Quantum Dots: A New-fangled Loom in Drug Delivery and Therapeutics

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ABSTRACT

Quantum dots (QDs) are luminescent nanoscale semiconductor crystal with surface chemistry and unique optical properties that make them useful as carriers for traceable targeted delivery and therapeutic applications. QDs combines with cancer specific ligands, antibodies and peptides etc., and were found to be more effective for identifying and imaging human cancerous cells. The present review gives an exhausted account of QDs including the synthesis, properties, toxicity and their optical and electrochemical applications in drug delivery and therapeutics. Moreover, special emphasis is given on QDs applicability in biomedicine, cancer diagnosis and therapy.

Keywords: Quantum dots, Nanomedicine, Drug Delivery, Toxicity, Cancer, Photodynamic therapy.

INTRODUCTION

In today’s scenario most of the drugs available are either poorly soluble and not permeable hence there is a huge demand to develop new delivery systems which can enable to overcome these issues. Various drug delivery systems and approaches have been evaluated but none has succeeded to great extent hence quantum dots (QDs) is one of the techniques which has been recently tried and it appears it has a lot of potential and can easily reaches the target tissue to deliver the drug [1-3]. Colloidal semiconductor QDs were first discovered by professor Louis Brus in 1982 [4-5]. QDs were introduced to biological imagine in 1998 [4-6]. The QDs are basically constitute nano particles and are primarily composed of various elements in the periodic table, like CdS, CdS, ZnS. The main advantage is because of its optical and electronic properties [7-8]. QDs are covalently linked to various biomolecules like antibodies, peptides, nucleic acid and ligand [9-10].

QDs have numerous properties but due to their narrow fluorescent emission and broad absorption spectrums it has attracted a lot of attention recently in the various fields especially biomedicine. This unique feature enables it to tag more than one molecule simultaneously. QDs contains electronic and optical properties, like larger absorption coefficients, size-tunable light emission, superior signal brightness, resistance to photo bleaching and simultaneous excitation of multiple fluorescence colours. Much more energy is needed to excite the dot; this is because of greater the difference in energy between the highest valence band and the lowest conduction band. The main agenda behind this is the smaller the size of the crystal larger the band gap, simultaneously, large energy is released when the crystal returns to its stable state [11].

Conventional QDs are made with heavy metal compounds as raw materials; the degradation of such QDs accumulated in the living body may lead disease called cytotoxic disease. It has been also reported that cadmium selenide (CdSe) nanoparticles exposed to Ultra Violet rays released cadmium ions and enhanced cytotoxicity in vitro and also reported the strong alkaline and acid instability of cadmium-based nanoparticles [12-13]. To prevent these instabilities, commercially available cadmium-based QDs are generally coated with some type of polymers and surfactants. However, an excessive increase in particle size because of the polymer coating of QDs may also lead to a critical deposition in the body over a long time. Since some of these negative aspects of the use of QDs for biomedical application have not
been resolved, further much more improved and highly safer QDs are expected.

An interesting aspect of QDs is their dimensional similarities with biological macromolecules, for example, nucleic acids and proteins. QDs have fluorescent properties which provide higher features to conventional organic dyes including high quantum yield, broad absorption, and narrow emission spectra. The properties of these materials contain the photo stability of coated QDs against photo bleaching and tolerance to variance in the alkalinity (pH) of biological electrolytes when fluorescent organic molecules are compared. QDs can be engineered by allowing particle size, shape, and chemical composition for modulation to match a given application. The two properties which are often manipulated are the size and composition of QDs; this will determine whether the QD is chemically excited in NIR light or UV light. For example, smaller nanocrystals of 2-nm size consist CdSe, emits light in the range 495 to 515 nm, whereas larger CdSe nano crystals of size 5-nm emits light in the range of 605 to 630 nm [7].

As mentioned above, one of the main and important features of QDs is that they are much more photo stable than conventional fluorophores, for example, it is reported that, under the same particular excitation conditions, 90% of the fluorescence of a normal organic dye fades within 1 minute, whereas the fluorescence of QDs remains intact even after 30 minutes also, a another feature of these materials is that they may be excited again and again [14]. When both the QDs and rhodamine green-dextran were exposed to 450 nm light for about 80 minutes, the fluorescence of rhodamine-dextran was lost while QDs stayed fluorescently stable. In addition to this, QDs have a wide excitation spectra and narrow emission spectra when compared to conventional dyes. These properties of QDs make these materials more suitable for multiplex imaging [14].

When we see in terms of the biological application of QDs, promising data has to be obtained regarding the toxicity of these materials in their surrounding atmosphere. When 108 QDs were injected into zebra fish embryos there was no notable observed effect on the embryogenesis. QDs combined with tumor cells have been used to study the extravasation step in the metastatic process. In this approach, tumor cells with QDs combined as well as native tumor cells were observed to extravasation into the surrounding tissue in a comparable mannering process, showcasing the utility of QDs for monitoring this complex process [7]. Figure 1 show QDs synthesized in laboratory.

Advantages of QDs

- **Physical stability**: QDs are more resilient to degradation as compared to other imaging probes, which allows them to track cell processes for longer periods of time.
- **Photo stability**: They have superior photo stability than traditional dyes due its inorganic composition and its fluorescence intensity do not fades with time while organic dyes lose their intensities in 20 s.
- **Signal to noise ratio**: QDs have high signal to noise ratio compared to organic dyes
- **Broader excitation and narrow emission**: QDs gives broader spectra and a very sharp and narrow emission peak. Hence, a single light source can be used to excite multi colour QDs simultaneously without overlap.
- **Brightness**: The brightness of QDs compared to organic dyes is 10 to 20 folds brighter [15].
- **Fluorescent lifetime**: They are highly photo-resistant with significantly longer fluorescence a lifetime which is the main advantage of it [16].
- **Sensitivity and precision**: Due to their large Stokes shift and sharp emission spectra, our conjugates have high signal intensity.
- **Shape flexibility**: They can be moulded into numerous shapes and coated with a variety of materials so that forming new shapes is more flexible.
- **Imaging agent**: As QDs are nanocrystals, they provide good contrast and good view for imaging with an electron microscope [15-16].

The Surface Chemistry and Toxicity of QDs

During early 1990s, Bawendi et al. first reported a synthesis protocol for QDs with highly monodisperse, regular core structure and tunable particle size. Up till now, the most successful and well-developed method to synthesis highly luminescent II–VI QDs is the TOP/TOPO synthetic approach. However, these QDs are insoluble in water thus which limits their biological applications. Therefore, a number of surface functionalization studies have been developed to make this QDs water-soluble and biologically compatible [16].

In first common approach, the original hydrophobic coatings are replaced by water-soluble functional molecules (e.g., dithiothreitol, mercapto carboxic acids, 2-aminoethanethiol, dihydroxipolic acid, oligomeric phosphates, peptides, and cross-linked dendrons through the ligand exchange reactions. Because the optical properties of the inorganic core are very sensitive to the surface, the ligands exchange process this may result in the very poorer performance, particularly in the case of QD [17].
The second approach is to encapsulate QDs in an amphiphile whose hydrophobic ends interleave with but do not replace the organic coating on QDs [18]. This improvement for QDs synthesis is significant in terms of:

1. Protecting the core/shell structure and maintaining the original photo physics of QDs;
2. Making QDs water-soluble;
3. Providing a biological interface and multiple functions.

However these kinds of QDs are not stable in biological settings because of relatively weak anchoring of the single and double hydrophobic tails to the particle. Additionally, the hydrophilic end groups of even biocompatible surfactants may not protect nanocrystals from non-specific biomolecular interactions [19-21]. Scientists have utilized amphiphilic polymers instead of simple amphiphile because single polymer chains can contain multiple hydrophobic units, their interactions with the native organic coatings on QDs can be numerous, and thus the encapsulant can be bound more strongly than conventional surfactants. However, the range of amphiphilic polymers for creating stable and non-aggregating QDs in biological settings has been relatively limited. Up till now, most of the amphiphilic polymers which are used for commercial and their hydrophobic/hydrophilic ratios are fixed; hence the cost is relatively high and it may be slightly different to control the process of forming water-soluble QDs and to optimize the forming conditions. Although QDs have great prospects, the toxicity of QDs can’t be overlooked. During the progressing of biological applications (e.g., cancer imaging, targeting and PDT treatment), the degradation products of QDs will do harm to the cells which they attach with or develop immune responses with the components present in blood.

The toxic degradation production routes are: first, the oxidation of the nanoparticle core/shell material can cause to make the release of free cadmium or other heavy metals, which will interrupt the normal activities of cell. Secondly, the photosensitized production of reactive oxygen intermediates (ROI) also plays a major role in mediating the cell damage; thirdly, the toxicity of capping materials must also be considered, several groups in capping materials such as mercaptoacetic acid and tri-n-octylphosphine oxide (TOPO) could produce toxicity in cells. In order to reduce the cytotoxicity of QDs, replacement of the cadmium by nontoxic or less-toxic metals such as indium (In), or encapsulation of the core with a bio compatible shell should be taken into considered. Though In-based semiconducting dots contain arsenic, another toxin, the cytotoxicity of these dots may be small enough to keep the toxicity low. Fisher et al. found that QDs could remain inside the body for very long periods. Kim reported that larger QDs generally get accumulated in the reticuloendothelial system (RES), such as the liver, spleen and lymphatic system for several months, but the size which is less than 5 nm could be removed by the kidney quickly. So in order to minimize the toxicity of QDs, QDs can be designed as smaller as they can be prepared through which can help them more easily to clean them out of the body. In spite of the fact that many investigators have paid close attention to and observed the side-effect of QDs, the definite metabolism of QDs in vivo remains uncertain to know. Thus, it is still a very necessary issue to investigate the detailed biochemical and pharmacological mechanism for further more application of QDs in the human body.

**Removal of QDs Toxicity**

QDs 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 QDs is their toxicity and therefore their application is problematic. E.g. cadmium telluride QDs (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 QDs thereby reducing the toxicity of the particles. Their approach could be useful for the development of other nanoparticle composites with low toxicity.

**Mode of Action of QDs** [22]

After administration of colloidal solution of QDs by S.C. or I.V. injection, they identify and stick to target [23]. Once stick to target, every quantum dot particle emits light and depending on their size they can fluorescence in a different variety of colours which can be identified or detected by different conventional techniques [24].

**Synthesis of QDs** [25]

High quality QDs have been synthesized through various types of approaches. But usually their synthesis is carried out in organic solvent such as toluene or chloroform at relatively temperature in the presence of surfactants. But those surfactant coated particle are not soluble in water as they contain polar surfactant head group attached to the inorganic core of QDs and the hydrophobic chain protruding into the organic solvent. Generally, all experiments with cells involve with water soluble materials. Various strategies approaches have been developed to make them water soluble, where either surfactant layer is replaced or coated with...
another additional layer such as hydrophilic or amphiphilic polymers. The hydrophobic coating of surfactant is replaced by ligand molecules carrying functional groups, one end binds to hydrophilic groups that make the QDs water soluble. In which employment of both hydrophilic and hydrophobic polymers as applied as additional coating on the surface of QD. Hydrophobic tail of the polymer react with the hydrophobic surfactant layer on the surface of QD; where the hydrophilic groups of the polymer on the outer end will be impart water solubility. QDs have also been encapsulated in phospholipid micelle [26-27].

Another ways of synthesizing QDs of chosen size and shape are now being fine-tuned with all the greater precision (i.e., low size relative standard deviations). In the early 1980s, QDs that were synthesized in aqueous media resulted in poor size distribution and low fluorescence efficiency. It was in the early 1990s when chemical synthesis of semiconductor nanocrystals turned to the use of high boiling point organic solvents. Below we discuss a few representative QDs synthesis methods.

High Temperature Synthesis
As mentioned earlier, it was Murray et al. who first reported on the synthesis of high-quality, monodisperse QD chalcogenide nanocrystals at very high temperatures. In this method, dimethyl cadmium (Cd(CH3)2) was used as precursor at elevated temperatures of ~300°C. However, Cd(CH3)2 is extremely toxic, pyrophoric, expensive, unstable at room temperature, and explosive at elevated temperatures by releasing large amount of gas. Thus, the use of less harmful precursors such as cadmium oxide (CdO) was exploited. Peng et al. introduced the one-pot CdO approach by incorporating CdO, trioctylphosphine oxide (TOPO), and either hexylphosphonic acid (HPA) or tetradecklyphosphonic acid (TDPA) as ligands at 250–300°C to generate a colorless solution. By introducing tellurium (Te), selenium (Se), and sulfur (S) stock solutions, the authors prepared high-quality monodisperse QDs. It is believed that the initial nucleation times are tens of second after the mixing yet appear to be slow and controllable due to the high stability of Cd-HPA–CdTDPA complexes. An important aspect with considerable effect on QDs synthesis is ligand selection. Several attempts have been reported where the nature of the ligand led to stable, high photoluminescence QYs. A wide variety of molecules such as thioglycolic acid, tiopronin, glutathione, l-cysteine ethyl ester hydrochloride, oleylamine, and polyethyleneimines of different molecular weights served as successful ligands for high PL yields.

Gamma-Irradiation Method
Yin et al. (1999) were able to prepare zinc sulfide (ZnS) QDs using γ-irradiation. However, ZnS preparation is less studied compared with CdSe, which maybe a consequence of ZnS possessing optical properties already in the UV region even before quantum confinement is attained. Using γ-ray, irradiation-free S2– anions could be obtained from sodium thiosulfate. The reagents employed in the synthesis included ZnSO4, NaS2O3, sodium dodecyl sulfate (as a surface active agent), and (CH3)2CHOH. Each solution was prepared in a given amount of distilled water and irradiated with differing doses of γ-rays to form the required colloidal products. Using recurring washes of ethanol and water, the nanoscale ZnS powder particles could be precipitated from the solutions and dried under vacuum at 60°C. Mechanistically speaking, the radiolytic free radical species were formed from water, which was used as the solvent with the source of energy for this molecular lysis being the γ-ray irradiation:

\[
\text{H}_2\text{O} \rightarrow e^{-}_{\text{aq}}, \text{H}, \text{OH}, \text{H}_2\text{O}, \text{H}_2\text{O}^4
\]

In the next step, the reductive species such as e−aq have the ability to reduce S2O3–, liberating S2– ions. When an alcohol such as isopropanol is introduced into the system, it assumes the role of a hydroxyl radical scavenger, mopping up the free radicals forming less reactive molecules. (CH3)2CHOH+ OH→ (CH3)2COH+H2O

A critical point is that the reducing nature of the solution has a positive effect on the yield of S2– that is obtained. The actual formation of the ZnS colloidal QDs occurs by the continuous ionic attraction and bonding of the S2– anions and the Zn2+ cations. This forms the crystalline seeds, which are then protected by the surfactant, hence preventing the crystals from growing to an unwanted size. It is important to note that the size as well as the size distribution of the QDs is very much dependent on the γ-ray absorption dose, the concentration of surfactant, and the concentration of the Na2S2O3.

Microwave-assisted Synthesis
Although high-energy electromagnetic radiation has been used to synthesize QDs using γ-radiation, reported that using radiation from the opposite end of the spectrum at much lower energy it is feasible to synthesize gold (Au) QDs. When chloroauric acid HAuCl4 is reduced in methanol for 0.5–5 min in the presence of a water-soluble polymer surfactant such as polyvinylpyrrolidone (PVP), small spherical monodispersed QDs can be synthesized. The PVP assumes the role of a stabilizer in the process and the microwave heating, which is used in between 480 and 1100 W. The synthesis rapidly takes only a few minutes and the
diameter of the Au QDs that are formed is within the quantum confinement region of <11 nm. By regulating reaction temperature, heating time, and rate, the size and morphology of the Au QDs could also be varied. Microwave irradiation can be performed in continuous or pulse wave modes. The pulse mode was found to give better control and accuracy over the heating process.

There are two kinds of microwave dielectric heating effects: thermal and non-thermal. It was found that thermal effects of microwave heating produced homogeneous heating of the reaction and its constituents. This fast uniform microwave heating accelerates the HAuCl4 decomposition, and provides uniform crystal nucleation and growth conditions, resulting in monodisperse QDs of small size. Nucleation and growth is considered to take place via the phenomena called Ostwald ripening. On the other hand, non-thermal effects are the effects that remain unchanged whether the use of microwave or oil-bath heating is used to heat the vessel. The presence of hot spots and hot surfaces are tell-tale signs of non-thermal effects of microwave heating in the preparation of QDs. The use of microwaves to heat solids, which may be involved in the reaction process, can give rise to these hot spots at regions where the solid and liquid meet each other. Hence, hot surfaces can be formed on solid metals at the regions where surfactants are adsorbed. Microwave irradiation was found to speed up the uniform heating of PVP at the surfaces on the gold metal, which it helped to stabilize thus giving rise to the formation of hot spots at these metal surfactant intersections. The critical roles which the hot spots and hot surfaces play in the QD formation are that they accelerate the reduction of HAuCl4 to form the free Au atoms.

They were also found to accelerate the precipitation and nucleation processes leading to uniform QDs. It was found that the intensity of the microwave radiation itself helps to dictate the size and shape of the QDs. Size distribution can also be heavily influenced by the concentration of the metallic precursor, the chain length of the surfactant polymer, the solvent and the reaction temperature. Apart from the preparation of Au QDs, microwave heating has also been used to synthesize cadmium sulfide (CdS), cadmium selenide (CdSe), lead sulfide (PbS), copper indium diselenide (CuInSe2), and molybdenum diselenide (MoSe2) QDs. The advantages of using microwave radiation in the synthesis of QDs include: the absence of convection processes while heating giving a homogeneous vessel temperature for uniform nucleation and growth, as well as shorter crystallization time.

Active and Passive Quantum Dot Targeting Mechanisms [27]

Quantum dot bioconjugates can be delivered to tumors in vivo by both active and passive targeting mechanisms although the passive targeting is much slower and less efficient than comparing to active targeting mechanism. In the passive targeting mechanism, bio conjugates deposited preferentially at tumor sites due to enhanced permeability and retention effect.

Effect can be attributed to the facts that angiogenic tumor:
(1) Produce vascular endothelial growth factors, which are responsible for enhanced permeability.
(2) Lack of an effective lymphatic drainage system [26].

Applications of QDs

Applications in Drug Delivery

QDs can be used in the variety of fields like solar cell, LEDs transistors, biomedicine and medical imaging.

Traditional solar cells are made of semi-conductor and maximum allowable limit is 36% of efficiency for converting sunlight to electrical energy in the cell. Variet of lipid based drug delivery systems have been examined for delivery of drugs but this QDs when combined to the ligand drug and target molecules can be designed which lends an edge. QDs in the presence of continuous UV radiation behave as a catalyst for semiconductor nanocrystals and increase the performance.

Although fluorescence based readouts are more widely used but as they are not cost effective, hence there is need for a better alternative where this QDs due to their superior optical properties can be utilised for higher drugs screening output.

The potential applications of QDs are mainly deals with the medical field and it’s mainly for cancer diagnosis. Luminescent and stable QD bio-conjugates enable visualization of cancer cells in the living animals. QDs has more bright and stable photoluminescence, makes them potential candidates for biomedical imaging and therapeutic interventions. QDs combines with cancer specific ligands/antibodies/peptides were found to be more effective for identifying and imaging human cells consist of cancer [28].

QDs in Nanomedicine

QDs are semiconductor nanocrystals which have sizes ranging from 2 to 10 nm. In general, it is well identified that the emission wavelength of the QDs can be tuned from 450 to 1800 nm by varying their size, shape, and composition of the nano crystals. QD exhibits a few more unique optical properties.
For example, they have very good resistance to photo-bleaching, very large absorption cross section, relatively long fluorescence lifetime, and excellent quantum yield that can be as large as 70-80%. The straight, narrow emission and broad excitation spectra makes possible to trace down the dynamics of several more interesting molecules in vivo or in vitro [29]. In addition to this two large photon absorption cross section of QDs, comparing to organic dyes makes them very promising and Believable optical agents for two-photon laser excitation, which can be performed in the near infrared window with much more better imaging penetration in epithelium tissue. These characteristics make QDs very attractable for bio photonics and nano medicine research based applications. To date, colloidal core/shell QDs such as CdSe/ZnS, CdSe/ZnCdS, CdTe/CdSe, and InP/ZnS are being commonly used in all biological and medical research. Among the many methods available in the literature for synthesizing QDs, hot colloidal synthesis approach stays the most promising approach for obtaining robust QDs for nano medicine based applications. For core QDs such as CdSe and CdTe, they can be prepared at very high temperature by the reaction takes place between cadmium oxide dissolved in oleic acid and trioctylphosphine (TOP) and/or TOP-Selenium. The reaction resulted in the production of mono-dispersed QDs. However, synthesized QDs are unable to be applied in biological applications unless the following critical challenges are name. First, it is important to passivate the core QD with a thin layer of high band gap materials, such as ZnS. There are many more advantages for core/shell QDs comparing with unpassivated ones. For example, it was been discovered that the chemical and optical stabilities of QDs can be maintained when the QDs are passivated with higher band-gap semiconductor materials [22]. Also, the shells will significantly reduce the QDs toxicity, which makes the biological applications to enable. Although many types of core/shell QDs were fabricated, only CdSe/ZnS, CdTe/ZnS, and CdSe/CdS/ZnS were found to be most useful for in vivo imaging applications. However, there exist toxicity concerns about CdSe and CdTe QDs due to the presence of cadmium and further development in studies are needed to resolve these challenges.

In recent years, many research teams conducted experiments and prepared cadmium-free QDs such as InP, CuInS2, AgInS2, and silicon for biological applications. Second, general high quality core/shell QDs are obtained by using hot colloidal synthesis and its surface is passivated with hydrophobic moieties, which doesn’t allows them to be dispersible in aqueous phase. Thus, water-dispersible QDs with reactive functional groups are essential for in vitro and in vivo applications [30]. The techniques for transferring organically dispersible core/shell QDs from organic phase to aqueous phase have been studied very extensively from the last decade. In general, the approaches employed for fabricating water-dispersible QDs includes (i) functionalizing QD surface with amphiphilic molecules such as mercapto acids, and hydrophilic dendrimers; and (ii) coating the QDs with biocompatible surface layer such silica-shell and amphiphilic polymers. E.g. Chan et al. demonstrated the formed of water dispersible CdSe/ZnS QDs for in vitro imaging by functionalizing the QD surface with mercaptoacetic acid by ligand exchange method. Using a similar type of approach; Uyeda et al. demonstrated that water-dispersible QDs can be formed by functionalizing the QD surface with the bi dentate dihydrolipoic acid (DHLA). Todate, surface modification of QDs using mercapto ligands has stays a popular method for forming water dispersible QDs. Third, combinations of biomolecules to the surface of water dispersible QDs is another most important requirement for in vitro and in vivo targeted delivery applications. Biomolecules such as antibodies, nucleic acids, peptides, and aptamers can be combined to the QD surface by either covalent or non-covalent bonds of interactions. QDs permeation through the cell membrane is depicted in Figure 2. Commonly, conjugation of proteins, antibodies, peptides, and drug molecules to the QD surface is requires for the targeted delivery to the area of interest. The QD surface can be added with functional groups such as carboxylic acid, primary amine, and thiol, which can be used for conjugation with targeting ligands by using conjugation chemistries such as carbo di imide, maleimide, and succinimide. Avidin-biotin cross-linking technique is another most popular method for conjugates the biomolecules on the surface of QDs [30].

Detection of Cancer Metastasis

The passive targeting mechanism based on the enhanced permeability and retention (EPR) effect is much more and most effective for targeting solid, primary tumours with fairly large size (at least 2 mm) and well-developed vasculature. Primary tumours at very early stage and micro-metastases do not require significant blood supply and are very small for the EPR effect [31]. In these cases, tumour-specific targeting or active targeting of QDs is more essential. To maximise active targeting, it is necessary to minimize non-specific uptake of QDs by the reticuloendothelial system (RES), often through proper surface modification, on the basis of which specific targeting ligands are conjugated. Demonstration of specific tumour targeting of QDs is faces much more challenging in
vivo than on tumour cells cultured in vitro due to complicated anatomical structure and physiology in tissues and organ systems which create barriers for QDs. Very few cell targeting ligands are truly specific to tumours, meaning that they only bind or attach to cancer cells but absolutely not to other cells or binding to off-target cells at very low rate. Identifying such ideal ligand receptor pairs is very crucial for QD cancer imaging to significantly reduce the frequency of false-positives and it requires very deeper understanding of cancer biology. Using QDs it has been found that changes occurs in membrane morphology and membrane protein dynamics based on its fluidity are critical for cancer metastasis. Among the various methods for SLN diagnosis, QDs have received greatly increasing attention as lymph node delivery agents [17-32].

Detection of Circulating Tumour Cells
The rapid and sensitive identification of low-frequency cancer cells is of great importance now because it employs a drastic positive effect on diagnosis and prognosis. In blood, the number of circulating tumour cells (CTC) is correlated very sensitively with the recurrence of cancer and relapse. In the early stage of a tumour, disseminated cells circulate in the blood at extremely very low concentrations thus making the detection or identification of low frequency cancer cells so difficult. QDs have been developed as a new class of fluorescent probes with several improved and important advantages over conventional dyes. In a recent study, human T-help cells were used as a model for CTC, and the membrane of T-help cells was labelled with QDs and magnetic beads using CD3 and CD4 markers, respectively. B cells and red blood cells were used as mixed cells to make interfere with the detection of T-help cells. Experimental results clearly demonstrated that the proposed method provides a simple, rapid and sensitive means of real-time measurement of the concentration of specific cells at very low frequency.

Cancer Therapy: QDs are also used for anticancer drug delivery. For simultaneous imaging and therapeutic uses, new smart multifunctional QD nanoparticles capable of simply sensing the release of therapeutics by a change in the fluorescence of the imaging modality have been reported. Researchers have designed a QD-aptamer conjugate that could concurrently deliver anticancer drugs to PCa cells and could sense drug delivery based on a fluorescence resonance energy transfer mechanism [33].

QDs for Photodynamic Therapy: It has been reported that QDs in photodynamic therapy (PDT) which can act as either photo-sensitisers themselves or make activation of another photo-sensitiser by serving or providing as the energy donor. The energy transfer between QDs and cell molecules (as triple oxygen, reducing equivalents and pigments) potentially could generate reactive oxygen species in order to provoke apoptosis in cells. As a good photo-sensitiser, QDs have several characteristics, such as a constant composition, simple and inexpensive synthesis, no toxicity in the absence of the light, but potential cytotoxicity under UV irradiation. Unlike the visible emission of most conventional photo-sensitisers, QDs can be make tuned to emit in the NIR regions, which can be very useful in PDT for deep-seated tumours as NIR is not scattered and absorbed by tissue [32, 34-36].

Various application areas of nanoscale pharmaceuticals along with their properties are quoted in Table 1.

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

EviComposites™
Quantum dot made of or composites. EviComposites which use the properties of Evident's proprietary EviDot QDs as well as common insulating polymer matrix materials [23].

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

EviFluors®
Water soluble QDs conjugated to antibodies and proteins. EviFluors are ready-to-uses superior or high quality, activated QDs coupled to secondary antibodies and proteins. Goat anti-Mouse, Goat anti-Rabbit, Goat anti-Rat, Streptavidin, and Biotin conjugated QDs are available in wavelengths ranging from 520nm-680 nm [23-24].

Future Prospective of QDs
1. Research is ongoing for designing hydrophilic QDs 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 QDs with normal physiology and production of QDs with higher biosafety.
4. NASA scientist working on QDs as drug carrier for Mars expedition in near future.
5. Single QDs 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 QDs, and combining them in polymeric micro beads [37-40].

CONCLUSIONS

In the area of nanomedicine, QDs 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 QDs expanded their use in biological applications, reduced their cytotoxicity and rendered QDs as a powerful device for the research of distinct cellular processes; like uptake, receptor trafficking and intracellular delivery.

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Table 1: Summary of application areas for nanoscale pharmaceuticals and medicine in diagnostics.

<table>
<thead>
<tr>
<th>Material/Technique</th>
<th>Property</th>
<th>Applications</th>
<th>Timescale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostics nanosized markers, i.e. the attachment of nanoparticles to molecules of interest.</td>
<td>Minute quantities of a substance can be detected.</td>
<td>E.g. detection of cancer cells to allow early treatment.</td>
<td>-</td>
</tr>
<tr>
<td>'Lab-on-a-chip' technologies.</td>
<td>Miniaturisation and speeding up of the analytical process.</td>
<td>The creation of miniature, portable diagnostic laboratories for use in the food, pharmaceutical and chemical industry; in disease prevention and control; and in environmental monitoring.</td>
<td>Although chips currently cost over $125 each to make, within three year the costs should fall dramatically.</td>
</tr>
<tr>
<td>QDs</td>
<td>QDs can be tracked very precisely the when molecules are 'bar coded'.</td>
<td>Diagnosis.</td>
<td>In early stage of development but there is enough interest here for some commercialization.</td>
</tr>
</tbody>
</table>
Figure 1: QDs synthesized in laboratory.

Figure 2: QDs permeation through cell membrane.
REFERENCES