Journal of Drug Delivery Science and Technology 80 (2023) 104156

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review article

Properties and application of carbon quantum dots (CQDs) in biosensors for disease detection: A comprehensive review

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ARTICLE INFO

Keywords:
Carbon quantum dot (CQD)
Diagnosis
Biosensor
Nanotechnology
Cancer

ABSTRACT

In the areas of bioimaging and detection, biosensors have attracted extensive attention recently. Specifically, biosensors based on nanostructures provide a more sensitive detection due to their prominent properties. Different biosensors have used quantum dots (QDs) due to their unique properties, like high quantum yield (QY) and photoluminescence. In addition to possessing the advantages of common QDs, carbon quantum dots (CQDs) have a higher solubility, lower toxicity, and easier synthesis, making them highly useful and a promising candidate for biomedical applications. The CQD is a zero-dimensional nanostructure with a size of less than 10 nm in every dimension. The unparallel features of CQDs, including good biocompatibility and unique optical properties, like high photoluminescence (PL) and Quantum yield (QY), make them attractive candidates for biosensor and bioimaging applications. This review examines the recent advances in biosensors based on CQDs and presents the properties, challenges, and future perspectives to pave the way for further studies in the future.

1. Introduction

From biological applications such as cancer diagnosis to environmental applications such as heavy metal detection, and even agricultural applications, biosensors have recently gained a great deal of attention [1–3]. Early detection of cancer cases is very crucial for the efficacy of treatment. Detecting cancer at an early stage and discriminating it from inflammations and infections are among the limitations of the most common diagnosis methods [4]. Additionally, common diagnostic approaches are costly and time-consuming [5]. In order to solve these problems, researchers are developing biosensors and nanobiosensors as a fast, sensitive, and precise way to detect various types of cancer in their early stages with high accuracy [1,6]. Moreover, biosensors have been used extensively in environmental fields. In light of the increasing environmental problem of hazardous heavy metals, biosensors are being considered for controlling the ionic heavy metal content in wastewater via monitoring [7]. Since nanomaterials possess unique properties that have been employed to enhance the efficiency of biosensing systems, various biosensing and bioimaging systems, which have been extensively investigated, rely on nanotechnology and nanomaterials to achieve rapid, facile and sensitive detection, specifically for early disease detection [6,8].

Biosensors are devices containing three main components: a signal transducer, a signal processor, and a biological recognition element (bioreceptor) to selectively measure a biological or chemical analyte by converting the biological signal into a measurable signal [9,10]. The bioreceptor is a specific agent that attaches to the target analyte [11] that includes the biological molecular species or the living biological

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https://doi.org/10.1016/j.jddst.2023.104156
Received 12 August 2022; Received in revised form 7 December 2022; Accepted 3 January 2023
Available online 4 January 2023
1773-2247/

species such as antibodies, antigens, enzymes, DNA, RNA, aptamers, a phage particle, organelles, cell membrane receptors, and even the whole cell [10,12,13]. Biosensors based on transducers are classified into optical biosensors (different types of spectroscopy, e.g., phosphorescence, fluorescence, absorption, refraction, Raman, dispersion spectrometry, surface-enhanced Raman scattering (SERS), etc.), electrochemical biosensors, and mass-based biosensors that apply piezoelectric crystals to measure small mass changes. Finally, the signal processor illustrates the measured response [11]. Electrochemical biosensors, for instance, are widely used in biomedical and environmental monitoring [14]. In these biosensors, biochemical reactions between the analyte and the bio-receptor are converted to electrical signals as a measure of analyte concentration [15].

Nanobiosensors are biosensors based on nanostructured materials as promising tools for improved detection [10]. The nanobiosensor systems utilize at least one nanostructure material that improves the diagnosis of a specific biological analyte due to prominent properties, including good electrical and thermal conductivities, high surface-to-volume to incorporate the biomaterials, high stability, optical and magnetic properties, easy fabrication methods, high carrier capacity, capability to be used as a transduction element, large dynamic range and color tenability [16–18]. Furthermore, functional groups in nanomaterials structure increase the electroactivity of the electrode surface, leading to more stability in the bioreceptor loading at the electrode surface [6]. The mentioned prominent properties of nanobiosensors provide more sensitive and efficient detection with an improved response time [10,17].

Nanomaterials' unique physical, optical, and electrical characteristics, such as gold and silver nanoparticles, carbon nanotubes, graphitic carbon nitride nanosheets, magnetic nanoparticles, quantum dots, etc., provide unique opportunities for cancer biomarker sensing and imaging [19–23]. Recently, quantum dots (QDs) are nanostructures with distinctive properties that have been vastly investigated in bioimaging and biosensors. Compared to dyes and classic fluorophores, QDs have remarkable optical properties, including high quantum yield, excellent photobleaching resistance, wide absorption, narrow emission spectra, and specificity to biological analytes [24]. QDs possess an inorganic core with a 4–10 nm size range that can be based on various nanomaterials such as CdS, CdTe/CdSe, PbSe, PbS/Ag_2S, or MoS_2 [24]. Due to poor water solubility, low chemical stability, and cytotoxicity limitations of the organic core, the surface must be coated with a biocompatible shell [25,26]. However, surface coating leads to size enlargement, which may adversely affect its specificity. Due to their structure and prominent properties, a wide variety of biosensors have been developed based on carbon quantum dots (CQDs) for various diagnosis approaches [27]. Despite the advantages of metal QDs like cadmium-containing QDs (CdQDs) for biomedical detection, the toxicity of these metal QDs impedes their application. Thus, biocompatible CQDs in biosensors for disease diagnosis could be much safer than common QDs. Furthermore, CQDs' production costs are less than QDs as their counterparts [28]. CQDs are emerging carbon-based zero-dimensional nanomaterials below 10 nm with sp^2/sp^3 structure that have applications in many fields like medical diagnosis, including biosensors, biochips, drug delivery, bioimaging as well as photocatalysis, metal ion recognition, and wastewater treatment [2,27]. CQDs have applications in bioimaging, biosensors, drug delivery systems, gen delivery, organic solar cells (OSCs), light-emitting diodes, and catalysis [29]. In addition to biocompatibility, CQDs have fascinating properties that make them highly useful probes in biosensors. High surface area, electroactivity, conductivity properties, physicochemical stability as well as great optical properties are some properties that make them an ideal candidate for developing biosensors. For instance, the high photoluminescence (PL) of CQDs is an important property in photoluminescent biosensors [30].

It is crucial to explore properties, synthesis, and various biosensors based on CQDs in recent years to keep track of the progress made so far and figure out the remaining challenges for future studies. This review has taken a step toward exploring the recent studies on CQDs for biosensing platforms and presenting the challenges and perspectives that should be considered in future research on CQDs-based biosensors.

2. CQD-based nanostructures: properties

CQDs are carbon-core, zero-dimensional nanostructures with less than 10 nm in all dimensions with a quasi-spherical shape [26]. In 2004, CQDs were discovered inadvertently during the purification of single-walled carbon nanotubes (SWCNTs) [29]. CQDs possess excessive carboxyl groups in the edges of their structure that give them exceptional aqueous solubility despite carbon's low water solubility [31]. CQDs have poorer crystallinity due to having a lower content of crystalline sp^2 carbon and having more surface defects compared to graphene quantum dots (GQDs) as another category of zero-dimensional carbon-based nanomaterials [7]. The structure of CQDs enables them to be both electron donors and receptors so that they can be used in photocatalyst systems [32].

During the past few years, CQDs have gained much attention because of excellent features such as superior PL, significant fluorescence emission, exceptional optical properties, good conductivity, suitable photochemical stability, chemical, and physical stability, safety, good biocompatibility, high water solubility as well as low cost and easy fabrication and functionalization process [28,33]. Carbon quantum dots are appropriate for clinical research due to their advantages over QDs. Among these advantages are strong fluorescence properties, biocompatibility, and lower toxicity [34,35]. Furthermore, carboxyl, carbonyl, hydroxyl, and amino functional groups in CQDs' structure pave the way for modifying their chemical structure, which leads to more sensitivity and selectivity and also causes improved optical features via expanding excitation and emission wavelengths [36]. CQDs possess various optical properties like optical adsorption at UV and visible spectra ranges, fluorescence, phosphorescence, chemiluminescence (CL), and electrochemical luminescence (ECL) [34,36]. Up-conversion photoluminescence (UCPL) is another important optical property of CQDs with shorter wavelength emissions that originates from two or more photons absorption. UCPL facilitates cell bioimaging using two-photon luminescence microscopy and biosensing [37]. So, they have great potential to be used in bioimaging, biosensing, and drug delivery [37]. Moreover, they can be useful in catalyst and energy technology [29]. Furthermore, CQDs have easy and quick synthesis and functionalization methods similar to GQDs. The modification and functionalization of CQDs' surface could improve the optical and chemical properties to achieve a more sensitive biosensor [38,39].

CQDs' optical characteristics are contingent on the fabrication process conditions. Krysmann et al. fabricated CQDs via the thermal treatment of ethanolamine/citric acid precursor at different temperatures (180, 230, 300, and 400 °C). The carbonaceous cores arise at high synthesis temperatures, and dual PL property, including PL of molecular fluorophores and PL of carbonaceous cores, was observed. At lower temperatures, the PL is mostly originated from molecular fluorophores, while at higher temperature conditions, it is mainly or exclusively relevant to the carbonaceous cores [29,40]. Furthermore, the PL emission is affected by the various sizes of CQDs.

CQDs not only have applications in different medical fields such as biosensing, bioimaging, in-vitro bioimaging, photodynamic therapy, drug delivery, and wound-dressing but also play a role as the photocatalyst in environmental and water treatment applications [31,41–44]. As mentioned, good fluorescence emission and biocompatibility of CQDs are the key factors that make them efficient bioimaging agents in detection platforms [29]. Moreover, sp^2 hybridization of CQDs could cause π - π interaction with biomolecules and aromatic drug molecules [42]. CQDs also indicate antibacterial properties that could be applied in wound healing applications [41].

3. CQD-based nanostructures: synthesis methods

In recent decades, many synthesis routes have been proposed to fabricate CQDs using various reactants and precursors in different studies. Generally, there are two major routes for the synthesis of CQDs: the "bottom-up" and the "top-down" routes [31,45]. In the bottom-up synthesis route, small-sized molecules and compounds (precursors) like carbohydrates are used to fabricate complex structures. However, in the top-down synthesis route, large-sized carbon substances like carbon nanotubes undergo some changes to be split into and form small-sized CQDs (Fig. 1) [27,28,46,47]. CQDs are modified through a post-modification process regardless of the synthesis approach to improving their properties via surface functionalization and passivation [26]. CQDs have also been produced using boron doping [48] and sulfur doping [49].

3.1. Bottom-up synthesis approaches

Bottom-up synthesis processes include methods such as pyrolysis, thermolysis, thermal combustion, hydrothermal/solvothermal treatment (or hydrothermal carbonization (HTC)), and microwave irradiation [27]. The bottom-up processes are commonly green and eco-friendly compared to top-down synthesis routes [27]. For instance, in the solvothermal method, CQDs can be synthesized using environmentally friendly waste biomass precursors like vegetable and fruit peels, coffee grounds, paper waste, etc. [26,50]. One bottom-up method is carbonization, in which various precursors like biomass undergo hydrolysis and a chain of chemical reactions occur to form nucleation clusters followed by forming carbon particles in micrometer size [51].

For instance, Gosh et al. applied the HTC method to fabricate CQDs from sweet lemon peel. After drying the pieces of peels, they were processed at a hydrothermal reactor lined with Teflon at about 180 °C for 3 h, then they were cooled and brown-colored CQDs were obtained [52]. The hydrothermal/solvothermal methods are more common due to their high fluorescence quantum yield (QY), quick and scalable synthesis process, and being environmentally friendly. In the hydrothermal/solvothermal treatment method, CQDs are fabricated through a chemical reaction of precursors that occurs in the solvent media at a closed vessel under high pressure and temperature conditions (Fig. 2) [31,53]. The various precursors that have been used in the hydrothermal treatment method include citric acid, hyaluronic acid, ethylenediamine, D-galactose, bacterial DNA, chitosan, mercaptosuccinic acid, polyacrylic acid, etc. [54–57]. For instance, Campos et al. used D-galactose as the precursor for fabricating the CQDs via the hydrothermal process [58]. The properties of the CQDs differ according to the synthesis process, precursor, and conditions. For example, Jiang et al. fabricated N-CQDs with a hydrothermal treatment method. The carbonization of chitin was done for 10 h at 240 °C while ammonia (alkaline solution) was present in the reaction media. The addition of ammonia positively affected the synthesis process by increasing the degradation and carbonization as well as enhancing the QY from 17.6% to 25.8% compared to the sample prepared without ammonia [46].

Microwave irradiation is an inexpensive and fast method to synthesize photoluminescent CQDs. In this method, microwaves (electromagnetic waves with wavelengths ranging from 1 mm to 100 cm) are irradiated for differential heating of precursors to fabricate CQD structures [31]. Zhao et al. used polyethylene glycol with 400 Da molecular weight (PEG400) as both the precursor and solvent to produce CQDs via the microwave irradiation route. For this approach, they heated 40 ml of PEG400 inside a microwave reactor at 100 °C in the specific reaction time and exposed it to bubbling with air, N_2, O_2, and CO_2 during the reaction to study their effect on the CQDs properties. Using O_2 increased the PL and QY and decreased the reaction time [59]. Furthermore, the microwave irradiation method could be as the post-treatment stage to increase the PL property and improve the biosensing. Omer et al. applied microwave irradiation. CQDs were fabricated from L-Arginine through a solvothermal method inside a hydrothermal reactor to enhance the PL and QY of CQDs [60].

3.2. Top-down synthesis approaches

The top-down synthesis processes are based on harsh chemical routes, including laser ablation, electrochemical carbonization, chemical ablation, and mechanical milling [27]. These routes cause to split off of the large-sized carbon source, such as C60 fullerenes, to the small-sized CQDs units with <10 nm size ranges [27]. For instance, Fig. 3 demonstrates the carbonization formation of the metal-free form of CQDs and the metal-doped form of CQDs (M-CQDs) synthesis from tetraphenylporphyrin (TPP) precursor or its metal complexes, like Pt and Pd precursors [61].

In the chemical ablation method, the oxidization process is applied to control the splitting of the reactants to produce CQDs. However, chemical ablation is the most simple and convenient method to produce CQDs. Still, it has some disadvantages, such as a multi-step process, harsh chemical conditions, and poor control over size [62]. The laser

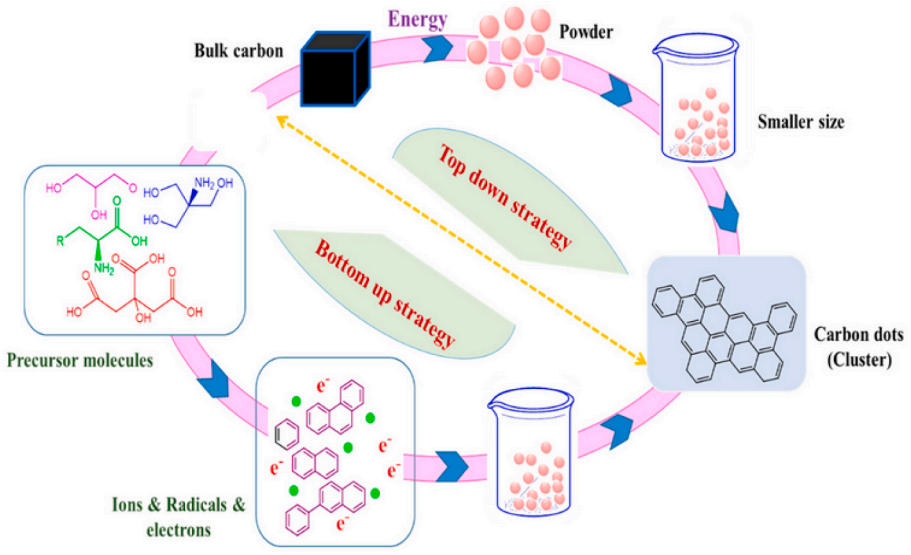

Fig. 1. Bottom-up and top-down approaches for the fabrication of CQDs. Reproduced with permission from [47].

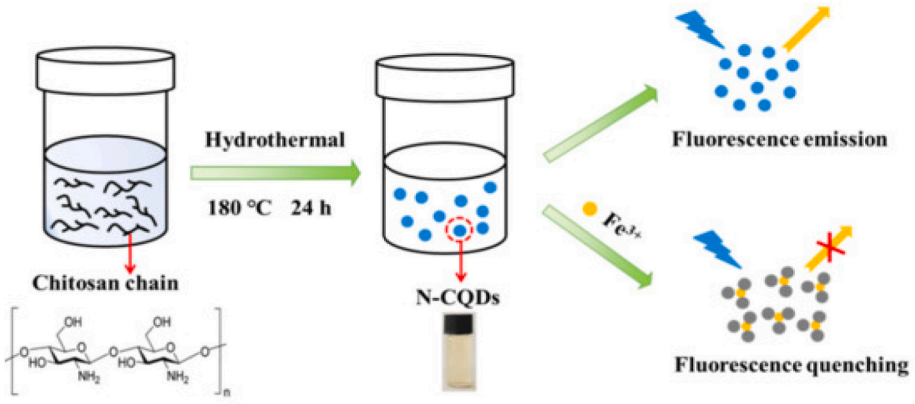

Fig. 2. Schematic of hydrothermal method production of nitrogen-doped CQDs (N-CQDs). Reproduced with permission from [53].

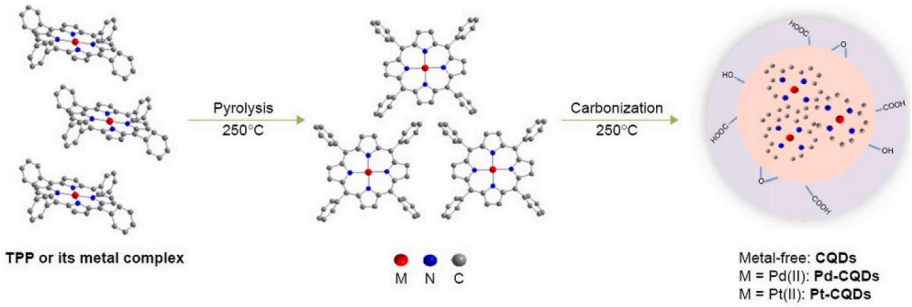

Fig. 3. The synthesis procedure of M-CQDs and metal-free CQDs by the pyrolysis and carbonization (TPP = tetraphenylporphyrin) precursors. Reproduced with permission from [61].

ablation method combines the laser pulses at definite time intervals to synthesize CQDs. The advantage is that this combination could decrease undesired thermal effects like laser-plasma interactions, evaporation, and melting. Ultrafast dual-beam laser ablation technique from cheap carbon cloth material was applied to prepare homogenous CQDs. The QY of the fabricated CQDs was 35% [63].

4. CQDs for detection

The photoluminescent characteristics of CQDs are one of its distinguishing features. With a significant UV absorbance band (260–320 nm) [64,65], CQDs have been controlled over the visible spectrum from blue to red [66–69] (Fig. 4), exhibiting attributes depending on the chemical milieu, including pH [70,71]. It is not completely evident where this PL is coming from. The luminescent features of CQDs can be attributed to flaws and surface conditions, but their amorphous nature hinders chemical modeling approaches [72]. Distinct precursors and synthesis processes produce various chemical and structural changes in CQDs [30,64,72]; nonetheless, they all act as powerful electron acceptors and donors [73,74]. Observations of photoluminescent upconversion in CQDs have been reported in a plethora of publications [75–77].

Although CQDs have been known for a long time, theoretical work defining their electrical characteristics has just lately begun. Although these mechanisms are less exact to explain, size and surface group alteration have comparable effects on their characteristics [72,79]. A direct relationship is observed between the surface conditions of CQDs, the existence of emissive traps (intermediary levels of energy that "capture" excited electrons and lead to a reduction in fluorescence), and surface passivation as a method of reducing the impact of these entrapments [80,81]. Employing the semiempirical molecular orbital hypothesis, Margraf et al. focused greatly on the CQDs' structure for estimating the bandgap, while sp^3 carbon atoms only contributed marginally [72,82]. Their research states that although CQDs exhibit confinement dependence, the sources of their bandgap energies are often complex and dependent on the conjugation level. The photoluminescent/electronic characteristics of amorphous CQDs are greatly influenced by surface electronic states [83].

Due to their amorphous nature and structure, CQDs are less suitable for electrochemical systems than GQDs, complicating direct interaction with physiological systems. Nonetheless, they exhibit the identical ECL process as GQDs and have comparable features. CQDs were used to lay the foundation for the early ECL research on carbon nanodots, which predates identifying this mechanism of GQDs [69,84].

CQDs have been the subject of less research than GQDs regarding their magnetic properties. The magnetic characteristics of GQDs can be studied more easily than those of CQDs because CQDs lack clear boundary structures and profiles. Despite this, studies have shown CQDs' inherent magnetic features and developed magnetic CQDs [85,86].

The catalytic efficiency of CQDs can be attributed to their enzymatic activity and the fact that they share numerous similar chemical and molecular processes [87–89]. Kinetically speaking, there are variances between the two compounds. It has been documented that GQDs have greater binding affinities, but it has also been observed that CQDs have greater maximal kinetic levels [88]. Depending on the system characteristics, this could be caused by changes in surface area, chemical doping levels, and terminal moieties. Nevertheless, both nanomaterials share this feature in general. Additionally, CQDs exhibit electrocatalytic and photocatalytic activity similar to GQDs [89].

4.1. Methods for detection based on CQDs

4.1.1. CQDs-based electrochemical biosensor

Electrochemical biotransducers are attractive platforms because they

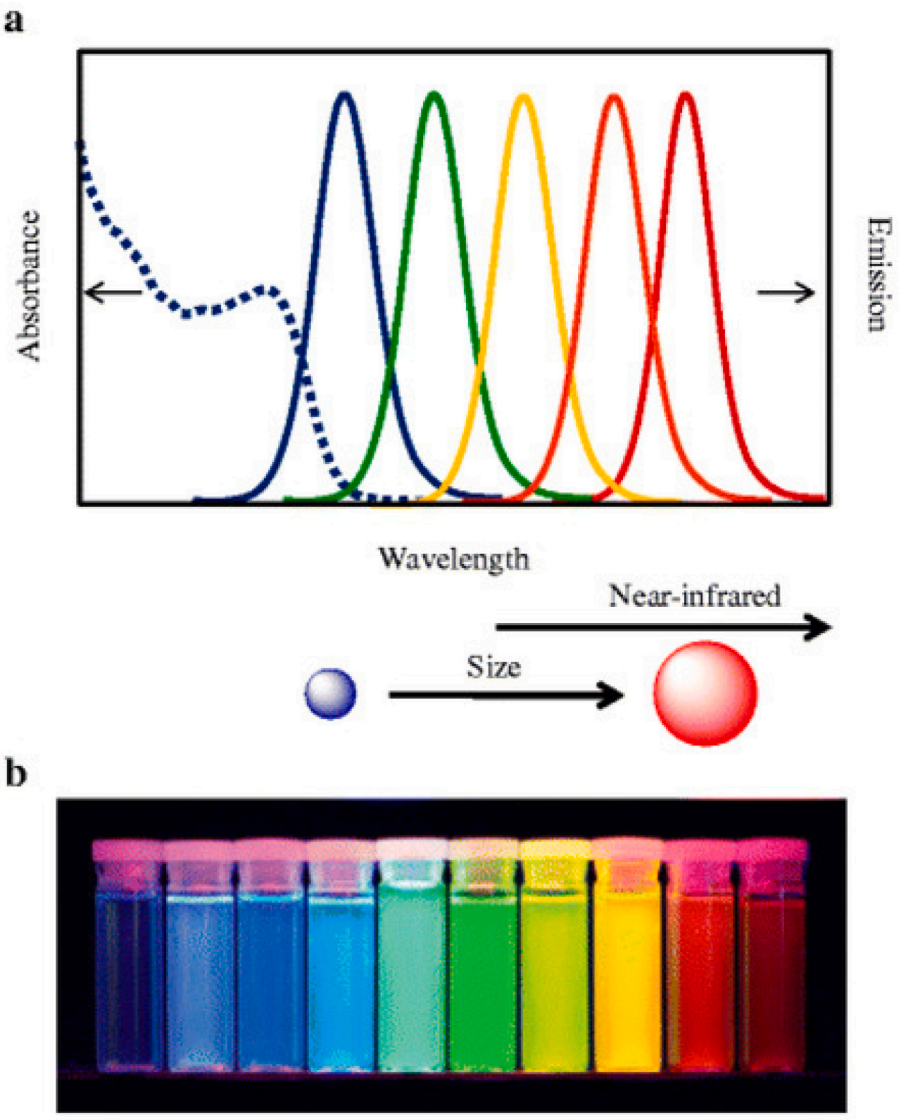

Fig. 4. Effect of size on excitation/emission of QDs. (a) Excitation/emission of QDs with various diameters. (b) The detectable emission color of ZnS-capped CdSe QDs by a near-UV lamp. Reproduced with permission from Ref. [78]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

can effectively detect and measure the transfer of electrons to determine analytes [90,91]. Electrochemical sensing offers a comprehensive range of electrical approaches, one of the system's remarkable advantages. Amperometric (current), potentiometric (voltage), impedimetric (AC impedance), and conductometric (DC resistance) measurements are among the options for determining outputs.

Various redox-active enzymes and nanomaterials have been used in electrochemical biosensors to demonstrate direct electron transport [92–96]. CQDs and GQDs are excellent alternatives for attaching to redox-active biological substances because of their length scale and electrical characteristics. In addition to the more typical amperometry and voltammetry, electrochemical sensing systems offer a large array of analytical approaches, such as impedimetry and electrochemical impedance spectroscopy [97,98]. A major downside of electrochemical sensing is that it may be impossible to identify if no electroactive species are present in the sample at all. Electroactive species, including ferrocyanide (II) $[Fe(CN)_6]^{-4}$/ferricyanide(III) $[Fe(CN)_6]^{-3}$], ferrocene/-ferrocenium, and quinone/hydroquinone redox systems are commonly used in impedance research to alleviate this issue [98]. Another shortcoming of these systems is their relative complexity. Therefore, significant interfacial engineering is required to establish stability and reproducibility in these systems. As part of interfacial engineering, preserving biomolecular function or structure is crucial [98].

Immobilized enzymes are one of the most common biosensing methods and serve as the biological identification component [99]. Initial experiments utilizing nature's machinery for detection and biotransduction used enzymes developed to catalytically transform the targeted analyte to a quantifiable byproduct, leveraging enzymes with high affinity to the analyte [99]. They also make up a significant component of the sensing devices used in therapeutic settings (for example, blood glucose monitoring and ELISAs). CQDs provide potential as simple immobilizing compounds for the development of enzymatic biosensors due to their excellent surface-to-volume ratios and adsorptive chemistry [97,98]. These compounds' advantages come from their robust electrical characteristics, which operate as electrode scaffolds while necessitating minimum passivation [97–99].

Utilizing redox-active enzymes is a great way to facilitate direct electron transport, which is suitable for electrochemical biosensing. CQDs' biosensing capabilities can be significantly enhanced in this way. Wang et al. [99] employed composites made of mixing carbon nanodots

and CoFe layered double hydroxide (LDH) with horseradish peroxidase (HRP) as a redox-active immobilized on the surface.

Analytes can only be specifically detected by using aptamers. Peptide strands can act similarly, with the apparent distinction being the chemical composition, which is made up of amino acids rather than nucleic acids [97–99]. Chemical library searches using brute force are widely used to create aptamers and portions of peptides; however, these molecules occur naturally, most notably in bacteria (RNA riboswitches). In addition to their numerous advantages of stability, specificity, and compact size, also, aptamers are compatible with many different chemical structures [97–99]. Nevertheless, the fundamental disadvantage is that building a functional construct is not trivial without the accessibility of a suitable aptamer for the analyte beforehand. Liu et al. [100] used nitrogen-doped CQDs functionalized with DNA to develop an ECL biosensor with enhanced signal to detect miRNA-21. An initial DNA sequence was used in the study to conjugate CQDs so that they could hybridize with both the miRNA and the assistance probe. The nicking enzyme detected this complex and cleaved the DNA, releasing the miRNA toward hybridizing for a second time. After cleaving the DNA, it can hybridize with a detection hairpin mounted on a GO electrode, which will result in an ECL readout. The LOD was set at 10 aM, and the system's dynamic ranged from 10 aM to 100 nM [100].

In addition, mixing nanomaterials with CQDs could improve the CQDs properties [4,101,102]. Pourmadadi et al. [4] developed a CQDs-gold nanoparticle electrochemical aptasensor for selective prostate-specific antigen (PSA) detection. CQDs interaction with gold nanoparticles resulted in enhanced electrical conductivity of CQDs following the rise in the current peak of cyclic voltammetry (CV) in CQD-gold nanoparticles compared to CQDs. Furthermore, compared to commercial chemiluminescence techniques, the electrochemical CQD-gold-based biosensors could be applied for sample detection.

4.1.2. *CQDs-based fluorescent biosensor*

For biomolecular imaging and biomarker identification, fluorescence nanomaterials and labels, which are extremely sensitive and specific, can be used with an acceptable spatiotemporal resolution [103]. Employing carbon nanomaterials, inorganic semiconductor quantum dots (QDs), organic dyes as fluorescent-based biosensors, multiple fluorimetric diagnostic examinations, and fluorescent indicators have been reported for biocatalyst performance [12,104]. The fluorescence event occurs whenever a fluorophore/fluorescent-labeled compound absorbs the associated electromagnetic radiation that lies at the heart of these biosensors' functioning. Fluorescent biosensors are classified into four groups based on the signal generation method: FI (Altered fluorescence intensity), FLIM (Fluorescence Lifetime Imaging), FCS (Fluorescence Correlation Spectroscopy), and FRET (Förster Resonance Energy Transfer) [105]. Fig. 5 depicts the fundamentals of fluorescence-based detection. Maximum sensitivity, low-invasiveness or non-invasiveness, the capacity to use fluorescence intensity and duration, and the provision of molecular structure and microenvironment are the primary benefits of fluorescence-based biosensors [106–108]. The manufacturing of fluorescent biosensors has relied on a variety of fluorescence-emitting nanomaterials, including lanthanide-doped nanomaterials, fluorescent gold/silver metal nanoclusters, dye-doped silica nanoparticles (DDSNs), fluorescent semiconductor QDs, carbon nanomaterials, and upconversion nanoparticles (UCNPs), to overcome the technical challenges of traditional organic labels [109,110]. The high surface-to-volume proportion of graphene nanomaterials and their outstanding distance-dependent fluorescence quenching capabilities based on FRET make them ideal options for improving fluorescent biosensors [104,111].

Carbon nanomaterials have been used in fluorescent biosensors, such as GO, RGO, GQD, CQD, etc., despite their unknown fluorescence process [89,112–114]. Due to the nanosheet's vast electron plane stimulating FRET to quench fluorescence, several carbon nanomaterials, including GO and graphene, are fluorescent quenchers [115–117]. For example, Singh et al. [118] designed a GO fluorescent biosensor to recognize guanine in human urine. As an efficient emission probe, the GO-functionalized organosilane receptor was applied in the fluorescent biosensor construction. This GO-based probe induces fluorescent spectra for sensitive detection of guanine with a response time of 10 s and LOD of 39 nM. Multicolor GQD, CQD, and CNT, on the other side, have strong fluorescence that renders them ideal for optical biosensors [119]. CNTs emit in the near-infrared spectrum, but their cytotoxicity has not been properly researched, which is their primary drawback [119]. CQD and GQD excitation-dependent emission is a unique fluorescent property; CQD and GQD emit at the matching wavelength [65,120–122]. Due to their large surface area, chemical and physical properties, and facile functionalization, GQD-based biosensors hold great promise for early and sensitive cancer biomarker detection. However, there is a challenge in using GQDs in biosensors related to the large-scale fabrication of stable and high-quality nanoparticles with definite shapes, sizes, and charges [39]. It was determined that the FRET process of CQDs was helpful for the identification of cysteine (Cys). There are several therapeutic conditions for which Cys, a sulfur-containing amino acid, can be used as a biomarker [123]. Orange juice combined with AuNPs was used in the hydrothermal preparation of CQDs [124]. Cys, AuNPs, and CQDs were the main components of this approach. In the exclusion of Cys, FRET occurs between CQDs and AuNPs, resulting in the quenching of CQDs. Because of the existence of Cys, AuNPs have a propensity to aggregate, which prevents FRET from occurring between AuNPs and CQDs and causes the latter to emit fluorescence. Human plasma and

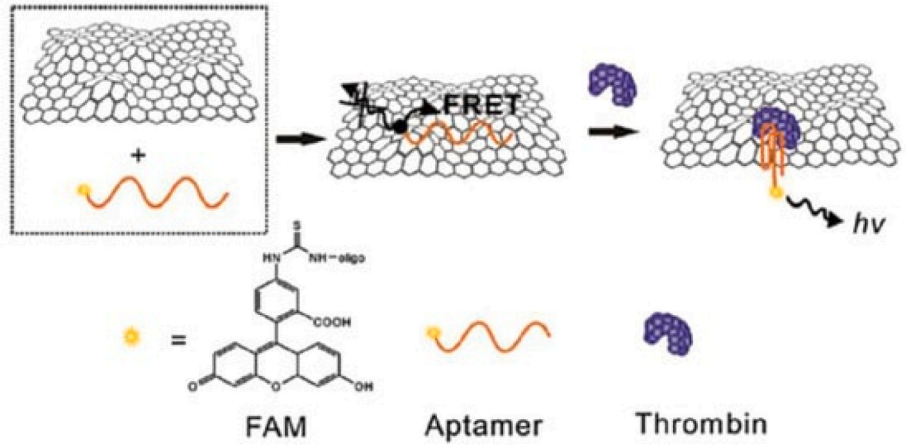

Fig. 5. Illustration of the design of fluorescence-based biosensor. Reproduced with permission from Ref. [6].

urine specimens have been tested using this technique to detect Cys.

Cho et al. [125] created a glucose biosensing ratiometric system using CQDs combined with rhodamine 6G. As glucose levels increased, they noticed a change in color from blue to green. Their technique achieved a linear range of 0.1–500 mM with a minimum LOD of 40 nM. Because CQDs are so biocompatible, a major application of CQDs-based sensors is biosensing; therefore, a study on biosensors using fluorescent probes could show them an extremely helpful instrument for the study of biological phenomena. To create a dopamine bioprobe, Tang et al. [126] directly conjugated tyrosinase to CQDs, addressing the fundamental shortcomings of fluorometric biosensors developed based on GQDs and CQDs. Although the whole system was similar to those proposed in the past, direct conjugation of the complete sensor in a single unit is a stride ahead in broadening the adaptability of these biosensors. Hemoglobin [127,128] and uricase [129], and urease [130] have also been studied as distinct proteins. A fluorescent ssDNA probe/CQD sensor for complementary DNA strands in solution was described by Loo et al. [131]. FRET quenching was made easier with this plan thanks to the π-π stacking that resulted from the DNA base pairs and the carbon quantum dot conjugated π-systems. For recovering the fluorescence of the DNA probe, this π-system connection was disrupted whenever the ssDNA hybridized with the target, and electrostatic repulsion prevailed. Liang et al. [132] used CQDs and CdTe quantum points to develop a ratiometric dsDNA biosensor.

Biosensors based on hybridization can benefit from the advantages of aptamers. To construct one of the earliest aptasensors using GQDs/CQDs, Wang et al. used CQDs as FRET receptors together with phosphors modified with thrombin aptamer oligonucleotides [133]. They stated that their aptasensor was able to detect thrombin. Nevertheless, in the existence of thrombin, CQDs interacted with oligonucleotide through π-π linkages, and the aptamer selectively attached to the analyte, releasing CQDs and recovering phosphors' fluorescence. Their technique demonstrated a high level of selectivity and showed a linear response ranging from 0.5 to 20 nM with a 180 pM LOD. Zhu et al. [134] prepared an aptasensor based on dopamine utilizing a competitive binding method several years later, in which CQDs were attached to a DNA aptamer using carbodiimide chemical reactions. As a result, a fluorescent biosensor was created by loading CQDs onto nanographite through π-π stacking and shifting them when dopamine was present. LOD was calculated to be around 55 pM, in the range of 0.10–5 nM. By employing graphene oxide (GO) and CQDs as scaffolds, Luo and colleagues demonstrated an advanced system for ATP aptasensing in a mixture [135]. In their mechanism, which was based on the strand displacement concept, signaling strand and CQDs were linked that could connect to aptasensing. Fluorescence was observed after binding, which inhibited the CQDs from associating with the GO. The availability of ATP caused an alteration in the structure of the aptamer, which in turn liberated the helper strand so that it could engage a fuel strand. This action then eliminated the complete aptasensing strand complex from the CQD, which made it possible to interact with the GO and become quenched. When Tan et al. [136] demonstrated the ability of Ir–Pd nanocube and CQD fluorophores to mimic peroxidase activity as a reference fluorophore in an immunosensor platform, it was a truly innovative development in immunosensing technology. They presented a sandwich immunosensor for myocardial troponin I detection during their study. The nanocubes would act as catalysts for the reaction and oxidize o-phenylenediamine to produce a fluorescent effect in the complexation process. This fluorescent product would subsequently quench the CQDs and provide a ratiometric sensor. Serum performance was particularly strong for their technique, which was also superior to enzyme-linked immunosorbent tests in terms of accuracy. Bagheri et al. [137] designed smart fluorescence aptasensors for the detection of S. aureus bacteria in skin wounds. These fluorescent biosensors were based on the nanofibers that were functionalized with CQDs and LOD 10 CFU mL^{-1} was obtained. By modifying nanofiber surfaces with CQDs, fluorescence emission was observed under UV light by the naked eye.

4.1.3. CQDs-based surface plasmon resonance (SPR) biosensor

SPR-based technology is an efficient tool for tracking molecular dynamics, as well as for measuring proteins, DNA, and whole cells quantitatively in real time [138–140]. The surface of the SPR biosensor is one of the most important components, as it is directly responsible for the total performance of the sensor. For more flexible strategies, intelligent sensing layers have also been a focus of numerous investigations [110,141,142]. To study noncovalent molecular interactions in a non-invasive manner, SPR sensing is a strong, label-free instrument. Protein-protein, Noncovalent protein–DNA, protein–cell, and other protein-protein interactions have all been studied extensively using SPR over the previous two decades [143]. Due to the very high sensitivity of surface plasmons to changes in the reflecting index (RI) of the dielectric medium, SPR biosensors can be widely implemented in biomarker diagnostics. During the immobilized sensors on the metal surface and the analyte compounds interaction, variations in the refractive index (dielectric) of the sensing medium lead to changes in the dispersion constant of surface plasmons. This mechanism influences the resonance setting of surface plasmons via surface plasmon waves (SPW) interacting with p-polarized incoming radiation with the identical propagation constant. A dramatic dip is formed in the SPR curve (reflectance according to the incident angle) as a consequence of the energy of light photons being transferred to surface plasmons at the resonance angle [144,145]. Light reflectance decreases dramatically as a result. Based on the interacting optical wave evaluated in the experiment, SPR biosensors can be constructed with angular, intensity, phase, or wavelength modulation [146]. Regarding the excitation of surface plasmons, the Kretschmann configuration is the most popular SPR option based on diminished overall reflection [147].

Errors in phase measurement are typically caused by the fact that coherence-based phase detection is extremely sensitive to mechanical motions in optical components and interference in the surrounding environment. The SPR biosensor must be stable in the time axis as well to track the biological reaction throughout time.

SPR phase biosensor for selective drug delivery screening was assessed by Wang et al. [148]. The sensor's sensitivity was measured by measuring the SPR signals of different sodium chloride concentrations. SPR signals fluctuated for 80 min while measuring a sodium chloride-containing specimen to determine the sensor's durability. Comparable to other high-sensitivity-phase SPR technologies, an optimal stability noise attenuation of 6×10^{-7} RIU/RU was observed throughout the 80-min test.

The color shift of S-doped CQD functionalized AuNPs was used by Amiri and colleagues to construct an extremely sensitive and specific dopamine detection [149]. It was discovered that the localized surface plasmon peak of S-doped CQDs@AuNPs shifted from 520 to 670 nm in the red region. The modified AuNPs have carboxylic groups on their surface that bind to the amino groups of dopamine and then aggregate with Fe^{3+}, resulting in this event. Fe^{3+} in the system causes this color shift from wine red to blue-purple. The analytical reaction is linear throughout the dopamine content in the range of 0.81–16.80 M when the circumstances are optimal. The detection and measurement limits are 0.23 M and 0.77 M, respectively. CQDs-modified AgNPs were successfully synthesized by Beiraghi et al. [150]. in a separate study to detect Cu^{2+}. Using CQDs-AgNPs, CQDs functional groups interact strongly with Cu^{2+} to develop the sensor. Because of the large wavelength transition in the SPR absorption peak, the CQDs-AgNPs aggregation resulted in a noticeable color alteration from orange to red-brown. A linear concentration spectrum of 0.3–8 M of Cu^{2+} is observed for the analytical reaction under optimal circumstances. UV–Vis spectrophotometry and physical observation have detection thresholds of 0.037 μM and 1 μM, respectively.

Additionally, employing a distance-dependent detection approach centered on CQDs as a donor of one oxygen atom and 9,10-diphenylanthracene-2-boronic acid (DABA) as an acceptor of one oxygen atom, Ding and his colleagues devised a novel sensing method for nucleoside

triphosphates (NTPs) detection [151]. To facilitate diffusion, the CQDs create singlet oxygen. Because of the contacts and subsequent development of a stable borate ester, CQDs@DABA-ATP began to aggregate whenever ATP was introduced, resulting in an absorption maximum at 387 nm, which subsequently declined under illumination owing to an O_2 entrapment. In concentrations ranging from 0 to 80 mM, the produced CQDs exhibit remarkable ATP specificity with a detection threshold as minimal as 4.35 mM.

4.1.4. CQDs-based surface-enhanced Raman scattering (SERS) biosensor

Fleischmann et al. [152] initially showed SERS in 1974. Raman scattering studies of pyridine compounds adsorbing to electrochemically roughened Ag surfaces were carried out, and the results were presented. According to Jeanmaire and Van Duyne [153] and Albrecht and Creighton [154], the Raman scattering from pyridine adsorbed on a roughened surface is 106 times stronger than from pyridine in solution. The substantial boost in signal sparked a lot of interest in the method, and it's one of its most compelling features even today. The approach has since been used in a variety of disciplines, particularly sensors.

The rough metal nanoparticles on their surfaces make it possible to analyze multiple analytes chemically using SERS. Due to the high local electromagnetic field created by the connection between surface plasmon resonance and laser light on metal nanoparticles at particular locations, the analyte's Raman signal is increased significantly [155]. The electromagnetic and chemical pathways are both accountable for SERS [156]. Electromagnetic impacts are the primary pathway underlying SERS operations. Electromagnetic amplification occurs when radiation with a frequency close to the plasmon-specific vibrations excites localized surface plasmons [157]. A large field-induced polarization and a consequently large local field on the surface are produced when the metal becomes particularly plasmon-polarizable [158]. It is possible to increase the Raman emission rate by using local fields, which are directly proportionate to the square of the supplied field. Where noble metal nanoparticles and metal substances attach together, hot spots can be formed, which are areas containing a significant local field at nanoscale edges [159].

The chemical impact is another pathway for SERS operations. The ensuing electrical field is strengthened as a consequence of the transport of electrons from the metal surface to the material that has been adsorbed, resulting in the inter-and intra-molecular charge transport [158]. Achieving an optimal homogenous distribution of hot spots requires considering metallic nanoparticles' morphology, degree of aggregation, and behavior. Consequently, for detecting analyte traces, the kinetics of the reduction mechanism resulting in the formation of nanoparticles is a crucial stage in producing repeatable SERS templates [157]. Surface functionalization can be applied to the SERS substrate to increase the adhesion of analytes, just like it can be applied to other types of substrates. Wang and colleagues utilized SERS quantitative analytical approach to identify metal ions [160]. An enzyme-like Ag-doped CQDs (Ag-CQDs) was found to imitate $HAuCl_4$–H_2O_2 reactions in their research. Victoria blue B (VBB) was used as a probe to produce nanogold particles via SERS and resonance Rayleigh scattering (RRS) impacts. The catalytic activity of Ag-CQDs can be weakened by the adsorption of the aptamer on its surface. Adding $Pb2^+$ resulted in the formation of the Pb-aptamer complex and the subsequent desorption of Ag-CQDs, resulting in the catalytic activity being restored. In the existence of a molecular probe, the nanogold produced has a significant RRS peak (375 nm) and a substantial SERS peak (1615 cm^{-1}). With enhanced Pb^{2+} concentration, the SERS and RRS dual-model signals decreased linearly. As a result, SERS and RRS had detection thresholds of Pb^{2+} as low as 0,0032 and 0,0048 μmol L^{-1}, respectively. Yao et al. [161] created a SERS/RRS dual-spectroscopic quantitative assessment approach with outstanding sensitivity to identify clenbuterol. This method was accomplished by employing a detection strategy analogous to the previously described one. Using the mixture of N/Ag-CQDs catalytic amplification and immunoreaction, clenbuterol was effectively detected at a detection threshold of 0.68 pg mL^{-1}. Focusing on the catalytic action that the CQDs have on the H_2O_2-3,30-dimethylbiphenyl-4,40-diamine (DBD) SERS reaction, Feng et al. [162] used a highly sensitive technique for the detection of acetamiprid. To oxidize DBD with H_2O_2, the generated codoped N/Ag-CQDs have excellent catalytic characteristics. The decreased SERS signal was caused by a catalytic function inhibited by the aptamer that was previously applied to cover the CQD surface. The CQDs were preferentially released by the mixture of acetamiprid and aptamer, restoring their catalytic function. As the concentration of acetamiprid elevated, there was a corresponding increase in the amount of CQDs that were released. The SERS peak at 1605 cm^{-1} grew linearly as additional DBD oxidation products were produced (Fig. 6). The catalytic function was recovered, and the SERS signal was linearly amplified by using the stabilized aptamer-acetamiprid complex and unbound N/Ag-CQDs.

4.1.5. CQDs-based photoelectrochemical (PEC) biosensor

PEC bioanalysis is a relatively novel technology that is quickly turning to the focus of modern study among the numerous methodologies owing to its appealing possibility for upcoming bioanalysis with excellent sensitivity and selectivity [163–165]. Bioanalytical PEC is fundamentally the next generation of traditional electrochemical bioanalysis. Therefore, due to its one-of-a-kind PEC set-up, which consists of totally distinct energy forms of light and electricity as the excitation source and detecting signal, respectively, it obviously acquires the benefits of electrochemical bioanalysis and exhibits superior sensitivity [166,167]. In addition, PEC bioanalysis equipment is simpler, relatively inexpensive, and better to miniaturize than optical techniques because of the employment of an electrical readout. Excitation sources like irradiation light, monochromator, cells, and an electrochemical workstation containing a three-electrode system (counter, working, and reference electrodes) are included in the PEC instrument arrangement. Several semiconductor compounds are used in the operating electrode, which connect to a metal interface, the outside electronics, and a metal counter electrode. The mixture used to integrate the circuit also connects the semiconductor-based operating electrode to the counter electrode [166,167].

Based on this system, the investigated biochemical data (including the analyte concentration) related to a particular biorecognition process might be effectively translated by semiconductors into output electrical signals [166,167]. Certain additional bioactive compounds (for example, anticalins, affibodies, and nanobodies) and recognition elements (for example, phages, whole cells, and molecularly-imprinted polymers) regarding the biological recognition elements, in complement to the common ones (namely, antibodies, DNA, and enzyme) may definitely provide one-of-a-kind frameworks for the creation of innovative PEC bioanalysis in the years ahead [163–167]. CQDs' varied features are exploited in ways that distinguish them from other nanomaterials within PEC biosensing [163–167]. To be more specific, this kind of interface engineering makes it possible to precisely design and couple different compounds to one another by combining the materials' conducting and valence bands in order to generate charge transfer pairings [163–167]. Tailor-made biotransduction systems can take advantage of CQDs' tunable character to specifically target analytes and the energetic/photonic transitions required for biotransduction. There are several downsides to these systems; notwithstanding, they provide a high level of freedom [163–167]. It is possible that redox coreactants or meticulous engineering of charge transport interfaces is required for these sophisticated biotransducers [163–167]. The construction of a PEC biotransducer necessitates the employment of specialized devices and electrodes, and these electrodes impose logistical challenges during integration, development, and scaling constraints [163–167].

Enzymatic disintegration of an oxide nanosheet accommodating CQDs was developed by Lin et al. [168] in a novel photoelectrochemical technique. The considered analyte was tagged using GOx, and the detection medium was pre-spiked in the developed platform. A

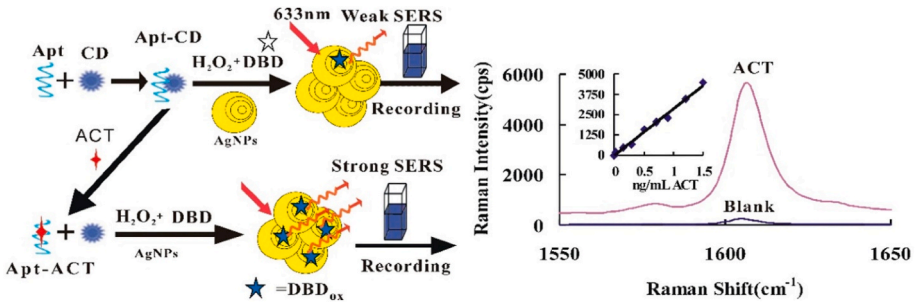

Fig. 6. N/Ag-CQDs impact on the amplification of catalytic performance of SERS analytical platform. Reproduced with permission from Ref. [162].

complexation would result in the localized generation of H_2O_2 on the nanosheet, which would etch the nanosheet and release the CQDs, which would eventually lead to a decrease in photocurrent. The etching of the sheet was prevented, and ECL was maintained due to the introduction of the native analyte, which outcompeted the compound. A sandwich method was used to create a quenching system by Lv et al. [169]. The CQD/g-C_3N_4 combination was responsible for generating the first photocurrent in their technique. Subsequently, upon creating the immunocomplex sandwich, the nanospheres released Cu^{2+} ions, which caused the photocurrent to be stopped. Unsurprisingly, the nanospheres were loaded onto an aptamer, releasing the Cu^{2+} ions following antibody attachment. Gong et al. [170] used an acid/base chemistry

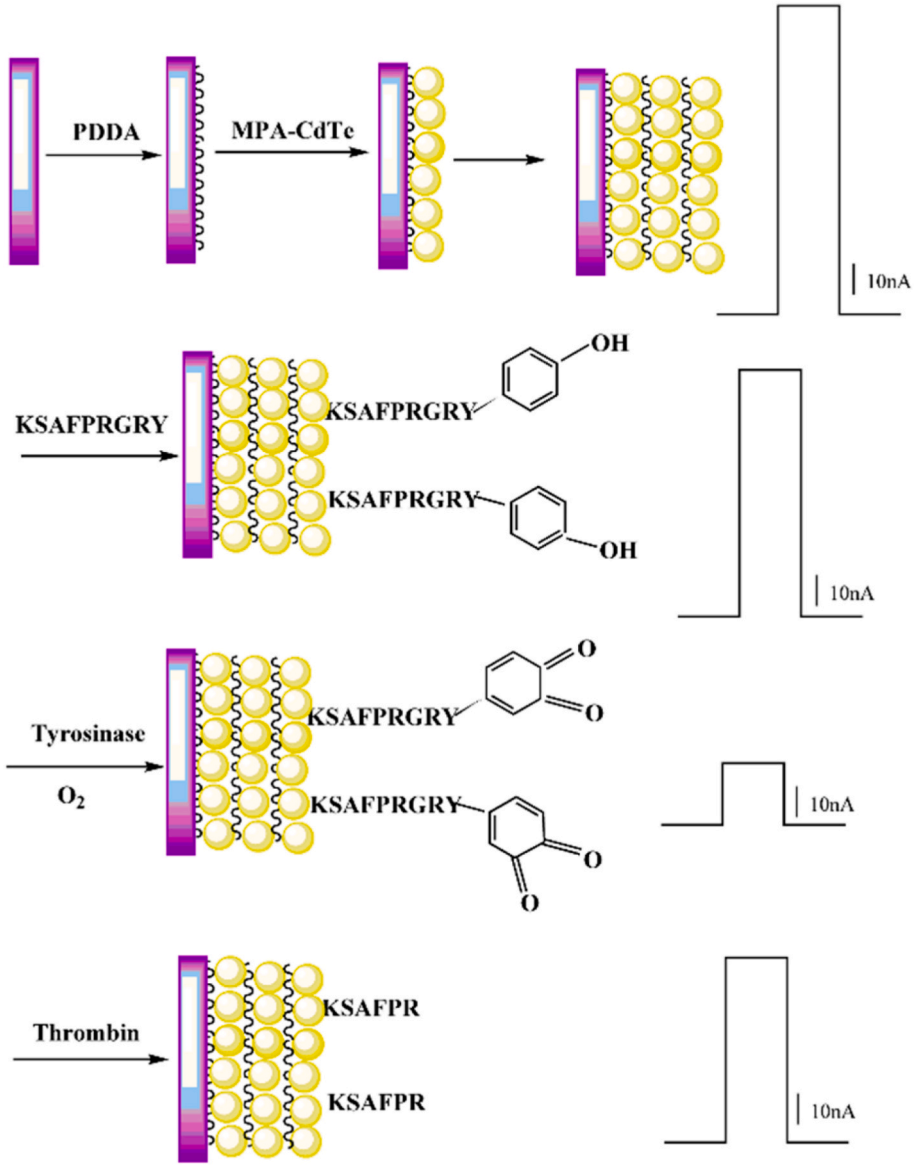

Fig. 7. (a) Schematic representation of fabrication procedure of QDs-based PEC biosensor for tyrosinase and thrombin detection. Reproduced with permission from Ref. [175].

technique. The initial significant photoelectrochemical capacity of oxidized CQD/TiO_2 nanoparticles was turned off in their system. The immunoassay was carried out in microwell plates, and alkaline phosphatase catalyzed the synthesis of ascorbic acid, decreasing the CQD combination and recovering the photocurrent.

Cheng et al. [171] reported the development of a turn-off CQD aptasensor for thrombin. This aptasensor was based on a comparable premise to the one developed by Jiang et al. [172]. Because of the reduction in photocurrent caused by thrombin attachment, a readable signal could be traced. An AChE-catalyzed photoelectrochemical system to convert acetylcholine into thiocholine was recently demonstrated by Cheng and colleagues [173]. Their system has a number of outstanding features. CQDs and visible light were employed as the photocurrent potentiator and excitation driving force, respectively. Thiocholine was used as an electron donor to enhance photocurrent production, and AChE antagonists reversed this effect. Using a LOD of 70 pg mL^{-1}, they could identify inhibitor concentrations between 1 ng mL^{-1} and 1.5 mg mL^{-1}. Using ZnO nanorods (NRs)/$CH_3NH_3PbI_3$/nitrogen-doped CQDs (NCQDs) nanocomposites, Peng et al. [174] created a highly sensitive sensor for early detection of rheumatoid arthritis (RA) (Fig. 7). LOD was calculated to be around 2 cell.mL^{-1}, with a linear range of 10^4 to 10 cell.mL^{-1}. Table 1 summarizes advantaes and disadvantages of discussed CQDs-based biosensors.

5. Conclusion

The unique properties of nanomaterials have led to the development of biosensors based on nanostructures in recent years. Regarding their capability to simplify early diagnosis and treatment options for patients, biosensors can effectively improve patients' quality of life. Besides, through quantifying various markers in a single unit, biosensors such as differential and semi-selective can be developed. Nanomaterials have prominent properties such as large surface area, excellent optical properties, electroconductivity, physicochemical stability, etc., that make them a candidate to be employed in the construction of biosensors. CQDs are one efficient category of nanomaterials that donate efficient features to the biosensing system providing a rapid, more sensitive, and more selectable diagnosis in various areas, from biomedical applications (like cancer diagnosis) to environmental applications (like heavy metals detection). CQDs are used in the construction of biosensors owing to their physical and chemical stability, optical properties (high PL and QY), high surface area, electrical conductivity, non-toxicity, biocompatibility, and electrochemical properties, and water solubility. In this review, the synthesis methods of CQDs have been reviewed. The bottom-up and the top-down approaches exist to synthesize the CQDs. The top-down approaches are simple, but in these methods, some harsh conditions are applied. CQDs often have easy and low-cost fabrication methods, such as hydrothermal/solvothermal routes. Chemical ablation is the most simple and convenient method to produce CQDs. However, they undergo post-treatment processes to be improved and to have more uniform size CQDs. Furthermore, the issues like being environmentally friendly, easy, and scalability of the process, as well as the cost of the fabrication, should be considered. CQDs and CQDs-based materials have been applied in different types of biosensors, including fluorescent, SPR, SERS, and PEC nano-biosensors, and have shown promising results in the detection area due to sensitive detection in the short response time. However, the drawback of the CQD nanoparticles that are used in the biosensors'probe is their low-depth penetration. The future challenges of CQDs-based biosensors would be to design high efficient nano-biosensors that are reproducible, more portable, and miniaturized as well as having more specific receptors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1
Advantages and disadvantages of CQDs-based biosensors.

Sensor type	Advantages	Disadvantages
Electrochemical	Cost-effective Quick response Sensitive Portable	Poor stability and reproducibility
Fluorescence	Cost-effective Quick response Portable	Photobleaching Confined specificity
SPR	Continuous assessment Sensitive	No direct detection of substances with low molecular weight
SERS	Non-destructive Low background signal Sensitive	High cost Poor reproducibility
PEC	High sensitivity Quick response	Desperate need for studies on the signal transmission mechanism

Data availability

No data was used for the research described in the article.

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