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Review On Quantum Dots: Fabrication, Characterization, Functionalization And Biomedicalapplication

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ABSTRACT
Quantum dots (QD), which are also known as nanoscale semiconductor crystals, these are nanoparticle which tend to have optical and electronic properties such as bright and intensive fluorescence and has different colors according to size. QD's are preferred over other organic label dyes because it emits light in a very specific gussian distribution and has high photo stability; resistance to photobleaching is 100-1000 times higher than other organic fluorophore. IT has narrow and symmetric peak of emission, strokes more than 200nm (ease to detection) and it is possible to control the emission by changing size and structure. There are many applications of quantum dots in medical fields such as cellular imaging, biomolecular tracking, tissue staining and targeted drug delivery and therapy. The review outlines the various biomedical applications of QDs such as (imaging, drug delivery system, immunoassay and sensor) and its optical characteristics.

KEY WORDS: Quantum dots, cellular imaging, photo stability, biomedical application.

I. INTRODUCTION

Quantum dots are substances which are having low dimensional material and the dimensions of these materials in all three dimensions are no larger than twice the exciton Bohr radius of their corresponding material. These are mostly spherical or quasi-spherical with a diameter between 2-20 nm and are roughly divided into semiconductor QDs, carbon ODs, two dimensional (2D) QDs (1).Quantum dots (QDs), which are also known as nanoscale semiconductor crystals, it was first reported by Ekimov and Onushenko in a glass matrix back in 1981,with first biological imaging application reported in 1988. As the field of QD is expanding successively and now include application in field of solar cell, photovoltaic device , light-emitting diode fabrication, photo detector, computing, biomedical imaging and so on(2). Colloidal QDs consist of element from different groups II-VI, II-V, III-V, IV-VI, I-VI, I-III-VI and V, its research was widely focused on material from group II-IV such as cadmium, lead and mercury for the core material but many of this material exhibit considerable toxicity in body even in low amount because of this heavy metal free QDs was proposed by Bawandi, who is known to be the pioneer in advancement of heavy metal free QDs by fabrication of group I-III-VI QDs via hot injection method (3).As most of the QDs are prepared with the help of non polar organic solvent, so to make it solubilize in aqueous medium the hydrophobic ligand present in the surface of QDs must be replaced with amphiphilic one, different techniques have developed over the past few years to increase the solubility of QDs in in aqueous preparation such as i) ligand exchange with simple thiol-containing molecule, ii) encapsulation with a layer of amphiphilic diblock, iii) combination of layer with different molecule granting the required colloidal stability to quantum dots (4).These crystals are promising nano-meter scale semiconductor which are having characteristics such as fluorescent emission, high resistance to photobleaching, broad absorption with narrow photoluminescence spectra, and long fluorescent lifetime(5). These merits allows the use of QDs in various biomedical fields such as labeling, immunoassay and bioimaging/sensing media(6). For application in these systems, QD were conjugated covalently with protein, antibodies, peptides, DNA, RNA, enzyme and pollutants. The method which are use for bioconjucation of QDs are electrostatic or hydrophobic attraction, bijunctional linkage with universal coupling agent such as 1-ethyl3-(3-dimethylaminopropyl)carbodiimide(EDC) (7). QDs have spectrally broad absorption with large molar absorption coefficient (in the range of 10^5 -10^7 M^{-1} cm^{-1}) and can be excited in the UV range, with subsequent photoluminescence (PL) emission detected in visible range. Quantum yield of QDs tends to be similar to those of fluorescent dyes, but

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the larger absorption coefficient of QDs make it 10-1000 times more brighter than many dyes (7).On atomic level, the emission wavelength of light depend on the QDs size, hence the emission wavelength can be modulated by synthesizing QDs of desired size. QDs which are of large size(>10 nm) emits lower wavelength (blue) of electromagnetic spectrum compare to the small one (2-10 nm)because as the size increases the difference in energy between conduction and valence band also increases, since the emission of light occurs when electron from valence band get exited and jumps to conduction band and then get de-exited therefore QDs emits specific wavelength depending on the energy difference between valence band and conduction band and that is why change in the size of QDs causes change in the emitted wavelength (8) .The downside of QDs uses in medical field are that it results in multi exponential decline of fluorescence and blinking of separate QDs, high background level of detection and accumulation of QDs in reticuloendothelial system, it may lead to Instability and increase hydrodynamic diameter after interaction with the serum proteins and high toxicity when used in invivo system followed by incomplete elimination of QDs(9) .Toxicity caused by QDs core (CdSe, CdTe) can by minimized by coating it with ZnS, which minimize Cd exposure and leakage/dissolution in cellular environment(10) .This review tells us about the various properties of QDs, their fabrication, characterization, uses in biomedicalfield, functionalization and the toxicity caused by it.

FABRICATION

Generally QDs are prepared by adding desirable organometallic substance to heated trioctylphosphine oxide which is vigorously stirred under ambient condition. Oddly the solution began to change color from blank to yellow, followed by orange and then to red/brown, depending on their size. when the QDs of desired size is obtained the hest is removed and the obtained QDs is screened by placing them under black light (11) .QDs can be synthesized with the help of various pathways but usually only two routes are used, top down processing method and bottom up approach (12). In top down method large substance are broken down to nanosize structure or particle, these methods are simple and work by removal or division of bulk material. One of the major problem with top down method is that is results in surface imperfection and impurities. On the other hand in bottom up approach substance are formed when small particles such as atoms, molecules and cluster comes together (13).

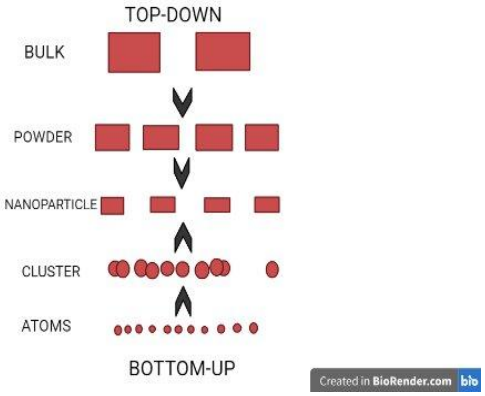

Fig.1) Top-down and bottom-up diagrammatic representation.

TOP-DOWN METHODS

ION IMPLANTATION METHOD

Ion implantation is one of the most versatile method for preparation of semiconductor crystals of the constituent species, later followed by annealing so that nanocrystals can be precipitated from the supersaturated solid solution (14). It is mostly a low temperature process in which ions of one element is projected to the target substance which result in change of the physical, chemical or electrical properties of the target (15).This method is can be used for studying the life span of QDs by applying different ion implantations over it and exposing them to the radiation (16).

international Journal of Pharmaceutical research and Applications
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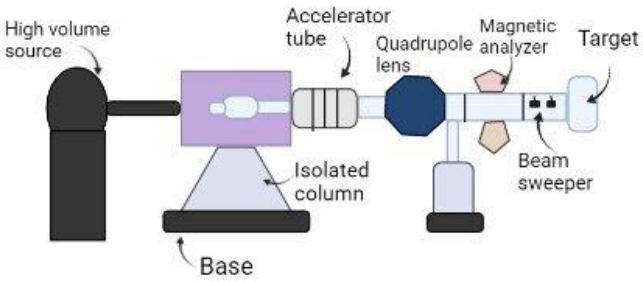

Fig.2) Schematic diagram of device for ion implantation .(17)

E-BEAM LITHOGRAPHY

Key fragmentation method, it was developed by modifying the design of scanning electron microscopy in the late 1960s. In this system a beam of electron is focused to the substrate covered with electron sensitive material, which leads to change in its solubility because of the energy deposition caused by the electron beam (18). The electron beam is controlled by magnetic lenses so that it would result in spot of small size. Scattering is very crucial for the function of electron beam liathography as scattering of electron after interaction with substrate is responsible for change in chemical properties(19).

Fig.3) Schematic diagram of E-beam lithography.(19)

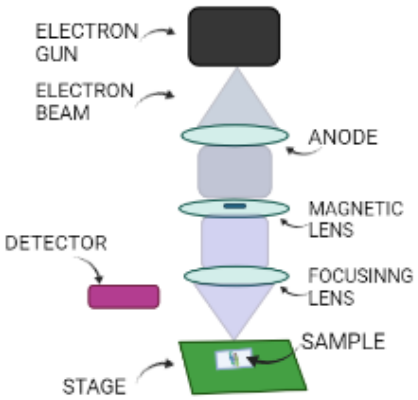

Fig.3) Schematic diagram of E-beam lithography.(19)

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BOTTOM UP APPROACHES

MOLECULAR BEAM EPITAXY

This technology has been employed for various purposes, for the growth of single crystal thin film, quantum wells, and superlattice and was evolved first as a research system for the formation of single crystal thin film and superlattice. With the help of this system mass production of compound such as semiconductor thin film under closed environment was feasible (20). The principle behind this method is that it forms atoms or cluster of atoms by heating of solid materials which are then transferred to the UHV environment so that it can be impinge on the surface of hot substrate and then be incorporated into the growing film (21). This method provides QDs of high-density, uniform and defect free array. These characteristics can be accomplished by two routes: nucleation through droplet epitaxy or strain derived process, both the path relies on stochastics nucleation method so that the resulting assembly of QDs are distributed randomly throughout the substrate (22).

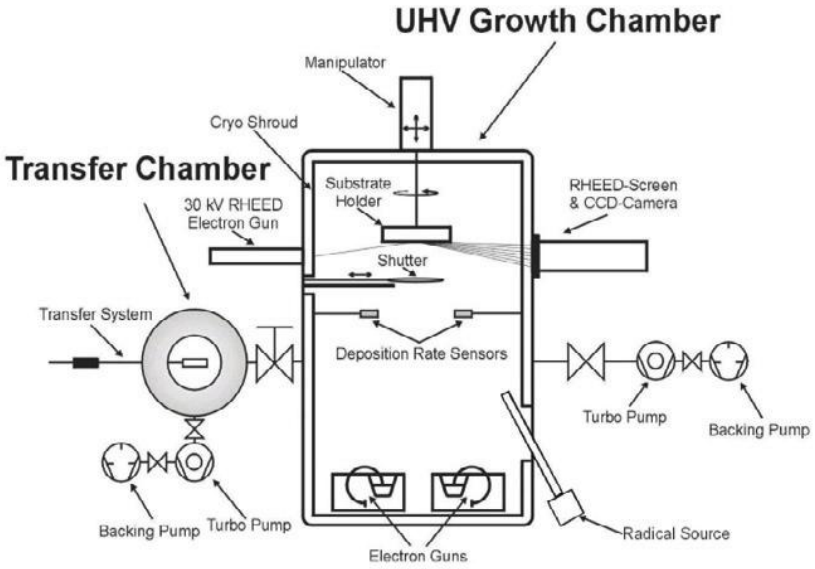

Fig.4) Schematic representation of reactive molecular beam epitaxy setup.(23)

CHEMICAL VAPOUR DEPOSITION (CVD)

In this process the substrate is exposed to the volatile precursors, which leads to the reaction and deposition of precursor on the surface of substrate. At high temperature vaporized precursor are firstly adsorb on the surface of the substrate and followed by reaction, which leads to production of crystals (24). There are wide range of advantages, one of them is that it gives high deposition rate where as the disadvantage is that precursor needs to be volatile near the room temperature(25).

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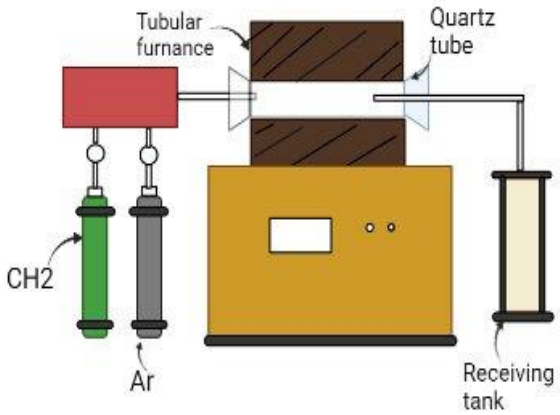

Fig.5) Schematic representation of chemical vapour deposition apparatus.(26)

CHRACTERIZATION

Characterization of optical properties of QDs are generally done with the help of UV-Visible and photoluminescence spectroscopy because they provide fast, contactless and non destructive result (27). Optical properties of QDs are size dependent as energy gap increases with decrease in the size therefore producing size dependent colored QDs. Small QD provides wavelength near blue spectrum where as large QD near red(fig5), thus it is clear that optical property is not only dependent on the material from which it is made but also the size of the QDs (28).

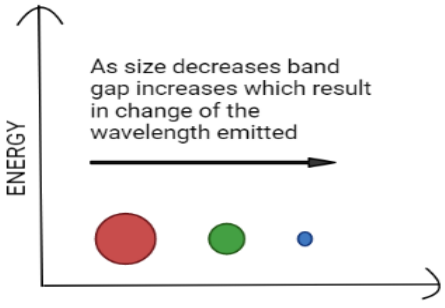

Fig.6) Size dependent band-gap energy.(28)

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Quantum dots size are usually calculated with the help of conventional techniques such as scanning electron microscope and transmission electron microscope (27). Transmission electron microscope provide particle size histogram from which one can clearly see the particle size distribution (29). For the quantitative analysis of quantum dots Energy-dispersive X-ray spectroscopy is used (EDS). To determine the change on the surface of QDs Fourier transform infrared spectroscopy is used (30)and x-ray photon electron spectroscopy was done to make sure the chemical state of synthesized quantum dots (31). With the help of X-ray defraction spectroscopy and scherrer equation size of the quantum was calculated by the author in table 1, scherrer equation $d = .9\lambda/\beta\cos\theta$ (30)(32).

Table 1.Size,luminescence quantity yields and luminescence maxima of QDs in solubilized water(32).

QDS	Size,nm	Λlumn,nm	ϕlum
TGA-CdSe	2.0	539	0.016
MPA-CdTe	2.7	563	0.47
GSH-CdSe/ZnS	2.8	580	0.61
GSH-CdTe/ZnS	3.1	600	0.41
MPA-CdTe/ZnS	3.1	557	0.72
TGA-CdTe	3.2	609	0.14
L-cysteine-CdTe	3.5	633	0.44

FUNCTIONALIZATION

Functionalization allude to modification of surface of the nano particles(NPs), that include conjugation with biomaterial or chemical like antibiotics, biotin molecule, peptide, oligo nucleotide, etc., on the surface of NP (33).

RATIONALE FOR FUNCTIONALIZATION

It is used to improve the property of NPs so that it can hit the target cell with high precision; it also provides particle good physical properties, anti-agglomeration, noninvasive and anticorrosion characteristics. Basically Functionalization is used to develop properties that we want to incorporate into the preparation (33) and also to stabilize it, as we know that bare QDs can result in photochemical degradation, leaching of metal ion from the core of QDs which may result in metal ion toxicity. Therefore surface of QDs are capped with stable compound (such as ZnS) to reduce the high reactivity and surface defects (34).

METHODS USED IMPROVING SOLUBILITY OF QDs

1) Ligand exchange - In this method the previous Ligand present on the surface of the QDs are replaced by the desirable one, example-dithiocarbamate is used to replace the original Ligand of QDs, in this experiment QDs were precipitated in MeOH and than they were redissolved in chloroform. Than dioctyamine was added in excess followed by addition of equimolar quantity of CS2. Then the solution was stirred for about 3 h at room temperature before the nanoparticle were precipitated with MeOH. The supernatant was discarded and newly coated dithiocarbamate QDs were obtained (35).

2) Surface silanization - Process of changing of QDs into more biocompatible and more effective species, in this process the surface of the QDs is covered with silica hence termed as surface silanization. First step involved in this process is exchange of surface Ligand with thiole derived saline (such as mercaptoproplytris silane). Cross linking of trimethoxysilane group can occur by formation of siloxane bonds. Most commonly used agents are phosphosilanes and aminopropylsilanes (36).

3) Amphiphilic combination - In this method the hydrophobic QDs are covered by Amphiphilic material without the removal of the original ligands. Encapsulation occurs by hydrobhobic-hydrobhobic interaction between these ligands (such as octyl chain of trioctylphosphine oxide and hydrophobic part of Amphiphilic chain). This is the most easiest and effective method of make QDs water soluble (37).

CHEMICAL FUNCTIONALIZATION STRATEGIES

For the application of QDs in biomedical field various conjugation are done with the help of protein, ligand, nucleic acid and peptides. Approaches used for immobilization of biomolecule

international Journal of Pharmaceutical research and Applications
Volume 6, Issue 6, pp: 509-524 www.ijprajournal.com ISSN: 2456-4494

on the surface of QDs are of two types 1) covalent linkage and 2) non covalent linkage (38).

Covalent linkage

Here QDs are covalently bound to the biomolecule with the help of certain tags such as ACP, SNAP and CLIC. ACP(acyl carrier protein) was used to couple QDs with COA in an 1:1 ratio, this coupling occurs via "straight forward thiol-reactive chemistry in an appropriate concentration of amine-blocking groups on the QDs" (39).

Non covalent linkage

Charged group present on the surface of QDs interact with the biomolecule of opposite charge, this leads to the coupling of biomolecule on the surface of QDs but are effected by various factors such as ionic strength, presence of competing molecule and ph (38).

Table2**.** Comparison between the methods used for conjugation of DNA on QDs.

S.NO.	Approach	Modification on DNA	Modification on QDs	Disadvantages	Advantages
1	Affinity for cationic shell of QDs	Thiol/polyhistidine/phosphorothioate	Positively charged or neutral	-unstable in high dilution -loss of DNA by photo-oxidation -ph sensitive	-rapid assembly -high yield -compact (40)(41)
2	Phospholipid encapsulation	Amine/thiol	Organic ligand	-stability issue -large size of particle -random fusion with the membrane	-one step procedure -DNA retain hybridizability -compatible with range of synthesis (40)(42)(43)
3	Affinity for specific ligand	Biotinylated DNA Polyhistidine modified	Streptavidin conjugation Ni-NTA modified	-increase in conjugated size due to the presence of protein -ph sensitive stability	-fast and easy -high QY(quantum yield) -conjugation of DNA independent of length(40)(44)(45) -one step -efficient -high QY (40)(46)
4	Electrostatic attraction with polymer on QDs	Unmodified :interaction with phosphate back bone	Positively charged hydrophilic ligand	-difficult to control stoichiometry of DNA -issue with stability and aggregation	-rapid -high DNA loading efficiency (47)

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BIOMEDICAL APPLICATION OF QDs

CHART 1: Biomedical application of quantum dots

BIOIMAGING

QDs are progressively used for invivo fluorescence imaging, this method is better that other as it is non invasive and has good level of sensitivity (48). Know a day's studies are focused on development of QDs that have near-IR luminescent property and emit walvelength ranging from 700-900 nm as this range provide maximum penetration and minimum interference (49). Major advancement in the use of QDs has been made in the field of live cell imaging, biomarker detection, and detection of tumor cell (50). Biomedical application, their transformation and various processing of biomaterial or drugs can be observe with the help of QDs, for example- Share thinning biomaterial (STB) are injected in conjugation with graphene QDs because it provides invivo and invitro biomedical application of STB (51).

Labeling of cell

As QDs are resistance to photobleaching and has unique optical property, they are widely used in the labeling of various cells. For examples, Biotinylated cholera toxinB with QD-avidin conjugate for labeling ganglion(52).

Table3. Reasons for identification of different non human cells with the help of quantum dots.

Labeled substance	Rationale
Single-virus labeling	Provide information about the relationship between virus and host by imaging of infectious process such as attachment, entry, replication and maturation.(53)(54)(55)
Bacterial labeling	One of the major biomedical concerns are error-free and brisk recognition of pathogenic bacteria, as these are responsible for various injection and leads to increase in global mortality rate. Monitoring of pathogenic bacteria is the first step in controlling their spread.(56)(57)

international Journal of Pharmaceutical research and Applications
Volume 6, Issue 6, pp: 509-524 www.ijprajournal.com ISSN: 2456-4494

Fungi labeling	Due to the severeness of fungal disease in immunocompromised patients (such as F.oxysporum) early detection is important.(58)

Detection of tumor cell

In 1988 QDs was first employed in the invitro imaging of cancer cell, this task was performed by conjugating QDs with various antibodies, ligand and peptides.(59)

Table4. Detection of various cancer cells with the help of quantum dots.

Type of cancer	QDs conjugates	Advancement
Prostate cancer	QD-Prostate specific membrane antigen(PSMA)	With the help of surface Plasmon-coupled emission the sensitivity of QD used for detection of prostate cancer can be enhanced. (60)(61)
Breast cancer	QD-IgG	AS various other studies used for detection of breast cancer by QD-HER2 (human epidermal growth factor 2) were successful, this method was extended to selectively labeled MCF-7 and BT-474 breast cancer cell for HER2. (62)(63)
Ovarian cancer	QD-Streptavidine(QD606)	QDs coated with natural protein such as SF (silk fibrion),used in bioimaging HEYA8 ovarian cancer cell. (64)(65)

DRUG DELIVERY

Side effects produced by delivery of drug with the help of QDs are less because it provides site specific delivery and its ability to distinguish between normal and the target cell. Main reason for the use of QDs in drug delivery system is because of its longer blood circulation time, high drug loading capacity, protection, sustained release of drug particle and ability to integrate various target ligands on its surface(52). In 2004 the use of QDs for the invitro diagnosis and therapy was first published (66). Single drug can be used for targeting various organs by using different QDs as carrier. For example- doxorubicin, used in breast cancer by conjugating with carbon quantum dots containing large quantity of transferrin (TF) receptor that allow the entry of drug into the breast cancer cells(67), it is used with Ag-In-Zn-S nanoparticle(QD) coated with 11-mercaptopuronic acid or L-cysteine or lipolic acid and then attached with FA(folic acid) resulting in QD-FA-DOX for treatment of lung cancer(68) and PEG-CdTe QDs loaded with doxorubicin are used in the treatment of Extramedullary multiple myeloma (69). Vaccination efficacy can be improved by employing it with QDs. It provides visualization of vaccine dynamics and there for provide adequate amount of information. QDs are conjugated with immune modulating agents such as antigen (Ovalbumin, OVA) and adjuvant (CPG) which acts as labels and nanocarriers. This provide QDs its site specific property by guiding through draining lymphnode and detection of sub cellular site at APCs (Antigen presenting cells) for better activation of APC and effective interaction of Tcells with antigen (70). QDs are mostly used as target drug delivery because of its distinct abilities such as uniform surface area, flexibility in drug doping and linking process and the surface to volume ratio provided by QDs are large with wide range of reactive group on the surface(71).

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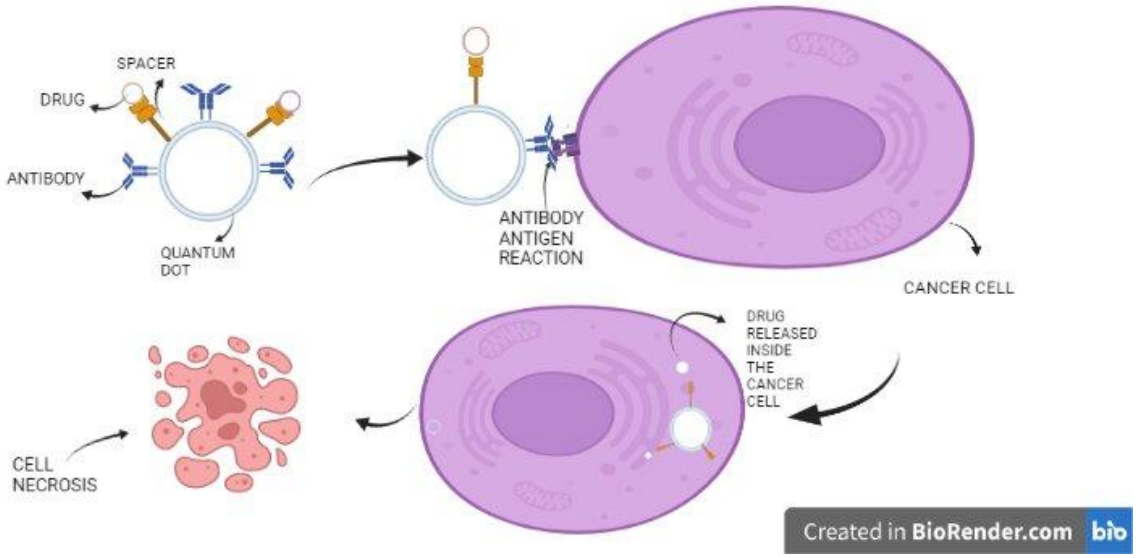

Table5. Different drug used in conjugation with QDs.

Type of quantum dots	Drugs	Uses	Reference
CdTe@CdS@ZnSQDs	Paclitaxel (PTX)	Anticancer	(72)
Carbon and ZnO QDs	Doxorubicin(DOX)	Used to treat breast and lung cancer	(67)
CdSe/CdS/NAC	Quercetin(QE)	Antibacterial	(73)
NH2-PEG-QDs	5-Fluorouracil(5-FU)	Used to treat colon, liver and breast cancer	(74)
Graphene quantum dots(GQD)	Cisplatin	Used In treatment of lung and hepatic cancer	(75)
Graphene quantum dots(GQD)	Glycine-Proline Glutamate	Anti Alzheimer	(76)
Graphene quantum dots(GQD)	Docetaxel(DTX)	Eradication of tumor	(77)
HA(hyaluronic acid)-L-cys-CdTe/CdS QD	Melphanan	Used in treatment of breast cancer	(78)
Carbon dots	Oxaliplatin	Used as theranostic agent	(79)
MAPA(mercaptopropionic acid)–capped CdTe QD	Celecoxib	Anti inflammatory property by inhibition of cox-2 pathway	(80)

international Journal of Pharmaceutical research and Applications
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IMMUNOASSAY

Immunoassay mechanism is based on antigen-antibody reaction which is used for various qualitative and quantitative analyses. It has various applications such as diagnosis of disease in patients, pharmacokinetic studies and quality control of commercially available products(81). Use of QDs in immunoassay was introduced because of the problem faced by the traditional technique such as use of colloidal gold-labelled LCS (lateral-flow immunochromatographic strip) system which used to provide low signal intensity and error-prone change in color. These problems were solved with the use of QDs with high stability, resistance to photobleaching and chemical degradation(82). Conjugating QDs with bio-recognizable antibodies will increase in the specificity as it result in QDs with narrow photoluminescence spectra that allows the measurement of the target substance with the help of fluorescent imaging(83). Lung cancer in human can be diagnosed by detection of specific markers (such as α-1-microglobulin/bikunin (AMBP), peroxiredoxine (PRDX2) and (PARK7) Parkinson disease protein) in bronchoalveolar lavage fluid (BALF) with the use of QDs conjugated with specific antibody for these markers. Flow cytometer is used to confirm the final result through colocalization of two colors(84).

USE OF QDs IN POCT (POINT-OF-CARE-TESTING)

POCT provide care near the site of need, especially in places where laboratories facilities are limited. QDs provide best signal to noise ratio, this is the reason why they are now a days in demand for point of care treatment(85). Different uses of QDs in POCT include bioimaging (such as invivo, signal molecule and live cell imaging), bio-targeting which include detection of genetic disease, clinical application and drug delivery, bio-sensing is also included which involve immunoassay and sugar sensing(86).

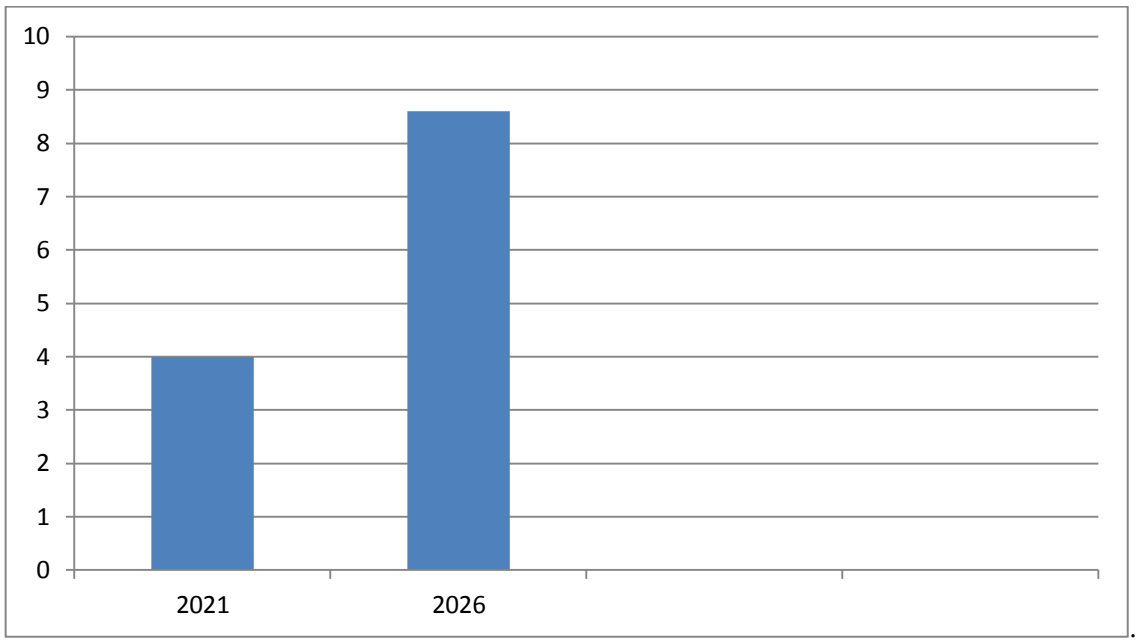

Chart3. According to marketstandmarkets.com the quantum dots market size is expected to grow from USD 4.0 billion in 2021 to 8.6 billion up to 2026. X axis denotes money in USD and Y axis denote years.

TOXIC EFFECTS OF QDs

In vivo and invitro toxicity caused by QDs differs, as both QDs and cell behave in different manner in both the cases. Most prominent way of assuring biosafety of QDs is determining its ADME (Absorption, Distribution, Metabolism and Elimination) parameters and comparing invitro data with invivo data. Major accumulation of QDs occurs in liver, spleen and kidney. With respect to time concentration of QDs decreases in liver and spleen, however its concentration increases in kidney as the time increases70(87). Majority of formulation inserted into the body pass through hepatic route before reaching systemic circulation therefore major accumulation occurs in liver which results in hepatotoxicity. CdSe core QDs was mostly responsible for this as it results in binding of cadmium with sulfhydryl group of critical

mitochondrial protein, which causes inactivation of thiol group and mitochondrial dysfunction(88). QDs results in increase in the MT1A and HMOX1 along with other factors such as proinflammatory cytokine tumor necrosis factor (TNF)-β, CXCL-8, CCL4 and CXCL10 in normal human hepatic cell 71(89).

II. CONCLUSION

This review includes preparation technique (top-down, bottom-up) and biological application of QDs (bioimaging, immunoassay, and labeling and drug delivery). Various functionalization techniques are discussed which are used to enhance the properties of QDs and how characterization can be done with the help of spectroscopic and electric techniques. Major advantages of QDs over other fluorescent dyes are that they provide narrow emission spectra, tunable emission peaks, long fluorescent lifetimes and negligible photobleaching. Now a day's QDs are progressively used in drug delivery, bioimaging and sensor because of this major concern is about the toxicity, body clearance, environmental stability of QDs on which scientist need to work to make it safer so that various other application of QDs can be determined.

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