Biochemical Characterisitcs of Quantum Dots for Cancer Research

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Abstract-A superb photoluminescence and electronic property of quantum dots (QDs) includes narrow emission spectra from visible to infrared wavelengths and broad and continuous absorption spectra. QDs are zero-dimensional materials made comprised of nanostructures that are no larger than a few nanometers in size, such as those found in InAs or II-IV groups such as CdSe, CdTe, CdS, and ZnS. the distinctive qualities of QDs, including their wide excitation range, limited emission, robust fluorescence, and good photobleaching resistance. In place of organic and inorganic fluorophores, QDs are employed. Application areas for ODs include the diagnosis and treatment of cancer as well as the early detection of primary tumours such breast, prostate, ovarian, and pancreatic cancer. The QDs nanocarrier technology is capable of monitoring, localising, and early disease site identification. With the use of QD-based nanotechnology, the biomedical imaging platform for cancer behaviour can be studied thanks to the optical and chemical benefits of quantum dots (QDs). The QDs were used in numerous clinical and bioanalytical applications, including medicines, immunology, and biosensing.

Keywords: Quantum dots, luminescence, fluorescence, chemiluminescence, phosphorescence, pharmaceutics, bioconjugation.

INTRODUCTION

At the end of the 1970s, Russian physicist Alexei Ekimov of the state optics institute Vavilov synthesized nanocrystals of copper chloride and then of cadmium selenide in a molten glass matrix. He then observed a fluorescence with a gradient of colours and published in 1980.Inspried by rom this colloidal Quantum dots obtained. ,the American chemist Louis Brus Labs tried and successfully produced nanocrystals but in a liquid form, QDs were first described by Ekimov and Onushenko in 1981. In 1982, Efros postulated that quantum size effects cause the change in optical and optoelectronic properties of nanoparticles. The Kavli Prize in Nanotechnology was given to Louis Brus in 2008 for his work in the field of colloidal semiconductor nanocrystals, which he invented in 1984. QDs were first introduced as biological probes in 1988. Their broad absorption spectrum, narrow tunable emission, and increased photostability compared with organic dyes made them attractive material for bioimaging

In the range of 1.5 to 10 nm in size, quantum dots (QDs) are extremely small semiconductor nanocrystals made up of 100 to 10,000 atoms. Due to variations in band gap energy brought on by quantum confinement phenomena, QDs have peculiar optical features.On absorption of light, electrons are promoted from the valence band (lower electronic energy state) to the conduction band (upper electronic energy state), producing an electrone hole pair, called an “exciton.” Radiative recombination occurs when an electron and a hole merge, releasing energy in the form of a photon. The exciton can disperse over the delocalized lattice in bulk materials. The energy needed to produce an exciton rises, though, when the particle size is smaller than the Bohr radius. This phenomenon, known as "quantum confinement," is frequently seen in extremely tiny, crystalline semiconductor materials. Greater band gap energy in smaller QDs causes them to emit higher-energy photons (blue shifted), and vice versa.. Tunability of optical properties of QDs QDs have been synthesized with emissions ranging from near ultravioleto infrared[1].

QDs have ahigh surface-to-volume ratio, which means a large percentage of the atoms are located on the particle surface. For example, a 5 nm diameter particle would have ~20% of its atoms on the surface, where as a 20nm particle would have ~5% surface atoms.[1] QDs are zero-dimensional materials made comprised of nanostructures that are no larger than a few nanometers in size, such as those found in InAs

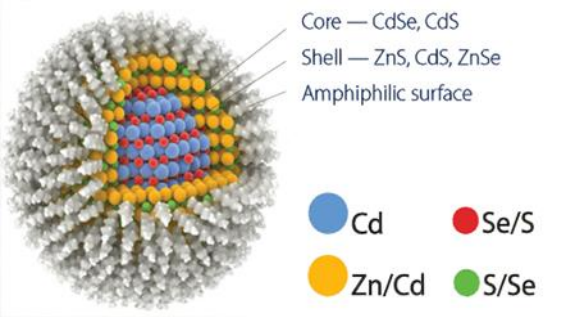

FIGURE:-1 Structure of QD

or II-IV groups such as CdSe, CdTe, CdS, and ZnS. Shown in Fig-1. When it comes to long-term, multi-color fluorescence imaging and detection, QDs have demonstrated excellent advantages. The discovery of QD labeling encourages cellular and even live animal research on nano-drugs. It is anticipated that the development of therapy-based multifunctional nano-drugs and QD fluorescence imaging technologies will be used in the diagnosis and treatment of cancer. Surface alterations with targeted ligands are also frequently used to improve medication delivery effectiveness at the same time [2].QDs are interesting options for luminous nano-probes and carriers in biological applications due to their distinctive optical characteristics. Drugs can be loaded into QD nano-carriers for drugs through coupling, adsorption, dispersion, and dissolution.[2]QD applications are mostly based on their exquisite optical properties and their role in light emission, conversion, and detection. QD applications are mostly based on their exquisite optical properties and their role in light emission, conversion, and detection[3].QD research was mostly done in group IV and III−V compounds, progress in the synthesis over the years has expanded the elemental composition. QDs are currently based on II− VI and I−III−VI compounds, as well as transition-metal dichalcogenides, perovskites, and carbon, among others[3].Quantum dots (QDs) with a bioinspired design derived from plant sources exhibit remarkable medication delivery and anti-cancer potential with minimal toxicity. QDs are widely employed in many different applications and can be specifically used for bio-imaging and medication administration in cancer therapy because to their well-known optical activity. Additionally, the use of bioinspired QDs as a delivery mechanism for anti-cancer drugs is poorly studied. Recruiting QDs to create more advanced, multifunctional nanostructures.

Various types of biomarkers such as proteins, specific DNA or mRNA sequences and circulating tumor cells have been identified for cancer diagnosis from serum samples.[4]Due to their significant benefits over traditional organic dyes, such as high QY, size-tunable emission, photostability, and enhanced signal brightness, semiconductor QDs have received enormous interest for biolabeling and bioimaging applications. A new generation of probes with integrated functions of labeling and drug/gene delivery has recently been developed as a result of surface modification on QDs (Guzelian et al. 1996)[5].

PROPERTIES OF QDS

QDs have three main components: a semiconductor core, shell, and cap. The cap offers solubility in aqueous conditions, and the shell serves as a protective block for the core and is in charge of capping ligands. The core forms optical and conductive characteristics.

- QDs have a broader excitation spectrum results in using a singlelight source to excite multicolor QDs. Also, a narrow sharp emission peak reduces spectral overlap [5]
- The significant difference between the absorption and emission wavelengths of QDs, the Stokes shift, allows collecting the full of emission spectra by separating the QDs fluorescence signal from the background auto-fluorescence, improving in sensitivity of detection.
- This is an essential factor for imaging tissue, especially in formalin-fixed and paraffin-embedded tissue specimens due to their high background auto-fluorescence Compared to organic dyes, QDs have a long fluorescence lifetime (about 10 to 40 ns) due to the inorganic composition of QDs, brighter emission, and higher signal to noise ratio. QDs brightness is about 10 to 20 times higher than the single organic fluorophores molecules.
- QDs are more resistant to degradation than other optical imaging probes and hence allow tracking of the cellular process for longer period of time.
- They have a longer-lasting photostability than traditional dyes, due to their inorganic composition and fluorescence intensity.
- QDs have high S/N ratio compared to organic dyes.
- QDs have broader excitation spectra and a narrow, sharply defined emission peak.[5]

QUANTUM DOT SYNTHESIS

Quantum dots can be synthesized (broadly) in two ways, Top-Down and Bottom-Up approach. In topdown synthesis, the bulk material is thinned to form quantum dot. The various techniques used in this approach are electron beam lithography, reactive ion etching, focused beam lithography, dip pen lithography. Some of the limitations from this approach are structural imperfections caused by patterning and contamination (addition of impurities) in quantum dots. When creating QDs top-down, a bulk semiconductor is cut into tiny pieces using techniques such laser ablation, chemical oxidation, arc discharge, reactive ion etching, and wet chemical etching. With the appropriate packing geometries, systematic research on the controlled shape and size as well as the quantum confinement effect is conceivable. back of this Techniques using concentrated ion or laser beams are employed to produce the arrays of zero-dimension quantum dots. The coupling of QD impurities and structural flaws with patterning is the fundamental drawstrategy . In the bottom-up process, chemical, physical methods are harnessed to form nanoparticles and clusters. Physical methods include molecular beam epitaxial growth, colloidal synthesis, and physical/ chemical vapor deposition techniques[6]

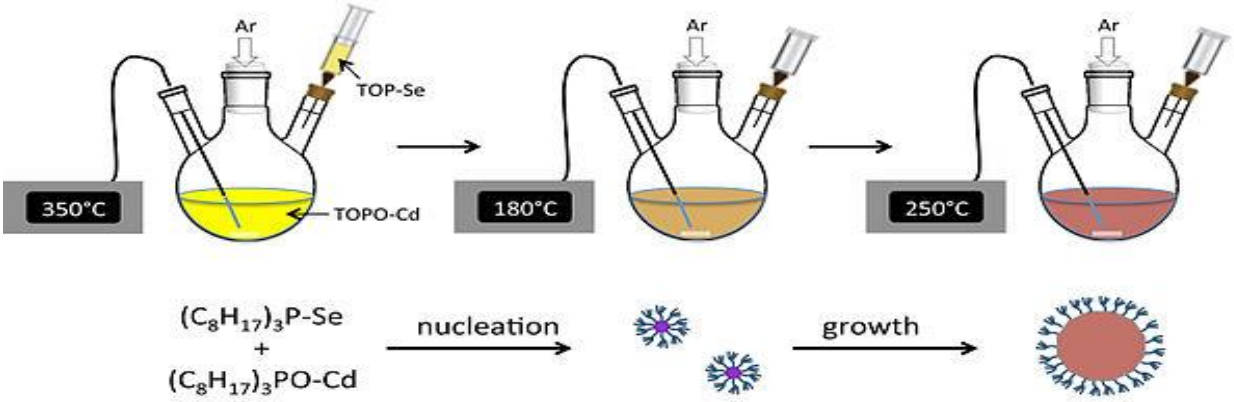

Fig 3: synthesis of quantum dots

COLLOIDAL SYNTHESIS

Preparation of CdSe QDs, Cd(Clo4)2.H20 salt dissolved in water 0.02 M is stirred and add thiol stabilizer. By adding the NaOH solution can control pH. This soln is deaerated by N_2 bubbling for 30 mins Solid Bulk Al_2Te_3 is reacted with dilute sulphuric acid to generate H_2Te gas. This gas along with slowly regulated nitrogen is introduced in the solution Cd-RSH precursor. After the exhaustion of H_2Te gas the solution is cooled in condenser to get quantum dot.[7]

QDS SYNTHESIS USING VAPOUR DEPOSITION TECHNIQUE

CdSe QDs are typically synthesized using an organometallic chemical bath method. This approach involves heating trioctylphosphine oxide (TOPO) to between 300 and 350 C in an inert environment. Trioctylphosphine (TOP) is diluted with a mixture of the necessary organometallic precursors (such as phosphine chalconide) and sucked into a syringe. As the heated TOPO is being vigorously stirred, the syringe's contents are injected into it. Due to the injection of the colder precursor, the bath's temperature will drop. The bath's initial temperature is referred to as the injection temperature, and the bath's current temperature when nucleation takes place is referred to as the growth temperature. The initially colorless solution changes to yellow, then orange, and finally red or brown.[7]

Vapor-phase methods, the layers of QDs are grown by an atom-by-atom process on an atomically smooth substrate. Therefore, self-assembly of QDs grown by molecular beam epitaxy (MBE), liquid metal ion sources, sputtering, aggregation forms on a substrate without any pattern. Most of the QDs synthesis approaches are complicated with multistep, cumbersome, expensive, requires the use of toxic solvents, and, consequently, the need for surface passivation. The technique applied to synthesize Cd-based semiconductor QDs can be generalized to other types of QDs. In this method, the possibility of chemical synthesis of large-scale colloidal quantum dots (CQDs) with an utterly desirable structure and a specified average size is achieved. The advantages of

the colloidal chemical synthesis approach of QDs are high quality and monodisperse nanosized particles [7]

GAS PHASE SYNTHESIS

Its is an economical way synthesis, Compared to liquid or solid state techniques, the vapor (gas) phase synthesis is a continuous process that delivers great purity. This method can be used to synthesis a variety of multi-component compounds, however it has the drawback of agglomeration. GaAs (III-V) was synthesized using the aerosol approach Deppert et al. As precursors, they employed gallium and adenine (AsH3). Utilizing an aerosol generator, ultrafine particles were produced (sprayed). Utilizing a differential mobility analyzer, which is based on the idea that electrical mobility of particles diminishes with particle size, the choice of particle size was made. Before or as the aerosol enters the reaction chamber, the flow is controlled to create nanocrystals[3]. In addition to the aerosol method discussed above, gas phase synthesis can also be carried out utilizing plasma reactors, laser reactors, flame reactors, and inert gas reactors (evaporating and condensing).and sputtering[6]

QD-BASED NANOTECHNOLOGY FOR CANCER RESEARCH

DETECTION OF PRIMARY TUMOR INVITRO

Researchers have created QD-based probes conjugated with cancer-specific ligands, antibodies, or peptides for cancer imaging and diagnosis in vitro since 1998when biocompatible QDs were first introduced for imaging of cancer cells in vitro. Traditional immunohistochemistry (IHC) is less accurate and exact at low protein expression levels than quantitative immunohistochemistry (QD-IHC), which will give significantly more information for individualized treatment. With excellent performance on biomedical imaging, QD-based imaging has become one of the most promising technologies for early diagnosis of cancer[8]

In between 25% and 30% of BC patients, the human epidermal growth factor receptor 2 (HER2) is overexpressed, and HER2 plays a significant role in the development of the disease. The importance of HER2 identification for BC treatment and prognosis has been proven by recent studies [15]. QD-HER2 conjugates' effective detection of BC. This method was furthered by Yezhelyev et al to specifically label MCF-7 and BT-474 BC cells for HER2, epidermal growth factor receptor (EGFR), estrogen receptor (ER), progesterone receptor (PR), and mammalian target of rapamycin (m-TOR) by visible and NIR QDs. This research demonstrated that QD-based nanotechnology is an effective method to provide multiplexed cancer biomarker imaging in situ. Chen et al. successfully detected BC with QD-based probes which demonstrated that lower expression of HER2 could be clearly detected by QD-IHC compared with conventional IHC and could also realize multiplexed QD-based detection simultaneously. The results showed that BC can be divided into 5 subtypes with different 5-year survival rate. Thus, QD-based multiplexed imaging will provide more information for the individual events of tumor, personalized diagnosis, prognosis, and treatment.[9]

Gao et al.'s labeling of human prostate cancer cells using a combination of QDs and an anti-prostate specific membrane antigen (PSMA) antibody is a well-known example of cancer detection. When compared to traditional fluorescent immunolabelling, QD-based immunolabelling has more steady photo-intensity, as demonstrated by Ruan et al. There have been reports of highly sensitive QD-based probes for multicolor fluorescence imaging of cancer cells in vivo. Shi et al.'s study demonstrated the higher quality of QD-IHC in comparison to traditional IHC and demonstrated the successful multiplexing of QDs for the simultaneous detection of PSA and the androgen receptor in prostate cancer cells. Surface plasmon-coupled emission, a novel biosensing method for detecting biosensors and prostate cancer biomarkers, has been introduced that can increase the detection sensitivity of QD-based prostate cancer and biomarkers.[10]

The ovarian cancer marker CA125 can also be found using QDs in a variety of materials, including fixed cells, tissue slices, and xenograft pieces. Additionally, QD signals' photostability is brighter and more focused than that of traditional organic dye. In order to demonstrate potential uses for intracellular pH sensors, Liu et al.[71] created pH-sensitive photoluminescent CdSe/ZnSe/ZnS QDs in SKOV-3 human ovarian cancer cells that are pH-dependent. EGFR single-molecules were successfully targeted by Kawashima et al. in human ovarian epidermal carcinoma cells.[11]

Using numerous tissue slides, each stained with one of the five separate biomarkers, Bostick et al.'sdetection of the five biomarkers on a single tissue slide allowed for the measurement of additional biomarkers. They also suggested developing a methodology for each biomarker's quantitative analysis. As a result of the system's effectiveness and convenience, it only took 7 hours to test six biomarkers, which was helpful for clinical application.[12]

Yang et al. used non-cadmium-based QDs as highly efficient and non-toxic optical probes for imaging live pancreatic cancer cells.By the aid of proteins and peptides targeted against overexpressed surface receptors on cancer cells and tissues, including as the transferring receptor, antigen claudin-4, and urokinase plasminogen activator receptor, QD-based imaging probes can target pancreatic cancer at a very early stage.Pancreatic cancer cell lines might be specifically targeted in vitro by bioconjugation of functionalized InP/ZnS QDs with pancreatic cancer-specific monoclonal antibodies, such as anti-claudin-4. Pancreatic cancer cell lines might be specifically targeted in vitro by bioconjugation of functionalized InP/ZnS QDs with pancreatic cancer-specific monoclonal antibodies, such as anti-claudin-4. With functionalized QDs, Lee et al. revealed quantitative molecular profiling of pancreatic cancer biomarkers. Because cancer cell populations are fundamentally diverse, they were able to acquire absolute quantitative values for the biomarker density in terms of the number of molecules per square micron on the cell surface. They also demonstrated highly selective targeting of molecular markers for pancreatic cancer with extremely low levels of nonspecific binding.[13]

INVIVO TUMOR IMAGING

The evolution process of tumor development may be visibly displayed using in vivo tumor imaging. Compared to in vitro molecular imaging, in vivo tumor imaging may provide more compelling data. However, for high-quality in vivo tumor imaging and fewer biological side effects on the animal model, sensitive and focused imaging agents are urgently required. By using "enhanced permeability and retention" (EPR) or targeted molecular imaging, QD-based imaging agents can address this requirement. The principle of EPR-based tumor imaging is the leakiness of tumor blood vessels.Tumor vasculature is quantitatively significant compared to normal tissues, but it is irregular, leaky, dilated, and the vascular endothelial cells are poorly aligned with massive fenestrations. For the imaging and therapy of cancer, a range of nanotherapeutics and nanoparticulates have been developed as a result of the EPR effect. The application of non-targeted QDs for cell trafficking, vascular imaging, sentinel lymph node (SLN) mapping and brain imaging has been described in several publications.[14]

Cancer surgery operation approach is influenced by the SLN diagnosis. Cancer cells first travel from the lymphatic system to the SLN during lymph node metastasis. To successfully execute SLN biopsy, the SLN attached to the tumor location must be able to identify cancer cells with high sensitivity. In SLN mapping, a typical practice in BC surgery, where the lymph node nearest to the targeted organ is checked for the presence of locally disseminated cancer cells, NIR QDs (emitting at 850 nm) have proven to be better. A high background-to-signal ratio, very sensitive, real-time intra-operative SLN imaging of the digestive system using NIR light and invisible fluorescent QDs has also been described in recent investigations.The surgeon may precisely identify the tumor boundary and reduce the extent of the dissection thanks to the great sensitivity and penetration (about 1 cm below the skin surface) of NIR QD fluorescence and the use of QD-based SLN mapping A significant advancement, this technology has shown promise in preclinical research, and more research will help it reach the clinic. Because integrin v3 is considerably increased in tumors but not in normal tissues, arginine-glycine-aspartic acid peptide-conjugated QDs have been employed to precisely target v3 in a mouse xenograft model [15]

The conclusion that the tumor contrast seen was from active, rather than passive, targeting is not supported by enough experimental data, though. A high-speed confocal microscope with a high-sensitivity camera was used to follow the movement of a single QD-antibody conjugate (the total number of QD particles injected was roughly 1.21014) inside the tumor through a dorsal skinfold chamber.This method documented the precise delivery of a single QD particle that entered circulation, extravasated from the vasculature into the interstitial space, attached to the tumor cell surface receptor, and then traveled on the intracellular train protein to the perinuclear area.[15]

Surface properties of QDs affect the luminescence character

The optical characteristics of QDs can be impacted by the chemical or physical interaction between analytes and QDs. On the basis of this modification, QDs have been widely used to detect a variety of analytes, including ions, drugs, small compounds, and biological macromolecules.. The selectivity and advantageous luminescent properties of QDs containing functional groups or biomolecules are improved by chemical surface modifications. The majority of detecting techniques are based on these QDs' fluorescence characteristics. Additionally, more research on using the natural phosphorescence of QDs has been published in the literature in recent years.[16]

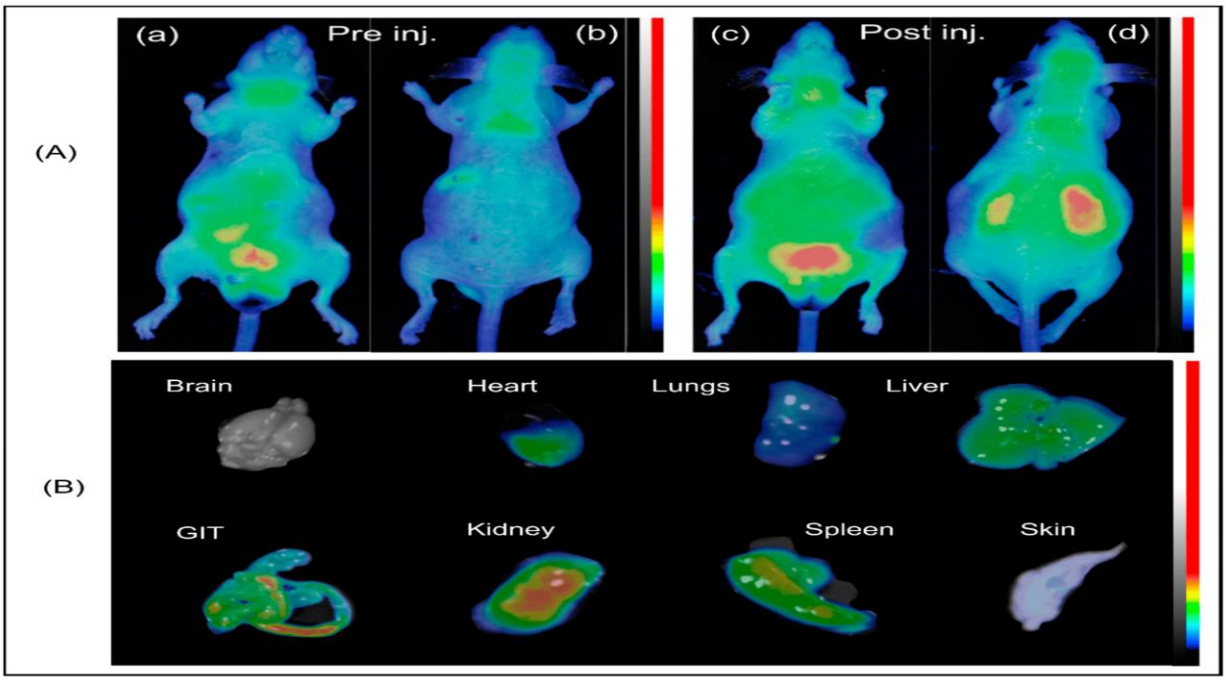

Figure:4 - Invivo images of QD, B – each particular cell imaging.

Fluorescence-based measurements

For qualitative or quantitative examination of diverse types of analytes, QDs' luminescent characteristics are employed. Initial research often focuses on determining how the interaction between the analyte and the QDs affects the luminescence signal of those particles. Due to the interaction of several biomolecules and structures, such as proteins, nucleic acids, or matrix substances, nonspecific binding is a significant issue, particularly in biomedical applications. It has been suggested and used to conjugate QDs with polymers, antibodies, amino acids, and proteins in order to enhance selectivity .Cd-based QDs have been reported for optical sensing of tiny molecules and ions in a ground-breaking study. The surface capping ligands had an impact on the luminescence response, as demonstrated by numerous studies in this field that concentrated on interactions between QDs and analyte.

For the investigation of drugs and biomolecules, numerous fluorescence techniques have been developed. These methods are generally based on quenching of fluorescence intensity of QDs[16].

Table 1. QDs based fluorescent probes for determination of pharmaceuticals

QD material	QD coating	Analyte	Matrix	Detection limit	Measuring signal
CdSe	TGA	Paraoxon	–	–	Fluorescence quenching
CdTe-Mn doped	TGA	Glutathione	Tablet	0.06 μM	Fluorescence quenching/ enhancement
CdTe	TGA	Doxycycline	Honey, human serum	1.1×10^{-7} M	Fluorescence quenching

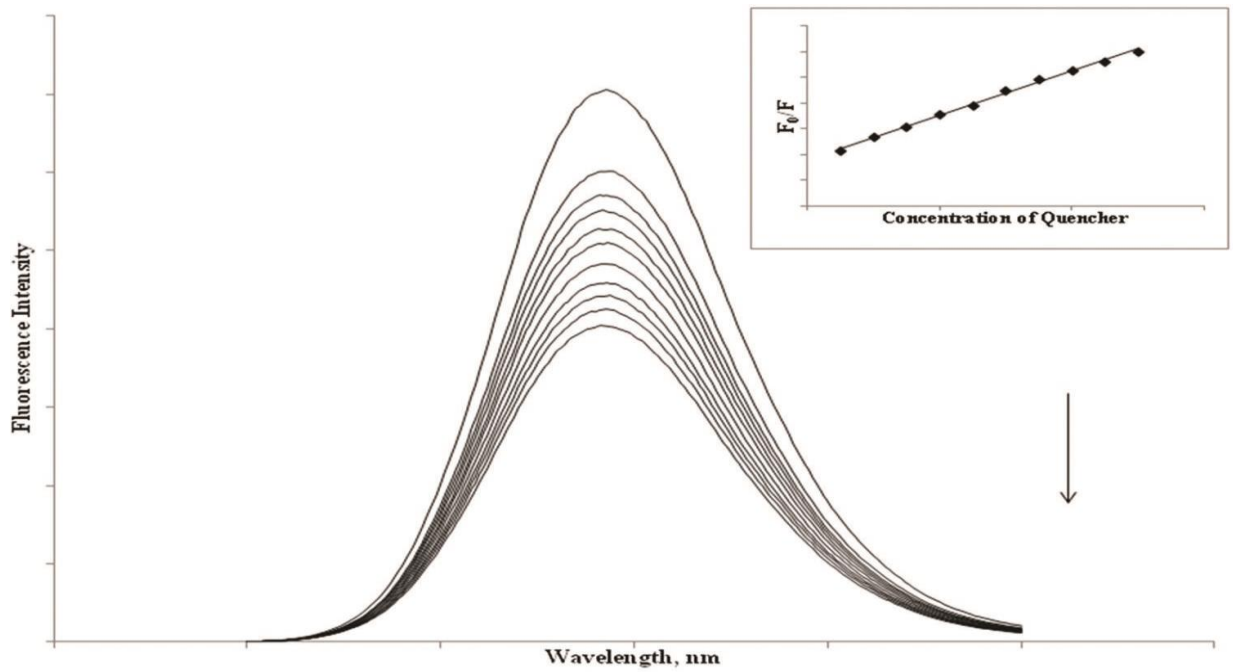

Figure 5 the general aspects of fluorescent spectra of QDs at different concentration of quencher. The inset is the calibration curve of Fo\F versus the concentration of quencher.

For biological imaging and detection, functionalized semiconductor QDs have been utilised as fluorescent labels. For example, avidin, highly positively charged tetramer, and functionalized CdSe/ZnS QDs were used in the detection of biotin.[6,19]

Chemiluminescence

Chemiluminescence (CL) is typically defined as the emission of light, as the result of a chemical reaction. Commonly, weak light is seen in chemiluminescent processes because to low QY. For analytical applications, it is required to increase the CL intensity. The ability to emit light at a variety of wavelengths without the need for a light source is another benefit of using QDs as chemiluminescent probes [17;19] Modern CL systems like CdTe, CdSe, and CdSe/CdS have utilised high-quality semiconductor QDs (core or core-shell) that are easily produced. Additionally, doped QDs are utilized in CL tests due to their catalytic properties. The improvements in QD use in CL allow for the creation of novel nanomaterials in addition to expanding their use in conventional applications.

According to Frigerio et al., there are three potential processes that could be used to explain how QDs can improve CL.

1. as emitter species after direct oxidation; direct oxidation happens when QDs is an only luminescent compound in the system;
2. as a catalyst of a reaction involving others luminophores; when more than one luminophores exist in the system, the final emitter is the luminophores due to the catalytic effect of QDs; and
3. as emitter species after chemiluminescence resonance energy transfer (CRET); the difference from catalytic effect, the final emitter is QDs.

QDs can be used in CL system as a catalyst, due to the redox properties of both conduction and valence bands. Imani-Nabiyyi and Sorouraddin showed that the CL emission was enhanced by combination of cysteine-capped CdTe QDs and luminol in the presence of KIO_4.[17]

Phosphorescence

The radiative transition known as phosphorescence occurs from the (singlet) ground state, S0, to the lowest excited triplet state, T1. Phosphorescence is a process that spin is disallowed, in contrast to fluorescence (singlet-singlet transition). The phosphorophore must be activated by electromagnetic radiation with the right wavelength in order to exhibit phosphorescence.

Some of the excited molecules can drop into the T state by an intersystem crossing if S energy levels and T energy levels are near to one another. Phosphorescence techniques have advantages over the fluorescence methods such as selectivity, sensitivity, longer emission lifetime, and a wider gap between excitation and emission spectra. [18,19]

Both capped and uncapped QDs are employed in phosphorescence research. The capping agents MPA and l-cysteine are frequently employed for this purpose. Using electrostatic self-assembly, MPA-capped Mn-doped ZnS QDs/CTAB nanohybrids, for instance, were created and used to detect rutin. A similar QDs technique was used to investigate how anticancer medication and DNA interacted. Here, a phosphorescent probe made of l-cysteine-capped Mn-doped ZnS QDs and idarubicin (IDA) nanohybrid was employed. Numerous bioanalyses, such as those involving the identification of proteins or nucleic acids, have employed phosphorescent QDs as a probe. Riboflavin (RF)-modulated MPA-capped Mn-doped ZnS QDs were created by Gong et al. and used as RTP sensors for DNA detection.[18]

(Bio)sensor and Immunosensor

Utilizing QDs in biological and clinical applications, such as the creation of biosensors and immunosensors, is another application. QDs are a suitable option for use in biosensing and immunoassay applications because they have distinctive optical properties, are biocompatible, have physicochemical stability, and may be linked to biomolecules including DNA, antibodies, proteins, or viruses.[7]

Quantum dots are a useful tool for imaging living cells because they can emit radiation at certain frequencies. For the purpose of identifying and detecting organisms inside the body, quantum dots can be affixed to the ends of big macromolecules like proteins or DNA strands. It is now possible to simultaneously apply numerous markers to living cell components and see how they interact thanks to the quantum dots' variable wavelengths. . Previously, color molecules were used that had less variability than color quantum dots. In fact, labeling cells is a technique that uses multiple colors to observe cellular structures such as cytoskeletal proteins or organelles. An electrochemical sensor based on the N-CQD@Co3O4/MWCNTs hybrid nanocomposite modified glassy carbon electrode (GCE) has been published by Muthusankar et al. (2020) for the simultaneous measurement of the antibacterial medication nitrofurantoin (NF) and the anticancer agent flutamide (FLU). With a detection limit of 0.0169 mM, the suggested sensor exhibits outstanding performance in the simultaneous determination of NF and FLU in the linear range of 0.05e1220 mM for NF.

QD material	Analyte	Matrix Detection limit	Measuring signal
CdSeQDs	Clopidogrel	Serum 7.55 10^8 M	AdSDPV
CS-Ag/N-GQD-Au electrode	Alprazolam	Serum 56 mM (DPV) e 73 mM (SWV)	DPV, SWV
	Diazepam	54 mM (DPV) e 56 mM (SWV)	
	Clonazepam	84 mM (DPV) e 54 mM (SWV)	
	Oxazepam	54 mM (DPV) e 56 mM (SWV)	
	Chlordiazepoxide	52 mM (DPV) e 70.4 mM (SWV)	
CdSe@ZnS	Glutathione	HeLa cells extracts (1%) samples 0.1 mM	Fluorescence lateral flow

Table:2 QD materials for the purpose of analyzing the bio [live] organisms within the detection limit

For the detection of disease biomarkers, Immunosensors are affinity solid-state based biosensors that rely on the creation of a stable immunocomplex as a result of the affinity between an antigen and corresponding antibody. Due to its ability to produce a focused and sensitive response, immunosensors are an effective method for clinical diagnosis.[20]

The oncofetal glycoprotein member carcinoembryonic antigen (CEA) is a malignant tumor biomarker for the diagnosis of several malignancies, including pancreatic, lung, colorectal, liver, gastric, and particularly breast cancer. CEA has a molecular mass of 180e200 kDa. High levels of CEA (>5 ng mL1) [20] In human blood are a sign that cancer cells are forming. Several researchers have reported determining CEA using various immunosensor types. For instance, Ganganboina et al. used a label-free impedimetric immunosensor based on nitrogen- and thiol-doped GQDs (N,S-GQDs) and goldembedded polyaniline (Au-PANI) nanowires to measure CEA in human serum samples [38]. The superior

electroconductivity of N,S-GQDs/AuPANI nanowires accelerates the transfer of electrons, and anti-CEA is immobilized on N,S-GQDs as a bifunctional probe that amplifies the electrochemical process. As a result of the conjugation of the antibody and antigen and the subsequent increase in charge transfer resistance, the label-free immunoassay platform's impedance changes, generating the measurement signal. The limit of detection for this impedimetric immunosensor is 0.01 ng mL1 over a broad linear range of 0.5 to 1000 ng mL1.[21]

Nie and coworkers reported on another GQDs-based immunosensor for the detection of CEA [23]. In this study, the main antibody (Ab1) was successfully immobilized using the poly(5-

Table :3 QD immunosensor to detect the sensitive and diagnosis within the ranges formylindole)/electrochemically-reduced graphene oxide nanocomposite (P5FIn/erGO) as a substrate, and graphene quantum dots (GQDs@Au NP) was employed for signal amplification.[21]

QD material	Analyte	Matrix	Detection limit	Measuring signal
GQDs	AXL	Serum of HF patients	0.5 pg mL^1	DPV
GQDs	Carcinoembryonic antigen	Human blood serum samples	0.01 ng mL^1	Impedance
GQDs	Carcinoembryonic antigen	Human serum	3.78 fg mL^1	Electrochemiluminescence
GQDs-N-S	Human chorionic gonadotropin (hCG)	Serum samples	12.5 fg mL^1	DPV
PbS	Procalcitonin	Human serum sample	0.02 pg mL^1	Photoelectrochemical
ZnSe@ZnS QDs	CEA	Human serum sample	0.029 pg mL^1	Electrochemiluminescence
Nickelecadmium QDs	Prostate-specific antigen (PSA)	Human serum samples	0.45 pg mL^1	DPV

Pharmacology of QDs

Pharmaceutical and biological applications, such as drug administration and targeting, depend on the pharmacology of QDs, which includes their absorption, distribution, metabolism, and excretion.

Although occupational and environmental exposures through cutaneous and respiratory routes are also feasible, the most significant route of administration for QDs at this time appears to be systemic distribution by parenteral dosing. According to Chithrani et al. (2006), QDs are taken in by cells via an endocytic pathway that is receptor-mediated. According to QD targeting studies, targeted QDs with targeting functional groups can accumulate in specific target tissues after intravenous delivery (24). The targeted QDs are absorbed into the cell by the endocytic route via a facilitated uptake mechanism.One of the first components that parenterally administered QD will come into contact with in terms of distribution is the blood environment. In this case, the knowledge of blood-QD interactions is very limited. Although the interaction between QDs and plasma proteins is still unclear, it is thought that the immune system can cause this degree of QD excretion [22].

However, the shell and coating appear to break down under photolytic and oxidative circumstances and produce poisonous cadmium cores. The QD core does not appear to be involved in substantial enzymatic metabolism. Despite the fact that QD shells and coatings seem to deteriorate under photolytic and oxidative circumstances, nothing is known about the deterioration products' biological impacts, which might control the release of hazardous cores.Since there are no extensive investigations of QD elimination through excretion, it represents yet another pharmacological barrier for QD research. Given that QDs contain cadmium and that cadmium is known to be toxic to the kidneys, the kidneys may be a key site for toxicological consequences. Size, the makeup of the coatings, and physico-chemistry will surely control excretion. According to several studies (22) QDs that are smaller than 5 nm can be easily excreted by the kidney.[22]

Drug delivery system

The use of QDs has negligible side effects as they can target the delivery system and can easily distinguish ailing cells from healthy cells by metal affinity-driven self-assembly between artificial polypeptides and the semiconductor core shell QDs. Nanoparticles of QDs has long blood circulation time, protection, large drug-loading capacity, controlled drug release profile, and

integration of multiple targeting ligands on surface. Further, the improvement can be gained through carbon nanotubes (CNTs) for intracellular delivery of antisense oligonucleotides tagged with QDs [23]

Toxicity of QDs

Numerous QDs have some level of cytotoxicity. The size, capping material, dosage, surface chemistry, coating bioactivity, and QD exposure pathway are the key determinants of QD cytotoxicity. According to Derfus et al (2004a, 2004b), the leftover organic compounds can also have a harmful effect on the target cells and tissues. As an illustration, Wistar rats were exposed to 0.52 mg cd/m3 for 5 days (6 h/day) by nasal delivery. After three days of exposure, Cd-based QDs were discovered upon histological investigation of the clinical variables in blood, bronchoalveolar lavage (BAL) fluid, and lung tissue. With minimal CNS toxicity, the Cd-based QDs were able to trigger local neutrophil inflammation in the lungs (22). Due to the protective effect of the ZnS shell preventing the escape of Cd ions from the inner side, a significant buildup of QDs was seen in the spleen. In Drosophila melanogaster, the long-term toxicity of CdSe-ZnS QDs with surface coating was investigated, as well as the genotoxic effects of QDs in vivo (Bazzi, 2008).[22,]

The in vivo disintegration of QDs and subsequent release of Cadmium ions are what cause toxic effects, and coated QDs showed lower overall toxicity. The coating has a significant impact on the longevity of the treated group. Depending on the processing conditions and dose of QDs, the surface oxidation of QDs can result in the creation of reduced Cd that can be liberated from QDs and cause cell death(22). Apoptosis is induced by the CdSe-core QDs. Human neuroblastoma cell mitochondrial membrane potential and cytochrome release were investigated by Chan et al. in 2004. According to reports, group III-IV QDs exhibit less cytotoxicity and appear to have more potential for application as an optical probe invivo (5,22). Therefore, the kind of core material chosen affects how harmful QDs are. Pericardial, ocular, and yolk sac edema, nano-depleted yolk, spinal curvature, and tail deformity are a few examples of the morphological endpoint toxicities (22). High mortality of embryos and larvae was discovered to be a consequence of selenite exposure.[22]

Overcome the toxic nature of QD

The semiconductor nanoparticle-based native QDs are poisonous by nature. As UV dissolves the CdSe and releases poisonous cadmium ions, it has been discovered that CdSe QDs are particularly toxic to cells exposed to UV for a prolonged period of time [24] However, in vivo investigations have shown that polymer-coated QDs are non-toxic in the absence of UV In addition, it has been demonstrated that the micelle-encapsulated QDs that were injected into the frog embryo had no impact on its growth. In order to make QDs water-soluble and resistant to chemical or enzymatic destruction, they are typically enclosed inside the outer coating of amphiphilic polymers.[24]

To avoid the development of aggregates, they are commonly produced in organic solvents with long alkyl chains and high boiling temperatures, such as tri-n-octyl-phosphine oxide (TOPO) [24] and hexadecylamine. The ability to change the surface chemistry of QDs to make them water soluble has advanced significantly in recent years [24] To make QDs biocompatible and lessen nonspecific binding, polyethylene glycol (PEG) or comparable ligands are most frequently used as a bridge. By conjugating them to various bioaffinity ligands like peptides, antibodies, oligonucleotides, etc. via various techniques, they are created specifically for the target site. A potential QD bioconjugate design for identifying tumor cell biomarkers is shown in below.[24]

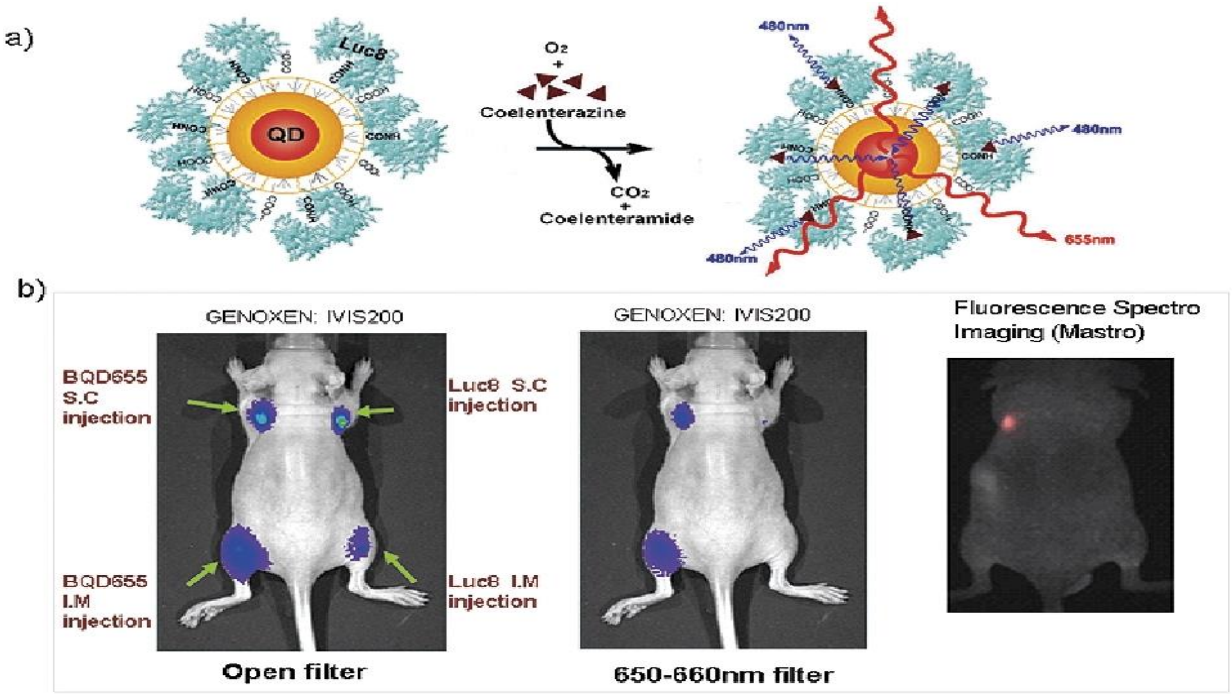

Figure6.Various steps in employing QDs for in vivo diagnosis of cancer. (a) Formation of QD bioconjugates, (b) Intravenous injection of QD bioconjugates into mouse.[24]

Applications of Quantum dot

- For diagnostic purposes, created ZnO QDs coated in BSA and functionalized them via EDC (ZnO@BSA-PEP-MPA) with the cationic antimicrobial peptide UBI29-41 (TGRAKRRMQYNRR, 1693Da) and MPA (NIR dye).
- The conjugate was examined in mouse infection models for Bacillus subtilis and Staphylococcus aureus. In these mice, tail-vein injections of S. aureus or B. subtilis suspensions into the right axillary fossa were followed by exposure to the QD conjugates. After 6 hours of treatment, QD fluorescence allowed for the detection of the infection location [1].
- Given the quick development of QDs and the quantity of knowledge on the molecular causes of cancer, this scenario seems attainable The design and fabrication of appropriate multimodal probes based on QDs should give cancer imaging a new dimension and momentum given that biomedical imaging technologies are now well-developed.[4]
- QD-based nanoplatforms are mainly integrated with MRI and PET. For example, Mulder et al.[]successfully targeted tumor angiogenesis by fluorescence and MRI imaging based on the MR-fluorescence bimodal QDs. This approach was extended to QD-based bimodal probes contained in a silica nanoparticle to improve biocompatibility. It was also successfully applied in lymphatic imaging or combined with other imaging modalities[4].
- In general, recent efforts to target tumor cells for therapeutic and diagnostic purposes have largely concentrated on a small subset of potential ligands whose receptors are overexpressed in tumor cells, such as folic acid and siRNA delivery. Due to its strong binding affinity with the folate receptor (FR), folic acid has been widely exploited as a targeting ligand to deliver therapeutic medicines to cancer cells. Furthermore, due to QDs' intrinsic fluorescence and distinctive optical characteristics (such as adjustable emission, photostability, and brightness), researching siRNA delivery in cells and small animals utilizing QDs should be a fantastic alternative.[2]
- Regarding various applications, magnetic particle detection in ferromagnetic materials was suggested using fluorescent CdTe QDs combined with maghemite nanoparticles.63 Other QD

applications include encapsulation and nanotags for product authentication. CdSe/ZnS QDs dispersed in liquid crystals produced micrometer-sized capsules with exceptional thermal stability up to 350 °C, while PbS and PbS/CdS QDs with hybrid coatings were proposed as fluorescent nanotags for liquid petroleum.[3]

- For the effective identification and treatment of cancer, advanced clinical studies use photodynamic therapy (PDT) with fluorescence imaging. These treatments give selective therapy while leaving the immune system and normal cells unharmed, in contrast to chemotherapy and radiation therapy. The most advantageous feature for PDT is QDs, which have outstanding photostability.[4]
- QDs were used in place of organic dyes in a number of imaging applications. However, it was discovered that these materials had a vast amount of promise when it was discovered that they continued to emit bright fluorescent light for days on end. This was a significant development in microscopic imaging technology that aided in the understanding of numerous biological processes.
- As the QD technology advanced, researchers were increasingly interested in it and began investigating its potential uses in a variety of industries. The same material had been used to create many QDs of varying sizes that, when activated by light of a single wavelength, can produce a variety of colors. The ability to identify specific molecules on the cell using QDs tagged with biomolecules like antibodies, peptides, etc. was then proven.[5]
- The technology will provide new insights in understanding the pathophysiology of cancer, and in imaging and screening tumors. QDs will definitely be one of the components of the envisioned multifunctional nanodevices that can detect diseased tissue, provide treatment and report progress in real time.[12]
- QDs are used as biomarkers. This is for clinical treatment, disease stage prediction, and diagnosis. In comparison to conventional fluorescent reporters, QDs are 20 times brighter and 100 times more stable). A gene-silencing tool known as siRNA may be delivered into cells much more effectively using QDs than with current delivery techniques [24]

CONCULSION

The most valuable and promising prospects in the fields of medication delivery, targeting, and imaging in recent years have been QDs. They are great prospects for in vivo bioimaging, gene/drug administration, and cancer detection due to their low toxicity, low cost, and strong biocompatibility. This has had a significant impact on a number of disciplines, including biotechnology, bioassays, intracellular tagging as photo sensitizers for cancer treatment, and illness detection. QDs are now being used more frequently in biological applications, which has decreased their cytotoxicity and made them an effective tool for studying various cellular processes like uptake, receptor trafficking, and intracellular delivery. There will be new prospects for drug screening, disease screening, gene sequencing, and a variety of biomedical research as the QD nanocarriers for pharmaceuticals method continues to advance.

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