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Biomedical applications of quantum dots

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Abstract: *currently, advanced drug delivery system includes vital roles of nanomaterials for the development of effective healthcare products. in this series, nanomaterial quantum dots (QDs) have pronounced biomedical drug application. quantum dots have a semiconductor outer shell that provides a surface for bioconjugation, resulting in improved pharmacokinetic properties such as increased water solubility and biocompatibility. quantum dots have capacity to efficiently transverse the drug across cell membranes and their large specific surface area, offers sites for attachment of different categories of drugs. here, in this paper synthesis of qds, their exclusive physicochemical features, and myriad biomedical applications in drug delivery, cell imaging, biosensing, gene delivery and roles in neuroscience study are comprehensively portrayed.*

Key Words: *Quantum dots, Nanomaterial, biomedical application, Drug Delivery, Semiconductor.*

1. INTRODUCTION:

A drug delivery system (DDS) is a method of introducing pharmacologically active substances into the body that combines one or more traditional procedures with designed technology, formulation, and devices. Controlling the time and place of medication release in the body can improve the efficacy of DDS. The drug delivery method includes administering a therapeutic medication, releasing the active substance into the systemic circulation, and then conveying the helpful material across biological membranes to the site of operation. The use of large-scaled particles in drug administration has a number of drawbacks, including in vivo instability, poor solubility, low bioavailability, poor absorption in the body, and the possibility of medication side effects. [1].

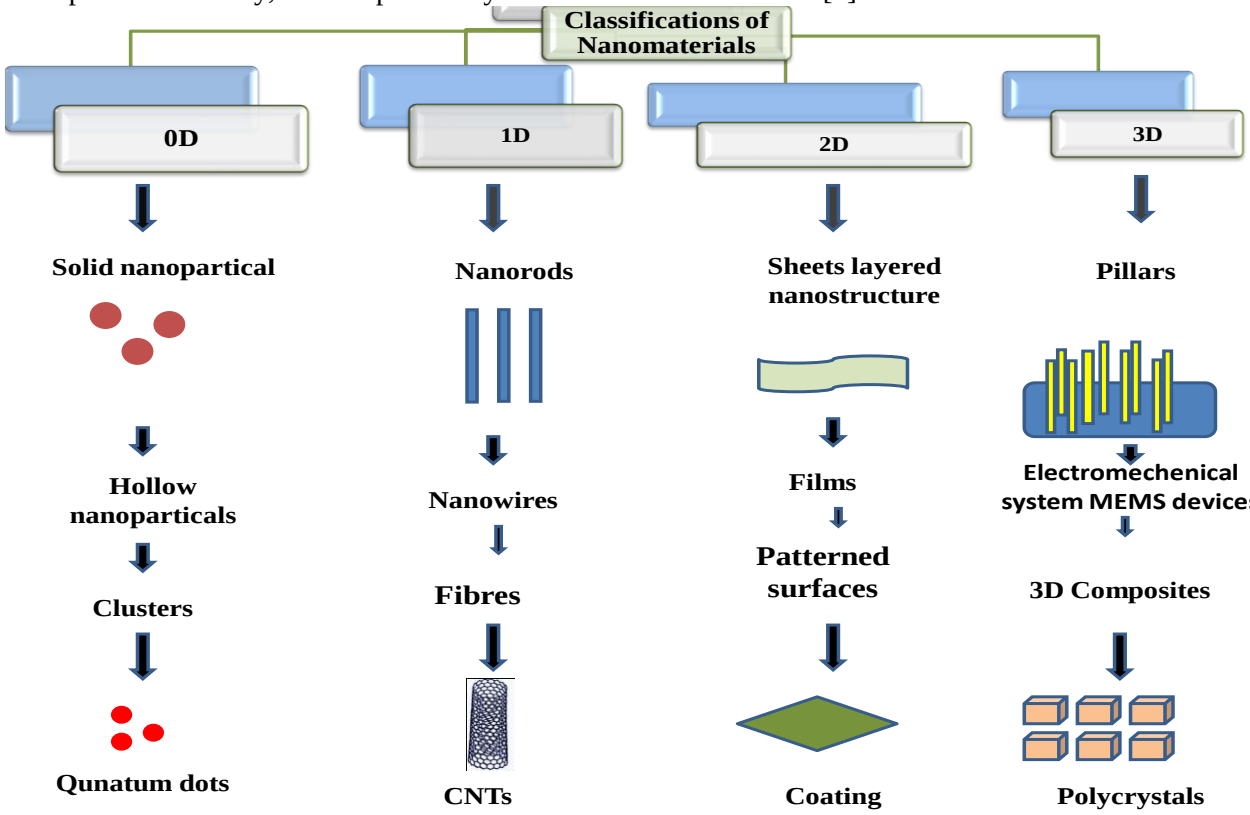

Figure 1: Classification of different nonmaterial's and their physical layout

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Nanotechnology is concerned with the study of matter structures with dimensions on the order of a billionth of a meter. Researchers learned that certain materials can exhibit diverse properties depending on their size, contain characteristics that distinguish them from bulk materials, such as a high fraction of surface atoms, high surface energy, spatial confinement, and reduced defects. The classification of Nonomaterial material depend upon dimension is shown in figure.1[2]. Quantum dots (QDs) for drug delivery have capacity to efficiently transverse the drug across cell membranes and their large specific surface area, offers sites for attachment of different categories of drugs. Furthermore, hydrophobic or noncovalent protein stacking interactions, as well as hydrogen bonding, can be used to load medicines into graphene quantum dots-based drug delivery. Quantum dots are available in variety of shapes and sizes, the size is so small 2-10 nm [3]. Quantum dots (QDs) also known as semiconductor nanocrystals, have become a vital tool in biomedical research, particularly for quantitative, multiplexed, and long-term fluorescence imaging and simultaneous detection [4-6]. In comparison to organic dyes and fluorescent proteins, QDs have emerged as a new class of fluorescent probes for bio molecular and cellular imaging Due to their unique optical and electrical properties such as size tunable light emission, improved signal brightess, photo bleaching resistance, and simultaneous excitation of multiple fluorescence colours. They were encapsulated with the production of core-shell nanocrystals to improve biocompatibility, quantum yield of fluorescence, and stability of these nanocrystals. The efficiency of luminescence was much improved due to passivation on the QDs surface of the semiconductor with a high energy gap band, which prevented metal ions from leaching from the core.[7-9]**.**

Table1. Description of Quantum dots.

	Quantum dots
Size	2–10 nm
Type	Semiconductor fluorescent material
Applications	Diagnosis, drug delivery system, boil - molecular imaging, In vivo imaging, etc.

QDs have three dimensional structure that falls in the nanometer range, the structure comprises of three parts including a core made of any semiconductor material (CdSe, CdTe, etc.), a shell surrounding the core that helps to improve the optical properties of the core, and a cap made of peptides, antibodies, oligo nucleotides, or poly ethylene glycol; the selection of which is made on the basis of required solubility or biological properties [10]. Quantum dots' name alludes to their quantum confinement and optical features. Various methods can be used to make semiconductor quantum dots and carbon quantum dots. Each method has its own set of benefits and drawbacks. Spectroscopic, microscopic, and electrical approaches can be used to characterise QDs. QDs can be easily shaped into a range of forms, sizes, and bioactive chemical coatings. Covalent and non-covalent binding are used to functionalize or modify the surface of quantum dots. This aids in the enhancement/improvement of a drug's physical, chemical, and pharmacological qualities. Quantum dots can be injected, inhaled, injected subcutaneously, or injected intramuscularly. Passive transport, assisted delivery, and active transport are all methods for cellular distribution. Quantum dots have uses in nanocarrier tagging, medication delivery, imaging, and diagnostic purposes. Quantum dots are increasingly being used for imaging, as a sensor, and as a probe. The basic structure of quantum dots is better explained in figure 2.

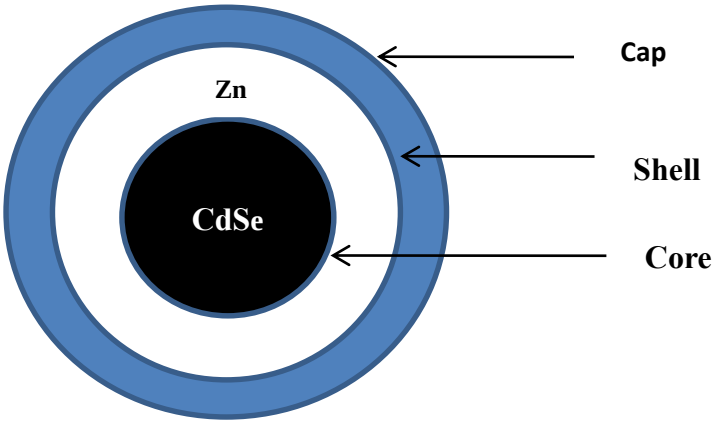

Figure 2: A typical structure of quantum dot

2. CHARACTERISTIC PROPERTIES OF QDs [11]:

QDs are formed of tiny metal particles and are about a thousand times smaller than a hair. These particles may be molded into a number of forms and coated with a diverse range of bio molecules. Under UV light, QDs have a luminescence property, with the size of the dots influencing the colour. For example, 2 nm Quantum dots have vivid green luminescence, while 5 nm Quantum dots have red luminescence. Further, Fluorescent quantum dots are often composed of compounds from periodic table groups II to VI and III to V such as Ag, Cd, Hg, Ln, P, Pb, Se, Te, and Zn. The size of QDs is proportional to the k (of light) they emit; that is, the smaller the QDs, the shorter the k it emits. QDs have a wide spectrum of excitation because QDs have a precise emission k, spectra in multiple fluorescence emission do not overlap. Moreover, quantum dots, often known as "designer atoms," have numerous optical and electrical features that make them ideal for use as semiconductors.

3. ADVANTAGES OF QDs:

- QDs are more resistant to degradation than other optical imaging probes, they allow researchers to watch cell processes for longer periods of time and provide fresh light on molecular interactions. The most remarkable aspect of QDs is real-time imaging**.**
- QDs are essentially nanocrystals, they provide good contrast for electron microscope imaging as scattering arises.
- QDs have size-tunable emission (from UV to IR).
- When compared to traditional dyes, QDs exhibit longer fluorescence.
- QDs have higher optical activity, which can be used in a variety of biotechnology and life science applications.
- Because of their small size, QDs can be injected into a wide range of environments, including liquid mixes, textiles, and polymer matrices.

4. LIMITATIONS WITH QDs:

- Cd and Se based quantum dots are highly toxic and require stable polymer shell.
- Particle size is difficult to manage.
- Quantum dot can undergo *in- vivo* degradation.
- The overall conversion efficiency is lower because QDs have generated more heat and their operational stability may be compromised. Phenomena of De-coherence is observed, since every system is weakly connected with the energy state of its surrounds, decoherence can be thought of as the loss of information from a system into the environment (typically depicted as a heat bath). [12]

5. SYNTHESIS OF QUANTUM DOTS: Two different methodologies can be used to for the production of carbon quantum dots (CQDs)[13-16].

Table 2: There are two different method of preparation

Method-A

Physical Method	Chemical Method
Arc discharge	Electrochemical Synthesis
Laser ablation/ Passivation	Combustion and acidic Oxidation
Plasma Treatment	Hydrothermal and Prolysis route Micro/Ultrasonic Synthesis.

Method-B

Top-down Approach	Bottom-up approach
(Large Carbon structures are broken off to smaller c-dots)	(C- dots are formed from molecular precursors)
Arc Discharge	Combustion / Thermal / Hydrothermal
Electro chemical Oxidation	Supported Synthesis
Laser ablation technique	Microwave / Ultrasonic .

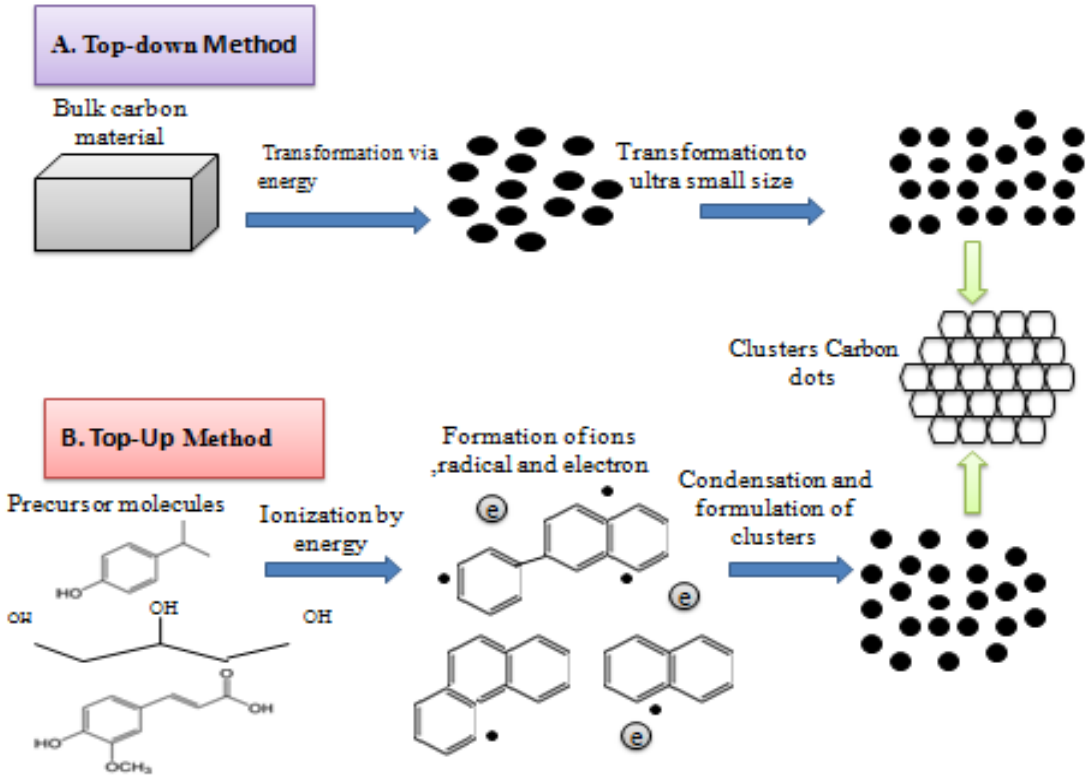

Figure 3: The top-down and bottom-up methods for the preparation quantum dots

5.1 General method of synthesis:

Cadmium and selenium QDs have been the most often manufactured using common method (CdSe). These dots could be made by infusing the necessary organometallic precursors into heated triocytlphosphine oxide (TOPO) that has been forcefully agitated under an inert environment. As the quantum dots grow in size, the solution begins to change in color from colorless to yellow, then orange, and finally red/brown. When the flask has reached the proper size, the heat is turned off. Finally, placing the synthesised quantum dots of various sizes under a "black light" allows them to be identified. Quantum dots emit different colors depending on their size i.e. 514nm (blue), 544nm (greenish blue), 559nm (green), 571nm (yellowish green), 577nm (yellow), 581nm (yellowish orange), and 610nm (yellowish orange) (orange) etc..

5.2 Physical Method

It includes mechanical grinding, polishing, ball milling, lithography, vapor deposition, Electric arc deposition, Ion beam technique, chemical ,etching, sputtering, Laser ablation, electro-explosion and molecular bean epitaxy modulated by top down and bottom up techniques.

5.2.1Top-down approaches

(a) Arc-discharge methods. When single-walled carbon nanotubes are produced and separated using electrophoretic methods [17]Using this technique, it is possible to create Carbon dots (C-dots) from unprocessed carbon nanotube soot (sediment). A stable dark-colored suspension was produced after the crude material (sediment) was oxidised with 3.3 M HNO3 to introduce carboxyl groups. The resultant substance was then extracted with NaOH and a basic solution with a pH of 8.4. The collected material was cleaned using gel electrophoresis. It was discovered that the separation of a rapidly moving band of highly fluorescent carbon-dot was 18 nm [18].

(b) Electrochemical oxidation. The working electrode's carbon nanoparticles are removed at a specific voltage after the electrolyte is anodized. Surface passivation transforms carbon nanoparticles into CQDs with fluorescent characteristics. discovered an effective approach for producing luminous carbon nanotubes after discovering for the first time that carbon nanotubes were broken by cyclic applied voltage. The fluorescent carbon dots that were produced were spherical, had small particle sizes and a narrow particle size distribution, and had a fluorescence quantum yield of up to 6.4%[19].

(c) **Laser-ablation methods**: C-dots are made by hot pressing a graphite powder and cement combination, then baking, curing, and annealing them in a series of steps at 900°C and 75 KPa under an argon flow. The surface of C-dots is passivated using various polymeric agents such as diamine terminated poly(ethylene glycol) and poly(propionyl-ethylenimine-co-ethylenimine), and the highly fluorescent pure C-dots are separated by dialysis against water and centrifugation [19]. To generate C-dots with a high quantum yield of 20%, a slightly modified process using 13C powder and more stringent control is used. developed a single-step technique that involved irradiating graphite or carbon black dispersed in diamine hydrate, diethanolamine, or PEG200N for 2 hours using a pulsed Nd:YAG laser, which served as a surface passivating agent.

5.2.2 Bottom-up approaches

(a) **Combustion/thermal/hydrothermal methods:** C-dots could be made by burning unscented candles or using natural gas burners. Through oxidative acid treatment, which added OH and COOH groups to the C-dot surfaces, water soluble multicolor fluorescent C-dots (less than 2 nm) were created from candle combustion soot. Polyacrylamide gel electrophoresis (PAGE) fraction is used to purify the final particles [19]

(b) **Microwave/ultrasonic synthesis [20]:** The synthesis of C-dots with electrochemiluminescence capabilities was reported using a microwave pyrolysis method that involved mixing PEG200 and a saccharide (e.g. glucose and fructose) in water to make a transparent solution, then heating in a 500W microwave oven for 2–10 minutes. The time of microwave heating affects the size and photoluminescence features of these C-dots. Later, using an ultrasonic treatment approach, C-dots with colourful PL covering the full visible-to-NIR spectral range were produced from glucose or active carbon. A one-step hydrogen peroxide-assisted ultrasonic process was also used to make water-soluble luminous C-dots from active carbon. These C-dots generated intense and colourful photoluminescence across the whole visible-tonear infrared spectral range, demonstrating up-conversion fluorescent characteristics [21]. Recently, one-pot ultrasonic synthesis of photo catalytic active fluorescent N-doped C-dots (NCDs) was used in the photo degradation of methyl orange under visible light.

5.3 Chemical method:

Chemical methods include wet chemical method, colloidals, aggregation, self-assembly, spinning plasma, flame spraying synthesis, Laser pyrolysis, hydrothermal method and Microwave method.

5.3.1 Electrochemical route [22]: An electrochemical method was used to make ZnO quantum dots at room temperature. A 4:1 mixture of acetonitrile and tetrahydrofuran, as well as the capping agent, is used in an electrochemical bath. The electrolyte was tetraoctylammoniumbromide (TOAB), which also served as a capping agent. The sacrificial anode was zinc, and the cathode was platinum. The ZnO QDs obtained were powders that were redispersed in acetonitrile for further characterisation.

5.3.2 Microwave synthesis

In ultrapure water, 4.2 g of citric acid and ethylenediamine were dissolved. The solution was then transferred to a sealed digestion vessel and placed in the microwave digestion furnace in 30 mL increments. The microwave digesting system had temperature units that could be adjusted by 1°C at the specified temperature. The system can work at a frequency of 2450 MHz with a power range of 0–1000W. The reaction temperature was quickly raised to 200 °C when the power was set to 600W. In 5 minutes, the synthesis process might be completed. The CD samples were naturally chilled to temperatures below 80°C . To obtain the CDs, the product, which was brown-yellow and translucent, was treated to dialysis (500-Da cut off). For optical characterization, the CD samples were diluted.

5.3.3. Hydrothermal synthetic method [23]: Aqueous solution of 1% Good's buffer (HEPES, BES, or MES) was placed in a Teflon-lined stainless steel autoclave and heated to 160 °C for 8 hours in a single step hydrothermal synthetic method. After allowing the solution to cool to ambient temperature, it was centrifuged, and the supernatant was collected and dialyzed against deionized water to eliminate any remaining unreacted molecules.

6. DRUG BINDING WITH QUANTUM DOTS:

Between the inorganic core and the amphiphilic polymer coating layer of the QDs, hydrophobic medicines can be implanted (**Fig. 4) [24].** Hydrophilic therapeutic agents (such as siRNA and antisense oligodeoxynucleotide, ODN) and targeting biomolecules (such as antibodies, peptides, and aptamers) are covalently or non-covalently linked to the hydrophilic side of the amphiphilic polymer. This nanostructure works like a magic bullet, identifying, binding, and treating sick cells while also emitting detectable signals to keep track of the target. The size of QDs is important in biomedical applications since small particles are quickly eliminated from the body by renal filtration, but larger particles have shown the ability to be uptaken by the reticulo endothelial system before reaching the disease sites. The activity of QDs with a polymer covering of 5-20nm size gives the best results. The QDs become bonded to the target after being injected as a colloidal solution through S.C. or I.V. injection. The connected QDs emit light and show

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variable fluorescence depending on their size, which can be determined by UV-VIS or photoluminescence spectroscopy or dynamic light scattering (DLS) experiments.

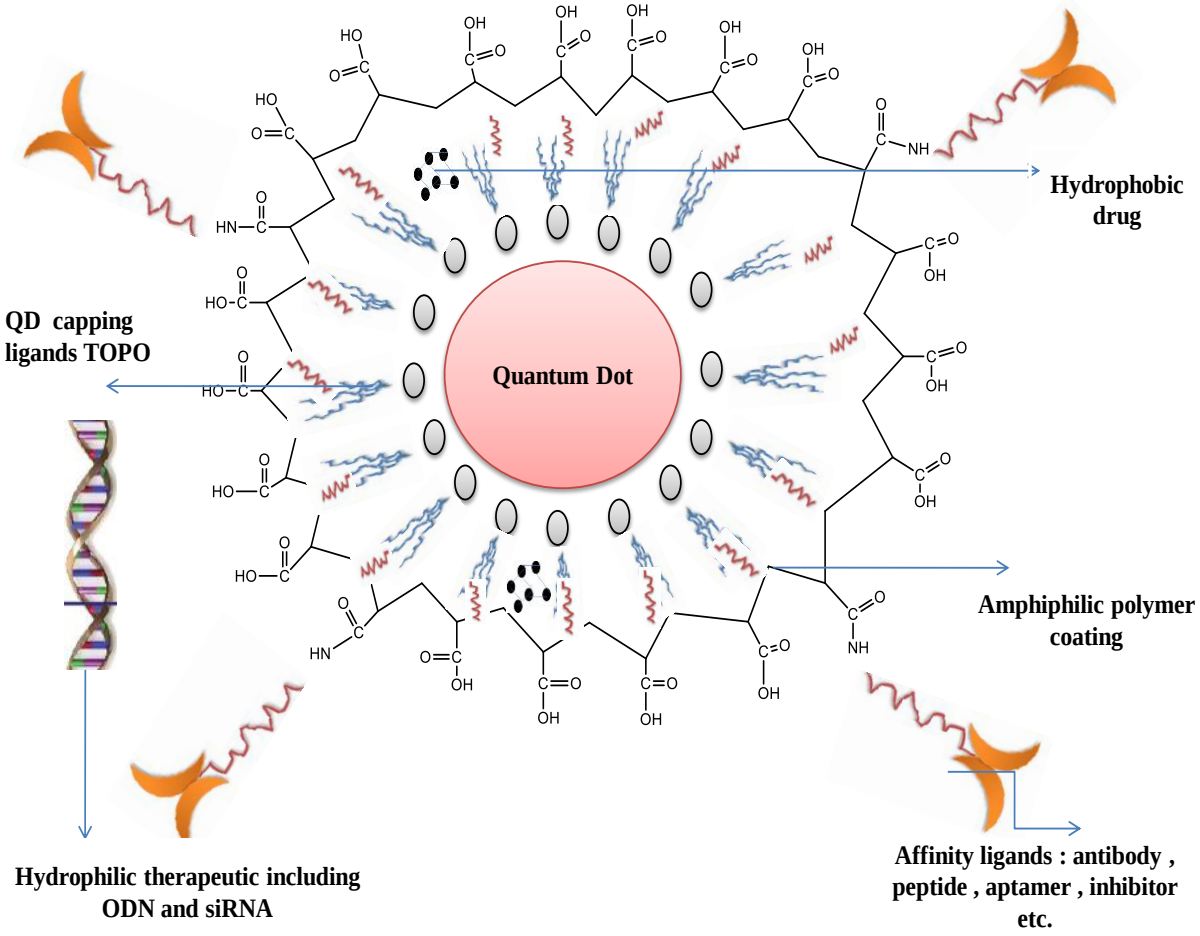

Figure 4: A multifunctional quantum dot covered with an amphiphilic polymer is shown schematically.

6.1. Fate of QDs:

The pharmacology of QDs, specifically their absorption, distribution, metabolism, and excretion, is critical in biomedical and pharmaceutical applications such as drug administration and targeting. Systemic distribution via parenteral delivery appears to be the most relevant mode of delivery for QDs at this time, however occupational and environmental exposures via cutaneous and inhalation routes are also feasible. A receptor-mediated endocytic mechanism is used to absorb QDs at the cellular level [25] The targeted QDs are absorbed into the cell via facilitated absorption via the endocytic route, and QD targeting experiments have shown that QDs with targeting functional groups can be deposited in specified target tissues following i.v. delivery [26].

7. CHARACTERIZATIONS:

Scanning transmission electron microscopy (STEM), X-ray fluorescence, and X-ray diffraction were used to determine the size, characterisation, and structure of QD-doped samples [27]. UV–Visible and photoluminescence spectroscopy are used to characterise QDs optically. Traditional techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and dynamic light scattering (DLS) are commonly used to determine the size of QDs (Yamashita et al. 2003). Photoluminescence, photoluminescence excitation, and Raman scattering spectroscopy were used to determine the size and composition of optically active QDs .Methods such as TEM, atomic force microscopy (AFM), scanning tunnelling microscopy, and magneto-tunneling experiments have also been reported for monitoring the size of epitaxially produced QDs. Nuclear magnetic resonance spectroscopy is another way for determining the properties of QDs [28]. In Table 3, the major techniques for characterization of quantum dots are compiled.

Table 3: Techniques for characterization of quantum dots

S.no.	Techniques	Examples
1	Electrical techniques	Electrochemistry, Electrophoresis
2	Spectroscopy techniques	Infra-red and Raman spectroscopy, Ultra-violet-visible, X-ray diffraction, Mass spectrometry
3	Scattering techniques	Small angle neutron scattering, Laser light scattering
4	Microscopy	Transmission electron microscopy, Scanning electron microscopy, Atomic force microscopy
5	Rheology, physical properties	Differential scanning calorimetry, Dielectric spectroscopy

8. BIOMEDICAL APPLICATIONS:

QDs have found uses in a variety of fields, including biology, photovoltaic devices, light emitting devices, optics, LEDs, solar cells computers, photo detector devices, and so on, due to their size-tunable optical qualities [29]. Drug delivery, targeted therapy, cell labeling, cell tracking, cancer therapy, bio imaging, and cancer therapy are some of the key applications of QD in biological sciences. This chapter goes through the use of QDs in drug delivery, bio imaging, and cancer therapy in detail in the parts that follow.

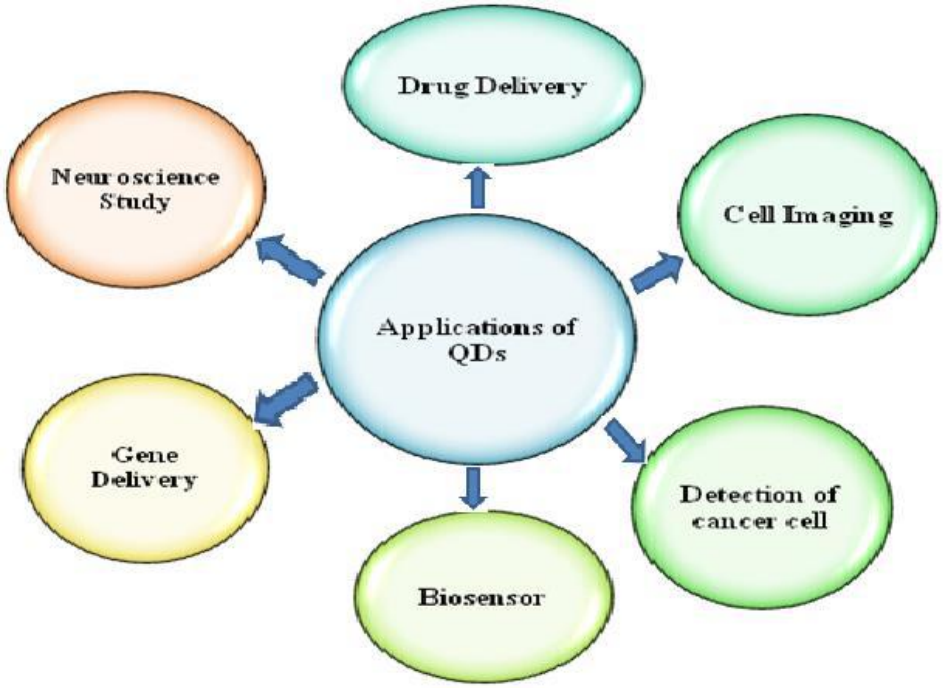

Figure 5: Myriad applications of QDs in pharmaceuticals and biomedicine.

8.1 Drug delivery:

Because of its unique optical qualities of QDs can operate as nano-carriers for medications and can identify and monitor specific disease locations. Anti–tumor medications have a variety of side effects, including toxicity to non–cancerous cells, non–selectivity, and inadequate targeting, among others. Tumors might be difficult to find and remove due to a lack of bioluminescence, especially in the case of tiny tumors. So it's highly desirable and crucial to target cancer cells with specificity, and in vivo imaging is a good way to do that. Only by introducing nanocarriers for medications will it be possible to target cancer cells with high selectivity. Nanovehicles such as micelles, dendrimers, nanotubes, QDs, and other nanovehicles are used as drug carriers. Through targeting of diseased cells, QDs nano carriers delivering medications would improve efficiency while reducing negative effects to non-affected cells. QD-based drug carriers are the most preferred nano carriers due to their small size and selective targeting. Liposomes, silica nanoparticles, polymer nanoparticles, chitosan, and other anti-cancer nano carriers are the most widely used.

The following features of QDs nano carriers are required for targeted medication delivery.

- Drugs should not interact with the nano carriers.
- A high level of medication loading capacity and encapsulation efficiency is required.
- The nano carriers must be prepared and purified in a proper manner.

- The materials are biocompatible and low-toxic, making them suitable for use as nano carriers.
- The nano carriers should have a specified mechanical strength and stability, as well as the right particle size and form, among other things.
- The duration of in vivo stay should be high .

8.2 QDs for labeling cells:

The size of QDs has a big impact on their optical properties, especially the wavelength of their fluorescence. Colloidal QDs are useful fluorescent probes for a variety of labelling experiments due toikkik their reduced tendency to photobleach. QDs are employed in cell marking because they exhibit constant and distinct optical characteristics [30]. For time durations ranging from seconds to months, QDs can simultaneously tag numerous inter- and intracellular components of live cells. Distinct colours of QDs can be used to mark different cell components, which can then be seen in vivo or using fluorescence microscopy. Plant bioimaging: CdSe QDs bind to cellulose and lignin in the cell wall, resulting in a fluorescent image of plant cells; animal bioimaging: biotinylated Cholera toxin B (CTxB) with QD–avidin conjugates for ganglion labeling ; CHPNH2 QD nanogel has potential for long-term cell imaging; prokaryotic bioimaging: anti E 7.

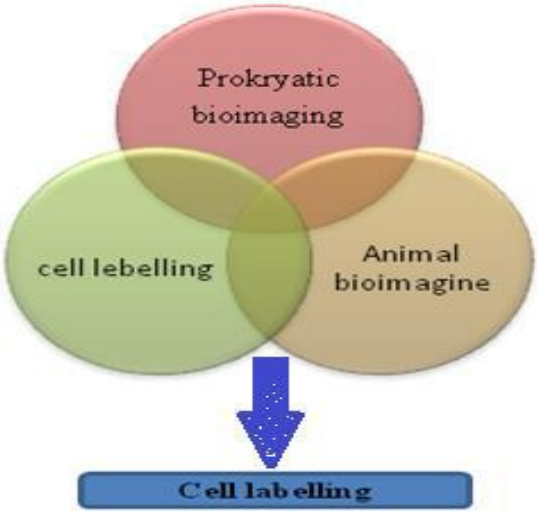

Figure 4: The uses of QDs in cell imaging.

(a) Tracking different particles: Single particle tracking (SPT) techniques were created to investigate the dynamics of biomolecules in living cells with single-molecule sensitivity and nanometer spatial resolution. Recent advancements in QD surface coating and bioconjugation methods have made them ideal probes for use in live cells [31].The greater stability of QD fluorescence allows for improved quantification of FISH (fluorescence in situ hybridization) investigation of human chromosomal alterations. QDs must be delivered intracellularly across the impermeable plasma membrane receptor.

(b) Imaging system: QDs are employed for diagnostic purposes and may have use in neurological manifestations due to their unique optical properties. In a culture of primary spinal cord neurons, antibody-functionalized QDs track the lateral diffusion of the glycine receptor [32]. In cultured neurons, biocompatible water-soluble QD micelles demonstrate absorption and intracellular dispersion. The interaction of QDs with ligands is used in DNA defection (induced by a variety of DNA flaws), biomolecular and protein detection, and cellular labeling .

8.3 Tissue imaging: In general, tissue has a variety of receptors and biomarkers that are difficult to detect and identify using fluorescence. To address this problem, quantum dots are recommended since they are better suited for imaging and have a narrow emission peak that aids in identifying the most receptors/biomarkers on a small cell surface. For tissue imaging, antibodies coupled with quantum dots are utilized. Quantum dots have also been utilized to identify several mRNAs in tissue samples [33]. For example, quantum dots were synthesized and functionalized with various groups to target endothelial cells of the liver, brain, and breast cancer cell in vivo and in vitro, according to the paper. Peptide attached quantum dots are also targeted to the nucleus or mitochondria by microinjection. The quantum dots were combined into a liposome delivery method for theranostic application in inflammatory-associated disorders and

used for tissue imaging, according to the study. Quantum dots have also been shown to be useful for in-vivo multiplex imaging of mouse embryonic stem cells .

8.4 Tumor imaging: Initially, tumor imaging was done using fluorescent microscopy, however because to its low intensity, it does not provide any spatial imaging. However, quantum dots have lately been employed for this purpose, i.e. for tumor imaging, due to their high intensity and brilliant fluorescence, which enhances retention and permeation, allowing the quantum dots to stay in the metastatic region for a long time [34]. Antibody-conjugated quantum dots are often utilized for tumor imaging because they facilitate quantum dot uptake by a specific cell. To make an immunological fluorescent probe, for example, QDs were conjugated with an alpha fetoprotein antibody that binds to the oncofetal glycoprotein of hepatocellular cancer. The use of peptide conjugate quantum dots for in-vivo target by reducing uptake in the RES system and increasing selective targeting was demonstrated in a 2002 study . Later in 2004, it was announced that a multifunctional quantum dots probe has been employed in live animals for tumour targeting and imaging. Another example is the coupling of alpha-fetoprotein with quantum dots, which resulted in a highly sensitive and immune-fluorescent probe for hepatocellular cancer diagnosis.

8.5 Detection of metastatis cancer cell: The term "metastases cancer" refers to the spread of tumour cells from one organ to another through the bloodstream. It can spread throughout the body and lead to a variety of cancers. Detection systems used to be based on radiation therapy with magnetic resonance; this was a costly technology that was also damaging to people. When circulatory tumour cells are present in low concentrations, it is difficult to isolate and detect them; for this reason, antibody conjugated quantum dots are utilised, as they also enable real-time imaging. Yali Wang et al. used magnetic nanoparticles and quantum dots to study the detection of micrometastases from lung cancer [35]. With the use of apatmer LY-1 incorporating quantum dot and magnetic nanoparticles, Fu-Bing Wang et al. revealed the detection and prediction of metastatis hepatocellular cancer. In a study, Hisatakakobayashi et al. explained how to monitor the B16 human meloma cancer cell within the lymphatic system using two nanomaterials: quantum dots and dendrimer. With the use of quantum dots, Yi-Heui Hsieh et al. were able to detect cancer cells at low concentrations, using human T cells as a model for circulating cancer cells. CD3 and CD4 markers were used to label them with quantum dots and magnetic beads.

8.6 Biosensors: Quantum dots have a unique optical property: they have a high fluorescence, a broad absorption spectrum, and a high photostability, making them ideal for sensors . In recent decades, quantum dots have been utilised as sensors for identifying and quantifying biological molecules, metal ions, and pesticide detection . CdSe/CdS coupled with thiourea, for example, can be used to detect mercury ions [36]. The detection of Hg++ was also done using carbon quantum dots modified with PEG and N acetyl cystine. The quantum dots conjugated BRET immunosensor was also created for the detection of small molecules, using enrofloxacin as a model target. Casein kinase was measured using a serine-containing peptide linked to CdSe/ZnS quantum dots, according to a study [37].

8.7. Neuroscience study through Quantum dots: The quantum dots play a role in neuron research. The selective penetration of biological molecules via the blood brain barrier, as well as their tiny size and lipophilicity, are key limitations in brain delivery studies . Carbon dots are said to easily traverse the blood-brain barrier, according to literature (BBB). Furthermore, quantum dots have a long-lasting fluorescence and optical feature that aids in brain imaging and drug delivery . The discovery of a new technology was responsible for the fabrication of biocompatible water soluble quantum dots micelles with optical properties and enhanced uptake in hippocampus neurons in one study . Quantum dots were also found to be antibody-conjugated and follow the transport of the glycine receptor in primary spinal cord neuron culture [38]. Quantum dots were coupled with nerve growth factor (NGF) and used in the culture of pheochromocytoma 12 cells to stimulate neuron-like development, which was effective for tracking and visualizing neuron function. For enhanced pharmacological activity, most natural and synthetic pharmaceuticals are packaged into quantum dots and administered.

8.8. Gene delivery: Gene therapy is a relatively recent strategy to treating hereditary disease and genetic disorders. For gene silence, genes such as plasmid DNA, mRNA, and siRNA are utilised [39]. Previously, gene delivery was limited by low cellular absorption, but quantum dots, which may be functionalized with a variety of materials, allow for greater cellular uptake. For example, siRNA was delivered using polyethyleneimine containing carbon quantum dots coupled with folate. Similarly, it was observed that the cadmium sulphoselenide/zinc sulphide quantum dots coupled with polyethyleneimine was the most effective in gene delivery, with two separate glioblastoma cell lines being successfully inhibited (U87 and U251). Various forms of quantum dots are employed in anticancer medications, antimicrobial pharmaceuticals, antibiotics, and other chemotherapeutic cytotoxic agents (Table 4).

Table 4: versatile applications of therapeutic agent enclosed QDs.

Drug	Type of quantum dots	Applications	References
Doxorubicin	ZnO, Graphene quantum dots, carbon dots	In lung cancer, NH2-ZnO quantum dots with hyaluronic acid pH responsive medication delivery. In MCF-7 cells, carbon dots were used to deliver drugs to patients with human breast cancer.	[40] [41]
Mitomycin	Carbon dots	For mitomycin drug delivery in MCF-7 and bacterial cells, fluorescent carbon dots were synthesised using Daucuscarota subsp. sativus roots.	[42]
Gemcitabine	CdSe/ZnS quantum dots QDs, Au doped CdTe quantum dots	. Through ROS production and apoptotic protein expression modulation, CdSe/ZnS QDs can be employed as a photosensitizer to suppress SW1990 cell proliferation. The fluorescence quenching of functionalized Au doped quantum dots (QDs) in biological samples was used to provide a quantitative assessment of the Gemcitabine medication.	[43] [44]
Alminoprofen	Silicon quantum dots	Created novel anti-inflammatory drug-conjugated Si-QDs, as well as innovative –Si medicines that improve the drug's functionality.	[45]
Oxaliplatin	Carbon dots	Theranostic Agent for Personalized Medicine with Oxaliplatin and a Highly Luminescent Carbon Dot	[46]
Bevacizumab	Quantum dots	Detect VEGF-expressing tumours in vitro and in vivo with QDs-bevacizumab nanoprobes, which allow VEGF-targeted noninvasive imaging in clinical practice**.**	[47]
Quercetin	Silicon quantum dots	Quercetin and fluorescent Silicon quantum dots (SiQDs) can be co-encapsulated in poly (ethylene glycol)-block-polylactide (PEG–PLA) nanoparticles for simultaneous in vitro imaging and to increase quercetin biocompatibility**.**	[48]

9. MARKETED PRODUCTS OF QUANTUM DOTS:

- **EviDots®:** These are core and core-shell quantum dots, with core quantum dots in the fundamental state and core shell coating quantum dots made of semiconductor nanocrystals. These have emission wavelengths ranging from 490 nm to 2100 nm, whereas PbSEviDots have emission wavelengths ranging from 850 nm to 1500 nm. These are manufactured by Evident technologies. They find applications in white LED(Light emitting diodes), solar cell, ink and thermoelectric products.
- **EviComposites™:** EviCompositesTM is a type of Quantum dot composite. The features of typical insulating polymer matrix materials are used in Evi Composites. Evident Technologies is the company that makes them.

Active LEDs (light emitting diodes), solar cells, and photovoltaic cells are all examples of where they can be used.

- **EviTags™:** Quantum dots that can be dissolved in water. Quantum dots with a bio-active surface that have been pre-functionalized. In the wavelength range of 490 nm to 680 nm, functionalized quantum dots with free carboxyl and amine groups are available. These are typically quantum dots that have been surface treated to give them a unique optical property. Evident Technologies also makes these, and their applications are similar to EviDots®.
- **EviFluors®:** These are also water soluble quantum dots that have secondary antibodies and proteins attached to them. They're really active. Quantum dots conjugated with goat anti-mouse, goat anti-rabbit, goat anti-rat, streptavidin, and biotin are available at wavelengths ranging from 520 nm to 680 nm [49].

10. REGULATORY CONSIDERATION: Strict standards and restrictions are required in the development of new drug products in order for them to be safe, effective, and cost-effective under the generally recognized as safe (GRAS) category. Toxicology is a key concern for quantum dot-based biological and pharmacological applications. However, as indicated in certain literatures, the regulatory features of QDs are divided into three components, which are discussed below in three categories —

Category I: Dealing with those QDs products utilized by the consumers for electronics and computing purpose.

Category II: It includes QDs dealing with medical, imaging devices and diagnostic agents.

Category III: QDs related to Pharmaceutical products and nanomedicine [50].

The first clinical trial utilizing quantum-dot technology in humans was recently approved by the US Food and Drug Administration (FDA). It signals the first time that inorganic material has been used in Quantum dots . It demonstrates that the US FDA has approved an inorganic material as a medication for the first time. Quantum dots labeled with radioactive iodine were used in the human study to demonstrate the amount of dots present in the body or tumor cell in a PET scan. Quantum dots are used to deliver drugs and radioactive agents into the body. This invention is being commercialized by Hybrid Silica Technologies (Cambridge, MA) [51-52].Table: 5 shows the patents for quantum dots.

Table 5: Patents on QDs.

Title of Patent	Assignee Company	Year of Issue	Patent no.
Fluorescent labels for immunoassays	Eastman Kodak Company	1987	4637988
Method of detecting an analyte in a sample using semiconductor nanocrystals as a detectable label	Quantum Dot Corporation	2001	6274323
Functionalized nanocrystals as visual tissue-specific imaging agents, and methods for fluorescence imaging	Bio-Pixels Ltd.	2001	6333110
Materials and methods for near infrared lymph node mapping	Massachusetts Institute of Technology	2007	7181266
Graphene quantum dot nuclear targeting medicine carrying system as well as preparation method and application thereof	-	2013	CN103432590B

11. CONCLUSION:

This review focuses on the classical synthesis and potential applications of quantum dots in a variety of fields (pharmaceutical, medical/biomedical/clinical). A brief overview of the types, general preparation methods, bioconjugation, and applications is provided, along with examples. Quantum dots are a new type of inorganic nanocarrier made up of a heavy metal or inorganic core and a shell. Quantum dots have been bioconjugated with bioactive agents and commonly utilized for drug delivery in the treatment of cancer and other life-threatening disorders. However, its toxicity is one of the key disadvantages that limit its application in biological systems. With all of this in mind, it can be concluded that QDs are multifunctional nano-sized particles that serve as important carriers

for overcoming the restrictions associated with the delivery of a variety of synthetic medications, hence lowering the dose, frequency of administration, and adverse effects.

Future prospect: Because toxicity in the biological field is a key worry with quantum dots, efforts will be made in the future to reduce this toxicity through enhanced pharmacological response. Various techniques to reducing the toxicity of quantum dots are available, but more research is still needed. Furthermore, the formation of hydrophilic quantum dots is a novel method for biological application and cell labeling.

Conflict of Interest: The authors declare no conflict of interest.

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