

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Quantum Dots for Pharmaceutical and Biomedical Analysis

Hayriye Eda Şatana Kara and Nusret Ertaş

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.70034>

Abstract

Quantum dots (QDs) are luminescent semiconductor nanocrystals that have extraordinary luminescence emission properties. Their semiconductor properties are different from bulk material because of the quantum confinement effects. These properties allow the use of QDs as a luminescent probe for pharmaceutical and biomedical analysis. Herein, we want to mention the synthesis, surface modification, characterization, and application of QDs. The aim of this chapter is to compile and discuss the advantages and disadvantages of QDs and their usage areas.

Keywords: quantum dots, luminescence, fluorescence, chemiluminescence, phosphorescence, pharmaceuticals

1. Introduction

The semiconductor nanoparticles known as quantum dots (QDs) are one of the most relevant developments in the nanotechnology area. Therefore, they are finding new important fields of application in pharmaceutical, biomedical, and food analysis and biomonitoring. QDs are zero-dimensional materials composed of II–VI groups (e.g., CdSe, CdTe, CdS, and ZnS) or III–V elements (e.g., InAs) [1–4]. Colloidal semiconducting QDs have spherical shape, and their radii are in between 2 and 10 nm in diameter, which is less than or equal to the excitation Bohr radius [5–8]. A decrease in the crystal size causes emission at longer wavelength due to increase of the Stokes shift. At such small sizes, these nanoparticles behave differently from the bulk form because of quantum confinement effect, which is responsible for the optoelectronic properties of QDs such as narrow spectral band and high quantum yield (QY).

In the last decades, QDs have gained great interests as luminescent probes for the determination of pharmaceuticals [9–12] in different sample matrices, *in vitro* bioimaging [13–18] and *in vivo* applications [19–21], as well as computing, light-emitting devices, and photodetector devices. Because of their unique optical properties, including good optical properties, stability against photobleaching and chemical reaction, broad excitation bands, sharp and symmetric emission bands, size control luminescence, as well as high photoluminescence QY, QDs are used as an alternative to organic and inorganic fluorophores [22–24].

QDs can be modified by different molecules such as polymers and biomolecules in order to make them water soluble and biocompatible. Modification of QDs with biomolecules (e.g., DNA, enzyme, antibody, antigen) [25–27] and metal ions [28–31] has formed an important field of sensor applications [32–34] for the analysis of ions [35–38], biomacromolecules, pharmaceuticals, and small molecules [12, 39–41]. In addition, the surface modification of QDs can increase their luminescent QYs, prevent them from chemical instability and aggregation, and give a special feature to interact with target molecules.

2. Structural and optical properties

2.1. Structural properties

Generally, QDs are composed of core, shell, and surface-coating parts, which gain high photoluminescence QY, surface activation, and stability to chemicals and photons [42, 43]. The core is composed of few monolayers of a semiconductor material, i.e., CdSe, CdTe, fluorescence emission, as well as excitation wavelengths, depends on the composition of the core. Shell part surrounds and stabilizes the core. Shell is also effective on the fluorescence QY, decay kinetics, and photostability of QDs. The organic capping determines its stability, biological functionality, and solubility [44]. Coating part at initially prepared QDs is hydrophobic, whereas nowadays hydrophilic polymers or molecules are used. These amphiphilic polymers increase the water solubility of QDs and allow incorporating ionizable functional groups. Both shell and capping are covered to the particle surface and optimize these characters. Typical QDs are core or core-shell structures. The passivation shell is chemical coating, and coated nanoparticles are called core-shell systems. Core (for example, CdTe) or core-shell (for example, CdSe/ZnS and CdTe/CdS) QDs are functionalized with different coatings. In core-shell system, the band gap of the shell is higher than the band gap of core [45–50]. Additionally, a slight red shift in absorption and emission is observed because of tunneling of charge carriers into the shell.

2.2. Characterization

Definition of size, structure, and shape of synthesized QDs is important. The characterization of QDs is evaluated by high-resolution transmission electron microscopy (HR-TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), X-ray fluorescence (XRF), X-ray diffraction (XRD), and Fourier transform infrared spectroscopy (FT-IR) methods. The size of QDs is generally detected by TEM and SEM [3, 51–53]. In addition to these methods, Brus equation is also used to calculate the diameter of QDs [39]. The optical characterization

is made by UV-visible (UV-vis), fluorescence, Raman, and nuclear magnetic resonance spectroscopy (NMR) [54, 55].

2.3. Optical properties of QDs

Although QDs are composed of semiconductor materials, their small size results in spectroscopic properties that are radically different from bulk forms. The electron of the valence band moves to conductance band when QDs absorb the photon. Absorption occurs as long as the energy of photon is higher than the bandgap energy of QDs; thus, excitons can be created with a wide range of energies within the core. The higher energy excitons relax to the lowest bandgap energy before emitting a photon. Therefore, excitation spectrum is broad, whereas the emission spectrum is narrow (**Figure 1**).

QDs are artificial atoms with typical dimensions ranging from 2 to 10 nm. QDs can be designed to have different emission wavelength by adjusting their size (**Figure 2**). The emission is adjusted by the particle diameter in the visible area and by particle composition in the longer wavelength. As diameter of QDs gets bigger, red shift is observed in the emitted light [56, 57]. The properties of QDs are changed by constructing the properties of the electron and hole. The electrons and holes of QDs also present discrete energy levels. As nanoparticles size get smaller, the band gap will be larger, and energy difference between the highest valence band and the lowest conduction band will be increased. As a result, the high energy is required to excite the dots, and therefore, more energy is emitted when nanoparticles return to ground state.

QDs have broad absorption band and a narrow symmetrical emission band; therefore, overlap with other emission colors is minimal. The wavelengths of absorption and emission are tunable by particle size as mentioned before. The broad absorption bands allow selection of the excitation wavelength, and consequently, excitation and emission wavelengths can be separated [48, 58–61]. Physicochemical and optical properties of QDs are summarized in **Table 1**.

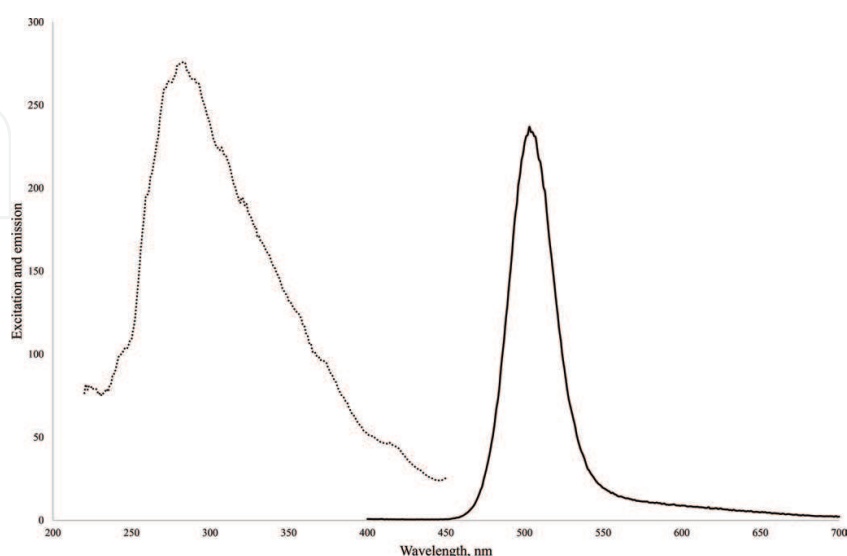


Figure 1. Excitation (dot line) and emission (line) spectra of MPA-capped CdTe QDs.

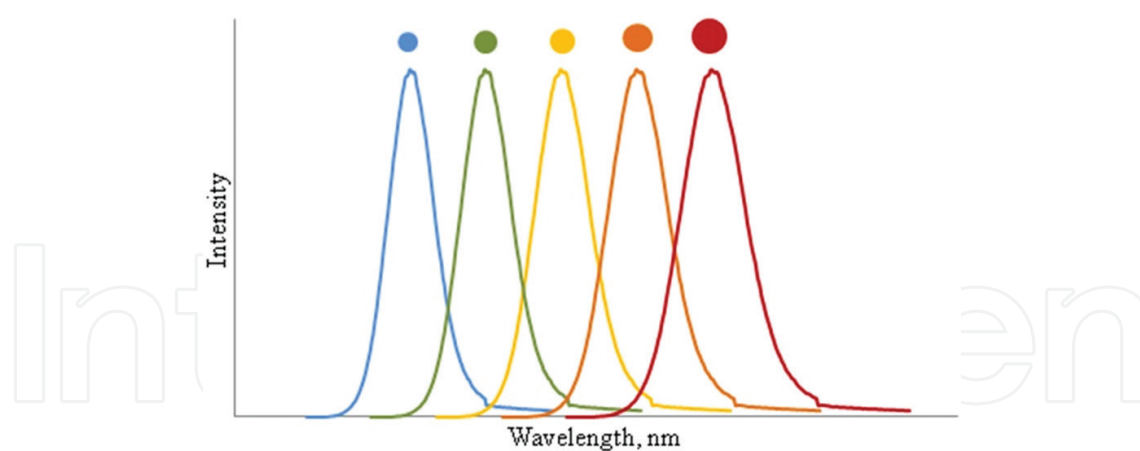


Figure 2. Photoluminescence spectra of the QDs by changing the size of the particle.

Property	Quantum dots
Size	2–10 nm
Thermal stability	High, depends on shell
Photostability	High, stable fluorophores due to their inorganic composition
Chemical stability	More resistant to degradation
Brightness	10–20 times more than organic dyes
Absorption spectra	Broader absorption spectra enables selection of excitation wavelength
Molar absorption coefficient	10^5 – 10^6 M ⁻¹ cm ⁻¹
Emission spectra	A narrow (30–90 nm), symmetric, sharply defined emission peak
Quantum yield	0.1–0.8
Stokes shift	Large stokes shift
Lifetime	Longer lifetime helps to eliminate background signal
Excitation by single or multiple sources	Ideal for the same source and multicolor experiments
Solubility	Depends on surface modification
Sensitivity	High S/N ratio
Applicability to single-molecule analysis	Good
Bioimaging	Better contrast with electron microscope

Table 1. Properties of QDs.

2.4. Synthesis and surface chemistry

Synthesis step of semiconductor nanocrystals plays a critical role. The solvent selection is crucial because this step is not only controlling nanocrystal size but also changing their polarity, solubility in aqueous or organic medium, functionality, and applicability. QDs can be synthesized in the organic or aqueous medium. When compared to organic way, water-based QDs synthesis is less toxic, useful for biological applications, and cheaper.

In order to prepare QDs, different types of materials and methods have been reported. In these methods, colloidal synthesis is commonly used technique for the preparation of QDs. During early 1990s, Murray et al. [62] first reported the synthesis for highly monodisperse, size-tunable QDs. In this method, trioctylphosphine (TOP) and trioctylphosphine oxide (TOPO) are used for the synthetic approach for II–VI QDs such as CdSe, CdS, and CdTe. Highly luminescent Cd-E (E = Se/Te/S) nanocrystals were synthesized by using dimethylcadmium ($\text{Cd}(\text{CH}_3)_2$) as QDs precursors in the coordinating solvent (TOPO) at high temperature (300°C). However, nowadays, cadmium oxide (CdO) is used instead of dimethylcadmium due to its toxicity. The commonly used method for synthesis of colloidal nanocrystal is based on core growth process, starting from organometallic precursor in a mixed solvent including organic surfactants and coordinating solvents. Briefly, reaction medium is heated to high temperature, and precursors are injected while solution stirring. At this step, precursors transform into monomers. As the process continues, nanocrystal growth starts with a nucleation process, and the color of solutions changes from yellow to red. Coordinating solvent caps the nanocrystal surface and stabilizes its surface, moreover, changes its solubility in organic and aqua media and prevents aggregation. Organic surfactants are used to avoid aggregation and give water soluble character [4, 63–66]. At nanocrystal-growth process, not only solvent but also temperature, pH, and growth time are important. Generally, when the heated and unheated forms of QDs are compared, heated QDs show emission, whereas unheated QDs do not have an emission band. Minor variations in pH values affect the diameter of nanocrystals.

Coordinating solvents can be hydrophobic or hydrophilic. Hydrophobic coatings are not suitable for aqueous assay especially biological analysis; therefore, hydrophilic capping agent must be introduced for this purpose. Various approaches have been developed to make water soluble. The hydrophobic layer can be changed with acidic and hydrophilic groups. Hydrophobic part reacts with the hydrophobic surface of QDs, whereas the hydrophilic part on the outer end will give water soluble character. The stability of water dispersed QDs is generally achieved by using charged organic molecules or polymers such as mercaptopropionic acid (MPA), mercaptoacetic acid (MAA), mercaptosuccinic acid (MSA), and cysteine [67–69].

Doping of QDs with transition-metal ions such as Mn^{2+} and Cu^{2+} has been widely studied to enrich the features of nanocrystals. These advantages include stability, large Stokes shift, and longer emission lifetime which allow phosphorescent measurement [70–72]. In these doped QDs, Mn-doped ZnS which have orange-yellow emission is widely used as a phosphorescent probe for analysis of different kinds of analytes [73–75]. The purification step is needed to remove unreacted precursors and other chemicals. A widely used method for this purpose is precipitation of QDs in methanol or ethanol and centrifugation.

Additionally, lithography [76, 77], epitaxy [76, 78], electrochemical assembly [79–81], plasma synthesis [82–86], biological synthesis [87, 88], gamma-irradiation [89–91], and microwave-assisted synthesis [92, 93] ways are also used for the synthesis of QDs.

3. Applications of QDs

Surface properties of QDs affect the luminescence character. The chemical or physical interaction of analytes and QDs can influence the optical properties of the QDs. Depending on this change, QDs have been widely applied to detect different kinds of analytes including ions, pharmaceuticals, small molecules, and biological macromolecules. In these analytes, direct analysis of pharmaceutical and biological samples is difficult due to interference molecules. However, chemical surface modifications of QDs with functional groups or biomolecules enhance the selectivity and favorable luminescence features. Most of the detection methods are based on the fluorescence properties of these QDs. Besides, in recent years, increasing number of work on making use of the inherent phosphorescent properties of QDs is in the literatures. In most QDs applications, the detection is based on quenching of luminescence signal, while new methods are developed on signal enhancing.

3.1. Fluorescence-based measurements

The luminescence properties of QDs are used for qualitative or quantitative analysis of different kinds of analytes. Initial studies are generally based on measuring the enhancement or quenching of luminescence signal of QDs resulting from the interaction of the QDs and the analyte. This surface interaction generally is not specific and allows interacting with simple and small molecules. Nonspecifically binding is a major problem especially in biomedical applications due to the interaction of a variety of biomolecules and structures including nucleic acids, proteins, or matrix compounds. In order to increase selectivity, conjugation of QDs with polymers, antibodies, amino acids, and proteins has been proposed and applied [94, 95].

In a pioneering work, Cd-based QDs have been reported for optical sensing of small molecules and ions. Many studies in this field, focusing on interactions between QDs and analyte, showed that the luminescence response was affected by the surface capping ligands. For example, the addition of Cd ions to a basic solution, including CdS nanoparticle, has caused increasing the luminescence QY of the nanoparticle. This effect was attributed to the formation of a $\text{Cd}(\text{OH})_2$ shell on the CdS core which eliminates the nonradiative pathways. Furthermore, addition of Zn^{2+} and Cd^{2+} ions to basic CdS or ZnS colloidal solutions caused similar photoluminescence-activation effect [96–98]. In addition, organic capping agents such as mercapto acids and mercaptoamines have been used for the modification of QDs surface [99]. Modification strategies are based on not only intensity enhancing but also quenching and emission wavelength shifting. Quenching mechanism depends on the interaction of quencher and nanoparticle and includes different deactivation pathways such as electrotransfer process, nonradiative pathways, inner-filter effect, and complex formation. Quenching occurs by two

different mechanisms called dynamic (collisional) and static quenching. In dynamic quenching, the quencher and fluorophore come into contact during the lifetime of the excited state, and the fluorophore returns to the ground state without emission. In static quenching, fluorophore and quencher form a nonfluorescent complex at the ground state. These quenching systems can be differentiated by their different dependence on temperature and viscosity. At higher temperatures, dynamic quenching increases due to faster diffusion. On the contrary, in the static quenching, dissociation of weakly bound complexes causes decreasing of quenching. In some cases, the fluorophore can be quenched by collisions and complex formation with the same quencher at the same time [100].

Literature survey shows that a great number of fluorescence methods have been developed for analysis of pharmaceuticals and biomolecules (**Table 2**). These methods are generally based on quenching of fluorescence intensity of QDs (**Figure 3**). Thioglycolic acid (TGA)-modified water-soluble CdSe QDs were synthesized and used for determination of paraoxon, which is acetylcholinesterase inhibitor. In this study, multilayers of chitosan, TGA-capped CdSe QDs, and organophosphorus hydrolase polyelectrolytes were incorporated into layer-by-layer architecture. The size of the nanoparticles was determined by HR-TEM and found 3.4 nm. The presence of paraoxon in the sample solution caused decreasing fluorescence emission of QDs, attributed to an interaction of the analyte with QDs and to change surface conformation [101].

QD material	QD coating	Analyte	Matrix	Detection limit	Measuring signal	Ref.
CdSe	TGA	Paraoxon	–	–	Fluorescence quenching	[101]
CdTe-Mn doped	TGA	Glutathione	Tablet	0.06 μM	Fluorescence quenching/enhancement	[102]
CdTe	TGA	Doxycycline	Honey, human serum	1.1×10^{-7} M	Fluorescence quenching	[103]
CdS	L-Cysteine	Ceftriaxone	Urine	1.3×10^{-9} M	Fluorescence quenching	[104]
CdSe	–	Spironolactone	Tablet	4.8×10^{-7} M	Fluorescence quenching	[105]
CdSe/CdS	TGA	Sparfloxacin	Tablet	0.1391 $\mu\text{g mL}^{-1}$	Fluorescence quenching	[106]
CdS	MPA	Penicillamine	Tablet	0.1123 $\mu\text{g mL}^{-1}$	Fluorescence enhancement	[107]
CdTe	MPA	Rifampicin, Rifaximin	Urine, tablet	1.5 mg mL^{-1} , 1.0 mg mL^{-1}	Fluorescence quenching	[108]
C	PEG 2000	Ceftazidime, Cefepime	Tablet	4.7×10^{-3} $\mu\text{g mL}^{-1}$, 5.1×10^{-3} $\mu\text{g mL}^{-1}$	Fluorescence quenching	[10]

Table 2. QD-based fluorescent probes for determination of pharmaceuticals.

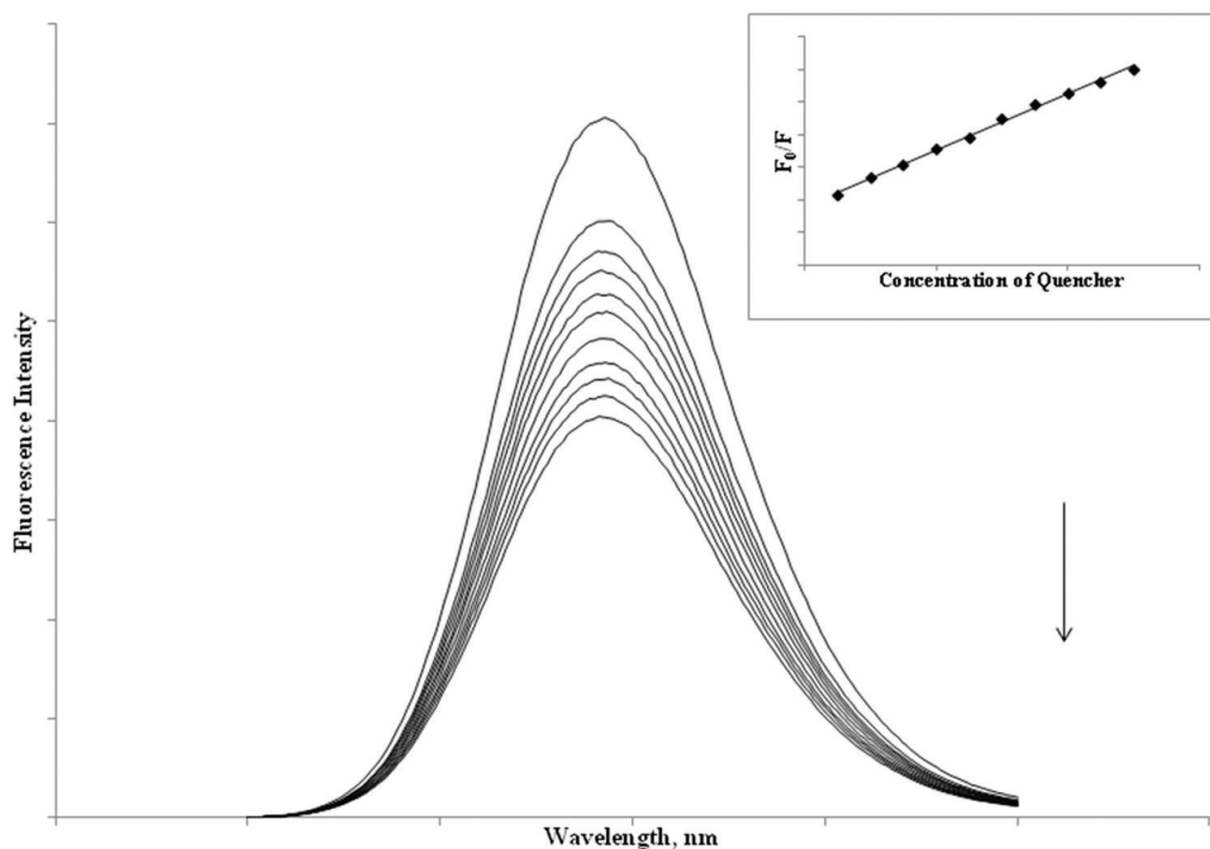


Figure 3. The general aspect of fluorescence spectra of QDs at different concentration of quencher. The inset is the calibration curve of F_0/F versus the concentration of quencher.

Yu et al. have developed a fluorescence switch sensor consisting of Mn-doped CdTe QDs-methyl viologen (MV^{2+}) nanohybrids to analyze bioactive peptide glutathione (GSH). Characterization of QDs was performed by TEM, XRD, and FT-IR methods. The results obtained from these studies showed that prepared QDs were monodisperse and have spherical shape with sizes 20 nm and hexagonal crystalline structure. In addition, TGA molecules and QDs conjugated successfully. In the sensor, MV^{2+} has two quaternary ammonium groups which link TGA on the surface of QDs through electrostatic interaction. Because of the electron transfer between QDs and quencher, the fluorescence signal is quenched. As the addition of GSH, the peptide can effectively replace TGA ligands on the surface of QDs, and fluorescence intensity is again recovered. Fluorescence recovery level of QDs is depended to the amount of GSH [102].

Synthesized by sonochemical technique, TGA-capped CdTe is used as a fluorescent probe for determination of doxycycline (DC), a member of tetracycline antibiotics, in honey and human serum. Prepared QDs were identified by FT-IR. In here, the peak related to SH group of TGA was not observed in the spectrum of TGA-QDs hybrids due to interaction between thiol and CdTe QDs. Furthermore, the TEM images showed that size distribution and shape were 4–6 nm and spherical, respectively. Similar to previous studies, the fluorescence intensity of QDs was quenched by adding of DC. To identify the mechanism of quenching process,

Stern-Volmer equation has been plotted at a different temperature. Obtained results showed that the quenching mechanism was dynamic [103].

L-Cysteine is also widely used surface modification agent which gives hydrophilic character to QDs. L-Cysteine-coated CdS QDs have prepared, characterized, and used to analyze ceftriaxone (CFX) in biological samples [104]. Optical characterization was identified by fluorimetry and UV-vis spectrometry. QDs have a broad absorption band in pH 7 buffer solution. Moreover, symmetric and narrow emission peak was at around 556 nm with excitation wavelength 359 nm. Recorded FT-IR spectra indicated that characteristic S-H band was absent in the L-cysteine-capped QDs. Also, the band at 3175 cm^{-1} belongs to CFX was not seen in the spectrum of L-cysteine/QDs/CFX complex. Prepared and characterized QDs were used in determination of CFX in urine. The effects of reaction time, temperature, and pH were identified, and 10 min, 25°C , and pH 7 were selected as optimum conditions.

Liang et al. have developed a method based on the quenching of the fluorescence of CdSe QDs by spironolactone in organic media. CdSe QDs were prepared from CdO as a precursor and stearic acid. After heating step under Ar flow, trioctylphosphine oxide and hexadecylamine were added, heated again at high temperature, and Se solution was injected. Obtained dried nanoparticles were redispersed in hexane. The emission spectra of QDs were recorded after titration with spironolactone [105].

Core-shell nanoparticles were also used for sparfloxacin in tablets. Water-soluble CdSe/CdS QDs modified with TGA have been synthesized and acted as a fluorescent probe. Hyperchromicity and forming of new absorption band were observed when the spectra of CdS and CdSe/CdS QDs were compared. This result indicated that CdS coated the surface of CdSe. After optimization of working conditions, TGA-capped CdSe/CdS QDs was used for the determination of sparfloxacin. Quenching mechanism was found static according to results of Stern-Volmer equation [106].

Besides these applications, fluorescence enhancement method has been developed for the determination of pharmaceuticals. Pawar et al. has used MPA-modified CdS nanoparticles as a turn-on probe to determine penicillamine. The obtained results showed that QDs aggregated after addition of the drug, the average size of QDs increased, and the fluorescence intensity of QDs was enhanced due to the interaction between QDs and penicillamine [107].

Nowadays, innovations and applications related to QDs are continuously increased. One of these is the using of QDs in automated systems. Rifampicin and rifaximin, which are complex macrocyclic antibiotics, have been analyzed by automated QDs-based analytical method using flow system. The automated flow system allows repeatable handling solutions, automation, miniaturization, lower reagent consumption, and waste. In this method, in the initial status, carrier ($\text{Na}_2\text{CO}_3/\text{NaHCO}_3$ buffer solution) flowed through the flow cell, and then valves of sample solutions and QDs were switched on. The analytical signal of QDs-sample mixture was recorded. A blank signal which is only QDs signal was also recorded before any sample analysis [108].

Most inorganic QDs such as CdX nanoparticles consist of highly toxic heavy metal ions, and this could be a major concern for *in-vivo* applications. Therefore, novel fluorescence

carbon-based nanoparticles have found wide using area in this field. They have some advantages over traditional QDs, for example, free of heavy metal ions, low toxicity, and excellent biocompatibility [10, 109]. Due to their small molecular mass, carbon nanoparticles easily enter the living cell and allow *in-vivo* monitoring [110]. Huang et al. have developed a sensitive method for the determination of ceftazidime and cefepime in their pharmaceutical forms based on fluorescence quenching of poly(ethylene glycol) (PEG) 2000-capped carbon QDs. The chemical oxidation method was used for preparation of nanocrystals. In this method, sawdust as a carbon source and nitric acid were mixed and heated. Then, pH of the solution was adjusted to neutral by adding NaOH and centrifuged. In the last step, for surface modification, PEG 2000 was added and heated in a microwave oven. Obtained carbon nanoparticles were characterized by TEM, and size of them was found in between 5 and 8 nm. Developed QDs were used for determination of drugs and method was sensitive, selective, and with high recovery value [10].

Functionalized semiconductor QDs have been used as fluorescence labels for biological detection and imaging. For example, avidin, highly positively charged tetramer, and functionalized CdSe/ZnS QDs were used in the detection of biotin [111]. Similarly, different sizes CdSe/ZnS QDs conjugated with different antibodies have been applied for simultaneous detection of four toxins (Shiga-like toxin 1, staphylococcal enterotoxin B, cholera toxin, and ricin) [112]. In another example, determination of 17β -estradiol has been done by using biotin-labeled antirabbit IgG and streptavidin conjugated by QDs [113]. As mentioned above, carbon-based QDs have low toxicity and biocompatibility. Li et al. have developed glucose sensor based on combining electrostatic attraction between anionic fluorescent carbon QDs that bear polar carboxy and hydroxy groups and cationic boronic acid-substituted bipyridinium salt. The interaction between them results in the formation of a ground state complex leading to a decrease in the fluorescence intensity. When glucose is added to the medium, the tetrahedral anionic glucoborane esters are formed which effectively neutralize the net charge of the cationic bipyridinium and recover the fluorescence intensity of QDs [114].

3.2. Fluorescence resonance energy transfer (FRET)

Fluorescence resonance energy transfer (FRET) is a powerful technique describing energy transfer between two light-sensitive molecules. In here, an excited donor chromophore group transfers energy to an acceptor chromophore through the nonradiative coupling. The efficiency of this energy transfer depends on the distance between both fluorophores, inversely proportional to the sixth power of the distance between acceptor and donor; therefore, FRET is more sensitive to small changes in distance [115, 116]. Photoemission properties and high QY of QDs allow efficient energy transfer when compared with the organic dyes. In addition, distinguishing the emission of the donor from acceptor is much easier due to narrow and symmetric emission spectrum of QDs. This technique is a useful tool to analyze biomolecules such as proteins and DNA. For this purpose, a FRET-based bioassay was developed by using QDs (donor) functionalized with a label (i.e., protein, antibody) which recognizes and binds to target. When FRET process occurs, the bioconjugate captures the dye-labeled

analog (acceptor), and fluorescence quenching takes place. In addition of target molecule to the medium, analyte competes with its analog and binds to the label. The acceptor is displaced from QD surface; thus, fluorescence enhancement is observed. Besides, different approaches have been developed toward the use of QDs in FRET assays, such as analyte displaces fluorescent ligands, analyte cleaves donor-acceptor linkage, analyte changes the conformation of acceptor-donor linkage, and analyte mediates donor-acceptor binding [117].

Several studies can be found that develop FRET-based assays for the detection of pharmaceuticals and biomolecules (**Table 3**). Generally, QDs and organic dye are used as donor and acceptor, respectively. However, the opposite situation, in which dye acted as a donor and QDs as acceptors, has been reported. Briefly, QD as a donor in an excited state transfers its excitation energy to an acceptor non-fluorescent dye in a nonradiative fashion. When the analyte introduces the medium, analyte replaces the dye, and fluorescence emission is recovered (**Figure 4**).

Similarly in this approach, amantadine has been determined in pharmaceutical form by using FRET mechanism. The optical sensor was designed by using water-soluble β -cyclodextrin (CD)-functionalized CdTe QDs and Rhodamine B (RB). The interior of the β -CD is not hydrophobic but considerably less hydrophilic than the aqueous environment and thus able to host other hydrophobic molecules. Therefore, RB could enter the cavity of β -CD by hydrophobic interaction, and the FRET process occurred between QDs (donor) and RB (acceptor). When amantadine introduced the system, it replaced RB in the cavity; the process of FRET was switched off. The authors also have used the developed sensor for *in-vivo* imaging. For this purpose, functionalized QDs with amantadine in the cavity were incubated with HepG2 cells and observed in the cytoplasm by fluorescence microscope [118].

Analyte	Donor	Acceptor	Detection limit	Ref.
Amantadine	β -CD-functionalized CdTe	Rhodamine B	8.82×10^{-6} mol/L	[118]
Atrovastatin/linezolid	β -CD-conjugated CdSe/silica atrovastatin and linezolid	Atrovastatin/linezolid	–	[119]
Vitamin B12	MPA functionalized CdS	Vitamin B12	$6.91 \mu\text{g mL}^{-1}$	[120]
DNA	Streptavidin-coated QDs	Cyanine dye		[121]
Biomarkers	Streptavidin labeled lanthanide complexes (europium and terbium)	Biotin coated CdSe/ ZnS	0.10–0.63 pM	[122]
Estradiol	Lanthanide (III), europium and terbium, chelate	Protein-coupled CdTe QDs	–	[123]

Table 3. FRET-based fluorescent probes for determination of pharmaceuticals.

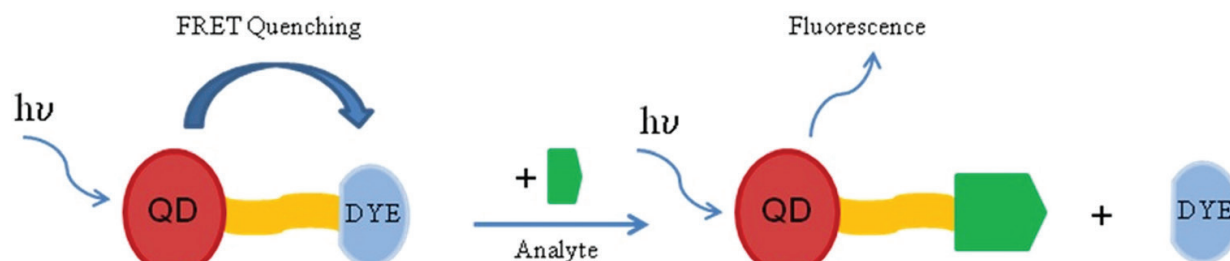


Figure 4. Schematic diagram of the quantum-dot based FRET sensor. QDs (donor) and non-fluorescent organic dye (acceptor).

Antony et al. [119] also used β -CD-conjugated CdSe/silica nanoparticles for determination of atrovastatin and linezolid. The FRET system occurred between CdSe/SiO₂ nanoparticles and the drugs encapsulated in the CD cavity. Coating and conjugation of prepared QDs were identified by FT-IR. FTIR spectra of CdSe and CdSe/SiO₂- β -CD complex were recorded and vibration bands at 1031.92 and 1117.29 cm⁻¹ appeared due to Si—O—Si bond. The Fröster distance between the encapsulated drugs and the CdSe nanoparticles was calculated and found below 3 nm.

More simple FRET method has been developed for analysis of Vitamin B12 in human serum, urine, and pharmaceutical forms. Herein, the MPA functionalized CdS QDs synthesized from cadmium chloride and sodium sulfide in aqueous media by a chemical method. FRET-based quenching mechanism was due to photoinduced charge transfer from QDs to drug. For investigation, the quenching mechanism, UV-vis absorption, and fluorescence spectra of QDs in the absence and presence of vitamin B12 were examined. Obtained results show that energy transfer from CdS QDs to vitamin B12 could occur with high probability resulting in the fluorescence quenching of QDs. Under the optimized conditions, the relationship between the fluorescence intensity of QDs and concentration of vitamin B12 was linear, and limit of detection was found as 6.91 $\mu\text{g mL}^{-1}$ [120].

Zhang et al. [121] has developed a method for detection of DNA using commercially available streptavidin-coated QDs. In this method, nanoparticle and cyanine dye were donor and acceptor, respectively. Cyanine-labeled DNA was assembled onto the QDs surface by specific streptavidin-biotin binding. The binding of molecules to QDs resulted in the formation of QD/DNA/Dye complexes. FRET was occurred between QDs and dye by excitation with the appropriate wavelength.

The use of QDs as energy acceptors in FRET-based techniques is not so common. QDs were inadequate acceptors when compared with molecular dyes because of a longer lifetime of QDs [95]. In addition to this, the donor used has to emit luminescence at a wavelength shorter than that of the QDs to allow the FRET process. A method based on this technique has been developed by Geissler et al. Herein, FRET process was realized between visible-emitting lanthanide complexes of europium and terbium, streptavidin labeled (as a donor) to CdSe/ZnS biotin-coated QDs (as acceptor). Developed method has been used for determination of five biomarkers [122]. Similarly, determination of estradiol was examined by using luminescent energy transfer between protein-coupled CdTe QDs and lanthanide (III), europium and terbium, chelate [123].

3.3. Chemiluminescence

Chemiluminescence (CL) is typically defined as the emission of light, as the result of a chemical reaction. Generally, chemiluminescent reactions show weak luminescence due to low QY. Therefore, it is necessary to enhance the CL intensity for analytical applications. For this reason, QDs have attracted great attention due to their properties as mentioned before such as brightness and reactivity. In addition, the use of QDs as chemiluminescent probe can give an advantage such as the emission at wide range wavelengths without light source [47, 124]. Nowadays, high-quality semiconductor QDs (core or core-shell) can be easily synthesized and have been used in CL systems such as CdTe, CdSe, and CdSe/CdS. Besides, doped QDs are also used in CL assays because of their catalytic features. The advances of using QDs in CL not only expand conventional usage of them but also give an opportunity to develop new nanomaterials.

There are three possible mechanisms that could be explained for the enhancement of CL by QDs as explained by Frigerio et al. [47]: (i) as emitter species after direct oxidation; direct oxidation happens when QDs is an only luminescent compound in the system; (ii) as a catalyst of a reaction involving others luminophores; when more than one luminophores exist in the system, the final emitter is the luminophores due to the catalytic effect of QDs; and (iii) as emitter species after chemiluminescence resonance energy transfer (CRET); the difference from catalytic effect, the final emitter is QDs.

Chen et al. have used MPA-capped CdTe QDs in H_2O_2 - HCO_3^- CL system and applied for the determination of ascorbic acid in serum [125]. The chemical process followed; peroxy-monocarbonate (HCO_4^-) was formed by reaction of hydrogen peroxide and sodium hydrogen carbonate. This unstable compound decomposed and caused to form superoxide ion radical ($\cdot\text{O}_2^-$) and finally singlet oxygen molecules with emission after several chemical steps. Radical scavenger, ascorbic acid, was used to study the emitting species. The proposed reaction mechanism based on the presence of four emitters: $^1\text{O}_2$, $(\text{O}_2)_2^*$, $(\text{CO}_2)_2^*$, and CdTe^* in the system. Authors also explained that the CL emission intensity depended on sizes of QDs, bigger nanoparticles decreased CL intensity.

In another work, Khateee et al. [126] used a flow-injection analysis system to investigate KMnO_4 -morin sensitized with CdS QDs and applied it to environmental water samples and pharmaceutical forms for determination of nalidixic acid. In addition, luminescence intensity was enhanced not only by adding L-cysteine-capped CdS QDs but also nalidixic acid. Possible CL mechanism was based on oxidation of morin and CdS by KMnO_4 in acidic media. Moreover, obtained UV-vis and luminescence spectrum showed that transmission of the energy of excited morin to CdS QDs can occur. According to the spectral knowledge, the addition of nalidixic acid to KMnO_4 -morin-CdS QDs system cannot generate new luminophore species. The final emitter species in the mentioned CL system is excited CdS QDs.

The same group also used a similar QDs system for the baclofen analysis in water samples and pharmaceutical forms. Various oxidants in basic and acidic aqueous medium were examined, and the best results were obtained with KMnO_4 in acidic media. In addition, $\text{Na}_2\text{S}_2\text{O}_3$ significantly enhanced the CL intensity of KMnO_4 L-cysteine-caped CdS QDs, while adding

of baclofen caused inhibition of intensity. There are two emissions bands observed, attributed to CdS QDs (at around 520 nm) and excited manganese (at around 725 nm). The process of CL is that (i) KMnO_4 oxidizes the L-cysteine to produce excited L-cysteine, (ii) excited L-cysteine transforms its energy to CdS QDs, and (iii) excited QDs produce the emission. Furthermore, the inhibition effect of baclofen was explained by incorporation of baclofen and KMnO_4 . The consumption of KMnO_4 by baclofen leads to decrease in the amount of excited CdS QDs and then CL emission [127].

QDs can be used in CL system as a catalyst, due to the redox properties of both conduction and valence bands. Imani-Nabiyi and Sorouraddin showed that the CL emission was enhanced by combination of cysteine-capped CdTe QDs and luminol in the presence of KIO_4 . The amplified CL was effectively quenched in the presence of naphazoline. According to spectroscopic and chemical investigations, weak CL emission was observed with the reaction between periodate and luminol in alkaline conditions; however, adding of QDs caused increasing of the CL emission. Based on these data, this phenomenon was explained by author that QDs could interact with the reactants catalytically and caused to form reactive oxygen species which reacts with luminol in order to give emission [128].

3.4. Chemiluminescence resonance energy transfer (CRET)

CRET is a nonradiative transfer of energy between chemiluminescent donors to a fluorophore acceptor. An essential condition is that there should be an overlap between CL emission spectrum and the absorption spectrum of the fluorescent acceptor. QDs are well-suited fluorescent acceptors due to their broad excitation spectra. In CRET, QDs are the final emitters, which can be confirmed by the emitted spectra. However, sometimes, it is also possible that direct oxidation and CRET take place simultaneously; thus with CRET, it is difficult to define that the excited forms of QDs are formed by a resonance energy transfer process or a redox process.

The water-soluble MPA-capped CdTe QDs as sensitizers are used for the chemiluminometric determination of the anti-diabetic drugs gliclazide and glipizide in their pharmaceutical formulations. Both glipizide and gliclazide quenched the CL emission of the $\text{Ce(IV)}\text{-SO}_3^{2-}\text{-CdTe}$ QD system, probably due to radical scavenging activity [129].

Golub et al. demonstrated CRET system for highly sensitive detection of DNA by the labeling of the probe-analyte complex with a hemin/G-quadruplex nanostructure [130]. The emission of CdS QDs was observed by stimulation with hemin/G-quadruplex-catalyzed luminol- H_2O_2 system. The detection limit for DNA is 2 nmol L^{-1} .

Similar nanostructure was modified with glucose oxidase and conjugated to CdSe/ZnS QDs for the CL detection of glucose. The glucose oxidase catalyzed the oxidation of glucose to compose gluconic acid and H_2O_2 . Then, in the presence of luminol catalyzed by hemin/G-quadruplex generated strong CL, which initiated a CRET process to the CdSe/ZnS QDs. Quantitative determination of glucose can be realized from the luminescence intensity of the QDs. The detection limit of glucose was calculated to 5 mmol L^{-1} [131].

3.5. Phosphorescence

Phosphorescence is the radiative transition from the lowest excited triplet state, T_1 , to the (singlet) ground state, S_0 . On the contrary to fluorescence (singlet-singlet transition), phosphorescence is a spin-forbidden process [100]. In order to obtain phosphorescence, the phosphorophore is excited by electromagnetic radiation of the appropriate wavelength. If S energy levels and T energy levels are close, some of the excited molecules can drop into the T state through an intersystem crossing. The intersystem crossing quantum efficiency can be enhanced by different approaches such as cryogenic conditions, micelle, and heavy atom effect. Phosphorescence techniques have advantages over the fluorescence methods such as selectivity, sensitivity, longer emission lifetime, and a wider gap between excitation and emission spectra. The longer lifetime of the triplet excited state allows using an appropriate delay time so that possible spectral interferences coming from system and light scattering can be avoided [132].

The optical, electrical, and magnetic character of QDs can be modified by using different types of dopants. Compared with traditional QDs such as CdSe, ZnS is a more attractive host nanoparticle for doping to form new type of QDs. Doping Mn^{2+} into ZnS QDs provides unique phosphorescence properties. Mn-doped ZnS QDs exhibit phosphorescence emission, which is produced by the energy transfer from the band gap of ZnS to Mn^{2+} dopant and the subsequent transition from the triplet state to the ground state of the Mn^{2+} involved in the ZnS host lattice [133]. Similar to fluorescent methods, mechanism of the system is quenching of phosphorescence emission of QDs. Adding quencher to QDs solution causes decrease of phosphorescence intensity due to adsorption onto the surface of QDs. When added, analyte interacts with the quencher, the new complex molecule is formed, and phosphorescence intensity is recovered due to removal of quencher from the surface. This type of QDs has been used in the phosphorescent sensing of drugs and biomolecules without any sample pretreatment [12].

General synthesis process of Mn-doped ZnS was explained by He et al. [134]. Briefly, capping agent such as L-cysteine and MPA, $ZnSO_4$, and $MnCl_2$ were added to a flask. pH of the mixture was adjusted to 11 with NaOH. Then, after air was removed with argon purging at room temperature, Na_2S was quickly added to the solution. The mixture was stirred, and then, the solution was aged at $50^\circ C$ under open air to form capped Mn-doped ZnS QDs. The heating step is vital for synthesis. For example, the phosphorescence spectrum of L-cysteine-capped Mn-doped ZnS QDs exhibited a maximum phosphorescence emission peak at 590 nm when excited at 290 nm. This peak was not observed without the aging step; however, after aging step, the peak appeared [39].

He et al. report Mn-doped ZnS QDs for the RTP detection of enoxacin in biological fluids. The fluorescence spectra of the Mn-doped ZnS QDs show two emission bands, at 435 and 590 nm, while the phosphorescence spectra exhibit only a single-emission peak at 590 nm. The emission at 590 nm presents typical characteristics of an RTP and shows a long decay time of 2 ms because of intersystem crossing. Reported Mn-doped ZnS QDs-based RTP method was not need the using of oxygen scavenger and other inducers and allowed the detection of enoxacin

in biological fluids without interference from autofluorescence and the scattering light of the matrix [134].

In phosphorescence study, not only uncapped but also capped QDs are used. For this purpose, widely used capping agents are MPA and L-cysteine. For example, MPA-capped Mn-doped ZnS QDs/CTAB nanohybrids were prepared through electrostatic self-assembly and applied to detection of rutin [135]. Cetyltrimethyl ammonium bromide (CTAB) is a cationic surfactant and has high stability to chemicals, heat, light, pressure, and pH; therefore, CTAB-based nanohybrid also shows highly stable features. Besides, adding of CTAB to QDs causes enhancement of phosphorescence intensity. Quantitative determination of rutin was done by using of linearity of RTP quenching value of QDs and rutin concentration.

N-acetyl-L-cysteine (NAC) and L-cysteine-capped Mn-doped ZnS QDs (NAC-Mn/ZnS QDs and L-cysteine-Mn/ZnS QDs) were prepared by hydrothermal methods and used for determination of L-ascorbic in the human serum sample. The characterization of QDs was made by TEM. Both NAC and L-cysteine-capped QDs were of spherical shape with size 8–10 nm. FT-IR spectra of NAC-capped QDs showed that the band of sulfhydryl group disappeared, and the band of carboxyl group was shifted. When it comes to L-cysteine spectra, their S–H vibration band disappeared. These results indicated that NAC and L-cysteine capped the QDs successfully. The proposed method was selective and sensitive. The Stern-Volmer plot and phosphorescence decay of nanohybrid QDs indicated the dynamic quenching mechanism [136].

Similar QDs system was applied to the investigation of the interaction of anticancer drug and DNA. Herein, L-cysteine capped Mn-doped ZnS QDs/idarubicin (IDA) nanohybrid was used as a phosphorescent probe. IDA was adsorbed on the surface of Mn-doped ZnS QDs and quenched of phosphorescence signal. With the addition of ds-DNA, IDA interacts with DNA, desorbed from the surface of the QDs, and the phosphorescence signal is increased. The quenching mechanism of phosphorescence of QDs by IDA was a combined dynamic and static quenching [12].

Same mechanism was used to investigate anticancer drug sanguinarine and DNA interaction [53]. Sanguinarine can adsorb on the surface of Mn-doped QDs and quench the phosphorescence emission. When the G-quadruplex-sanguinarine complex formed, the phosphorescence intensities of the QDs sensors would be restored.

The macromolecules such as DNA and ATP are also used for capping agents. An ultrasonic-assisted approach was developed for the synthesis of adenosine triphosphate (ATP)-capped Mn-doped ZnS QDs. The prepared QDs were combined Mg^{2+} -ATP-arginine ternary system and used a phosphorescent probe to detect arginine and methylated arginine [137]. The supramolecular interactions of Mg^{2+} and arginine with ATP have been investigated. Arginine and Mg^{2+} acted as a cofactor, interacted specifically, and catalyzed the hydrolysis of ATP. The binding of ATP-capped Mn-doped ZnS QDs to arginine in the presence of Mg^{2+} caused to quenching of the phosphorescence intensity of the QDs, which allowed detection of arginine with a detection limit of 0.23 mM.

Phosphorescent QDs have been used as a probe in numerous bioanalysis such as for nucleic acid or protein detection. Gong et al. developed riboflavin (RF)-modulated MPA-capped Mn-doped ZnS QDs and utilized as RTP sensor for DNA detection. As an electron acceptor, RF could quench the RTP emission of QDs via photo-induced electron transfer (PIET) and form Mn-doped ZnS QDs/RF nanohybrids by electrostatic attraction. RF also effectively interacted with DNA in groove-binding mode. In Mn-doped ZnS QDs/RF nanohybrids system, adding of DNA to medium caused the removal of RF from the surface of QDs due to interaction with DNA double helix. Therefore, releasing the RTP of Mn-doped ZnS QDs was observed. The degree of recovery of Mn-doped ZnS QDs depended on DNA concentration. The developed QD-based RTP sensor acted in a turn-on mode and offered high sensitivity to DNA [138].

Another study for detecting DNA is based on self-assembly of nanohybrids from octa(3-aminopropyl) octasilsequioxane octahydrochloride (OA-POSS) and MPA-capped Mn-doped ZnS QDs (MPA-1) [139]. OA-POSS has eight quaternary ammonium groups on each corner and acts as cubic linkers between MPA-1 through electrostatic interaction. MPA-1 and OA-POSS form spherical nanohybrids (1/OA-POSS) in aqueous solution with these linkers. DNA possesses negative charge in phosphate groups and competes with MPA-1 for forming complexes with OA-POSS. This competition led to the decrease of the emission intensity of 1/OA-POSS nanohybrids and allows developing a method for quantitative determination of DNA.

4. Conclusions

A pervasive trend in the pharmaceutical and biomedical analysis is the development of ultra-sensitive and high-throughput technologies for the rapid detection and quantification of drugs, proteins, and nucleic acid. QDs have an important role in this field. QDs have unique structural and surface properties such as stability, tunable size, wide spectrum band, and large surface-to-volume ratio that have enabled a new avenue of research to be opened. QD-based nanotechnology will be constantly expanding its applications due to their continued development of specialized nanoparticles. Chemical-surface modifications of the QDs allow enhancing the selectivity of the systems and to profit from their favorable emission features. Moreover, different approaches such as the combination of the nanoparticles with energy-transfer processes and phosphorescence detection are helping to open new research areas. These intelligent, multifunctional, low-toxic or nontoxic nanoparticles are achievements for the future.

Author details

Hayriye Eda Şatana Kara* and Nusret Ertas

*Address all correspondence to: eda@gazi.edu.tr

Department of Analytical Chemistry, Faculty of Pharmacy, Gazi University, Ankara, Turkey

References

- [1] Costa-Fernandez JM, Pereiro R, Sanz-Medel A. The use of luminescent quantum dots for optical sensing. *Trends in Analytical Chemistry*. 2006;**25**:207-218
- [2] Niemeyer CM. Nanoparticles, proteins and nucleic acids: Biotechnology meets materials science. *Angewandte Chemie International Edition*. 2001;**40**:4128-4158
- [3] Murphy CJ, Coffey JL. Quantum dots: A primer. *Applied Spectroscopy*. 2002;**56**:16A-27A
- [4] Kuang H, Zhao Y, Ma W, Xu L, Wang L, Xu C. Recent developments in analytical applications of quantum dots. *Trends in Analytical Chemistry*. 2011;**30**:1620-1635
- [5] Ozkan M. Quantum dots and other nanoparticles: What can they offer to drug discovery?. *Drug Discovery Today*. 2004;**9**:1065-1071
- [6] Yoffe AD. Semiconductor quantum dots and related systems: Electronic optical, luminescence and related properties of low dimensional systems. *Advances in Physics*. 2001;**50**:1-208
- [7] Efros AL, Rosen M. The Electronic structure of semiconductor nanocrystals. *Annual Review of Material Sciences*. 2000;**30**:475-521
- [8] Gill R, Zayats M, Willner I. Semiconductor quantum dots for bioanalysis. *Angewandte Chemie International Edition*. 2008;**47**:7602-7625
- [9] Ma J, Wang F, Fan M, Wang T, Bian W, Shuang S. Phosphorescence detection of hydrochlorothiazide using Mn-doped ZnS quantum dots. *Analytical Methods*. 2013;**5**:6094-6099
- [10] Huang Y, Zhang Y, Yan Z, Liao S. Assay of ceftazidime and cefepime based on fluorescence quenching of carbon quantum dots. *Luminescence*. 2015;**30**:1133-1138
- [11] Lopez JJ, Molina-Garcia L, Rodrigues SSM, Santos JLM, Ortega-Barrales P. Automated determination of rifamycins making use of MPA-CdTe. *Journal of Luminescence*. 2016;**175**:158-164
- [12] Ertas N, Satana Kara HE. L-Cysteine capped Mn-doped ZnS quantum dots as a room temperature phosphorescence sensor for in-vitro binding assay of idarubicin and DNA. *Biosensors and Bioelectronics*. 2015;**70**:345-350
- [13] Chan WC, Nie S. Quantum dot bioconjugates for ultrasensitive nonisotopic detection. *Science*. 1998;**281**:2016-2018
- [14] Hoshino A, Hanaki KI, Suzuki K, Yamamoto K. Applications of T-lymphoma labeled with fluorescent quantum dots to cell tracing markers in mouse body. *Biochemical and Biophysical Research Communications*. 2004;**314**:46-53
- [15] Parak WJ, Gerion D, Pellegrino T, Zanchet D, Micheel C, Williams SC, et al. Biological applications of colloidal nanocrystals. *Nanotechnology*. 2003;**14**:R15-R27
- [16] Jaiswal JK, Mattoussi H, Mauro JM, Simon SM. Long-term multiple color imaging of live cells using quantum dot bioconjugates. *Nature Biotechnology*. 2003;**21**:47-51

- [17] Dahan M, Levi S, Luccardini C, Rostaing P, Riveau B, Triller A. Diffusion dynamics of glycine receptors revealed by single-quantum dot tracking. *Science*. 2003;**302**:442-445
- [18] Wu X, Liu H, Liu J, Haley NK, Treadway JA, Larson JP, et al. Immunofluorescent labeling of cancer marker Her2 and other cellular targets with semiconductor quantum dots. *Nature Biotechnology*. 2003;**21**:41-46
- [19] Larson DR, Zipfel WR, Williams RM, Clark SW, Bruchez MP, Wise FW, et al. Water-soluble quantum dots for multiphoton fluorescence imaging *in vivo*. *Science*. 2003;**300**:1434-1436
- [20] Dubertret B, Skourides P, Norris DJ, Noireaux V, Brivanlou AH, Libchaber A. *In vivo* imaging of quantum dots encapsulated in phospholipid micelles. *Science*. 2002;**298**:1759-1762
- [21] Akerman ME, Chan WC, Laakkonen P, Bhatia SN, Ruoslahti E. Nanocrystal targeting *in vivo*. *Proceedings of the National Academy of Science of the United States of America*. 2002;**99**:12617-12621
- [22] Resch-Genger U, Grabolle M, Cavaliere-Jaricot S, Nitschke R, Nann T. Quantum dots versus organic dyes as fluorescent labels. *Nature Methods*. 2008;**5**:763-775
- [23] Wang F, Tan WB, Zhang Y, Fan X, Wang M. Luminescent nanomaterials for biological labeling. *Nanotechnology*. 2006;**17**:R1-R13
- [24] Pham W, Choi YD, Weissleder R, Tung CH. Developing a peptide based near-infrared molecular probe for protease sensing. *Bioconjugate Chemistry*. 2004;**15**:1403-1407
- [25] Dybiec M, Chornokur G, Ostapenko S, Wolcott A, Zhang JZ, Zajac A, et al. Photoluminescence spectroscopy of bioconjugated CdSe/ZnS quantum dots. *Applied Physics Letters*. 2007;**90**:263112
- [26] Gerion D, Chen F, Kannan B, Fu AH, Parak WJ, Chen DJ, et al. Room-temperature single-nucleotide polymorphism and multiallele DNA detection using fluorescent nanocrystals and microarrays. *Analytical Chemistry*. 2005;**75**:4766-4772
- [27] Baron R, Willner B, Willner I. Biomolecule-nanoparticle hybrids as functional units for nanotechnology. *Chemical Communications*. 2007;**4**:323-332
- [28] Ma H, Liu X, Wang X, Li X, Yang C, Iqbal A, et al. Sensitive fluorescent light-up probe for enzymatic determination of glucose using carbon dots modified with MnO₂ nanosheets. *Microchimica ACTA*. 2017;**184**:177-185
- [29] Wei F, Yu H, Hu C, Cai Z, Yang J, Liu L, et al. A simple method for copper ion determination in beverages using Mn-modified CdTe/CdS quantum dots as a fluorescence probe. *Journal of Nanoscience and Nanotechnology*. 2016;**16**:12282-12287
- [30] Uppa Y, Kulchat S, Ngamdee K, Pradublai K, Tuntulani T, Ngeontae W. Silver ion modulated CdS quantum dots for highly selective detection of trace Hg²⁺. *Journal of Luminescence*. 2016;**178**:437-445
- [31] Zhang H, Kang S, Wang G, Zhang Y, Zhaou H. Fluorescence determination of nitrite in water using prawn-shell derived nitrogen-doped carbon nanodots as fluorophores. *ACS Sensors*. 2016;**1**:875-881

- [32] Shojaei TR, Salleh MAM, Sijam K, Rahim RA, Mohsenifar A, Safarnejad R, et al. Detection of Citrus Tristeza virus by using fluorescence resonance energy transfer-based biosensor. *Spectrochimica ACTA Part A-Molecular and Biomolecular Spectroscopy*. 2016;**169**:216-222
- [33] Ahmed F, Arshi N, Dwivedi S, Koo BH, Azam A, Alsharaeh E. Low-temperature growth of ZnO nanotubes for fluorescence quenching detection of DNA. *Journal of Materials Science-Materials in Medicine*. 2016;**27**:189
- [34] Pratiwi FW, Hsia CH, Kuo CW, Yang SM, Hwu YK, Chen P. Construction of single fluorophore ratiometric pH sensors using dual-emission Mn²⁺-doped quantum dots. *Biosensors & Bioelectronics*. 2016;**84**:133-140
- [35] Chen JL, Zhu CQ. Functionalized cadmium sulfide quantum dots as fluorescence probe for silver ion determination. *Analytica Chimica Acta*. 2005;**546**:147-153
- [36] Li J, Bao D, Hong X, Li D, Li J, Bai Y, et al. Luminescent CdTe quantum dots and nanorods as metal ion probes. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*. 2005;**257-258**:267-271
- [37] Xie HY, Liang JG, Zhang ZL, Liu Y, He ZK, Pan DW. Luminescent CdSe-ZnS quantum dots as selective Cu²⁺ probe. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2004;**60**:2527-2530
- [38] Chen Y, Rosenzweig Z. Luminescent CdS Quantum dots as selective ion probes. *Analytical Chemistry*. 2002;**74**:5132-5138
- [39] Kara Satana HE, Demirhan B, Demirhan Er B. Mn-doped ZnS quantum dots as a room-temperature phosphorescent probe for analysis of glutamic in food stuff. *Turkish Journal of Chemistry*. 2016;**40**:762-771
- [40] Peng CF, Li ZK, Zhu YY, Chen W, Yuan Y, Liu LQ, et al. Simultaneous and sensitive determination of multiplex chemical residues based on multicolor quantum dot probes. *Biosensors and Bioelectronics*. 2009;**24**:3657-3662
- [41] Peng H, Zhang L, Kjallman THM, Soeller C, Travas-Sejdic J. DNA hybridization detection with blue luminescent quantum dots and dye-labelled single-stranded DNA. *Journal of American Chemical Society*. 2007;**129**:3048-3049
- [42] Bawja N, Mehra NK, Jain K, Jian NK. Pharmaceutical and biomedical applications of quantum dots, Artificial Cells. *Nanomedicine and Biotechnology*. 2016;**44**:758-768
- [43] Moriyama S, Fuse T, Suzuki M, Aoyagi Y, Ishibashi K. Four-electron shell structures and an interacting two-electron system in carbon nanotube quantum dots. *Physical Review Letters*. 2005;**94**:186806
- [44] Santos BS, Farias PMA, Fontes A. Handbook of self assembled semiconductor nanostructures for novel devices in photonics and electronics. In: Henini M, editor. *Semiconductor Quantum Dots for Biological Applications*. Netherlands: Elsevier; 2008. pp. 773-799

- [45] Peng X, Schlamp MC, Kadavanich AV, Alivisatos AP. Epitaxial growth of highly luminescent CdSe/CdS core/shell nanocrystals with photostability and electronic accessibility. *Journal of American Chemical Society*. 1997;**119**:7019-7029
- [46] Talapin DV, Rogach AL, Kornowski A, Haase M, Weller H. Highly luminescent monodisperse CdSe and CdSe/ZnS nanocrystals synthesized in a hexadecylamine–triocetylphosphine oxide–trioctylphosphine mixture. *Nano Letters*. 2001;**1**:207-211
- [47] Frigerio C, Ribeiro DSM, Rodrigues SSM, Abreu VLRG, Barbosa JAC, Prior JAV, et al. Application of quantum dots as analytical tools in automated chemical analysis: A review. *Analytica Chimica Acta*. 2012;**735**:9-22
- [48] Gerion D, Pinaud F, Williams SC, Parak WJ, Zanchet, D, Weiss, S, et al. Synthesis and properties of biocompatible water-soluble silica coated CdSe/ZnS semiconductor quantum dots. *The Journal of Physical Chemistry*. 2001;**105**:8861-8871
- [49] Bruchez M, Moronne M, Gin P, Weiss S, Alivisatos AP. Semiconductor nanocrystals as fluorescent biological labels. *Science*. 1998;**281**:2013-2016
- [50] Kim S, Bawendi MG. Oligomeric ligands for luminescent and stable nanocrystal quantum dots. *Journal of American Chemical Society*. 2003;**125**:14652-14653
- [51] Yamashita K, Nakate T, Okimoto K, Ohike A, Tokunaga Y, Ibuki R, et al. Establishment of new preparation method for solid dispersion. *International Journal of Pharmaceutics*. 2003;**267**:79-91
- [52] Miao Y, Zhang Z, Gong Y, Yan G. Phosphorescent quantum dots/doxorubicin nanohybrids based on photo-induced electron transfer for detection of DNA. *Biosensors and Bioelectronics*. 2014;**59**:300-306
- [53] Wen LN, Xie MX. Competitive binding assay for G-quadruplex DNA and sanguinarine based on room temperature phosphorescence of Mn-doped ZnS quantum dots. *Journal of Photochemistry and Photobiology A: Chemistry*. 2014;**279**:24-31
- [54] Banin U, Lee JC, Guzelian AA, Kadavanich AV, Alivisatos AP. Exchange interaction in InAs nanocrystal quantum dots. *Superlattice and Microstructures*. 1997;**22**:559-568
- [55] Rajh T, Micic OI, Nozik OJ. Synthesis and characterization of surface-modified colloidal cadmium telluride quantum dots. *Journal of Physical Chemistry*. 1993;**97**:11999-12003
- [56] Chan WCW, Maxwell DJ, Gao X, Bailey RE, Han M, Nie S. Luminescent quantum dots for multiplexed biological detection and imaging. *Current Opinion in Biotechnology*. 2002;**13**:40-46
- [57] Norris DJ, Bawendi MG. Measurement and assignment of the size dependent optical spectrum in CdSe nanocrystals. *Physical Review B Condensed Matter and Materials Physics*. 1996;**53**:16338-16346
- [58] Pinaud F, Michalet X, Bentolila LA, Tsay JM, Doose S, Li JJ, et al. Advances in fluorescence imaging with quantum dot bio-probes. *Biomaterials*. 2006;**27**:1679-1687

- [59] Yu WW, Qu L, Guo W, Peng X. Experimental determination of the extinction coefficient of CdTe, CdSe, and CdS nanocrystals. *Chemistry of Materials*. 2003;**15**:2854-2860
- [60] Kuçur E, Boldt FM, Cavaliere-Jaricot S, Ziegler J, Nann T. Quantitative analysis of the CdSe nanocrystal concentration by comparative techniques. *Analytical Chemistry*. 2007;**79**:8987-8993
- [61] Rueda D, Walter NG. Fluorescent energy transfer readout of an aptazyme-based biosensor. *Methods in Molecular Biology*. 2006;**335**:289-310
- [62] Murray CB, Norris DJ, Bawendi MG. Synthesis and characterization of nearly monodisperse CdE (E = sulphur, selenium, tellurium) semiconductor nanocrystallites. *Journal of American Chemical Society*. 1993;**115**:8706-8715
- [63] Modani S, Kharwade M, Nijhawan M. Quantum dots: A novelty of medical field with multiple applications. *International Journal of Current Pharmaceutical Research*. 2013;**5**:55-59
- [64] Pandurangan DK, Mounika KS. Quantum dot aptamers-an emerging technology with wide scope in pharmacy. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2012;**4**:24-31
- [65] Bandyopadhyay S, Menon L, Kouklin N, Zeng H, Sellmyer DJ. Electrochemically self-assembled quantum dot arrays. *Journal of Electronic Materials*. 1999;**28**:515-519
- [66] Murray CB, Kagan CR, Bawendi MG. Synthesis and characterization of monodisperse nanocrystals and close-packed nanocrystal assemblies. *Annual Review of Materials Research*. 2000;**30**(1):545-610
- [67] Tada H, Higuchi H, Wanatabe TM, Ohuchi N. *In vivo* real-time tracking of single quantum dots conjugated with monoclonal anti-HER2 antibody in tumors of mice. *Cancer Research*. 2007;**67**(3):1138-1144
- [68] Obonyo O, Fisher E, Edwards M, Douroumis D. Quantum dots synthesis and biological applications as imaging and drug delivery systems. *Critical Reviews in Biotechnology*. 2010;**30**(4):283-301
- [69] Lakshmeesha R, Afrasim M, Gowda DV, Santhosh TR, Abhilasha TP, Gritta S, Osmani RAM. Quantum dots: A new-fangled loom in drug delivery and therapeutics. *World Journal of Pharmaceutical Sciences*. 2016;**4**(4):125-134
- [70] Norris DJ, Yao N, Charnock FT, Kennedy TA. High-quality manganese-doped ZnSe nanocrystals. *Nano Letters*. 2001;**1**:3-7
- [71] Yang H, Santra S, Holloway PH. Syntheses and applications of Mn-doped II-VI semiconductor nanocrystals. *Journal of Nanoscience and Nanotechnology*. 2005;**5**:1364-1375
- [72] Sotelo-Gonzalez E, Fernandez-Arguelles MT, Costa-Fernandez JM, Sanz-Medel A. Mn-doped ZnS quantum dots for the determination of acetone by phosphorescence attenuation. *Analytica Chimica Acta*. 2012;**712**:120-126

- [73] Wei B, Jing M, Wenrong G, Dongtao Lu, Meng F, Yanli W, et al. Phosphorescence detection of L-ascorbic acid with surface-attached N-acetyl-L-cysteine and L-cysteine Mn-doped ZnS quantum dots. *Talanta*. 2013;**116**:794-800
- [74] Demirhan Er B, Demirhan B, Satana Kara HE. Room-temperature phosphorescence determination of melamine in dairy product using L-cysteine capped Mn-doped zinc sulfide (ZnS) quantum dots. *Journal of Dairy Science*. 2015;**98**:2992-3000
- [75] Wu P, He Y, Wang HF, Yan XP. Conjugation of glucose oxidase onto Mn-doped ZnS quantum dots for phosphorescent sensing of glucose in biological fluids. *Analytical Chemistry*. 2010;**82**:1427-1433
- [76] Mishra S, Tripathy P, Sinha SP. Advancements in the field of quantum dots. *International Journal of Advancements in Research & Technology*. 2012;**1**:1-5
- [77] Henini M, Sanguinetti S, Brusaferrri L, Grilli E, Guzzi M, Upward MD, et al. Structural and optical characterization of self-assembled InAs-GaAs quantum dots grown on high index surfaces. *Microelectronics Journal*. 1997;**28**:933-938
- [78] Franchi S, Trevisi G, Seravalli L, Frigeri P. Quantum dot nanostructures and molecular beam epitaxy. *Progress in Crystal Growth and Characterization of Materials*. 2003;**47**:166-195
- [79] Kim YT, Han JH, Hong BH, Kwon YU. Electrochemical synthesis of CdSe quantum-dot arrays on a graphene basal plane using mesoporous silica thin-film templates. *Advanced Materials*. 2010;**22**:515-518
- [80] Huang H, Zhu JJ. The electrochemical applications of quantum dots. *Analyst*. 2013;**138**:5855-5865
- [81] Penner RM. Hybrid electrochemical/chemical synthesis of quantum dots. *Accounts of Chemical Research*. 2000;**33**:78-86
- [82] Mangolini L, Thimsen E, Kortshagen U. High-yield plasma synthesis of luminescent silicon nanocrystals. *Nano Letters*. 2005;**5**(4):655-659
- [83] Sankaran RM, Holunga D, Flagan RC, Giapis KP. Synthesis of blue luminescent Si nanoparticles using atmospheric-pressure micro discharges. *Nano Letters*. 2005;**5**:537-541
- [84] Kortshagen U. Nonthermal plasma synthesis of semiconductor nanocrystals. *Journal of Physics D: Applied Physics*. 2009;**42**:113001
- [85] Mangolini L, Kortshagen U. Plasma-assisted synthesis of silicon nanocrystal inks. *Advanced Materials*. 2007;**19**:2513-2519
- [86] Pereira RN, Almeida AJ. Doped semiconductor nanoparticles synthesized in gas-phase plasmas. *Journal of Physics D: Applied Physics*. 2015;**48**:314005
- [87] Mao C, Flynn CE, Hayhurst A, Sweeney R, Qi J, Georgiou G, et al. Viral assembly of oriented quantum dot nanowires. *Proceedings of the National Academy of Sciences*. 2003;**100**(12):6946-6951

- [88] Borovaya MN, Burlaka O, Yemets A, Blume Y. Biosynthesis of quantum dots and their potential applications in biology and biomedicine. In: Fesenko O, Yatsenko L, editors. Nanoplasmonics, Nano-Optics, Nanocomposites, and Surface Studies. Switzerland: Springer International Publishing; 2015
- [89] Bekasova OD, Revina AA, Rusanov AL, Kornienko ES, Kurganov B. Effect of gamma-ray irradiation on the size and properties of CdS quantum dots in reverse micelles. *Radiation Physics and Chemistry*. 2013;**92**:87-92
- [90] Jovanović S, Marković Z, Budimir M, Spitalsky Z, Vidoeski B, Marković BT. Effects of low gamma irradiation dose on the photoluminescence properties of graphene quantum dots. *Optical and Quantum Electronics*. 2016;**48**:259
- [91] Jovanovic SP, Syrgiannis Z, Markovic ZM, Bonasera A, Kepic DP, Budimir MD, et al.. Modification of structural and luminescence properties of graphene quantum dots by gamma irradiation and their application in a photodynamic therapy. *ACS Applied Material Interfaces*. 2015;**7**:25865-25874
- [92] Xuan T, Wang X, Zhu G, Li H, Pan L, Sun Z. One-step microwave-assisted synthesis of water soluble CdSe quantum dots for white light-emitting diodes with excellent color rendering. *Journal of Alloys and Compounds*. 2013;**558**:105-108
- [93] Moghaddam MM, Baghbanzadeh M, Keilbachb A, Kappe CO. Microwave-assisted synthesis of CdSe quantum dots: Can the electromagnetic field influence the formation and quality of the resulting nanocrystals. *Nanoscale*. 2012;**4**:7435-7442
- [94] Kairdolf BA, Qian X, Nie S. Bioconjugated Nanoparticles for biosensing, *in vivo* imaging, and medical diagnostics. *Analytical Chemistry*. 2017;**89**:1015-1031
- [95] Esteve-Turrillas FA, Abad-Fuentes A. Applications of quantum dots as probes in immunosensing of small-sized analytes. *Biosensors and Bioelectronics*. 2013;**41**:12-29
- [96] Spanhel L, Haase M, Weller H, Henglein A. Photochemistry of colloidal semiconductors. 20. Surface modification and stability of strong luminescing CdS particles. *Journal of American Chemical Society*. 1987;**109**:5649-5655
- [97] Sooklal K, Cullum BS, Angel SM, Murphy CJ. Photophysical properties of ZnS nanoclusters with spatially localized Mn²⁺. *Journal of Physical Chemistry*. 1996;**100**:4551-4555
- [98] Moore DE, Patel K. Q-CdS photoluminescence activation on Zn²⁺ and Cd²⁺ salt introduction. *Langmuir*. 2001;**17**(8):2541-2544
- [99] Gao M, Kirstein S, Mohwald H. Strongly photoluminescent CdTe nanocrystals by proper surface modification. *Journal of Physical Chemistry B*. 1988;**102**:8360-8363
- [100] JR Lakowicz. *Principles of Fluorescence Spectroscopy*. 2nd ed. New York: Plenum Press; 1999
- [101] Constantine CA, Gattás-Asfura KM, Mello SV, Crespo G, Rastogi V, Cheng TC, et al. Layer-by-layer films of chitosan, organophosphorus hydrolase and thioglycolic acid-capped CdSe quantum dots for the detection of paraoxon. *Journal of Physical Chemistry*. 2003;**107**:13762-13764

- [102] Yu L, Li L, Ding Y, Lu Y. A Fluorescent switch sensor for glutathione detection based on Mn-doped CdTe quantum dots-methyl viologen nanohybrids. *Journal of Fluorescence*. 2016;**26**:651-660
- [103] Tashkhourian J, Absalan G, Jafari M, Zare S. A rapid and sensitive assay for determination of doxycycline using thioglycolic acid-capped cadmium telluride quantum dots. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2016;**152**:119-125
- [104] Samadi N, Narimani S. An ultrasensitive and selective method for the determination of Ceftriaxone using cysteine-capped cadmium sulfide fluorescence. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2016;**163**:8-12
- [105] Liang J, Huang S, Zeng D, He Z, Ji X, Ai X, et al. CdSe quantum dots as luminescent probes for spironolactone determination. *Talanta*. 2006;**69**:126-130
- [106] Hou M, Yan X, Xiong L. Determination of sparfloxacin with CdSe/CdS quantum dots as fluorescent probes. *Journal of Luminescence*. 2015;**157**:58-62
- [107] Pawar SP, Gore AH, Walekar LS, Anbhule PV, Patil SR, Kolekar GB. Turn-on fluorescence probe for selective and sensitive detection of d-penicillamine by CdS quantum dots in aqueous media: Application to pharmaceutical formulation. *Sensors and Actuators B*. 2015;**209**:911-918
- [108] Jimenez-Lopez J, Molina-Garcia L, Rodrigues SSM, Santos JLM, Ortega-Barrales P, Ruiz-Medina A. Automated determination of rifamycins making use of MPA-CdTe quantum dots. *Journal of Luminescence*. 2016;**175**:158-164
- [109] Lin L, Rong M, Luo F, Chen D, Wang Y, Chen X. Luminescent graphene quantum dots as new fluorescent materials for environmental and biological applications. *Trends in Analytical Chemistry*. 2014;**54**:83-102
- [110] Cao L, Wang X, Meziani MJ, Lu F, Wang H, Luo PG, et al. Carbon dots for multiphoton bioimaging. *Journal of American Chemical Society*. 2007;**129**:11318-11319
- [111] Goldman ER, Balighian ED, Mattoussi H, Kuno MK, Mauro JM, Tran PT, et al. Avidin: A natural bridge for quantum dot-antibody conjugates. *Journal of American Chemical Society*. 2002;**124**(22):6378-6382
- [112] Goldman ER, Clapp AR, Anderson GP, Uyeda HT, Mauro JM, Medintz IL, et al. Multiplexed toxin analysis using four colors of quantum dot fluororeagents. *Analytical Chemistry*. 2004;**76**:684-688
- [113] Sun M, Du L, Gao S, Bao Y, Wang S. Determination of 17 β -oestradiol by fluorescence immunoassay with streptavidin-conjugated quantum dots as label. *Steroids*. 2010;**75**:400-403
- [114] Li YH, Huang J, Liang RP, Qiu JD. Fluorescent graphene quantum dots with a boronic acid appended bipyridinium salt to sense monosaccharides in aqueous solution. *Chemical Communications*. 2013;**49**:5180-5182

- [115] Harris D. Quantitative Chemical Analysis. 8th ed. New York: W. H. Freeman and Co; 2010
- [116] Clapp AR, Medintz IL, Mattouss H. Förster resonance energy transfer investigations using quantum-dot fluorophores. *Chemical Physics and Physical Chemistry*. 2006;**7**:47-57
- [117] Coto-Garcia AM, Sotelo-Gonzalez E, Fernandez-Argüelles MT, Pereiro R, Costa-Fernandez JM, Sanz-Medel A. Nanoparticles as fluorescent labels for optical imaging and sensing in genomics and proteomics. *Analytical and Bioanalytical Chemistry*. 2011;**399**:29-42
- [118] Ai X, Niu L, Li Y, Yang F, Su X. A novel β -cyclodextrin-QDs optical biosensor for the determination of amantadine and its application in cell imaging. *Talanta*. 2012;**99**:409-414
- [119] Antony EJ, Shibu A, Ramasamy S, Paulraj MS, Enoch IVMV. Loading of atorvastatin and linezolid in β -cyclodextrin-conjugated cadmium selenide/silica nanoparticles: A spectroscopic study. *Materials Science and Engineering C*. 2016;**65**:194-198
- [120] Gore AH, Kale MB, Anbhule PV, Patil SR, Kolekar GB. A novel FRET probe for selective and sensitive determination of vitamin B12 by functionalized CdS QDs in aqueous media: Applications to pharmaceutical and biomedical analysis. *RSC Advances*. 2014;**4**:683-692
- [121] Zhang CY, Johnson LW. Quantum dot-based fluorescence resonance energy transfer with improved FRET efficiency in capillary flows. *Analytical Chemistry*. 2006;**78**:5532-5537
- [122] Geissler D, Charbonniere LJ, Ziessel RF, Butlin NG, Löhmansröben HG, Hildebrandt N. Quantum dot biosensors for ultrasensitive multiplexed diagnostics. *Angewandte Chemie International Edition*. 2010;**49**:1396-1401
- [123] Harma H, Soukka T, Shavel A, Gaponik N, Weller H. Luminescent energy transfer between cadmium telluride nanoparticle and lanthanide (III) chelate in competitive bioaffinity assays of biotin and estradiol. *Analytica Chimica Acta*. 2007;**604**:177-183
- [124] Chen H, Lin L, Li H, Lin JM. Quantum dots-enhanced chemiluminescence: Mechanism and application. *Coordination Chemistry Reviews*. 2014;**263-264**:86-100
- [125] Chen H, Lin L, Lin Z, Guo G, Lin JM. Chemiluminescence arising from the decomposition of peroxy-monocarbonate and enhanced by CdTe quantum dots. *The Journal of Physical Chemistry A*. 2010;**114**:10049-10058
- [126] Khateee A, Lotfi R, Hasanzadeh A, Iranifamb M, Joo SW. A flow injection chemiluminescence method for determination of nalidixic acid based on KMnO_4 -morin sensitized with CdS quantum dots. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2016;**154**:243-251
- [127] Khataee A, Hasanzadeha A, Iranifamb M, Jooc SW. A novel flow-injection chemiluminescence method for determination of baclofen using L-cysteine capped CdS quantum dots. *Sensors and Actuators B*. 2015;**215**:272-282

- [128] Imani-Nabiyyi A, Sorouraddin MH. Determination of naphazoline hydrochloride in biological and pharmaceutical samples by a quantum dot-assisted chemiluminescence system using response-surface methodology. *Luminescence*. 2014;**29**:994-1002
- [129] Fortesa PR, Frigerio C, Silvestre CIC, Santos JLM, Limab JLFC, Zagatto EAG. Cadmium telluride nanocrystals as luminescent sensitizers in flow analysis. *Talanta*. 2011;**84**:1314-1317
- [130] Golub E, Niazov A, Freeman R, Zatsepin M, Willner I. Photoelectrochemical biosensors without external irradiation: Probing enzyme activities and DNA sensing using hemin/G-quadruplex-stimulated chemiluminescence resonance energy transfer (CRET) generation of photocurrents. *The Journal of Physical Chemistry C*. 2012; **116**:13827-13834
- [131] Niazov A, Freeman R, Girsh J, Willner I. Following glucose oxidase activity by chemiluminescence and chemiluminescence resonance energy transfer (CRET) processes involving enzyme-DNAzyme conjugates. *Sensors*. 2011;**11**:10388-10397
- [132] Kuijt J, Ariese F, Brinkman UAT, Gooijer C. Room temperature phosphorescence in the liquid state as a tool in analytical chemistry. *Analytica Chimica Acta*. 2003;**488**:135-171
- [133] Bi L, Dong XT, Yu YH. Room-temperature phosphorescence sensor based on manganese doped zinc sulfide quantum dots for detection of urea. *Journal of Luminescence*. 2014;**153**:356-360
- [134] He Y, Wang HF, Yan XP. Exploring Mn-doped ZnS quantum dots for the room-temperature phosphorescence detection of enoxacin in biological fluids. *Analytical Chemistry*. 2008;**80**:3832-3837
- [135] Miao Y, Zhang Z, Gong Y, Zhang Q, Yan G. Self-assembly of manganese doped zinc sulfide quantum dots/CTAB nanohybrids for detection of rutin. *Biosensors and Bioelectronics*. 2014;**52**:271-276
- [136] Bian W, Mab J, Guo W, Lu D, Fan M, Wei Y, et al. Phosphorescence detection of L-ascorbic acid with surface-attached N-acetyl-L-cysteine and L-cysteine Mn-doped ZnS quantum dots. *Talanta*. 2013;**116**:794-800
- [137] Ren HB, Yan XP. Ultrasonic assisted synthesis of adenosine triphosphate capped manganese-doped ZnS quantum dots for selective room temperature phosphorescence detection of arginine and methylated arginine in urine based on supramolecular Mg^{2+} -adenosine triphosphate-arginine ternary system. *Talanta*. 2012;**97**:16-22
- [138] Gong Y, Fan Z. Room-temperature phosphorescence turn-on detection of DNA based on riboflavin-modulated manganese doped zinc sulfide quantum dots. *Journal of Fluorescence*. 2016;**26**:385-393
- [139] He Y, Wang HF, Yan XP. Self-assembly of Mn-doped ZnS quantum dots/octa(3-aminopropyl)octasilsequioxane octahydrochloride nanohybrids for optosensing DNA. *Chemistry-A European Journal*. 2009;**15**:5436-5440

