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# Versatile semiconductor quantum dots: synthesis, bioconjugation strategies and application

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## ABSTRACT

**Purpose:** The present work aimed to synthesize organic and inorganic quantum dots (QDs) and discuss their bioconjugation strategies.

**Design/methodology/approach:** We have prepared 3 different QDs, organic (Carbon [CQDs]) and inorganic (Cadmium Sulphide [CdS] and Zinc Mercury Selenide [ZnHgSe]) quantum dots (QDs) and bioconjugation through in-situ and ex-situ route. These QDs have been characterized through UV-Vis spectroscopy and photoluminescence (PL) emission spectra. Their surface functional groups have been identified through Fourier-transform infrared (FTIR) spectroscopy. The bioconjugated quantum dots were tested through PL emission shift, Agarose electrophoresis, and Bradford assay technique.

**Findings:** Successful synthesized QDs, and their bioconjugation has been confirmed through the previously listed characterization techniques. There are distinct differences in their emission peak, FTIR spectroscopy, and Bradford assay, which confirms their successful bioconjugation.

**Research limitations/implications:** These bioconjugated QDs are difficult to filter from their unconjugated counterpart. Bioconjugation steps are extremely crucial.

**Practical implications:** These QDs could be utilized for highly effective biolabelling and bioimaging *in-vivo* as well as *in-vitro* applications.

**Originality/value:** The synthesis has been majorly modified, and the bioconjugation has been prepared in a novel method. There is limited reported work with this much description of the differences in conjugated and unconjugated QDs.

**Keywords:** Quantum dots, Quantum dot synthesis, Quantum dot bioconjugation, Eco-friendly synthesis, Photoluminescence

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BIOMEDICAL AND DENTAL MATERIALS AND ENGINEERING

## 1. Introduction

Investigation of various biological processes relies on quick, sensitive, selective and reproducible detection [1]. Fluorescence techniques for biological and clinical applications, especially bioimaging processes, have seen revolutionary developments in the past decade owing to their high sensitivity and visual and rapid response [2-4]. A fluorophore is a chemical compound that can absorb and emit light at different wavelengths [5]. Over the years, organic fluorophores have been extensively utilized for cell labelling and tissue imaging [6]. These are biocompatible and aqueous in nature; however, they suffer from poor photostability and background-interfering auto-fluorescence. Moreover, the close proximity of the excitation and emission bands often tends to overlap during the imaging process, thus giving misleading results [7]. In comparison, inorganic fluorophores have shown much better photostability and narrow emission bands with appreciable isolation from the excitation peak [8].

Amongst the inorganic fluorophores, quantum dots (QDs) or semiconducting quantum dots (SQDs) are a class of semiconducting nanocrystals with a size of a few tens of nanometres [9,10]. Their size is much smaller as compared to the wavelength of electrons, thus leading to quantum confinement [11]. This enables unique size-dependent tunability in optical and electronic properties. The most commonly explored QDs are compounds from elements of group II-VI (ZnSe, CdSe), III-V (InP, InAs), and IV-VI (PbS, PbSe) [12]. Facile wet colloidal-based synthesis of QDs makes its usage very common. However, in general, most of the QDs are cytotoxic and unsuitable for in-vivo application; these are also often synthesized using toxic precursor materials with limited water solubility [11]. To overcome these challenges, QDs are either coated or encapsulated within amphiphilic materials such as polymers or biomolecules [13-15]. Organic quantum dots (Carbon QDs) can also be synthesized; this makes them biocompatible with minimal toxicity and hydrophilic in nature [16].

Using inorganic QDs and organic QDs like carbon is growing as an indispensable biological tool [17-19]. Bioconjugation of QDs ensures diverse biological applications; for instance, QD–antibody conjugates in immune assays, flow-cytometry, and immune-histochemistry, where the antibody provides the biorecognition and targeting. Another major utility includes in-vivo imaging. Some other active uses of QDs include conjugation with biomolecules for monitoring changes in the emission of the QD as a type of dynamic signal transduction.

Although QDs have shown several benefits over organic fluorophores, most of the QD surface functionalization and bioconjugation strategies are complex and hence tricky and more challenging than bioconjugation of organic fluorophores. Improper conjugation may often affect excitation and emission peak intensities, such as auto-fluorescence, scattering, etc. Bioconjugation of QDs can be done through *in-situ* (pre-synthesis) or *ex-situ* (post-synthesis) reactions. In the in-situ method, biomolecules are added during the QD synthesis. This causes the QDs to be synthesized from within the biomolecule cavity. In general, biomolecules can be conjugated through physical (electrostatic, affinity, etc.) or chemical (using surface-activated functional group binding) routes [12].

It is apparent that QDs have an inevitable role to play in biological activities, but a systematic and comprehensive knowledge of surface functionalization of these QDS, followed by an appropriate bioconjugation strategy, is highly desired to ease off its utility in real-life application. This work presents a comprehensive approach to meeting the challenges faced with the synthesis, functionalization and bioconjugation of QDs. Here in we have discussed the synthesis and detailed characterization of three different categories of QDs, namely carbon (elemental form), CdS (compound form), and ZnHgSe (complex compound form). Further, an extensive and systematic study is described for surface functionalization and bioconjugation of these QDs with proteins using *in-situ* and *ex-situ* methods.

## 2. Materials and methods

### 2.1. Materials

Urea, citric acid, cadmium sulphate [$Cd(SO_4)$], sodium sulphide [$Na_2S$], zinc acetate [$Zn(CH_3CHO_2)_2$ or $Zn(OAc)_2$], mercury chloride [$HgCl_2$], 11-mercaptoundecanoic acid [MuA], ammonium bicarbonate [$NH_4HCO_3$], sodium borohydride [$NaBH_4$], selenium [Se] powder, sodium dodecyl sulfate [SDS], bradford reagent, acetic acid, EDC/EDAC (1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydrochloride), and bovine serum albumin [BSA] were purchased from Sigma Aldrich. S-NHS (N-hydroxysulfosuccinimide) was purchased from Thermo Fisher. Agarose, tris base, ethylenediaminetetraacetic acid [EDTA], glycerol, bromophenol blue, and methanol were purchased from Merch. Green tea leaves were bought from Organic India. Distilled water (DW) was used for the synthesis, purification, and bioconjugation. All the chemicals used were of analytical reagent grade purity and were used without any further purification.

### 2.2. Synthesis of QDs

Carbon quantum dots

Carbon quantum dot (CQD) synthesis was a pyrolysis method taken from previously published literature with major modifications [20]. Briefly, 5:1 (w/w) urea and citric acid were heated and kept at 200°C for 15 min. A dark brown-coloured slurry containing CQD was obtained. The as-formed CQDs were purified by centrifugation at 15,000 rpm in the presence of dilute NaOH solvent.

Cadmium sulfide quantum dots

This synthesis process was inspired by previously published literature wherein black tea leaves were used to synthesize CdS QDs [15]. Here, green tea leaves capped cadmium sulfide (CdS) QD was synthesized in a dark environment at room temperature. 3 g of green tea leaves were soaked in 15 ml methanol for 24 h. The extract was then filtered out using Whatmann filter paper (No. 42). 1 ml of $Cd(SO_4)$ (25 mM) was added to the extract and was kept undisturbed at a dark condition for 72 h. Thereafter, 0.25 ml of $Na_2S$ (25 mM) was added to the mixture and kept for another 96 h. Finally, the mixture was centrifuged at 15000 rpm, and the supernatant was collected. Further purification was performed using 10 kDa Amicon filter. The QDs were then vacuum dried and stored under refrigeration for further use.

Zinc mercury selenide quantum dots

MuA-capped Zinc Mercury Selenide (ZnHgSe) QDs were synthesized at room temperature via rapid injection method. The method was inspired by previous literature with minor modifications [21]. Briefly, a 0.2 M solution of $NH_4HCO_3$ at pH 12.7 was prepared as a medium. 125 µl of (100 mM) $Zn(OAc)_2$, 37.5 µl of (500 mM) MuA, and 6.25 µl of (100 mM) $HgCl_2$ were added into the medium (final volume of 500 µl). Sodium hydrogen selenide (NaHSe) was prepared by mixing 98.5 mg of Se powder and 100 mg of $NaBH_4$ in 5 ml of water in presence of an inert $N_2$ environment. NaHSe solution was then rapidly injected into the mixture of the medium. As the colour of the medium changed to brown, it indicated the formation of ZnHgSe QDs. For in-situ conjugation with BSA protein, 20 µl of (0.5 mM) BSA was added into the mixture of the medium before injecting NaHSe solution. Purification was done using a 10KDa Amicon filter to remove any unconjugated QDs.

### 2.3. Bioconjugation process

Bioconjugation of the QDs has been done through both *in-situ* (pre-synthesis) and *ex-situ* (post-synthesis) methods using a standard bovine serum albumin (BSA) protein.

*Ex-situ* method:

Carbon quantum dots – 100 µl of CQD stock solution was vacuum dried. 10 µl of (500 mM) EDAC and 20 µl of (500 mM) S-NHS were mixed with dried CQD and incubated for 15 min. 20 µl of (5 mM) BSA was then added to the solution and incubated for 2h at room temperature. The final volume of the solution mixture was 100 µl volume. The solution was filtered using a 10 kDa Amicon filter for the separation of unconjugated QDs.

CdS quantum dots – 10 mM of CdS and 10 mM of MuA were mixed in methanol and incubated for 1 h. Then the mixture was vacuum dried. EDAC – S-NHS treatment and BSA protein incubation were similar to the CQD bioconjugation process, followed by filtration to remove any unconjugated QDs.

*In-situ* method:

ZnHgSe quantum dots – Bioconjugation was done during the QD synthesis. BSA protein was added to the solution medium before the reduction process (i.e. NaHSe injection). The molar ratio of ZnHgSe to BSA was 1:1.

### 2.4. Characterization

Absorbance measurement was carried out using Shimadzu UV-2600_spectrophotometer. Photoluminescence (PL) emission peak was recorded using an optical fibre-based portable photoluminescence spectrophotometer from Research India. Fourier-transform infrared spectroscopy (FTIR) was carried out using a Perkin Elmer Infra-red spectrometer. Bradford assay was carried out using a Bradford assay kit purchased from Thermo Fisher.

### 2.5. Gel electrophoresis

QD-protein samples were mixed in a 1:1 ratio in 1X gel loading dye to verify QD-protein conjugation. They ran on 1.5% Agarose gel using TAE buffer (40 mM Tris, 20 mM acetic acid, 1 mM EDTA, 8.5 pH) at 80V for 70 min. The free protein and QD-conjugated protein bands were visualized by staining the gel with Coomassie Brilliant Blue stain for 20 min.

## 3. Results and discussion

### 3.1. Formation of quantum dots

The synthesized QDs were purified and refrigerated till further use. Absorbance spectra of CQD, CdS QD and

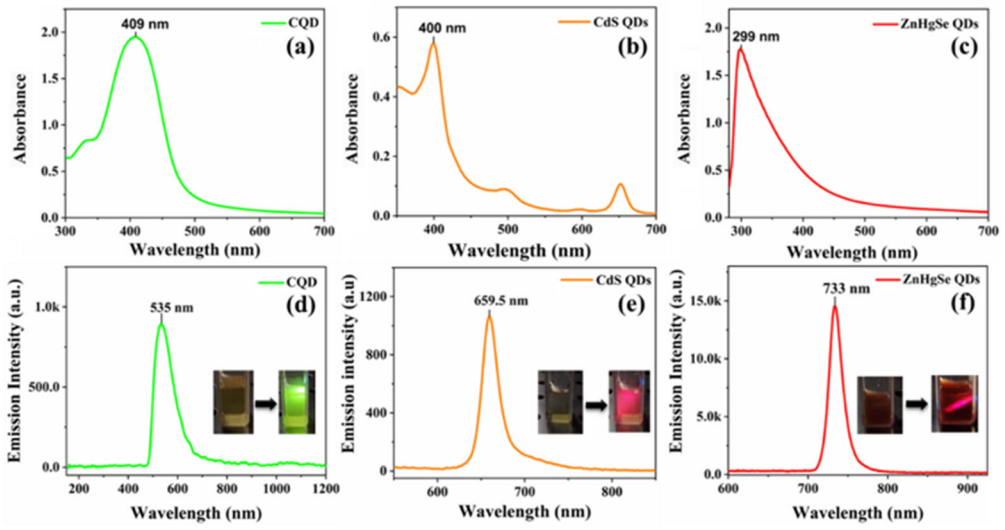


Fig. 1. Absorbance spectra of (a) CQD, (b) CdS QD, and (c) ZnHgSe QD. Emission Spectra of (d) CQD, (e) CdS QD, and (f) ZnHgSe QD

ZnHgSe QDs were recorded to detect the excitation wavelength. Maximum absorbance of CQD, CdS QDs and ZnHgSe QDs was observed at 409 nm, 400 nm, and 299 nm, respectively, as shown in Figures 1a, 1b, and 1c. The maximum absorbance peak corresponds to the excitation wavelength of these QDs. Figures 1d, 1e, and 1f represent the corresponding emission spectra of each of these QDs when excited with the respective absorbance maxima wavelengths. The emission peak for CQD was observed at 535 nm (Fig. 1d), which was also evident through visible green colour emission, as shown in the inset in Figure 1d. Similarly, the emission peak for CdS and ZnHgSe QDs were observed at 659 nm and 733 nm, respectively, with a visible orange and red colour fluorescence (Fig. 1e and 1f). However, the orange and red colours could not be visibly distinguished.

### 3.2. Bioconjugation

It is to be noted that organic quantum dots, like carbon, can only be bioconjugated through *ex-situ* methods. This is due to high-temperature synthesis and/or fluctuating environmental conditions, which is unfavourable for most biomolecules. However, inorganic quantum dots, specifically semiconducting quantum dots, can be synthesized under ambient conditions; thus, biomolecules remain stable. This makes *in-situ* bioconjugation possible for semiconductor QDs.

Bioconjugation of QDs can be taken up by immobilizing the biomolecules on the surface of QD by either non-covalent binding such as electrostatic interactions, or covalent binding via various conjugation chemistries using activated functional groups at the surface of the QDs. In this study, a well-known protein EDAC-NHS covalent cross-linking chemistry has been used. The cross-linking chemistry for QD conjugation with BSA protein is schematically represented in Figure 2. EDAC, a carbodiimide compound, provides a versatile method for cross-linking to carboxylic acids. Hence, the QD surface was initially carboxylated using the MuA compound. The EDAC compound reacts with the carboxyl groups (-COOH) to form

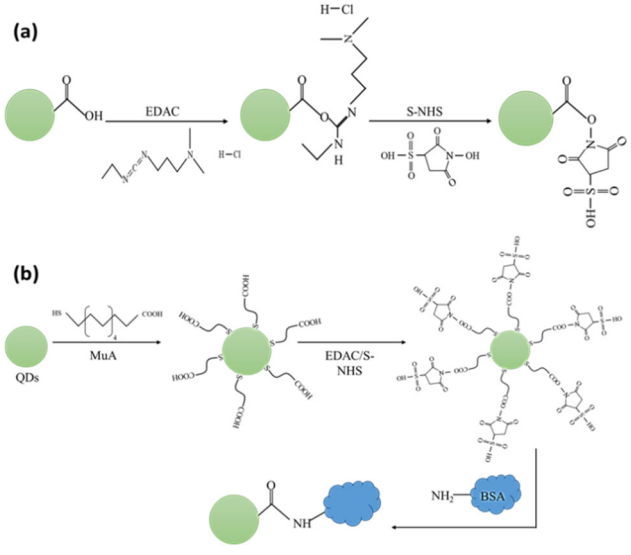


Fig. 2. (a) EDAC/S-NHS cross-linking with MuA-capped QDs; (b) QD-BSA bioconjugation strategy

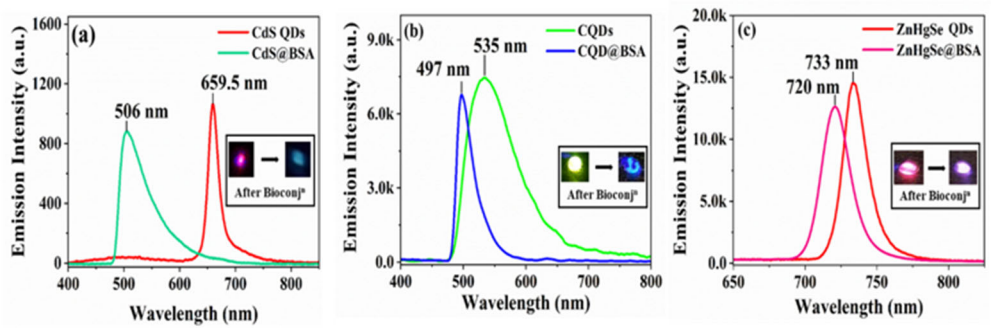


Fig. 3. PL spectra of (a) CdS QD and CdS@BSA conjugate, (b) CQD and CQD@BSA conjugate, and (c) ZnHgSe QD and ZnHgSe@BSA conjugate

an active O-acylisourea intermediate compound readily displaced by nucleophilic attack from primary amino groups from a protein. The primary amine from the protein comprises an amide bond with the original carboxyl group, and an EDAC by-product is released as a soluble urea derivative.

QD bioconjugation was verified using PL emission spectrum, gel electrophoresis, Bradford assay, and FTIR spectrophotometry.

Photoluminescence emission

Photoluminescence (PL) emission spectra were observed before and after bioconjugation, as shown in Figure 3. An excitation wavelength of 365 nm was used for CdS QD and ZnHgSe QD and 405 nm for CQDs. In Figure 3a, the emission peak of CdS QDs was observed to be significantly blue-shifted by 153 nm from red to greenish blue after bioconjugation. The emission peak at 506 nm was initially (i.e. before bioconjugation) observed as a suppressed peak. In Figure 3b, the emission peak of CQD was observed to be shifted by 39 nm from green to blue after bioconjugation. Minimum emission peak shift was observed by only 13 nm on bioconjugation of ZnHgSe QDs where an in-situ conjugation process was undertaken (Fig. 3c). In addition to the facile synthesis process, in-situ bioconjugation also showed a minimum shift in the emission peaks as compared to the pristine QD counterparts. The blue shift that is often observed in the bioconjugation of QDs is mostly due to oxidation. It is clear that the in-situ conjugation process largely prevents this blue shift from occurring. This is a beneficial feature that is highly desirable for bioimaging in-vitro applications.

Visualization of QD-conjugated protein by gel electrophoresis

Agarose gel electrophoresis results of bioconjugated quantum dots verified the successful binding of the protein. Free QDs owing to their small dimensions, had more mobility on an agarose gel than BSA conjugated QDs, as seen in the gel image shown in Figure 4. Figures 4a and 4b represent the Coomassie blue-stained gel electrophoresis image of CQD, CdS QD, and ZnHgSe QD conjugated with BSA. Lane 1 in each image corresponds to only BSA used as a control. It was observed that as compared to the free BSA, the CQD@BSA Figure 4 (lane 2) conjugate band and the CdS@BSA band (lane 3) had retarded mobility. In addition, the CdS@BSA conjugate band (lane 3), due to the heavier mass of CdS, showed the least mobility. A similar trend was observed for the ZnHgSe@BSA conjugate (lane 2) in comparison to the BSA band in lane 1 (Fig. 4b).

A LASER first imaged the gels at a specific excitation wavelength (405 nm) and then stained them using the

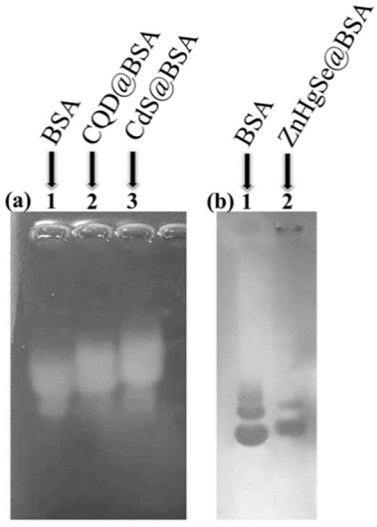


Fig. 4. Gel Mobility shift assay of QD-conjugated BSA on 1.5% agarose gel; (a) free BSA (lane 1), CQD@BSA, and CdS@BSA conjugated (lanes 2 and 3); (b) BSA (lane 1), and ZnHgSe@BSA conjugated (lane 2)

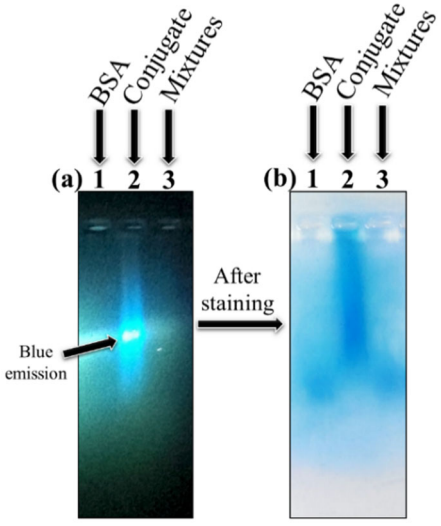


Fig. 5. Electrophoresis gel (a) under 405 nm LASER excitation and (b) after staining with Coomassie blue

protein-binding dye - Coomassie blue. A comparison of the fluorescence gel image (Fig. 5a) and stained gel image (Fig. 5b) showed the regions of co-staining, suggesting successful conjugation of protein and CQD. Lane 1 consisted of the BSA band as control. Lane 2 contained BSA@CQD conjugate band, and lane 3 was a mixture of unconjugated BSA and CQD. As the unstained gel was excited with 405 nm LASER, lane 2 emitted a blue fluorescence. Further, lanes 1 and lanes 3 did not show any visible fluorescence as expected.

Bradford assay

Bradford assay of bioconjugated CdS QD was further performed to validate the presence of BSA in the conjugate. It can be observed in Figure 6 that the original brown colour of the Coomassie reagent in the Bradford assay remained unchanged in the presence of only CdS QD due to the absence of any protein. Whereas the blue colour in the CdS@BSA conjugate clearly indicated the presence of protein with QDs. The blue colour is primarily attributed to the strong non-covalent interaction of the protein with the Coomassie blue reagent.

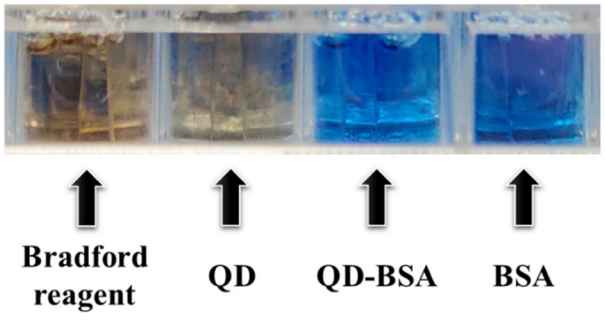


Fig. 6. Bradford assay of QD-protein conjugate

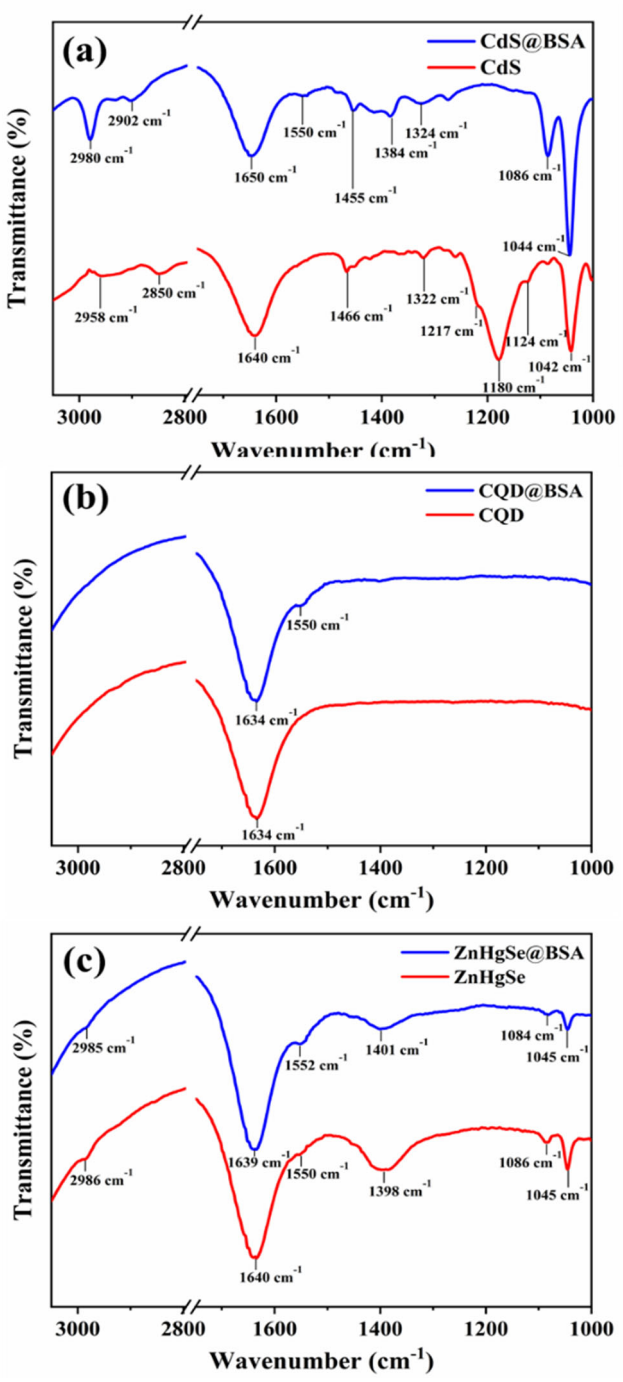


Fig. 7. FTIR spectra of (a) CdS QDs and CdS@BSA conjugate, (b) CQDs and CQD@BSA conjugate, and (c) ZnHgSe QDs and ZnHgSe@BSA conjugate

FTIR analysis

FTIR studies were carried out to study the surface functional groups of QDs and QD@BSA conjugate. The measurements were carried out before and after conjugation to understand the BSA-induced change. In Figure 7a, multiple peaks can be seen in CdS QDs representing the green tea organic moieties on the quantum dots that indicated the capping of green tea residues on the CdS quantum dot. Similar peaks have also been indicated in other reports on the biogenic synthesis of quantum dots [22]. Typically, peaks near 1634 $cm^{-1}$ to 1650 $cm^{-1}$ represent C=O stretching due to amide groups like polyphenols, proteins, amino acids, etc. In Figures 7a and 7c, peaks near 2958 $cm^{-1}$ and 2986 $cm^{-1}$ represents C-H stretching, and 1086 $cm^{-1}$ and 1045 $cm^{-1}$ represent C-OH stretching due to the presence of MuA. In Figure 7b, the absence of these peaks in CQDs is due to the absence of MuA. Peak at 1550 $cm^{-1}$ is due to peptide bonds formed during bioconjugation. Figure 7a shows some peaks at around 1217 $cm^{-1}$, 1180 $cm^{-1}$, 2850 $cm^{-1}$, and 1124 $cm^{-1}$ have been quenched after conjugation with BSA.

## 4. Conclusions

In this study, successful synthesis and bioconjugation of various quantum dots have been demonstrated. The study describes the tips and tricks to overcome various challenges often faced during the bioconjugation of quantum dots.

A comparison of ex-situ and in-situ bioconjugation concludes that QDs bioconjugated with an in-situ process can save substantial time and effort and render better stability to the QDs. For instance, in-situ bioconjugation of ZnHgSe QDs has shown a minimal shift in emission peak, thus indicating its suitability for various in-vitro imaging applications. Further, an eco-friendly green synthesis of CdS QDs capped with organic moieties of green tea leaves may benefit in *in-vivo* applications.

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## Additional information

The work presented in this paper was presented in "Two Days Virtual National Meet on Nano Interface Science (NIS-2021)", Chettinad Academy of Research & Education, Chennai, India, 2021.

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