Progress in Chemical and Biochemical Research

Journal homepage: www.pcbiochemres.com

Review Article

A review on Bioimaging, Biosensing, and Drug Delivery Systems Based on Graphene Quantum Dots

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ARTICLE INFO

Article history

Submitted: 2020-06-28
Revised: 2020-09-03
Accepted: 2020-09-17
Available online: 2020-10-24
Manuscript ID: PCBR-2006-1102
DOI: 10.22034/pcbr.2020.237134.1102

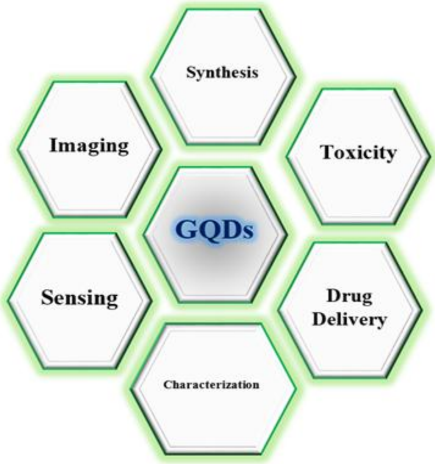
KEYWORDS

Graphene, Quantum Dots,
Nanotechnology,
Drug Delivery,
Bioimaging,
Biosensing

ABSTRACT

Graphene quantum dots (GQDs), which are the most capable carbon-based nanostructures, play a significant role in biological studies. These nanostructures show significant attributes including low toxicity, high solubility in numerous solvents, notable electronic characteristics, strong chemical inertness, high specific surface areas, and abundant sites for functionalization. In addition, GQDs have adaptability as well as capability to be improved via absorbent surface chemicals as well as the addition of modifiers or nanoparticles. Accordingly, we have presented here the fundamental properties, synthesis techniques, and the applications of GQDs in biosensing, bioimaging, and drug delivery. It is worth mentioning that toxicity is a significant issue which has restricted biological applications of QDs. Hence, the toxicological features of GQDs have been covered in this review paper.

GRAPHICAL ABSTRACT



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1. Introduction

No doubt, nanotechnology is one of the rapidly progressing fields which is penetrating in many areas of science[1-5]. Noteworthy, with the development of quantum dot (QD)-based optical methods, a dramatic revolution has taken place in medical investigations, particularly biological imaging and biomedical diagnostic applications[6-9]. Graphene quantum dots (GQDs), which are flat 0D nanomaterials, have received distinctive attention owing to their biocompatibility, abundant active sites, water solubility, low toxicity, bandgap opening due to quantum confinement, and better tunability in chemicophysical properties[10, 11]. These features have provided quite a few applications for GQDs such as biological imaging [12, 13], drug/gene delivery[14], antibacterial and antioxidant activity[15], fluorescence sensors[16-18], electrochemiluminescence sensors[19], and electrochemical sensors[20, 21]. Several studies have demonstrated that GQDs are capable of support charge transfer and transport which happen at the interfaces with electrolytes, reactants, or other nanoparticles and are facilitated by local active parts or sp2 carbon sites[22]. Therefore, the quantum-confinement effect and the difference in density and nature of sp2 domains obtainable in GQDs create their optical features which significantly depend on their dimensions so that the energy band gap of GQDs can be adjusted by controlling their size[23, 24]. In this review, we intend to discuss synthesis, optical properties, and cytotoxicity of GQDs. In addition, the recent applications of GQDs in three critical areas namely biomedical imaging, biosensing, and drug delivery are investigated and evaluated.

2. Synthesis of GQDs

In general, there are two techniques for the synthesis of GQDs: Top-down approaches and bottom-up methods. The top-down methods such as hydrothermal or solvothermal, assisted by microwave, sonication, electrochemical processes, laser ablation and chemical vapor deposition (CVD) techniques, include cutting down carbonic precursors into the micrometer-sized pieces. On the other hand, the bottom-up approaches are based on growing small molecules. The latter methods are suitable for modulating the size of GQDs but require multistep reactions and purification at different steps[25-27]. Small aromatic molecules, glutamic acid, glucose, and citric acid are common carbon precursors in bottom-up routs. Hydrothermal and solvothermal processes require water and oxidizing agents such as strong acids or alkali which are crucial to cut the carbon sources into GQDs. Although hydrothermal method is the most frequently used technique to fabricate GQDs, electrochemical techniques are more manageable and environmentally friendly which provide nanoparticles with the anticipated properties and structures. However, for the manufacture of nanoparticles with high level of reproducibility and scalability, laser technology is a practical, fast, and reliable technique that can be applied directly in liquid environments. It is worth mentioning that chemical vapor deposition is a widely employed method for synthesis of nanoparticles with monolayer structures and less deficiencies in the graphene sheets[28-30].

3. Sensing strategies based on GQDs

Recent studies revealed that the synthesized nanoparticles can be very attractive probes for biosensing applications[31-34]. Therefore, with progress in various methods of the synthesis of GQDs with remarkable attributes including high purity, controlled particle size and proper quantum yield, it was predictable that this type of nanoparticles would hold the capacity to obtain a significant position among the classes of nanoparticles used in biosensing applications, due to their biocompatibility, chemical reactivity, and suitability in size[35-39].

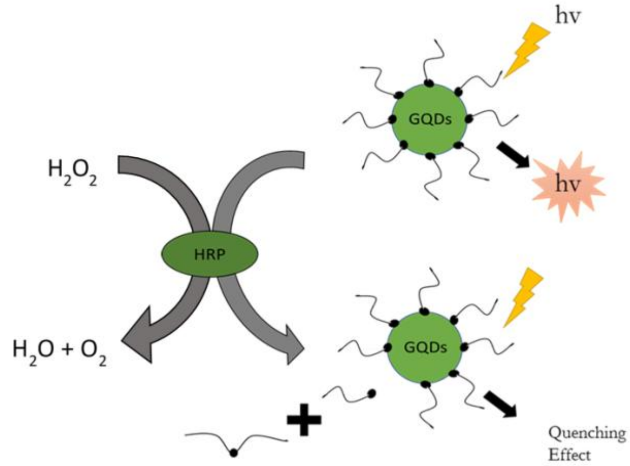

Figure 1. A schematic of the GQDs/HRP system in the presence of H2O2, where H2O2 quenched the GQDs and led to the reduction of the fluorescence intensity of the system. Reprinted from[40].

Mastar et al.[40] specified hydrogen peroxide (H2O2) content using GQDs-horseradish peroxidase (HRP) as a promising biosensor (Figure 1). According to their records, H2O2 can quench the emission intensity of GQDs system which is proportional to the H2O2 concentrations. G-quadruplex/hemin DNAzyme and caffeic acid can be used for uric acid fluorescence determination. Uricase can decompose uric acid to produce hydrogen peroxide allantoin. By calculating the concentration of hydrogen peroxide, detection of uric acid is indirectly possible[41]. Detection time is an essential parameter in sensing applications. To handle this item, Cui et al. explored determination and separation of circulating tumor cells (CTCs) using a magnetic fluorescence bio-sensing platform with GQDs, Fe3O4, and molybdenum disulfide (MoS2) nanosheets which was acting in a short time. They successfully fabricated the GQDs using electrochemical synthesis method and employed epithelial cell adhesion molecule (EpCAM) as the functional agent which reduced the detection time[42].
Moreover, GQDs are attractive nanomaterial for the construction of electrochemical sensors[43-45]. For instance, ZnO@GQD is a promising candidate for 6-mercaptopurine (6-MP) electrochemical sensing. To do so, the pencil graphite electrode (PGE) is coated with a sol-gel binder reinforced with polypyrrole (PPy) based molecularly imprinted polymer (MIP), and ZnO@GQD core-shell nanoparticles[46] (Figure 2).

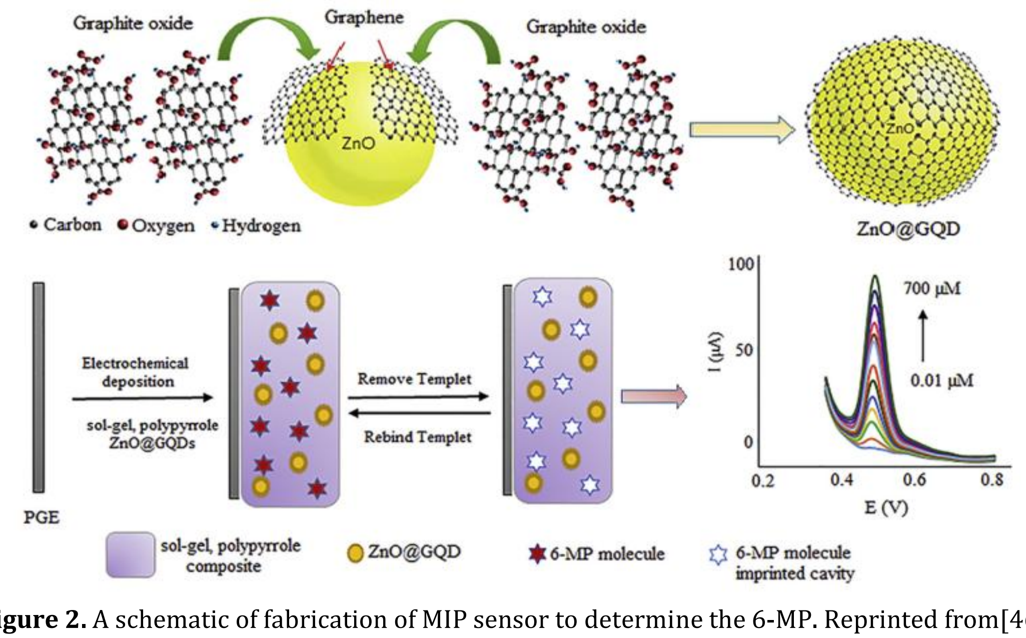

Figure 2. A schematic of fabrication of MIP sensor to determine the 6-MP. Reprinted from[46].

By a comprehensive study, Ag+ detection was explored by He et al. based on luminescence resonance energy transfer technique between sodium citrate functionalized upconversion nanoparticles (Cit-UCNPs, energy donor) and graphene quantum dots (GQDs, energy acceptor). Amino-labeled single-stranded DNA (NH2-ssDNA), which includes several cytosine (C), was conjugated on the Cit-UCNPs. By doing so, the upconversion luminescence can be quenched owing to the π–π stacking interaction between NH2-ssDNA and GQDs. In the presence of Ag+ and the creation of the hairpin structure of C–Ag+–C on the UCNPs, the π–π stacking interaction will be destroyed and GQDs will be separated from the surface of the UCNPs (Figure 3). By enhancing the upconversion luminescence, a "Turn-On" biosensing platform based on upconversion nanoparticles and GQDs can be constructed[47].

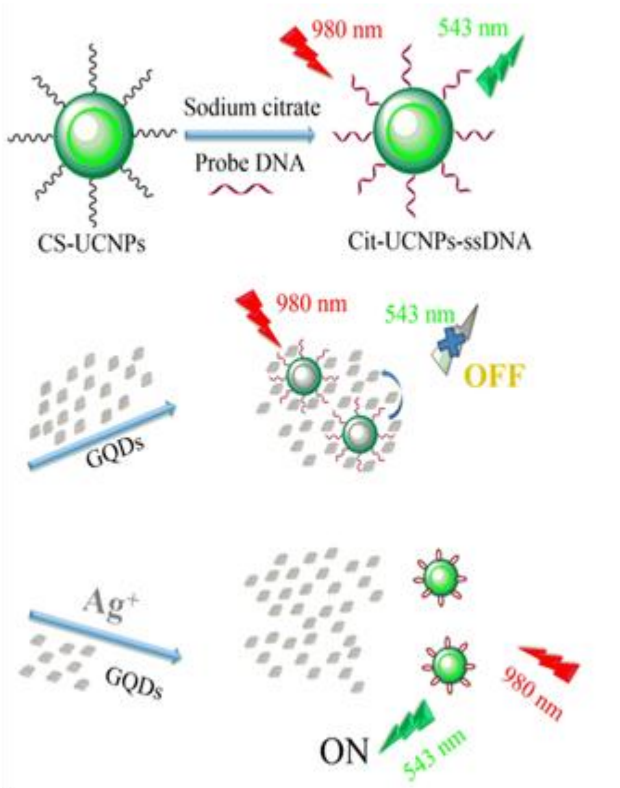

Figure 3. Schematic illustration of the upconversion LRET-based mechanism for the detection of Ag+. Reprinted from[47].

It has been reported that electrochemical sensors based on GQDs can be promising sensing techniques in the real samples. Li and associates studied hydrothermally fabrication of N-doped GQDs/N-doped carbon nanofibers (NGQDs@NCNFs) and its application in precise detection of nitrite. The mentioned electrochemical sensor was designed based on electrospinning, carbonization, and a hydrothermal method[48].

Although the GQDs have many applications in biosensing, GO and GO@QDs are the useful material for sensor constructing[49-54]. Cheeveewattanagul et al.[55] designed a novel biosensing approach using straightforward immunosensing platform based on Graphene Oxide-decorated nanopaper (GONAP), which works by a single antibody. GONAP quenches the fluorescence emission of CdSe@ZnS QDs complexed with antibodies (Ab-QDs). However, the emission is recovered upon immunocomplex (antibody-antigen) creation. The antigen is subsequently attached onto the GONAP surface operating as spacer between GONAP and Ab-QDs and obstructing effective nonradiative energy transfer. Noteworthy, the immunosensing platform can be turned "On" by pathogens and proteins (Figure 4).

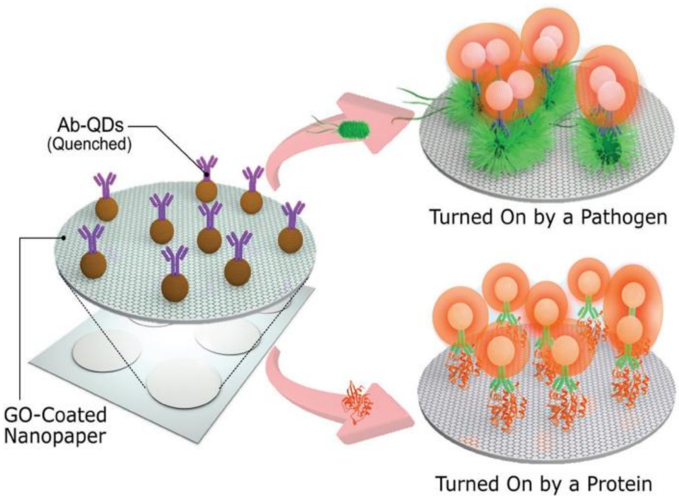

Figure 4. Operational concept of the immunosening approach. Reprinted from[55].

Photoelectrochemical biosensing of cell surface N-glycan expression based on the improvement of nanogold-assembled mesoporous silica amplified by GQDs[56] and pentaethylenehexamine and histidine-functionalized GQDs for ultrasensitive fluorescence detection of microRNA[57] are more examples for GQDs based sensors.

4. GQDs based drug delivery systems

Before development of nanotechnology, organic fluorescent dyes were considered to be as promising tools for bioimaging applications. However, recently introduced types of fluorescent nanomaterial changed the former understanding[58-60]. Quantum dots, which play a significant role in nanomedicine, enable accommodation of drugs, affinity ligands, and imaging moieties within a single nanostructure to reach targeted and noticeable drug delivery. These semiconductor nanoparticles not only enhance pharmacologic properties of existing therapeutics, but also facilitate delivery of different types of effective anti-cancer drugs for gene therapy and immunotherapy. In general, nanoparticle-based drug delivery systems reduce drug toxicity, develop bio-availability, improve circulation times, and control drug release as well as targeting. As a result, drug delivery based on nanocarriers offers various advantages over conventional drug delivery systems[61-65].

Coating mesoporous silica nanoparticles (MSNPs) with N-GQDs, loading with DOX, and then, coating with hyaluronic acid (HA) will lead to HA-DOX-GQD@MSNPs. The synthesized nanoparticles facilitate HeLa cells imaging by fluorescence microscopy[66]. Chiral GQDs, which have various types of applications in drug delivery, optoelectronics and bioanalysis, can be synthesized by covalent edge modification using levo/dextro cysteine. Carbodiimide/N-hydroxysuccinimide cross-linking between the carboxylic acid group on GQDs and amine group of cysteine can provide chiral center on GQDs. These structures can interact with cells and biological molecules depending upon the chirality of attached stereoisomer[38]. Hence, chirality has a significant role in biological activities, toxicity determination, and enatioselective reactions. Toxicity is an important parameter in fabricating nanocarriers for drug delivery purposes. Various in-vivo and in-vitro studies have demonstrated that GODs can be the biocompatible and non-toxic nanocarriers for delivering a drug. However, many methods for reducing cytotoxicity of GQDs are reported based on encapsulating GQDs in a PEG nanoparticle[67]. In addition, GQDs provide the active sites by oxygen-containing groups on the surface and a large specific surface area, effectively carries the drug molecules[68, 69]. Therefore, in comparison with graphene and GO, GQDs enjoy some unique properties. With regard to cancer therapy, multifunctional GQDs can be used as drug carriers and targeted cellular imaging simultaneously. It is possible to handle a drug delivery system in the cells in real time based on the inherent fluorescence of GQDs without using external fluorophores[11]. In addition, GQDs are prosperous nanostructures for numerous optical and luminescence based applications by providing quenching mechanism of FRET[70]. Fluorinated Graphene Oxide (FGO) is a new nanocarrier which controllably and precisely can deliver single or mixed anticancer drugs. Synthesis of FGO by mild process and modifying its surface with oxygen groups, and then functionalizing its structure with folic acid (FA) pre-linked amino-polyethylene glycol (PEG) can provide a proper strategy for cancer cells[71] (Figure 5). Poly(N,N-diethyl acrylamide)/ functionalized graphene quantum dots hydrogels loaded with doxorubicin as a nano-drug carrier for metastatic lung cancer[72] and using graphene quantum dots based systems as HIV inhibitors[73] are other examples of drug delivery systems based on GQDs.

5. Biological imaging based on GQDs

Because QDs are more resistant to degradation than other optical imaging probes, bioimaging based on quantum dots have attracted great attention in recent years. Hence, this type of fluorescent nanoparticles allows the cellular procedure tracking for longer period of time and provide decent contrast for imaging under electron microscope due to an increasing scattering nature[74]. However, concerns of toxicity are noticeable among semiconductor QDs, and restricted their imaging applications. Therefore, several techniques, such as surface modification and polymeric coating have been offered to reduce the semiconductor QDs' toxicity[75]. Recent reports have demonstrated that GQDs can be a reliable choice for cellular imaging with a visible excitation wavelength due to their luminescent properties, low toxicity, and high solubility[76]. Nurunnabi et al. synthesized photoluminescent GQDs based on an oxidation process, and coated them with polydopamine (pDA) to improve their luminescence stability in water and reduce their toxicity in vivo. Then, they evaluated in vitro and in vivo biocompatibility of pDA-coated GQDs in nude mice. The obtained results revealed that pDA-coated GQDs can be a promising candidate for optical imaging and drug delivery[77]. Table 1 shows more studies in biological imaging based on GQDs with the details of probe type, precursor, method of synthesis, and cells.

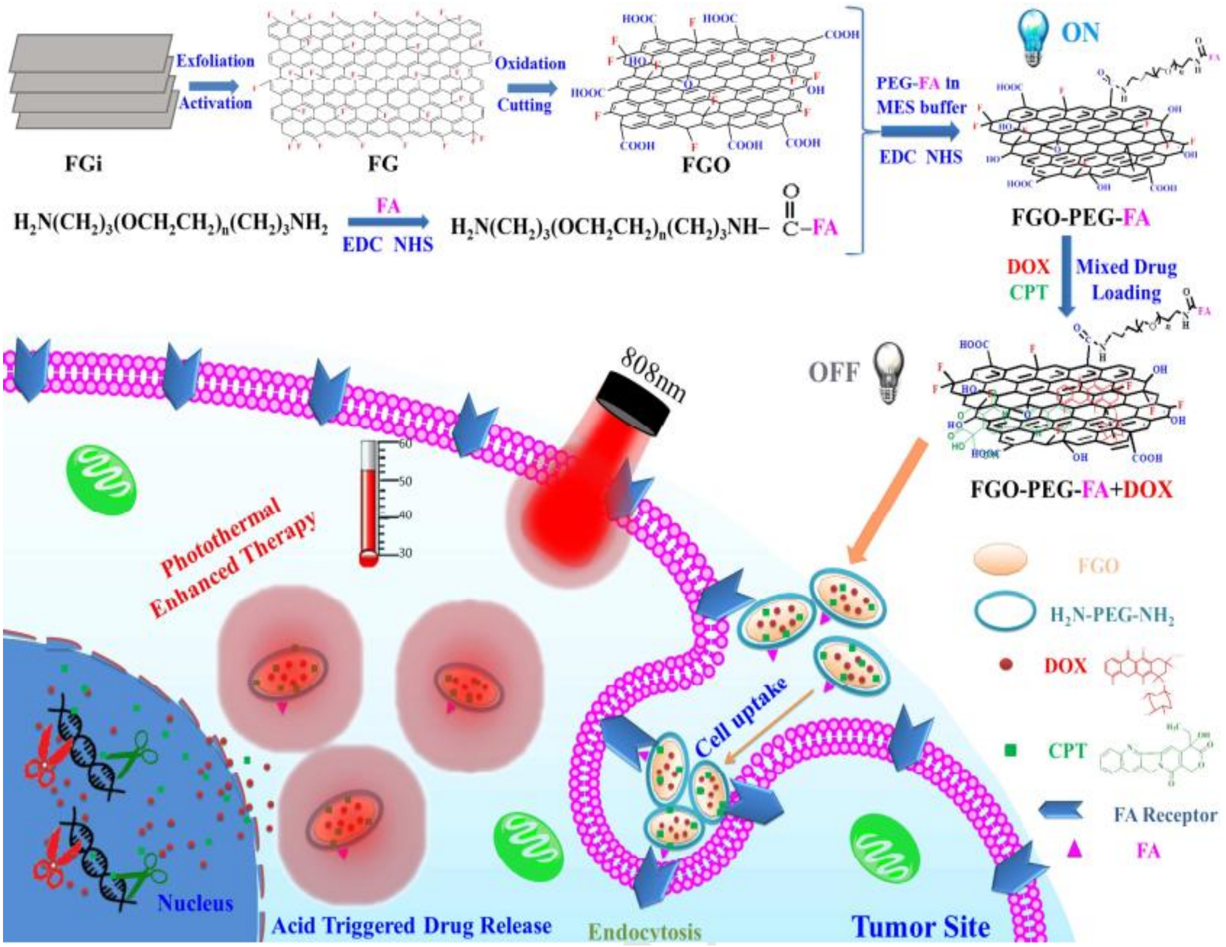

Figure 5. Schematic illustrations of synthesizing FGO-PEG-FA for targeting delivery of single or mixed anticancer drug of DOX and CPT. Reprinted from[71].

Table1. Biological imaging based on GQDs.

REF.	PROBE	PRECURSOR	METHOD OF SYNTHESIS	CELL
[42]	aptamer@Fe3O4@GQDs@MoS2	Graphite rods	Electrochemical	A549, Hep G2
[78]	N-GQDs	Citric Acid, PVP K90, Glutamate	Hydrothermal	MCF-7
[79]	GQDs-GO	GO	Hydrothermal	A549
[80]	N-GQDs	GO, Ethylenediamine	Hydrothermal	Hela
[81]	GQDs-Bi NP	Citric Acid	Pyrolysis	HeLa
[82]	Galactose- GQDs	Pyrene	Hydrothermal	HepG2, MCF-7, HeLa, MCF-10A
[83]	DOX-GQDs-RGD	GO	Hydrothermal	U251 Glioma
[84]	GQDs-PEI	Pyrene	Hydrothermal	Hela
[10]	S-GQDs	Citric Acid	Hydrothermal	Hela
[85]	GQDs	Grape seed extract	Thermal	L929, HT-1080, MIA PaCa-2, HeLa, and MG-63
[86]	GQD-DNPTYR	Pyrene	Hydrothermal	MCF-7
[87]	N,P-GQDs	THPC and PEI-EC	Hydrothermal	T24
[88]	GQDs/AgNPs	Citric Acid	Pyrolysis	L-02
[89]	Cl-GQDs-N	D-fructose	Hydrothermal	MDA-MB231
[90]	GQDs-scFvB10	CX-72 carbon black	Chemical oxidation	MDA-MB-231
[91]	GQDs-PEG	GO	Hydrothermal	A-375, Hela
[92]	GQDs	Neem plant root Extract	Hydrothermal	RAW
[93]	Fe3O4@SiO2@GQD-FA/DOX	Citric Acid	Pyrolysis	Hela
[94]	Boron- GQDs	4-vinylphenylboronic acid (VPBA) and with boric acid	Polymerization and decomposition	SF763, BT474, and HEK293T
[95]	GQDs	1,3,6-trinitropyrene	Electron-beam irradiation (EBI)	MCF7
[96]	GQDs functionalized by SO_3^- and OH groups	Pyrene	Molecular fusion	MCF7, Hela
[97]	GQDs	Amine and sulfo groups	Hydrothermal	Hela
[98]	N-B-GQDs	3-aminophenylboronic acid monohydrate (APBA)	Thermal	SF763, 4T1, B16F10
[99]	GQDs-Fe/Bi NP	Citric Acid	Pyrolysis	HeLa, MCF-7

6. Conclusion

Fluorescence techniques are widely used in biochemistry[100]. Hence, because of their size which is comparable with the sizes of antibodies, fluorescent QDs have various applications in imaging, biosensing, and drug delivery. It is worth mentioning that toxicity is a critical issue in QDs based strategies[101, 102]. However, GQDs have an exceptional position among the QDs due to low toxicity, high solubility, high specific surface areas, and adaptability as well as capability to be improved via absorbent surface chemicalss[103, 104]. In other words, GQDs-based drug delivery systems reduce drug toxicity, develop bio-availability, improve circulation times, and control drug release as well as targeting. As a result, drug delivery, biosensing, and imaging based on GQDs offer various advantages over conventional systems. Nevertheless, further improvement in GQDs probes seems to be mandatory since some issues such as using QDs for in vivo applications of human, development of single nanocarriers, clinical applications, and QDs characterization are questionable.

Acknowledgments

The authors wish to express their gratitude to Farabi Research Center and Sharif University of Technology for supporting this work.

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HOW TO CITE THIS ARTICLE

Abdollah Khosravanian, Ahmad Moslehipour, Hossein Ashrafian, A review on Bioimaging, Biosensing, and Drug Delivery Systems Based on Graphene Quantum Dots, Prog. Chem. 4 (*2021) 44-56*

DOI: 10.22034/pcbr.2020.237134.1102

URL: http://www.pcbiochemres.com/article_118343.html