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Fluorescent quantum dots: An insight on synthesis and potential biological application as drug carrier in cancer

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ABSTRACT

Quantum dots (QDs) are nanocrystals of semiconducting material possessing quantum mechanical characteristics with capability to get conjugated with drug moieties. The particle size of QDs varies from 2 to 10 nm and can radiate a wide range of colours depending upon their size. Their wide and diverse usage of QDs across the world is due to their adaptable properties like large quantum yield, photostability, and adjustable emission spectrum. QDs are nanomaterials with inherent electrical characteristics that can be used as drug carrier vehicle and as a diagnostic in the field of nanomedicine. Scientists from various fields are aggressively working for the development of single platform that can sense, can produce a microscopic image and even be used to deliver a therapeutic agent. QDs are the fluorescent nano dots with which the possibilities of the drug delivery to a targeted site and its biomedical imaging can be explored. This review is mainly focused on the different process of synthesis of QDs, their application especially in the areas of malignancies and as a theranostic tool. The attempt is to consolidate the data available for the use of QDs in the biomedical applications.

1. Introduction

Quantum dots are semiconducting nanocrystals with intermolecular distance of approximately 2–10 nm. The use of QDs extends from the commonly seen items like lights, reflectors, photovoltaic devices and sign boards to the more sophisticated, delicate and precise medicines to be administered to humans. In case of medicines, QDs are useful as drug carriers and are also used as tools for diagnosis of diseases when seen under light of particular wavelength [1]. QDs can be synthesized by many well established documented procedures and uniqueness lies in the fact that different QDs emit different emission spectra when excited under same wavelength. This is based on the composition of materials used for their synthesis and resultant particle size obtained for fluorescent dot [2]. The ease of conjugating QDs with drug delivery vehicles viz; a polymer, solid lipid nanoparticles, micelles, liposomes and carbon based nanomaterials allows the use of such fluorescent nano dots in the field of nano medicine [3]. Very recently the application of nanomaterials is seen in the areas of diagnosis as well as treatment for even complicated conditions like diabetes, cardiovascular ailments, neuro-muscular diseases and cancer. Due to the property of photo

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excitation, QDs finds its place in various nano biomedical examinations in chronic conditions particularly cancer for detecting the extent and site of actual damage caused by the disease [4]. Cancer is the leading cause of death as one of the WHO reports in the year 2018 documented 9.6 million deaths solely due to cancer [5,6]. Globally, one in every 6th death is reported due to cancer. This calls for the urgent need to find newer and precise treatment strategies for the better management of cancer.

The nanomaterials as discussed above in conjunction with QDs are accepted in the treatment strategies due to their biocompatibility and absolutely no toxic effects to the human physiology. They come with the properties of surface functionalization with which both hydrophilic and hydrophobic drug moieties can be conjugated to form a release control delivery vehicle [4]. Scientists working in the field of drug therapy, diagnostics and medical science are interested in developing a nano-theranostic tool that can simultaneously detect the origin of the disease and direct the nanocouture for therapy. QDs qualify as ideal material for drug delivery, imaging tool and as nanosensor as promising scientific findings are published in the area of biomedical sciences. The present review is based on consolidation of such data for the use of QDs in biomedical application particularly in the area of cancer theranostics.

2. Optical properties and cellular toxicity of QDs

Optical properties exhibited by QDs along with their unique electronic properties impart various advantages to new fluorophores to be used as biological dyes, florescent proteins, and lanthanide chelates [7]. QDs show extensive emission spectra, which allow excitation by a wide range of wavelengths, a characteristic that may be exploited to energize numerous distinctively coloured QDs utilizing a single wavelength. Regular colours likewise have broad emission spectra, which mean the spectra of diverse colours may be exhibited to a vast degree. This exhibits that the fluorescent material can be conjugated to distinctive natural particles for analysing their fluorescence properties. Surprisingly, QDs having narrow emission spectrum can be inhibited in a relatively straightforward way by a variation in core dimensions, and through different structures [8].

Cellular toxicity of QDs has been reported in a number of *in vitro* tests, influencing cellular development furthermore, feasibility. The degree of cytotoxicity has been found to be dependent upon various elements including size, fluorescence, surface chemistry, and bioactivity and handling parameters. Regardless of instigating noteworthy modifications in cell physiology, QDs are capable of causing inconspicuous changes that could suggest the toxic behaviour of formed QDs [9]. These contain elution of free Cadmium (QD core degradation), free radical formation, and interaction of quantum dots with inner cellular environment. Recently, investigation of QDs toxicity in a hepatocyte culture model demonstrated that the accumulation of Cadmium Selenide core within an oxidative surrounding of cell could result in degradation of core leading to elution of Cadmium ions [10].

3. Molecular targeting with QDs

Luminescent QDs are a potential alternative in contrast to natural dyes for fluorescence-based applications. Inferable from their narrow emission, wide ultra violet ray excitation, brilliant fluorescence, and high photostability makes QDs extremely attractive candidates for visualization techniques [11]. QDs of transferrin (an iron-transport protein) conjugates were prepared by covalently binding zinc sulfide-cadmium selenide QDs s to a protein with the help of mercaptoacetic acid (MA). At the point when the conjugates were fused with HeLa cells, the transferrin particles were separated from the receptors over cell surface and also inside the cells by receptor-interceded endocytic mechanisms. Prior endeavours have been made to apply quantum dots in live cells *invitro*. This could allow constant examination of molecular processes in living cells along with ligand receptor interactions [12]. Further engineered scientific investigations for developing long-term and multifaceted imaging techniques which can be used in humans are essential. Walling et al. mentioned in their communication about the use of QDs for live cell imaging. The synthesized fluorescent dots gets attached to cell proteins resulting in insightful imaging of live cancer cells. In this investigation, the cells remained stable for over seven days as they developed into a live imaging tool. This showed the non-toxic impact on cell capacity/morphology; thus making QDs ideal for long term and deep imaging of living cells [13].

4. Theranostics platform with QDs

Theranostics is the term given when a system/tool/delivery vehicle is capable of instantaneous detection of a disease along with its treatment. Warner described the term as the integrated system/platform which is smart enough to assist in diagnosis as well as provides a treatment for a disease. The nanotherapeutics is now shifting towards concept of theranostics by which coordinated approach is utilized for simultaneous treatment and also examining the disease regression [14,15]. It has resulted in a more sophisticated image-assisted nanotherapeutics for chronic disease conditions particularly for cancers [15,16]. The striking feature of the therapy is that it comes with biocompatibility, diminished side effects and lowered risks affecting the healthy human cells.

Early stage detection of cancer is still a fantasy which calls for the development of modern and sophisticated tools for its detection. Conventional methods viz; physical examination, biopsy and blood tests are less precise, time consuming and are performed with tedious procedures. So, the introduction of theranostics into the field of oncology is the need of the hour and recent investigations have proved that such application will provide additional molecular level information along with superior treatment options [17]. The Fig. 1 below shows the use of QDs for gathering the multidimensional information based on *invitro* cell imaging, assays and *invivo* animal studies.

From the past one decade theranostic tools are developed for better understanding of cancer cell biology [18,19]. QDs coupled with ligand molecules like antibodies and aptamers have led to the development of more effective therapeutics. This has opened the field of personalized medicine for cancer, diabetes, cardiovascular and patients with neurological disorders [20]. The concept of theranostics has now extended to genomics, proteomics and other 'omic techology' that have contributed a lot for development of superior diagnostic tools.

5. Theranostic nanomaterials in tumour microenvironment

The medicinal or therapeutic viability of any theranostics can be decided by the intensity of the response generated for the therapeutic after its administration into the living cells. Typically, the nanomaterials are stimulus-responsive (for example, pH, attractive field and light), therefore, the circulation life of the nano material in the human physiology system is dependent upon the factors responsible for disease onset and its progression [21]. For, example, gold nanostructures gathered at the tumor site can be effortlessly illuminated by near infrared (NIR) light leading to unconstrained build-up of heat that brings about diseased cell's death by means of hyperthermia [22]. Doxorubicin (DOX), an anticancer medicine, is an example of a drug that can detect malignant growth and cause cell death after its transportation to the tumor site in a controlled fashion depending upon the nanomaterial used for synthesis of its nanocargo. The cumulative movement to the cancer cells and drug discharge from the nano-delivery vehicle can be observed using their fluorescent properties of QDs [23,24]. Hence, with QDs it is observed that the pharmacodynamics of nanomaterials can be judged, which lead to in-depth knowledge of the disease and its progression [25].

In the year 2015, Pawar et al. documented CdS nanoprobes for estimation of penicillamine content in the nanoparticles formed. The authors reported an increase in size of the QDs in presence of the drug

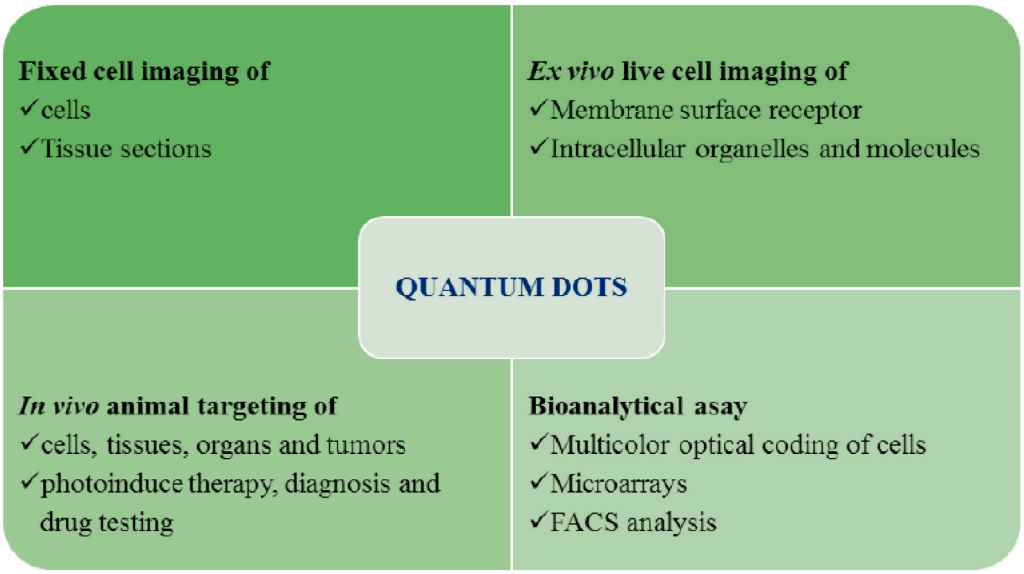

Fig. 1. Use of Quantum dots as various contrasts mediators in bioimaging.

and enhanced fluorescence attributed towards synergistic interaction between the drug and the QDs [26]. Similarly, QD based tools are developed for cancer therapy and genetic material delivery especially for siRNA. These are useful for MRI imaging, multiplexed molecular imaging and can be used for monitoring the dynamic nature of tumour microenvironment [25,26]. Moving on same lines Sun et al. reported successful detection of HER2 (human epidermal growth factor receptor found on the surface of breast tumours) with QDs based immunohistochemistry even at lower expression levels of the HER2 protein. The authors also reported that with the developed system, multiplexed QDs based analysis was also possible [27]. Fig. 2 below depicts the unique characteristics of QDs employed in the modern age oncology therapeutics.

6. Use of theranostics in targeted cancer treatment and imaging

As the branch of theranostics is concerned with providing treatment as well as diagnostic attributes to the delivery vehicle, this serves dual purpose in the complicated oncology strategy followed for cancer remission. QDs with surface functionalization also provide the opportunity to target the therapeutic at the specific site, thus minimising the peripheral side effects associated with therapy [28]. Very recently, the omic technology in association with the QDs has been able to develop symptomatic diagnostic kits for cancers. In this, ligands specific for cancers like antibodies, peptides and aptamers attached to the surface of kits which can detect the corresponding cancer biomarker present in the sample [29].

Cai et al. developed DOX encapsulated ZnO QDs with dimensions of ~ 3 nm with biocompatible materials like polyethylene glycol and hyaluronic acid. The system was synthesized to target the overexpressed CD44 glycoprotein in the lung cancer. The drug loading was done to fulfil the therapeutic component of QDs and it resulted in controlled release inside the acidic tumour microenvironment when imaged using confocal laser scanning microscopy [30]. The cancer imaging using QDs was successfully reported by Yezhelyev et al. done on breast tumour cell line and on clinical specimens. The authors investigated the comparative study with the developed system vis-à-vis conventional available techniques of western blotting and fluorescence in situ hybridization (FISH). MCF-7 cells line was used to evaluate HER2, ER, and mTOR in the tumour microenvironment. The relevance of the study was proved by the fact that the diagnostic tool was in the position to detect even low concentration of these protein markers in breast tumour [31]. Fig. 3

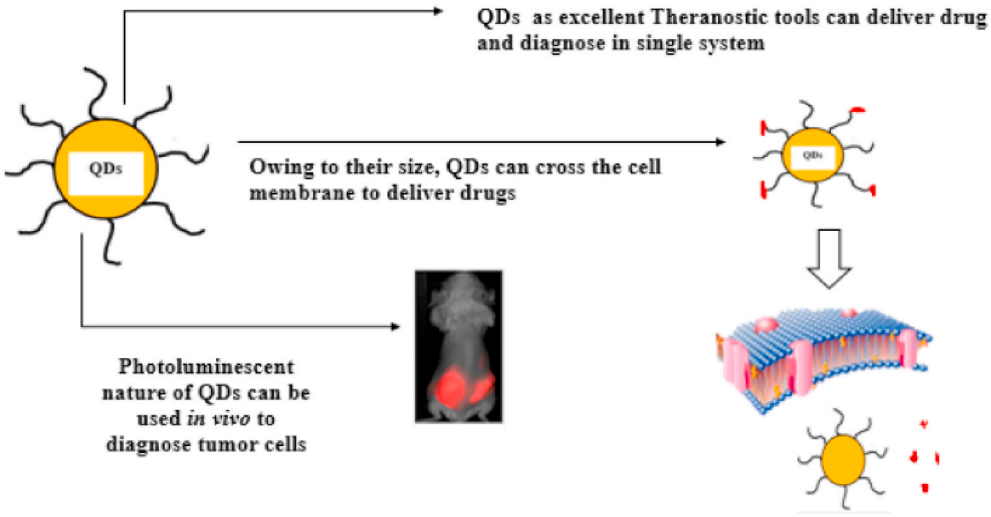

Fig. 2. Attributes of QDs useful in the cancer therapy.

Fig. 3. Theranostic utilization of QDs for delivery of therapeutic inside cancer microenvironment.

below depicts the associated benefits with QDs when applied in the oncology segment.

7. Various methods used for quantum dots synthesis

7.1. Wet-chemical methods (microemulsion process/sol-gel process/hot-solution decomposition process)

QDs with tunable dimensions can be synthesized through chemical methods. Epitaxial hetero structures can be constructed using a variety of wet-chemical methods, including the direct synthesis from molecular precursors (e.g., solution epitaxial growth) and the post-synthesis, treatments of the existing seeds or templates (e.g., ion exchange) [32,33]. In the solution of epitaxial growth methods, the nucleation of the second material is allowed on the defined sites of existing seeds. Ion exchange methods, especially the cation exchange in which the cations in a nitrocellulosde host lattice are substituted for those in solution, have been used as a particularly powerful tool for the construction of epitaxial hetero structures [34,35].

Similar to sol-gel processes, microemulsion and hot-solution decomposition process can be carried out at atmospheric temperature. One can adjust the dimension of QDs by altering the concentration of surface-active agent and can furthermore have the smallest possible size when synthesized from the sol-gel process. Low yield, risk of contamination and deformations of formed crystal lattice are major disadvantages of these techniques. The inverse micelle techniques is most favoured for preparation of QDs, where water globules scattering may be improved with the use of surface-active agents like acetyl tri methyl-ammonium-bromide (CTAB), sodium lauryl sulfate (SLS) and other non-ionic surfactant. As these surface-active agents have both hydrophilic and hydrophobic characteristics, numerous minute aggregates called micelles surround the oil phase. Such micelles are thermodynamically stable and are called as 'nonreactors'. Formation of resultant QDs is facilitated by micelle particles which in turn is dependent upon molar concentration of water and surfactant [36,37].

7.2. Hot-arrangement decay process

This strategy incorporates reactivity of the organometallics at a maximum temperature and a brief description was first given by Bawendi and partners in 1993. Process involves injecting a cool solution of precursor molecules into a hot liquid of tri-octylphosphine oxide (TOPO) between 295 and 305 °C under vacuum in a three-necked round bottom flask. The injection leads to the formation of tri-*n*-octyl-phosphine selenide nuclei which can be controlled by variation in temperature. Consistent nucleation to produce QDs is done through a mechanism of dominant particle growth called 'Ostwald ripening' which results in broadening of their size distribution and increase in the free energy of QDs which further influences their photoluminescence [38]. The tri-octyl-phosphine oxide solution (purity nearly to 90%) controls the QDs scattering, enhance the surface coating, and imparts surface aggregating property for adequate development of QDs. This strategy involving the use of heat transfer fluids provides a convenient means to control growth and results in mono scattered QDs. Additionally, a progression of QDs dimensions may improve after a similar antecedent growth by tweaking the temperature. In any case, this procedure faces limitations over its higher expenses for the utilization of higher heat, the toxicity potential of organo-metallic precursors, and low scattering in water [39].

7.3. Vapor-stage phase techniques (molecular beam epitaxy (MBE)/ physical vapor deposition (PVD)/chemical vapor deposition (CVD)

In vapor-stage strategies, layers of QDs are created within a molecule through particle processes with no structuring rather by the hetero-epitaxial migration of self-assembled QDs [40]. This has brought a paradigm shift in research since the past few years owing to their exceptional properties, crystallinity and potential for biomedical application. In the III-V system for synthesis of QDs according to Stranski-Krastanow (SK) the formation of uniform QDs, like nano structures can be well controlled by the nucleation conditions [41]. The entire synthesis process is dependent upon the precursors, their concentration and the controlled temperature conditions during the reaction.

7.4. Physical vapor deposition method (PVDM)

Vaporization occurs from dense material or fluid obtained in different natures of atom/molecules and is directed through an evacuated/low pressure gas in the PVD process where distillation is carried out. The most customarily utilized PVDM in the mechanical application is when the surface of the sputtering target is blocked with vaporous molecules with increased electrical frequency for QD production. The molecules/atoms are produced using this method by energy exchanged from the colliding molecules in solution [42].

7.5. Chemical vapor deposition method (CVDM)

In CVDM, powder/solid film is deposited over the substrate at increased temperature using different precursors. These precursors are formed by a chemical interaction converting the molecules or atoms into gaseous phase. This process commonly occurs with evaporation induced by the secondary products as well as starting materials [43]. CVDM are of different types, such as vapor phase epitaxy method (VPEM) when CVDM is used to deposit single crystal film, metal-organic CVDM (MOCVDM) when precursors are metal-organic species, plasma increased CVDM (PECVDM) when a plasma is utilized to increase the reaction and if the breakdown is taking place at decrease pressurize gas is known as low-pressure CVD (LPCVD) [42]. Likewise, atmospheric pressure CVDM (APCVDM), photochemical vapor deposition (PCVDM), laser chemical vapor topping (LCVDM) are also well recognized. Correspondingly, ecological weight CVD, photochemical vapor articulation (PCVD) are furthermore outstanding techniques for QDs synthesis [44].

7.6. Substantial metal-free quantum dots or green method for synthesis

For business reasonability, a scope of cadmium-free quantum dots, for example, Indium Phosphide/Zinc Selenide and Copper Indium Sulfide (CuInS2)/Zinc Selenide have been synthesized. They represent brilliant discharges in the regular near infrared range with comparable optical characteristics to that of CdSe QDs. A green technique for combining the hydrophilic CuInS2 and CuInS2/ZnS colloidal quantum dots was devised utilizing N, *N*-dimethylformamide in soluble form. Ionic liquids (IL) are beneficial due to their eco-friendly green nature and can be utilized as elective response media by replacing conventional unstable organic solvents. Another technique was detailed by Wang Y. Q, and colleagues utilizing ionic fluids as microwave absorbing solvents for the synthesis of ZnS quantum dots [45,46]. Fig. 4 below portray the simplest lab scale injection method of synthesis for graphene quantum dots.

8. DNA-functionalization of QDs

QDs can also function as fluorophores by a process known as quantum confinement which leads to emission of electromagnetic radiation perceived as fluorescence and helps in imaging of various cellular and sub-cellular structures. In this regard, conventional CdSe/ZnS quantum dots are not the most attractive preference as they may cause damage to characteristic cells. To make cell compatible features, superficial alterations of QDs are done. Recent changes made to address these limitations include synthesis employing hydrogel or covalent link between layers to explicitly attach with DNA, which can be utilized for cellular as well as molecular discovery [47]. Fig. 5 depicts the sequential steps involved in DNA functionalized QDs to reach the target site. In a hydrogel system, the outer surface of Zinc Selenide might possess electric charge to bind the hydrophobic core of a micelle which enables the hydrophilic surface to stay associated with organic frameworks. Nevertheless, during bio conjugation, two covalently reinforced biomolecules can form a defensive coat over the QDs. Hydrophobic bio conjugation hinders breakdown of the QDs structure inside the body [48].

Xiaohu Gao et al. utilized tri-*n*-octylphosphine oxide for attachment with receptor site, and a trisquare polymer comprising of two hydrophobic and one hydrophilic portion, with an entirely hydrophobic hydrocarbon sequence. The intense hydrophobic relationship among trinoctylphosphine oxide and polymer hydrocarbon empowers them to assume a hydrophobic conformational nature [49,50].

9. Biological use of quantum dots

Fluorescence resonance energy transfer (FRET) includes the transmission of fluorescence energy initiated from donor particle to a receiver particle at all points. FRET can be an accurate measure of molecular proximity at angstrom distances (10–100 Å) and highly efficient if the donor and acceptor are positioned within the Förster radius (the distance at which half the excitation energy of the donor is transferred to the acceptor, typically 3–6 nm) [51]. It is a sensitive technique suitable for estimating variations in inter-molecular separation, investigating various biological phenomena causing changes in molecular proximity, estimating protein conformational deviations, and analysis of protein interaction. A collective effort to utilize QDs in FRET has led to several advances, mostly after coupling to peptides and antibodies used for immunoassays. QD-FRET remains useful for observing protein reactions in the Holliday Junction, an intermodal recombinant DNA which undergoes conformational modification after interacting withMg2+ ions [52]. A large number of references demonstrate that QD-conjugated oligonucleotide arrangements (coupled by means of surface carboxylic acid groups) bind with DNA or mRNA1 [53]. The optical properties of QDs were utilized to identify the clinically valuable ERBB2/HER2/new locus, which is useful for breast cancer. Coupling of oligonucleotides to the QDs surface leads to low stability because these QDs develops free carboxylic acid groups on the surface, making them much less useful than predictable organic fluorophore probes [54].

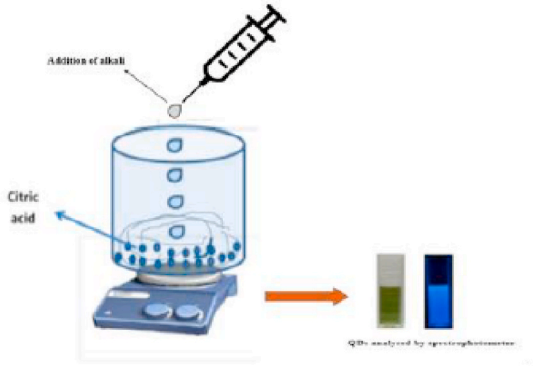

Fig. 4. Green synthesis method for the preparation of graphene quantum dots (GQDs). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

9.1. Blood and biochemical markers

The QDs being minute particles may influence the resistance mechanisms or initiate a rapid reaction, which would be demonstrated by changes in hematological factors, for which standard hematological and biochemical markers are evaluated. Hematological outcomes demonstrated in the mice with CdTe QDs and PBS infused appeared to be ordinary wherein the actions of hematological and biochemical markers showed extraordinary results at the samplings intervals of 0, 7, 15 and 30 days post administration. Besides, the mice infused with CdTe QDs demonstrated an altogether increased WBC number in samples taken at 7, 15 and 30th day with the greatest increase at 30 days after infusion. This may be because of likely irritation caused by the QDs in kidney tissues [55]. The increased dimensions of WBCs at a high dose (100 g) of QDs are also reported. Also, serum organic chemistry examinations were conducted on weekly basis and hinted at no liver damage as both the AST and ALT were within ordinary range. Markers of kidney function such as blood nitrogen urea and creatinine were observed to be higher in CdTe QDs infused animals. Overall, the consequences of hematology and blood estimations demonstrated that the CdTe QDs cause mild to moderate renal harm [56].

9.2. In vivo imaging

Current known advancement in superior QDs for whole body imaging is still at developmental stage. Whole body imaging poses a few critical challenges with the goal of developing more significant diagnostic tool over the existing methods already utilizing QDs in this domain. In contrast to single-layered cells and thin tissue segments, imaging in live subjects acquaints confusions owing to scrambling and auto-fluorescence of tissue due to UV and the bright range. Hence, images have been acquired at proximity of a couple of mm beneath the surface of the skin [58]. QDs can be employed for inner body imaging as they can radiate infrared radiations in the near infrared window (700–900 nm). Such wavelengths are harmless for skin and appropriate for biomedical use, due to low energy conduction of QDs. A vital limitation for *in vivo* applications is their escape from the circulatory system [57].

9.3. Drug transportation

As of late, collaborations in organic frameworks have led to increased interests in science and medicine. QDs, otherwise called modest light-radiating NPs, have incredible photophysical

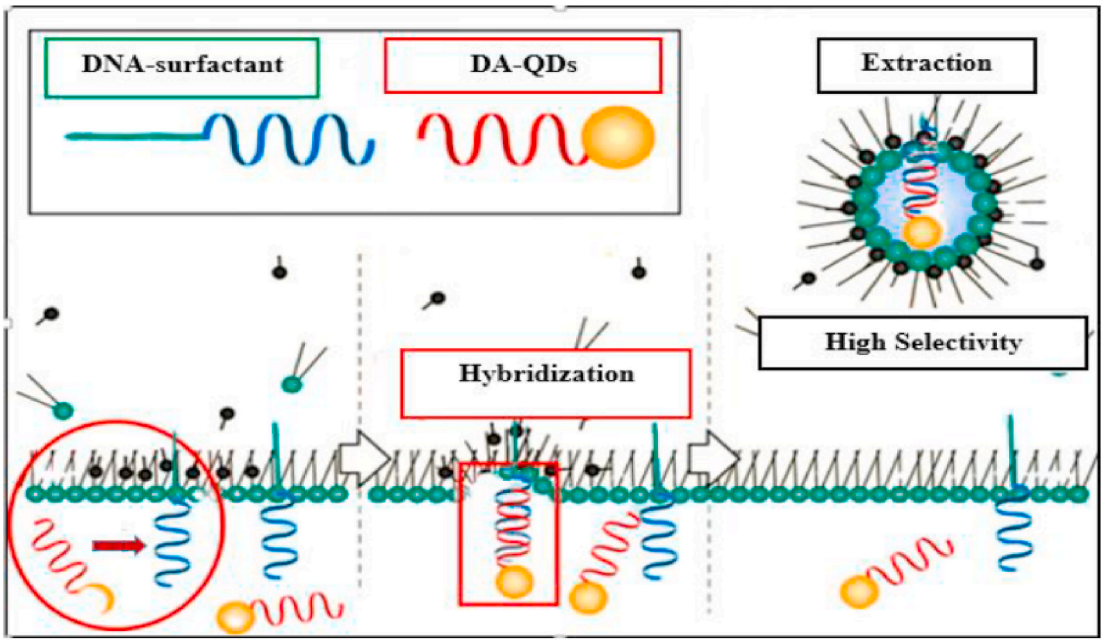

Fig. 5. Schematic representation of liquid-liquid extraction process of DNA functionalized quantum dots.

characteristics that are involved in effective extension of the application and also possess extraordinary possibilities in disease detection as well as treatment progression. In order to uphold their numerous abilities, existing QDs are innovating rapidly. QDs can be cross-linked to biomolecules, for example, antibodies, peptides, or small ligands which can be preferred over conventional organic frameworks and can be utilized in developing drug therapies as highlighted in Table 1 below.

The use of QDs in the field of biomedical sciences fascinates the scientific community for its potential advantageous aspects. The spectra of scope for these fluorescent dots to be used in understanding and revealing newer concepts in cellular biology is far more enormous which calls for further scientific investigations.

10. Conclusions

Theranostics is a rapidly evolving area of drug development in the dynamic research and in various fields of material science, imaging specialties and atomic science. Theranostic nanomaterials have been widely investigated in the area of oncology for complex purposes, such as chemotherapeutic drug delivery, quality delivery, photothermal treatment, and photodynamic treatment/management. In addition, theranostic agents may also find wide application in agricultural sciences and chemotherapy of cancer. As of late, theranostic nanomaterials have likewise been investigated, though to a lesser degree, in cardiovascular indications, renal complications and immunological disorders for their improved treatment and monitoring of disease progression. Advances in therapeutic science, hereditary patterns, physical science, biomedical development, and nanotechnology are being made for improvement of diagnostic tests in terms of multi-modality and molecular visualization of disease with remedial specialists focusing majorly on cancer treatment. Peptides, nanoparticles, peptidomimetics, proteins, and antibodies labeled with radioisotopes, fluorescent dyes, super paramagnetic nanoparticles, and QDs have been studies extensively in this regard. This gives the guarantee that the fluorescents dots (QDs) can definitely illuminate the complicated terrain of oncology sciences with newer diagnostic tools, novel biomarkers and a patient compliant treatment regimens in near future.

Table 1
QD conjugated/loaded with drug molecules acting as a carrier system for cancer therapy.

Type of quantum dots (QDs)	Drug Moiety	Outcome	Ref
Mn/ZnS QDs	5-Fluorouracil	5-FU loaded FACS-Mn: ZnS nanocomposite for targeted delivery for breast cancer therapy	[58]
Tri-element doped magneto-fluorescent carbon QDs (GdNS@CQDs)	Doxorubicin	QDs showed a maximum drug filling and pH-depending drug release.	[59]
Graphene QDs (GQDs)	Cisplatin	Enhancement to cisplatin cellular uptake in cisplatin-resistant cells	[60]
ZnO QDs	Doxorubicin	Biodegradable pH-responsive drug delivery platform	[61]
$Cu^2(OH)$ PO4 QDs	photodynamic treatment/ photothermal method of treatment	The developed system worked on photoactivated development of reactive oxygen species and photothermal adaptation of the synthesized QDs	[62]
ZnSe:Mn/ZnS QDs	Paclitaxel	Hybrid nanocapsules with tunable fluorescence and sustain release behaviour	[63]
CdTe/CdsS/ZnS QDs	Paclitaxel	Parenteral multifunctional delivery system (NLC)	[64]
ZnO QDs	Doxorubicin	The developed system developed surface protonation/ deprotonation controlled charge switch	[65]

Declaration of competing interest

There is no conflict of interest.

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References

[1] Z. Ning, X. Gong, R. Comin, G. Walters, F. Fan, O. Voznyy, E. Yassitepe, A. Buin, S. Hoogland, E.H. Sargent, Quantum-Dot-in-Perovskite solids, Nature 523 (2015) 24–328.
[2] T.R. Pisanic, Y. Zhang, T.H. Wang, Quantum dots in diagnostics and detection: principles and paradigms, Analyst 139 (12) (2014) 2968–2981.
[3] N.G. Zaorsky, T.M. Churilla, B.L. Egleston, S.G. Fisher, J.A. Ridge, E.M. Horwitz, J. E. Meyer, Causes of death among cancer patients, Ann. Oncol. 28 (2) (2017) 400–407.
[4] N. Ahmed, H. Fessi, A. Elaissari, Theranostic applications of nanoparticles in cancer, Drug Discov. Today 17 (18) (2012) 928–934.
[5] WHO report on Cancer, Accessed on 02022021, https://www.who.int/news-room/fact-sheets/detail/cancer.
[6] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global Cancer Statistics, GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, Ca - Cancer J. Clin. 68 (2018) 394–424, 2018.
[7] S. Tomic, N. Vukmirovic, Quantum dots, in: Handbook of Optoelectronic Device Modeling and Simulation: Fundamentals, Materials, Nanostructures, LEDs, and Amplifiers, CRC Press, 2017.
[8] V.I. Klimov, A.A. Mikhailovsky, S. Xu, A. Malko, J.A. Hollingsworth, C. A. Leatherdale, H.J. Eisler, M.G. Bawendi, Optical gain and stimulated emission in nanocrystal quantum dots, Science 290 (2002) 314–327.
[9] A. Hoshino, K. Fujioka, T. Oku, M. Suga, Y.F. Sasaki, T. Ohta, M. Yasuhara, K. Suzuki, K. Yamamoto, Physicochemical properties and cellular toxicity of nanocrystal quantum dots depend on their surface modification, Nano Lett. 4 (11) (2004) 2163–2169.
[10] N. Chen, Y. He, Y. Su, X. Li, Q. Huang, H. Wang, X. Zhang, R. Tai, C. Fan, The cytotoxicity of cadmium-based quantum dots, Biomaterials 33 (5) (2012) 1238–1244.
[11] S.N. Baker, G.A. Baker, Luminescent carbon nanodots: emergent nanolights, Angew. Chem. Int. Ed. 49 (38) (2010) 6726–6744.
[12] L.P. McGuinness, Y. Yan, A. Stacey, D.A. Simpson, L.T. Hall, D. Maclaurin, S. Prawer, P. Mulvaney, J. Wrachtrup, F. Caruso, R.E. Scholten, L.C.L. Hollenberg, Quantum measurement and orientation tracking of fluorescent nanodiamonds inside living cells, Nat. Nanotechnol. 6 (2011) 358–363.
[13] M.A. Walling, J.A. Novak, J.R.E. Shepard, Quantum dots for live cell and in vivo imaging, Int. J. Mol. Sci. 10 (2) (2009) 441–491.
[14] M.K. Yu, J. Park, S. Jon, Targeting strategies for multifunctional nanoparticles in cancer imaging and therapy, Theranostics 2 (1) (2012) 33–44.
[15] J.V. Jokerst, S.S. Gambhir, Molecular imaging with theranostic nanoparticles, Accounts Chem. Res. 44 (10) (2011) 1050–1060.
[16] B.A. Goins, W.T. Phillips, Nanoimaging, Pan Stanford Publishing Pt. Ltd., 2011.
[17] C. Fang, M. Zhang, Nanoparticle-based theranostics: integrating diagnostic and therapeutic potentials in nanomedicine, J. Contr. Release 146 (1) (2010) 2–5.
[18] V. Vijayan, S. Uthaman, I.K. Park, Cell membrane-camouflaged nanoparticles: a promising biomimetic strategy for cancer theranostics, Polymers 10 (9) (2018) 983–999.
[19] F. Pene, E. Courtine, A. Cariou, J.P. Mira, Toward theranostics, Crit. Care Med. 37 (2009) S50–S58.
[20] G. Galina Nifontova, A. Efimov, O. Agapova, I. Agapov, I. Nabiev, A. Sukhanova, Bioimaging tools based on polyelectrolyte microcapsules encoded with fluorescent semiconductor nanoparticles: design and characterization of the fluorescent properties, Nanoscale Res. Lett. 14 (2019) 29.
[21] M. Holzinger, A. Le Goff, S. Cosnier, Nanomaterials for biosensing applications: a review, Front. Chem. 2 (2014) 63–74.
[22] D. Kim, S. Jon, Gold nanoparticles in image-guided cancer therapy, Inorg. Chim. Acta. 393 (2012) 154–164.
[23] F. Wang, Y.C. Wang, S. Dou, M.H. Xiong, T.M. Sun, J. Wang, Doxorubicin-tethered responsive gold nanoparticles facilitate intracellular drug delivery for overcoming multidrug resistance in cancer cells, ACS Nano 5 (5) (2011) 3679–3692.
[24] D.N. Price, L.R. Stromberg, N.K. Kunda, P. Muttil, In vivo pulmonary delivery and magnetic-targeting of dry powder nano-in-microparticles, Mol. Pharm. 14 (12) (2017) 4741–4750.
[25] M. Nishikawa, Pharmacokinetic properties of nanomaterials, in: Methods in Pharmacology and Toxicology, vol. 39, Humana Press, 2016.
[26] S.P. Pawar, A.H. Gore, L.S. Walekar, P.V. Anbhule, S.R. Patil, G.B. Kolekar, Turn-on fluorescence probe for selective and sensitive detection of d-penicillamine by CdS quantum dots in aqueous media: application to pharmaceutical formulation, Sensor. Actuator. B 209 (2015) 911–918.
[27] J.Z. Sun, C. Chen, G. Jiang, W.Q. Tian, Y. Li, S.R. Sun, Quantum dot-based immunofluorescent imaging of Ki67 and identification of prognostic value in HER2-positive (non-luminal) breast cancer, Int. J. Nanomed. 9 (2014) 1339–1346, https://doi.org/10.2147/IJN.S58881.
[28] Z.M. Bhujwalla, S. Kakkad, Z. Chen, J. Jin, S. Hapuarachchige, D. Artemov, M. F. Penet, Theranostics and metabolotheranostics for precision medicine in oncology, J. Magn. Reson. 291 (2018) 141–151.
[29] B. Bahrami, M. Hojjat-Farsangi, H. Mohammadi, E. Anvari, G. Ghalamfarsa, M. Yousefi, F. Jadidi-Niaragh, Nanoparticles and targeted drug delivery in cancer therapy, Immunol. Lett. 190 (2017) 64–83.
[30] X. Cai, Y. Luo, W. Zhang, D. Du, Y. Lin, pH-Sensitive ZnO quantum dots–doxorubicin nanoparticles for lung cancer targeted drug delivery, ACS Appl. Mater. Interfaces 8 (34) (2016) 22442–22450.
[31] M.V. Yezhelyev, A.A. Hajj, C. Morris, In situ molecular profiling of breast cancer biomarkers with multicolour quantum dots, Adv. Mater. (19) (2007) 3146–3151.
[32] U. Resch-Genger, M. Grabolle, S. Cavaliere-Jaricot, R. Nitschke, T. Nann, Quantum dots versus organic dyes as fluorescent labels, Nat. Methods 5 (2008) 763–775.
[33] M.L. Landry, T.E. Morrell, T.K. Karagounis, C.H. Hsia, C.Y. Wang, Simple syntheses of CdSe quantum dots, J Chem. Educ. 91 (2) (2014) 274–279.
[34] I.U. Arachchige, S.L. Brock, Sol-gel methods for the assembly of metal chalcogenide quantum dots, Acc. Chem. Res. 40 (9) (2007) 801–809.
[35] F. Glas, G. Patriarche, J.C. Harmand, Growth, structure and phase transitions of epitaxial nanowires of III-V semiconductors, in: Proceedings of the Journal of Physics: Conference Series; 209 012002, 2019.
[36] N. Ghows, M.H. Entezari, Quantum dots of CdS synthesized by micro-emulsion under ultrasound: size distribution and growth kinetics, Phys. Chem. Res. 1 (2) (2013) 166–174.
[37] Y. Wang, A. Hu, Carbon quantum dots: synthesis, properties and applications, J. Mater. Chem. 2 (2014) 6921–6939.
[38] Y. Zeng, D.F. Kelley, Two-photon photochemistry of CdSe quantum dots, ACS Nano 9 (10) (2015) 10471–10481.
[39] C.J. Barrows, J.D. Rinehart, H. Nagaoka, D.W. DeQuilettes, M. Salvador, J.I. L. Chen, D.S. Ginger, D.R. Gamelin, Electrical detection of quantum dot hot electrons generated via a Mn2+-enhanced auger process, J. Phys. Chem. Lett. 8 (1) (2017) 126–130.
[40] M. Saadoun, N. Mliki, H. Kaabi, K. Daoudi, B. Bessais, H. Ezzaouia, R. Bennaceur, Vapour-etching-based porous silicon: a new approach, Thin Solid Films 405 (2) (2002) 29–34.
[41] S.D. Singh, T.K. Sharma, C. Mukherjee, S.M. Oak, Impact of growth parameters on the structural properties of InP/GaAs type-II quantum dots grown by metal-organic vapour phase epitaxy, in: Proceedings of the Proceedings of the 14th International Workshop on the Physics of Semiconductor Devices, IWPSD, 2007, pp. 1–4.
[42] D. Sun, N. Miyatake, H.J. Sue, Transparent PMMA/ZnO nanocomposite films based on colloidal ZnO quantum dots, Nanotechnology 18 (21) (2007) 215606. IOP Publishing Ltd.
[43] N.S. Kulkarni, Y. Guererro, N. Gupta, A. Muth, V. Gupta, Exploring potential of quantum dots as dual modality for cancer therapy and diagnosis, J. Drug Deliv. Sci. Technol. 49 (2019) 352–364.
[44] M. Bacon, S.J. Bradley, T. Nann, Graphene quantum dots, Part. Part. Syst. Char. 31 (4) (2014) 415–428.
[45] Y.P. Sun, B. Zhou, Y. Lin, W. Wang, K.A.S. Fernando, P. Pathak, M.J. Meziani, B. A. Harruff, X. Wang, H. Wang, P.G. Luo, H. Yang, M.E. Kose, B. Chen, L.M. Veca, S. Y. Xie, Quantum-sized carbon dots for bright and colorful photoluminescence, J. Am. Chem. Soc. 128 (24) (2006) 7756–7757.
[46] J. Zheng, P.R. Nicovich, R.M. Dickson, Highly fluorescent noble-metal quantum dots, Annu. Rev. Phys. Chem. 58 (2007) 409–431.
[47] S.Y. Lim, W. Shen, Z. Gao, Carbon quantum dots and their applications, Chem. Soc. Rev. 44 (2015), 362-281.
[48] M.P. Monopoli, A.S. Pitek, I. Lynch, K.A. Dawson, Nanomaterial interfaces in biology, in: Nanomaterial Interfaces in Biology: Methods and Protocols, Methods in Molecular Biology, Humana Press, 2013.
[49] W.C.W. Chan, D.J. Maxwell, X. Gao, R.E. Bailey, M. Han, S. Nie, Lumnescent quantum dots for multiplexed biological detection and imaging, Curr. Opin. Biotechnol. 13 (2002) 40–46.
[50] F. Wang, W.B. Tan, Y. Zhang, X. Fan, M. Wang, Luminescent nanomaterials for biological labelling, Nanotechnology 17 (2006) R1–R13.
[51] V.V. Didenko, DNA probes using fluorescence resonance energy transfer (FRET): designs and applications, Biotechniques 31 (5) (2001) 1106–1121.
[52] A.P. Alivisatos, W. Gu, C. Larabell, Quantum dots as cellular probes, Annu. Rev. Biomed. Eng. 7 (2005) 55–76.
[53] J.-J. Zhu, J.J. Li, H.P. Huang, F.F. Cheng, Quantum Dots for DNA Biosensing, Springer Press, 2013.
[54] C. Würth, M. Grabolle, J. Pauli, M. Spieles, U. Resch-Genger, Relative and absolute determination of fluorescence quantum yields of transparent samples, Nat. Protoc. 8 (2013) 1535–1550.
[55] L. Ye, K.T. Yong, L. Liu, I. Roy, R. Hu, J. Zhu, H. Cai, W.C. Law, J. Liu, K. Wang, J. Liu, Y. Liu, Y. Hu, X. Zhang, M.T. Swihart, P.N. Prasad, A pilot study in non-human primates shows No adverse response to intravenous injection of quantum dots, Nat. Nanotechnol. 7 (2013) 453–458.
[56] J. Ruan, K. Wang, H. Song, X. Xu, J. Ji, D. Cui, Biocompatibility of hydrophilic silica-coated CdTe quantum dots and magnetic nanoparticles, Nano Res. Lett. 6 (1) (2011) 299–312.

[57] A. Orte, J.M. Alvarez-Pez, M.J. Ruedas-Rama, Fluorescence lifetime imaging microscopy for the detection of intracellular PH with quantum dot nanosensors, ACS Nano 7 (7) (2009) 6387–6395.
[58] I.B. Bwatanglang, F. Mohammad, N.A. Yusof, J. Abdullah, N.B. Alitheen, M. Z. Hussein, N. Abu, N.E. Mohammed, N. Nordin, N.R. Zamberi, S.K. Yeap, In vivo tumor targeting and anti-tumor effects of 5-fluororacil loaded, folic acid targeted quantum dot system, J. Colloid Interface Sci. 480 (2016) 146–158, 2016.
[59] S.H. Chiu, G. Gedda, W.M. Girma, J.K. Chen, Y.C. Ling, A.V. Ghule, K.L. Ou, J. Y. Chang, Rapid fabrication of carbon quantum dots as multifunctional nanovehicles for dual- modal targeted imaging and chemotherapy, Acta Biomater. 46 (2016) 151–164.
[60] N. Suzuki, Y. Wang, P. Elvati, Z.B. Qu, K. Kim, S. Jiang, E. Baumeister, J. Lee, B. Yeom, J.H. Bahng, J. Lee, A. Violi, N.A. Kotov, Chiral graphene quantum dots, ACS Nano 10 (2) (2016) 1744–1755.
[61] X. Cai, Y. Luo, W. Zhang, D. Du, Y. Lin, PH-sensitive ZnO quantum dots-doxorubicin nanoparticles for lung cancer targeted drug delivery, ACS Appl. Mater. Interfaces 8 (34) (2016) 22442–22450.
[62] W. Guo, Z. Qiu, C. Guo, D. Ding, T. Li, F. Wang, J. Sun, N. Zheng, S. Liu, Multifunctional theranostic agent of Cu2(OH)PO4 quantum dots for photoacoustic image-guided photothermal/photodynamic combination cancer therapy, ACS Appl. Mater. Interfaces 9 (11) (2017) 9348–9358.
[63] Q. Zhang, C. Nie, C. Chang, C. Guo, X. Jin, Y. Qin, F. Li, Q. Li, Highly luminescent red emitting CdZnSe/ZnSe quantum dots synthesis and application for quantum dot light emitting diodes, Opt. Mater. Express 7 (11) (2017) 3875–3884.
[64] F. Wei, X. Lu, Y. Wu, Z. Cai, L. Liu, P. Zhou, Q. Hu, Synthesis of highly luminescet CdTe/CdS/ZnS quantum dots by a one-pot capping method, Chem. Eng. J. 226 (2013) 416–422.
[65] Y. Wang, L. He, B. Yu, Y. Chen, Y. Shen, H. Cong, ZnO quantum dots modified by PH- activated charge-reversal polymer for tumor targeted drug delivery, Polymers 10 (11) (2018) 1272.