

Research Article

Quantum Dots: A Promising Tool for Biomedical application

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Abstract

Quantum dots the colloidal semiconductor nanocrystals showing variety of applications because of its size tuneable optical properties. The bioconjugated colloidal nanoparticles showing similarities with biological macromolecules leads its applications to biological fields such as detecting, imaging and drug delivery. This chapter provides a brief description of QDs in biomedical applications especially in bio imaging, tumour cell targeting and drug delivery. In addition to macro scale in vivo imaging techniques nanoscale QD based probes were well matched for fluorescence imaging in biomedical applications.

INTRODUCTION

Nanotechnology is the study of creation, manipulation, and application of structures in the nanometer size that is between 1 to 100 nm. Metal and semiconductor nanoparticles which are in the 2-6 nm size range shows very good dimensional similarities with biological macromolecules like nucleic acids and proteins. So the integration of nanotechnology and biology leading to open up new endeavour in the field of medical diagnostics, targeted therapeutics, molecular biology and cell biology. Recently several groups has incorporated colloidal nanoparticles to biomolecules and these bioconjugated nanoparticles are then being used for producing homogeneous bioassays and multicolor fluorescent labels for ultrasensitive detection and imaging. Quantum dots (QDs) are colloidal semiconductor nanocrystals having ~1-10 nm diameters. The QDs can be made based on different materials such as inorganic semiconducting materials, carbon, graphene and black phosphorus [1]. Quantum dots shows size-dependent optical and electronic properties and these properties makes quantum dots a good material in the field of biomedical applications such as bio imaging and sensing, drug delivery, diagnostics, cancer therapy etc [2]. Quantum dots have been developed in different shapes, size and configurations and one of the main applications of the QDs in biomedical field. Compared to conventional organic dyes and fluorescent proteins, QDs shows typical features such as size-tunable light emission, improved signal brightness, resistance against photo bleaching and simultaneous excitation of multiple fluorescence colors. These properties are the basic motivation for using QDs in bio medical field compared to individual molecules or bulk semiconductor solids [3].

All the three dimensions of QDs are in nano metre range and QDs have mainly three parts as shown in Figure 1, one core part made from any semi conductor material such as CdSe, CdTe etc, secondly shell surrounding the core part which helps to improve the optical properties of the core and finally a cap which may be of peptides, antibodies, oligo nucleotides or poly ethylene glycol depending on the required solubility or biological properties [4].

Different sized QDs emit different colour light due to quantum confinement effect. By changing the particle size QD probe give different colours. The biggest quantum dots produce the longest wavelengths or lowest frequencies and shows red light while the smallest dots has bigger band gap make shorter wavelengths or higher frequencies and emits blue light.

The size tuneable optical properties of QDs are shown in Figure 2(A). The fluorescence properties of quantum dots are related to the size of the QD core and the colour of emitted light

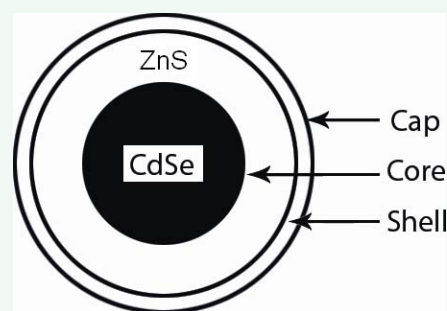
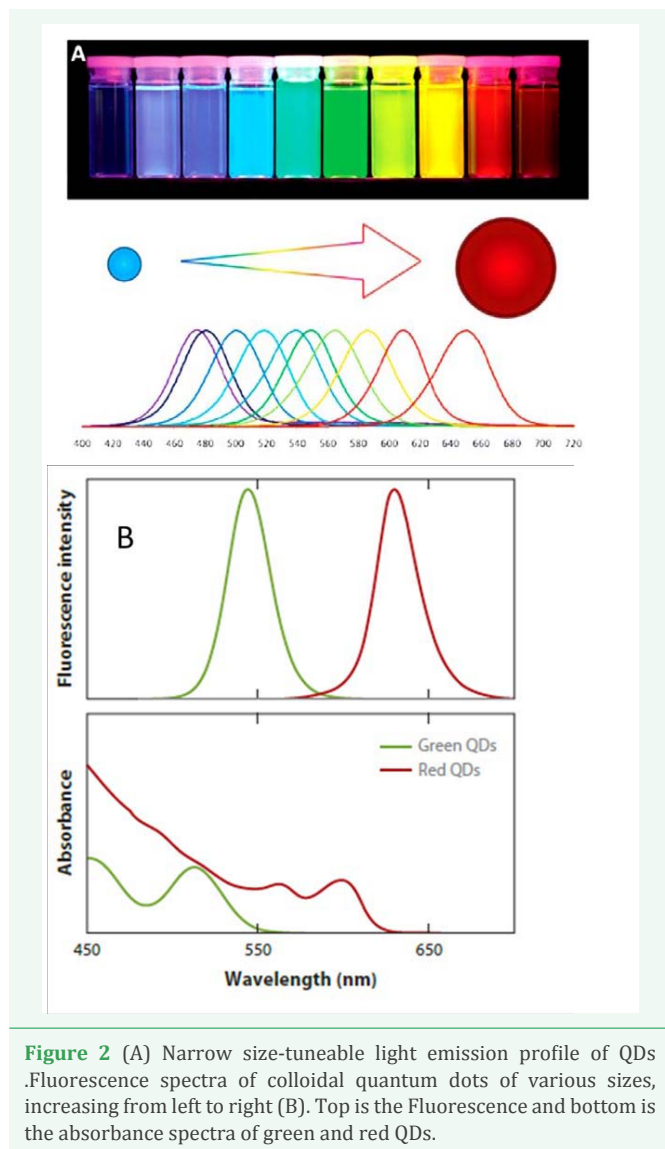


Figure 1 Schematic representation of a quantum dot [4].



and can be adjusted by changing the QD size. As the particle size decreases the degree of confinement increases and gives a narrow fluorescence emission which allows getting multiple colours. Because of the broad absorption profile multiple excitations is possible with a fluorescent lifetime of 20 second opens doors for bioimaging [5].

Narrow and symmetric fluorescence spectra facilitate accurate modelling for deconvolution and spectral unmixing to differentiate probes with significant emission overlaps. The broad absorption profile shown by absorbance spectra allow a wide wavelength range for excitation of QDs and a single excitation source for emitting multiple QD colours (Figure 2B) [6]. The present chapter discussing the properties of quantum dots its biocompatibility and its application in biological field.

METHODS OF PREPARATION OF QDS

Organometallic method/ organic phase method

Monodispersed QDs with uniform surface derivatization and regularity in core structure can be prepared through

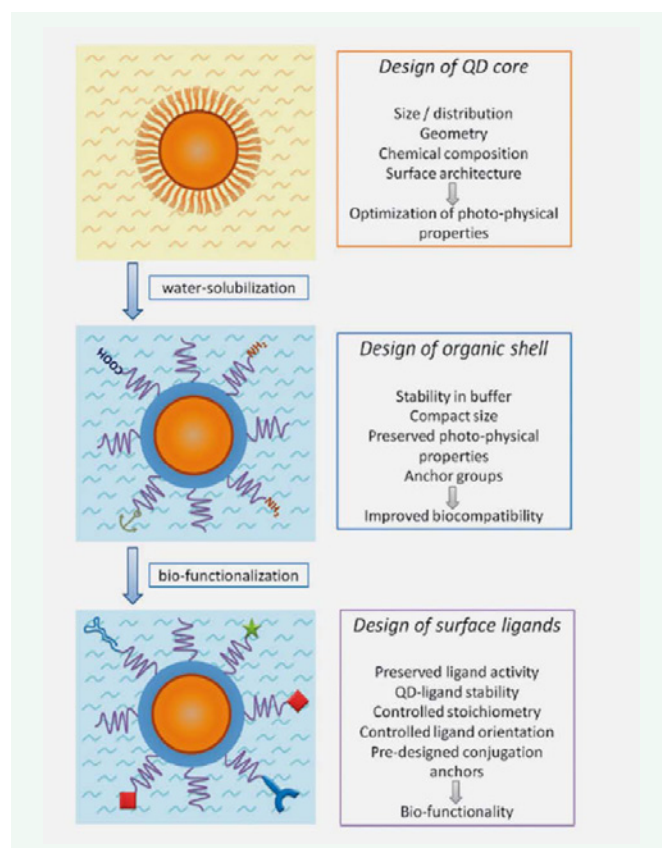
organometallic method. The generally used organometallic precursors are Me₂Cd and Bis(trimethylsilyl)selenium. Monodisperse CdSe was obtained from the pyrolysis of organometallic reagents by injection into a hot coordinating solvent between 250°C to 300 °C [7]. Depending on the temperature conditions QDs with different sizes were produced. Organometallic method is currently considered as the most important method to synthesize QDs. Because sing this method different QDs showing high quantum yield can be produced and the size distribution of QDs is easily controlled by changing the temperature or by changing the reaction time [8].

Aqueous solution method/water phase method

In this method ionic perchlorates are used as precursors. CdTe QDs were prepared using ligands such as 3-mercaptopropionic acid (3-MPA), glutathione (GSH), or other hydrosulphyl-containing materials in aqueous medium. This is an environment friendly method the cost for the synthesis is very low. Also the QDs produced through this method can be directly applied into the biological systems. The thiol capped QDs shows poor stability in aqueous solution, low quantum yield and wide size distribution compared to QDs produced from organometallic method [9].

Hydrothermal method

Another method to synthesis QDs are Hydrothermal Method/ Microwave-Assisted Method. Through this method QDs with narrow size and high quantum yields were produced. The surface defects introduced during the synthesis process will be reduced



using these methods. In hydrothermal method first the reagents are introduced into hermetic container and giving temperature upto supercritical temperature, and the reaction time and surface defects of QDs will effectively reduced by the high pressure produced from this temperature.

Microwave-assisted method

The Microwave-assisted irradiation was first introduced by Kotov group and followed by Qian and co-workers. The heating source microwave irradiation and the solvent used were water. The reaction system is heated above 100°C to yield homogeneous QDs and obtained a quantum yields of 17% [10].

QDs produced through organic phase synthesis give hydrophobic QDs. But for the biological application the QDs should be soluble in water. Because the nano crystals produced from the water solubilisation method will be stable in biological systems and without changing/affecting the photo-physical properties.

The water soluble QDs prepared in the initial stage provides only a low quantum yield with poor fluorescence. Later with the advanced synthetic procedures and surface modifications give water soluble QDs with higher quantum yield that is up to 50%. But controlling the photo physical and chemical properties of QD in aqueous is a big challenge. Different methods have been introduced to develop QDs soluble in water and showing with small particle size.

One method is ligand exchange: In this method the hydrophobic groups on QD surface will replace using hydrophilic groups through ligand exchange mechanism. Because of the simplicity of this method by the use of monodentate ligands it will affect fluorescence efficiency and leads nano particle aggregation. That is ligands left some vacant sites when it is detached from the surfaces and the vacant sites act as trap centers and that makes nanoparticles aggregation. This problem can be solved using ligand cross linking and usage of di tio group instead of mono

thio group. Another method for producing water soluble QD is through the incorporation of amphiphilic molecules such as polymers or phospholipids [11].

QD -polymer nanocomposites can be prepared using two methods ligand exchange method and by polymer encapsulation. In ligand exchange polymer molecules is used to replace original hydrophobic ligands on the QD surface but in polymer encapsulation the native surface of QD ligand layer does not changed. The increased number of hydrophilic groups present in the long-chain polymer molecules acts as agents to increase the dispersibility of QD in biological buffer solutions and also provide chemical functional groups for conjugations of bio-probes. The polymers coated on QDs not only increase the biocompatibility of QD -polymer nanocomposites but also reduce their cytotoxicity.

The photo-physical properties of QD probes are changed with change in chemical composition, size and structure of the inorganic nano particle used for the development of QD probes. Because of the lack of biological functioning the nano particle cannot interact with biological systems. For better biological application the inert QDs must be decorated with biomolecules such as proteins, nucleic acids which give interaction with living cells. Incorporation of biomolecules makes QDs more biocompatible with living systems. The process of conversion of bare QDs to biocompatible QDs is a multistep process as shown in Figure 3 [12].

Bioconjugation of QDs

Labelling of QDs with bio recognition elements such as oligonucleotides, aptamers, peptides and proteins is an essential step required for using QDs in biological field. Specific recognition and binding of QDs with the biomolecular targets are take place through bio conjugation of QDs (Figure 4).

The mainly used approaches for making bio conjugated QDs with biorecognition elements are covalent or non covalent binding. QDs with bio recognition elements containing covalent

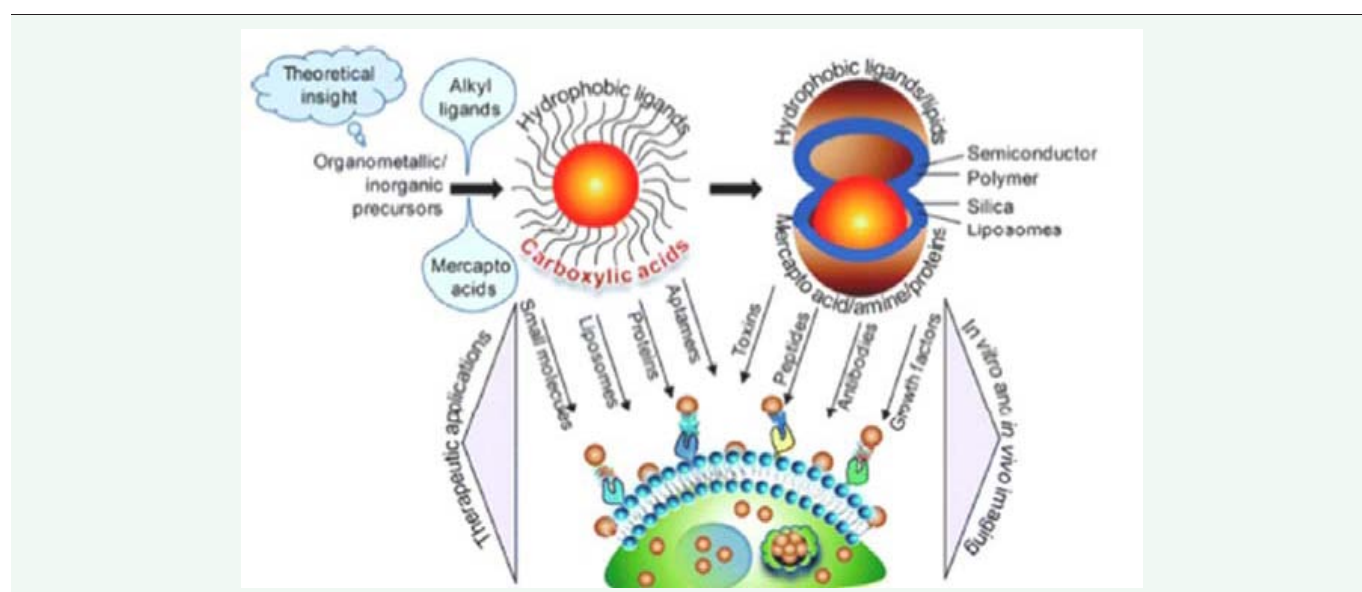


Figure 4 Schematic representation of different approaches for bioconjugation of QDs.

or non covalent conjugates are considered as bio conjugated QDs and can be used for specific targeting and bio imaging applications.

In covalently conjugated QDs a covalent bond will establish between QD and conjugate through the reaction of functional groups present both in QD and the conjugate. The covalent binding depends on the nature of functional group present in the QD surface. The generally used functional groups for bioconjugation are carboxylic acid, amino, thiol, epoxide, hydroxyl groups etc. Among these functional groups the most popularly used one is carboxylic acid groups because they can be easily attached to free amino groups of immune globulins, proteins and peptides through the formation of simple amide bonds [13]. Also covalently attached avidin and biotin to biomolecules or QD surface are also used as bio conjugates.

A hydrophobic, electrostatic or high affinity interaction is required to exist non covalent conjugation between QD and functional group. Electrostatic coupling is the simplest and most widely used non covalent conjugation method. However the electrostatic interactions between QDs and biomolecule affected by the various factors like, pH, ionic strength, pressure of competing molecules or chelating ligand. Also these interactions are not controllable and sometimes it may negatively affect the activity of the coupled biomolecules. Because of the positive charge on the protein surface we can easily self assembled the proteins in oppositely charged QD surface. For QD-protein coupling the effective methods are the self assembly of proteins, another method is interaction between positively charged histidine residue with dihydrophilic acid capped QD.

Peng Wu et al., synthesized conjugated phosphorescent Mn-doped ZnS quantum dots for glucose bio sensing application. QDs are conjugated with glucose oxidase(GOD) using 1-ethyl-3-(3 dimethylaminopropyl) carbodiimide (EDC)/N-hydroxysuccinimide (NHS) as coupling reagents and the room temperature phosphorescence (RTP) of Mn doped ZnS QDs is quenched by the H₂O₂ generated from GOD. Glucose bio sensing using this conjugated QD is takes place through the above mentioned mechanism [14].

Working of Quantum dots

Hydrophobic drugs can be implanted between the inorganic core and the amphiphilic polymer coating layer of the QDs (Figure 5) [15]. Hydrophilic therapeutic agents (including small interfering RNA [siRNA] and antisense oligodeoxynucleotide [ODN]) and targeting biomolecules (such as antibodies, peptides and aptamers), are attached onto the hydrophilic side of the amphiphilic polymer through covalent or non-covalent bonds. This nanostructure act as a magic bullet that will identify, bind and treat diseased cells as well as emit detectable signals in order to monitor the target.

The size of the QDs have a very good significance in the bio medical application because small size QDs easily removed from body by renal filtration but bigger particles has showed the possibility to uptaken by the reticulo endothelial system before reaching the targeted disease sites. The QDs having polymer coating with 5-20nm size shows optimum activity. After the incorporation of QDs in the form of colloidal solution through S.C or I.V. injection the QDs got bound to the target. Depending on the size the attached QDs will emit light and shows different fluorescence which can be identified using UV-VIS or photoluminescence spectroscopy or dynamic light scattering (DLS) studies.

Quantum dots characterization

UV-VIS and photoluminescence spectroscopy are the mainly used optical characterizations of quantum dots which is fast, non destructive and contactless methods. The optical properties can be tuned by quantum dots' size. QD size is determined using scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), scanning tunneling microscopy (STM) and dynamic light scattering (DLS) studies [4].

APPLICATIONS OF QDS

Because of the size tuneable optical properties the QDs have shown applications in many field such as biology, photo voltaic

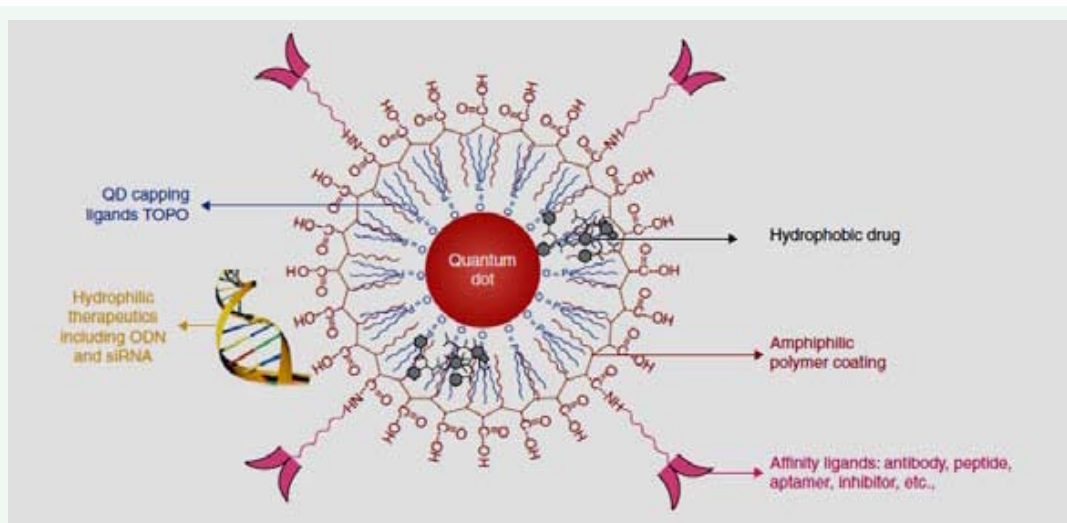


Figure 5 Schematic representation of a multifunctional quantum dot coated with amphiphilic polymer [15].

devices, light emitting devices, optics, LEDs, solar cells computing, photo detector devices etc. The major specific applications of QD in biological fields are drug delivery, targeted therapy, cell labelling, cell tracking, cancer therapy, bio imaging and cancer therapy [16,17]. In the following sections this chapter discusses the application of QDs in drug delivery, Bio imaging and in cancer therapy in detailed.

Drug delivery

QD act as nano-carriers for drugs and has the potential to detect and monitoring the specific disease sites because of its characteristic optical properties. Anti-tumour drugs have various side effects such as toxicity to non cancerous cells, nonselectivity and poor targeting etc. Due to the lack of bioluminescence, tumours can be difficult to locate and remove especially in the case of smaller sized tumours. So it is very desirable and important to target the cancer cells with specificity and it's *in vivo* imaging. The targeting of cancer cells with high specificity will achieve only through the introduction of nanocarriers for drugs. Nanocarriers for drugs are nanovehicles such as micells, dendrimers, nanotubes, QDs etc.

QD nano carrier containing drugs will enhance the efficiency and reduce the side drugs to non diseased cell through targeting of the diseased cells. Because of smaller size and the selective targeting QD based drug carriers are most popular among other nano carriers. The most commonly used anti cancer nano carriers for drug are liposome, silica nano particle, polymer nano particle, chitosan etc. For targeted drug delivery the QD nano carriers must have some properties as following.

1. The nano carriers should be inert with drugs
2. The drug loading capacity and encapsulation efficiency should be high.
3. The nano carriers should possess some appropriate preparation and purification method

4. The materials shows good biocompatibility and low toxicity can be used as nano carriers.
5. The nano carriers should have certain mechanical strength and stability and appropriate particle size and shape etc.
6. The *in vivo* residence time should be high [18].

QD Forster Resonance Energy Transfer (FRET) is a new method to study the nano drug release *in vivo*. The surface modification of QDs with anti bodies that bind to antigen present in the target cells or tissue has resulted in the development of sensitive and specific targeted imaging and diagnostic modalities for *in vivo* and *in vitro* application. Bagalkot et al., reported a method for imaging and deliver anticancer drug to prostate cancer cells (PCa) based on the mechanism of FRET using QD-aptamer (Qd-APT).

In the recent years tumour cell targeting is focussed on ligands whose receptors are over expressed in tumour cells such as folic acid and siRNA. Due to the high binding affinity of folic acid with folate receptor folic act as a targeting ligands to deliver drugs in cancer cells. siRNA delivery in cells using QDs are excellent choice because of optical properties and intrinsic fluorescence.

Small interfering RNA (siRNA) delivery approach was discussed by Chen and his co-workers by co-transfection of siRNA and QDs with Lipofectamine™2000 [19]. Here the authors allow the siRNA to condense on the cationic membrane following standard cell transfection protocol, and the lipoplex was then incubated with fluorescent QDs. The results that the intracellular QD fluorescence intensity showed a direct correlation with the degree of silencing, which is identified from fluorescence intensity, because stronger fluorescence represents a higher level of lipoplex uptake by cells at a fixed ratio of Lipofectamine and QD concentrations. Concentration of QDs have a significant role in the biological applications that is if the concentration of QD is lower, then it is not enough to provide noticeable fluorescence

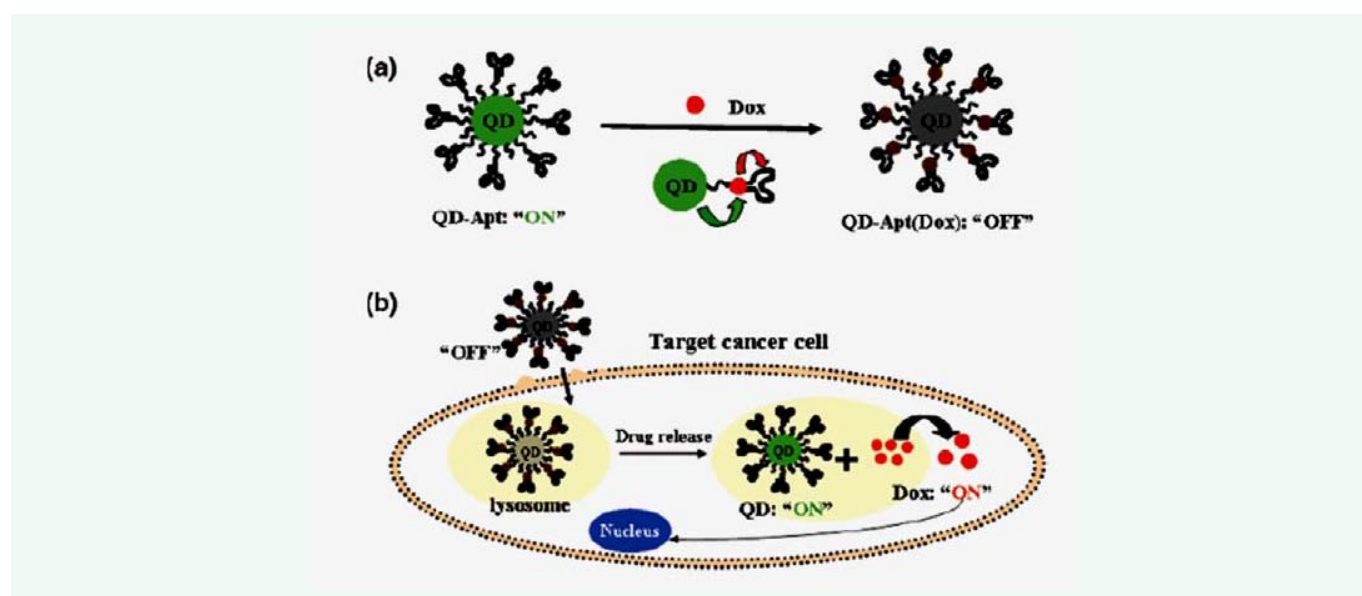


Figure 6 Schematic representation of QD-Apt(Dox) Bi-FRET system [8,22].

while higher amount of QDs reduce the silencing efficiency. The uniform QD-doped chitosan nanobeads have synthesized by Tan et al., for traceable siRNA delivery [20]. Jia et al., provide a route for antisense ODN delivery by combining PEI-coated carbon nanotubes with QDs [21].

The working method for QD-FRET is schematically illustrated in Figure 6. A donor-acceptor model FRET is formed between QD and Dox, and the fluorescence of QD is quenched by the absorbance of Dox which leads to the formation of a donor-quencher model FRET between Dox and aptamer. The fluorescence of Dox is quenched by double-stranded RNA aptamer in donor quencher model between Dox and aptamer. After the loading of QD-Apt with Dox both QD and Dox of the conjugate are in the fluorescence "OFF" [QD-Apt (Dox)]. When the particle is enter into the cancer cells, Dox is gradually released from the conjugate, which helps the activation of QD and Dox and both of these particles emit fluorescence and it is designated as "ON" state. Using fluorescence the cancer cells can be imaged easily. Bagalkot and his co-workers used CdSe/ZnS core-shell QD490 as a model QD, and the A10 RNA aptamer, as a model aptamer-targeting molecule [22]. Several groups reported the use of QDs for the preparation of drug carriers and for drug delivery [23].

Biological imaging

QDs show quantum confinement effects which means that the optical properties of these QDs are controlled by their size, than their composition, thus by considering the ability of QDs to emit spectacular colours QDs act as useful bio imaging agents. Because of the biological imaging capabilities, photo stability, bright fluorescence and the narrow and size tuneable emission spectrum, QDs shows a great role in the biological imaging area [24]³⁸. QDs which have a water soluble and paramagnetic micellular coating can be used in both fluorescence microscopy and magnetic resonance imaging. Targeting bio molecular affinity ligands like antibodies, peptides or small molecules can be conjugated with QDs via male imide or other functional groups which is used to detect molecular biomarkers and tumour cells at high sensitivity and specificity.

In vitro diagnostics the toxic nature of cadmium-containing QDs is no longer a considering factor but in the case of *in vivo* and clinical imaging the solubility and potential toxicity of QDs are a potential issue, so the use of multicolour QDs having hydrophilic surface passivating ligands was need to be introduced before *in vitro* and clinically relevant applications.

Consider the molecular imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) is not enough to attain all the necessary information of an affected area. In the case of tissues having a depth more than few millimetres with in a specimen the optical fluorescence imaging using MRI and PET are difficult to quantify MRI has low sensitivity and PET has poor resolution. This problem can be resolved by using the multiple molecular imaging techniques. The ability to see inside the body of a human being and understand the biological complexities which helped for the treatment of disease is very important and fastly growing areas and is happened through molecular imaging. The early detection and characterization of disease is the primary challenge in the treatment of medical field.

The QDs which showing an emission wavelength ranging from 700 to 900 nm can be used for biological imaging, because the QDs have near-IR luminescent property has maximum depth of penetration in tissue and the interference of tissue auto fluorescence is minimum [25,26]. Many factors such as aggregation, nonspecific binding of QDs, and specific target imaging should be considered when using QDs in biological imaging. In order to meet these requirements the system should be planned suitably. Surface modification of QDs another requirement for the use of QD in the biological application [27-29]. PbS and PbSe capped with carboxylic groups obtained ligands exchange method can be used to label cells [30]. *Salmonella typhimurium* cells can be imaged using CdTe capped with 3-mercaptopropionic acid (3-MPA) [31]. The labelling of HeLa cells was achieved through acid-capped CdSe/ZnS QDs [27].

CdS quantum dots (QDs) synthesized by Li et al., provide a practical and economical approach for single-target imaging application due to good photo luminescence of aqueous CdS QDs and the feasibility of aqueous CdS QDs as imaging tool was demonstrated with *Salmonella typhimurium* cells using 3-mercaptopropionic acid (MPA) as the capping molecule [32].

Mulder et al., developed MRI detectable and targeted quantum dots for targeting human endothelial cells *in vitro*. The paramagnetic quantum dots conjugated with cyclic RGD peptide conjugated and were synthesized and used for the detection of (tumour) angiogenesis [27].

Cao et al., were used near-infra red QDs with an emission wavelength of 800 nm (QD800) to label squamous cell carcinoma cell line U14 (U14/QD800). The authors also claimed that QD800-based *in vivo* imaging for early detection of cancer cells is 100 times better than the traditional cancer recognition methods. The present study also evaluated the effect of tissue depth and animal fur on the detection sensitivity and duration of near infra red QD-based *in vivo* imaging [25].

Hyun et al., introduced a protocol for making water soluble Pbs and PbSe quantum dots. They used carboxylic group functionalized QDs for specific labelling of cells and they demonstrated the use of these QDs in imaging human colon cancer cells. Initially the human colon cancer cells were recorded at wavelengths beyond 1000 nm but the prepared QDs give a near infra red fluorescence images for these cells which illustrate the potential of the water-soluble lead-salt QDs in biological applications [30].

Jiang et al., describes optimized synthetic parameters for preparing near infra red fluorescence emitting QDs for biological application. And they prepared CdS capped alloyed CdTexSe1-x QDs which are stabile against photo bleaching and shows >30% quantum yield, and <50% fluorescence full width at half-maxima [26].

Taniguchi et al., synthesized Water soluble, near infrared emitting CdTe/CdSe/ZnSe quantum dots for deep tissue monitoring through Successive Injection Precursors in One-Pot (SIPOP) procedure [32].

Another group synthesized CdTeSe and CdTeS ternary quantum dots (QDs) shows fluoresce in the red to near-IR regions

using chemical aerosol flow synthesis (CAFS) for cellular imaging [29].

Tumour cell targeting

In cancer treatment the surgeons remove both the tumour cells and surrounding lymphatic vessels and nodes in order to prevent the spreading of cancer cells to other parts of our body. The surgeons have to remove more number of lymphatic nodes to reduce the risk of spreading of cancer cells. But the removed lymphatic nodes may contain healthier vessels too; surgeons can't identify the affected area [33].

This problem is solved using the detection of tumour cells through imaging using dyes or other fluorescent emitting materials. Compared to healthy tissues the tumour cells and their surrounding membranes are more permeable and reactive towards dyes and radio isotopes because of the abnormal growth rate of tumour cells. If the primary tumour cells are injected with this radio isotopes, only the affected area is absorbs these isotopes very fastly and can be identified the presence of this dye. But the dyes used were migrating rapidly from the site of injection to the entire lymphatic system. This problem can be solved using QDs instead of dyes, and QDs show relatively slow migration and they maintain their ability to fluoresce for many hours.

Several studies have been reported for the use of QDs in cancer cell detection, imaging and treatment [18]. Due to the optical and chemical advantages of quantum dots (QDs) over traditional organic fluorophores QD-based nanotechnology act as an emerging candidate in biomedical imaging for cancer imaging tracking and diagnosis. Table 1 shows the properties and application of QDs compared to conventional organic fluorophores [32].

There are two methods called active targeting and passive targeting to locate and mark tumour cells by using QDs. Quantum dots which conjugated with tumour-specific active binding sites can attach themselves to tumour cells in active targeting. These tumours are then detected through the immunofluorescent probes which are manufactured with antibodies. In the case of quantum dot probes which do not have the tumour-specific active

binding sites the cancer cell detection is takes place through another mechanism called passive targeting.

Cai et al. evaluated the tumour-targeting efficacy of dual-function QD-based probes using both PET imaging and NIRF imaging. This approach reduces the potential toxicity and overcomes the tissue penetration limitation of NIRF imaging, which facilitate future biomedical applications of QDs [34].

Zeng et al., reported a two-step aqueous synthesis for the production of highly luminescent CdTe/CdSe QDs and a homogeneous shell of CdSe is shown in the CdTe core. The emission range of the prepared CdTe/CdSe QDs can be tuned from 510 to 640 nm by controlling the thickness of the CdSe shell. They also assessed the effect of folate conjugated QDs in Hela cells. The folate conjugated QDs efficiently enter in to the tumour cells and this investigation used for tumour cell recognition [5]. Current achievements, challenges and future directions in cancer therapy using QDs are summarized in Table 2 [35-39].

ADVANTAGES OF QUANTUM DOTS

- Quantum dots show good physical stability. The optical imaging probes other than QDs undergo degradation very fastly compared to these QDs shows more resistant to degradation and tracks cell processes for longer periods of time.
- QDs have greater photo stability than traditional dyes because of its special inorganic composition and the fluorescence intensity of QDs do not diminish with in 20s as shown by organic dyes.
- Compared to organic dyes QDs shows high value of signal to noise ratio.
- Organic fluorophores has a narrow absorption spectrum and organic dyes don't have a sharp emission peak. Compared to these particles Quantum dots shows broader excitation spectra and a narrow emission peak. Because of these properties, small amount of energy is enough to excite the QDs not considering of the QD size. So a single blue or ultraviolet wavelength beam is enough to excite

Table 1: Comparison of the characteristics and applications between traditional organic fluorophores and QDs [32].

Property	Traditional organic fluorophores	Quantum dots
Chemical properties	Chemical resistance is often poor	Resistant to chemical degradation; sensitivity to pH, determined by coatings
Size scale	Molecular, <0.5 nm	Colloidal, 1.5 nm to 10 nm diameter
Absorption spectra	Discrete bands, FWHM ^a , 35 nm ^b to 80 nm to 100 nm ^c	Strong and broad
Quantum yield	Variable, 0.05 to 1.0	High, >20% ^d
Fluorescence lifetime	Short, <5 ns, mono-exponential decay	Long, >10 ns, typically multi-exponential decay
Solubility or dispersibility	Control by substitution pattern	Control via surface chemistry (ligands)
Thermal stability	Usually poor	Excellent resistance to photo bleaching; observation time of minutes to hours
Toxicity	Variable, based on dye	Related to the heavy metal

a: FWHM, full width at half height of the maximum.

b: Dyes with resonant emission, such as fluoresceins, rhodamines and cyanines.

c: CT dyes.

d: Ligand, coating and solvent-dependent

Table 2: Summary of quantum dot applications in cancer diagnosis and treatment.

QD applications in cancer	Current achievements	Challenges	Goals for future development
SLN mapping	Map SLNs in mice and pigs		SLN mapping in cancer that involve visceral organs
Detecting primary tumour and metastasis	Detect primary tumour in xenograft models in mice	RES uptake	Detecting metastasis, especially micro-metastasis
Identifying molecular targets to aid targeted therapy	Reach tumour vascular in vivo	RES uptake: Difficulty in extravasating to reach tumour cells in vivo	Reach tumour cells; measure the level of molecular targets quantitatively; predict response post therapy.

multicolor quantum dots.

- Quantum dots are 10 to 20 times brighter and show significantly longer fluorescence lifetimes compared to organic dyes.
- Excitation of QDs by single sources is possible, and the multi colour QDs permits the application of different probes to track several targets *in vivo* simultaneously
- The QD-conjugates shows high signal intensity with low background interference because of the large Stokes Shift and sharp emission spectra.
- Moulding of QDs into different shapes is possible. QDs can be moulded into different shapes such as small crystals, quantum dust, in bead form and can be coated with a variety of biomaterials also.
- The manufacturing methods of QDs are cost effective and easy. QDs shows numerous manufacturing methods like lithographic techniques, epitaxial techniques, and colloidal synthesis

DISADVANTAGES OF QUANTUM DOTS

- The size of the QDs have a very good significance in the bio medical application because small size QDs easily removed from body by renal filtration but bigger particles has showed the possibility to uptaken by the reticulo endothelial system before reaching the targeted disease sites. The QDs having polymer coating with 5-20nm size shows optimum activity. Quantum dots when positioned in live cells may kill the cells Due to aggregation of QDs in live cells; it may kills or interferes with cell function [4,16,17].
- They have surface defects which can affect the recombination of electrons and holes by acting as temporary traps results in blinking and detoriates yield of the dots.
- The delivery of QDs into the target is difficult due to biconjugation of QD.
- Cytotoxicity:
- The metabolism and excretion of QD is unknown and its accumulation in kidney spleen and liver body tissues leads to toxicity.

Coating of QDs like Mercaptoacetic acid is toxic. Not only the coating the core part or building material of the quantum dots (Cdse) itself is toxic.

- The photolysis and oxidation cause leakage of heavy metal ions from the core which also leads to cytotoxicity [16].
- The surface defects in QDs act as temporary traps and negatively affect the recombination of electrons and hole which leads to blinking of QDs and that reduces the quantum yield of the dots.

CONCLUSION

Quantum dots are of highly attractive in the area of optics, photo voltaic devises, light emitting devices, LEDs, solar cells, computing, and in medical field. This chapter discusses the major areas of QDs in the field of bio medical application. The preparation methods and its working in biological systems are discussed in detail. The current trend of QDs and their applications mainly in bio imaging in drug delivery and in cancer therapy are also discussed. The chapter also discusses the main advantages and limitations of QDs.

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