



Quantum Dots in Medical Devices: Recent Advances and Emerging Healthcare Applications

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Abstract

Because of quantum mechanics, quantum dots, or QDs, are tiny semiconductor crystals that have unique optical and electrical features that set them apart from bulk materials. With their size-dependent emission wavelength, broad excitation range, and small emission peak, QDs are a valuable tool for a range of biological applications, including molecular imaging, biosensing, and diagnostic systems. A few good things have happened as a result of the discovery of quantum dots (QD) nano-transporters. The excretion of QD shows conversion in natural imaging, and photographs have demonstrated remarkable applicability in bio-imaging, targeted gene delivery, drug development, biosensing, photodynamic therapy, and diagnosis. The present review aims to impart fundamental insight as well as conception of Quantum Dots (QDs) its merits, properties, utilization as well as mode of action. Researchers are motivated to advance the development of quantum dots (QDs) for clinical and translational research due to their efficacious use in biological imaging, sensing, and detection. The goal of this article is to provide readers with a basic understanding of quantum dots (QDs), including their benefits, characteristics, applications, and mechanism of action. Researchers are motivated to advance the development of quantum dots (QDs) for clinical and translational research due to their efficacious use in biological imaging, sensing, and detection.

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1. Introduction

Semiconductor nanoparticles known as quantum dots (QDs) have special optical and electrical characteristics. Quantum dots have the ability to spread beyond volume and molecular levels because their particle size is less than 100 nm. Quantum dots enable novel approaches, particularly in biological research, biomedical, pharmaceutical, and healthcare. Louis E. Brus synthesised QDs for the first time in the

1980s, attracting interest from a variety of fields. Russian physicists Alexei Ekimov and Onushchenko observed the quantum size influence on optical spectra of nanocrystals for the first time in 1982. They discovered that by shrinking the size of the substance, the optical properties alter. Murray and his colleagues discovered colloidal monodispersed quantum dots (QDs) using organometallic precursors in 1993. QDs

are nanostructures with no dimensions. It has distinct optical features, such as higher absorption and smaller emission spectra [2].

Murray and his colleagues discovered colloidal monodispersed quantum dots (QDs) using organometallic precursors in 1993. As, QDs are nanostructures with no dimensions. It has distinct optical features, such as higher absorption and smaller emission spectra. A few applications of the QDs are shown in Figure 1. Due of their small size and large surface area, these particles have distinct optical and electrical properties, as well as features such as a low detection limit peak, broad excitation range, and size-dependent emission wavelength. The adjustability in emission wavelength, exceptional brightness, and photostability are distinguishing features of Quantum Dots (QDs). These attributes render QDs well-suited for various medical applications, encompassing imaging, diagnostics, and therapy. As fluorescent probes for in vivo and in vitro imaging, QDs are frequently used. A vast array of biological targets, including as cells, tissues, and malignancies, can be imaged by them [3].

In comparison to typical organic fluorophores, QDs have various advantages. QDs have the potential to be exploited to create highly sensitive and selective diagnostic assays. QDs for example, can be coupled to antibodies in order to detect certain biomarkers in blood or urine. QDs based assays can be used to diagnose diseases including as cancer, infectious infections, and genetic disorders. Furthermore, surface modification using antibodies or DNA is simple. Additionally, QDs can be made from the same material while emitting different colours by altering varying their size. To attach to specific cell surface receptors, QDs can be functionalized using targeted ligands. QDs can be absorbed by cells and release their payload once bound. QDs based medicines have the promise to provide more targeted and effective disease therapy. Drugs, genes, and other therapeutic agents can be delivered to specific cells or tissues using QDs. QDs have various other attributes that make them well-suited for medical applications in addition to their optical properties. They are biocompatible, which means they can be put into the body without harm. They're also photostable, which means their

fluorescence won't fade over time. They can also be conjugated to a variety of targeting ligands, allowing them to be delivered to sick cells specifically. QDs are among the most promising new medical imaging tools. QDs, which function as robust imaging probes have been crucial to in-vitro illness diagnosis and prognosis as well as general biology. Targeted and traceable drug delivery is a new area of study that has been sparked by their remarkable structural and surface features, which include a high surface-to-volume ratio, a variable and uniform size, flexible drug linking and doping techniques, and a wide variety of surface reactive groups. QDs represent a transformative technology with the potential to revolutionize medicine. Already applied in various medical contexts, QDs are expected to have an even greater impact in the future, being effective in identifying both organic and inorganic drug carriers, with further advancement potential [4].

Quantum dots (QDs) are commonly manufactured from cadmium selenide (CdSe), cadmium sulphide (CdS), and lead sulphide (PbS). Because QDs have a size-dependent emission wavelength, their colour can be adjusted by varying their size. Because of their adaptability, they are suitable for use in fluorescence imaging, where they can track cells, mark proteins, and photograph tumours. Crystalline molecules comprising hundreds to millions of atoms, semiconductor quantum dots exhibit a low count of free electrons. Visible, luminous nanostructures colloidal semiconductor quantum dots are predominantly composed of atoms from groups II-VI, III-V, or IV-VI. Group II-VI compounds like CdSe, CdS, and CdTe are gaining popularity, particularly in medical applications [5].

This sector has grown enormously in the last 20 years or more into a large, high-tech, global stage with undisputable significance and possibilities for the present and future. The key feature of QDs is their capacity to combine small particles or devices Sizes range from a few nanometres to millimeters are combined in a single system. They have a significant clinical influence in the fields of pharmaceuticals and clinical diagnostics, particularly in point-of-care testing (POCT) [5].

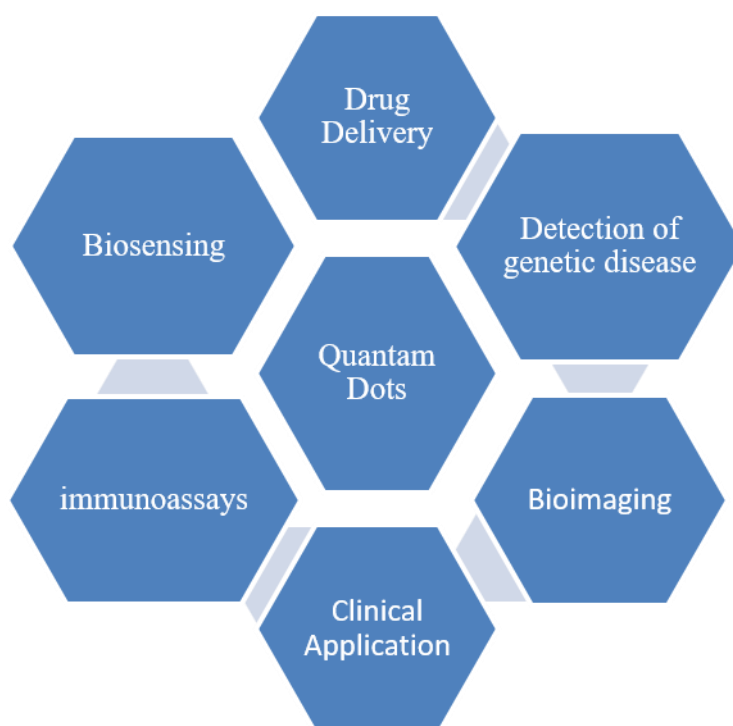


Figure 1: Applications of quantum dots.

2. Properties of Quantum Dots

The term "quantum dots" refers to semiconductor nanocrystals that possess semiconductor characteristics. Features of quantum dots lie in the center they are much smaller than bulk semiconductor materials, but slightly larger than individual atoms. The different size of quantum dots causes quantum effects that determine their behavior (Figure 2).

Different energy levels are occupied by electrons in a bulk semiconductor. The valence band is considered the lower level, whereas the conduction band represents the greater energy level. The energy differential between the two bands is represented by the band gap. Electrons in the valence band shift to the conduction band as they absorb energy, such as heat or light. A hole is created when an electron departs the valence band. Together, the hole and electron form an exciton. The exciton Bohr radius represents the typical separation between a hole and an electron. When a semiconductor is smaller than the Bohr radius, it experiences quantum confinement and transforms into a quantum dot [5]. In this sense, confinement refers to the limitation or restriction of electrons' random mobility within quantum dots. As

particle size reduces, energy levels become more distinct, resulting in a larger band gap. There is more gap energy as a result of this larger band gap. Thus, a crystal's band-gap energy is determined by its size, and this in turn affects the photon's radiated energy [1]. With a broad absorption spectrum, QDs can be activated by a wide range of wavelengths. Furthermore, the user can narrow the emission spectrum as needed; because the size of the energy of the emitted photon is determined by QDs. Red QDs have a broader band gap than blue QDs, which have smaller diameters.

Quantum dots (QDs) are broadly classified into semiconductor QDs, carbon dots (CDs), and graphene quantum dots (GQDs). Semiconductor QDs such as CdSe and InP offer strong, tunable fluorescence and are widely investigated for bioimaging and biosensing. CDs provide good water dispersibility, surface functionalization, and relatively low toxicity, supporting applications in imaging, drug delivery, and therapy. GQDs combine graphene-like properties with quantum effects and are explored for imaging, sensing, drug delivery, and theranostic applications.

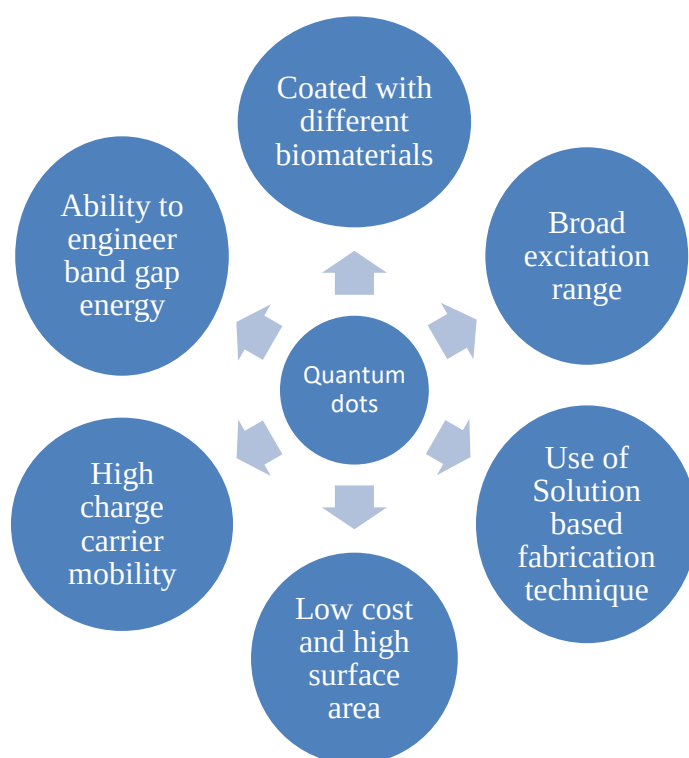


Figure 2: Properties of semiconductor quantum dots.

3. Fluorescence in QDs

3. Fluorescence in QDs

Quantum dots (QDs) exhibit fluorescence as a result of quantum confinement, making them useful as fluorescent probes for imaging cellular and subcellular structures. Unlike bulk semiconductor materials, which possess continuous energy bands, QDs exhibit discrete energy levels because of quantum confinement. The optical properties of QDs can therefore be tuned by controlling their size, composition, and surface characteristics [2]. In addition to fluorescence, interactions such as energy transfer and charge transfer can modify the spectroscopic behavior of QDs. One important energy-transfer mechanism is Förster resonance energy transfer (FRET), in which an excited donor transfers energy non-radiatively to a nearby acceptor through dipole–dipole interactions. FRET is highly dependent on the distance between the donor and acceptor and generally occurs over a range of approximately 1–10 nm. In contrast, when the donor and acceptor are separated by very short distances, orbital overlap may facilitate electron or charge transfer, involving transfer between the donor and acceptor molecular orbitals [3]. These processes can alter the fluorescence intensity and emission characteristics of QDs and have been explored in sensing, bioimaging, and other biomedical applications.

4. Synthesis and Fabrication of Quantum Dots

Quantum dots (QDs) are extensively employed in diverse biomedical applications. Those intended for

biomedical purposes commonly possess a core made of a distinct semiconductor material, such as CdSe, enveloped by a shell composed of another semiconductor material like ZnS. This structural arrangement improves the optical characteristics of the QDs [7][8]. To mitigate the toxicity associated with certain QDs containing harmful ions like Cd^{+2} , Se^{-2} , and Te^{-2} , a coating based on oxides becomes necessary for biological applications [4]. QDs exhibit emission wavelengths spanning from ultraviolet to infrared, and they are synthesized in various types such as ZnS, ZnSe, CdSe, CdS, CdTe, PbSe, PbS, and so on.

Quantum dots (QDs) can be produced using three methods: type I, reverse type I, and type II. In type I, the core material has a narrower band gap than the shell material, confining both holes and electrons within the core. The shell acts as a barrier, isolating the core from the surrounding medium and reducing interference from oxygen and water molecules. This keeps oxygen and water molecules from altering the optical properties of QDs. The most common type I core/shell QD is CdSe/ZnS[10], with the ZnS shell increasing photo-degradation stability and optical properties[5]. In the reverse type I scenario, the core material band gap exceeds that of the shell material, leading to the partial or complete entrapment of holes and electrons in the shell. Consequently, the emission wavelength is influenced by the thickness of the shell. The extensively studied systems in this context include CdS/HgS[6], ZnSe/CdSe [7], and CdS/CdSe[10]. Surface modification plays an important role in

determining the biological behavior of quantum dots (QDs). Appropriate surface coatings can improve water dispersibility and colloidal stability while reducing nonspecific interactions with proteins and cell membranes. The surface chemistry and charge of QDs can also influence cellular uptake, as positively charged or ligand-functionalized surfaces may enhance interaction with negatively charged cell membranes and facilitate internalization. In addition, attachment of targeting ligands such as antibodies, peptides, or other biomolecules can improve selective recognition and accumulation of QDs in specific cells or tissues. Surface coatings may also reduce aggregation and protect the QD core from the surrounding biological environment, thereby improving physicochemical stability and reducing the release of potentially toxic ions [4][7][8]. Importantly, surface modification can influence protein adsorption, biodistribution, retention, and biological clearance. Hydrophilic and biocompatible coatings may reduce nonspecific uptake by the reticuloendothelial system and alter the residence time of QDs in the circulation. However, excessive surface functionalization or highly stable coatings may also prolong their persistence in biological tissues. Therefore, the selection of coating material, surface charge, ligand density, hydrophilicity, and particle size should be carefully optimized to achieve an appropriate balance between cellular uptake, targeting efficiency, stability, and clearance.

The type II structure has a staggered alignment in which the shell's valence or conduction band aligns with the core material's band gap [8]. This accord is smaller than the first semiconductor materials utilized for core and shell formation in quantum dots (QDs). Type II essentially seeks to fine-tune the size and, as a result, energy of the radiated photon. Type II quantum dots, such as CdSe/ZnTe and CdTe/CdSe, are widely used in infrared applications [9]. Their fabrication involves two distinct approaches known as top-down and bottom-up, which are detailed below.

4.1. Top-Down Approach

Top-down procedures for manufacturing quantum dots (QDs) include a variety of processes, including ion implantation, e-beam lithography, molecular beam epitaxy (MBE), and X-ray lithography [10]. These procedures include thinning bulk semiconductors, which leads to the formation of quantum dots by material reduction. QDs with a diameter of ~30 nm are created using electron beam lithography, focussed ion, and wet chemical processes on bulk semiconductor materials. Alternatively, the fabrication of arrays of zero-dimensional dots has been achieved using focused ion or laser beams. However, these methods have notable drawbacks, including the

introduction of impurities into the quantum dots and the occurrence of structural imperfections through the patterning process.

This process uses a lot of energy and involves breaking down a large carbon material to reach the anode electrode. This degradation occurs in the presence of plasma created by two ideally positioned electrodes. This technique includes high electrical currents which creates intense heat, due to which it vaporises the carbon rods which led to the formation of CQDs when this vapour condenses. CQDs were produced utilizing this arc discharge process. While trying to create SWCNTs using the same method, Xu and his team accidentally produced three different types of carbon-based nanomaterials, each with its own molecular weight and glowing characteristics. When stimulated at 365 nm, these CQDs generated fluorescence in colors of orange, yellow, and blue-green. Further research showed that these CQDs had water-loving carboxyl groups on their surfaces, making them dissolve in water. However, the CQDs made this way often had a wide range of particle sizes because the discharge process created nanocarbon compounds of varying sizes [11].

This is a laser-based method which uses high beam of laser to blasts the carbon particles. This is a unique and promising approach which is widely employed for the production of CQDs of various shapes. Sun and his team first proposed that this pulse creates a state with extremely high pressure and temperature. This causes the target material to rapidly turn into plasma, which then cools and crystallizes into CQD nanoparticles. The large-scale synthesis of heteroatom-doped CQDs utilizing a sequential technique was proven in a noteworthy improvement. First, the carbon structure was altered by acid oxidation, which was followed by a hydrothermal reduction procedure. This method permits the addition of heteroatoms, which can improve the CQDs' optical and electrical characteristics, in addition to providing exact control over the surface chemistry of the particles. This is a technology that uses high-energy ultrasound to accelerate the creation of nanocarbon materials in a variety of circumstances, including high temperature and pressure. This procedure is highly recommended because it has many advantages, like being eco-friendly, low-cost, able to penetrate deeply, and providing consistent results [12].

4.2. Bottom-Up Approach

The integration of Quantum Dots (QDs) into medical devices signifies a groundbreaking convergence of nanotechnology and healthcare, leveraging the unique electronic and optical properties of nanoscale semiconductor materials. Quantum dots, with their

tunable characteristics and size-dependent fluorescence, hold immense potential for diverse medical applications, including imaging, diagnostics, drug delivery, and therapy across visible and infrared spectra. The key to harnessing their potential lies in the Bottom-Up Approach for the synthesis and fabrication of quantum dots, offering precise control over size, shape, and composition.

In this approach, the careful selection of precursor materials, often metal salts or organometallic compounds, initiates the process, influencing subsequent quantum dot properties [13]. Nucleation, the formation of small clusters of atoms, is crucial for uniformity in quantum dot properties, especially in medical imaging and diagnostics. Controlled growth follows nucleation, where adjustment of parameters such as temperature, pressure, and reaction time tailors quantum dots for specific medical device applications, including targeted drug delivery. Capping agents, introduced during synthesis, prevent uncontrolled growth and enhance stability, ensuring the biocompatibility of quantum dots within complex biological systems. The fine-tuning of synthesis conditions allows precise control over size and shape, critical for achieving uniformity in medical imaging applications. The Bottom-Up Approach supports the incorporation of biocompatible capping agents, essential for in vivo medical devices, and enables customization of optical properties, advantageous for accurate diagnostics [14].

Designed with specific surface modifications, quantum dots synthesized through this approach facilitate targeted drug delivery, particularly relevant for precision medicine and therapies. The tunable electronic properties of quantum dots find application in theragnostic devices, where both diagnostics and therapy converge. Challenges, including long-term stability and toxicity considerations, underscore the need for careful evaluation in medical applications. Quantum dots unique optical properties make them well-suited for medical imaging, offering the development of contrast agents with enhanced brightness. Integrated into diagnostic devices, quantum dots enable the detection of biomarkers with highly sensitive and accurate diagnostic tools [15]. Engineered for targeted drug delivery, their small size, surface modifications, and biocompatibility make quantum dots ideal carriers for delivering therapeutic agents to specific cells or tissues. The adjustable electronic properties of quantum dots can be used for treatments like photothermal or photodynamic therapy, providing precise and localized treatment. The Bottom-Up Approach for quantum dot synthesis and fabrication holds immense promise for revolutionizing medical devices, ushering in a new era

of precision medicine. From enhancing medical imaging to enabling targeted drug delivery and theranostic applications, the tailored properties of quantum dots provide a pathway to more advanced and effective healthcare technologies. As research and development in this field progress, the seamless integration of quantum dots into medical devices is poised to redefine diagnostics, treatment, and patient care, promising a transformative impact on the future of precision medicine [16].

This method is straightforward, economical, and efficient, yielding high quantities of CQDs. It utilizes microwave irradiation, a rapid technique where electromagnetic radiation with wavelengths ranging from 1 mm to 1 m is applied to the reaction mixture. Microwave irradiation offers notable advantages such as ease of handling and shortened processing times. It ensures even distribution of internal energy by uniformly heating the substrate, thereby facilitating the production of pure, size-controlled CQDs in significant quantities. Moreover, this method stands out for its reduced reaction times, energy efficiency, and environmental friendliness compared to traditional heating methods. However, a key challenge in CQD synthesis via ultrasonic techniques is the uneven sample heating, which, in contrast to direct or microwave heating techniques, can affect reaction efficiency. Pioneered microwave pyrolysis for CQD production, employing substances like polyethylene glycol-200 (PEG 200) and saccharides such as fructose or glucose in a water-based solution. This solution becomes transparent and is subsequently treated in a microwave oven for controlled synthesis [17].

This is a widely adopted synthesizing method used by the researchers. This method involves burning a carbon-rich material, like glucose, citric acid, or other organic compounds, with an oxidizing agent. Successfully created fluorescent GQDs through the combustion of citric acid. This method entails burning an oxidizing agent-containing carbon-rich precursor, such as glucose, citric acid, or other organic molecules. By burning citric acid, fluorescent GQDs with success in 2017. By adding acetic acid moieties and functionalizing them with carboxyl groups at high temperatures, they improved these GQDs even further. This modification resulted in GQDs that maintained a uniform size of 8.5 nm and featured a substantial number of carboxyl groups on their surfaces. The thermal oxidation method is valued for its simplicity and scalability, making it suitable for producing CQDs in large quantities. By carefully controlling the combustion process and subsequent functionalization steps, researchers can tailor the properties of CQDs to meet specific application

requirements, such as enhanced fluorescence or improved biocompatibility [18].

These techniques are among the most widely used ones for creating CQDs, and they are highly valued for their high quantum yields and simple experimental setups. They are more cost-effective and applicable due to their ability to function well over a wide range of temperatures, enhancing their adaptability. Also, the synthesis techniques can use a variety of precursors, including proteins, glucose, and chitosan, which are environmentally friendly and non-toxic. These techniques usually involve dissolving tiny organic compounds or polymers in an organic solvent (solvothermal) or water (hydrothermal). After that, the resultant solution is put into an autoclave. Carbon cores are first generated at high temperatures, which serves as the starting point for the formation of CQDs. This step allows exact control over the size and the structure of the CQDs produced [19].

This approach is the most extensively used, commercially feasible, and highly effective way to create CQDs. These nanoparticles are created by electrochemical exfoliation or electro-oxidation of carbon sources. Because it can function in standard temperature and atmospheric pressure circumstances, it is very popular. This process is well known for being easy to manage in terms of both the final CQDs' photoluminescence properties and particle size. A noteworthy benefit of this method is its dependence on easily accessible and environmentally benign precursors. But obtaining high-purity CQDs requires labor-intensive and time-consuming purifying procedures, which presents a major obstacle to this synthesis approach. This method to prepare deep-blue luminescent CQDs using multiwalled carbon nanotubes (MWCNTs) as starting materials. This pioneering work has paved the way for further advancements in tailoring the properties of CQDs through electrochemical routes, promising broader applications in various fields. This method to prepare deep-blue luminescent CQDs using multiwalled carbon nanotubes (MWCNTs) as starting materials. This pioneering work has paved the way for further advancements in tailoring the properties of CQDs through electrochemical routes, promising broader applications in various fields.

4.3. Wet Chemical Methods

In order to produce QDs with high crystallinity and narrow dispersion using this approach, various alternative self-assembly methods (bottom-up) were employed. These methods are classified as either wet-chemical or vapor-phase techniques. The process encompasses sol-gel, micro-emulsion, and hot solution decomposition methods, building on

conventional precipitation techniques that employ one or a combination of solutions with carefully controlled parameters [20]. Nucleation, whether homogeneous, heterogeneous, or involving secondary nucleation, plays a crucial role in the precipitation process by controlling the limited growth of nanoparticles. During the hot-solution decomposition process, quantum dots (QDs) are synthesized at high temperatures using organometallic precursors along with growth solvents or stabilizing ligands such as trioctylphosphine or trioctylphosphine oxide. These agents play a vital role in enhancing QDs dispersion and improving surface passivation. The synthesis method is simple and may be completed in a single step (one-pot), producing ample thermal energy capable of rectifying defects and enabling the uniform production of quantum dots in significant quantities, including the alloying process [21].

This process combines three main steps: hydrolysis, condensation (forming a sol), and growth (forming a gel). In this technique, a sol is formed by dispersing nanoparticles in a solvent through random motion. A metal precursor, like alkoxides or metal chlorides, is used in an acidic or basic solution. The metal precursor reacts in this solution, undergoing hydrolysis and condensation to create the sol. This is followed by polymerization, which leads to the formation of a networked solid, or gel. The formation of metal oxides occurs through the connection of metal centers by oxygen bridges (M-O-M) or hydroxyl bridges (M-OH-M), resulting in polymers of metal oxides or hydroxides in the solution. This solution changes into a system with both liquid and solid parts, which can include separate particles or continuous polymer networks. Removing the remaining solvent causes significant shrinkage and densification, influenced by the gel's porosity distribution. To strengthen and stabilize the material, further polymerization often requires heating or firing to improve its mechanical properties and structure through processes like sintering, densification, and grain development. The precursor sol can be used to manufacture microspheres or nanospheres, molded into molds for specified forms, or deposited on surfaces by spin- or dip-coating to make films.

For example, Zinc Oxide Quantum dots are produced by combining Zn-acetate with sodium hydroxide, followed by a controlled aging process. Researchers have also used sol-gel methods to produce Zinc Oxide thin films for quantum dot solar cells. Despite its advantages like low temperature requirements, cost-effectiveness, and scalability, this method suffers from imprecise size distribution and high defect concentrations. For example, Zn-acetate and sodium hydroxide solutions have been used to create Zinc

Oxide Quantum dots, which are then aged under controlled conditions. Sol-gel techniques have also been utilized by researchers to create thin sheets of zinc oxide for quantum dot solar cells. Though this technology has benefits such as low temperature requirements, low cost, and scalability, it has drawbacks such as imprecise size distribution and high concentration of defects [22].

This method can be used at room temperature, just like the Sol-Gel process. In contrast to the Sol-Gel approach, one may control the size of quantum dots and produce a tighter size distribution by varying the quantity of surfactant to water. Lower yield and the introduction of contaminants and faults are disadvantages, though. The reverse micelle process is commonly employed to synthesize quantum dots, where nanometer-sized water droplets are dispersed in n-alkane solutions using surfactants like aerosol OT (AOT), cetyl trimethylammonium bromide (CTAB), sodium dodecyl sulfate (SDS), or Triton-X. Quantum dots are commonly created by the reverse micelle technique, in which surfactants like aerosol OT (AOT), cetyl trimethylammonium bromide (CTAB), sodium dodecyl sulfate (SDS), or triton-X are employed to disperse nanometer-sized water droplets in n-alkane solutions. These surfactants create a large number of tiny micelles in the continuous oil phase because they have both hydrophilic and hydrophobic ends. These stable micelles serve as minuscule reaction channels. The dynamic collisions created by actively stirring micellar solutions allow for the continuous interchange of reactants. The size of quantum dots is controlled by the size of the micelles, which can be adjusted by changing the water-to-surfactant ratio. The reverse micelle technique has been used to make various quantum dots, including CdS, CdS/ZnS, IV-VI quantum dots, and carbon quantum dots, using hydride reducing agents. Darbandi and his team showed a simple one-step method to embed single quantum dots into spherical silica nanoparticles, using cyclohexane as the oil and Synperonic NP-5 as the surfactant. A recent study also looked at how ultrasonic waves affect the creation of hexagonal-phase CdS quantum dots in a microemulsion.

As described by Bawendi and associates in 1993, this technique entails raising the temperature of organometallic compounds to a high point. Air is usually removed, and a solvent like tri-octyl-phosphine oxide (TOPO) is dried in a three-necked flask under vacuum at about 300°C. At this temperature, a dry mixture of tri-n-octyl-phosphine selenide and a cadmium precursor is prepared and then added to the flask while stirring vigorously. This leads to the formation of quantum dots through uniform nucleation, and the gradual development that

follows through 'Ostwald ripening'. At a reaction temperature of roughly 250°C, smaller quantum dots with higher free energy lose material to larger ones during Ostwald ripening, which results in a progressive rise in quantum dot size. The nearly 90% pure coordinating solvent TOPO improves surface passivation, stabilizes the quantum dot dispersion, and inhibits quantum dot growth by blocking adsorption. During the first few hours, samples can be obtained from the flask at regular intervals to reach the required particle size through optical absorption.

This technique has been extensively used to synthesize various types of quantum dots, including II-VI, IV-VI, and III-V. The size, shape, and control of the reaction are influenced by several factors, such as reaction duration, temperature, choice of precursors, solvents, coordinating agents, and the purity of coordinating solvents like TOPO. A thorough explanation of numerous precursor and process characteristics. This process creates uniformly sized quantum dots by applying enough heat to anneal flaws. By varying the temperature, the same precursor solution can yield a variety of quantum dot sizes. This process is costly due to the high temperature requirements, the toxicity of certain organometallic precursors, and the generally poor dispersion in water.

4.4. Vapor Phase Methods

Achieved in a single step (one-pot), the synthesis process is uncomplicated, generating sufficient thermal energy to rectify defects and ensure the consistent production of quantum dots in substantial quantities, including the alloying process. In biomedical applications vapor phase method is significantly used, the CdSe/ZnS core/shell is commonly employed, with a CdSe core covered by a ZnS shell possessing a broader bandgap. This shell functions to passivate the surface and stabilize the photophysical characteristics of the CdSe core quantum dot [23].

One method that is frequently used to create semiconductor crystals in III-V and II-VI is called molecular beam epitaxy, or MBE. Ultra-pure elements like arsenic and gallium are heated individually in quasi-Knudsen effusion cells in solid-source MBE until they slowly sublime. Following their formation, the gaseous components condense on the wafer and can react to generate quantum dots of gallium arsenide, for example. In comparison to other epitaxy techniques, MBE operates at a lesser throughput. Sources can also be mixtures of gases and solids (AsH₃, PH₃, or metal-organics like trimethyl or triethyl gallium). Reflection High Energy Electron Diffraction (RHEED) tracks the development of crystal layers while it is in operation. Each furnace has

computer-controlled shutters in front of it that allow for exact control over layer thickness, even down to the level of an individual atom. As previously indicated, MBE is mainly employed for self-assembling quantum dots employing materials with significant lattice mismatches, like InAs on GaAs, which exhibits a 7% mismatch and causes SK development.

In the Physical Vapor Deposition (PVD) process, material is turned into vapor from a solid or liquid source. This vapor then travels through a vacuum or low-pressure gas to the surface where it cools and forms a layer. The most common industrial application of PVD is sputtering, where ions bombard the surface of a target material under high voltage, causing atoms or molecules to be ejected due to the momentum transfer from the incoming particles. Other PVD techniques include vacuum deposition, arc vapor deposition, ion plating, and pulsed laser ablation. These methods have been employed to prepare materials such as Nb₂O₅, CdSe/CdTe quantum dots, and various nanocrystals.

Chemical reactions in the gas phase, referred to as "precursors," transform atoms or molecules into solid films or powders that are deposited at high temperatures on substrates in the process of Chemical Vapor Deposition (CVD). Usually, this method yields wasted precursors and volatile byproducts. Chemical Vapor Deposition (CVD) includes several techniques: Vapor Phase Epitaxy (VPE) for single crystal films, Metal Organic CVD (MOCVD) using metal-organic materials, Plasma Enhanced CVD (PECVD) with plasma, and Low-Pressure CVD (LPCVD) at lower pressures. Other methods are Atmospheric Pressure CVD (APCVD), Photochemical Vapor Deposition (PCVD), and Laser Chemical Vapor Deposition (LCVD). Kim and his team made ZnSe/ZnS quantum dots using MOCVD in Atomic Layer Epitaxy (ALE) mode. Dhawan and his team used MOCVD to create InAs quantum dots on a germanium substrate and studied how temperature and InAs coverage affected the size, density, and height of the dots. Jinsup Lee and his team showed how to control the size of graphene quantum dots using a block copolymer as a mask on graphene films. Current research is focusing on making graphene quantum dots on a large scale and studying how to grow and recrystallize 2D graphene using mobile hot-wire CVD processes.

4.5. Other Synthetic Methods

Alternative methods for creating Quantum Dots (QDs) include hydrothermal synthesis, electrochemical assembly, bio-template synthesis with microorganisms, and ultrasonic or microwave irradiation. Quantum dots (QDs) with sizes ranging

from 1 to 5 nm can be produced using ultrasonic or microwave irradiation, where ultrasonic or microwave waves are passed through an inert aqueous medium containing the precursor. The hydrothermal technique involves encapsulating inorganic salts from aqueous solutions, with control over pressure and temperature. Bio-templates derived from microorganisms are used in the bottom-up production of QDs, offering a cost-effective, rapid growth method with adjustable size and structure. For example, genetically engineered phages like M13 and Fd, which can detect specific semiconductor surfaces through randomized phage display, are applied in this process. The electrochemical technique involves an ionic reaction at the interface of an electrolyte and metal, resulting in the self-assembly of quantum dots onto the metal.

Since 2000, researchers have utilized ultrasonic or microwave energy to produce quantum dots ranging in size from 1 to 5 nm by passing them through a mixture of precursors dissolved in water. This process induces acoustic cavitation, creating localized hotspots due to the rapid compression of gas inside collapsing bubbles. These conditions facilitate the growth of quantum dots.

Zinc acetate dispersed in a solution was combined with selenourea and subjected to sonication for an hour under an argon atmosphere. This method resulted in the formation of ZnSe nanoparticles approximately 3 nm in size. Throughout the process, the solution temperature rose to 80 °C.

Scientists have employed hydrothermal synthesis methods or similar approaches to create quantum dots. These methods involve carefully controlling the crystallization of inorganic salts from water solutions at certain pressures and temperatures. As the temperature or pressure drops, the solubility of the salts decreases, causing them to form crystalline particles called quantum dots. By changing factors like pressure, temperature, reaction time, aging time, and the ingredients used, researchers can create quantum dots with different shapes and sizes. Several other wet-chemical processes have also been documented in the literature for synthesizing quantum dots. Additionally, methods involving the introduction of H₂S gas into precursors have been utilized to prepare quantum dots based on sulfides.

The solvothermal synthetic method resembles hydrothermal processes, but with a key distinction: it uses a stainless-steel autoclave to facilitate chemical reactions, typically with non-aqueous precursor solutions. This method has been instrumental in producing various nanostructures, such as nanostructured TiO₂ and graphene nanosheets,

through a step-by-step approach. For example, ethanol and sodium react to create an intermediate solid. This material is then heated to produce a collection of graphene sheets, which are spread out using gentle sonication. In a significant study by Du and his team, they made ultra-small CuInSe₂ quantum dots with diameters smaller than 10.6 nm using a solvothermal method in oleylamine, without using any organometallic materials.

Researchers have also created well-organized arrays of quantum dots using electrochemical methods. In this process, a template is made by starting an ionic reaction at the interface between an electrolyte and metal. This reaction causes nanostructures, including quantum dots, to assemble onto the metal surface. The metal then acts as a mask for etching these nanostructures onto a chosen surface. This method has several benefits: it's inexpensive, avoids radiation damage to nanostructures (unlike beam lithography), and produces a high yield, making it great for mass production. It also allows for patterning on curved surfaces. Bandyopadhyay and his team described two electrochemical self-assembly techniques for making well-organized arrays of quantum dots and studied the special optical properties of self-assembled CdS quantum dots. In a 2000 study, Raman spectroscopy was used to analyze these arrays of CdS quantum dots that were electrochemically assembled within a porous anodized alumina film.

Nigel Pickett developed a method for producing technique allows for making large amounts of quantum dots in one batch. It uses clusters of Cd₁₀Se₄(SPh)₁₆ to start the growth of CdSe quantum dots. The number of quantum dots produced depends on how many clusters are added during the process. Further advancements were made by "The Snee Group" at the University of Illinois, Chicago. They conducted research on synthesizing CdSe nanocrystals, observing a linear correlation between the number of clusters introduced and the number of nanocrystals synthesized. Their studies revealed that a higher concentration of clusters leads to the formation of smaller quantum dots, as there is increased competition among a larger number of dots for limited precursor materials. Importantly, they found that without clusters, no quantum dots are synthesized. The group also pioneered a method to synthesize individual CdSe quantum dots doped with four copper ions. They achieved this by using [Na(H₂O)₃]₂[Cu₄(SPh)₆] as a cluster seed. This approach builds upon the cluster-seed method, where organometallic clusters act as pivotal nucleation centers for the formation of quantum dots.

5. Surface Coating and Functionalization of QD

Quantum dots (QDs) possess unique size- and composition-dependent optical and electronic properties, making them attractive materials for a wide range of biomedical applications. However, QDs synthesized using conventional methods are frequently capped with hydrophobic ligands and dispersed in nonpolar organic solvents, which restricts their direct use in aqueous and physiological environments. Therefore, surface coating and functionalization are essential steps in the development of QDs for biomedical applications. Appropriate surface modification can improve aqueous solubility, colloidal stability, cellular uptake, target specificity, and biocompatibility, while also providing functional groups for the conjugation of biomolecules [26].

5.1 Surface Coating for Improving Stability and Biocompatibility

Surface coating protects the QD core from the surrounding biological environment and can reduce undesirable interactions with water, oxygen, proteins, and other biomolecules. This is particularly important for QDs containing potentially toxic elements such as cadmium, selenium, or tellurium. Appropriate surface coatings can reduce the release of toxic ions and improve the overall stability and biocompatibility of QDs in biological systems [4]. Several strategies have been developed to convert hydrophobic QDs into water-dispersible and biologically compatible nanomaterials. These include ligand exchange, polymer encapsulation, silica coating, phospholipid or micellar encapsulation, and multilayer surface modification. In ligand-exchange approaches, the original hydrophobic ligands are replaced with hydrophilic or amphiphilic molecules containing functional groups such as thiols, phosphines, carboxylates, or peptides [26]. Although ligand exchange can preserve the original particle size, changes in the surface environment may influence the photoluminescence intensity and other optical characteristics of QDs.

An alternative strategy involves encapsulating QDs within amphiphilic polymers, silica shells, phospholipid micelles, polymer beads, polymeric shells, or amphiphilic polysaccharides. This approach provides an additional protective layer around the QD core and can improve aqueous dispersibility, colloidal stability, and resistance to environmental degradation. Polymers such as polyacrylic acid and maleic anhydride-based polymers have been investigated for this purpose. Encapsulation within micelles or lipid-based structures also provides flexibility in controlling the surface chemistry of QDs. PEG-containing phospholipids and related materials can improve water solubility and reduce nonspecific interactions

with biological components [34]. Thus, appropriate surface coating can help maintain QD stability while reducing potential cytotoxic effects.

5.2 Surface Functionalization for Cellular Uptake

Surface functionalization also plays an important role in determining the interaction of QDs with cellular membranes and their subsequent internalization. The physicochemical characteristics of the QD surface, including surface charge, hydrophilicity, ligand density, and functional-group composition, can influence cellular interactions and uptake. Functional groups introduced onto the QD surface can be further modified with specific biomolecules to facilitate receptor-mediated cellular internalization. Functionalized QDs can be conjugated with proteins, peptides, antibodies, and receptor-specific ligands to improve their interaction with selected cell types. For example, streptavidin, antibodies, epidermal growth factor (EGF), recognition peptides, and biotin-avidin/streptavidin affinity systems have been employed for the functionalization and biological targeting of QDs [26]. Such modifications can promote interactions between QDs and specific receptors expressed on the cell surface, thereby improving cellular uptake and intracellular delivery. However, increased cellular uptake does not necessarily indicate improved biomedical performance. Excessive surface charge or nonspecific interactions may increase cellular internalization while simultaneously contributing to membrane damage or cytotoxicity. Therefore, surface functionalization should be optimized to achieve an appropriate balance between cellular uptake, target specificity, and biocompatibility.

5.3 Surface Functionalization for Targeted Delivery

One of the major advantages of QD surface functionalization is the ability to introduce specific recognition molecules for targeted biomedical applications. The presence of amino, carboxyl, and sulfhydryl groups on the QD surface enables the attachment of antibodies, peptides, proteins, and other targeting ligands through covalent or affinity-based interactions [28,35]. These biomolecular conjugates can improve the selective recognition of specific receptors, cells, or tissues and thereby enhance the targeting efficiency of QD-based systems.

For example, streptavidin-coated QDs have been used for the detection of human epidermal growth factor receptor 2 (HER2) on the surface of SK-BR-3 human breast cancer cells through a biotinylated secondary antibody and a HER2-specific antibody [28,29]. Similarly, QD-based labeling has been employed to

visualize individual glycine receptors in cultured spinal neurons, allowing high-resolution monitoring of receptor diffusion in synaptic and extrasynaptic regions [30]. These examples demonstrate the potential of surface-functionalized QDs for selective molecular recognition and high-resolution biological imaging. Targeting can also be achieved by incorporating receptor-binding peptides, antibodies, or other affinity ligands onto the QD surface. Such functionalization can improve the accumulation of QDs at desired biological targets and may enhance their application in targeted imaging, diagnosis, drug delivery, and theranostics.

5.4 Role of Surface Modification in Improving Biocompatibility

Biocompatibility is a critical consideration in the development of QDs for biomedical applications. The biological response to QDs is influenced not only by their core composition but also by their surface chemistry, particle size, surface charge, coating material, and functional groups. Appropriate surface modification can reduce nonspecific protein adsorption, minimize aggregation, improve aqueous stability, and decrease direct exposure of potentially toxic QD components to biological tissues. Hydrophilic polymeric coatings and lipid-based encapsulation can provide a protective interface between the QD core and biological environment. In particular, PEG-based coatings are widely investigated because they can improve aqueous dispersibility and reduce nonspecific interactions. Surface modification can therefore contribute to improved compatibility of QDs with cells and biological fluids while maintaining their desirable optical properties.

Nevertheless, surface functionalization does not completely eliminate the potential toxicity of QDs. The nature and density of surface ligands, coating stability, degradation behavior, and possible release of toxic ions must be considered when designing QDs for biomedical applications. Consequently, the selection of coating and functionalization strategies should be based on the intended application, required stability, cellular interaction, targeting mechanism, and overall safety profile. Surface coatings primarily contribute to aqueous stability, protection of the QD core, and improved biocompatibility, whereas functional ligands can facilitate cellular uptake, molecular recognition, and targeted delivery. The appropriate combination of coating material and targeting ligand can therefore provide QDs with application-specific physicochemical and biological properties. The major surface-modification strategies and their roles in improving the stability, cellular uptake, targeting capability, and biocompatibility of QDs are summarized in Figure 3.

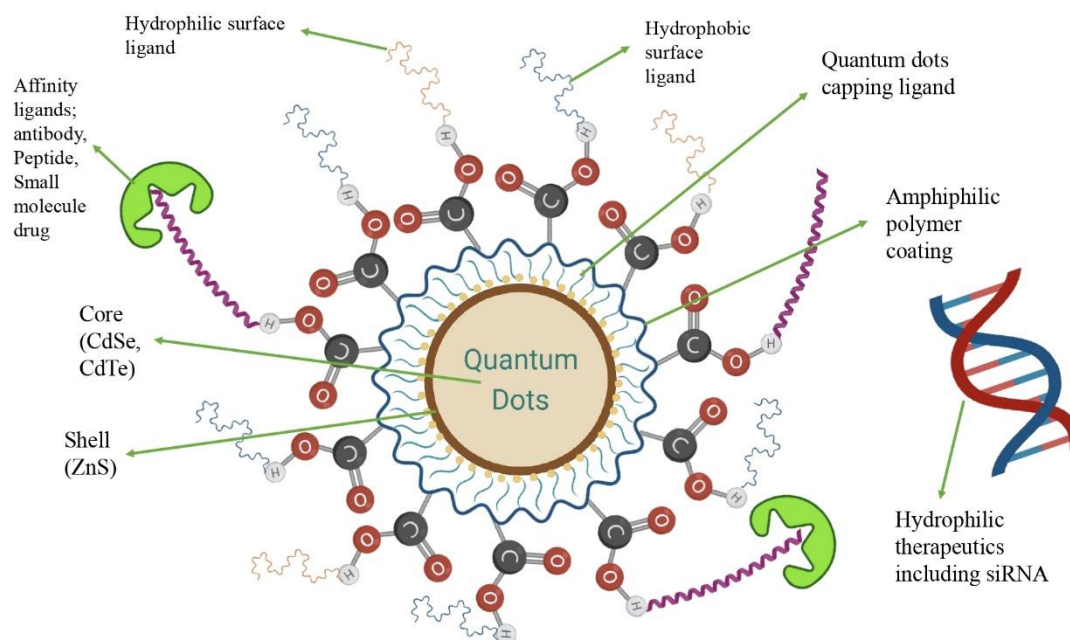


Figure 3: A schematic picture of a quantum dot coated with amphiphilic polymer. Hydrophobic therapies have the ability to trap hydrophilic targeting molecules and therapeutic substances on the outer surface between the hydrophobic nanoparticle core and the amphiphilic polymer coating layer.

6. Bioconjugation of QDs

The special optical and physical properties of Quantum Dots (QDs) make them useful in bioimaging, medical diagnostics, and treatments. For biomolecule specificity or targeting in these applications, various biomolecules can be effectively linked to QDs through methods such as adsorption, electrostatic interaction, mercapto (-SH) exchange, and covalent bonding [36].

6.1. Conjugation of QDs to Proteins

Quantum Dots (QDs) exhibit a unique capacity, enabling the intricate linking of a single QD to multiple protein molecules, with adaptability for diverse applications based on desired specificity; for example, a 6-nm QD can accommodate approximately 15–20 maltose binding proteins. The conjugation process typically employs crosslinkers like 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) or succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC). EDC, a zero-length crosslinker, is commonly used in QD-protein conjugations, facilitating amide bond formation [37]. Researchers have utilized EDC for conjugating transferrin and TAT peptide to QD surfaces, showcasing diverse strategies for achieving QD-protein conjugations with potential applications in biomedicine. Peptides can undergo direct conjugation to QDs, with straightforward approaches involving linkage to thiol-rich domains.

Direct binding method, enhancing QD solubility using synthetic phytochelatin-related peptides. Strategies for QD-antibody conjugation, such as controlled orientation through fusion proteins and metal-affinity coordination of histidine residues, highlight versatile methods for achieving controlled and functional QD-peptide or QD-protein conjugations with potential applications in biomedicine [38].

6.2. Conjugation of QDs to Oligonucleotides

Table 1 summarizes the various strategies have been devised to conjugate single-stranded (ssDNA) and double-stranded DNA (dsDNA) to Quantum Dots (QDs), preserving DNA selectivity and QD photophysical properties for detecting single or multiple DNA targets. Essential requirements include achieving water solubility, stability under physiological conditions, and minimizing nonspecific DNA binding to QD surfaces. One approach involves direct ligand exchange with thiol-modified oligonucleotides, replacing surface-bound mercaptopropionic acid to create stable, highly fluorescent QD-oligonucleotide conjugates. Another method uses thiol-bearing silanized QDs, stabilized by PEG and phosphonate, enabling a two-step process with sulfo-SMCC to achieve stable and specific DNA-QD conjugation [39].

Table 1: Quantum dot-protein/peptide conjugation approaches.

S. No.	Biomolecule	QD surface cap	QD type	Strategy	Application	References
1.	Concanavalin A protein	TGA	CdTe	QD surface carboxy group crosslinking with concanavalin A's reactive amine groups	FRET-based glucose biosensor	[76]
2.	Maltose binding protein	DHLA	CdSe/ZnS	Electrostatic interaction between the QD's negatively charged DHLA cap and the protein's positively charged leucine zipper tail leads to self-assembly.	An alternative conjugation strategy for conjugating proteins to the surface of CdSe/ZnS DHLA-capped QDs other than using EDC crosslinker	[77]
3.	Multifunctional peptides contain protease recognition/cleavage sequence for caspase-1, collagenase and chymotrypsin	DHLA	CdSe/ZnS	Self-assembly of peptides with the amino-terminal hexahistidine domain on DHLA-capped QDs	Detect proteolytic activity of caspase-1, thrombin, collagenase and chymotrypsin	[78]
4.	Transferrin protein	Mercaptacetic acid	CdSe/ZnS	Crosslinking of QD surface carboxylic groups with reactive amine groups	Labeling and imaging of cultured HeLa cells	[79]
5.	TAT peptide	Thiol	CdTe	Crosslinking using EDC	Labeling and imaging of human hepatocellular carcinoma (QGY) cells and human breast cancer (MCF7) cells	[80]
6.	Phytochelatin-related peptides	TOPO	CdSe/ZnS	Direct interaction with thiolated peptide that contains cysteine residues.	Labeling and imaging of HeLa cells	[38]

7. Applications

This review looks at the great potential of quantum dots (QDs) in biology, including tracking macromolecules in cells, monitoring different cell types in tissues, labeling organelles and cells, exploring clinical uses, and investigating other possible applications.

7.1. Applications of QDs in the Clinical Laboratory

Quantum Dots (QDs) are widely used in diagnostics, imaging, and treatments, serving as labels in immunoassays, staining, cellular imaging, and multiplex diagnostics. Delivering QDs into cells efficiently is key for imaging and labeling, and this can be done through endocytosis or physical methods. Attaching QDs to specific peptides or molecules helps

them enter cells by using receptor-mediated or assisted endocytosis. For instance, QDs linked to folic acid can target tumor cells that have high levels of folate receptors. Encapsulating QDs in micelles also improves their entry into cells. Additionally, linking QDs to peptides like TAT allows for peptide-based delivery, showing their flexibility in targeted applications.

7.2. *In vitro* Diagnostics

Quantum Dots (QDs) are better than traditional labels in medical tests. They can be activated by a single light color, enabling multiple tests simultaneously. QDs have been used to detect disease-causing germs like those responsible for tuberculosis and hepatitis, and to identify conditions such as cancer and heart problems. Table 2 provides examples of diagnostic applications using QDs.

7.3. Immunoassays

Researchers have used Quantum Dots (QDs) in various immunoassays to detect specific markers and antigens. In one study, Zeng and his team developed an immunoassay to detect hepatitis B surface antigen using CdTe/CdS QDs attached to antibodies, with protein G as a linking bridge. This method detected as little as 15.6 ng/ml. Luo and his team worked on a microplate immunoassay for the cardiovascular marker C-reactive protein, using a sandwich format that captured the protein with antibodies and used streptavidin-coated QDs to generate a fluorescent signal, detecting as little as 0.19 µg/l in 1.5 hours. Sapsford and his team created a multiplex immunoassay to simultaneously detect staphylococcal enterotoxin B and chicken IgY in a 96-well plate. The antigens were sandwiched between capture antibodies and QD-labeled detection antibodies, achieving detection limits of 9.8 ng/ml for chicken IgY and 7.8 ng/ml for staphylococcal enterotoxin B [42]. Cao and his team developed a multiplex fluoroimmunoassay to detect lung cancer markers NSE and CEA in human serum using a sandwich format on filter microplates with capture antibodies on polystyrene microspheres. They used different QDs with varying emission wavelengths for detection. Another study used a multiplex immunoassay for Enterovirus 71 and Coxsackievirus B3, combining QDs, the FRET phenomenon, and graphene oxide as a superquencher. When the viruses were present, the QD conjugate detached from the graphene oxide, causing visible fluorescence changes that helped identify and measure the viruses. These studies show the flexibility of QDs in various immunoassays, offering sensitive and multiplexed detection for different biomarkers and pathogens. Quantum dots (QDs) are important in detecting tough-to-find pathogens like mycobacteria, which cause diseases such as tuberculosis and leprosy. Researchers combined a technique called immunomagnetic separation with QD-based fluorescence to identify *Mycobacterium bovis* bacillus. They used special antibodies attached to magnetic beads to capture the bacteria, followed by adding another antibody and separating the bacteria using a magnet. The bacteria were then detected under UV light, showing how versatile QDs are in spotting pathogens. Additionally, QDs were used to create a sensor that could measure glucose levels in serum with a detection limit of 50 nM, similar to clinical tests, while only needing a tiny 1 µL sample [45].

7.4. Molecular Diagnostics

Quantum dots (QDs) have a big advantage over traditional organic dyes for labeling DNA because they don't break down or produce harmful free radicals when exposed to light. QDs with magnetic

nanoparticles to quickly detect human papilloma virus 16 DNA, which is linked to cervical cancer, in under an hour. In another study, Algar and Krull created a test using CdSe/ZnS QDs to identify single nucleotide changes (SNPs) with a very low detection limit of 1 nM and a high contrast ratio of 12:1. Their test used green- and red-emitting QDs on an optical fiber to detect multiple SNPs at once by measuring the energy transfer between QDs and other fluorescent markers [47].

7.5. Imaging

QDs coated with streptavidin to watch how acetylcholine receptor clusters form in muscle cell cultures from frogs. QDs with a special focus on hepatitis C virus (HCV) to study how the virus affects liver tissue, helping them understand where infected liver cells are located. QDs with antibodies to measure several pancreatic cancer markers in individual cells, detecting as few as four markers per square micrometer. CdTe QDs were used for detailed deep-tissue imaging, reaching about 2 mm into the tissue with two-photon microscopy. Silicon QDs with manganese for imaging using both MRI and two-photon techniques, successfully imaging mouse immune cells in the lab [49].

Quantum dots (QDs) to detect a specific marker for Epstein-Barr virus infection, called EBER, in tissue samples that had been preserved and embedded in paraffin. This marker helps provide important information about nasopharyngeal cancer. They used QDs in a technique called Fluorescence In Situ Hybridization (FISH) to detect EBER accurately.

In another application, near-infrared-emitting QDs were used to locate sentinel lymph nodes in pigs, which were about 1 cm below the skin. Additionally, streptavidin-coated QDs linked to special antibodies were used to label HIV particles on a microfluidic chip, making it possible to image individual viruses in a small blood sample. Quantum dots (QDs) that emit near-infrared light to track the movement of immune cells called dendritic cells into lymph nodes in mice. They were able to monitor these cells with fluorescence imaging while keeping the cells healthy and active.

Researchers have also discovered a new type of quantum dot made from zinc oxide (ZnO) that looks promising for cancer imaging and detection. ZnO QDs, which are about 5–10 nm in size, attached to transferrin (a protein) to study breast cancer cells that have transferrin receptors. These ZnO QDs worked similarly to the commonly used CdSe QDs but were less toxic, making them a promising option for cancer research (see table2). Quantum dot (QD)-based technologies are currently distributed across different

stages of development. At the experimental level, QDs are mainly investigated in laboratory-based studies for fluorescence imaging, biosensing, drug delivery, photodynamic therapy, and theranostic applications using cell-free systems and cultured cell lines. Preclinical applications extend these findings to animal models, where QDs have been evaluated for tumor imaging, targeted drug delivery, biodistribution, pharmacokinetics, and therapeutic efficacy. These studies provide important information regarding biological behavior and safety under in vivo conditions. In contrast, the clinical translation of QD-based

technologies remains limited, primarily because of concerns related to long-term toxicity, accumulation in organs, degradation products, immunogenicity, and clearance from the body. Although considerable progress has been made with heavy-metal-free QDs and improved surface coatings, most QD-based diagnostic and therapeutic platforms remain at the experimental or preclinical stage. Therefore, further systematic toxicological evaluation, standardized manufacturing, and regulatory validation are required before their widespread clinical application.

Table 2: Quantum dot-based diagnostic applications.

S. No.	QDs	Application	References
1.	CdSe/ZnS/SiO ₂ QDs	QDs were employed to count bacterial cells (<i>Escherichia coli</i>) in samples, replacing the traditional viable count culture procedures. The method employed glutaraldehyde as a crosslinker to covalently bind QDs to bacteria. The bacteria were then combined with the QD-glutaraldehyde mixture, and any excess QDs were removed using ultrafiltration. The method utilized was direct bacterial counting with a detection limit of 3×10^2 CFU/ml, which is 10-20 times lower than plate counting. Reduction of detection time to 2 hours.	[81]
2.	CdTe QDs conjugated to oligonucleotides (molecular beacon structure)	QDs conjugated with oligonucleotide molecular beacons and capillary electrophoresis may detect single-base alterations in synthetic DNA targets simultaneously. The detection limit is 16.2 pg of DNA.	[82]
3.	CdTe/CdS QDs conjugated to goat anti-mouse IgG secondary antibodies	Mouse antibodies were used in sandwich and reverse-phase immunoassays to detect cancer biomarkers CEA and AFP. The detection was performed using a microfluidic chip with femtomolar sensitivity for both biomarkers. When applied to human serum, the detection limit was around 2.5 pM for CEA and 250 fM for both AFP and CEA in buffer. Commercial ELISA kits have detection limits of 5 pM for CEA and 7 pM for AFP. CEA and AFP concentrations were measured simultaneously (range: 25 fM to 25 nM).	[83]

7.6. QDs for Labeling Cells

Quantum dots (QDs) are often better than organic dyes for labeling cells because they have stable and unique optical properties. Combination of biotinylated cholera toxin B (CTxB) and QD-avidin conjugates to label live HeLa cells. This method let them create images showing the staining of the cell membrane for a specific molecule (GM1 ganglioside) with QDs, and also stain the cell nucleus using Hoechst [51, 52].

7.7. Labeling of Microorganisms.

Biologically linked quantum dots (QDs) have shown promise as multi-wavelength fluorescent markers for bioassays and eukaryotic cells, but their use with bacteria hadn't been studied much before. There were concerns because QDs are relatively large (3 to 10 nm), which might affect how bacteria recognize attached molecules or their ability to pass through

bacterial cell walls. However, a recent study used CdSe QDs to label different types of bacteria and fungi, showing that they can be applied in various ways depending on the strain and metabolism [53].

Studying microorganisms where they interact with water and surfaces is important because bacteria sticking to surfaces can lead to problems like corrosion. Extracellular polymeric substances help bacteria attach to surfaces. To understand how substances move and diffuse in bacterial cells and biofilms under different flow conditions, researchers used two types of quantum dots (QDs) with different surface chemistries (amine and carboxyl). These QDs were used to study how bacteria behave in various environments, such as water systems. They made predictions about how QDs would interact with bacterial cells and biofilms based on general

measurements of the QDs' surface chemistry [54]. Researchers are exploring how quantum dots (QDs) can be used in drug delivery. Surface-modified CdS QDs as removable caps to hold drug molecules and neurotransmitters inside a mesoporous silica nanosphere system. These CdS caps keep the drug safe until a chemical trigger releases it. In this case, QDs are used for their capping ability rather than for fluorescence. Additionally, an optical biosensor has been developed to quickly and accurately detect Troponin I in the blood, which is important for diagnosing heart attacks. This sensor uses a method called fluorescence resonance energy transfer (FRET) to detect Troponin I. In this setup, a Protein A molecule, labeled with QDs, acts as the energy donor, and a capture antibody, labeled with an organic dye, acts as the energy acceptor. When Troponin I is present, it causes a change in the distance between the donor and acceptor, leading to a detectable change in energy transfer. This biosensor is very sensitive, detecting Troponin I at levels as low as 32 nM in saline and 55 nM in human plasma.

7.8. Tumor Targeting and Imaging

Initially, quantum dots (QDs) were used as stable fluorescent tracers to study how substances are taken up by cells and to map lymph nodes in living animals. Later, researchers improved this method by coating QDs with polyethylene glycol (PEG) and attaching antibodies that target a specific prostate cancer marker. These modified QDs were injected into mice to image tumors more accurately. A recent innovation involves using self-lighting quantum dots as imaging probes. Scientists attached QDs to antibodies for alpha-fetoprotein (AFP), a marker for liver cancer cells. This setup allows for targeted imaging of liver tumors in living animals using fluorescence. The QD probes were tested for their ability to reveal the distribution of tumors, showing their potential for cancer detection. Quantum dots are also useful for high-resolution imaging of cells and tissues. While traditional immunofluorescence labeling has limits in resolution, QDs can be used in electron and X-ray microscopy for better detail. CdSe QDs in both standard and advanced electron microscopy to show how they can reveal cell structure and sample aggregation. Getting the best results requires careful adjustment of imaging conditions for single QD experiments [55].

7.9. Quantum Dots in Imaging and Diagnostics

Quantum dots outperform traditional imaging technologies. Their high-resolution imaging ability provides a detailed understanding of biological processes at the molecular level, which is notably useful in disease detection and treatment response assessment. Quantum dots enhanced imaging

capabilities help in precise diagnosis, allowing for quick and focused therapeutic interventions [15].

The surface properties of Quantum Dots permit accurate functionalization with targeting ligands like antibodies or peptides. This enables specific interactions with designated cells or tissues, introducing a precision in drug delivery that was previously challenging to achieve. Targeted drug delivery systems hold the promise of transforming the treatment landscape for diverse diseases, particularly in the case of cancer, where minimizing harm to healthy tissues is of utmost importance. The incorporation of Quantum Dots with imaging functionalities enables the real-time tracking of drug delivery. This not only improves treatment precision but also offers healthcare professionals valuable insights into the dynamics of drug interactions within the body. Real-time monitoring allows for adjustments to treatment plans based on individual patient responses, thereby contributing to the implementation of personalized medicine approaches [60].

Since the first successful use of quantum dots with biological molecules in 1998, these materials have become powerful tools for fluorescent imaging, including inside cells and at the single-molecule level. This discussion covers the progress of quantum dots and their use in biological imaging, diagnostic tools, and treatments. Recent research has focused on creating specialized quantum dots to improve the detection of important disease-related molecules in samples outside the body [61].

Quantum dots (QDs) are very promising for cancer imaging because they are stable and exceptionally bright. Researchers have used two-photon microscopy to image blood vessels in live mice after injecting them with QDs. This method showed that QDs provide better contrast and deeper imaging with less power compared to traditional dyes. Another study found that coating QDs with a substance called polyethylene glycol (PEG) helps prevent them from building up in the liver and bone marrow. These coated QDs stayed visible in the bone marrow and lymph nodes for several months. Early uses of peptide-QDs included targeting specific tissue markers, like blood vessels in the lungs and cancer cells, by injecting them into live mice. [62].

8. Recent Progress and Trends in Biomedical Applications

Quantum dots (QDs) are now widely used in real-time biomedical imaging, diagnosis, and guided surgeries, showing their broad potential. QDs with dopamine to create a new type of test for the cancer marker alpha-fetoprotein (AFP) in human serum. This test used a

method where an enzyme reaction on the QD surface reduced fluorescence when AFP was present.

In another approach, QDs were used in a competitive test to detect human serum albumin (HSA) in urine. Despite the QDs being larger due to their binding with other molecules, they remained stable for up to two months and successfully identified high levels of HSA in urine, demonstrating their effectiveness in fluorescence tests.[63]. A new device using quantum dots (QDs) on paper to monitor levels of carcino embryonic antigen (CEA) in human serum. This device used CdTe/CdSe QDs and glucose oxidase on paper to visually detect very low concentrations of CEA, down to 0.05 ng/mL.

Besides these assays, QDs are also useful for non-invasive cell labeling and diagnostic imaging in cancer research. They were used for multicolor imaging of specific markers like human epidermal growth factor (HER2) and type IV collagen in tissue samples from breast cancer patients. This technique showed a connection between high HER2 levels and increased damage to the extracellular matrix, cancer cell invasion, and possible new blood vessel formation, providing important diagnostic information [66]. In another study, researchers used multiple quantum dot (QD)-antibody combinations and advanced imaging techniques to map the diversity of tumors in prostate cancer samples. They looked at four different protein markers and discovered significant differences at the molecular, cellular, and structural levels within prostate glands as cancer progressed [67].

Near-infrared-II (NIR-II) quantum dots that can penetrate deep into tissues, provide high-resolution images, show multiple colors, and capture images quickly. These advanced QDs can be customized in terms of their composition and surface features, making them useful for various imaging applications inside living organisms [68]. A test to identify the Her2 receptor on breast cancer cells using quantum dots (QDs) linked with streptavidin. This method effectively detects targets inside cells. These advancements show how important QDs are becoming in medicine, from sensitive cancer tests to detailed molecular mapping in clinical samples. QDs provide deep tissue imaging, accurate molecular detection, and real-time visualization, making them valuable for improving diagnostics, understanding disease progression, and developing treatments. As research continues, QDs' versatile properties are making them essential in nanomedicine and biomedical imaging.

Quantum Dot-based imaging has emerged as a transformative technology in medical diagnostics. Moreover, the versatility of Quantum Dots extends

beyond mere imaging. They can serve as multifunctional probes, simultaneously carrying therapeutic agents while enabling real-time monitoring of biological processes. This dual functionality is a testament to the versatility and potential of Quantum Dots in advancing medical diagnostics and treatment. One of the most promising applications of quantum dots in medicine is their use as carriers for targeted drug delivery [70].

9. Toxic Effects of Quantum Dots

Quantum dots (QDs), particularly those containing cadmium or lead, have raised considerable safety concerns because of the potential release of toxic metal ions under biological and environmental conditions. The toxicity of these materials can be influenced by their composition, particle size, surface chemistry, coating stability, concentration, and duration of exposure. Photodegradation is another important concern, especially for QDs exposed to prolonged UV or other high-energy illumination. For example, CdSe QDs can cause significant toxicity in cultured cells following UV irradiation, which may promote photolysis and the release of harmful Cd^{2+} ions into the surrounding medium. Therefore, maintaining an effective and stable protective coating is important for reducing the biological exposure to toxic components of the QD core. Several coating strategies have been investigated to improve the stability and biocompatibility of QDs. Low-toxicity organic molecules and polymers, including polyethylene glycol (PEG), as well as inorganic coatings such as ZnS and silica, can provide a protective barrier around the QD core and reduce the release of toxic ions. Water-soluble CdSe and CdSe/ZnS QDs can therefore show improved biological compatibility when an appropriate surface coating is applied. In contrast, incomplete surface coverage or inadequate purification may result in extracellular cytotoxicity associated with the release of Cd^{2+} . Silica-coated QDs, particularly those further modified with PEG on the outer surface, have demonstrated reduced toxicity compared with QDs stabilized only with relatively simple surface ligands. QDs coated with molecules such as mercaptoacetic acid or mercaptopropionic acid have been reported to exhibit greater toxicity than silica-coated systems, highlighting the importance of both the composition and stability of the surface coating in determining biological responses [71].

Cellular uptake is another factor that needs to be considered when evaluating QD toxicity. Endocytosis enables QDs to enter cells, where their accumulation and interaction with intracellular components may influence cell viability. QD uptake was associated with cellular toxicity, although the extent of this effect

depended on the properties of the QDs and their surface coatings. Interestingly, QDs encapsulated within more complex polymeric or amphiphilic systems and appropriately functionalized for biomedical applications have often shown considerably lower toxicity. For example, tumor cells labeled with QDs exhibited survival and tumor-forming abilities comparable to those of unlabeled cells in mice, without evident adverse effects on the overall physiology of the animals. Similarly, water-soluble QDs encapsulated within amphiphilic polymers, including PEG-containing systems, have shown negligible cellular toxicity at concentrations below 100 nM. These findings indicate that appropriate surface engineering can substantially influence the biological behavior of QDs; however, coating alone cannot completely eliminate toxicity, particularly when QDs undergo degradation or prolonged exposure within biological environments. The toxicity concerns associated with heavy-metal-containing QDs have also encouraged the development of alternative QD systems containing less toxic or heavy-metal-free components. Carbon-based quantum dots, including carbon quantum dots (CQDs) and graphene quantum dots (GQDs), have attracted particular interest because of their favorable aqueous dispersibility, tunable surface chemistry, and generally improved biocompatibility compared with many conventional heavy-metal-based QDs. Their surfaces contain functional groups that can be readily modified with polymers, peptides, proteins, antibodies, or other biomolecules, making them attractive for bioimaging, biosensing, drug delivery, and theranostic applications. Other alternatives, including silicon-based QDs and selected III–V semiconductor QDs such as indium phosphide, are also being explored to reduce dependence on cadmium- and lead-containing materials. Nevertheless, these alternatives should not automatically be considered completely non-toxic.

Their biological effects can still depend on particle size, synthesis conditions, surface functionalization, impurities, concentration, degradation products, and exposure duration. Consequently, comparative and systematic toxicological evaluation remains necessary before their widespread biomedical application. Despite the development of improved coating strategies and alternative materials, efforts are continuing to produce QD systems with reduced toxicity while maintaining their desirable optical properties. Synthesized Cu- or Mn-doped ZnSe QDs with reduced cytotoxicity as an alternative approach for minimizing both extracellular and intracellular toxicity associated with highly toxic components [61]. Such approaches demonstrate that modifying QD composition can provide an additional strategy for improving their safety profile while retaining useful

optical characteristics.

QD toxicity may also arise from intrinsic physicochemical properties rather than solely from the release of toxic metal ions. Several QD systems, including CdS, CdSe, CdSe/ZnS, and CdTe, have been reported to generate reactive oxygen species (ROS), such as free radicals and singlet oxygen. Excessive ROS production can disturb cellular redox balance and cause oxidative damage to lipids, proteins, mitochondria, and DNA. Interestingly, the same ability of QDs to generate ROS can be advantageous in certain biomedical applications, particularly photodynamic therapy (PDT), where ROS-mediated cellular damage is intentionally used to destroy diseased cells. Thus, the biological effects of QDs may vary according to their composition, surface properties, dose, and intended application. Another important issue is the persistence and clearance of QDs following administration. Some QDs have been reported to accumulate in organs such as the bone marrow, spleen, and liver for several months after administration, raising concerns regarding their long-term retention and potential biological effects. QD size, surface charge, coating, and aggregation state can influence their biodistribution and elimination. Larger particles may have limited renal clearance, while their surface characteristics may favor uptake by the mononuclear phagocyte system and subsequent accumulation in organs such as the liver and spleen. These factors highlight the importance of evaluating not only short-term cytotoxicity but also the pharmacokinetics, biodistribution, degradation, and long-term clearance of QDs before their clinical use [72].

Overall, the development of QDs for biomedical applications requires a careful balance between their excellent optical and functional properties and their biological safety. Reducing the use of highly toxic elements, improving surface-coating strategies, developing carbon-based and other low-toxicity QDs, and adopting safe-by-design approaches may help overcome some of the limitations associated with conventional QDs. However, the absence of highly toxic heavy metals alone does not guarantee complete safety. Comprehensive evaluation of cytotoxicity, oxidative stress, genotoxicity, immune responses, biodistribution, degradation, and long-term clearance is essential for establishing the safety profile of emerging QD systems. Continued refinement of surface engineering and the development of novel low-toxicity QDs may therefore provide a more appropriate balance between performance and safety for their future biomedical applications [73].

10. Future Directions and Challenges

Integrating quantum dots into biosensor technologies offers considerable potential for future developments. QD-based biosensors can provide rapid and sensitive detection of biomolecules, which may support the early diagnosis of diseases. Their applications include point-of-care diagnostics, environmental monitoring, and personalized medicine [74]. At present, QD-based technologies range from laboratory investigations to early stages of clinical translation. Experimental studies primarily investigate their performance in cells and laboratory models, whereas preclinical studies focus on their safety and effectiveness in animal models. Only a limited number of QD-based technologies have progressed toward clinical use, where their safety, efficacy, reproducibility, and regulatory requirements need to be carefully established.

Future research may focus on improving the properties of quantum dots for applications such as photothermal therapy and combination treatment approaches, with the aim of achieving better therapeutic outcomes in cancer. QDs may also provide new possibilities for signal transduction and device integration in areas such as neuroprosthetics and brain-machine interfaces. However, their use in medical applications requires careful consideration of safety and performance. Toxicity remains an important concern, particularly for QDs containing heavy metals such as cadmium. Therefore, continued efforts are needed to develop more biocompatible QDs and safer alternative materials. A better understanding of the long-term behavior of QDs in the body, including their distribution, degradation, and clearance, is also necessary. In particular, further studies are required to determine whether QDs may accumulate in specific organs or tissues following prolonged exposure.

The large-scale production of QDs and maintaining consistent quality between batches remain important challenges for their wider use in medical devices. Future manufacturing approaches should therefore aim to be scalable, cost-effective, and reproducible. Standardized methods for synthesis, characterization, and quality control will be important for maintaining consistent particle size, surface characteristics, optical properties, purity, and biological performance. Long-term stability during storage and following incorporation into medical devices also needs to be carefully assessed, as changes in QD properties over time could affect their safety and effectiveness. In addition, suitable sterilization methods need to be established because sterilization conditions may alter the surface properties, stability, or biological performance of QDs. Regulatory approval is another important consideration for the clinical translation of

QD-based medical technologies. Clear standards and guidelines will be needed to ensure appropriate assessment of safety, efficacy, manufacturing consistency, stability, sterilization, and overall product quality [75].

Conclusion

Quantum dots (QDs) have attracted considerable interest in biomedical research because of their distinctive optical and electronic properties. Their tunable fluorescence, high photostability, and ability to be modified with different surface groups have made them useful for investigating bioimaging, biosensing, targeted drug delivery, photodynamic therapy, and theranostic applications. Surface modification and polymer coating have also been explored to improve their water dispersibility, stability, targeting ability, and interaction with biological systems. These developments have supported the use of QDs in a range of experimental and preclinical studies. However, several challenges still need to be addressed before QD-based technologies can be widely translated into clinical practice. Safety remains one of the major concerns, particularly for QDs containing toxic elements such as cadmium and lead. Their possible long-term accumulation, degradation products, persistence in tissues, and biological effects require further investigation. The development of heavy-metal-free QDs and biocompatible surface coatings may reduce some of these concerns, but comprehensive studies on their long-term toxicity, pharmacokinetics, and clearance are still needed.

Another important challenge is the large-scale and consistent manufacture of QDs. Differences in particle size, composition, surface characteristics, and functionalization can influence their biological and optical properties. Maintaining these characteristics consistently from one batch to another is therefore essential for reproducible results. In addition, regulatory requirements for QD-based products remain complex and require well-defined standards for material characterization, quality control, manufacturing, stability, safety, and efficacy. Overall, QDs offer considerable potential for combining diagnostic, imaging, and therapeutic functions within a single platform, but their clinical application is still developing. Most reported applications remain at the experimental or preclinical stage. Future research should therefore focus not only on improving the performance of QDs but also on addressing their safety, scalable manufacturing, reproducibility, and regulatory requirements. Close collaboration among researchers in nanotechnology, pharmaceutical sciences, toxicology, medicine, and regulatory science will be important for translating the promising

properties of QDs into safe and clinically useful technologies.

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Author Contribution

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