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A review on CdSe quantum dots in sensing

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ABSTRACT

The primary aim of this review is to survey the literature on the ion sensing ability of quantum dots. Sensing of both cations and anions is important, since both play significant roles in various ecological and biological processes, which makes it important to ensure their concentration at balanced level. Contamination by heavy metal ions and various anions poses a serious threat to humans, aquatic organisms, and to the environment; therefore detection of these ions (in presence of other cations and anions), which are the major cause of environmental pollution is of immense significance at the present time. Owing to their enhanced fluorescence properties and photostability, QDs offer tremendous scope to be used for ion sensing. They offer several advantages over traditional chemical fluorophores. This review throws light on the mechanism adopted by CdSe QDs to act as flourophores. Owing to their enhanced photoluminescence properties, QDs offer selective and sensitive determination of various ions, which is a function of the capping on the surface of the QD nanosensor, i.e. it is possible to tune their sensing ability by changing the capping layer, which influences the QD's interaction with various analytes. Hence, these quantum dots may prove promising candidates in future for sensing approximately all types of analytes. Copyright © 2014 VBRI press.

Keywords: Core/shell quantum dots; analyte detection; luminescence; fluorescence; fluorophore; metal ions sensing; photoluminescence; quantum dots quenching; nanonanosensors.

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Rita Kakkar, after obtaining a PhD degree in Physical Chemistry from the University of Delhi, undertook research on various topics. She has been teaching Physical Chemistry at the University of Delhi for the past three decades. Prior to that, she taught at Miranda House, University of Delhi. In the field of chemistry education, she is actively involved in designing syllabi of various universities and conducting teacher-training workshops, and for popularizing the use of Molecular Modelling in teaching chemistry. Her main research interests are in Computational Chemistry and related fields. She heads a large research group, which is carrying out computational and experimental studies on catalysis by nanomaterials and by enzymes. The focus of the research on nanomaterials is to understand the growth, morphologies and stabilities of nanocrystalline forms of metals and metal oxides, their reactivities, and their catalytic role in various reactions, particularly those involving degradation of organic pollutants. Her research on nanoscale materials also includes theoretical and experimental studies on quantum dots and their size-dependent properties for use as semiconductor devices and sensors. Professor Rita Kakkar has over 95 research publications in international journals. She has successfully supervised the work of 35 PhD and 7 MPhil students. She has delivered invited several talks at scientific conferences. She also regularly reviews manuscripts for many international journals, including those published by the American Chemical Society, Royal Society of Chemistry, Wiley and Elsevier.

Contents

1. Introduction

In recent years, there has been considerable thrust into the development of sensors in the nanoscale **[1-5]**. In this review, we discuss the recent advancements in ion sensing using CdSe based quantum dots (QDs). Since metal ions are important, both biologically and ecologically, their detection is essential. Living organisms need varying amounts of heavy metal ions. Humans mainly require metal ions such as iron (Fe), cobalt (Co), manganese (Mn), zinc (Zn), and molybdenum (Mo), but various other heavy metal ions such as lead (Pb) **[6]** and mercury (Hg) **[7]** are toxic even at very low concentration and produce serious ill-effects. These are known as toxic metal ions. The ability of toxic metal ions to cause toxicity even at moderately low concentration and their tendency to accumulate in the ecosystem, agriculture and the human body has led to special and widespread attention to them in recent years. As we know, pollution is the result of release of undesirable materials, which leads to the contamination of the environment, as a result of which we are always under the threat of living in a biosphere with some imbalance. Although there are various causes of environmental pollution, the major cause is the industrial effluents, since they ultimately end up in aquatic systems. For example, a high concentration of gaseous oxygen in the atmosphere is highly favorable for causing corrosion of metals and the metal ions from the corroded metal structures eventually enter into the aquatic media by dissolution in rain water. Also, combustion of fuels releases heavy metals and causes pollution of the environment, which further enters into the aquatic environment by the rain water. Due to the above factors, metal ion concentration in aquatic media is much higher than the tolerance limit, which further enters the biological system when the living beings intake the polluted water, and affects their physical condition. The concentration of these metal ions mainly increases in the vicinity of the dumping area and nonstop practice of waste dumping may result in further increments of metal ion aggregation and pollution of groundwater sources. Thus, heavy metal release poses severe trouble for the environment, since they cannot be biodegraded and remain in the soil/water for longer periods, thereby affecting humans and domestic animals. Hence, determination of heavy metals in the biological system and in aquatic environment has become a necessity for the well-being of society, due to their toxicity and retention by the ecological system **[8, 9]**.

Besides metal ions, various anions, such as carbonate ion (CO_3^{2-}) are important biologically, and some others such as cyanide (CN^-) are harmful. Some anions, such as nitrate ions, which are formed as a result of rain water interaction with atmospheric forms of nitrogen, are responsible for ground water pollution. In addition, various anthropogenic sources of nitrate are septic tanks, and excessive use of nitrogenous fertilizers (which leach to the ground water), applied in order to improve crop productivity. The harmful effects of nitrate are blue baby syndrome or methemoglobinomia (reduced ability of RBCs to release oxygen to tissues). Hence, preventive measures must be taken so as to avoid this situation. The concentration of all these ions should be maintained in a fine limit, as a slight excess or deficiency produces undesirable, unwanted and toxic effects. In order to minimize the pollution caused by heavy metal ions, various detection methods have been employed, such as atomic absorption spectrometry **[10]**, inductively coupled plasma mass spectrometry **[11]**, capillary electrophoresis **[12]**, X-ray fluorescence spectrometry **[13]** and microprobes **[14]** with high sensitivity, but, due to high cost, complicated instruments and the need of trained people to handle them, these are not in much use **[15]**. Thus, it is necessary to develop highly selective and responsive analytical tools to avoid the damaging effects of pollution due to heavy metals in the very early stage and has long been a focus of research. QDs offer several advantages over traditional chemical fluorophores for ion sensing. Many reports on sensing cations and anions of both biological and ecological importance using quantum dots (QDs) have been published **[1]**. In this review, we focus on the utilization of CdSe and CdSe based core/shell QDs for sensing various such ions. We first discuss quantum dots and their use as sensors.

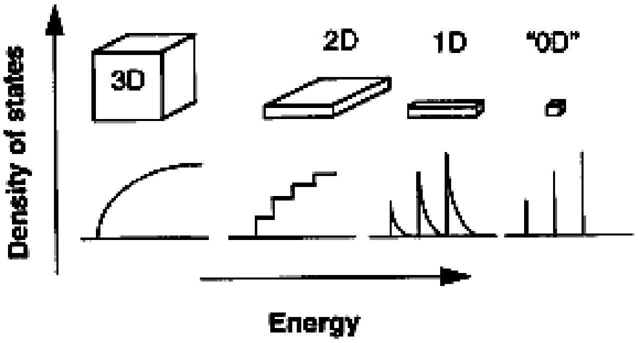

Fig. 1. Illustration of density of states in semiconductors as a function of dimension **[19]**.

2. Quantum dots

Quantum dots are a special class of inorganic semiconductor nanocrystal materials, composed of atoms of periodic groups of II-VI, III-V, or IV-VI materials. They are constrained in three dimensions to a somewhat spherical shape, typically with a diameter of 2 - 8 nm, containing approximately 200 - 10,000 atoms **[16, 17, 18]**. **Fig. 1** shows that in semiconductors, the density of states is a function of dimension, and since QDs are zero-dimensional semiconductors, their density of states is sharp and discrete **[19]**.

QDs are exciting candidates in the field of nanotechnology due to their unique optical and electronic properties, such as high quantum yield, narrow, tunable and symmetric emission spectra, broad absorption spectra, their ability to span the electromagnetic spectrum from visible to infrared and resistance towards photo-oxidation and photobleaching **[20, 21]**. They exhibit size tunable fluorescence properties and simultaneous excitation of multiple fluorescence colors due to quantum confinement effects **[22-30]**. Their long-term photostability makes them attractive in the area of sensing. Sensing by QDs is based on their fluorescence property. Fluorescence is a type of photoluminescence, but can be distinguished from other types of photoluminescence, as the excited electron returns immediately to the ground state. In earlier days and even till now, molecular sensing continues to be dominated by organic dye-based fluorescent sensors. However, QDs, the new class of fluorescent compounds, have proven to be better alternatives to conventional organic dyes and have almost replaced them due to their remarkable photophysical properties **[18]**.

Stuczynski et al. **[31]** first reported, in 1989, the formation of metal-chalcogen bonds by the reaction of metal alkyls with silyl chalcogenides. The most studied colloidal QDs are Cd-chalcogenide QDs due to the ready availability of precursors and the simplicity of crystallization. These are referred to as II-VI semiconductors due to the positions of Cd and the chalcogenide in the periodic table. Amongst all the Cd-chalcogenide QDs, the CdSe QD is found to be of great interest due to its familiar physical properties and its band-gap energy, which covers almost the whole of the electromagnetic spectrum **[32]**. It is a direct band gap semiconductor.

As a result of their unique optical and electronic properties, such as broad absorption spectra, very narrow emission spectra, long fluorescence lifetime and high photostability, CdSe nanocrystals are considered to be the ideal candidates for various applications such as in biological imaging, laser media, light emitting diodes, in photovoltaics and, most importantly, in analytical chemistry **[33-39]**. Among the various applications of CdSe QDs, in this review, we are focusing on the ion sensing abilities of CdSe based QDs and core/shell QDs, which depend on the fluorescence efficiency of the QDs. The fluorescence efficiency of QDs is found to be sensitive to the presence of and also on the nature of adsorbates at the surface of QDs **[38]**.

The remarkable properties shown by QDs are a function of their size and a consequence of the effect called the quantum confinement effect, which arises due to change in density of states **[16, 19]**. A QD-based chemical sensing system employs fluorescence changes induced by the analyte present at the surface or close to the surface of the QD. Sensing via QDs is based on the interaction of the QD with the analyte of interest, thereby influencing the optical properties, which in turn are quite sensitive to the type of capping ligand used, indicating that surface phenomenon cannot be neglected. The analyte present close to the QDs leads to dramatic changes in the luminescent properties of these QDs, i.e. results either in fluorescence quenching or enhancement, which promotes them to be applied for analytical sensing. Hence, enhancement or quenching of luminescence of QDs due to analyte-quantum dot interaction may guide researchers to design new, specific nanoparticle-based sensors **[39]**. In this review, an effort has been made to understand the mechanism employed by CdSe and CdSe based core/shell QDs to act as chemical sensors for various ions of biological and environmental interest.

3. Properties of quantum dots

3.1. Quantum confinement

A significant property which makes QDs applicable to be employed for sensing purposes arises from a property known as quantum confinement, which was first reported by Ekimov and Onushchenko in CuCl nanocrystals **[40]**. A lot of research has been done in the field of quantum confinement effect in semiconductors and in low dimensional nanostructures **[41, 42]**. This effect is the widening of the band-gap (i.e. gap between the conduction and valence band) with a reduction in the size of the QD. This effect is analogous to the "particle in a box" model in which the energy gap of the particle increases as the size of the box decreases **[18]**. It is because of the quantum confinement effect that the QDs of identical material but with dissimilar sizes display various colors **(Fig. 2) [18]**. QDs exhibit exclusive electronic and optical properties due to this effect. The band gap in a material is the energy required to create an electron and a hole at rest (i.e. with zero kinetic energy) at a distance far enough apart that their coulombic attraction is negligible. If one carrier approaches the other, they may form a bound electron-hole pair, i.e. an exciton, whose energy is a few meV lower than the band-gap. The distance between the electron and hole is known as the exciton Bohr radius **[43]**.

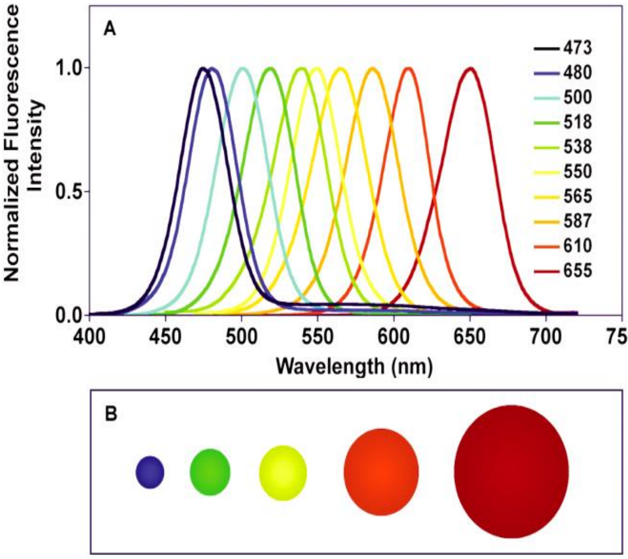

Fig. 2. (**A**) and (**B**) Illustration of size-tunable fluorescence spectra of CdSe quantum dots **[18]**.

3.2 Luminescence properties

As already discussed, CdSe QDs are nowadays being widely employed in various applications and have received extensive attention owing to their unusual electronic and optical properties. These properties can be altered by merely manipulating the number of atoms in the QDs while maintaining the same chemical composition. The optical and electronic properties of semiconductor nanoclusters come up from interactions between electrons, holes, and their local environments **[44]**. QDs undergo photoexcitation on absorption of photons when the excitation energy exceeds their band gap and electrons get promoted from the valence band to the conduction band. The electron in an excited state is a high energy electron. The excited electron and hole form an exciton. The electron and hole may recombine and relax to a lower energy state, ultimately reaching the ground state. The excess energy resulting from recombination and relaxation may be either radiative (emits photon) or nonradiative (emits phonons). The luminescence of QDs is due to radiative relaxation. Measurements of UV–visible spectra reveal a large number of energy states in QDs. A remarkable peak is observed as the first observable peak from the lowest excited energy state. Excitations at shorter wavelengths are also likely due to multiple electronic states present at higher energy levels. The size of CdSe QDs is used to tune the optical gap across a major portion of the visible spectrum **[19, 45] (Fig. 2)**. In case of CdSe QDs, the optical gap can be tuned from deep red (~1.7 eV) to green (~2.4 eV) by reducing the dot diameter from 20 to 2 nm. Thus, tuning their size allows tailoring their optical properties, thereby making QDs hopeful resources for developing various sensing devices **[46]**.

4. Surface modification of quantum dots

QDs, being nano-sized, have very high surface to volume ratio, as a result of which, most of the atoms are present on the surface. These surface atoms are with unsatisfied valencies and act as sites of preferential photodegradation and luminescence quenching, thereby making the surface of QDs highly prone to photobleaching and photooxidation. Therefore, it is highly desirable to modify the surface of these QDs with appropriate ligand molecules in order to make them suitable for interaction with various analytes. These surface ligands alter the sensitivity and selectivity of QDs towards various analytes of interest by altering their fluorescence response, and this response can be further modified by modifying the capping layer. In addition, it has been found that, for the successful development of sensors and for allowing flexibility and functionality of QDs for efficient coupling of these fluorescent probes to various analytes, a control of the surface chemistry of QDs is highly essential **[47-52].** However, studies also show that surface modification of QDs may lead to enhancement in their cellular toxicity **[53-56]**.

Alloyed QDs, which offer continuous tuning of quantum confinement by alteration in the size of the QDs or by variation of their chemical composition, have been synthesized. QDs generally do not exhibit aqueous solubility, as they are synthesized in organic solution and are surface-stabilized with hydrophobic organic ligands. Surface modification with various bifunctional ligands makes them water soluble and enhances their bio-compatibility and absorption by cells. Generally, surface modifications involve the conversion of hydrophobic ligands to hydrophilic ones on QD surfaces. This includes ligand exchange (done by exchanging the hydrophobic surfactant molecules with bifunctional molecules, i.e. molecules having a hydrophilic end on one side and a hydrophobic end on the other, the most commonly used bifunctional molecules being cysteine, mercaptosuccinic acid, glutathione and mercaptoacetic acid), silica coatings (done by introducing silica shell covering onto the QDs), adding another ligand layer, and incorporation of QDs into polymeric molecules, or by coating the hydrophobic QD surface with a cross-linked amphiphilic polymer, the hydrophilic component of which provides water solubility and the hydrophobic part interacts with the hydrophobic surface of the QD **[57]**. Various other coating techniques include electrostatic interaction, micelle encapsulation, and hydroxylation. There are various kinds of interactions by which QDs interact with biomolecules; importantly, hydrophobic and van der Waals interactions, peptide linkages or S-S disulfide bonds, and electrostatic interactions. Various reports based on the sensing capabilities of QDs focus on either organically capped or inorganically capped, i.e. core/shell QDs **[36, 58-63]**.

4.1. Organically capped quantum dots

Organic capping layer allows one to achieve colloidal suspension and the ability to bio-conjugate the QDs. However, to choose the organic ligand that bond with the surface atoms of the QDs is a very delicate subject. The most commonly used organic ligands are phosphenes (e.g., tri-n-octyl phosphene oxide–TOPO) or mercaptans (-SH). The coverage due to these ligands may be sterically hindered due to the size (which is larger than the surface site) and shape of these ligands. Some dangling bonds on the surface are always present when the surface is passivated by organic ligands, since these ligands do not passivate both the cationic as well the anionic sites. Also, QDs passivated with the organic ligands are photounstable due to weak bonding between the surface atoms and capping molecules that leads to the generation of trap states **[43, 64-67]**.

4.2. Inorganically capped QDs: Core/shell QDs

An alternative method employed for passivating the surface of QDs is by the utilization of inorganic layers, mainly a material with a larger band gap. These inorganically capped QDs are called core/shell QDs. Core/shell QDs have improved luminescence quantum yields and acquired properties due to the tailoring of relative band gap positions between the two materials **[68-75]**.

Fig. 3 shows the photoluminescence (PL) spectra of bare CdSe QDs (dashed lines) and CdSe/ZnS (solid lines) QDs. The results of Dabbousi et al. **[21]** show that the PL quantum yield increases from 5 to 15% for bare CdSe QDs to 30 to 50% for ZnS overcoated CdSe QDs. Also, the quantum yield is higher for smaller dots **[21]**. Hence, QDs passivated with inorganic material have been found to be more robust than organically passivated dots **[76]**. Some examples of core/shell quantum dot structures reported include CdS on CdSe and CdSe on CdS **[73]**, ZnS grown on CdS **[75]**, ZnS on CdSe and the inverse structure **[70]**, CdS/HgS/CdS quantum dot quantum wells **[72]**, ZnSe overcoated CdSe **[68]** and so on. **Fig. 4** illustrates the emission colors of different-sized CdSe/ZnS core/shell QDs excited with a near-UV lamp.

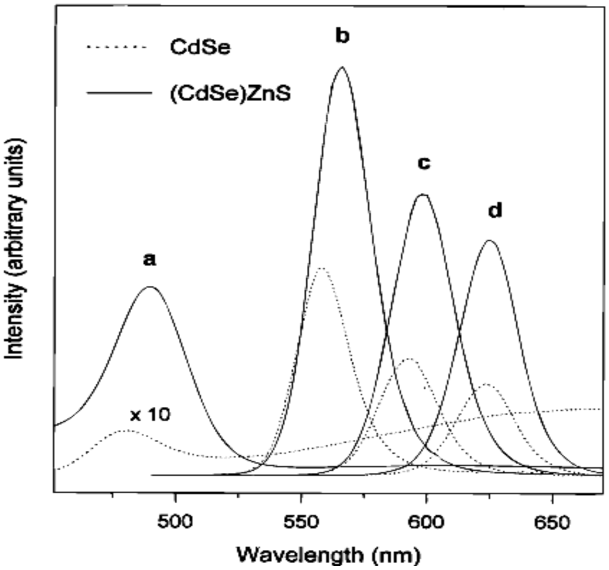

Fig. 3. Photoluminescence spectra for bare CdSe QDs (dashed lines) and CdSe/ZnS core/shell QDs (solid lines) **[21].**

Fig. 4. Ten distinguishable emission colors of ZnS capped CdSe QDs excited with a near-UV lamp. From left to right (blue to red), the emission maxima are located at 443, 473, 481, 500, 518, 543, 565, 587, 610, and 655 nm **[20]**.

4.3. Comparison with organic fluorophores

Conventionally employed organic fluorophores undergo quite severe problems, both chemically and photophysically. QDs, on the other hand, due to their unique optical and electronic properties, exhibit interesting properties, such as size tunable light emission, broad absorption spectra, narrow emission spectra, simultaneous excitation of multiple fluorescence colors, resistance against photobleaching and hence high photochemical stability which makes them superior to organic dyes and fluorescent proteins. Different excitation wavelengths are required in order to excite each organic dye in a sample of several dyes which is not required in the case of QDs due to their broad absorption spectrum which enables the excitation of a combination of QDs of different emission wavelengths with a single excitation wavelength **[19, 21, 77-80]**.

Fig. 5(A) gives the comparison of the absorption spectrum of the organic dye fluorescein isothiocyanate (FITC) with that of CdSe QDs. FITC shows a narrow absorption band and can only be effectively excited at a wavelength around 470 nm whereas QDs exhibit a broad absorption spectrum that extends from 350 nm to 520 nm. **Fig. 5(B)** reveals that the emission spectrum of QDs is sharp and symmetric, while that of FITC is broad and has a tail extending to long wavelengths **[18]**.

As can be seen from **Fig. 5**, QDs possess a broad absorption spectrum which allows the excitation of multiple fluorophores with a single light source. QDs are very much resistant to photobleaching, a common trouble with organic fluorophores **[81]**. QDs exhibits bright fluorescence due to their large molar extinction coefficients and high quantum yields **[82]**. QDs also have long fluorescence lifetimes of the order of 20-50 ns, which allow them to be distinguished from background and other fluorophores, thereby exhibiting amplified sensitivity of detection **[83]**.

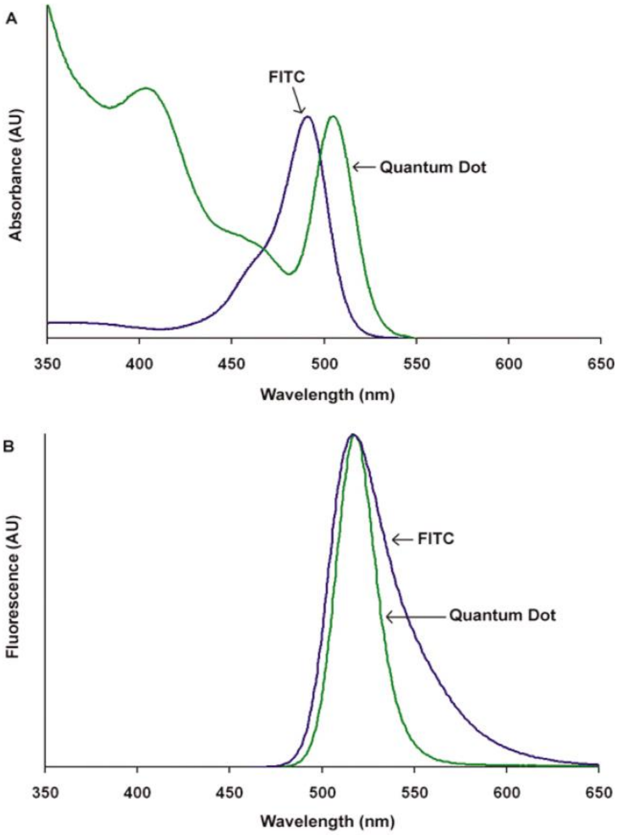

Fig. 5. Comparison of absorption spectra (A) and emission spectra (B) of QDs and fluorescein isothiocyanate organic dye (FITC) **[18]**.

5. Quantum dots as sensors

As has already been discussed, development of robust and sensitive environmental sensors for various ions is in progress and is of main concern currently. Ion sensing can be carried out using QDs via analyte-induced changes in the photoluminescence of QDs **[84]**. These sensors may be classified into luminescence based sensors, which mainly involve the principle of photoluminescence and chemiluminescence, and absorbance-based sensors which employ changes of the spectral absorbance. The sensing abilities of surface-modified CdSe QDs and core/shell QDs such as CdSe/ZnS have been intensively studied **[85]**. For ion detection, fluorescence quenching is the most usual process observed after interaction between quantum dot and organic analytes, usually involving photo-induced electron transfer (PET) and Förster resonance energy transfer (FRET) **[86]** which are discussed in the next section. The first use of cadmium based QDs was reported in 2002 when CdS quantum dots capped with L-cystein and thioglycerol were employed for the detection of zinc and copper in physiological buffer samples **[87]**.

6. Mechanism involved in sensor design

As discussed, out of the various mechanisms involved in the design of fluorescent sensors, QDs based sensors majorly make use of photoinduced electron transfer (PET) and Förster Resonance Energy Transfer (FRET) mechanisms **[86]**.

6.1. Photoinduced electron transfer (PET)

The mechanism of PET involves the separation and intramolecular charge relocation, such as in photosynthesis. The energy absorbed from sunlight is utilized in promoting an electron to a higher energy level and reduces a chain of electron acceptors with lowered redox potentials, thus producing chemical energy. This PET principle has led researchers to incorporate this mechanism into sensing systems due to its sophistication and modular design. The “switching off” of the PET process by complexation with metal ions leads to the restoration of emission of the fluorophores, such as during cation sensing, the linkage of cation to ionophore prevent the quenching of ionophore leading to increase in quantum yield **[88-90]**. The idea of the PET mechanism for sensing cations has also been explored for anion sensing **[91-93]** and sensing of molecules of biological significance like glucose **[94, 95]**. PET sensors are composed of three distinct and separate components **(Fig. 6)**.

A fluorophore, consisting of aromatic groups or cyclic molecules with π bonds is joined to a receptor via a spacer **(Fig. 6)**. A signaling component of the sensor, the fluorophore extracts information from the analyte via fluorescence. The receptor recognizes the analyte and binds to it through chelation or through some kind of bonding (e.g. hydrogen bonding) by taking part in redox processes with the fluorophore **[97]**. The use of a spacer is to keep the fluorophore and receptor far apart from each other.

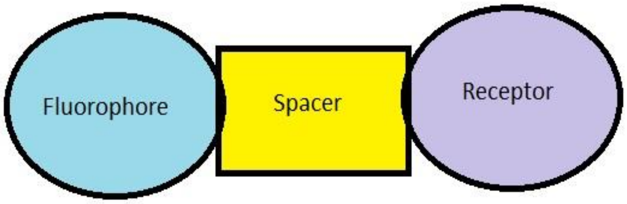

Fig. 6. The "fluorophore-spacer-receptor" format of fluorescent PET sensors.

Fig. 7 explains the molecular orbital energy diagrams of the "OFF" and "ON" states of the sensor. In an "OFF" state of the sensor, the receptor HOMO lies above that of the fluorophore, while in an "ON" state, there occurs stabilization of the HOMO of an analyte bound receptor and it is found below the fluorophore’s HOMO. PET occurs if the oxidation potential of the receptor is smaller in magnitude than that of the fluorophore but, if opposite is the case; there is an "ON" situation **[96]**.

6.2. Förster resonance energy transfer (FRET)

Another important technique frequently employed for sensing analytes using QDs is the Förster Resonance Energy Transfer (FRET) **[98-105]**. Upon photoexcitation, there occurs generation of electron-hole pairs. Fluorescence light is emitted upon recombination of the electron and hole. This property forms the basis of fluorescence resonance energy transfer (FRET). The FRET process involves the nonradiative transfer of energy from an excited donor fluorophore to a ground-state acceptor fluorophore when these two are in close proximity, typically 1-10 nm, i.e. FRET is the distance dependent nonradiative transfer of electronic energy from a donor to an acceptor molecule. Thus it can be employed very effectively for investigating distances in the range of 1 - 10 nm and can be extremely useful to study molecular interactions in various chemical and biological systems. Hence, by measuring FRET effectiveness, one can determine the distance between two fluorophores [**106, 107]**.

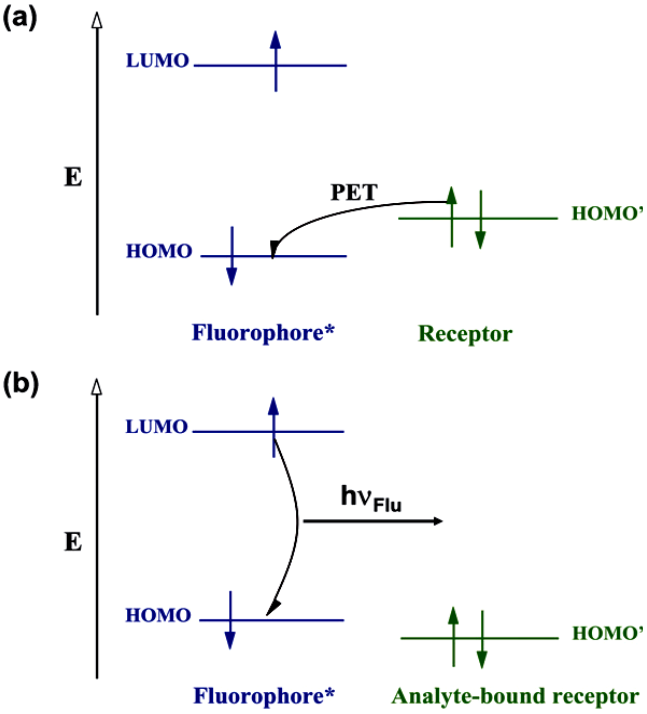

Fig. 7. Molecular orbital energy diagrams which show the relative energetic dispositions of the frontier orbitals of the fluorophore and the receptor in (a) the analyte-free situation and (b) the analyte-bound situation **[96**-Reproduced by permission of The Royal Society of Chemistry, http;//dx.doi.org/10.1039/b912527m**]**

For an effective FRET to occur, the emission spectrum of the donor must overlap the absorption spectrum of the acceptor molecule. The greater the overlap, the higher is the transfer efficiency of electronic energy. FRET takes place via the weak dipole-dipole coupling mechanism (inversely proportional to the sixth power of the distance between the donor and acceptor and directly proportional to the square of the coupling between them) between the transition moments of donor and acceptor molecules **[108-114]**. With the process of FRET, there occurs a fall in the fluorescence efficiency of the donor molecule, with a simultaneous increase in the emission intensity of the acceptor molecule **[115, 116]**.

FRET between QDs and various chemical and bio-molecules such as QDs and fluorescent proteins **[111-116]**, CdSe/ZnS and rhodamine B for light harvesting **[117]**, QDs and various ions and in pH sensing, and so on has been studied in the literature. Research is still continued to explore the importance of FRET in QDs by investigating their optical properties to determine their possible consequent applications in analytical as well as in life sciences **[118]**. Due to their broad absorption spectra, QDs are ideal energy acceptors. QDs were investigated as effective FRET donors for the first time by Bawendi et al. **[102]** who showed that like the organic fluorophores, CdSe QDs could also exhibit nonradiative energy transfer.

In general, the interaction of QDs with various ions leads to a fluorescence quenching that can be ascribed to inner-filter effects, nonradiative recombination pathways and electron transfer processes **[119]**. In some other cases, fluorescence improvement could also be observed due to passivation of trap states or defects on the surface of the QDs **[120]**.

7. Detection of cations using surface modified CdSe QDs

QDs were first employed as ion probes in 2002 by Chen and Rosenzweig when they made use of L-cystein and thioglycerol capped QDs for detection of zinc and copper **[87]**.

7.1. CdSe: Zinc

Zinc is one of the most important transition metal ions of physiological importance, both extracellular and intracellular, for example, in the synthesis of insulin and serves as a mediator for cell-cell signaling in the central nervous system where the brain tissue contains a high concentration of zinc. Zinc is also a part of two main enzymes carbonic anhydrase, which is vital to the process of conversion of CO_2 into bicarbonate and transformation of bicarbonate to CO_2 and carboxypeptidase for regulation and digestion of proteins. Due to the participation of zinc in various other physiological processes, development of highly sensitive and selective chemical sensors for the Zn^{2+} ion is of great importance at the biological level, i.e. at low concentrations in the presence of other relevant cations and at physiological pH values. Various fluorescent sensors for Zn^{2+} detection based on the linking of a receptor to a fluorophore employing PET or FRET have been reported.

Earlier in 2009, Frasco and Chaniotakis **[121]** first demonstrated that the calixcrown moiety can be conjugated to the QD surface and the resulting structure could be employed as an ion sensor due to its sensitivity towards the presence of low concentrations of metal ions. They carried out their studies on the metal ions copper (0.73 Å) and sodium (1.02 Å), and ammonium (1.47 Å) which differ in their ionic radii and correlated the fluorescence quenching of QDs with the increase of cation concentration. Later in 2010, Frasco et al. **[122]** reported a novel hybrid structure based on tetrapyridyl substituted porphyrin (5,10,15,20-tetra(4-pyridyl)porphyrin $[H_2P(pPyr)_4]$) functionalized CdSe QDs for the selective sensing of Zn^{2+} ions with a 0.5 μM limit of detection. This conjugated structure upon coordination with zinc ions, shows an increase in the fluorescence efficiency of CdSe QDs which increases with increasing concentrations of zinc ions.

7.2. CdSe : Copper

Copper is an essential element, an important part of electron transport chains (where mainly blue copper proteins like azurin and plastocyanin are involved) in plants and animals. It is vital for the functioning of various enzymes like cytochrome c oxidase and superoxide dismutase. Due to its antibacterial and antimicrobial properties, it is also employed in hospital surfaces and fittings. Various diseases like Alzheimer's disease and Parkinson's disease are linked to copper **[123, 124]**. In India, cirrhosis of liver is related to cooking acidic food in copper pots **[125]**. Therefore, detection of Cu^{2+} is of considerable importance. Various spectrophotometric based methods are preferred due to the requirement of reasonably priced instruments which offer reasonable sensitivity when chromogenic reagents such as sodium diethyldithiocarbamate trihydrate, N-ethyl-2-naphthylamine **[126]**, di-2-pyridylketone benzoylhydrazone **[127]**, and thiomichlersketone **[128]** are employed. Various other methods such as spectrofluorometric methods have also been used for Cu^{2+} determination employing various fluorescent reagents mainly europiumterpyridine-polyaminopolycarboxylate chelate **[129]** and 5-(3-fluro-4-chlorophenylazo)-8-aminoquinoline **[130]** due to their advanced sensitivity.

A novel method for the sensitive determination of Cu(II) ions with a detection limit of 0.2 μg L^{-1} based on water-soluble luminescent CdSe QDs surface functionalized with 2-mercaptoethane sulphonic acid or with 2-mercaptoacetic acid has been developed by Fernández-Argüelles et al. **[131]**. They observed that the presence of even ultratrace amounts of copper ions could cause a decrease of the emission luminescence of the modified QDs which could be explained in terms of substitution of surface Cd^{2+} ions by Cu^{2+} ions to form CuSe (with extremely low solubility) on the surface of CdSe QDs. No interference from other cations such as Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, Mn^{2+}, Co^{3+} and Fe^{3+} even at concentrations upto 300 mg L^{-1} was observed on the emission signals of the surface modified CdSe QDs **[131]**. Quintaneg and Santos synthesized CdSe QDs using Horizontal Vapor Phase Crystal (HVPC) Growth Technique in order to analyze Cu^{2+} ion concentration based on the fluorescence quenching mechanism of CdSe QDs **[132]**.

7.3. CdSe: Silver

Liang et al. **[133]** developed a chemodosimeter for Ag(I) by synthesizing biocompatible, water soluble CdSe QDs surface modified with mercaptoacetic acid and further absorption of bovine serum albumin (BSA) onto the surface in order to improve their fluorescence intensity and stability in water with detection limit of 7.0×10^{-8} mol L^{-1} of Ag(I). Ultrasmall particles of Ag_2Se formed at the surface of CdSe QDs by the chemical displacement of surface Cd(II) by Ag(I) and the extremely low solubility of Ag_2Se could quench the luminescence of BSA functionalized CdSe QDs **[133]**. Later in 2010, Ingole et al. **[134]** synthesized water soluble, citrate-capped, luminescent CdSe QDs for the selective detection of silver ions in the presence of various ions including physiologically important metal ions such as K^+, Ca^{2+}, Fe^{3+}, Zn^{2+}, Mg^{2+}, Mn^{2+}, Cu^{2+}, Ag^+ and toxic metal ions like Pb^{2+} and Cd^{2+}. They found the selective luminescence quenching of conjugated QDs predominantly with Ag^+ ions due to its highest positive redox potential compared to other metal ions under investigation and the limit of detection obtained was between 1.7 and 18 μM for silver ions.

7.4. CdSe: Barium

Barium behaves toxic even at low concentrations since it blocks potassium ion channels which are important for the proper functioning of the nervous system. Therefore, higher doses affect the nervous system causing cardiac irregularities, tremors, weakness, anxiety, dyspnea and paralysis. Mahmoud **[135]** first reported the detection of barium ions by using water soluble 2-mercaptoethanol capped CdSe QDs with a detection limit of 4.2×10^{-9} mol L^{-1}. He found enhancement in fluorescence emission from CdSe QDs on interaction with barium ions whereas the presence of other metal ions had no significant effect on the PL of QDs **[135]**.

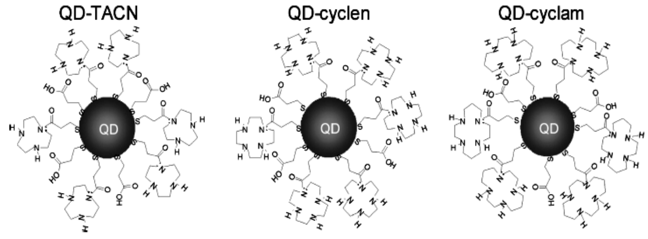

Fig. 8. Structure of QD-TACN, QD-cyclen, QD-cyclem **[143]**.

7.5. CdSe: Mercury

The analysis of Hg (II) ions has been one of the most essential topics because of the significant health hazards it causes even when its concentration is extremely low, of the order of ppm. Deposition of mercury in water bodies can also have an impact on ecosystems and wildlife **[136-140]**. Chen et al. **[141]** developed water soluble and biocompatible highly fluorescent L-cysteine CdSe nanosensors for sensing of Hg^{2+} ions with the limit of detection 6.0×10^{-9} mol L^{-1} based on fluorescence quenching of surface modified-CdSe QDs **[141]**. Shang et al. **[142]** have demonstrated the detection of an ion pair by utilizing photoluminescent CdSe QDs surface modified with triethanolamine (TEA-CdSe-QDs) for the detection of Hg^{2+} ions in the presence of I^- ions and vice versa for the first time. The fluorescence of TEA-CdSe-QDs was found to be quenched in presence of both the above ions while no significant effect on fluorescence was observed in the presence of the individual ions. The limit of detection was found to be 1.9×10^{-7} mol L^{-1} for Hg^{2+} and 2.8×10^{-7} mol L^{-1} for the I^- ion. Formation of a complex between TEA-CdSe-QDs and Hg^{2+} occurs with I^- acting as a bridge (QDs–I^-–Hg^{2+}) and fluorescence quenching has been explained in terms of the electron transfer mechanism from QDs to Hg^{2+} ions **[142]**.

8. Detection of cations using surface modified CdSe based core/shell QDs

8.1. CdSe/ZnS: Zinc

The first zinc ion sensors developed using QD nanoparticles in a host-guest and receptor-fluorophore system with a detection limit lower than 2.4 μM were based on the azamacrocycle derivatization of CdSe/ZnS core/shell QD nanoparticles. Three azamacrocycles **(Fig. 8)** chosen as receptors were : TACN (1,4,7-triazacyclononane), cyclen (1,4,7,10-tetraazacyclododecane), and cyclam (1,4,8,11-tetraazacyclotetradecane). Azamacrocycle adsorbed at the surface of the QD causes fluorescence quenching which could be reversed when the zinc ion enters the azacrown, i.e. an increase in fluorescence intensity was observed on exposure to zinc ions due to the involvement of the lone pair of nitrogen with the zinc ion, thereby disturbing the hole-transfer mechanism and hence switching on the QD emission **[143]**.

Ganguly et al. **[144]** synthesized CdSe/ZnS QDs surface modified with the multidentate ligand, salen. This hybrid material exhibits selective metal ion sensing towards Fe(II) and Cu(II) by photoluminescence quenching with a limit of detection 30 μM and 25 μM respectively. The selective sensing of ferrous ions could be attributed to the fluorescence energy transfer between the QDs and the surface ferrous-salen complexes while the selective sensing of copper is due to both the fluorescence energy transfer and surface adsorption mechanism. The authors had also investigated the photoluminescence response of QD-Salen towards different biologically relevant metallic cations including Na^+, K^+, Cu^{2+}, Mn^{2+}, Ca^{2+}, Co^{2+}, Ni^{2+}, Fe^{2+}, VO^{2+}, Zn^{2+} and Cd^{2+} and found that Na^+, K^+, Mn^{2+}, Ca^{2+}, VO^{2+}, Zn^{2+} and Cd^{2+} had no significant influence on the fluorescence properties of QDs-Salen, although Co^{2+} and Ni^{2+} also quenched the fluorescence to some extent. This conjugated system could be used for sensing Fe in biological systems since the iron content in physiological fluids is much higher than those of copper, nickel and cobalt.

8.2. CdSe/ZnS: Copper

A variety of research has been done to develop novel hybrids based on CdSe/ZnS core/shell QDs for detection of copper concentration as low as possible. High-quality luminescent CdSe/ZnS QDs, surface modified with bovine serum albumin (BSA) were used as selective copper (II) ion probes with satisfactory results and the detection limit achieved was 10 nM **[145]**. The authors explained it in terms of the strong binding of Cu^{2+} onto the surface of

CdSe leading to a chemical displacement of Cd^{2+} ions and the formation of CuSe on the surface of the QDs due to the extremely low solubility of CuSe which further quenches the luminescence of BSA capped QDs. **Fig. 9** shows that the fluorescence of BSA-QDs was effectively quenched by Cu^{2+} and Fe^{3+} ions in presence of other physiologically vital cations even if their concentrations were 50 times higher than that of Cu^{2+}. The interference of Fe^{3+} with Cu^{2+} ion analysis could be eliminated by adding fluoride ions to form the colorless FeF_6^{3-} complex. The BSA coated QDs can principally be used for the analysis of Cu^{2+} in the presence of a small concentration of Zn^{2+} ions which is of particular importance, since Cu^{2+} and Zn^{2+} generally exhibit analogous reaction to many organic fluorescent indicators **[145]**.

Later in 2007, Jin et al. synthesized water-soluble CdSe/ZnS QDs for the analysis of Cu^{2+} by overcoating the QD surface with thiacalix[4]arene carboxylic acid (TCC) which are highly fluorescent QDs. It was found that the fluorescence of the TCC-QDs was efficiently quenched by Cu^{2+} ions. The presence of other transition metal ions such as Cd^{2+}, Zn^{2+}, Co^{2+}, Fe^{2+} and Fe^{3+} did not cause any interference. These conjugated TCC-coated QDs were highly selective as was determined by the fluorescence response towards transition metal ions such as Fe^{2+}, Fe^{3+}, Co^{2+}, Zn^{2+}, Cd^{2+} and more or less insensitive to other biologically important ions such as Na^{+}, K^{+}, Mg^{2+}, and Ca^{2+} implying that TCC-coated QDs could be used as a fluorescent Cu^{2+} ion probe for biological samples **[146]**.

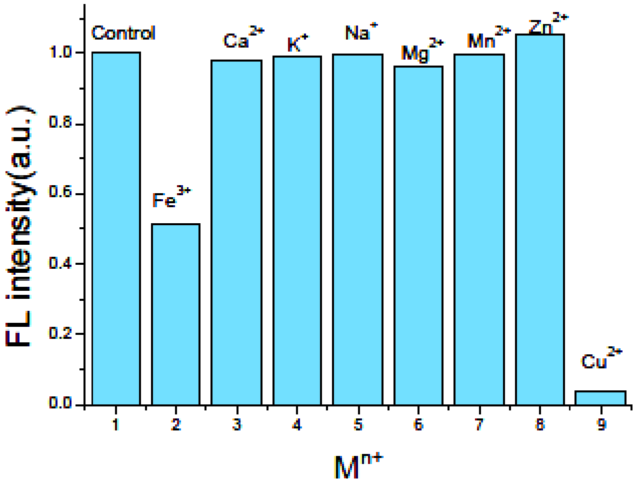

Fig. 9. Effect of biologically relevant ions on the fluorescence of BSA-QDs: concentration of Cu^{2+}: 10^{-6} M; for others: 5×10^{-4} M **[145]**.

In the work presented by Callan and Mulrooney **[147]**, CdSe and CdSe/ZnS QDs were surface functionalized with mercaptosuccinic acid (MSA) rendering them water soluble. MSA plays two important roles: at physiological pH, the negatively charged MSA ensures water solubility and electrostatically attract positively charged substrates close to the QD surface. Thus, this QD conjugate could be employed for sensing positively charged metal ions. It was observed that in a solution with concentration 1×10^{-5} M containing Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, Fe^{2+}, Mn^{2+} and Cu^{2+} as their chloride salts in the presence of MSA capped CdSe/ZnS QDs, a photoluminescence quenching was observed in case of Fe^{2+} and Cu^{2+} ions only. Photoluminescence quenching was explained due to competitive absorption in case of Fe^{2+} ions and due to the formation of CuSe and Cu_2S/CuS at the surface of the MSA capped CdSe and CdSe/ZnS core/shell QDs respectively. Also, greater range of quenching was observed in case of MSA capped CdSe/ZnS core/shell QDs than MSA capped CdSe QDs due to an increased insulation of the CdSe core by the ZnS shell in case of MSA capped CdSe/ZnS core/shell QDs. In another work done by Sutter et al. **[1]**, CdSe/ZnS core/shell QDs Qdot800 (Invitrogen) were synthesized and employed for sensing Cu^{2+} ions as $Cu^{2+}(H_2O)_8$ at concentration as low as 1 ppb by fluorescence quenching of QDs, most likely due to resonance energy transfer. In the same year, Sung and Lo (2012) synthesized a fiber-optic sensor for Cu^{2+} detection, where silica shell-encapsulated CdSe/ZnS QDs were overcoated with the polyvinyl chloride (PVA) polymer which exhibits strong quenching of QDs fluorescence in presence of Cu^{2+} ions. They demonstrated that the silica shell plays a key role in fluorescence quenching as it prevents the aggregation of CdSe/ZnS QDs and promotes the adsorption of Cu^{2+} ions on the QD-conjugated nanosensor **[148]**. Very recently, Zeng et al. **[149]** have systematically carried out a study in which the effect of different capping ligands on CdSe/ZnS QDs has been discussed in order to demonstrate that the quenching mechanism of QDs upon metal ion binding not only depends on the inherent properties of metal ions but also on the nature of ligands capped on the surface of QDs. The metal ions studied were Cu^{2+}, Pb^{2+}, Hg^{2+}, Fe^{3+}, Co^{2+}, Cr^{3+}, Ni^{2+}, Cd^{2+}, Zn^{2+}, Ba^{2+}, Mn^{2+}, Ca^{2+}, Mg^{2+} and Al^{3+} and the nine ligands chosen were thiolate ligands, namely mercaptoacetic acid (MAA), 3-mercaptopropionic acid (MPA), 11-mercaptoundecanoic acid (MUA), 3-mercapto-1-propanol (MPO), 2-aminoethanethiol (AET), L-cysteine (Cys), D-penicillamine (DPA), glutathione (GSH) and mercaptosuccinic acid (MSA). They observed a strongest fluorescence quenching by Cu^{2+} ions in no consideration to the capping ligand while Hg^{2+} ions also caused fluorescence quenching along with red shifting of the emission band. They had also found that the ligands with long aliphatic chains could protect the QDs from penetration of metal ions and hence lesser fluorescence quenching should be observed on metal binding when the QD is capped by such ligands **[149]**. Various papers on the use of CdSe/CdS core/shell QDs for Cu^{2+} ion detection have also been published which have been reviewed below:

8.3. CdSe/CdS : Copper

Lai et al. in 2006 synthesized mercaptoethanol modified CdSe/CdS QDs for the sensitive and selective determination of Cu^{2+} ions in the presence of other biologically important ions **[150]**. Then, in 2008, Zhang et al. **[151]** had synthesized L-cysteine coated water soluble CdSe/CdS QDs for the selective determination of Cu^{2+} ions in the presence of other physiologically essential cations such as Ca^{2+}, Mg^{2+}, Zn^{2+}, Al^{3+}, Fe^{3+}, Mn^{2+} and Ni^{2+} etc. with the limit of detection 3.0×10^{-9} mol L^{-1} for Cu^{2+} ions. They observed that fluorescence quenching of the PL of QDs could only be observed with copper ions and was insensitive to the presence of other cations **[151]**.

Promising flouroionophore candidates sensitive to Cu^{2+} ions have been synthesized by conjugating fluorescent CdSe/CdS core/shell QDs either with oleic acid or with MAO-mPEG in aqueous solutions **[152]**. Fluorescence quenching was observed when copper ions in both oxidizing and reducing environments i.e. Cu^{2+} and Cu^{+} bind the above conjugated nanostructure with limit of detection found to be 16 nM and no interference from other metal ions such as Ag^{+}, Al^{3+}, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cr$^{3+,}$ Fe^{2+}, Fe^{3+}, Hg^{2+}, K^{+}, Mg^{2+}, Mn^{2+}, Na^{+}, Ni^{2+}, Pb^{2+}, Sn^{2+} and Zn^{2+} was observed **[152]**.

8.4. CdSe / ZnS: Mercury

Mercury is a well-known dangerous and widespread global pollutant **[153]** and is considered to be harmful for water and soil due to the long atmospheric residence time of Hg(0) vapor and its oxidation to the soluble inorganic Hg^{2+} **[154]**. Sulfur calixarene capped CdSe/ZnS QDs have been reported for the selective and sensitive determination of Hg(II) using the QD's fluorescence changes. The influence of other metal ions such as Li^{+}, Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, Cu^{2+}, Zn^{2+},Mn^{2+}, Co^{2+}, Ni^{2+} was very weak even if present at relatively higher concentration **[27]**.

The use of luminescent and stable L-carnitine capped CdSe/ZnS core/shell QDs, which on interaction with mercury ions lead to quenching of photoluminescence and thus allow a sensitive determination of Hg^{2+} ions via analyte-induced changes in the photoluminescence of nanosensors has been reported **[155]**. The detection limit was as low as 0.18 μM with no interference of even very high concentrations of other metal ions such as alkali metal ions, alkaline earth metal ions, Ni^{2+}, Zn^{2+}, Fe^{2+} and Ag^{+} and anions such as NO_3^-, SO_4^{2-}, CO_3^{2-} and halogen ions. Freeman et al. **[156]** in 2009 had employed nucleic acid modified CdSe/ZnS core/shell QDs for multiplexed optical detection of both Hg^{2+} and Ag^{+} ions. CdSe/ZnS QDs were modified with thymine-rich nucleic acid for the selective analysis of Hg^{2+} and cytosine-rich nucleic acid for the selective analysis of Ag^{+} and a luminescence quenching of CdSe/ZnS QDs was observed on interaction with both of these ions **[156]**. Water-soluble CdSe QDs, surface modified with β-cyclodextrin (β-CD-QDs) have been synthesized in order to discuss the effect of various anions on their photoluminescence and to compare the degree of quenching caused by them **[157]**. The observed degree of quenching by various anions decreases in the order: monoanion > dianion >> trianion. The fluorescence could be restored by exposing the QDs to sunlight which could further be employed for the detection of various ions such as Ag^{+}, Hg^{2+} and Co^{2+} which could quench the restored fluorescence of the β-CD-QDs efficiently.

8.5.CdSe/ZnS: Potassium

Chen et al. (2006) have synthesized 15-crown-5 modified CdSe/ZnS QDs in aqueous solution exhibiting excellent selectivity towards K^{+} ion and this recognition is due to the 15-crown-5/K^{+}/15-crown-5 sandwich type of complex formation via the Förster type of energy transfer between two different color QDs with the detection limit of the order of 10^{-6} M. The emission intensities were insensitive to the presence of various physiologically important cations like Li^{+}, Cs^{+}, Mg^{2+} and Ca^{2+}. The authors had observed similar energy transfer phenomenon for Ba^{2+} ions as that for the K^{+} ions by carrying out Ba^{2+} titration. Due to the almost similar sizes of K^{+} (1.52 Å) and Ba^{2+} (1.49 Å) ions, the 15-crown-5/Ba^{2+}/15-crown-5 sandwich type of association could also be run **[158]**.

8.6. CdSe/ZnS: Cadmium

Cadmium is considered as a widespread health dangerous global pollutant and its level has been increased considerably in many areas due to human activity **[159]** as a result of mining, smelting, fossil fuel combustion, industrial use as in phosphate fertilizers and waste water sludge **[160]**. All of these are the cause of large scale environmental contamination by cadmium. Cadmium enters in biological systems through these sources and may lead to renal dysfunction, calcium metabolism disorders and an increased incidence of certain forms of cancer, possibly due to direct inhibition of DNA mismatch repair by cadmium **[160-162]**. With time, cadmium gets accumulated in tissues and produces severe health hazards. Thus, the sensitive and selective detection of cadmium in primary sources is highly needed. Currently, techniques for cadmium screening are labor intensive and high-priced **[160, 163]**. Since Cd^{2+} and Zn^{2+} ions occur mutually in nature, most of the chemosensors available are not able to distinguish them. Li and coworkers **[164]** have developed a sensor which selectively binds to Cd^{2+} in presence of Zn^{2+} by synthesizing L-carnitine (LC) capped CdSe/ZnS core/shell QDs. LC capped QDs are sensitive to cadmium ions (**Fig. 10**) over other metal ions such as Na^{+}, K^{+}, Mg^{2+}, Ca$^{2+,}$ Ni^{2+}, Zn^{2+}, Fe^{2+}, Ag^{+} and Pb^{2+} with a detection limit of 0.15 μM for Cd^{2+} ions. This could be applied for the determination of cadmium ions both biologically and environmentally.

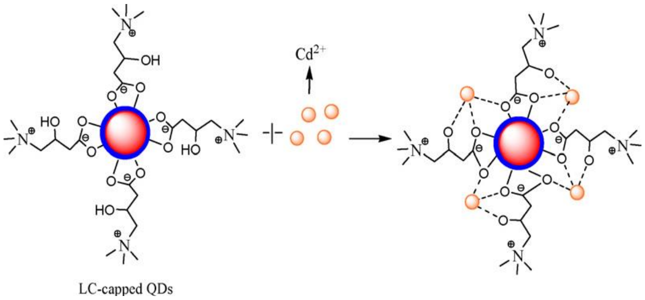

Fig. 10. Schematic illustration of interaction of LC-CdSe/ZnS with Cd^{2+} ions **[164]**.

8.7. CdSe/ZnS: Lead

Although lead is important industrially as it is extensively used in making alloys, batteries, glasses and paints, its compounds are carcinogenic, interfere with the body processes and are considered to be toxic for biological systems as they can harm various body organs and tissues like heart, kidneys, bones and reproductive and nervous systems with symptoms like headache, abdominal pain, memory loss, weakness and pain **[165, 166]**. Therefore in order to evade heavy metal poisoning by Pb^{2+} ions, it is highly desirable to produce sensors which can selectively analyze Pb^{2+} ions.

Highly luminescent CdZnSe QDs capped with glutathione shells have been developed for the ultrasensitive analysis of Pb^{2+} ions with a 20 nM limit of detection **[167]**. Fluorescence quenching of the conjugated QD system was observed on interaction with Pb^{2+} ions due to stronger binding between heavy metal ions and the surface glutathione capping. CdSe/ZnS core/shell QD conjugates have been developed for the multiplexed detection of the heavy metal ions, Pb^{2+} and Cu^{2+} with the limit of detection 0.2 nM for Pb^{2+} and 0.5 nM for Cu^{2+}. For this, carboxyl-silanized QDs coupled to DNAzymes were employed and the detection was based on FRET. In the absence of metal ions, quenching of QDs fluorescence was observed due to the presence of DNAzymes, which act as quenchers, but in the presence of the target metal ion, due to the cleavage of DNAzymes from QDs, the emission from QDs was restored **[168]**. Luan et al. **[169]** have synthesized mercaptopropionic acid modified CdSe/ZnS QDs for the sensitive detection of Pb^{2+} ions in water. Photoluminescence quenching was observed due to the cation exchange reaction (Zn^{2+} by Pb^{2+}) in water. However, this ion probe has a limitation that if in a sample Ag^+ and Cu^{2+} ions are also present, there is equal probability of replacing Zn^{2+} ions by these ions as that of Pb^{2+} ions and hence a similar quenching phenomenon is observed.

8.8. CdSe/ZnS: Cobalt and nickel

Baranov et al. **[170]** investigated a different type of optical sensing mechanism by utilizing dissociative luminescence sensors in which they had put in CdSe/ZnS QDs and 1-(2-pyridilazo)-2-naphtol (PAN). Formation of CdSe/ZnS-PAN complexes where PAN binds to the surface Zn^{2+} ions was observed to occur. Due to an efficient spectral overlap between the QDs photoluminescence and the PAN/Zn^{2+} absorption bands, the QD luminescence is quenched via efficient FRET but in the presence of Co^{2+} and Ni^{2+} ions, reappearance of QD luminescence occurs due to dissociation of the QD/PAN complex and formation of PAN/Co and PAN/Ni complexes **[170]**.

8.9. CdSe/ZnS: pH sensors

Semiconductor based biosensors EIS (electrolyte-insulator-semiconductor) have been employed **[171]** as pH sensors whose sensitivity depends on the properties of the sensing membrane surface. CdSe/ZnS QDs were deposited on the SiO_2 surface using a layer of chaperonin GroEL protein template and the pH sensitivity of bare SiO_2 were compared with the CdSe/ZnS modified sensing membranes. A more positively charged surface was observed at low pH due to more of H^+ ion concentration and a less positive surface was observed at high pH.

9. Detection of anions using surface modified CdSe QDs

Sensing and recognition of anions is of great importance, as they play a primary role in a wide range of areas such as in medicine, catalysis and various biological processes **[172]**. A lot of research has been focused on developing colorimetric **[173]** and fluorescent **[174]** techniques for sensing various anions. However, these days major attention has been laid on the development of new fluorescent probes for sensing due to their simplicity and sensitivity. Although the detection technique is at a nascent stage, still QDs can be looked upon as promising candidates for anion sensing **[175]**. Here also, the same QDs i.e. CdSe and CdSe/ZnS were chosen to have a detailed overview of the work done in the sensing area.

9.1. CdSe: Cyanide

Cyanide finds applications in various industries such as in petrochemicals, polymers like nylon and acrylic plastics (which are also associated with environmental issues) metal extraction, gold mining, metal electroplating, fertilizer factories. These industries are majorly responsible for cyanide poisoning which affects the ability of cells to make use of oxygen. Concentrations of 0.5–3.5 mg per kg of body weight are lethal to humans since it immediately diffuses and binds with target sites very rapidly. Cyanide is also a constituent of tobacco smoke **[176-183]**. Cyanide containing compounds such as mercury cyanide, copper cyanide, gold cyanide, and silver cyanide release hydrogen cyanide gas which further reacts with acids which are harmful. Cyanide immediately spreads in the body and death can occur within seconds or minutes after a large dose mainly due to permanent neurological disability **[184, 185]**. Smoke inhalation from structural fires is the main cause of cyanide poisoning in Western countries **[186]**. Unfortunately no tests have been developed so far which leads to rapid confirmation of cyanide poisoning. Hence, there is a need to develop a novel inexpensive system which is simple to use for the detection of this ion. Jin et al. **[187]** synthesized novel and highly photoluminescent CdSe QDs surface-modified with *tert*-butyl-*N*-(2-mercaptoethyl)-carbamate (BMC) for the optical determination of cyanide ions and a detection limit of 1.1×10^{-7} M for cyanide ions was obtained. The important thing to be noted is that the effect of other inorganic anions like NO_3^-, Cl^- or SCN^- was negligible even if their concentration was 200 times than that of the CN^- ion concentration. Also, the sensitivity of the BMC-CdSe QDs to CN^- recognition was unchanged even after more than two months of storage **[187]**. The authors also have synthesized **[84]** surface-modified CdSe QDs with polar unidentate 2-mercaptoethane sulfonate **[188]** or mercaptoacetic groups **[82]** to analyze cyanide ion selectively through fluorescence quenching of the luminescent QD-conjugate in aqueous solution with a detection limit of 1.1×10^{-6} M. The presence of other common ions such as SO_4^{2-}, SO_3^{2-}, NO_3^-, NO_2^-, Cl^-, Br^- and acetate did not cause any interference in cyanide ion detection. Only I^- and SCN^- ions that too at concentrations higher than 2×10^{-4} M produce fluorescence quenching of the QD-conjugate **[84]**. A combination of TOPO-coated CdSe QDs, 2,2'-bipyridine(bipy) and $CuCl_2$ has been employed **[178]** as a cyanide probe. Fluorescence quenching of the QDs is observed as a result of electron transfer between the QD and the complex [(bipy)$CuCl_2$] formed as a 1:1 mixture of bipy and $CuCl_2$ **[189]**. On addition of cyanide ions, the cyanide reacts with copper ions and forms a stable $[Cu(CN)_n]^{(n-1)-}$ complex **[190]** and this reaction is called demetallation of the [(bipy)$CuCl_2$] complex which can be used as a tool to detect cyanide ions.

This probe has an advantage that it works at the physiological pH 7.5, in the presence of water and in presence of other anions such as NO_3^-, AcO^-, SO_4^{2-}, F^-, Cl^-, Br^-, I^-, ClO_4^-, $HCO_3^-$and $H_2PO_4^-$ at pH 7.5 **[178]**.

9.2. CdSe: Nitrite

Nitrite ion detection is also of immense significance both ecologically and for public health fields. A variety of methods based on spectrophotometric **[191]**, chromatographic **[192]**, chemiluminescent **[193]** and electrochemical techniques **[194, 195]** have been developed for determination of nitrite ions but many of them are difficult to employ, time consuming and involve tedious sample pretreatment **[194]**. Liu et al. **[196]** demonstrated an electrochemiluminescent (ECL) method for the detection of nitrite based on the quenching of ECL emission of thioglycolic acid capped CdSe QDs with a limit of detection in the range from 1 μM to 0.5 mM, where the nitrite ions act as electroactive quenchers. This method is highly selective since the presence of other anions such as NO_3^- and Cl^- ions and cations such as Na^+, K^+ and NH_4^+ does not cause any interference even at the concentration of 20 mM **[196]**.

9.3. CdSe: Carbonate

Carbonate (CO_3^{2-}), a polyatomic anion, works as an important buffer in our blood and is also important industrially as in detergents, paper liquors, glasses, a chief constituent of limestone and so on.

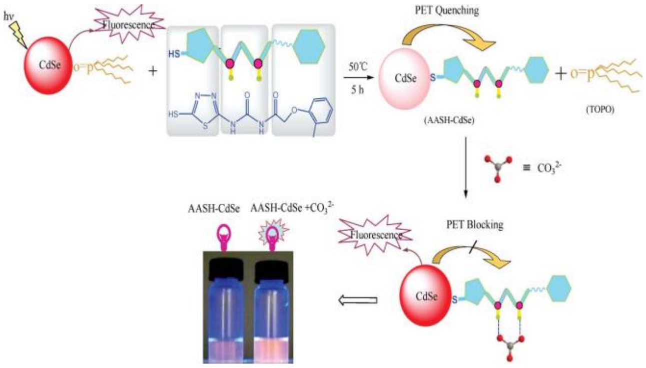

Fig. 11. Synthesis procedures of AASH functionalized CdSe QDs and a possible model for carbonate recognition **[197]**.

A highly selective fluorescence nanosensor for carbonate anion detection has been designed **[197]** where the CdSe QDs were modified with thio ligands containing urea groups, i.e. N-(5-mercapto-1,3,4-thiadiazol-2-ylcarbamoyl)-2-(*o*-tolyloxy) acetamide (AASH-CdSe QDs). The synthesized AASH-CdSe QDs could selectively analyze CO_3^{2-} ion by turning "on" the fluorescence response with a limit of detection 2.3×10^{-8} M. In the absence of CO_3^{2-} ions, recombination of the photogenerated electron is prevented due to transfer of this electron to the low lying π* energy level on the ligand and hence charge separation occurs and “switches off” the QD emission but in the presence of carbonate anion, an electron transfer mechanism is prevented due to the formation of a complex AASH....CO_3^{2-} (**Fig. 11**), thereby "switching on" the fluorescence emission. The above conjugated nanosensor can even analyze CO_3^{2-} anion in presence of anions like F^-, Cl^-, Br^-, I^-, HCO_3^-, CO_3^{2-}, HPO_4^{2-}, $H_2PO_4^-$, NO_3^-, NO_2^- and HSO_3^-.

10. Detection of anions using surface modified CdSe based core/shell QDs

Callan et al. **[198]** demonstrated that the surface functionalized CdSe/ZnS quantum dot fluorophore with a receptor 1-(2-mercapto-ethyl)-3-phenyl-thiourea can be adopted as a PET based organic dye sensor with comparable selectivity and sensitivity when an identical receptor was bound to the anthracene fluorophore.

10.1. CdSe/ZnS: Fluoride

Fluoride is of particular interest owing to its role in preventing dental caries and its use as a treatment for osteoporosis. As mentioned above, Callan et al. **[198]** reported an example of a PET operated quantum dot probe for sensing of anions by selecting 1-(2-mercapto-ethyl)-3-phenyl-thiourea as a receptor bound to CdSe/ZnS QDs. Charge neutral thioureas are useful as receptors for anions when bound to an anthracene fluorophore in a PET format **[199]**. Addition of Cl^-, F^- and AcO^- caused about 90% of fluorescence quenching due to hydrogen bonding interaction which led to an enhancement in the reduction potential of the receptor thereby increasing the rate of PET from the HOMO of the receptor to the quantum dot **[199, 93, 200]**. Mulrooney et al. **[201]** synthesized a sensor for anions using QDs as the signaling unit by modifying the surface of CdSe/ZnS core/shell QDs with 1-(bis(η^5-cyclopentadienyl)iron)-methyl-3-(5,7-dimercapto-heptyl)-urea (ferrocenyl urea) and demonstrated the effect of the presence of fluoride ions on fluorescence emission of the conjugated structure. They observed that there is no fluorescence emission in the absence of fluoride ions most probably due to the electron transfer mechanism but fluorescence emission was "on" upon binding to fluoride ions due to modulation of the rate of PET between ferrocene units and the QDs.

10.2. CdSe/ZnS: Hydroxide

Gauci et al. **[202]** investigated the fluorescence quenching of CdSe/ZnS core/shell QDs by an aryl carboxylate moiety by synthesizing surface functionalized CdSe/ZnS core/shell QDs with *p*-mercaptomethyl benzoate to which the addition of hydroxide ions leads to fluorescence quenching as a result of hydrolysis of the ester via a carboxylic acid intermediate to the aryl carboxylate and afterwards photoinduced electron transfer reaction from an electron-rich benzoate moiety to the QD valence band **[202]**.

10.3. CdSe/ZnS: Chloride

Chloride ion sensing is important both biologically and ecologically. Wang et al. **[203]** demonstrated chloride ion sensing by employing luminescent QDs in order to measure chloride ion concentration in the intracellular range. They had synthesized a QD-conjugate by conjugating a chloride ion receptor, 1-(2-mercapto-ethyl)-3-phenyl-thiourea with the water soluble CdSe/ZnS QDs. It was observed that binding of chloride ions to the above conjugated QD leads to an electron transfer mechanism which leads to the fluorescence quenching of the QDs. The higher the Cl^- ion concentration, higher is the fluorescence quenching of the QD conjugate. They also verified the effectiveness of these nanosensors by employing them to dynamic $[Cl^-]_i$ measurements in epithelial cells. The above QD-conjugated structure proves to be a sensitive and selective chloride ion nanosensor with properties that can be utilized for drug discovery **[204, 205]**.

Ruedas-Rama et al. **[206]** analyzed the chloride ion concentration using Cl^- ion sensitive QD-lucigenin conjugates where lucigenin serves as a chloride-sensitive indicator dye. A drastic drop off in the photoluminescence lifetime of both the QD and lucigenin was observed on combining these two, but on binding the chloride ion, the photoluminescence lifetime of QDs increased while that of the lucigenin dye decreased and an overall linear response was observed for Cl^- ion in the limit of 0.5 to 50 mM concentration. The above conjugate nanosensors can be widely employed for intracellular sensing of Cl^- ions.

11. Conclusion

CdSe and CdSe/ZnS core/shell quantum dots have emerged as promising candidates in the area of sensing of ions. This is due to the presence of extraordinary electronic and optical properties possessed by these nanostructures, thereby making them one of the most prolific nanomaterials alternatives to traditional fluorophores in a wide range of applications. This is attributed to the quantum confinement effect which makes them so unique. The tendency of tuning the band gap by varying the size of QDs has allowed scientists and researchers to play with these magical nanoclusters. All the colors of QDs can be excited by a single excitation source which makes it much easier to achieve multiplexed detection than traditional dyes that requires the excitation light source to be tuned into its respective absorption. In this review, we have reported how photoluminescent semiconductor nanocrystals, CdSe QDs and CdSe based core/shell QDs have been employed as selective and sensitive ion detectors by utilizing their optical properties. The mechanisms involved in sensing are mainly PET and FRET. In the majority of the sensing cases, we observe quenching of fluorescence while in some others enhancement is also observed depending on the electron transfer mechanism. We presume that this approach could lead to invention of novel luminescent sensors in the area of sensing various other types of analytes.

12. Future perspectives

Quantum dots, owing to their unique optical and electronic properties have emerged as potential analytical tools for the multiplexed, selective and sensitive determination of various analytes. Although quantum dot expertise is not in much use biologically due to their toxicity, hydrophobicity and difficulty in understanding the fluorescence quenching or enhancement mechanism, once the mechanism is fully understood, they can further be employed to detect ions at still lower concentrations and by carrying out various surface modifications. In future these novel nanosensors will drastically enlarge the scope to use them for studying various biologically important ions in intracellular fluids. Prediction also exists to build up superior sources and detectors for use in optical gas sensors for analyzing concentrations of various harmful gases in the environment. This will provide helpful information aiming to design fluorophores with great versatility and flexibility.

13. Abbreviations

AASH N-(5-mercapto-1,3,4-thiadiazol-2-ylcarbamoyl)-2-(*o*-tolyloxy) acetamide, **β-CD** β-Cyclodextrin, **bipy** 2,2'-bipyridine, **BMC** *tert*-butyl-*N*-(2-mercaptoethyl)-carbamate, **BSA** Bovine serum albumin, **Cys** L-cysteine, **DPA** D-penicillamine, **ECL** Electrochemiluminescent, **EIS** Electrolye-insulator-semiconductor, **FITC** Fluorescein isothiocyanate, **FRET** Förster Resonance Energy Transfer, **GSH** Glutathione, **LC** L-carnitine, **MAA** Mercaptoacetic acid, **MPA** 3-mercaptopropionic acid, **MPO** 3-mercapto-1-propanol, 2-aminoethanethiol, **MSA** Mercaptosuccinic acid, **MUA** 11-mercaptoundecanoic acid, **MSA** Mercaptosuccinic acid, **PAN** 1-(2-pyridilazo)-2-naphtol, **PL** Photoluminescence, **PET** Photoinduced Electron Transfer, **PVA** Polyvinyl chloride, **QDs** Quantum dots, **TEA** Triethanolamine, **TCC** Thiacalix[4]arene carboxylic acid.

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