Quantum Dot: A Boon for Biological and Biomedical Research

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Abstract Quantum dots (QDs) are mostly semiconductor nanocrystals, having properties in between bulk semiconductors and discrete atoms or molecules. Quantum dots can be synthesised using several methods from colloidal synthesis to chemical vapor deposition, for QDs synthesis, but the cheapest and the convenient method is benchtop colloidal synthesis. Due to exceptional optical and chemical behavior, QDs are broadly used in different areas, including light-emitting diodes, laser technology and solar cells, as well as in the biological and biomedical fields. This chapter provides the brief idea about QDs, including their synthetic approaches, biological relevance, and potentials in clinical applications like bio-imaging (cancer cell imaging), and targeted molecular therapy (drug delivery), as well as the leftover issues and future perspectives.

Keywords Quantum dots · Bioimaging · Drug delivery · Cancer cell

Abbreviations

2D	Two dimensional
3D	Three dimensional
ACE	Angiotensin I-converting enzyme
BSA	Bovine serum albumin
CPPs	Cell-penetrating peptide
DDS	Drug delivery system
DOX	Doxorubicin
EPR	Enhanced permeability retention

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GFP	Green-fluorescent protein
MUA	11-Mercaptoundecanoic acid
NIR	Near infrared
NPs	Nanoparticles
OSCC	Oral squamous cell carcinoma
PAR_1	Protease-activated $receptor_1$
PC3	Prostate cancer cells
PEG	Polyethylene glycol
PL	Photoluminescence
QDs	Quantum dots
QY	Quantum yield
SLNs	Sentinel lymph nodes
UV	Ultraviolet
VCAM-1	Vascular cell adhesion molecule 1
VEGFR2	Vascular endothelial growth factor receptor 2

1 Introduction

Crystalline semiconductor nanoparticle (NP) QDs are attractive candidate in the biological and biomedical research field due to their several unique features. NPs are different from bulk materials due to their exceptional structural and functional properties. Their unique quantum features, like quantum size, small surface and quantum tunneling effects, are responsible for their outstanding electrical and optical features [1]. There are several types of inorganic NPs like quantum dots (QDs; e.g., CdSe, CdS, CdTe/CdS, PbS and InP), carbon NPs, silica nanoparticles, magnetic compounds (e.g., Fe_3O_4, $CoFe_2O_4$, and CoPt), prompted the development of nanotechnology. Among them, QDs have the most exceptional features to be applied in the field of biology and medicine [2–5]. Quantum dots (QDs) are a heterogeneous class of inorganic NPs, having physical size close to or smaller than exciton Bohr radius [6]. QDs are zero dimension NPs having particle sizes <10 nm. The quantum confinement effects and reduced size make QDs an intermediate between a molecule and bulk solids. This confinement effect of QDs is also responsible for their extraordinarily attractive photophysical property like intensive photoluminescence (PL) [7]. In comparison with the usual organic dyes, QDs have better sensitivity, 100-fold more photostability, excellent biocompatibility and less invasiveness, and these features made them superior candidates for bio-imaging, bio-sensing, cell targeting and drug delivery applications [8–10]. QDs also behave as a good candidate for multicolor imaging in cellular and molecular label because of their exceptional optical features, like size-tunable broad absorption spectra, narrow emission spectra and large stokes shift [11]. Relying upon their size and composition, the optical properties of QDs can be tuned from ultraviolet (UV) to near-infrared (NIR) region. Mainly NIR emitted QDs are the promising candidates for both in vitro and in vivo deep-tissue imaging, in

the biological and biomedical purposes [12–14]. Having high molar adsorption coefficients and high quantum yields (QY), QDs do not require intense photon beams for their photochemical excitation purpose, which in turn avoid photo-damaging. QDs require functionalization with antibodies, proteins, peptides or drugs to enhance their water solubility and biocompatibility [15]. Regardless of the above-mentioned exclusive features of QDs, their extensive use in biomedical purposes is restricted due to their toxic side effects and biodegradability [16, 17]. Therefore, researchers paid attention to design non-toxic and biocompatible high-quality QD-based fluorescent probes, and some successful solution has been achieved in this context [18]. Herein, we discussed the properties and synthesis of QDs for their biological relevance or potentials in clinical applications like bio-imaging, cancer cell imaging, cancer cell targeting, drug delivery and their perspectives and shortcoming for in vivo biological and biomedical applications.

2 Quantum Dots (QDs)

Quantum dots are solid spherical-shaped (may exist with other shapes, for example, rods and tetra-pods) nano-size crystals, having diameter <10 nm (10–50 atoms). QDs consist of only a few numbers of free electrons and 10^2–10^6 numbers of atoms. The conventional type colloidal semiconductor QDs comprise mainly atoms of groups II–VI, III–V or IV–VI (e.g., CdSe, PbSe, CdTe, GaAs, InP, etc.) of the periodic table, among which Cd-based QDs have received more attention in biomedical uses. QDs contain a semiconductor core [e.g., cadmium selenide (CdSe)], covered with a semiconductor outer shell (e.g., ZnS) (Fig. 1).

First traditional lithography-based QDs were synthesized in 1980s by Louis E. Brus and Alexei Ekimov, which shows exceptional electronic and optical properties [20]. QDs being very tiny in size exhibit attractive photophysical behavior like they

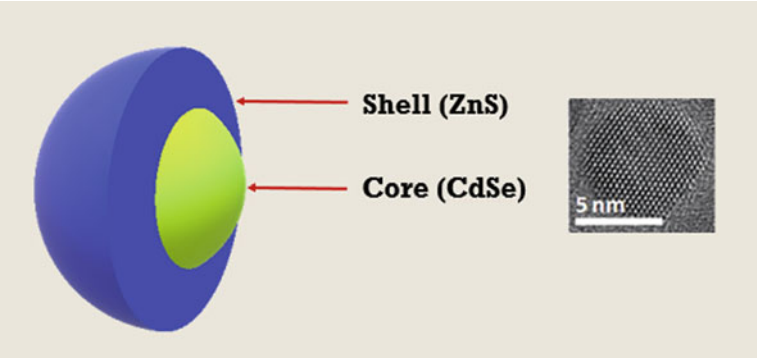

Fig. 1 Schematic representation of a core/shell QD and TEM image of the QD core. Reproduced with permission from Ref. [19]. Copyright 2015, The Royal Society of Chemistry

have narrow emission peak and broad excitation range, and their emission wavelength is also dependent on their particle size [21–23]. The size-tunable properties and high molar excitation coefficients of QDs made them a good fluorophore for biological, biomedical research and pharmaceutical industries [24–26]. Although a bare nanocrystal core is highly reactive and toxic, cap-enabled (using ZnS or SiO_2) and surface-modified QDs (adding biomolecules) have improved optical properties, water solubility, reduced toxicity and enhanced biocompatibility [27]. Although Carbon Quantum dots (C-QDs) are widely applied in electronics, sensors and catalysis due to their excellent electrical and electronic properties, but now a days they are also used in biomedical research [28] (detailed discussions about C-QDs fall beyond the scope of this chapter).

3 Properties of QDs

QDs, small crystalline semiconductor NPs, contain a few hundred to a few million atoms having size <10 nm with excellent optical and electronic properties due to their quantum confinement effect. Lower and higher energy levels of the semiconductors are called valance and conduction band, respectively. The resultant energy difference between the two bands is called band gap. After absorbing heat or light energy, electrons move from the lower energy level to the higher energy level, and thus, a hole is created at the valance band. The separation distance or gap between electron and hole is known as the exciton Bohr radius. If the exciton Bohr radius is greater than double of QDs size, then they will experience quantum confinement, and the particle in a box model can be used to evaluate their energy level. The energy involved with QDs is comprised of band gap energy, confinement energy and bound exciton energy. Since the electron of a semiconductor NPs is confined by the exciton Bohr radius, so their properties are dependent on the properties of electron and hole pair. Electrical conductive properties of semiconductor NPs can be changed by changing their size and shape; that is, lower the particle size, higher will be the band gap and vice-versa (Fig. 2) [29, 30].

That is to say, the photon's emission wavelength is directed by the size of the band gap, which can vary from UV to NIR region (400–1350 nm). For example, QDs with larger particle sizes have smaller band gaps and release red light, whereas QDs with smaller particle sizes and larger band gap release blue light (Fig. 3) [31, 32]. A quantum confinement effect of QDs is not only dependent on the size of the core, but also the chemical composition of the same. QDs are very similar to electron-bound nuclei; therefore, QDs act as an artificial atom, and it can excite and emit light together with sharp signal intensity. Compared to conventional organic fluorophores, inorganic QDs have very high fluorescence efficiency, elongated fluorescence lifetime of >10 ns and less photobleaching tendency. QDs also have a high molar excitation coefficient, large stokes shift, longer signal acquisition times and good photostability [33]. The diameter tunability and brightness (emission wavelength) properties of QDs make them suitable for multiplex detection [34]. Highly

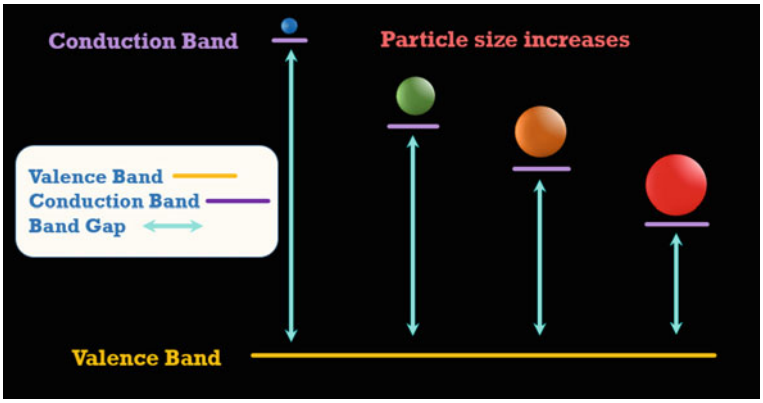

Fig. 2 Schematic representation of the size changes of the semiconductor NPs with band gap

luminescent, stable colloidal QDs are promising candidates for biological research and biomedical studies in vivo. The major drawback of heavy metal-containing QDs is their toxicity, which can be reduced by the modification of the QDs surface.

4 Surface Modifications of QDs

Semiconductor QDs required surface modification to reduce their toxic effects and to improve the optical property. Surface modification is a synthetic technique where the hydrophobic surface of the QDs is modified by attaching a variety of inorganic and organic or biological materials through sequential physical and chemical reactions. The surface of QDs can be modified by using thiol group coupling, multimodal ligand, cavity chain, group coupling and dendrimer (Fig. 4). For instance, polyethylene glycol (PEG) coatings are used to increase circulation time and stability and to minimize non-specific deposition of QDs for in vivo imaging [35].

Another advancement of surface modification of QDs is electrostatic interaction of the charged surfaces of QDs with a protein through polylysine chain. Encapsulation of a phospholipid micelle inside the QDs surface, through hydrophobic interaction, is also another effective strategy of surface modification. Here, hydrophilic part of micelle is attached to biomolecules and effectively improves efficiency of QDs for biological and biomedical experiments [37].

5 Synthesis of QDs

To synthesize QDs for biological purpose, one should pay attention to the material with high water solubility, less toxicity and having a wide range of emission

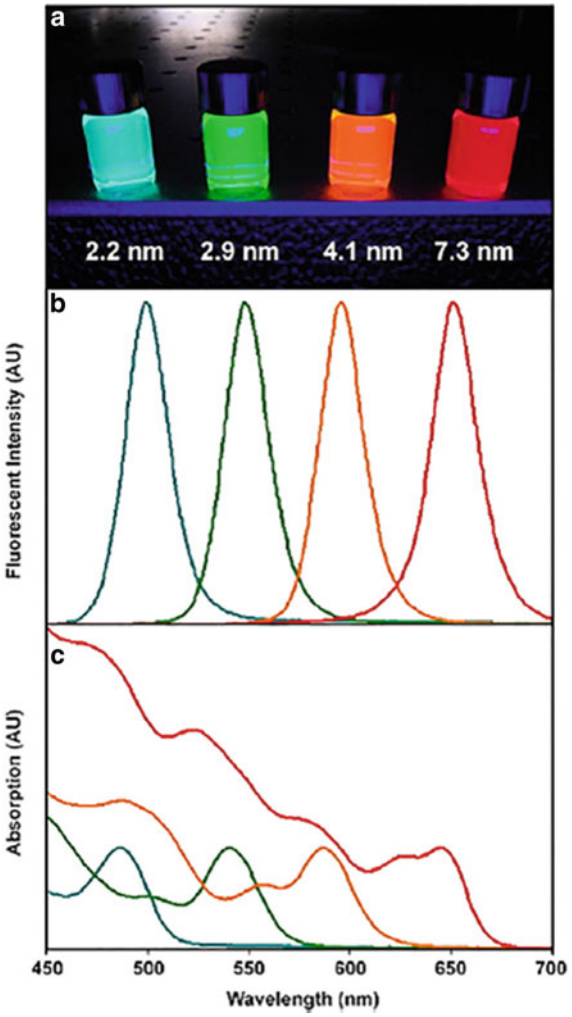

Fig. 3 Schematic representation of the change in fluorescent image (**a**), emission wavelength (**b**) and absorption spectrum (**c**) with the size of QDs. Reprinted with permission from Ref. [23]. Copyright 2019, Acta Materialia Inc., Elsevier Ltd.

wavelengths, ranging from ultraviolet to the infrared region. Among the frequently reported QDs like CdS, CdSe, ZnSe, ZnS, PbS, PbSe or CdTe, typically CdSe/ZnS, core/shell QDs are mainly used in the biological and biomedical purposes [38]. QDs that are usually used for biological and biomedical applications are prepared in such a way that they must have a semiconductor core such as CdSe, which is then shelled by another semiconductor material like ZnS. These core/shell QDs have improved optical properties and reduced toxicity [39].

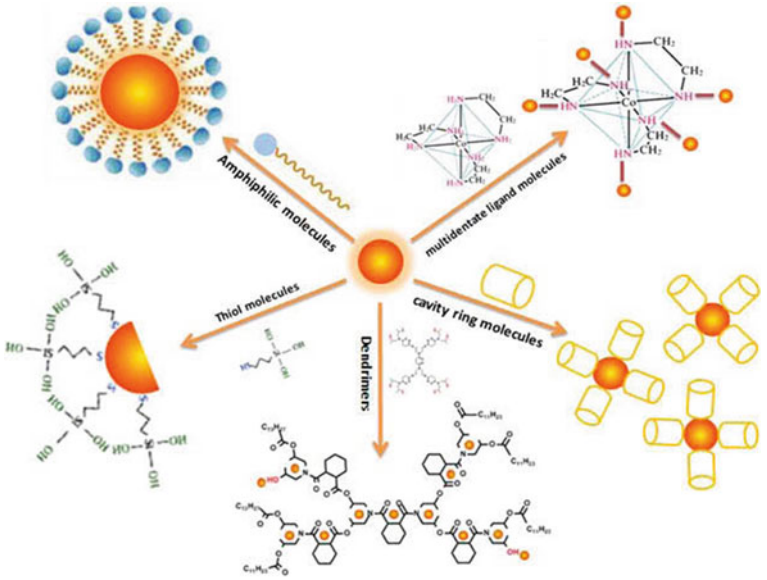

Fig. 4 Schematic representation of different surface modification techniques of QDs. Reprinted with permission from Ref. [36]. Copyright © 2014, Elsevier B.V.

General synthetic approaches for QDs are classified into two classes: one is the 'top-down' approach, and another is the 'bottom-up' approach (Fig. 5). Top-down synthetic methods consist of processing techniques such as X-ray lithography, molecular beam epitaxy (MBE), electron beam lithography and ion implantation [40]. In bottom-up approach, the colloidal QDs prepared in the solution phase via self-assembly of precursor materials [41–43].

5.1 'Top-Down' Approach

A bulk semiconductor is thinned by the top-down approach for making the QDs. These synthetic routes are fundamentally more straightforward and depending upon either on the removal or division of bulk material or on the tininess of bulk fabrication procedures to manufacture the desired structure with suitable properties. Commonly used methods to achieve QDs via this approach are electron beam lithography, high-energy wet ball milling, atomic force manipulation, gas-phase condensation, wet chemical etching, etc. This approach also suffers from some disadvantages such as low yield, incorporation of impurities, non-controllable size, shapes and structural imperfections *and so on* [44]. Uniformly shaped small nanoparticle preparation maintaining their proper crystallographic pattern is very difficult using conventional top-down techniques.

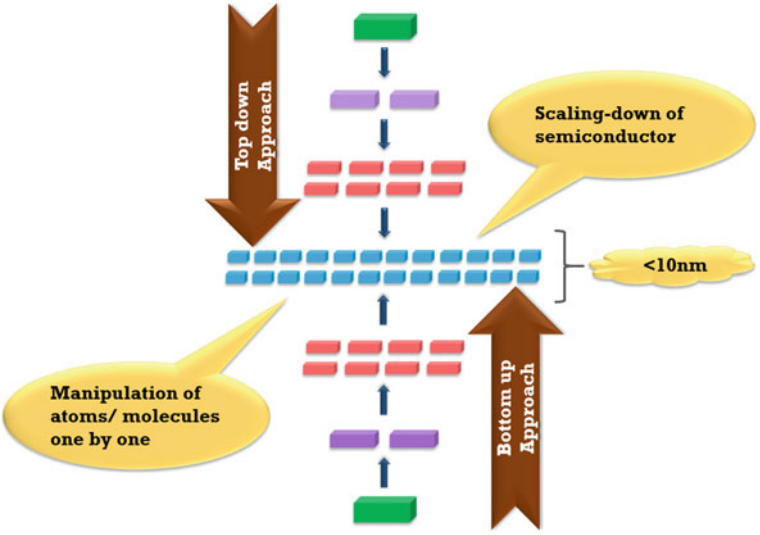

Fig. 5 Cartoon representation of general synthetic methods ('top-down' and 'bottom-up') of quantum dots

5.2 'Bottom-Up' Approach

In bottom-up synthesis, semiconductors QDs were build up of material from the bottom following atom-by-atom, molecule-by-molecule or cluster-by-cluster approach. This cost-effective approach produces less waste material. Some familiar techniques of QDs preparation using bottom-up routes are sol–gel synthesis, colloidal precipitation, oraganometallic chemical route, reverse-micelle route, hydrothermal synthesis, template-assisted sol–gel, electro-deposition, etc. The major challenge in the applying inorganic semiconductor QDs for biological purposes was the reproducible synthesis of highly luminescent, mono-disperse water-soluble QDs. In 1993, Murray et al. developed a groundbreaking bottom-up synthetic methodology to synthesize uniform colloidal mono-disperse nanocrystal QDs with a relatively high polydispersity and moderate PL and QY [45]. This high-temperature organometallic-based method, which resulted in a CdSe/ZnS core/shell structure to widen the band gap, inactive the surface, stabilizes the photophysical properties of CdSe core QDs [46]. First, aqueous phase synthesis of thiol-stabilized CdTe with small particle size and excellent QY was reported by Rogach et al. in 1996 [47]. In 2001, Peng et al. reported safe and larger scale synthesis of QDs using CdO instead of toxic $Cd(CH_3)_2$ that reduces toxicity by restricting leaching of the Cd^{2+} metal ion [48]. In 2013, Au et al. evaluated that the aqueous phase-synthesized QDs have better conjugation efficiency and stability than organic-synthesized QDs in biological media [49]. CdTe QDs with altered emission wavelength and improved QYs can be produced using a milder reaction conditions, i.e., lower temperatures (~100 °C), green chemicals (viz.

cadmium acetate; $Cd(Ac)_2$) and thiolated capping agent in aqueous solution [50, 51]. Nie et al. have even developed SeTe-alloyed QDs with different morphologies and unique optical properties independent of size by controlling the cadmium feed into the reaction mixture [52, 53].

6 Biological and Biomedical Applications

6.1 Bio-imaging

Bio-imaging is a non-invasive process that enables us to visualize, characterize and quantify biological processes taking place at the cellular and sub-cellular levels in a specific period within intact living subjects. It helps to depict different cellular and molecular mechanisms and pathways related to the disease of a living subject without inhibiting the various processes of life such as movement and respiration. It also helps to elucidate the 3D structure of specimens. QDs possess exceptional optical and electronic properties, viz broad absorption spectra, composition and size adjustable narrow emission spectra, high absorption extinction coefficients, increased quantum yields, large stokes shift, photochemical robustness which made them suitable for bio-imaging [54–57]. QDs show higher emission wavelength (near-IR > 650 nm) compared to the most commonly used optical organic probes [58–60]; for this reason, their depth of penetration into living tissue is maximum and are suitable for target specific sites [61, 62].

6.2 In Vitro Imaging

QDs NPs made of inorganic core material have unique photophysical properties that make them suitable for immune-fluorescent labeling. There is a big challenge to deliver them into the cell for cellular imaging. The core–shell structure and surface functionalization of QDs make them biocompatible, stable and soluble in the biomatrix. Specific tissues and cells can be targeted by QDs conjugated with antibodies, peptides and DNA [63–70]. In 1998, Bruchez and Chan et al. first demonstrated QDs application as immunofluorescent for antigen detection in fixed cellular monolayers [71, 72]. Osaki et al. revealed that QDs mainly transported within the eukaryotic cells by engulfing activity of the cells, where they consume external objects like, here, QDs along with the plasma membrane (Fig. 6) [73]. Another route for cell penetration of QDs is done via electrostatic interaction with the plasma membrane. Small size, amine surface, cationic charge, cell incubation media and human body temperature sometimes help cellular uptake. Libchaber et al. reported intracellular imaging of QDs by covalently conjugating mercaptoacetic acid-coated CdSe/ZnS QDs, which

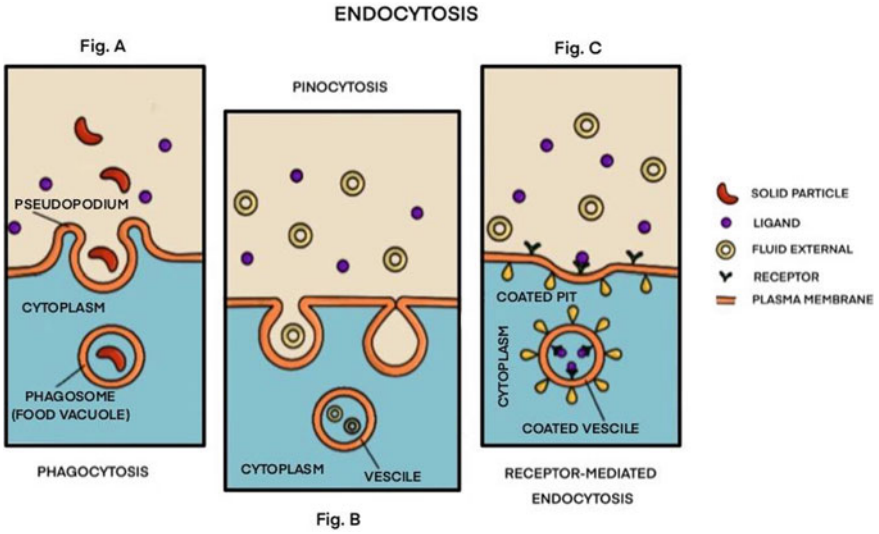

Fig. 6 Schematic representation of **a** phagocytosis, **b** pinocytosis, **c** receptor mediated endocytic pathway in mammal cell

spontaneously endocytosed by cancer cells and retained their bright fluorescence. PEG-coated CdSe/ZnS QDs used for intracellular staining of cells [37].

Non-invasive and invasive cancer cell lines can be distinguished by a quick-quantitative-easy in vitro 2D invasion assay using QDs, relying upon the process of phagocytosis (Fig. 6). In this 2D assay, cancer cells (both invasive and non-invasive) were seeded on top of a homogenous layer of QDs and are incubated. It was observed that the invasive cancer cells engulf (phagocytose) the QDs as they migrate. As the fluorescent QDs are engulfed by the aggressive cancer cells, this phenomenon leaves behind a non-fluorescent phagokinetic track, free of QDs [74]. Nisman et al. demonstrated to label the nuclear protein on cell sections. They also employed QDs in conjunction with immuno gold to co-localize proteins at the ultrastructural level [75]. A few different techniques that have been employed to deliver QDs into the cells are micro-injection, non-specific uptake of QDs via endocytosis or conjugation of QDs with translocating proteins or cationic peptides [37, 76, 77].

6.3 In Vivo Imaging

Size and composition tunable strong fluorescence signal made QDs a promising fluorescent probe for the in vivo imaging. In live mice, tissue-specific vascular markers were targeted using peptide conjugated QDs, by intravenous injection. The high in vivo specificity of these peptide conjugated QDs is attributed to the identifying of specific molecular markers expressed by blood vessels of organ/tissue/tumor by a

unique set of homing peptides. These peptides guide the QDs to the suitable vascular site in the live mice. So, when CdSe/ZnS QDs coated with a lung-targeting peptide are injected intravenously in live mice, it binds only in the lungs' blood vessels [78]. Stroh et al. demonstrated in vivo multi-photon imaging using semiconductor QDs. They also demonstrated the ability of QDs to monitor tumor vasculature and cell trafficking [79]. The lymphatic system can be called the drainage system of our body that helps our body to fight against infections and diseases, and it is made up of nodes, vessels and capillaries, containing lymphocytes. When tumor cells attack the local lymph node, they spread quickly over the whole body through extensive lymphatic network. Sentinel lymph nodes (SLNs) are the closest lymphatic nodes of the tumor cell. For effective cancer treatment and its surgery, it is essential to know the mapping of SLNs. The first demonstration of SLN mapping using NIR QDs was done by Kim et al. for image-directed surgery. The QDs entered into the animal lymphatic system through intradermal injection can be monitored through real-time images of lymphatic nodes and selectively identify the SLN for the surgical purposes [80]. Morgan et al. showed that the semiconductor nanocrystals of CdMnTe/Hg coated with bovine serum albumin (BSA) have significant photostability and cheaper than competing MRI technology [81]. Mapping of lymphatic drainage is problematic due their difficult accessibility and smaller size. NIR QDs can be used in non-invasive manner for imagining of multiple lymphatic drainage simultaneously as reported by Hema et al. and Kobayashi et al. Their study reveals the advantages of NIR QDs for in vivo multiplexed diagnostics [82, 83]. Noh et al. demonstrated NIR QDs guided non-invasive in vivo tracking of dendritic cells migration in the lymph nodes [84]. Their study helps to track immunotherapeutic cells. Accumulation of QDs inside the specific region of lymphatic nodes was demonstrated by Pic et al. [85]. Due to the lack of appropriate methods, it is difficult to track the real-time flow of lymph, which was resolved by Kosaka et al. combining macro-zoom fluorescence microscopy and QDs optical lymphatic imaging [86].

6.4 Tumor Cell Targeting and Imaging

In this century, cancer is a significant challenge for global public health. After several studies regarding cancer invasion, now it is clear that it is an adaptive process with the tumor microenvironment. For in vivo cancer imaging and its research are essential to know its biology, the location and distribution of tumors cell environments. Due to the unique optical and chemical properties of QDs over conventional organic fluorophores, they act as a promising candidate in biomedical imaging for cancer imaging, tracking, and diagnosis. Usually, antibodies tagged with QDs applied to target tumor cells [87, 88]. Antibody-labeled QDs entered into cell membrane through the blood vessels and are delivered to the perinuclear region [89]. Identifying the antibody delivery pathway significantly improves therapeutic efficacy. Membrane fluidity, morphology and membrane protein dynamics play a vital role in cancer metastasis. QDs-labeled metastasis-promoting factor [protease-activated

receptor$_1$ (PAR1)] inside cell membrane combined with anti-PAR1 antibody gives in vivo imaging of cancer cells and PAR1 during metastasis [90]. QDs (Qdot 800 QDs) functionalized with cell-penetrating peptide (CPPs) shows high sensitive image in oral carcinoma cell [91]. Another promising approach to improve cancer detection and treatment is multiplexed imaging. In this technique, green-fluorescent protein (GFP) coupled with QDs helps to distinguish tumor vessels from both perivascular cell and the matrix [79, 92]. An effective strategy for cancer treatment is cell-based cancer immunotherapy. Here, various therapeutic cells (e.g., lymphocytes, dendritic cells and natural killer cells) are tagged with QDs (e.g., Qdot 705, Life Technologies) and then systematically circulated into cancer patients' body. Since this is patient's own immune system-based therapy, so major advantage of this strategy is the effective tracking of injected therapeutic cells and less side effects on normal cells [93, 94]. The most effective method for cancer treatment is complete surgical resection of lymph nodes where high resolution image guidance is required. In image-guided surgery, NIR QDs (e.g., CdTe) attached with tumor-specific peptides (cyclic Arg-Gly-Asp peptide, cRGD) were injected into the U87 MG tumor xenografted mice through tail veins. This NIR QD-based bioconjugate shows significant enhancement of NIR signal within the vessels consequently, helps to locate the tumor cells and resects them [95]. QDs functionalization with vascular cell adhesion molecule 1 binding peptide (VCAM-1) enhances fluorescence intensity in vivo and ex vivo experiments which helps to visualize the VCAM-1 expressing endothelium in vivo [96]. Kwon et al. showed that how NIR QDs help to visualize anti-VEGFR2 (vascular endothelial growth factor receptor 2) antibody conjugated QDs for angiogenesis of cancer cell. Fluorescence enhancement at the tumor region of the prostate cancer (PC3) xenografted mouse after 12 h of injecting QD-conjugated antibody indicates that this technique can further be used to selectively monitor cells having up regulated expression of VEGFR2 [97].

7 Drug Delivery

A drug delivery system (DDS) is mainly used to enhance of the efficacy of the existing medication. It is an engineered technology to administer a pharmaceutical compound to achieve its therapeutic effect. It helps in selectively discharging the active constituent in the systemic circulation and thereby transferring them through the biological membranes to the operation site. The effectiveness of DDS can be optimized by controlling the time, rate, and site of release of drugs in the body. Currently, applications of QDs appear to be an emerging field of research as DDS, especially for cancer research. The preference of QD over other nano-carriers like dendrimer, micelles, silica nano-sphere, or nano-tube arises from its inimitable optical properties that make it a potential candidate as a carrier or delivery vehicle for biological applications. There are different techniques by which drugs can be laden into QD nano-carriers like adsorption, coupling, dispersion, dissolution, etc. The physical, chemical, or biological response of the drugs is altered due to their conjugation with

QDs and thus, the absorption, distribution, metabolism, and excretion of drugs are also affected. Eventually, QD nano-carriers for drugs can boost their effectiveness and decrease their harmful side effects to increase the therapeutic index. Ideally, any QD nano-carrier materials for the drugs should not react with drugs, should have high drug loading capacity and encapsulation efficiency, must be biocompatible, and less toxic, have longer dwelling time in biological systems, specific mechanical strength and stability and proper shape and particle size. Detectable drug delivery of therapeutics in vitro and in small animal models has a significant influence on biological research. In living systems, non-invasive recognition of any therapeutics tagged with drug carriers, in real-time requires specialized imaging techniques. QDs have the potential to elucidate the pharmacokinetics and pharmacodynamics of drug candidates. QDs can deliver a specific doses of the drug to the appropriate sites via enhanced permeability retention (EPR) effect. QDs being nanoscopic in size (<10 nm) and having a high surface-area-to-volume ratio can easily interact with biological molecules via surface adhesion and thereby found an exceptional opportunity as drug carriers in biomedical applications. Captopril, an antihypertensive drug, when conjugated with QDs, in vitro and in hypertensive rat model, reduces blood pressure by inhibiting the activity of angiotensin I-converting enzyme (ACE) [98]. CdSe/ZnS QD as DDS can reduce side effects and drug resistance of chemotherapeutic drug erlotinib used against non-small cell lung carcinoma [99]. Hypoxia-induced chemoresistance in oral squamous cell carcinoma (OSCC) overcome by the use of QD as DDS. Under hypoxia, PEG-modified graphene QDs loaded with platinum induce apoptosis via S phase cell cycle arrest in OSCC and a prominent tumor growth, inhibitory effect with less systemic drug toxicity was also reported in an OSCC xenograft mouse tumor model [100]. Carboxymethylcellulose hydrogel nanocomposite films conjugated with graphene QDs and doxorubicin (DOX) act as a pH-sensitive anticancer drug delivery system in blood cancer cell line K562 [101]. Despite having anti-cancerous properties and aqueous solubility sesamol was less bio available i.e, it has difficulties in penetrating cell membrane and thereby its cellular uptake is retarded. Its bio-availability and thereby cytotoxicity increase considerably after conjugation with CdS modified chitosan [52]. QD-based DDS have enormous prospects in treating cancer in terms of drug loading, targeting and enhanced efficacy. Many cancers (like breast, lung, kidney, ovarian, etc.) are known to express folate receptors in an appreciable quantity; folate receptor targeting DDS can be useful in treating these types of cancers with the existing chemotherapeutic drugs [102]. AgIn/ZnS QDs coupled with 11-mercaptoundecanoic acid (MUA)/L-cysteine/lipoic acid, when further loaded with folic acid and doxorubicin (a chemotherapeutic drug), behaved as targeted DDS to treat human lung cancer (A549 cell line) in vitro [103].

8 Conclusions

QDs, the tiny light-emitting nanocrystals of semiconductor materials, are a blessing for biological and biomedical research because of their numerous promising applications in real-time in vivo, cellular imaging, cell labeling and drug delivery. QDs have several advantages in comparison with usual organic dyes used for the bio-imaging purposes. They have exceptional optical and electronic properties, for example, size-tunable emission spectra, broad absorption range, narrow emission spectra, negligible photobleaching, better brightness, etc. In spite of QDs remarkable photochemical and photophysical properties, its in vivo applications are quite restricted owing to the relatively large size, degradation and toxicity. Typically, the toxicity of QDs is dependent on different parameters like their size, charge, coating, experimental conditions, surroundings, etc. Quantum dots that possess heavy metals like cadmium, arsenic, mercury or lead in the inner core may release toxic ions due to oxidation or photolysis [65, 104]. The escaped metal ion from the inner core may be enriched and stay for longer time inside the body that may cause a potential threat to that host [105]. Quick removal of QDs from the body circulatory system by phagocytic cells in systemically fixed tissues or entrapment QDs in the spleen or liver gives rise to heightened background noise or poor quality bio-image. Another challenge is the batch-to-batch variations or lack of reproducibility in the production of QDs. Clinical translation of QDs remains a challenging task because of the availability of less number of information in the literature regarding the relationship between physicochemical properties and pharmacokinetics/pharmacodynamics of QDs. Various synthetic techniques or strategies were adapted to enhance their effectiveness in different biological and biomedical applications. Finally, we hope that researchers will address these shortcomings and continue to move forward with modified QDs that may be suitable for human use.

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