Quantum Dots as multifunctional nanoparticles - A review

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Abstract

Quantum Dots (QDs) are one of the nanoparticles that use in imaging, recognition and targeting. QDs are nanometer-size luminescent semiconductor crystals and have unique chemical and physical properties due to their size and their highly compact structure. They emit different wavelengths over a broad range of the light spectrum from visible to infrared, depending on their size and chemical composition. Eventual use of QDs is to dramatically improve clinical diagnostic test for the early detection of cancer. The use of QDs is an indication of revolution in biological imaging. The current and widely used organic fluorophores have two shortcomings associated with their fluorescence. Signals from the labeled molecules can be obscured by cell autofluorescence, occurring in the visible spectrum and by photobleaching which seriously limits observation time. Colloidal QDs are bright, photostable fluorophores of a few nanometers in diameter. Despite their advantages the best materials for QDs; cadmium sulfide, CdS and cadmium selenide, CdSe can be highly toxic. While enhancing the biocompatibility of this nanoparticle various encapsulation techniques have also aided in their water dispersibility and functionalization. QDs were introduced to cell biology as alternative fluorescent probes in recent years.

Key words: QDs, nanoparticle, targeting, bio-nanotechnology, imaging, detection.

Introduction

QDs (QDs) are spherical nano-sized crystals. They can be made of nearly every semiconductor metal (e.g., CdS, CdSe, CdTe, ZnS, PbS), but alloys andother metals (e.g. Au) can also be used [1,2]. The prototypical QD is cadmium selenide (CdSe).QDs range between 2 and 10 nm in diameter (10 to 50 atoms). Generally, QDs consist of a semiconductor core, over coated by a shell (e.g.,ZnS) to improve optical properties, and a cap enabling improved solubility in aqueous buffers.

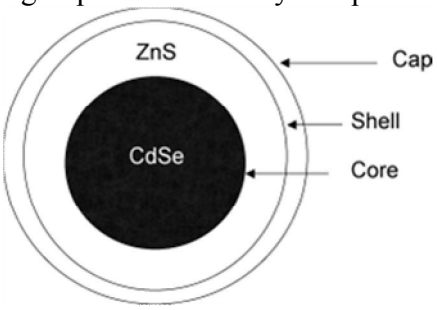

Fig.1. Schematic representation of a QD

The cadmium selenide core is surrounded by a shell of zinc sulphide. Finally, a cap can be encapsulating the binary QD by different material such as silica (Fig. 1). The diameter of QDs ranges between 2-10 nm (Fig. 2).

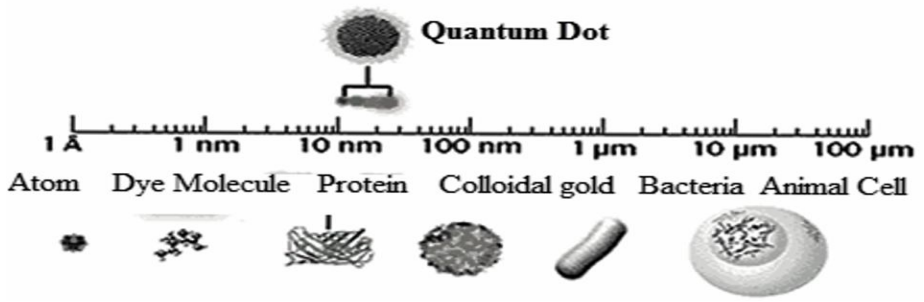

Fig.2. Relative size of QDs

The traditional lithography based techniques (a combination of electron beam lithography and etching) were used to make QDs in 1980s. However, these QDs are only in the nanometer scale in one dimension. The other two dimensions are limited by the resolution of the lithography. In the early 1990s, QDs were mainly prepared in aqueous solution with added stabilizing agents. This procedure yielded low-quality QDs with poor fluorescence efficiencies and large size variations. From 1993 onwards, the high-temperature organometallic procedure was used for growing QDs [3]. This procedure yields nearly perfect crystal structures and narrow size variations, but the fluorescence is still relatively low. The deposition of a surface- capping layer such as ZnS or CdS was found to dramatically increase the fluorescence properties of CdSe nanocrystals [4]. The resulting QDs are highly hydrophobic and only soluble in nonpolar solvents. The art of QD synthesis is evolving as alternative precursor materials, such as CdO, can be used to prepare high quality CdS, CdSe, and CdTe nanocrystals [5]. In contrast to traditional binary QDs, and core/shell nanocrystals, the QDs synthesized show excellent quantum yields without an inorganic capping layer. The size of the QD can be controlled by temperature (>300°C) and period of time, ranging from minutes to hours depending on the desired particle size [6]. So, it can be summarizes that the QDs are manufactured broadly in two step reaction process in a glass flask (Fig. 3).

The first step is nucleation. This is initiated by heating a solvent to approximately 500 degrees Fahrenheit and injecting precursors such as cadmium and selenium. They chemically decompose and recombine as pure CdSe (cadmium selenide) nanoparticles. Once these nanocrystals form, the next step

involves growth in which sizes of the nanocrystals can be determined based upon varying the length of time of reaction. QDs can then be functionalized for various biological uses.

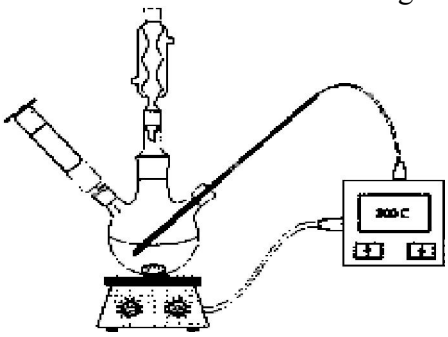

Fig.3. QDs are manufactured in the glass flask

Properties of Quantum dots

QDs take advantage of the quantum confinement effect, giving these nanoparticles unique optical and electronic properties. A theoretical framework for these properties was already described in 1982 by two research teams in the former Soviet Union [7,8]. Fluorescence semiconductor QDs offer advantages in that they have a tunable absorption spectrum, which is very broad, extending from the ultraviolet to a cut-off wavelength in the visible spectrum. Emission is confined to a narrow band and can also be tuned. Absorption and emission characteristics are dictated by size for binary QDs or by composition/internal structure independently of size for alloyed semiconductor QDs, such as CdSeTe. Moreover, QDs have brighter emission and good photostability [9]. In addition, QDs can be conjugated to biological molecules such as proteins, oligonucleids, small molecules, etc. which are used to direct binding of the QDs to areas of interest for biolabelling and biosensing [10, 11]. QDs 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 [12,13,14,15,16], amphiphilic polymers conjugated with poly (ethylene glycol) [17], and surface coating with phytochelatin-related peptides. All these synthesis strategies have effectively solubilized CdSe or CdSe/ ZnS QDs. The T2-MP EviTags™ offer a potential range of benefits over traditional QDs, especially the possibility of lower toxicity, and a wider range of colours into the near infrared.

The modification in QDs has also been done, which is very potential. Since the QDs were coated with hydrophobic surfactant molecules, it can be only solved in organic solution. Before QDs can be applied to biological analysis, they have to meet several criteria. First, most of the biomolecules, e.g. protein, DNA, peptides exist in aqueous environment. Modifying the surface of QDs to be hydrophilic and compatible to varieties of biomolecules is important. Second, designing the techniques for specific labeling cells and biomolecules with QDs is necessary. Third, nontoxic performance of QDs is request for in vivo applications.

Potential applications of Novel Quantum dots

1. QDs in optical imaging

QDs in fixed cells and tissue imaging:

The feasibility of using QDs for antigen detection in fixed cellular monolayers was first demonstrated in 1998. By labelling nuclear antigens with green silica-coated CdSe/ZnS QDs and F-actin filaments with red QDs in fixed mouse fibroblasts, these two spatially distinct intracellular antigens were simultaneously detected. For cellular labelling QDs are ~20 times brighter and dramatically morephotostable over many weeks after injection than organic fluorophores [13].

QDs in live cell bio imaging:

Live cell imaging is a more difficult task compared to fixed cells and tissues due to the care that must be taken to keep cells alive and due to the challenge of delivering probes across the plasma membrane for studying intracellular targets. In vivo applications of QDs have been demonstrated for labelling

cellular surface antigens. By covalently conjugating mercaptoacetic acid-coated CdSe/ZnS QDs to the transferrin protein, QDs were spontaneously endocytosed by cancer cell and retained their bright fluorescence, indicating that QDs can be used as intracellular labels.

QDs in in-vivo imaging:

In order to benefit from the advantageous optical properties of QDs as *in vivo* labels, a number of issues must be addressed. First, the relatively large size and surface area of QDs allow the attachment of multiple targeting probes to each label of enhanced binding specificity. The accessible targets for systemically administrated QD probes could be limited to those of vascular exposure, such as endothelial receptors. Also, nanoparticles are non-specifically taken up by phagocytic cells in the organs of the reticulo-endothelial system (most notably by the liver and spleen). This non-specific targeting can be reduced by coating nanoparticles with hydrophilic polymers such as poly(ethylene glycol) to allow greater vascular circulation time, but non-specific uptake cannot be eliminated completely [18]. QDs were first used to target tissue-specific vascular markers by intravenous injection in live mice [19].

QDs in Visualizing Vitreous:

Vitreous is transparent tissue located between the lens and the retina of the eye, thus, difficult to look at by even ophthalmological microscope. But vitreous is connected with some sight-threatening eye diseases, for example, retinal detachment, macular hole, epi-retinal membrane, and so forth. QDs (QDs) have been applied to a wide range of biological studies by taking advantage of their fluorescence properties. We established a novel technique of aqueous colloidal QD (ACQD) as a vitreous lesion detector. When compared with some conventional dyes used for clinical situation, i.e. fluorescein, indocyanine green, and triamcinolone acetonide, ACQD exerted a higher performance to detect a Weiss Ring. Furthermore ACQD is also effective to perform vitrectomy, an eye surgery to cut and eliminate vitreous. Some functional structures in vitreous are detected clearly when ACQD was injected into an enucleated porcine eye. We demonstrated that ACQD enabled any ophthalmic surgeon to perform vitrectomy reliably, easily, and more safely. Taken together, the ACQD oriented vitreous staining system will promote ophthalmological science, and it will raise the cure rate of eye diseases [20].

2. QDs in Cancer Cells

QDs are nanoscale material used for cancer imaging and treatment, being nanoparticles they will reduce the drug exposure of health tissues by limiting drug distribution to target organ, so, are highly effective [21]. Many forms of malignant cancer cells have a high concentration (when compared to healthy cells) of epidermal growth factor receptor (EGFR) on there exterior. Using a technique called labeling, scientists can coat Q-dots with an antibody for EGFR, making the Q-dots attach to the cancer cells. These antibodies coated Q-dots are injected into a patient's bloodstream or tissue. The area of suspected cancer is then illuminated with either ultraviolet or white light, and doctors literally look for the Q-dots; if cancer is present a very noticeable brightly-colored region (red, green blue, etc. depending on the Q-dots used) will be seen .

In vivo tumour targeting and imaging was primarily due to antibody-antigen binding, but was also aided by the enhanced permeability and retention effect characteristic for tumor vasculature. Moreover the permeability and retention effect is due to the inherent vasculature permeability of the microenvironment of cancerous tissue, combined with the lack of lymphatic drainage [22]. Due to the permeability and retention effect alone, it was found that nonconjugated poly (ethylene glycol) QDs accumulated in induced mouse tumours, demonstrating tumour contrast, but much less efficiently than actively targeted probes. QDs can be customized to concurrently image and differentiate tumour vessels from both perivascular cells and matrix and to monitor the trafficking of bone marrow-de QD: magic nanoparticle for imaging, detection and targeting 163 rived precursor cells to the tumour vasculature allowing to investigate the degree to which the vascular and perivascular structures are formed or remodeled in response to cell homing (Fig. 4).

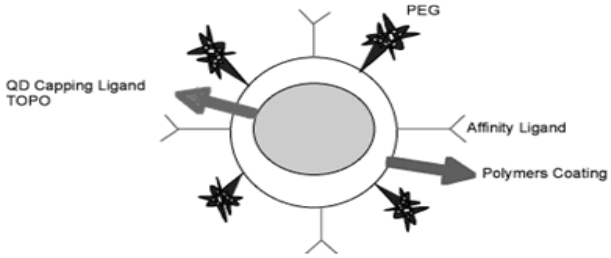

Fig.4. Structure of a Multifunctional QD probe
(PEG- polyethylene glycol, TOPO- tri-n-octylphosphine oxide)

3. QDs in Vascular Graft Engineering

A novel QD (QD) were used to developed a system for polymeric microencapsulated drugs which is conjugated to near infrared (NIR) absorbing QDs and tested the feasibility of burst release of a model drug, heparin, from microcapsules triggered by irradiation. This system is designed to externally modulate drug release in response to physiological needs by control of the intensity and period of irradiation. QD are the key component to be used for triggering the release of drugs for various clinical applications [23].

4. QDs in cardiovascular disease

Cell and molecular imaging has a long and distinguished history. Erythrocytes were visualized microscopically by van Leeuwenhoek in 1674, and microscope technology has evolved mightily since the first single-lens instruments, and now incorporates many types that do not use photons of light for image formation. The combination of these instruments with preparations stained with histochemical and immunohistochemical markers has revolutionized imaging by allowing the biochemical identification of components at subcellular resolution. The field of cardiovascular disease has benefited greatly from these advances for the characterization of disease etiologies [24]. In this review, we will highlight and summarize the use of microscopy imaging systems, including light microscopy, electron microscopy, confocal scanning laser microscopy, laser scanning cytometry, laser microdissection, and atomic force microscopy in conjunction with a variety of histochemical techniques in studies aimed at understanding mechanisms underlying cardiovascular diseases at the cell and molecular level.

5. QDs in Biomedical Research and life science

QDs are devices or particles are so small that they are invisible to the naked eye. Such entities could be used to patrol our bodies and autonomously augment endogenous defense and repair mechanisms. Imagine the defeat of illness at a fraction of the current costs. Bionanotechnology is the field of science that deals with just that: the development of imaging, tracking, targeting, sensing, diagnostic, and eventually therapeutic capabilities based on particles in the nanometer range, *i.e.*, “nanoparticles”. Within the extensive group of nanoparticles, semiconducting QDs play a central and prominent role. QDs excel at a myriad of physical properties, most notably their fluorescent properties, such as high quantum yield, photo-stability, broad absorption spectra, and their remarkable size-dependent emission-tunability.

QDs are multifunctional research and diagnostic tools. Multiplex pseudocoloured image of cellular structures visualized with QDs. Fixed human epithelial cells were stained to show the nucleus (blue; 655-nm QDs), Ki-67 cell proliferation proteins in the nucleus (magenta; 605-QDs), mitochondria (orange; 525-QDs), microtubules (green; 565-QDs), and actin filaments (red; 705-QDs). Courtesy of QD Corp./Invitrogen [25].

Example of QD-based imaging capabilities in intact animals by simultaneous imaging of multicolor QD-encoded microbeads (0.5 μm diameter) emitting green, yellow or red light. Approximately 1–2 million beads in each color were injected subcutaneously at three adjacent locations on a host animal. There is the significant brightness and spectral shifting advantages away from auto-fluorescence. The

ultimate goal would be to use functionalized QDs for the simultaneous detection and concomitant treatment of disease states in human patients.

6. QDs in Digital Logic

A QD is a semiconductor whose excitons are confined in all three spatial dimensions. As a result, they have properties that are between those of bulk semiconductors, and those of discrete molecules. Also, due to confinement in all 3 dimensions, they also differ from Quantum Wires and Quantum Wells in certain properties. The ability to tune the size of QDs is advantageous for many applications. For instance, larger QDs have a greater spectrum-shift towards red compared to smaller dots, and exhibit less pronounced quantum properties. Conversely, the smaller particles allow one to take advantage of more subtle quantum effects. Hence QDs find applications in various fields like Biology, Optics, Quantum Computing and Digital Electronics.

7. Other applications of QDs

These include: LEDs (light emitting diodes); solid state white light, lasers, displays, memory, cell phones, optical nanocodes and biological markers. To date, biological marker applications of QDs have been the earliest commercial applications of QDs. In these applications, QDs are tagged to a variety of nanoscale agents, like DNA, to allow medical researchers to better understand molecular interactions. Molecular imaging and therapy.

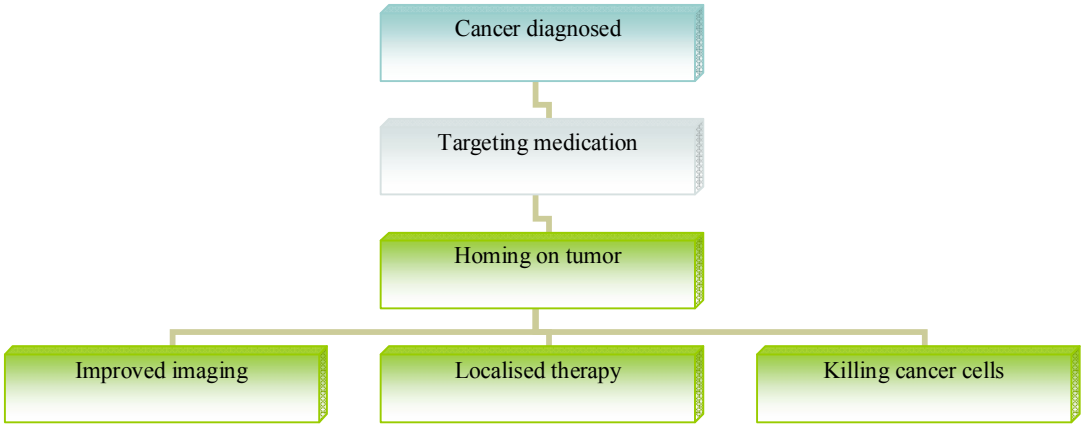

Fig.5. Nanoparticles of QDs in imaging and therapy of ailment

When injected, the functionalized QDs can target cancer tumors. The surgeon can see the glowing tumor, and use it as a guide for more accurate tumor removal (Fig. 5).

Finally, new concepts can exploit specific pathophysiological situations, e.g. when an enzyme is upregulated, and activate particle delivery at the affected site on demand [26]. A first promising approach was presented by Zhang et al. In this study, non-specific, transduction peptide- driven uptake of QDs was rendered cell-selective by linkage to a negatively charged, transduction-inhibiting peptide, which was additionally a substrate for matrix metalloproteases (MMPs). After cleavage of the negatively charged peptide by MMPs, the colloid could enter the target cells [27]. Since MMPs are upregulated in many tumors and in arthritic tissues, this approach should be selective for these targets. This example shows that the design of effective, cell-targeting colloids probably requires several targeting strategies to be combined on one particle. Exploiting differently expressed enzymes or other forms of regulation specific for certain (patho) physiological events inside cells to 'switch on' colloids on the intracellular level could be an issue for the future development of advanced colloids.

Nanoparticles emerged as promising tool in drug targeting, since, after appropriate modification, they are able to deliver their payload to specific sites, like tissues, cells, or even certain cellular organelles. For example viva gel is a particularly unique microbicide in that its active ingredient is a nanoscale dendrimer highly effective at stopping the transmission of both HIV and genital herpes in macaque monkeys [28]. In this context, the delivery of nanoparticles from the circulation into the target cells

represents a crucial step. Here, model drug delivery systems such as QDs are ideal candidates to elucidate this process in more detail, since they provide outstanding features like a small and uniform size, unique optical properties for most sensitive detection and modifiable surfaces. Recent progress in the surface chemistry of QDs expanded their use in biological applications, reduced their cytotoxicity and rendered QDs a powerful tool for the investigation of distinct cellular processes, like uptake, receptor trafficking and intracellular delivery. In this review, we will not only describe the ideal attributes of QDs for biological applications and imaging but also their distinct specific and non-specific pathways into the cells as well as their intracellular fate.

Conclusion

QDs have been received as innovative technology with novel characteristics that could greatly developed biological imaging, detection and could be used for treatment of various diseases. Nanoparticles as colloidal drug carriers seem to be promising tools for targeting specific cells, tissues or organs. These drug carriers have not only to head for specific cell types but should also address distinct cellular uptake processes to deliver their payload into cells. In order to investigate the pathways for nanoparticles into specific cells, model colloids of defined size and shape, which in addition have to be easy to detect, are a powerful tool. As presented above, the use of QDs for the investigation of cellular uptake and intracellular delivery of nanoparticles offers new possibilities in order to study sub-cellular processes, due to the small, uniform size and the unique optical properties of the QDs. However, there is still a need for more information on the distinct mechanisms of this uptake. A better understanding of such processes would obviously aid in the design of targeted nanoparticles for numerous applications. In the field of nanomedicine, QDs can make a worthy contribution to the development of new diagnostic and delivery systems as they offer unique optical properties for highly sensitive detection, are well defined in size and shape and can be modified with various targeting principles.

It can help to improve different field of biomedical sciences as it is useful to design and produce of nanoparticles and nanodevise with multiple functions. Furthermore, QDs can be used for analyzing the biomarkers and detection of disease. Design and make of biocompatible and biodegradable nanoparticles to sole the problem like nonspecific organ uptake and RES scavenging is the another application of Q dots. In addition deliver of nanoparticles for of imaging and therapeutic aim into solid tumors beyond the vascular endothelium can be achieved with Q dots.

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