2$ (AIS) and $(AgInS_2)_x(ZnS)_{1-x}$ (AIZS) QDs, which could be excellent alternatives to Cd-based QDs.[16, 35-40].

The cytotoxicity of QDs depends on several factors related to their intrinsic properties, such as QDs size, chemical composition, capping agent or surface chemistry, but also to environmental conditions (light, temperature, oxidative conditions,..).[41] For instance, it was demonstrated in several studies that the capping ligand, and therefore the surface charge, has a significant impact on QDs cytotoxicity with positively charged QDs being more toxic than negatively charged

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ones.[42, 43] Others studies also highlighted the importance of surface chemistry and QDs size in determining the cytotoxicity of QDs.[41, 44, 45]. For example, it was found that the cytotoxicity of small and positively-charged green emitting CdTe QDs (D=2.2 ± 0.1 nm) was more pronounced than that of larger and equally charged red emitting ones (D=5.2 ± 0.1 nm) at equal concentrations.[46].

The multiplicity of factors that impact QDs toxicity makes complex and controversial the mechanisms described in the literature. The early published results generally ascribed the toxicity of QDs to the metal (Cd^{2+}, Zn^{2+}, etc) released in biological medium.[47] It was found later that Cd-based QDs are more toxic to cells than their equivalent content in Cd^{2+} salts, which means that metal release is not the only cause of toxicity.[48] In this context, the ability of QDs to photo-generate reactive oxygen species (ROS), such as free radicals and singlet oxygen, was also considered as a potential source of toxicity toward biological material.[49] In a recent article, our group demonstrated that metal release and ROS generation don't fully explain the toxicity of ZnO QDs against bacteria cells and proposed that other alternative phenomena such as direct interactions between QDs and bacterial cell surfaces should also be considered [50].

In the present work, we report a comparative study of water dispersible ZnSe:Mn/ZnS and CdTe/CdS core/shell QDs taken as an example of Cd-free and Cd-based QDs, respectively. Both QDs were synthesized through a single step synthesis in water using 3-mercaptopropionic acid (MPA) as capping agent. The synthesis conditions were adjusted to yield similar ZnSe:Mn/ZnS and CdTe/CdS QDs in terms of PL emission and average nanocrystal diameter. The objective of this study was to dissociate the impact of QDs size, surface ligand and PL wavelength-related stress, as discussed above, from the intrinsic cytotoxicity due to the chemical composition (*i.e*. Cd, Zn) of the QDs.

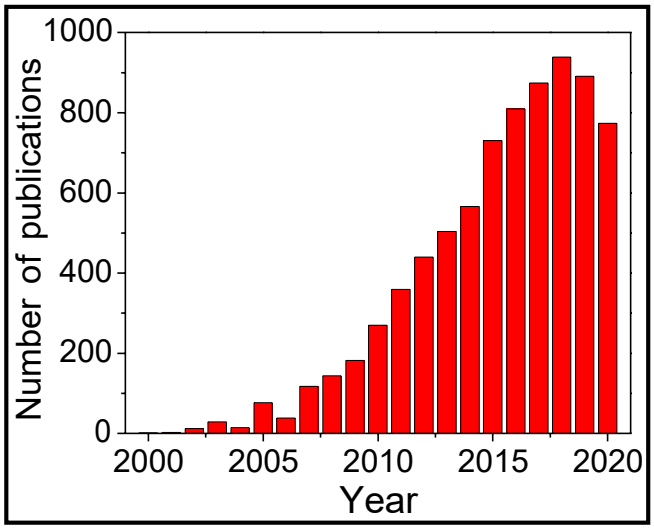

Figure 1: Evolution of publications (containing the keywords ''quantum dots'' and ''toxicity'') number vs year from 2000 to 2020.

MATERIALS AND METHODS

Chemicals

Zinc sulfate heptahydrate ($Zn(SO_4).7H_2O$, extra pure, MRCK), Manganese acetate pentahydrate ($Mn(OAc)_2.4H_2O$, 99%, ABCR), 3-mercaptopropionic acid (MPA, 99%, Aldrich), Selenium powder (99.5%, Aldrich), tellurium powder (99.9%, Aldrich), $CdCl_2$, $2.5H_2O$ (99%, Aldrich), Sodium borohydride ($NaBH_4$, 98%, Aldrich) and iso-propanol (i-PrOH, HPLC grade) were used as received without additional purification.

Synthesis of MPA-capped ZnSe:Mn/ZnS core/shell QDs

The 0.05 M NaHSe solution was prepared according to the method we have already described in our previous report.[35] The theoretical Mn/Zn/Se/MPA molar ratio in the solution was 1/25/23/500. MPA-capped ZnSe:Mn/ZnS core/shell QDs were prepared in two steps according to the method described previously with some modifications.[35] In the first step, 0.286 g (1 mmol) of $Zn(SO_4).7H_2O$ and 2.12 g (20 mmol) of MPA were dissolved in 10 mL and 40 mL of water, respectively. The solutions were mixed and then 3 mL of a 13 mM $Mn(OAc)_2.4H_2O$ solution were added to the mixture. The pH of the mixture was carefully adjusted by adding a 2 M NaOH solution until pH=10.3. The solution was then transferred to a three-necked flask fitted with a septum and valves and degassed with N_2 bubbling for at least 1 h in order to remove the air contained in the flask. Under continuous stirring, 18 mL of fresh 0.05 M NaHSe solution were injected into the Zn/Mn/MPA solution at room temperature and the mixture was refluxed for 24 h (under Ar flow). The resulting MPA-capped ZnSe:Mn QDs were precipitated by ethanol, washed several times with ethanol and collected by centrifugation. The obtained precipitate was then dried at room temperature under vacuum. In the second step, a ZnS shell was grown on the surface of ZnSe:Mn nanocrystals. Briefly, 10 mL of a 0.2 M $Zn(OAc)_2$ solution and 0.7 mL of MPA were mixed together and diluted with 88 mL of water. The pH of the mixture was adjusted to 10.3 with a 2M NaOH solution followed by N_2 bubbling for 1 h. Then, 20 mL of this Zn-MPA complex solution was added dropwise to ZnSe:Mn solution, prepared by dispersing 20 mg of crude ZnSe:Mn powder in 130 mL water, and the mixture was heated at 100°C for 12 h in an air-free three-necked flask fitted with a septum and valves. The solution was then concentrated down by removing about 90% of water, using a rotary evaporator system, and precipitated by adding ethanol. The collected ZnSe:Mn/ZnS@MPA nanocrystals were finally dried in vacuum for 12 h and dispersed in water for further use.

Synthesis of MPA-Capped CdTe/CdS core/shell QDs

MPA-capped CdTe/CdS core/shell QDs were prepared according to our previous report with some

modifications.[51] Noteworthy is that MPA serves both as capping ligand and as sulfur source. First, a NaHTe solution was prepared from $NaBH_4$ and tellurium powder with molar ratio of 2.5/1. In a typical experiment, 37 mg (1 mmol) of sodium borohydride and 50 mg (0.4 mmol) of tellurium powder were introduced into a small air-free Schlenk flask. Then, 10 mL of ultrapure water were added. The reaction mixture was heated at 80 °C for 30 min under inert N_2 atmosphere. During this step, a deep red 0.04 M NaHTe solution is prepared. This fresh solution is immediately used to prepare CdTe/CdS core/shell QDs. In the second step, CdTe/CdS QDs were prepared by reacting $CdCl_2$ with NaHTe using MPA as capping agent with Cd^{2+}/Te^{2-}/MPA molar ratio of 2/1/5. In a typical experiment, $CdCl_2$, $2.5H_2O$, and MPA were dissolved in 100 mL of N_2-saturated ultrapure water with $[Cd^{2+}]$ molar concentration of 1.25 mM. The pH of the mixture was adjusted to 9.0 using 1 M NaOH solution. Then, the NaHTe solution was added to the mixture before heating at 100 °C for 15 h. The resulting CdTe/CdS core/shell QDs were precipitated by adding i-PrOH and collected by centrifugation at 5000 rpm. QDs were dried in vacuum at room temperature and redispersed in water for further use.

Characterization of ZnSe:Mn/ZnS@MPA and CdTe/CdS@MPA core/shell QDs

For TEM analysis, samples were prepared by placing a drop of the particles suspension in water onto a carbon film-supported copper grid and images were recorded at different magnifications. A Panalytical X'Pert Pro MPD diffractometer with Cu Kα radiation (λ = 1,5405 A°) was used to record X-ray powder diffraction (XRD) diagrams of QDs samples. UV-Visible absorption spectra of the samples were recorded from 300 to 800 nm using a Perkin-Elmer (Lambda 2) UV-Visible spectrophotometer. PL emission and excitation spectra as well as PL quantum yield (QY) values were measured using a C9920-02G PL-QY measurement system from Hamamatsu. The setup comprises a 150 W monochromatized Xe lamp, an integrating sphere (Spectralon Coating, Ø = 3.3 in.) and a high sensitivity CCD spectrometer for detecting the whole spectral luminescence.

Cytotoxicity Tests

Bacterial cells have been systematically cultured at 30°C in 100 mL conical flasks containing 20 mL LB broth Miller [Difco] (1% Tryptone, 0.5% Yeast Extract, 1% NaCl) using a water bath shaker (Innova 3100, New Brunswick Scientific) stirred at 160 rpm. Escherichia coli MG1655 [52] was used as a model for growth inhibition tests following our previously described procedure.[44] In a typical test, bacteria were pregrown in LB medium in the absence of QDs until the cultures reached the mid log phase with an optical density at 600 nm (OD600) of 0.2. Then, cultures were diluted (1/10th) in prewarmed LB medium amended with the desired concentration of QDs (0, 1 and 10 µM) and the DO600 was monitored at 20 min intervals using an UV-visible spectrometer (safas UVmc2, Safas Monaco). In order to assess the toxicity of the QD studied in this work, the doubling time of exponentially growing E. coli MG1655 cultures in the absence of QDs was calculated to reach 34 min with a standard deviation ± 1 min. This doubling time was compared to the one calculated in the presence of given QDs at different concentrations in order to estimate the effect of the QDs on the growth kinetics.

RESULTS AND DISCUSSION

Figure **2** shows typical XRD patterns of the ZnSe:Mn/ZnS@MPA and CdTe/CdS@MPA QDs. CdTe/CdS@MPA QDs exhibit a cubic structure while ZnSe:Mn/ZnS@MPA QDs belong to the zinc blende structure. The results also show that XRD peaks for CdTe/CdS@MPA QDs are located between those of pure cubic CdTe and pure cubic CdS. A similar result is obtained with ZnSe:Mn/ZnS@MPA QDs where XRD peak positions are located between those of pure ZnSe and pure ZnS with a zinc blende structure, which is consistent with the formation of ZnS and CdS shell around ZnSe and CdTe core, respectively.

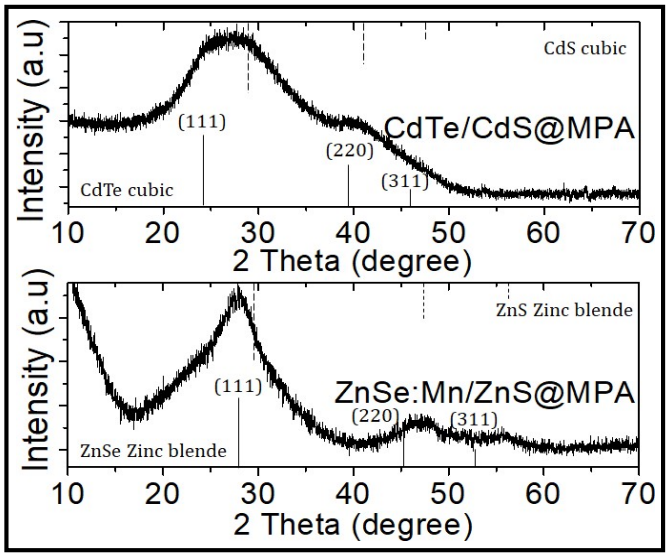

Figure 2: XRD pattern of ZnSe:Mn/ZnS@MPA and CdTe/CdS@MPA QDs.

The as-prepared ZnSe:Mn/ZnS@MPA and CdTe/CdS@MPA QDs have also been characterized by TEM as shown in Figure **3**. TEM images revealed the formation of well dispersed and spherical nanocrystals with an average diameter of 3.5 nm and 3.9 nm for ZnSe:Mn/ZnS@MPA and CdTe/CdS@MPA QDs, respectively. As shown by the digital photographs of the QDs aqueous solution (inset of TEM images, Figure **3a** and **b**), both QDs emit homogeneous and intense orange light and the corresponding QDs were stable over time upon storage at room temperature. This result indicates that the surface of the QDs is efficiently covered with the hydrophilic MPA surface ligand which keeps the particles stable in water and prevents them from aggregation.

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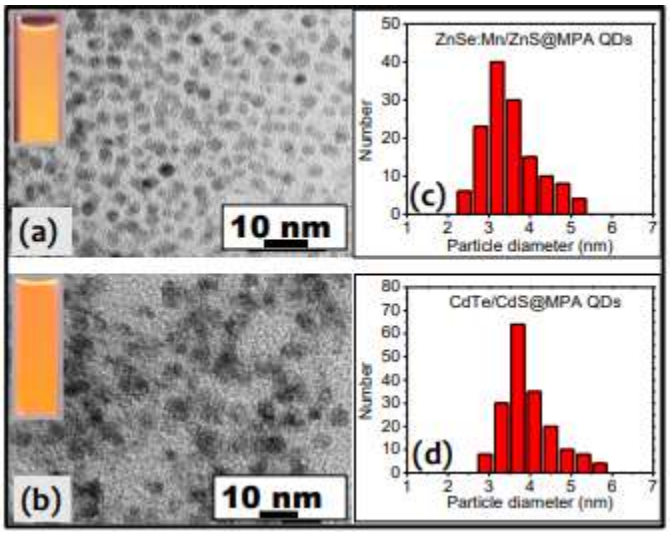

Figure 3: TEM image of (a) ZnSe:Mn/ZnS@MPA QDs and (b) CdTe/CdS@MPA QDs and the corresponding particle size distribution (c) and (d), respectively. The insets of figures (a) and (b) are digital photographs of QDs aqueous dispersions upon excitation at 365 nm.

The PL emission and UV-Visible absorption spectra of ZnSe:Mn/ZnS@MPA QDs and CdTe/CdS@MPA QDs are given in figure 4. Both QDs show a strong orange emission upon excitation at 360 nm. Table **1** compares the optical properties, such as PL wavelength maximum, full width at half maximum (FWHM) and PL QY of the as-prepared QDs. As shown by figure 4 and table **1**, ZnSe:Mn/ZnS@MPA QDs exhibit a relatively broad PL emission spectrum (FWHM = 72 nm) centered at about 600 nm, characteristic of the Mn^{2+} $^4T_1 \rightarrow f$ $^6A_1$ electronic transition, as reported in the case of Mn-doped ZnS nanocrystals.[53] When compared to ZnSe:Mn/ZnS@MPA QDs, CdTe/CdS@MPA QDs have narrower emission spectrum, with FWHM of about 60 nm, and higher PL QY (65 % vs. 25 %). The emission of both QDs has been adjusted to have approximately the same color emission (600 nm and 604 nm, for ZnSe:Mn/ZnS@MPA and CdTe/CdS@MPA QDs,

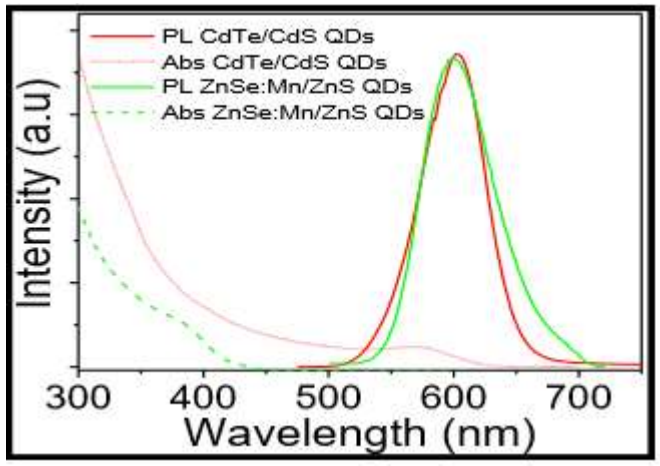

Figure 4: PL and absorption spectra ofZnSe:Mn/ZnS@MPA and CdTe/CdS@MPA QDs. PLspectra were recorded upon excitation at 360 nm.

Table 1: Optical properties of ZnSe:Mn/ZnS@MPA and CdTe/CdS@MPA QDs.

QDs	λ_{em} (nm)	Abs.	FWHM (nm)	PL QY (%)
ZnSe:Mn/ZnS@MPA	600	UV	72	25
CdTe/CdS @MPA	604	UV-Vis	60	65

Due to the high potential of these nanocrystals in bio-imaging and bio-sensing, it is mandatory to assess their cytotoxicity towards biological cells. For that purpose, the toxicity of the as-prepared ZnSe:Mn/ZnS@MPA and CdTe/CdS@MPA QDs was evaluated using a simple sensitive test based on the growth inhibition of *E. coli* cells in culture [44] (Figure **5**).

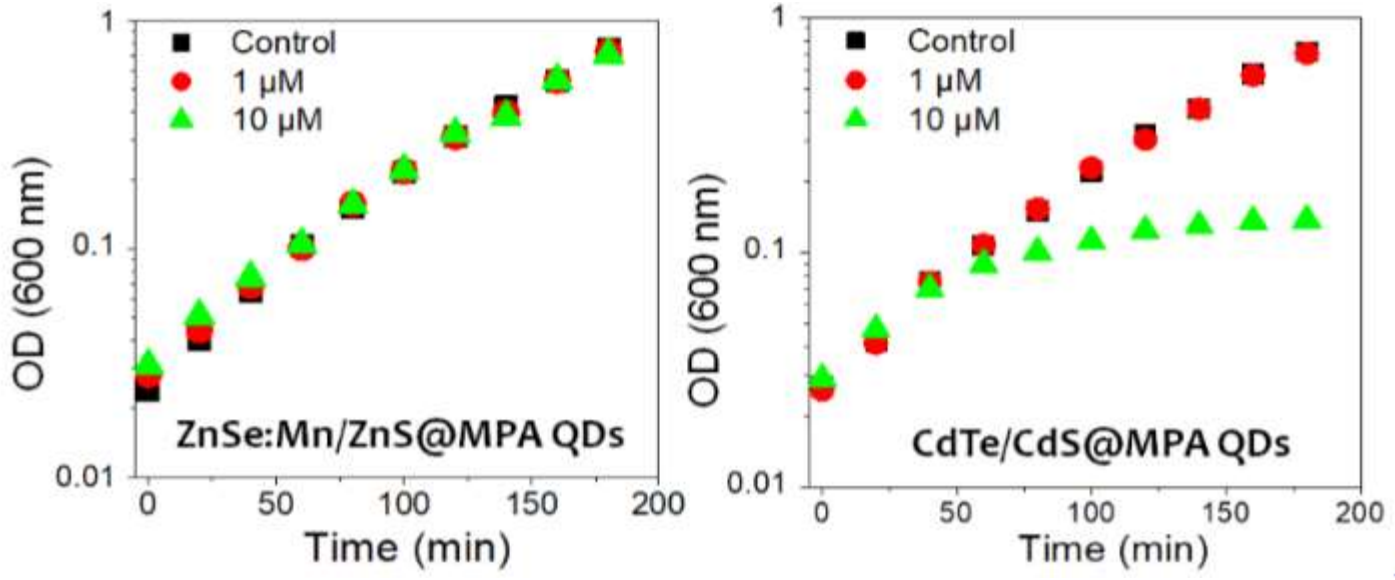

Figure 5: Growth inhibition of E. coli MG 1655 in the absence and presence of different concentrations of ZnSe:Mn/ZnS@MPA and CdTe/CdS@MPA QDs.

Results showed that at a concentration of 1 μM none of the QDs exhibit any toxicity towards the E.coli cells as indicated by a doubling time almost identical to that of the control culture (34 ± 1 min) maintained in the same growth conditions. However, at a 10 μM concentration, the cytotoxic effect of CdTe/CdS@MPA QDs can clearly be observed after about 40 min of cultivation for which bacteria cells gradually entered into a growth arrest state. On the contrary, even at 10 μM, ZnSe:Mn/ZnS@MPA QDs still displayed no cytotoxicity against E. coli cells in these growth conditions. It is worth noting that this concentration is far higher than those classically used in in-vivo or in-vitro live cells labeling with QDs, which are typically in the range of 10 – 100 nM.[54, 55] These results clearly show that ZnSe:Mn/ZnS@MPA QDs are much safer than CdTe/CdS@MPA QDs and thus exhibit a higher potential for bio-imaging and nano-diagnostic applications. The ability of QDs to be conjugated with a great number of bioactive molecules (e.g., antibodies, receptor ligands) makes these nanocrystals promising candidates to target various specific biological events and cellular structures such as tumoral cells.[19, 56, 57] Bioconjugated QDs could also be potentially explored as biomarkers for site-specific gene and drug delivery through a suitable surface modification of QDs with polymer containing active molecules.[58].

CONCLUSION

This work was mainly focused on comparing the Cd-free ZnSe:Mn/ZnS to the Cd-based CdTe/CdS QDs prepared in similar synthesis conditions and having similar physico-chemical properties (i.e. particle diameter, PL emission wavelength and surface ligand) in order to demonstrate the potential of using ZnSe:Mn/ZnS QDs as non-toxic and efficient bio-probes. The synthesis conditions were adjusted to yield QDs with similar nanocrystals diameter and emission wavelength. The average crystallite sizes determined by TEM are 3.5 nm and 3.9 nm for ZnSe:Mn/ZnS and CdTe/CdS QDs, respectively. The maximum emission wavelengths are 600 and 604 nm for ZnSe:Mn/ZnS and CdTe/CdS QDs, respectively. CdTe/CdS QDs had a higher PL QY (i.e. 65% vs. 25%) and narrower FWHM (i.e. 60 nm vs 72 nm) compared to ZnSe:Mn/ZnS QDs. In terms of cytotoxicity, bacteria growth inhibition tests showed that Cd-based QDs almost stopped the cells growth at concentration as high as 10μM while no toxicity was observed with ZnSe:Mn/ZnS@MPA QDs in similar conditions. Application of these nanocrystals in bio-imaging and nano-diagnostic is currently under investigation.

ASSOCIATED CONTENT

No Supporting Information is provided by the authors.

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