REVIEW PAPER

Quantum Dots in Therapeutic, Diagnostic and Drug Delivery Applications "A Brief Review"

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Abstract: *Synthesis of materials at nano scale is one of the main challenges in nanotechnology for different applications such as semiconductor, superconductors, electro-optics devices, advanced ceramics, refractories, diagnostic imaging and drug delivery. Semiconductors nanocrystals, known as "Quantum Dots", have emerged as new generation of nanomaterials due to their unique optical, electrical and electrochemical properties for variety of applications such as contrasts agents, fluorescent labels, localized targeted drug delivery and new generation of biosensors. Quantum dots advantages over traditional nanomaterials are due to quantum confinement effect, which bring broad absorption spectra, superior brightness and durability for different applications. The most important factor in developing nano carriers for biological applications is the toxicity, so recent researches have been focused on heavy metal-free formulations and nontoxic ceramics and polymers. So, one of the main goals in this paper is to explicate efficiencies and deficiencies of recent advances in quantum dot based formulations with the least toxicity for bioimaging, therapeutic and drug delivery applications. Another area of quantum dot's application is the determination of dopamine (DA). Due to basic role of DA in some diseases like Parkinson and Schizophrenia, its determination is important and thus, it is desirable to develop new, simple and rapid analytical methods for the determination of DA with high selectivity and sensitivity, especially for diagnostic applications. Recently, developments in nanotechnology and preparations of semiconductors quantum dots cause open a new field in photo-electrochemical methods based on semiconductors quantum dots for determination of DA. In this review, an attempt was made to elaborate the mentioned goals of the paper in details.*

Keywords: *Quantum Dots, Diagnostic, Toxic; Therapeutic, Contrast agents, Graphene, Drug delivery.*

1. INTRODUCTION

Quantum dots are zero dimensional nanomaterials with size ranging from 1 to 20 nm which is comparable to Bohr radius of the exciton and causes to three dimensional quantum confinement effect. Restricting electron movement in three dimensions makes the electronic configuration of quantum dots similar to that of atoms, that is why some expert calls quantum dots "artificial atoms" [1, 2]. Quantum dots have been emerged as contrast agent in cellular bioimaging and nano carrier for therapeutic purposes due to their unique electrical, optical, electrochemical and physicochemical properties [2-4]. Detection of nano carrier entrance to cells and its interaction with cellular processes is the key point in drug discovery and developing new drug delivery systems [2]. Fluorescence property of quantum dots makes it conceivable to trace nano carrier and molecular mechanisms for diagnosis and therapeutic applications via drug or gene therapy[5]. Quantum dots advantages over traditional fluorescent dyes are their narrow emission spectra, size tunable emission wave length due to quantum confinement effect, broad absorption spectra, superior brightness, very high and controllable electrical and optical properties and durability to photo-bleaching. For example, designing bio-conjugated quantum dots to target special biomarkers can provide simultaneous diagnostic imaging and therapy through targeted drug delivery. Quantum dots of group II-VI including CdSe, CdTe, CdS as well as graphene quantum dots (GQD) have dedicated the most research in bioimaging, therapeutic and targeted drug delivery applications among other quantum dots [6, 7, 8] whereas the toxicity of some atoms such as Cd ions has been proved both in vitro and in vivo [9, 10]. Thereupon; recently group III-V and Cd-free quantum dots such as InP [11-16] and $CuInS_2$ [17-19] have attracted much attention in biological applications to develop safer formulations.

Graphene, with extraordinary properties such

as high specific surface area, high mechanical flexibility, thermal conductivity, unique optical properties, excellent electrical conductivity, and high mobility of charge carriers one of the most studied materials in the past 30 years [20-23] Graphene, graphene oxide (GO), reduced graphene oxide (RGO), functionalized graphene oxide (FGO) and graphene quantum dots (GQD) with these exceptional properties, when mixed with other materials such as ceramics or polymers, improve their electrical properties [24-28]. On the other hand, although single-layer graphene has a zero band gap, but with increasing the number of layers and formation of oxygen groups and structural defects, it acquires a band gap and alter its optical, electrochemical and electro-optical properties. For example, it can provide photoelectric activity [29-31]. Due to basic role of (DA) in some diseases like Parkinson and Schizophrenia, its determination is important and thus, it is desirable to develop new, simple and rapid analytical methods for the determination of DA with high selectivity and sensitivity, especially for diagnostic applications [32,33]. One of the candidates for this purpose is GQD.

In this article, recent advances in development and applications of a few quantum dots for simultaneous diagnosis, therapy and localized targeted drug delivery, have been discussed.

2. QUANTUM DOTS FOR BIOIMAGING APPLICATION

One of the main Quantum Dots characteristics for bioimaging application is their optical Properties. Restricting the size in three dimensions result in discrete electron states emersion and quantum confinement effect [34]. Unique optical, electrical and electrochemical properties of quantum dots are due to quantized energy levels of electrons that lead to size-tunable emission wavelength and makes quantum dots convenient fluorescent probes [3, 35]. Fluorescence criteria for bio-labeling are the expanse of absorption and emission spectrum, photo stability and deterioration lifetime. Conventional dyes deficiency as bio-label, especially for multiplexed analysis is their narrow excitation and broad emission spectra, short life time and low signal to noise ratio. Narrow excitation spectrum leads to specific wavelength requirement for excitation of each in multiple dyes. Overlapping the emission spectra of different dyes is the result of broad emission spectrum that limits the multiplexed analysis. Monitoring simultaneous multiple-labeled biological molecules is possible using quantum dots as bio-label due to their broad excitation and narrow emission spectrum and excitation of quantum dots with different emission wavelength is feasible via single source of light [36-37]. Emission wavelength of quantum dots can be tuned via alteration of core size, composition and surface chemistry from ultraviolet (UV) to infrared (IR), the best window for bioimaging because body tissues are transparent in this range [38]. Moreover quantum dots have higher photo stability and brightness in compared with conventional dyes and they can endure several consecutive excitation and emission cycles [3, 4, 35, 37-41]. Higher molar extinction coefficients of quantum dots in compare with organic dyes leads to improved brightness of the quantum dots [42]. Quantum yield of bio-conjugated quantum dots is preserved and it is higher than bio-conjugated organic dyes, howbeit the quantum yield of fluorescent dyes can reach 100% in absence of biological molecules [37]. The core material of core/shell quantum dots is responsible for optical properties of the collection but the low quantum yield and stability of the core makes it inapplicable for bioimaging probes. Improvement of optical properties and quantum yield of the core has been accomplished by coating it with another semiconductor with wider band gap through surface passivation [37, 43-44].

Graphene is a symbol of a stable two-dimensional structure and is known as a basic part of graphite, a flat monolayer of honeycomb carbon atoms. Distance between each carbon atom with σ bond is about a =1.42 °A from its three neighbors. The fourth bond is a π-bond in vertical direction out of the plane. All π-bonds from each atom are hybridized together to form π and π* bands. Graphene is a name given to a flat/2D monolayer of sp2 bonded carbon atoms closely packed into a honeycomb lattice with a nearest neighbor distance of 0.14 nm. Graphene can be considered as the mother structure of all the carbon based materials. It has been generally used in the approximation of the crystal structure and properties of graphite, carbon nanotubes and Bucky balls. For instance, graphite is made up of loosely stacked (ABAB type) graphene layers

with an interlayer distance of 0.34 nm. This large interlayer separation, compared to the in-plane nearest neighbor distance, makes graphite a quasi 2D system. Carbon nanotubes are usually considered as graphene layers rolled into hollow seamless cylinders and a C60 Bucky balls can be considered as a graphene sheet, where some hexagons are replaced by pentagons, which cause a crumbling of the sheet into a final formation of a graphene sphere or a graphene football. Graphene has been extensively studied in the last several years despite the fact that it was discovered only several years back, for the first time. Andre Geim and Konstantin Novoselov won the 2010 Nobel Prize in Physics for this trailblazing discovery (Fig. 1) [45, 46].

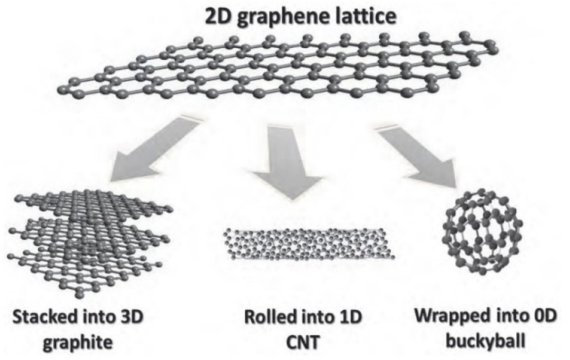

Fig. 1. Graphene, mother structure of various carbon based materials [45, 46].

The electronic properties of graphene are originated from these bands. The charge carriers can move on the thousands interatomic distances of honeycomb without scattering. Optical properties of different graphene systems have been widely investigated. The optical transmittances for monolayer and bilayer graphene are reported to be around 98% and 96% in the visible range. Also, graphene is a zero-gap semiconductor with a very high Fermi velocity VF = 106 m/s and individual graphene sheets have very high in-plane conductivities. The best optical property was observed in GQD. GQDs have high stability and can be dissolved in most polar solvents. Because of fine biocompatibility and low toxicity, GQDs are demonstrated to be excellent bioimaging agents. In theoretical and experimental studies, quantum confinement and edge effects of "small" graphene (less than 10 nm) have shown to induce photoluminescence (PL) [47,48, 49]. Graphene quantum dots have been developed for bioimaging applications in many research groups [8, 50]. Strongly fluorescent graphene quantum dots (GQDs) have been prepared by one-step solvothermal method with PL quantum yield as high as 11.4% in this study [8, 50]. Choi et al [51] presented a solution method to prepare emissive hybrid quantum dots (HQDs) in which zinc oxide core is covered by a single graphene layer shell. They presented photoluminescence spectra at 300 K for the ZnO–GQDs, poly-TPD and pure ZnO QDs. The PL peaks for the pure zinc oxide QDs and poly-TPD were located at 379 nm (3.26 eV) and 460 nm (2.69 eV) wavelengths, which are in agreement with the values of excitonic emission with a band gap. There were two extra emissions peaks at 406 nm (3.05 eV) and 432 nm (2.86 eV) wavelengths for the ZnO–GQD quasi core shells, in which the peak positions are different from pure zinc oxide. It is believed that these peaks can be used for bio imaging application. The optical properties and correlation between band gaps are presented in Fig. 2.

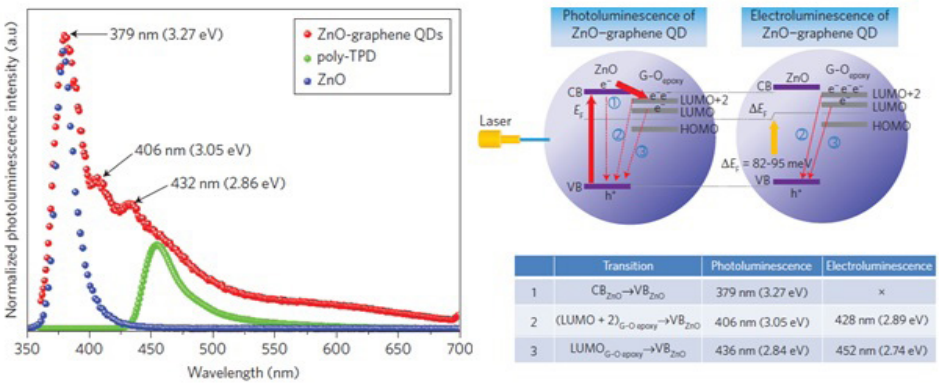

Fig. 2. Optical characteristics of ZnO–graphene quasi core shell [8, 50].

3. BIO-CONJUGATED QUANTUM DOTS IN TRACEABLE TARGETED DRUG DELIVERY

Localized drug delivery is one the main issue and concern in medical treatment to lower the side effects of chemotherapy and other methods. There are many ways for targeted drug delivery, such as: through pH control, via temperature control, using optical waves, application of ultrasonic waves and using magnetic field. Different nanoparticles have used for the targeted drug delivery which have been shown in Fig. (3). Fig. (4) shows a few targets for localized drug delivery [52].

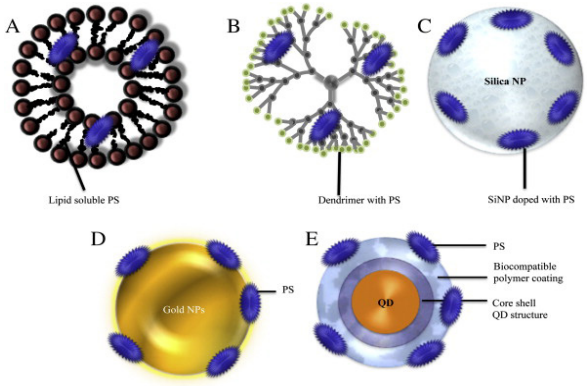

Fig. 3. Different nanoparticles used for localized drug delivery [100-101]

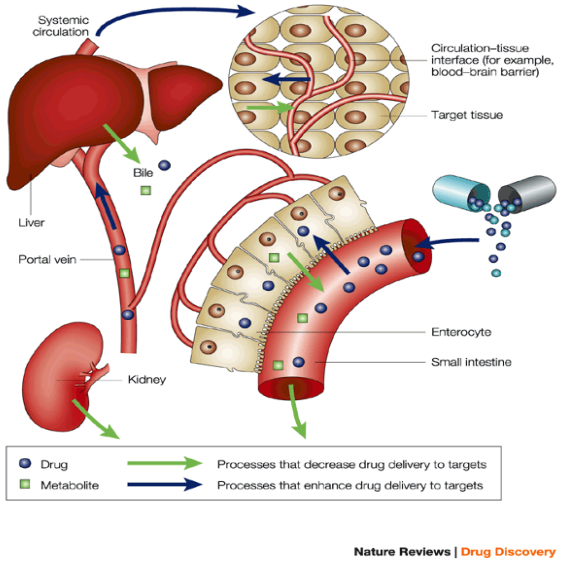

Fig. 4. A few targets for localized drug delivery [52]

Targeted delivery of therapeutic agents requires cell membrane penetration that is impermeable to hydrophilic species. Some proteins and peptides have been shown that are capable of penetrating cell membrane and delivering the bio-conjugated nano carrier including quantum dots. Cell penetrating peptides (CPPs) are the most popular bio-molecules used for ingression of nano carriers comprising therapeutic agents [5, 53]. Most of the proteins, nucleic acids, toxic therapeutic drugs and liposome are compatible with CPPs, so it can be used for a variety of cargoes delivery [17, 54]. Nevertheless some studies assert that optimizing some factors including size, charge and surface properties of quantum dots ultimate internalization to cell without need to bio-fictionalization. They showed that positively charged quantum dots penetrate the cells readily and the larger quantum dots are maintained in cytoplasm whilst the smaller ones go through nucleus [55, 56]. Pursuant to the target, conjugated bio-molecule to quantum dot should be selected. For targeting special antigens, quantum dot should be functionalized with appropriate antibody. As well as recognizing a peculiar receptor exclusive to any kind of cell needs quantum dot bio-conjugating to proper molecule ligand, peptides or aptamers [57]. Quantum dots functionalized with foliate is the most studied bio-conjugation to target foliate receptor, over expressed in many types of tumor cell [7, 11, 58-59]. Likewise functionalized quantum dots could be act as a specific bio-molecule sensor like sugar maltose by quantum dot surface conjunction to protein with binding affinity to maltose [36, 54]. Recent researches have shown the capability of quantum dots in targeted delivery of drugs to peculiar cells and tracing the fate of drug simultaneously. Chakravarthy et al. approved doxorubicin delivery of functionalized quantum dot to alveolar macrophages, critical cells in pulmonary diseases [6]. Savla et al. used conjugation of quantum dots-mucin 1 aptamer for targeting ovarian cancer cells and delivery of doxorubicin anti cancer drug [60]. In vitro release of temozolomide, anticancer drug conjugated to quantum dots, was also demonstrated by Wu et al. [58]. Quantum dots encapsulated in biodegradable polymers like chitosan are appropriate candidate for targeted delivery of anti cancer drugs. Encapsulating quantum dots in chitosan prevent drug release before attaching to target cell membrane [61]. Effect of quantum dot size on its emission spectra makes it beneficial for simultaneous multicolor imaging of different parts in the body [62].

4. CADMIUM FREE QUANTUM DOTS IN BIOLOGICAL APPLICATIONS

Most of the last decade researches on bioimaging and therapeutic applications of QDs have been focused on cadmium based QDs despite the cyto-toxicity of cadmium. Recently some studies on toxicity of Cd-based QDs have impelled researchers to develop toxic elements-free QDs for biological applications. CdTe quantum dots recognizable cyto-toxicity in PC12 and N9 cell have been demonstrated even at low concentrations [15, 55].V. Brunetti et al. [9] studied the toxicity of water-soluble InP/ZnS and CdSe/ZnS quantum dots both in vitro and in vivo. Different concentrations from 1pM to 5nM of InP/ZnS and CdSe/ZnS QDs toxicity on epithelial cell line A549 and neuronal cell line SH SY5Y was investigated and cell viability decrease was higher in cell lines incubated with CdSe/ZnS QDs. Toxic effect of CdSe/ZnS quantum dots on cell lines was obvious even at 1nM concentration after 24hours lapse, whiles InP/ZnS QDs showed inconsiderable decline in cell viability at 5nM concentration after 48h incubation. Release of Cd ions is the main reason of CdSe quantum dots even in the presence of ZnS shell around CdSe core, in contrast InP/ZnS quantum dots showed better biocompatibility [8]. Cadmium toxicity is due to its DNA-damaging effect and some studies claim that reactive oxygen species formation leads to cell death in presence of cadmium. Actually cadmium agglomerates in calcium channels of cell membrane and hinders the formation of DNA, RNA and proteins [10]. Drawing a conclusion from cyto-toxicity researches on quantum dots is difficult because each type of QDs encompasses different cyto-toxic effect owing to the variety in physicochemical properties of various QDs and multifarious test methods used for studying cyto-toxicity of quantum dots [63]. Inspiring cadmium base quantum dots in nano gels [58, 64] and coating with polymers [36] could decrease the risk of cadmium ion release in biological applications [65], however the harm of Cd, Pb or Hg elements for the environment and human health is inevitable. Accordingly, recent researches have been focused on toxic elements-free quantum dots biological application. The most studied Cd-free quantum dots are InP/ZnS [11, 15], AgInS2/ZnS [66], CuInS2/ZnS [18, 67] and ZnO [61].

Conjugating QDs with special molecules leads to achieve higher efficiencies of nano carrier penetration through particular cell membranes. Bharali et al. synthesized foliate conjugated InP/ZnS QDs in order to study the uptake of them in foliate-receptor containing cell lines using confocal microscopy (Fig. 5) and the bio-conjugated InP/ZnS QDs potential for profound in vivo imaging of tissue was indicated. Human KB cells (nasopharyngeal epidermal carcinoma cells) with over expressed foliate receptor surfaces was used versus foliate receptor deficient human A549 cells (lung carcinoma) as negative control to monitor the effect of folic acid on targeted delivery of nano carrier into calls [11].

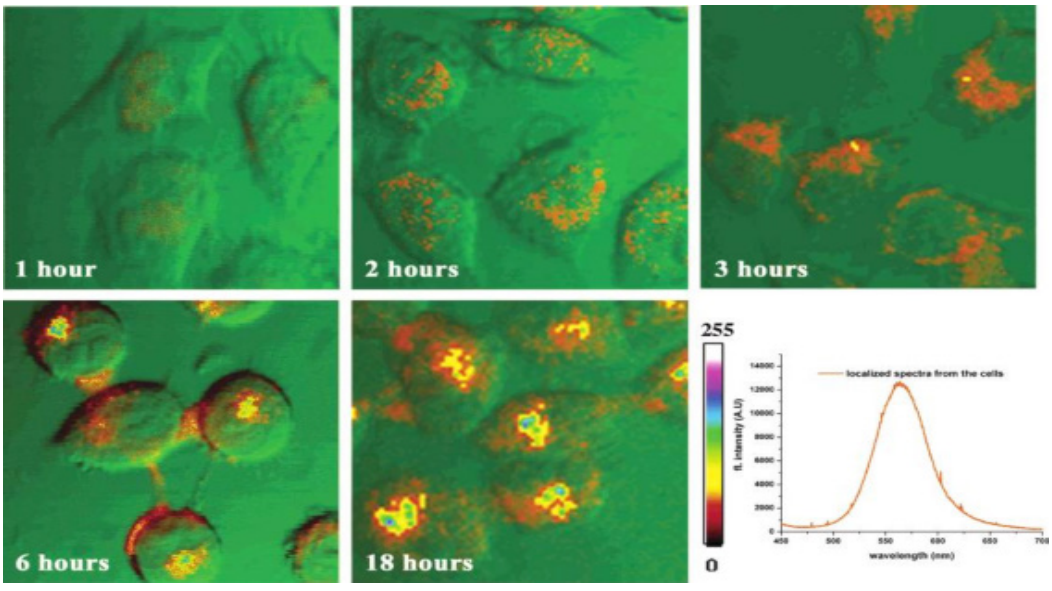

Fig. 5. Folate conjugated InP/ZnS QDs uptake in folate-receptor containing cell lines confocal images [11].

Functionalization of quantum dots with particular mono clonaland polyclonal antibodies of any type of cancer cells make it possible to trace the delivery of anti cancer drug or gene therapy more specific. Yong et al. demonstrated the antibody- conjugated InP/ZnS quantum dots susceptibility to in vitro targeting of pancreatic cancer cells. Water dispersible InP/ZnS quantum dots [14]. Potential of InP/ZnS QDs functionalized by carboxyl group and polyethylene glycol, for bioimaging and drug delivery was demonstrated by Liu et al. and cell penetrating peptides (CPPs) was used for in vitro internalization of bio-functionalized quantum dot to human A549 cells [13]. Hussain et al. showed the internalization of InP/ZnS quantum dots synthesized using PEG as recycling solvent for the first time to HeLa cell lines confirmed by fluorescent microscope [12].

$CuInS_2$/ZnS quantum dots are among more studied cadmium-free quantum dots. Foda et al. demonstrated the biocompatibility of $CuInS_2$/ZnS quantum dots as contrast agent for imaging of live HeLa cell lines. Lipophilic silane micelles and silica shell on quantum dots were used for transferring them into aqueous solution. Further fictionalization of quantum dots was accomplished by attaching holo-transferring (Tf) to water dispersible $CuInS_2$/ZnS quantum dots [68]. $CuInS_2$/ZnS quantum dots can be synthesized directly in aqueous media without need for further changing of quantum dots surface chemistry to transfer them into aqueous solution in order to be applicable in biological media. Potential of $CuInS_2$/ZnS quantum dots synthesized via aqueous route for a disease biomarkers diagnosis specially cancer had been shown by Xiong et al. [69]. MUC1 aptamer functionalized $CuInS_2$ quantum dots loaded with anti-cancer chemotherapy drug, daunorubicin (DNR), was used by Lin et al. for in vitro investigation of its potential for simultaneous cancer cell therapy and imaging [70]. $CuInS_2$ quantum dots can be used as fluorescence nano sensors for detecting special biological macromolecules like heparin and heparinase [71]. Also CuInS2 quantum dots functionalized with DA have been developed as fluorescence probes [18] and biosensor [72]. Another quantum dot among ternary semiconductor nanocrystals $AgInS_2$, conjugated with methotrexate (MTX) anticancer drug have been shown to possess low cyto-toxicity and effective uptake by Hella cells [66]. Folic acid conjugated $AgInS_2$-ZnS quantum dots capability in targeting HepG2 tumor cells via foliate receptors have been confirmed in vitro by Chang et al. [73].

In addition quantum dots are remarkable candidate for multimodal imaging applications. Rosenberg et al. demonstrated that attaching InP/ZnS quantum dots to MRI contrast agent is executable to make bimodal MR contrast agent with noticeable potential for tracking of fluorescence in high-field MR applications [16]. As well as quantum dots can be used in magneto fluorescent nanocomposites with multimodal attributes for imaging and therapeutic applications. The magneto fluorescent nanocomposite developed by Demillo et al. is composed of $MnFe_2O_4$ magnetic nanoparticles and $CuInS_2$/ZnS quantum dots and the capability of the resulted nanocomposite for biological applications have been revealed through physical, chemical and biological characterization [74]. Mn-doped $CuInS_2$/ZnS quantum dots susceptibility for bimodal bioimaging including fluorescence and magnetic resonance imaging (MRI) of tumors have been shown via in vivo experiments (Fig. 6) by Ding et al. research on nude mouse enduring subcutaneous tumor [17].

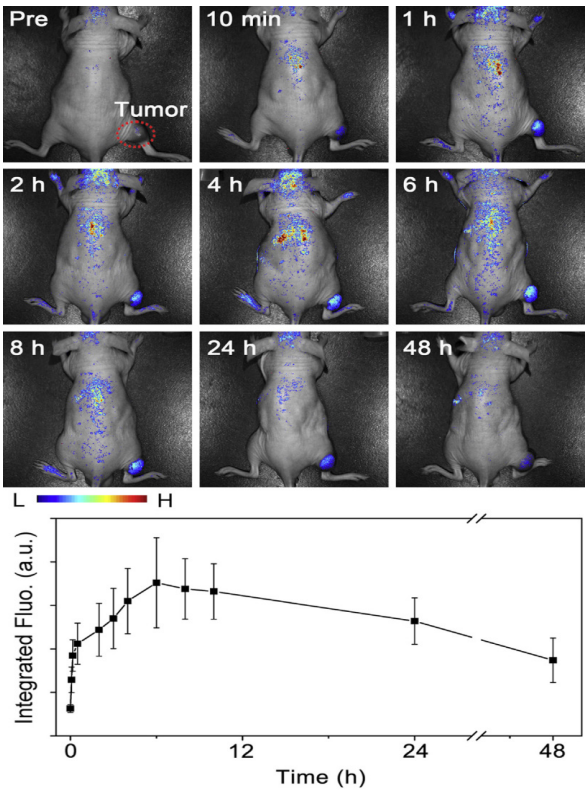

Fig. 6. In vivo fluorescent imaging of nude mouse enduring subcutaneous tumor at different times after injection. The graph in lower frame shows the temporal evolutions of recorded fluorescence signals of tumor [17].

The only deficiency of Cd-free quantum dots is their low quantum yields; however coating the core with multiple shells could solve the problem. Kim et al. demonstrated the effect of second shell on quantum yield of ZnSe/InP/ZnS capable of being applied in biological applications without remarkable toxicity [75].

5. SYNERGIC EFFECTS IN GQD NANOCOMPOSITES AS A BIOSENSOR

Graphene, graphene oxide (GO), reduced graphene oxide (RGO) and GQD with these exceptional properties, when mixed with other materials such as nano-ceramics, nano-metalic and nano-polymers, improve their electrical, optical and electrochemical properties. New nanocomposites with semiconducting property from Fe_3O_4, TiO_2, CeO_2 and SiO_2, and metallic nanoparticles (such as gold) along with GQD are gaining more attention in the biomaterials research and results are promising for many applications [76-84]. On the other hand, although single-layer graphene has a zero band gap, but with increasing the number of layers and formation of oxygen groups and structural defects (formation of GO or RGO), it acquires a band gap and provides photoelectric activity [85-91]. Therefore, synergistic effects of constituents of graphene-based nanocomposites are expected to improve the electrical, optical, electrochemical and photoelectric properties of nanocomposite [92-97].

Based on literature, the DA detection is limited due to the similarity of the oxidation potential of DA with Ascorbic acid (AA) and Uric acid (UA) (as shown in Fig. 7).

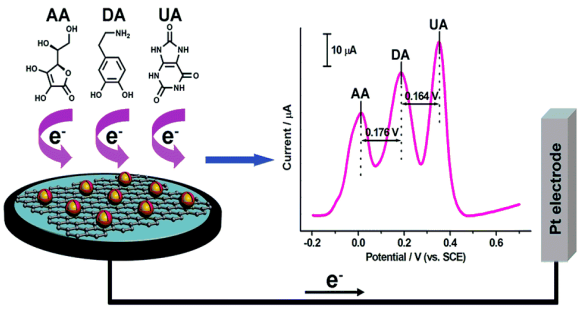

Fig. 7. The difference between DA with AA and UA [98]

In a study by nemati el al. [98, 99], a GQD contaning nanocomposite was prepared and the photo-electrochemical responses of a modified glassy carbon electrode with them was evaluated by electrochemical methods. A Titania-Ceria-GQD nanocomposite electrode was synthesized (Fig. 8) and characterized and their synergistic effect on the biosensor performance was evaluated. The modified electrodes showed outstanding response in the present of light in comparison to dark condition towards DA. Affecting parameters like pH, bias potential and DA concentration on photo-electrochemical responses of the modified electrodes were studied. Linear ranges, Fig. of merits and detection limits of the modified electrodes by the prepared semiconductors were calculated and compared with together. Figs. 9 and 10 show the XRD and PL analysis of the synthesized GQD. Fig. 11 shows the PL analysis of the synthesized nanocomposites. Fig. 12 shows the electrochemical behavior of the biosensors for the detection of DA.

Fig. 8. Schematic presentation of preparation processes for TC-GQD

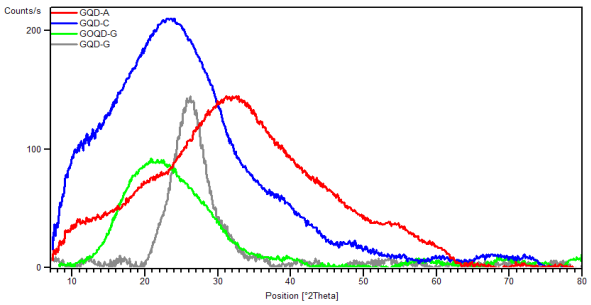

Fig. 9. XRD analysis of GQDs

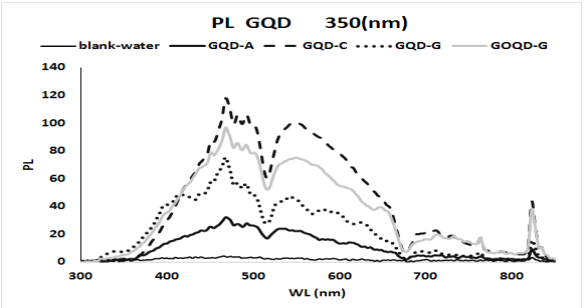

Fig. 10. PL analysis of GQDs:

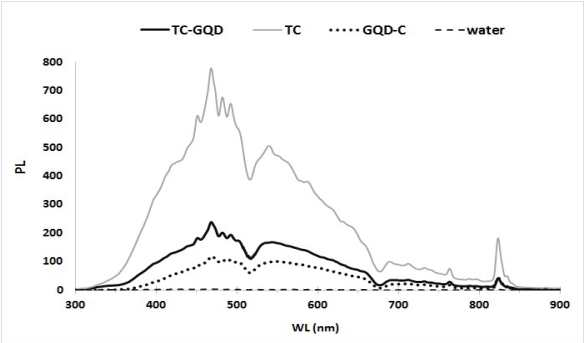

Fig. 11. PL Analysis of nanocomposites

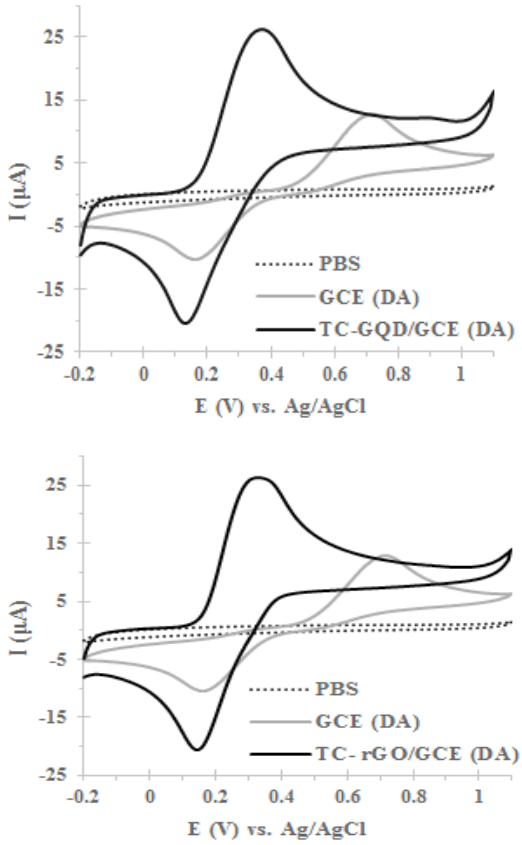

Fig. 12. Electrochemical characteristics of the biosensors for the detection of DA

The results indicated that selection of" Titania-Ceria-graphene quantum dot" nanocomposite with an electrical conductivity of about 89 (μS/cm) and an indirect band gap of approximately 1.3 eV in the production of photo-electrochemical biosensors to detect DA with wide linear detection range. A schematic model was proposed to show the synergic effect in this system in Fig. 13 [98-99].

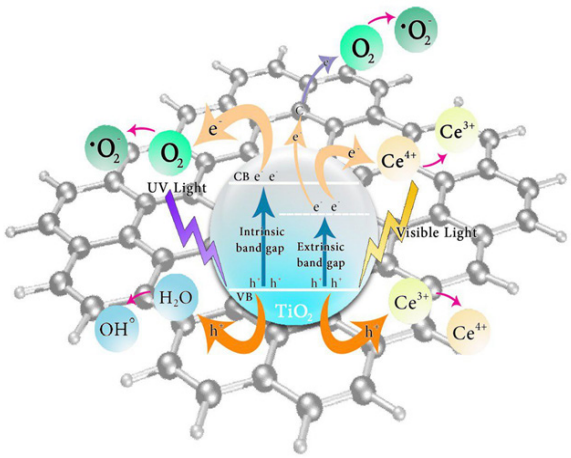

Fig. 13. Schematic presentation of synergistic effect of components on the photoelectric behavior of Ce-doped TiO_2-GQD nanocomposite [98, 99]

6. CONCLUSION

Unique optical and electrical and electrochemical properties of quantum dots have made them appropriate for many applications such as contrast agent for cell labeling, imaging and drug delivery. Quantum dots high surface area and its chemistry allow conjugation of different kinds of biomolecules in order to target specific cells and drug or gene delivery that can be traced because of fluorescent and electrochemical properties of quantum dots. So the fate of drug, gene or any kind of biomolecule could be followed after injection in vitro and vivo investigations. The most important matter in biological applications is cyto-toxicity and biocompatibility of nano carrier and developing nontoxic quantum dots and functionalizing of them with appropriate biocompatible species could solve many problems to make the resultant quantum dot applicable for simultaneous therapy and diagnosis. There is more to do on cadmium-free quantum dots field to approve quantum dots capability in vitro and vivo conditions. The results of the case study conducted for DA detection indicated that selection of "Titania-Ceria-graphene quantum dot" nanocomposite with an electrical conductivity of about 89 (us cm) and an indirect band gap of approximately 1.3 ev in the production of photoelectron-chemical biosensors to detect DA with wide linear detection range.

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