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Research Article

QUANTUM DOTS: A NOVELTY OF MEDICAL FIELD WITH MULTIPLE APPLICATIONS

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ABSTRACT

Quantum dots are considered as a new class of fluorescent labels which are robust and bright light emitters. Quantum dots are semiconductor nanocrystals ranging typically between 1-10 nanometers and have ability to glow or fluorescence brightly when excited by a light source such as a laser. They are composed of microscopic metal, thousand times smaller than width of a hair or semiconductor boxes such as cadmium selenide-zinc sulphide. They are considered as one of the highly innovative technology having wide applications in the field of biomolecular and cellular imaging. This makes it suitable for application such as *in vivo* imaging including live cell and whole animal imaging, blood cancer assay, cancer detection and treatment. The focus of this article is mainly on the brief introduction related to their synthesis, properties and applications.

Keywords: Quantum dots, Semiconductor nanocrystals, Organic dyes, Fluorescence.

INTRODUCTION

Nanotechnology is the science of nanolength scale size that deals with the processes that occur at molecular level and cellular level. Quantum dots are tiny semiconductor crystals of size 1-10 nanometres made up of compounds from group II to VI and III to V e.g. Ag, Cd, Hg, Ln, P, Pb, Se, Te, and Zn etc**.** These fluorescent quantum dots are glow or fluorescence brightly in different colours such as Adirondack Green (520nm), Blue (514 nm), Greenish blue (544 nm), Green (559 nm), Yellowish green (571 nm), Yellow (577 nm), Yellowish orange (581 nm), Fort Orange (600nm), Orange (610 nm), Maple Red-Orange (620nm), depending on their size by a light source such as a laser. The communication with the cells by the researcher is done by using molecular photodetectors. Traceable drug delivery is a recent and promising application of quantum dots having potential which explains the pharmacokinetics and pharmacodynamics of drugs which helps in drug designing and discovery. Quantum dots are currently limited to cell and small animal uses in testing of drug candidate because of long-term *in vivo* toxicity and degradation (1-6).

By filling polymer beads with multiple colors and intensity of dots in various combinations, the researchers created "quantum beads" with distinct optical signatures analogous to merchandise barcodes. When linked to different antibodies, peptides, or oligonucleotide probes, the bar-coded beads should enable sensitive, high throughput detection of tens of thousands of different proteins or gene sequences in clinical specimens or other samples.

A quantum dot has all three dimensions in the nano range. Materials can be nanostructured for new properties and novel performance. Quantum dots consists of three parts i.e. core, shell and cap (Fig 1.).

Core is made up of semiconductor material i.e. CdSe. Shell is the coat of ZnS surrounds the semiconductor core for improving its optical properties and cap encapsulates the double layer quantum dots by different materials e.g. silica which helps in improving solubility in aqueous buffers (7-9).

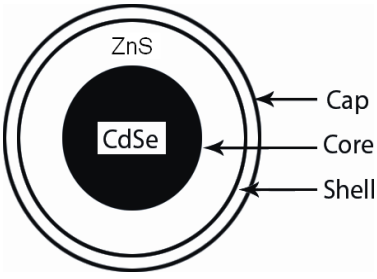


Fig. 1: Schematic representation of a quantum dot.

Advantages of Quantum Dots (10-13)

- **Physical stability**: Quantum dots are more resistant to degradation than other optical imaging probes, allowing them to track cell processes for longer periods of time
- **Photostability:** They have greater photostability than traditional dyes due its inorganic composition and its fluorescence intensity do not diminish with time while organic dyes lose their intensities in 20s.
- **Signal to noise ratio:** Quantum dots have high signal to noise ratio compared to organic dyes.
- **Broader excitation and narrow emission:** Quantum dots have broader excitation spectra and a narrow more sharply defined emission peak. Due to these properties, a single light source can be used to excite multicolor quantum dots simultaneously without overlap.
- **Brightness:** The brightness of quantum dots compared to organic dyes is 10 to 20 times brighter
- **Fluorescent lifetime:** They are highly photo-resistant with significantly longer fluorescence lifetimes. Researchers can use their intense fluorescence to track individual molecules.
- **Excitation by single or multiple sources:** Quantum dot can be excited by the same source and multicolor quantum dots allows the use of many probes to track several targets *in vivo* simultaneously.
- **Sensitive and precise:** Due to their large Stokes Shift and sharp emission spectra, our conjugates have high signal intensity with minimal background interference.
- **Shape flexibility**: They can be moulded into different shapes and coated with a variety of biomaterials.
- **Imaging agent:** As Quantum dots are nanocrystals, they provide good contrast for imaging with an electron microscope as scattering increases.

Limitations (14)

- Quantum dots when positioned in live cells may kill the cells due to aggregation.
- 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.
- Biconjugation of quantum dots leads to delivery into the target difficult.

- Building material of the quantum dots can be cytotoxic e.g. Cdse.
- Their metabolism and excretion is unknown so the accumulation in body tissues can leads to toxicity.

Production

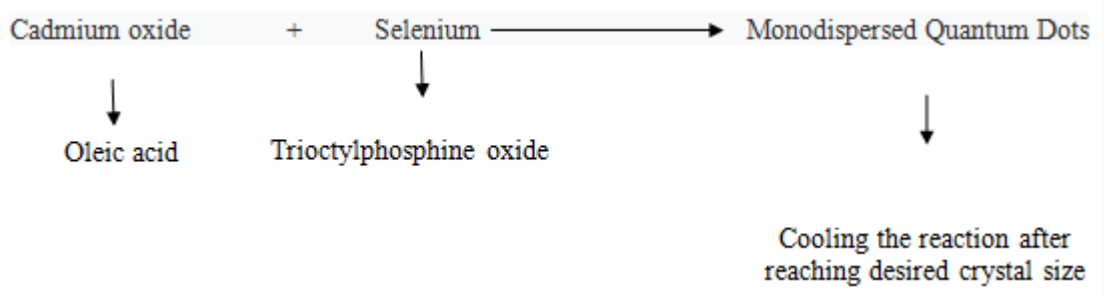
Chemical synthesis of quantum dots represents a typical approach, which is generally divided into organic and water phase approaches (15-16).

1. Organic phase method

a) Colloidal synthesis: This method is the cheapest, less toxic and occurs at bench top condition.

The synthesis of colloidal quantum dots is based on a three-component system composed of precursors, organic surfactants, and solvents. A reaction medium is heated to a sufficiently high temperature (e.g. 300°C) and under vigorous stirring the precursors are injected through syringe which chemically transform into monomers. Once the monomers reach a high enough super saturation level, the nanocrystal growth starts with a nucleation process. The solution immediately begins to change from colourless to colours like yellow, orange and red/brown, as the quantum dots increase in size by placing them under a "black light". This reaction results in the formation of monodispersed quantum dots. Surfactant is used to avoid aggregation, to make the quantum dots water-soluble.

Typical dots are made of binary alloys such as cadmium selenide, cadmium sulfide, indium arsenide, and indium phosphide. Although, dots may also be made from ternary alloys such as cadmium selenide sulfide. The reaction between cadmium oxide dissolved in oleic acid and selenium dissolved in trioctylphosphine oxide (TOPO) (1).



These quantum dots can contain as few as 100 to 100,000 atoms within the quantum dot volume, with a diameter of 10 to 50 atoms (14).

b) Lithography: By growing the quantum dots in a semiconductor heterostructure which refers to a plane of one semiconductor sandwiched between two other semiconductors. If this sandwiched layer is very thin i.e. about 10 nanometers or less, then the electrons can no longer move vertically and thus are confined to a particular dimension. This is called the quantum well. When a thin slice of this material is taken to create a narrow strip then it results in a quantum wire, as it gets trapped in a 2 dimensional area. Rotating this to 90 degrees and repeating the procedure results in the confinement of the electron in a 3 dimension which is called the quantum dot. According to quantum mechanics and Heisenberg's uncertainty principle, the more confined an electron is, the more uncertain is its momenta; and hence, the wider the range of momentum is, the higher is the energy possessed by the electron i.e. may be infinite in case the electron is confined to an infinitely thin layer. The electrons confined in an electron wire are free only in one dimension, those confined in a plane are have no freedom in the 3rd dimension, and those confined in a quantum dot are not free in any dimension (17).

c) Epitaxy: Self-assembled dots can also be grown by depositing a semiconductor with larger lattice constant on a semiconductor with smaller lattice constant eg. Germanium on Silicon. These self-assembled dots are then used to make quantum dot lasers. Hence, the quantum dots are actually formed when very thin semiconductor films buckle due to stress of having lattice structure slightly different in size from those on which the films are grown. The organic phase method produces quantum dots, which are generally capped with hydrophobic ligands (e.g. trioctylphosphine oxide – TOPO or trioctylphosphine - TOP) and hence cannot be directly employed in bioapplications. To be used in biological applications, quantum dots need to be soluble in aqueous solutions and require surface modifications to achieve biocompatibility and stability (17).

Compared with organic approach, aqueous synthesis is effective, less toxic and more reproducible method. Furthermore, the products often show improved water solubility biological compatibility and stability.

2. Water phase method

a) Cap exchange: The hydrophobic layer of organic solvent can be replaced with bifunctional molecules containing a soft acidic group (usually a thiol, e.g. mercaptoacetic acid, mercaptopropionic acid, mercaptoundecanoic acid or reduced glutathione (GSH) ,sodium thioglycolate) and hydrophilic groups (e.g. carboxylic or amino groups) which point outwards from the quantum dots surfaces to bulk water molecules. In fact, substitution of monothiols by polythiols or phosphines usually improves stability. From these ligands, GSH seems to be very perspective molecule, since provides an additional functionality to the Quantum dots due to its key function in detoxification of heavy metals in organisms.

b) Native surface modification: Adding a silica shell to the nanoparticles using a silica precursor during the polycondensation quantum dots are rendered water-soluble using several synthesis strategies, such as water soluble ligands, silanization , organic dendrons, cysteines, dihydrolipoic acid, encapsulation with block-copolymer micelles, with amphiphilic polymers, amphiphilic polymers conjugated with poly(ethylene glycol), and surface coating with phytochelatin-related peptides. All these synthesis strategies have effectively solubilized CdSe or CdSe/ ZnS quantum dots. In addition, quantum dots can be conjugated to biological molecules such as proteins, oligonucleids, small molecules, etc. which are used to direct binding of the quantum dots to areas of interest for biolabelling and biosensing (9,18-20).

QUANTUM DOTS CHARACTERIZATION

Optical characterization of quantum dots is usually done by UV-VIS and photoluminescence spectroscopy, which offer fast, non destructive and contactless option. The optical properties (fluorescence emission) of Quantum dots can be fine-tuned by the Quantum dots' size and is calculated using conventional techniques like scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM) or more preferably scanning tunneling microscopy (STM) and dynamic light scattering (DLS) studies. Besides these techniques, field flow fractionation was also successfully employed an excellent complement to characterization of water soluble quantum dots by the conventional tools (21).

MODE OF ACTION OF QUANTUM DOTS

After administration of colloidal solution of quantum dots by S.C. or I. V. injection, they identify and bound to target. Once bound to target, each quantum dot particle emits light and depending on their size, they can fluorescence in a variety of colours which can be identified or detected by different techniques (16, 22).

APPLICATIONS

Quantum dots as carriers with integrated functionalities

In quantum dot core, small molecule hydrophobic drugs can be embedded between the inorganic core and the amphiphilic polymer coating layer. Polymer coating of quantum dots is powerful tool toward diagnostics. Small size Quantum dots easily cleared from body by renal filtration whereas bigger particles are more likely to be uptaken by the reticuloendothelial system before reaching the targeted disease sites. So size of the Quantum dots is maintained by coating with suitable polymer at 5-20nm for optimum activity. Larger particles have limited penetration depth into solid tissues and high surface-to-volume ratio of nanomaterials, due to which it is possible to link multiple functionalities on single Quantum dots while keeping the overall size within the optimal range.

Hydrophilic therapeutic agents (including small interfering RNA [siRNA]) and antisense oligodeoxynucleotide [ODN] and targeting biomolecules (such as antibodies, peptides and aptamers), in turn, can be immobilized onto the hydrophilic side of the amphiphilic polymer. This can be done either covalent or non-covalent bonds. This fully integrated nanostructure may behave like a MAGIC BULLET that will not only identify, bind to and treat diseased cells, but will also emits detectable signals for real-time monitoring of its trajectory (3, 23).

Quantum dots as tags for other drug carriers

The research and development of various drug nanocarriers is an important part for the advance of nanomedicine. In traceable drug delivery – labelling a conventional drug carrier such as poly(lactic-co-glycolic acid) and polyethyleneimine (PEI) with quantum dots, which serve as photostable fluorescent reporters. They have been used to label both organic and inorganic drug carriers and potentially even bacteria and viruses, with a burst of activity in the area of ODN and siRNA delivery. Small interfering RNA was first condensed on the cationic membrane following standard cell transfection protocol, and the lipoplex was further incubated with fluorescent quantum dots.

When a targeting functionality was added to quantum dots by linking them with RNA aptamers (A10) that specifically bind to prostate specific membrane antigen (PSMA). Doxorubicin, a DNA-interacting drug widely used in chemotherapy, was immobilized onto Quantum dots. The resulting nano-complexes were non-fluorescent – the quantum dots fluorescence is quenched by the Doxorubicin molecules and subsequently the energy is relayed to the A10 aptamer. When the nano-complexes are up taken by PSMA-positive cells, the slow release of Doxorubicin results in recovery of both quantum dots fluorescence and Doxorubicin fluorescence, which can be monitored by confocal microscopy (3, 24-26)

Bimodal molecular imaging

The synthesis of quantum dots with a water-soluble and paramagnetic micellular coating as a molecular imaging probe for both fluorescence microscopy and magnetic resonance imaging. The quantum dots preserve their optical properties and have a very high relaxivity. Targeting ligands can be coupled to these Quantum dots via maleimide or other functional groups. In this study, the paramagnetic quantum dots were functionalized by conjugating them with cyclic RGD peptides and were successfully targeted to human endothelial cells in vitro. This nanoparticulate bimodal contrast agent may be of great use for the detection of (tumor) angiogenesis (1, 27).

Detecting Cell Death

By combining a quantum dot with a novel carrier of the magnetic resonance imaging (MRI) agent gadolinium - a nanoparticle that can spot apoptosis, or programmed cell death, using both MRI and fluorescence imaging is designed. This nanoparticle can provide anatomical information using MRI and cellular level information using fluorescence imaging. Imaging programmed cell death in the body could provide an early indication that an antitumor therapy is indeed killing cancer cells. MRI experiments showed that the nanoparticles produced an imaging signal that was approximately40 times stronger than that produced by the gadolinium carrier alone. Subsequent imaging experiments were able to detect injury-induced apoptosis in mice (1, 28).

***In-vivo* imaging**

EviTags (Non-targeted near infrared emitting quantum dot) as non-invasive optical molecular imaging probes will have a great impact on the early detection, diagnosis and treatment monitoring of cancer. No uptake in the tumor was observed, suggesting the next round of imaging to be done with tumor targeted EviTags will have minimal background signal within the tumor (1, 14, 16, 29-31).

Tumor Cell Markers

There are two methods by which quantum dots locate and mark tumor cells. These two schemes are active targeting and passive targeting.

In active targeting, quantum dots can be conjugated with tumor-specific active binding sites so as to attach themselves to tumor cells. Sequentially, immunofluorescent probes are manufactured with antibodies to detect these tumors.

In passive targeting, the quantum dot probes do not have the tumor-specific active binding sites. Instead, certain properties of the tumor cells are exploited. The growth rate of tumor cells greatly surpasses that of normal cells and thus the membranes of such cells are more permeable. This increased permeability sufficiently enables the absorption of nanocrystalline quantum dots. Through tumor cells' lymphatic drainage system deficiency and keen retention capabilities, further quantum dot absorption and multiplication can take place. In this way, tumor cells have bittersweet adaptations. Consequently, through tumor cells' abilities to efficiently take in and retain nanoparticles, passive targeting is made possible (32).

Immunoassay

Immunoassay was carried out on a glass chip using a sandwich assay approach, where antibody covalently bound to a glass chip was allowed to capture antigen specially. The ZnS-coated CdSe quantum dots (ZnS/CdSe Quantum dots) were linked to a detection antibody. Antibody labeled with quantum dot was allowed to bind selectively to the captured antigen. The fluorescent signals of the sandwich conjugate were detected by a laser confocal scanner.The specificity of the Quantum dots-labelled immunoglobulin (IgG) was tested by using goat IgG and human IgG samples. A diode laser was used to excite efficiently the fluorescent signals while bovine serum albumin was used to eliminate nonspecific binding sites (1, 16, 27, 33, 34).

Gene technology

A number of studies have revealed that quantum Dot-conjugated oligonucleotide sequences (attached via surface carboxylic acid groups) may be targeted to bind with DNA or mRNA. Using precise la beling like red, green and blue Quantum dots in a number of combinations, identification of target sequences of DNA can be achieved. This was exploited by using quantum dot microbeads for an assay of single nucleotide polymorphism (SNP) (35).

Pathogen and toxin detection

Several different pathogens have been targeted so far, including Cryptosporidium parvum and Giardia lamblia, Escherichia coli and Salmonella Typhi and Listeria monocytogenes. Simultaneous multiplexed labelling of both C. parvum and G. lamblia using immunofluorescent staining methods with quantum dots fluorophores produced a good signal-to-noise ratio of 17, with better photostability and brightness compared with two commonly used commercial staining kits. However, one study found that the quantum dots -based assay was not as sensitive as ELISA based techniques (35).

Detection of viral infections

Quantum dots bind to molecular structures that are unique to the virus coat and the cells that it infects. Rapid and sensitive diagnosis of Respiratory Syncytial Virus (RSV) is important for infection control and development of antiviral drugs. Antibody- conjugated Quantum dots rapidly and sensitively detects RSV. Quantum dots system can detect the presence of particles of the RSV in a matter of hours. RSV virus infects lung cells; it leaves part of its coat containing F and G proteins on the cell's surface. Quantum dots have been linked to antibodies keyed to structures unique to the RSV coat. As a result, when Quantum dots come in contact with either viral particles or infected cells they stick to their surface and they illuminate bright fluorescence (16, 36).

Neuroscience

Quantum dots can be used to visualize, measure, and track individual molecular events using fluorescence microscopy, and they provide the ability to visualize and track dynamic molecular processes over extended periods (e.g., from seconds to many minutes). These properties are difficult to achieve using other techniques or approaches. For example, quantum dots are useful for experiments that are limited by the restricted anatomy of neuronal and glial interactions, such as the small size of the synaptic cleft, or between an astrocyte process and a neuron. Because of their extremely small size and optical resolution, they are also well suited for tracking the molecular dynamics of intracellular and/or intercellular molecular processes over long time scales. It should be appreciated that the hydrodynamic radius of functionalized quantum dots is larger (15–20 nm) than their actual size of 5–8 nm.

Recent studies using quantum dots in neuroscience illustrate the potential of this technology. Antibody functionalized quantum dots are used to track the lateral diffusion of glycine receptors in cultures of primary spinal cord neurons. They were able to track the trajectory of individual glycine receptors for tens of minutes at spatial resolutions of 5–10 nm, demonstrating that the diffusion dynamics varied depending on whether the receptors were synaptic, persynaptic, or extrasynaptic (1, 37, 38).

Drug discovery

The features of quantum dots such as their multiplexing potential, photostability, and inorganic nature make them of value for drug discovery. For example, they would allow monitoring of multiple drug candidates over extended time periods in cell culture simultaneously, thus saving time and cost (39, 40).

Biosensor and biolabels

A number of analytical tools have been developed with application of this smart and potential technology. These tools are employed for determination of various pathological proteins and physiological-biochemical indicator associated with disease or disrupted metabolic conditions of body (8, 16, 27, 41).

Surgical guidance

Quantum dots also have a potential surgical utility by providing optical guidance that can result in reduction of cancer metastases. Scientists such utility by mapping sentinel lymph nodes at 1 cm tissue depth using oligomeric phosphine-coated quantum dots that emit in the nearinfrared region. The sensitivity and stability were superior to conventional dyes and thus this approach could improve the sensitivity of surgical lymphatic resectioning (40, 41).

BARRIERS TO USE *IN VIVO*

Although these studies have produced some successful results, the significance of quantum dots for *in vivo* applications is controversial. The size of quantum dot complexes limits tissue penetration. The only data currently available comes from observation of experimental animals over the short term. Considerable problems can be anticipated.

1. Quantum dot complexes, including their capping materials may be immunogenic, which could result in both dangerous immune reactions in subjects, and could also render the quantum dots ineffective as a result of antibody binding.
2. The heavy metals contained in the core, and the materials used for capping (e.g. MPA) may be toxic to the host.
3. The size of quantum dot complexes precludes renal excretion, making clearance from the bloodstream unlikely. This will result in eventual uptake and concentration in the liver, which is particularly sensitive to cadmium toxicity.

A large number of high-quality and high powered trials specifically addressing these issues will need to be undertaken before quantum dots can be considered for human use, and such a process is likely to be lengthy (1, 28, 35).

REMOVAL OF QUANTUM DOTS TOXICITY

Quantum dots can be considered as an alternative for organic dyes in the imaging of biological systems, due to their excellent fluorescent properties, good chemical stability, broad excitation ranges and high photo bleaching thresholds. The main shortcoming of quantum dots is their toxicity and therefore their application is problematic.

e.g. cadmium telluride quantum dots (CdTe - which is toxic) used as fluorescent probes for biological imaging, they can also be utilized to monitor targeted drug delivery. Scientists have been using gelatin during the production of CdTe quantum dots thereby reducing the toxicity of the particles. Their approach could be useful for the development of other nanoparticle composites with low toxicity as well (1, 29).

QUANTUM DOT PRODUCTS (16, 26)

EviDots® Core & core-shell quantum dots EviDots are available as core quantum dots in their fundamental state, or enhanced with our proprietary coating technologies as core-shell semiconductor nanocrystal quantum dots. EviDots are available in wavelengths ranging from 490nm - 2100nm. PbS EviDots® are available in emission wavelengths from 850 nanometers (nm) to 1500 nm.

EviComposites™ Quantum dot composites. EviComposites use the properties of Evident's proprietary EviDot quantum dots as well as common insulating polymer matrix materials.

EviTags™ Water soluble quantum dots. EviTags are conjugation-ready with a bio-active surface. Carboxyl or amine functionalized dots are available in wavelengths ranging from 490nm - 680nm.

EviFluors® Water soluble quantum dots conjugated to antibodies and proteins. EviFluors are ready-to-use high quality, activated quantum dots coupled to secondary antibodies and proteins. Goat anti-Mouse, Goat anti-Rabbit, Goat anti-Rat, Streptavidin, and Biotin conjugated quantum dots are available in wavelengths ranging from 520nm - 680nm.

FUTURE PROSPECTIVE OF QUANTUM DOTS

1. Research is ongoing for designing hydrophilic quantum dots that are luminescent.
2. More selective and specific approach of labelling cells and biomolecules is undergoing research.
3. Work is being carried to study interference effect of quantum dots with normal physiology and Production of quantum dots with higher biosafety.
4. NASA scientist working on quantum dots as drug carrier for Mars expedition in near future.
5. Single quantum dots of compound semiconductors were successfully used as a replacement of organic dyes in various bio-tagging applications. This idea has taken one step further by combining differently sized and hence having different fluorescent colours quantum dots, and combining them in polymeric micro beads (1, 38).

CONCLUSION

In the area of nanomedicine, quantum dots add to the expansion of new diagnostic and delivery systems. As they are well defined in

size, shape, provide sole optical properties for highly sensitive detection and can be customized with various targeting principles. It has created powerful impact in various fields of disease diagnosis, intracellular tagging as photo sensitizer for treatment of cancer, biotechnology and bioassays. Current advancement in the surface chemistry of quantum dots expanded their use in biological applications, reduced their cytotoxicity and rendered quantum dots a powerful device for the research of distinct cellular processes, like uptake, receptor trafficking and intracellular delivery.

REFERENCES

1. Dey NS, Rao MEB. Quantum Dot: novel carrier for drug delivery. IJRPBS 2011;448-458.
2. Rathore KS, Lowalekar R, Nema RK. Quantum dots: a future drug delivery system. The Pharma Review 2006;4:30-32.
3. Lifeng Qi, Xiaohu Gao. Emerging application of quantum dots for drug delivery and therapy. Expert Opin. Drug Deliv 2008;5(3):263-267.
4. Roger S. Quantum dot advances studies show that nanoparticles have potential biological applications. Chemical and Engineering News. Am Chem Soc 2003;81:10-23.
5. Johuson RC. Scientists active neurons with quantum dots. EE times PM EST.2001;5:24- 28.
6. Choi HS, Liu W, Misra P, Tanaka E, Zimmer JP, Itty Ipe B, et al. Renal clearance of quantum dots., Nat Biotechnol 2007; 25(10):1165-1170.
7. Bhushan, B. Introduction to Nanotechnology, In. Spring Handbook of Nanotechnology, New York: Springer, 2007:1-3.
8. Varshney HM, Shailender M. Nanotechnology" Current Status in Pharmaceutical Science: a review. International Journal of Therapeutic Applications 2012;6:14-24.
9. Ghasemi Y, Peymanib P, Afifi S. Quantum dot: magic nanoparticle for imaging, detection and targeting. Acta Biomed 2009;80:156-165.
10. Patel HR. Quantum dots: A novel technique for drug delivery and therapy 2007; available at http://www.pharmainfo.net/reviews/quantum-dots-novel-technique-drug-delivery-and-therapy accessed on 31 july 2013.
11. Bakalova R, Ohba H. Zhelev Z, Ishikawa M, Baba Y. Quantum dots as photosensitizers. Nature Biotech 2004; 22:1360-1361.
12. Sattler KD. Handbook of Nanophysics: Nanomedicine and Nanorobotics, USA: CRC Press, 2010:1-5.
13. Resch-Genger U, Grabolle M, Cavaliere-Jaricot S, Nitschke R, Nann T. Quantum dots versus organic dyes as fluorescent labels. Nat Methods 2008;5(9):763-75.
14. Pandurangan DK, Mounika KS. Quantum dot aptamers-an emerging technology with wide scope in pharmacy. Int J Pharm Pharm Sci 2012;4(3):24-31.
15. Bandyopadhyay S, Menon L, Kouklin N, Zeng H, Sellmyer DJ . Electrochemically self-assembled quantum dot arrays, Journal of Electronic Materials 1999;28(5):515-519.
16. Mishra P, Vyas G, Harsoliya MS, Pathan JK, Raghuvanshi D, Sharma P. et al. Quantum dot probes in disease diagnosis. International Journal of Pharmacy and Pharmaceutical Science Research 2011;1(2):42-46.
17. Mishra S, Tripathy P, Sinha SP. Advancements in the field of quantum dots. International Journal of Advancements in Research & Technology 2012;1(3):1-5.
18. Yuan J, Guo W, Yin J, Wang E. Glutathione-capped CdTe quantum dots for the sensitive detection of glucose, Talanta. 2009;77(5):1858-1863.
19. Chomoucka J, Babula P, Hubalek J synthesis and modification of quantum dots for medical applications a Nanocon 2009.
20. Zhang J, Zhao1 S-Q, Zhang K, Zhou J-Q, Cai Y-F. A study of photoluminescence properties and performance improvement of Cd-doped ZnO quantum dots prepared by the sol–gel method, Nanoscale Research Letters 2012,7:405,1-7
21. Drbohlavova J, Adam V, Kizek R, Hubalek J. Quantum Dots-characterization, preparation and usage in biological systems, Int J Mol Sci 2009;10:656-673.
22. http://www.americanelements.com/quantum-dots.html
23. Srinivasan C, Lee J, Papadimitrakopoulos F, Silbart LK, Zhao M, Burgess DJ. Labeling and intracellular tracking of functionally active plasmid DNA with semiconductor quantum dots. Mol Ther 2006;14(2):192-201.
24. Zrazhevskiyn P, Gao X. Multifunctional Quantum Dots for Personalized Medicine, Nano Today 2009;4(5):414–428.
25. Wang Y, Chen L, Quantum dots, lighting up the research and development of nanomedicine. Nanomedicine: Nanotechnology, Biology, and Medicine 2011;7:385–402.
26. Vengala P, Dasari A, Yeruva N, Quantum Dots For Drug Delivery And Therapy International Journal Of Pharmacy&Technology, IJPT 2012;4(2):2055-2074.
27. Mukherjee S, Das U, Quantum Dots: An Optimistic Approach To Novel Therapeutics, International Journal of Pharmaceutical Sciences Review and Research 2011;7:59-64.
28. Akerman ME, Chan WCW and Laak KP. Nanocrystal targeting *in vivo*. Proc Nall Acad Sci.2002;2:198-210.
29. Maestro LM, Rodriguez EM, Vetrone F, Naccache R, Ramirez HL, Jaque D, Capobianco JA, Solé JG."Nanoparticles for highly efficient multiphoton fluorescence bioimaging" Opt Express 2010;18(23):23544-23553.
30. Michalet X, Pinaud FF, Bentolila LA. Quantum Dots for Live Cells, *in Vivo* Imaging, and Diagnostics. American Association of the Advancement of Science 2005;307:538-544.
31. Shi C, Zhu Y, Cerwink WH, Zhau HE, Marshall FF, Simons JW, et al. Quantum Dots: Emerging applications in urologic oncology. Seminars and Original Investigations 2008;26:86-92.
32. Fang M, Peng C-W, Pang D-W, Li Y. Quantum Dots for Cancer Research: Current Status, Remaining Issues, and Future Perspectives. Cancer Biol Med 2012;9(3):151–163.
33. Dubertret B, Skourides P, Norris DJ, Noireaux V, Brivanlou AH, Libchaber A. *In vivo* imaging of quantum dots encapsulated in phospholipid micelles. Science 2002;298:1759–62.
34. Jaiswal JK, Mattoussi H, Mauro JM, Simon SM. Long-term multiple color imaging of live cells using quantum dot bioconjugates. Nat Biotechnol 2002;21:47–51.
35. Jamiesona T, Bakhshi R, Petrovaa D, Pococka R, Imanib M, Seifaliana AM. Biological applications of quantum dots. Biomaterials 2007;28:4717–4732.
36. Salisbury DF. Quantum dots detect viral infections. PHYSorg.com. 10 Jun 2005 available at http://phys.org/news4479.html accessed on 30 July 2013.
37. Pathak S, Cao E, Davidson MC, Jin S, Silva GA. Quantum Dot Applications to Neuroscience: New Tools for Probing Neurons and Glia. The Journal of Neuroscience 2006;26(7):1893–1895.
38. Cheki M, Moslehi M, Assadi M, Marvelous applications of quantum dots. European Review for Medical and Pharmacological Sciences 2013;17:1141-48.
39. Ozkan M. Quantum dots and other nanoparticles: what can they offer to drug discovery? Drug Discov Today 2004;9:1065–71.
40. Azzazy HME, Mansour MMH, Kazmierczak SC. From diagnostics to therapy: Prospects of quantum dots. Clinical Biochemistry 2007;40:917–927.
41. Smith AM, Dave S, Nie S, True L, Gao X. Multicolor quantum dots for molecular diagnostics of cancer, Expert Rev Mol Diagn 2006;6(3):231-244.