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Mini-Review

Boronic-Acid-Modified Nanomaterials for Biomedical Applications

Yu-Yu Aung, Alfinda Novi Kristanti, Hwei Voon Lee, and Mochamad Zakki Fahmi*

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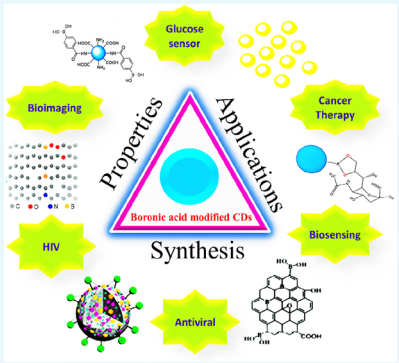
ABSTRACT: Boronic-acid-modified nanomaterials have inspired significant research interest owing to their unique biocompatibility and excellent reversible interaction with diol groups containing saccharides, protein, DNA, and other related glucose compounds. However, the different sources and methods change the application of nanomaterials. Thus, surface-functionalized nanomaterials are of interest as one of the best ways to improve the application of the biomedical field. In this mini-review, we summarize recent studies on boronic-acid-modified nanomaterials, based on the carbon dot group and graphene oxides, which have been used in the fields of bioimaging, biosensing, antiviral inhibitors, etc. Moreover, the multivalent interaction on boronic-acid-modified materials has become the main key improvement for targeting treatment in the future. We mainly focused on any previously reported papers for synergistic future opportunities of superior biomedical applications of carbon dots (CDs) in the management and diagnostics of nanomedicine fields.



1. INTRODUCTION

Carbon is generally exhibited as an allotropic structure. The carbon dot (CD) group consists of carbon quantum dots (CQDs), graphene quantum dots (GQDs), and polymer dots (PDs). Various sources of carbon and synthesis methods have been applied to prepare the CDs, and the resulting CDs' structures are also diverse.[1] Each type of carbon family has interesting features and has been widely exploited in biological applications due to their unique properties, such as chemical inertness, excellent fluorescence emission, water solubility, low toxicity, photobleaching resistance, high luminescence, optical absorption, and high conductivity.

For biomedical concepts, the design of a material that is specific to the biological target was the most crucial aspect besides the toxicity issue. Although lethal dose consumption as high as commercial salt is well known, boron and its derivate compounds became favorable elements for theranostic studies of the biological environment. Among the other boron derivative compounds, many researchers have reported the utilization of boronic acid functionalized onto nanoparticles for many applications. Recently, various boronic-acid-modified nanomaterials have been applied in biomedical applications, containing selective separation of glycopeptides and glycoproteins, therapeutic agents for cancer therapy, boron neutron capture therapy, sensing, hydrogels, and diabetes.

In aqueous media, the Lewis acidity of boronic acid can interact with other Lewis-base sites, which produce the boronate anions and sufficiently bind to *cis*-diol groups containing saccharide compounds such as glucose, mannose, and adenosine triphosphate (ATP). This opened a new avenue to using boronic acid as a specific targeting ligand to biorelated compounds like sialic acid and glycoprotein groups in the various cells. Various boronic acid derivatives were reported to be utilized for saccharide detection and to treat a cancer cell line via a sialic acid connection. Considering HIV infection, the strong in vivo interaction between the gp120 immunogens on the HIV-1 surface and the CD4 receptor has been reported, which results in conformational changes that alter the immunogenicity of the glycoprotein subunit. This was highlighted through special binding of gp120 to the CD4 receptor directly. Therefore, many researchers paid intensive research attention to the boronic-acid-modified materials that indirectly block the CD4 binding by changing the gp120 substructure or disturb the stability interaction of gp120 and CD4. Regarding the above information, the boron-modified nanomaterials brought attractive potency to biomedical applications, even still on limited and nonintegrative reports. Moreover, evaluation of carbon dots attributed to boronic acid has never been explored, and there are remaining questions to discuss regarding their benefits. Therefore, in the present mini-review, we focus first on digging into information on the performance of boron, its derivative, and carbon dots (including CQDs, GQDs, and PDs). Also, we further focus on the advanced potential application of boronic-acid-modified carbon dots. The discussion next explores any application reports of boronic-functionalized carbon dots with its work mechanism for bioimaging, biosensing, glucose sensing, HIV inhibitors,

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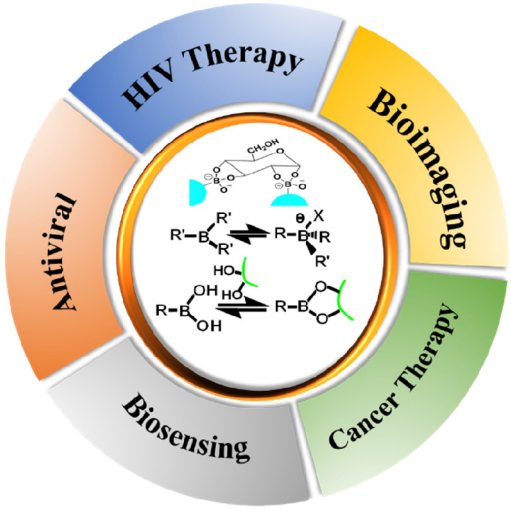
bioimaging of cancer therapy, and antiviral inhibitors as the main focus of applications (Scheme 1).

Scheme 1. Boronic-Acid-Modified Carbon Dots (CQDs, GQDs, and PDs) for Biomedical Applications

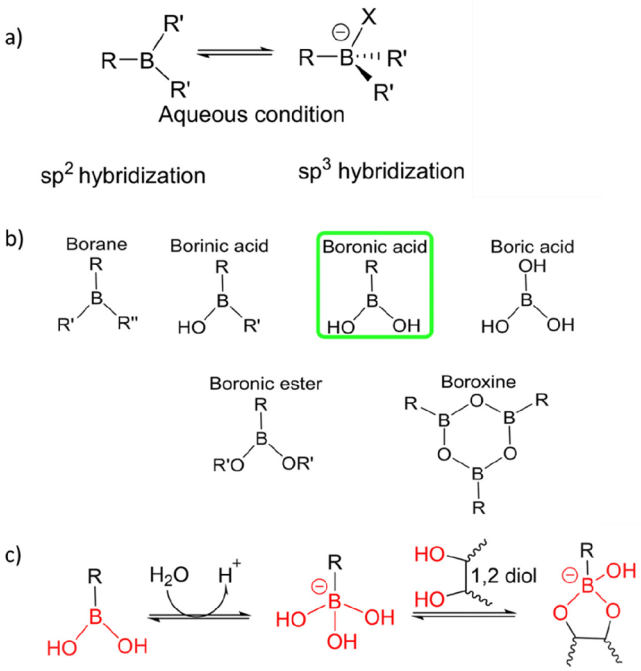


1.1. Boron. Boron is part of a semiconductor organization in elemental groups. The ability of boron is intermediate among metals and nonmetals. This element can be found in nature with certain oxygen and is never found in pure elements. There are two types of nonradioactive isotopes of boron, ^{10}B and ^{11}B, which are naturally found in the Earth's crust. The small atom of boron has three valence electrons, allowing its electrons to covalently bond with other elements or molecules to fill its outer shell. The vacant p-orbital on boron acts as a Lewis acid and interchanges from sp^2 to sp^3, allowing it to capture other Lewis bases. This interchanging can also be quickly made by interacting with water in an aqueous solution. In neutral conditions, sp^2 hybridization of boron is transferred to an anionic sp^3 hybridization form in equilibrium[2] (Scheme 2a).

Boron can be found abundantly in nature as boric acid due to its strong attraction to oxygen as organoboron. Any organoboron is capable of combining with biological materials including polysaccharides. As part of organic molecules, boric acid and borane molecules are found in tissues, fluids, and blood in the human body. By the hydrolyzing process of borane, boronic acid can be produced along with other boron compounds such as boric acid, boronic ester, and boroxine. The family of boron-containing organic compounds as organoboron compounds is shown in Scheme 2b. Boronic acid is a trivalent organic molecule containing boron, which bonded two hydroxyl groups and one alkyl/aryl substituent group to occupy the valence electrons in the atom of boron, making it more stable than a borane. For boronic acid, it can bind with polysaccharides and other ionization transition materials for diabetes diseases and other biomedical applications including cancer therapy, antiretroviral therapy, sensing, and catalysts.[3] These were considered to be due to the fact that boronic acids perform trigonal planar to form a boron atom, which donates a bond with a group of alkyl substituents as well as with two hydroxyl groups in neutral aqueous solution.

1.2. Reactivity of Boronic Acid. Since the late 19th century, the ability of boronic acid to interact with sugar alcohol groups has been recognized, and the detailed interactions

Scheme 2. (a) Transfer in Geometry to the Center of Boron on an Interaction with a Nucleophile, (b) Various Oxygenated Organoboron Compounds, and (c) Esterification Equilibria of Boronic Acid in Aqueous Solution[a]



[a]Adapted with permission from refs 3 and 2. Copyright 2006 John Wiley & Sons. Copyright 2011 Elsevier.

involving diol moieties in the early 20th century have also been reported. Boronic acid is analogous with carboxylic acid, which can serve as a proton donor. However, they act as Lewis acids with hydroxide anions or fluoride or as electron-donating groups, such as oxygen or nitrogen. In aqueous solution, the acid property of boronic acid increases as it interacts with 1,2- or 1,3-*cis*-diols to form cyclic boronic ester (Scheme 2c).[4]

The neutral form of boronic acid exhibits sp^2-hybridized boron (trigonal planar) and two hydroxyl groups. The formation of boronate esters has reversible molecular assemblies with the boronic acid and diol groups under the actual conditions. This is a beneficial interaction for saccharide reaction because it forms cyclic boronate ester, as exhibited on the complexation between boronic acids (Lewis acids) and proximal tertiary amines (Lewis bases). The precise character of boron−nitrogen (B−N) interplay has been reported to provide two advantages. First, at neutral pH, the B−N interaction is enhanced by the formation of a tetrahedral boronate complex, which allows strong binding to a particular target with chemical interaction. Second, the B−N interaction enhances binding due to the Lewis acid feature from the boron atom, and it modulates fluorescence property by moving the photoinduced electron from the nitrogen and stabilizing the obtained structure of the B−N interaction. In particular, the Lewis acidity of the boron atom increases the electron-withdrawing character, and the Lewis base of nitrogen increases electron-donating character. Wulff and co-workers revealed that the boronic acid's pK_a value decreased through the intramolecular coordination of the boron-supplied nitrogen atom and the boron with an oxygen atom (Scheme 3a).[5] This observation showed that the dative bond was formed between boron and nitrogen atoms, changing

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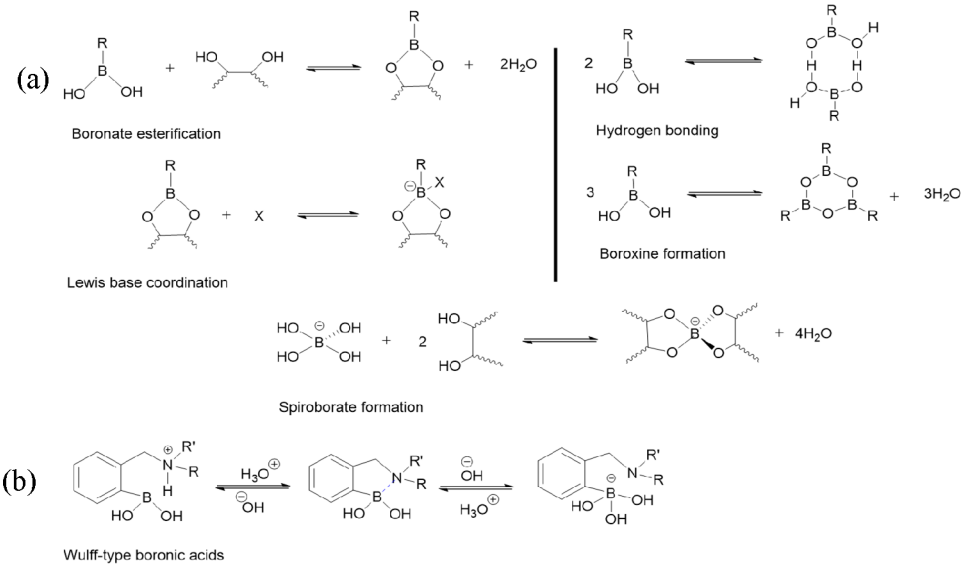
Scheme 3. Main Boronic Acid Interactions Concerning the Self-Assembly (a) and Intramolecular Interaction between Boronic Acid and a Nitrogen Atom (b)[a]



[a]Adapted with permission from refs 5 and 4. Copyright 2016 American Chemical Society. Copyright 2013 American Chemical Society.

the hybridization type of the boron, from sp^2 to sp^3, which forms the fast and more stable bond formation boronate esters. The dative B−N bond is usually favored on protic media like water or methanol. However, this protic solvent insertion prepares a hydrogen-bonded zwitterionic species, which can contribute to enhancing the binding of *cis*-diols at pH-neutral conditions.[5] The complexation of the dative bond between boron and nitrogen is extremely influenced by some aspects, like containing the structure of boronic acid, steric hindrance on the nitrogen atom, various solvents, different concentrations of diols, and different pH solutions. The substitution of bulky groups was also reported to influence the dative bond (B−N) formation by decreasing the binding strength between the boron and nitrogen atom. Boronate ester formation is highly dependent on the various pH conditions and the solvent used. At low pH conditions, the amine group protonated to the boron center and changed to trigonal planar sp^2 hybridization. Therefore, the boron center of boronic acid interacted with a hydroxide anion and released nitrogen at higher pH conditions. After that, in neutral pH conditions, the nitrogen atom deprotonated and coordinated with the boron center of boronic acid and transferred to a tetrahedral boronate anion. Boronate ester formation appears with a higher pK_a of boronic acid. It can interact immediately and reversibly with groups of *cis*-diol to make a boronate ester compound due to the basicity of the liquid system (Scheme 3b).

The above discussion informed us that the boronic acid site was revealed to be an excellent binding agent with another nucleophilic substance, such as dicarboxylic acids and α-hydroxy-carboxylic acids. Boronate ester formation was favored for the analysis of saccharides, glycoprotein detection, glucose sensing, HIV barriers, and staining along with cancer therapy, and it is discussed in the following section.

1.3. Unique Features of Boron-Based Nanomaterials.

Boron-based nanomaterials have been one of the most researched until recently. These nanomaterials are extensively used as chemical functional groups for biomedical applications. Boron-based nanomaterials possess diverse great advantages such as chemical stability, excellent optical performance, and good biocompatibility. Under these conditions, boronic acid acts as a Lewis acid and interacts with vicinal diol groups to generate boronate esters. In addition, they can react with various precursors of disease such as the saccharide group, glycoprotein, and sialic acid as targeting agents. Therefore, they can be applied for bioimaging and inhibition of targeting materials after suitable creation of the nanoparticle's surface. Boronic acid moieties on the nanoparticle surface act as reactive oxygen species (ROS), pH-responsive groups, diol-responsive nanomaterials, and targeting agents. By using H_2O_2, the hydroxyl groups containing dextran from 4-(hydroxyl methyl) phenylboronic acid pinacol ester changed to a hydrophobic dextran form, which has been applied for ROS-responsive cargo release in vitro and in vivo. In addition, due to regular cellular metabolic activity, the pH value is stable and regulated in our body. However, the metabolism process changed into an abnormality in the regulation of pH levels from pathological environments such as cancer and diabetes. In this context, a class of pH-responsive boronate−cross-linked polysaccharides displayed water solubility and biocompatibility, which can be effectively used in specific targeting (pH-dependent targeted drug delivery system) for cancer treatment. In addition, boronic-acid-based nanomaterials effectively linked with 1,2- and 1,3-containing glucose, fructose, galactose, gp 120, and ribose in a neutral pH medium. Also, they act as a neutral specific targeting agent for a glucose sensor and HIV inhibitor due to their size and structure. Similarly, boronic-acid-modified nanomaterials interact with sialic acid on the HeLa cancer cell due to their ester ring formation and reversible covalent interaction. Hence, the boronic-acid-modified nanomaterials are widely useful for cancer imaging and diagnosis.

2. CATEGORIES AND SYNTHESIS OF NANOPARTICLES

As in boronic acid moieties, nanoparticles can also exhibit interesting features that may be totally different from the bulk phase. Investigations of the interactions of nanoparticles within

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clinical research, diagnostics, and therapy with biomolecular compounds have existed for a long time due to their superior electrical and optical properties and morphology. In particular, nanoparticles have been improved as biomolecules with specific targeting agents for optical imaging amd as sensors for detection of polysaccharides and drug delivery to specific cell lines (e.g., cancer and inhibition of HIV and viral infection). Nanoparticles have also been synthesized using various methods for biomedical applications, which can adjust their size and structure in terms of their physicochemical activities. Generally, the most popular nanoparticles for biomedical applications are carbon-based nanoparticles such as fullerene, carbon nanotubes, carbon dots (CDs), carbon quantum dots (CQDs), graphene quantum dots (GQDs), and polymer dots (PDs), which are of intense interest, as demonstrated by their ability to successfully penetrate a cell membrane and tissues because of their small size, high surface area, enhanced mechanical properties, and ease of modification with functional groups on the quantum dot surface.[1] Nowadays, there are two approaches for preparing functional carbon dots, namely, "top-down" and "bottom-up". With the former, the carbon dots are designed from larger carbon cluster structures by using methods such as arc discharge, laser ablation, electrochemical oxidation, etc. In the "bottom-up" approach, the production of CDs on the surface of CDs can easily possess a large number of functional groups by using bottom-up methods, including the hydrothermal method, microwave-assistance method, ultrasonic method, and pyrolysis method.

Researchers reported numerous kinds of carbon-based fluorescent materials such as carbon dots (CDs), carbon nanodots (CNDs), graphene quantum dots (GQDs), carbon quantum dots (CQDs), and polymer dots (PDs), and so on.[1] Due to overlap and conflict separation of the various CD families, unification and standardization are important for further improvement of CDs. As fluorescent nanomaterials are developed, the analysis of fluorescent behaviors of CDs was still improved although challenging.

2.1. Classification of Reported CDs. As part of nanoparticles, CDs are a family of quantum dots that are semiconductor nanoparticles commonly coated by a capping ligand as a passivating agent to maintain its colloidal stability. For typical QDs, when this material has a size diameter that is smaller than the radius of the Bohr exciton, the PL properties are essentially dominated by the quantum confinement effect. Therefore, the size of quantum dots (QDs) depends on the exciton confinement. The regulation of intrinsic energy levels on QDs correlated to particle size, and the doping process, along with the surface effect, correlated to defects and ligands. Therefore, the homogeneous size distribution of QDs exhibits excitation-independent emission and narrows the full width half-maximum.[6] QDs composed with active elements have been widely used in a variety of devices and applications. The common QDs are prepared from II−VI or III−V element groups, which have been significantly developed in biological science and clinical applications. Therefore, they can act as valuable luminescent probes in drug delivery and specific targeting, glucose sensing or glucose detection, and bioimaging.

On the other hand, carbon dots (CDs), as developing fluorescent nanomaterials, possess at least one-dimensional shape less than 10 nm in size and excellent fluorescence as distinct optical properties. The structure of CDs exhibits a pure carbon core as an sp^2/sp^3 carbon and surface passivation group (oxygen/nitrogen-based groups) or various polymeric precursors. The optical properties of CDs were correlated with sp^2/sp^3 features from carbon and oxygen/nitrogen-based groups. The fluorescent CDs are classified into three types, namely, GQDs, CQDs, and PDs. All types of CDs create a new class of semiconductor nanoparticles with ultrasmall size (2−10 nm) and similar photoelectrochemical properties, but they differ in the internal construction and functional groups on the surface due to their specific properties, such as water stabilities, chemical stability, biocompatibility, and low toxicity. The types of CDs are discussed below.

2.1.1. Graphene Quantum Dots (GQDs). From their typical structure, GQDs exhibit a graphite structure of less than five layers and are correlated with functional groups on their edges, which are anisotropic and make them become an ultrasmall two-dimensional material. The triple carbene from zigzag edges, oxygen-based groups, and resonance properties of amine groups are exhibited on the surface/edge state of a graphene sheet. Diverse types of edges, armchair and zigzag edges, can be obtained, after cutting the graphene sheet along different crystallographic directions. As a result, the GQDs can be ideal to analyze the photoluminescent (PL) mechanism of CDs. In this context, the chemical PL process is derived from the graphene oxide (GO) because the GO is mainly used as raw molecular particles for the preparation of GQDs. In addition, the chemical structure of GO and GQDs is similar. Therefore, the aromatic sp^2 domains on the GQDs exhibited a linearly aligned epoxy and sp^3 C−O (hydroxyl bond) structure.

2.1.2. Carbon Quantum Dots (CQDs). CQDs have spherical structure and amorphous nature (if crystallinity shows a lattice parameter up to 0.24 nm), which contain a sp^2/sp^3 carbon core and rich oxygen. CQDs possess a multiple-layer graphite structure with the same horizontal and vertical dimensions that made it different from the planar structure of GQDs, which set graphene the as main structure with a honeycomb lattice of carbon atoms and sp^2 hybridization carbon structure.[6] In this regard, CQDs are suitable for chemical modification and surface passivation using organic or inorganic molecules, diverging polymers, and biological materials. Therefore, CQDs have been effectively developed by surface passivation. Also, due to the various molecules, the surface energy traps controlled the PL mechanism of CQDs.

2.1.3. Polymer Dots (PDs). PDs, generally named polymer CDs, have also been reported as a new structure of the CD family. The structure of PDs consists of either polymeric cross-linked/aggregated polymer chains or linear polymer chains assembled around the spherical carbon. However, a vast majority of PDs are a tangled coil, which consisted of high cross-linking and a hydrophilic chain on the external PD surface. PDs further enhanced the fluorescence emission due to the highly cross-linked enhanced emission effect, which described the excellent emission in their species nonconjugated polymer structure. The PL of the PD nanoparticles can have a diverse lifetime, and the intensity of the emission wavelength depends on their surface group, size, and structure. Due to the carbonization, the chemical stability of PDs is better than that of simple polymers. Also, the aggregated polymer chain provided better compatibility of PDs than that of QDs. This proves that the correlation between the polymer and carbon core brings about advantages for the development of eco-friendly materials due to the nontoxic and low-cost properties of these materials.

2.2. Synthesizing the CD Nanoparticles. Table S1 (Supporting Information) lists many reports that successfully

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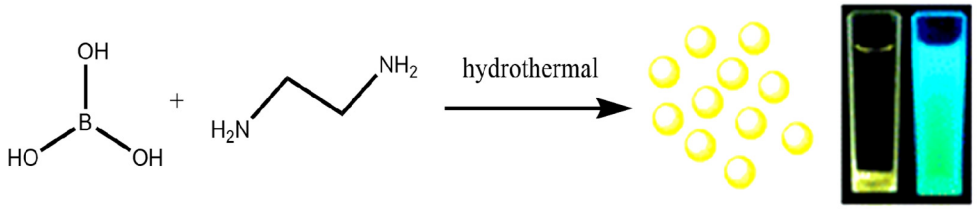

Figure 1. Synthesis process of the fluorescence properties of B-doped carbon dots (CDs) on both aqueous and solid conditions. Photograph courtesy of C. Shen. Reprinted with permission from ref 8. Copyright 2015 Royal Society of Chemistry.

obtain CDs with divergent synthesis methods such as hydrothermal, laser irradiation, microwave assistance, pyrolysis, electrochemical, and cross-linking and assembly methods, which summarize the advantages and disadvantages by using different methods. These results indicated an ease of preparing CDs. Therefore, we can easily understand from Table S1 that one of the most common organic precursors is prepared from the hydrothermal or solvothermal method. Their advantages and disadvantages create restrictions for further applications. As a result, the achievement for further synthesis design is the physical form, and it should produce uniform size, easy modification, and high QY. Even so, the hydrothermal method was widely utilized because it is effective and fast and has low cost, biosafety, and environmental friendliness. Therefore, we discuss the as-prepared boron-based nanoparticles by using hydrothermal/solvothermal methods in the next section of this mini-review.

2.3. Current Strategy for the Synthesis of Boron-Based Nanoparticles. So far, the synthetic methods for the preparation of CDs have been established into two main approaches: "top-down" and "bottom-up" routes. Both approaches exhibit inherent benefit. Nevertheless, surface passivation or functionalization for the synthesis of CDs usually needs the next step through "top−bottom" methods. Compared with the "bottom-up" methods, no next step is necessary, and the functionalization can be established in a "one-step" hydrothermal method. Hydrothermal methods are simple and easy to functionalize due to their good synthetic control and good size control, and the hydrothermal method has the advantage of creating the properties of carbon-based nanoparticles. To improve the optical properties as fluorescent properties, both the surface functionalization and heteroatom doping are the most effective ways to do so for carbon-based nanoparticles such as CDs, GQDs, CQDs, and PDs. By heteroatom doping (B, N, S, and P), the intrinsic properties as electronic properties, optical properties, and surface reactivity are effectively influenced on the nanoparticles. Many researchers have investigated improving the optical, electrical, and chemical properties of nanoparticles by introducing the heteroatoms. Due to their electronic structure, CDs can be adjusted, creating n-type or p-type carriers. Hence, by utilizing certain types and amounts of doping materials, the optical and electronic properties of carbon nanoparticles can be tuned. Although nitrogen is widely used for doping processes, it is unstable in the carbon skeleton at high temperature. Therefore, using boron atom doping into the carbon-based nanoparticles, the ionic charge (positive and negative) was effectively balanced in the carbon skeleton of the nanoparticles. For instance, our previous report showed that heteroatom doping of carbon dots was performed by a one-step furnace and microwave-assisted method with high QY. Compared to the heteroatom (B, N, S, and P) carbon dots, the boron-doped carbon dots displayed the highest photoluminescence (QY = 32.96%) and low toxicity (above 80%) and demonstrated bioimaging with strong emission in the cytoplasm of HeLa cancer cells. Besides, doping and functionalization of carbon dots effectively used the hydroxyl group containing boron derivative compounds as boric acid and boronic acid, respectively.[7] In this condition, the boronic acid (B-$(OH)_2$)-based carbon nanoparticles anticipated correlation with polysaccharide groups such as mannose, gp 120, and sialic acid on the host cell membrane, which can help us understand the inhibition of the viral mechanism. Therefore, very recently researchers have demonstrated boron doping and functionalization of carbon nanoparticles with CDs, CQDs, GQDs, and PDs by using one-pot synthesis as hydrothermal/solvothermal methods.

2.3.1. Hydrothermal/Solvothermal Synthesis. Although there are diverse ways to prepare heteroatom-doped carbon-based nanoparticles, hydrothermal/solvothermal methods are widely adopted due to their eco-friendliness, ease of operational control, high efficiency, and one-step process. In a typical synthesis, the precursors, a mixture of small organic molecules, are dissolved with solvent and transferred to a Teflon-lined stainless steel autoclave by heating at a high temperature of approximately 100−270 °C for suitable hours. At that time, all of the small molecules interact together to change carbonaceous structure and form into CDs with a size range from 2 to 10 nm. As previously reported, the synthesis of CDs using hydrothermal/solvothermal methods with a divergent boron source is summarized in Table S2 (Supporting Information). The QY can be enhanced by using suitable experimental conditions such as varying boron source, solvent nature, heating time, and temperature. For instance, Shen and co-workers[8] adopted the hydrothermal process and prepared the B-doped carbon dots (CDs) with boric acid and ethylenediamine, which have good solubility and excellent fluorescence on both aqueous and solid conditions (Figure 1). B-doped CDs' fluorescence was well controlled at yellowish-green emitted light in the solid state. Note that the above-explained synthesis strategies of CDs applied cell (cellular) imaging in the living cell. It has less toxicity and higher fluorescent staining property in living cells. Some B-doped CDs have also been an effective strategy for the metal-free electrocatalyst for the oxygen reduction reaction (ORR). Modifying the surface of carbon dots with boron reveals that the B atoms are incorporated with a positive charge on the carbon atom because their electronegativity is lower than that of C atoms.

By combining the graphene oxide (GO) and BGQD, we show the metal-free electrocatalyst for ORR. It has excellent operational stability for a long time and a strong ability to tolerate methanol crossover effectively and has the potential to be applied as a substitute for the Pt-based catalyst in ORR as well as other electrochemical applications. Moreover, Xu et al. found that the synthesized BCQDs with 3-pyridine boronic

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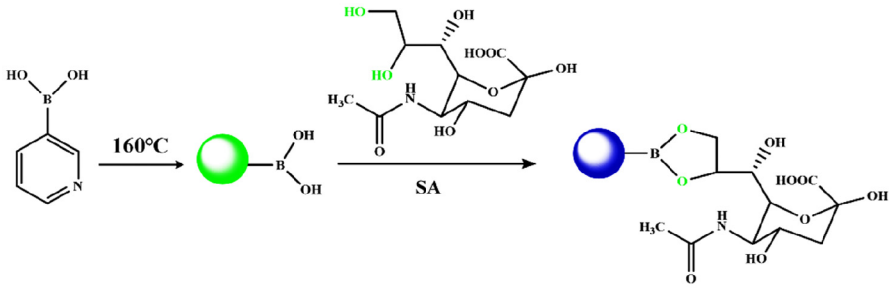

Figure 2. Process of the B-CD synthesis for the detection of SA. Adapted with permission from ref 9. Copyright 2019 Elsevier B.V.

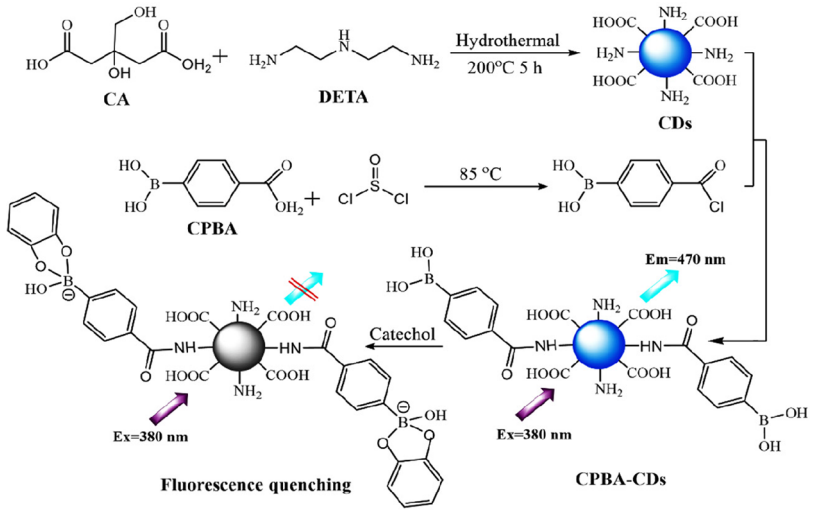

Figure 3. Synthesis process of the CPBA-CDs as nanosensors for catechol based on CPBA-CDs. Adapted with permission from ref 10. Copyright 2017 Elsevier B.V.

acid are much better for the determination of SA (Figure 2).[9] BCQDs were prepared by a one-step hydrothermal process and were effectively used for determination of SA with a linear range from 80 μM to 4000 μM (R^2 = 0.992) with a LOD value at 54 μM. It should be noted that BCQDs could successfully monitor the SA concentration in samples of human serum with sufficient data. In addition, the CDs can be applied as a dopamine (DA) biosensor for the detection of dopamine on the solid surface. Covalently linked CDs are beneficial to better adjust the size, form, physical properties, and chemical properties of the CD surface.

The application of boron-doped CDs for the detection of specific compounds was also observed by Ye et al., who synthesized the 4-carboxyphenylboronic-acid-functionalized carbon dots (CPBA-CDs) by a one-pot hydrothermal method by applying anhydrous citric acid (CA) and diethylenetriamine (CDETA) as the source of carbon and 4-carboxyphenylboronic acid as a functionalizing agent.[10] In addition, CPBA-CDs have effectively examined the catechol concentration. In various concentrations of catechol, boronic acid functional sites on the carbon dot surface react with the vicinal diols of catechol molecules, which formed the borate ester structure (Figure 3). The functionalization of CPBA-CDs found that they could be used in human umbilical vein endothelial cells and that they are mostly applicable for multicolor real-time cell staining.

By hydrothermal reaction, Jiang et al. fabricated boronic-acid-functionalized N-doped carbon quantum dots (APBA-NCQDs) from a collagen and ammonia solution, continued with modification using 3-aminophenylboronic acid (APBA) grafting as a glucose sensor (Figure 4).[11] APBA-NCQDs showed sensitivity and selectivity to fluorescent quenching properties and have been effectively applied in glucose detection and diabetes diagnostics.

The as-prepared N-B-GQDs demonstrated in vivo NIR-II imaging and used the internal organ of mouse model. The fluorescence properties of N-B-GQD nanoparticles were capable for use in imaging-related cancer therapy and

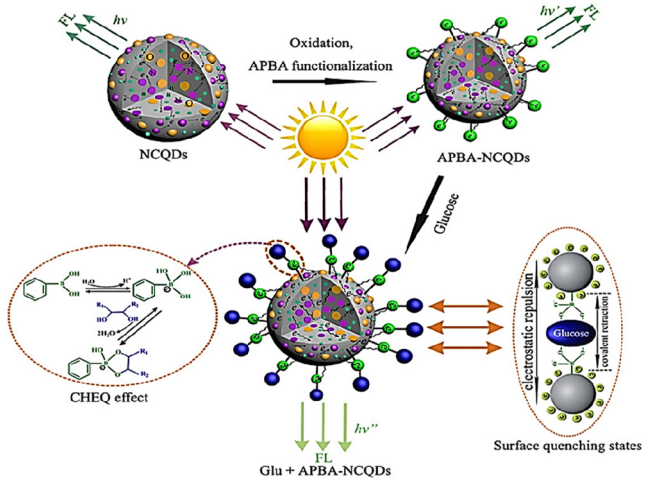

Figure 4. Synthesis process of the fluorescent behavior of APBA-NCQDs with and without the presence of glucose. Reprinted with permission from ref 11. Copyright 2014 IOP Publishing Ltd.

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monitoring. They displayed great fluorescence intensity with quantum yield and excellent stability. All the above-mentioned studies showed the interference of doping atoms on the natural emission of CDs. Although the fluorescent CDs have relatively low QY, they can be effectively used in cell imaging for sensors.

3. BORONIC-ACID-MODIFIED NANOMATERIALS FOR BIOMEDICAL APPLICATIONS

The advantages of boronic acid and CDs as part of nanoparticles open the possibility for this material to be combined to promote multipurpose applications. On further discussion, several reports on using boronic-acid-modified nanomaterials were presented for biological application.

3.1. Bioimaging. To date, carbon dots have been used as bioimaging agents to label into many cells because they are strong, stable, and highly PL. Under these conditions, the size and surface states of carbon dots greatly influence their PL properties. Table S3 (Supporting Information) summarizes the boron-containing carbon dots as a staining agent in various cell lines for cell imaging and cancer treatment. Due to their high photostability and resistance to photobleaching, carbon dots successfully stained the cell lines under prolonged illumination. It is interesting that even though the carbon dots surface is passivated with substituent groups their luminescent properties are not lost. However, many studies investigated how to improve the PL properties by using chemical modification. For example, Liu et al.[12] reported staining of sialic acids on live cells with a novel class of imaging probes on the basis of phenylboronic-acid-doped quantum dots. Quantum dots showed that they could be efficiently one-step labeled and simultaneously interacted with the sialic acid moieties of the cell's surface with no treatment of living cells. For labeling design, the QDs entered endocytic pathways together with SA into the PC12 cells for different times (10−90 min), where the amount of the quantum dots (QDs) was combined with the cell membrane and formed a ring-fluorescent shape after 10 min of incubation (shown in Figure 5). The APBA-QDs were gradually internalized and displayed bright color in the intracellular scope even under a longer incubation time from 20 to 60 min, and then over 60 min, the spread emission did not change in the cell, undertaking longer incubation time.

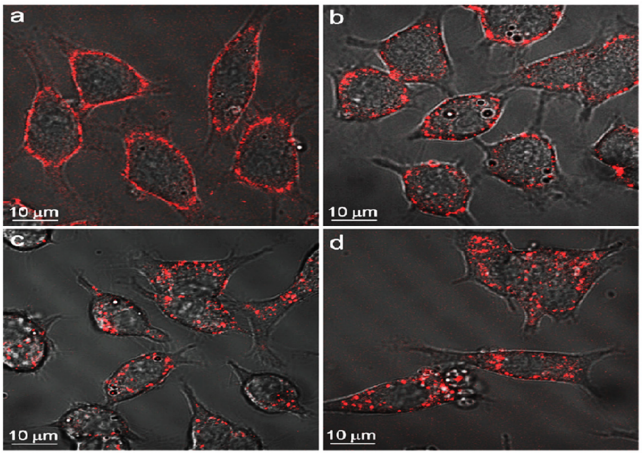

Figure 5. Confocal images of PC12 cells that were incubated using APBA-QDs and the intracellular dissemination of QD-labeled SA using various times: (a) 10 min, (b) 20 min, (c) 60 min, and (d) 90 min. Reprinted with permission from ref 12. Copyright 2010 American Chemical Society.

More remarkable progress was reported by Zhang and co-workers who reported the functionalized graphitic carbon nitride quantum dots (PCQDs) from 3-aminophenylboronic acid (APBA) through Schiff base reaction at 180 °C for 60 min.[13] The results indicated that PCQDs could efficiently and selectively label sialic acids on living cells and tissue, with a size range of 3−5 nm. Due to the abundant passivity by PBA on the structure of PCQDs, it could be more soluble in water and efficiently strained in distinct cell lines (H460, BEAS-2B, and Jurkat T cells) within 30 min. In Figure 6, the confocal images

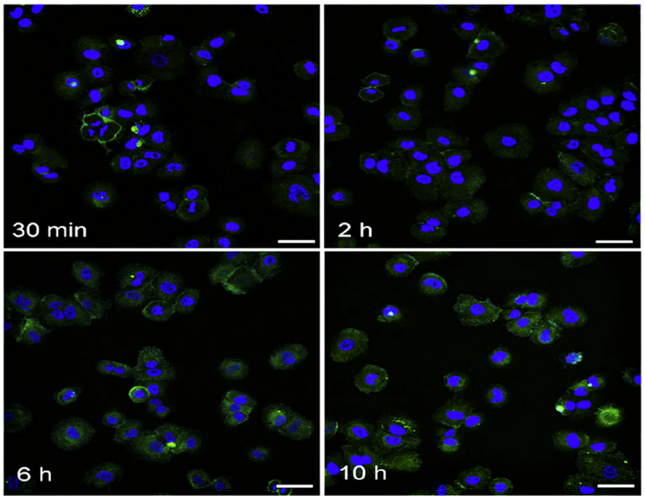

Figure 6. Confocal laser scanning images of H460 cells that were incubated with PCQDs (50 mg/mL) for various times: 30 min, 2 h, 6 h, and 10 h. Reprinted with permission from ref 13. Copyright 2019 Elsevier B.V.

of H460 cells stained with PCQDs revealed an interplay between probes and the target at varied times. After incubation for 30 min, the PCQDs were mostly bound to the cell membrane. The PCQDs are still labeled on the surface of cells even under prolonged incubation from 2 to 10 h. The QY% values of the PCQDs are also diverged due to their synthetic mechanism and structure. Note that PCQDs possessed strong stability and high QY%, which efficiently probed for labeling to the SAs on the cancer cell.

In addition, the existence of heteroatomic doping on CDs opens a change to the complex structure with a particular element. Thus, it can be modified as a nanosensor based on fluorometric as well as colorimetric assays with specific metal ions (such as Fe^{3+}). In particular, carbon dots could be used for sufficient determination of Fe^{3+} with a notable sensitivity ranging between 0.3 and 546 μM with a detection limit value of 90 nM, which is supported by the quenching of red fluorescent emission as shown in Figure S1 (Supporting Information). Nevertheless, the cell imaging experiments noted that the red fluorescence BNS-CDs can serve in the investigation of intracellular Fe^{3+}. Another study on modifying CDs with boron was proposed by Ngo et al., in which the higher fluorescent aminoboronic-acid-functionalized graphitic carbon nitride quantum dots (g-CNQDs/3APBA) exhibited labeling fluorescent potency in the cells. After being incubated with g-CNQDs/3APBA for 8 h, the HeLa cells released bright blue and green emission colors at 405 and 488 nm excitation.[14] The

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fluorescent emission of g-CNQDs/3APBA was shown in the cell membrane and cytoplasmic part of the cells in Figure 7. The

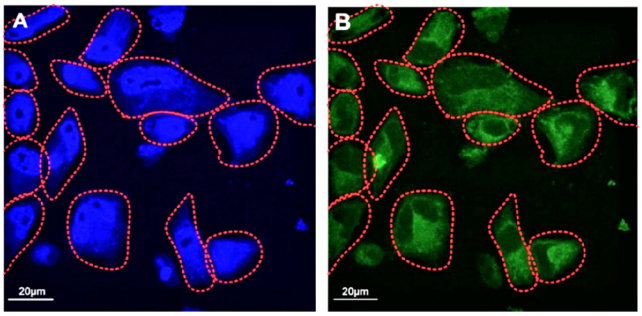

Figure 7. Confocal laser scanning images of HeLa cells with g-CNQDs/3APBA under excitation wavelengths of 405 nm (A) and 488 nm (B). Reproduced with permission from ref 14. Copyright 2019 Elsevier Ltd.

g-CNQDs/3APBA is not able to strain into the inside of the nucleus, even though it can enter into the nuclei, which makes it show low cytotoxicity and exhibit excellent bioimaging properties on the living cell surface.

In addition, boron-doped carbon nanoparticles (B-CNPs) were used to label cells because they have different diameters and size-dependent fluorescent color (red to blue). For the cell labeling experiment, HeLa cells were incubated with 30 μL of BCQDs (BC-31, BC-61, and BC-101) in the MEM medium for 5h. According to the cell imaging results, the HeLa cells with BC-101 (Figure S2d, Supporting Information) showed stronger fluorescence than BC-31 and BC-61 (Figure S2b and c). In Figure S2a, after the HeLa cells were incubated without BCQDs, the colorless images were observed. Although the QY of BCQDs was 0.5%, it could be applied well for bioimaging in HeLa cells. Investigation of a nanohybrid based on boron-doped carbon dots (BCQDs) active on both fluorescence and magnetic resonance (MR) was performed for imaging by Zhao et al.[15] BCQDs possessed great fluorescence intensity as well as higher longitudinal relativity (r_1 = 5.13 mM^{-1} s^{-1}), which exhibited red-shifted fluorescence emission. Due to the high fluorescence intensity and relaxation rates of BCQDs, they were further investigated for imaging in HeLa cells and fluorescent MR imaging in nude mice. After incubation of the HeLa cells with BCQDs (30 μg mL^{-1}) for 2 h, the cells showed bright green florescent emission under 458 nm excitation, which is in significant contrast with control cells where no fluorescence

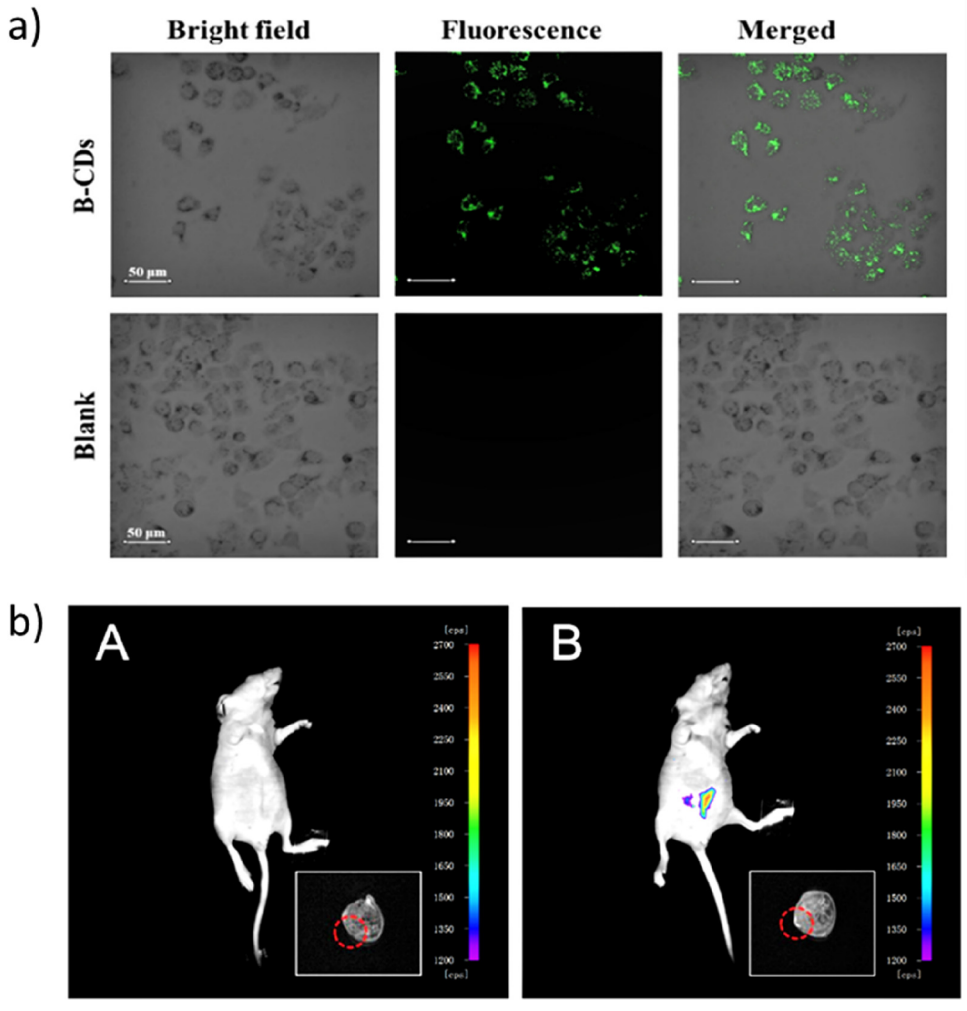

Figure 8. (a) Confocal laser scanning microscopy bright-field and fluorescence images of HeLa cells with BCQDs (30 mg/mL) and without BCQDs (blank) for 2 h. (b). In vivo fluorescence and MR imaging (inset) images without injection using BCQDs (A) and after subcutaneous injection with B-CDs into nude mice. Reprinted with permission from ref 15. Copyright 2019 Elsevier B.V.

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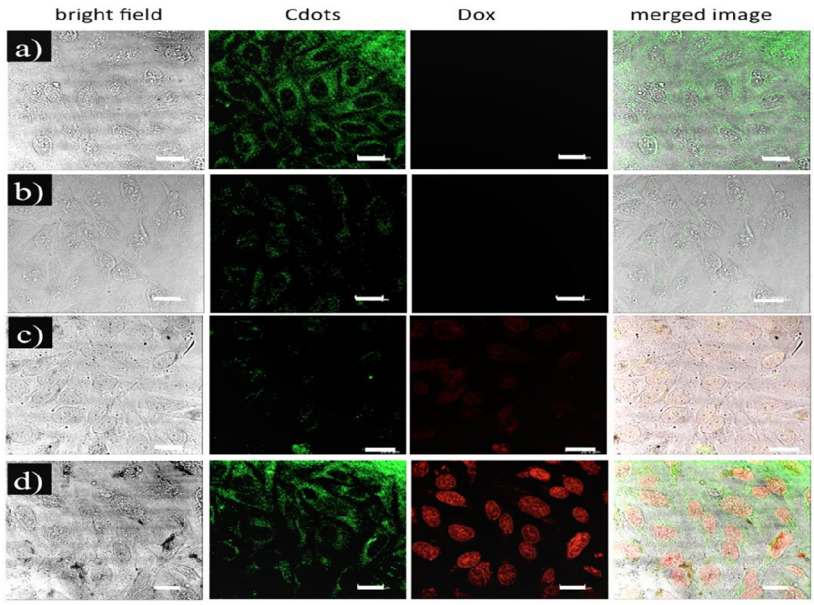

Figure 9. Confocal microscopy images showing HeLa cells incubated with CCM (a) and free CDs (b) for 1 h. Confocal microscopy images showing HeLa cells incubated with DCCM for 20 min (c) and 1 h (d). Reprinted with permission from ref 16. Copyright 2015 Royal Society of Chemistry.

color appeared (Figure 8a). For in vivo imaging, after nude mice were injected with BCQD (200 μL) solution, the MR images of the nude mice showed brighter fluorescence MR enhancement than the control conditions (Figure 8b). Zhao's group found that BCQDs with fluorescence and MR imaging properties can become true alternative beneficial agents for dual-modality imaging because of their low level of toxicity, good biocompatibility, as well as high contrast efficiency.

3.2. Cancer Cell Imaging and Diagnosis. Creating groundbreaking work, a targeted cancer investigation of various cell lines using boronic-acid-containing CDs has also been done. Recently, CDs were prepared as fluorescent probes by phenylboronic acid and citric acid (CA) and as precursors and utilized in cell imaging using HeLa cells. Due to the good water solubility and high quantum yield, the fluorescent imaging and microscopy displayed that the tiny CD nanoparticles could be internalized into the cell membrane. Nevertheless, this study suggests that CDs are suitable nanoparticles for bioimaging for future research. The CDs could be spread easily in the cytoplasm without the nucleus and agglomerated on the cell membrane.

Most of the research on applying the boronic acid moiety took advantage of forming boronate−diol bonding on the target with abundant hydroxyl groups. This feature will open a change in its application as a therapy and diagnostic (theranostic) tool simultaneously. In equivalent conditions, HeLa and B16F10 cells exhibited strong green fluorescence; however, there was no efficient fluorescence exhibited by NIH3T3 cells (Figure S3, Supporting Information). This study revealed that boronic acid worked with dual functions to increase the photoluminescent emission as well as drive the RCD1s-specific targeting on the cell. Additionally, boronic acid could be used as drug binding agent and deliver it as well. Therefore, the drug delivery of a pharmaceutical agent into the body could be done through a variety of approaches. Drug delivery systems (DDSs) using CDs have been used a lot for anticancer drug delivery. Doxorubicin (Dox), known as a commercial anticancer agent, works by inhibiting the DNA helix structure by stabilizing the enzyme (topoisomerase II complex) within the replication system and thus destroying the cancer cell. For example, Fahmi et al. synthesized magnetofluorescent nanoparticles (NPs), which were modified with phenylboronic acid and conjugated to fluorescent carbon dots (CDs).[16] The as-prepared CD−phenylboronic-acid-modified nanoparticles with doxorubicin (Dox) in aqueous solution participated in doxorubicin delivery with HeLa cancer cells. The hydrophobic properties of $MnFe_2O_4$ NPs were changed to hydrophilic materials by interaction with 4-carboxyphenylboronic acid molecules. The superior phenylboronic acid moieties were capable of interacting with a targeting specific cancer cell. Doxorubicin (Dox), a water-insoluble chemotherapy drug, was bound in magnetic nanoparticles (CCM) through $\pi-\pi$ stacking and hydrophobic interaction. Phenylboronic acid has a strong interaction ability with glycoprotein, including sialic acid, which is found on several pathologic cells. For in vitro investigation of fluorescent CCM and DCCM by confocal laser scanning microscopy, HeLa cells were used as a design cell line to examine the specificity on the cell surface (Figure 9). After incubation of the HeLa cells with the nanoparticles for 1 h, the CCM-treated cells had strong green fluorescence in the cell membrane according to the CLSM images (Figure 9a). In comparison with phenylboronic acid CDs with CCM, the CDs did not show strong fluorescence in the cytoplasm of HeLa cells (Figure 9b). The CCM is labeled into the cells through endocytosis mediated by a glycoprotein receptor. According to this result, boronic acid moieties on the CCM surface are capable of promoting intracellular uptake by receptor-mediated endocytosis. Dox connected to the surface of CCM particles to have a look at whether CCM is suitable for use as a carrier for delivering anticancer drugs. First, the HeLa cells were incubated with DCCM for 20 min, and the fluorescent images observed weak green and red fluorescence color. This result showed that DCCM cannot efficiently enter into the cells within a short incubation time (Figure 9c). After incubation for 1 h, the fluorescent green color was observed in the cytoplasm of cells (Figure 9d).

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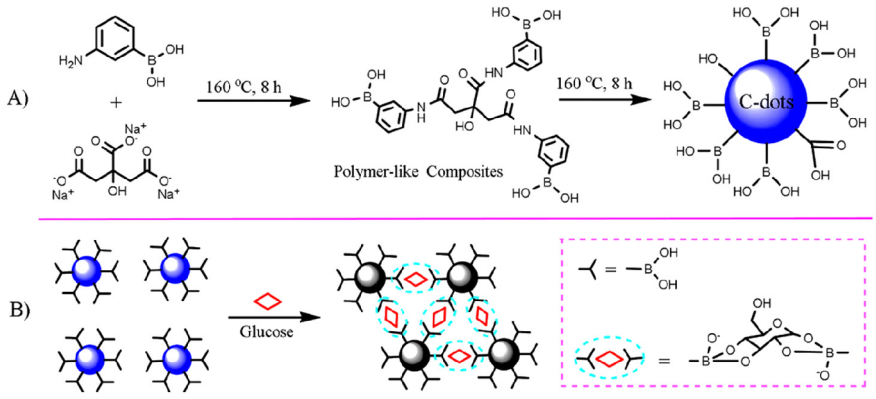

Figure 10. Schematic diagram of the synthesis process to fabricate boronic-acid-functionalized C-dots (A) and the interaction of CDs between boronic acid and *cis*-diol groups for glucose sensing (B). Reproduced with permission from ref 17. Copyright 2018 Elsevier B.V.

The boronic-acid-modified nanoparticles could interact with sialic acid moieties on the cancer cell surface, which was confirmed by a hemolysis assay. Moreover, the fluorescent CDs were attracted through an interplay between boronic acid and sialic acid moieties on the surface of the cancer cell.

3.3. Biosensing. It was well-noted on various applications that CDs have also been applied for fluorescent biosensing to examine such ions, biological pH value, protein, DNA, carbohydrates, enzymes, and vitamins. In the early state, the fluorescent properties of CDs were used to analyze biological sensors, and sensing was due to their intrinsic fluorescent properties. Furthermore, the surface modification gave excellent properties of a variety of CDs for sensing applications by transferring their surface functional groups, which act as a receptor or donor site. The features of the diverse sensors using boronic-acid-modified nanomaterials as sensor probes are discussed below.

3.3.1. Fluorescent Sensing. Traditionally, the fluorescent spectrophotometer is an extensively employed and attractive sensing technique for saccharide compounds according to their operational simplicity and high sensitivity. Interestingly, CDs can be applied in numerous fields, such as sensing and bioimaging, owing to their higher optical and fluorescent properties. In principle, the fluorescent properties of CDs are formed from the exciton radiative recombination. In theory, the fluorescence is produced from the conjugated domains in the bandgap transitions and the defected surface at the center of the carbonyl electron. The photoluminescence from CDs could be quenched well by either electron donor or electron acceptor molecules, which can efficiently enable nonradiative electron−hole recombination by an effective electron-moving process. Therefore, surface passivation or surface functionalization by doping with elements (boron, nitrogen, and sulfur) on CDs is one of the best ways to develop fluorescent features of CDs. The interaction of functionalized CDs influenced by biomolecules can exhibit the turned off−on feature, which is effective for detecting several biomolecules and improving the recovery of fluorescence. An interesting synergistic quenched effect of B-MoS_2 QDs toward dopamine (DA) by a coupling interaction was found. Boronic-acid-functionalized CDs were also often used to detect glucose for medical purposes because the sites of boronic acid on the surface of CDs will react to glucose diols. Currently, boronate affinity chemosensors are popular research topics in the field of glucose sensing. For instance, Zou et al. fabricated the boronic-acid-functionalized CDs to detect glucose concentration by sodium citrate and 3-aminophenyl boronic acid as precursors. Their impressive work is based on enhancing synchronous fluorescence quenching and resonance light scattering (RLS) (Figure 10).[17] As mentioned above, the boronic acid moieties are assembled with the *cis*-diol group of glucose, which resulted in the aggregation state of fluorescence quenching on CDs and induced strong RLS enhancement. Accordingly, the CDs exhibited good emission at pH 6−8 within the excitation wavelength of 340 nm. Especially, the hybrid radiometric chemosensor was improved for facile and selective glucose sensing in the urine sample at pH 8. The CDs had great RLS enhancement properties at a glucose concentration (LOD) of 10 μM about their specific interaction, which leads to strong fluorescence quenching of CDs and can be efficient for quantitative glucose monitoring, due to its great sensitivity, wide linear response range, and decreasing cost. For great improvement, the CD-based sensing could also be efficiently applied for not only glucose detection but also nonenzymatic glucose sensing. The boronic-acid-modified CDs demonstrate a coupling interaction with the conjugated aromatic rings of CDs and boronic acid functional groups, which can exhibit excellent fluorescent enhancement and a blue shift effect.

Postsurface modification of GQDs created oxygen-rich CDs, and the GQDs possessed negatively charge anions, which easily conjugated with glucose to form negatively charged boronate complexes. Note that the electrostatic repulsion and covalently cross-linked interaction developed a counterbalance of aggregation and disaggregation between the glucose and diol groups of boronic-acid-modified CDs. Therefore, the fluorescent APBA-CDs for glucose were suitable to use as fluorescent sensors for glucose detection. Recently, in an impressive work, the boronic-acid-functionalized nitrogen-doped carbon dots were synthesized by Anjali Devi et al. (Figure 11).[18] The high pH conditions supported that the electron pair from the nitrogen atom of the amino group on dopamine (DA) successfully transferred to the surface defects of CDs. As a result, the CDs improved the fluorescence efficiency. The fluorescent probe had a slightly blue shift behavior when adding the high DA concentration (0−61 μm). From this result, the CDs exploited a good linear correlation (R^2 = 0.99498) and an LOD of 89 pM. Consequently, the as-mentioned NCD-APBA was sufficiently utilized to investigate DA in the human serum (spiked) to obtain a good recovery percentage.

3.4. Boronic-Acid-Modified Nanomaterials for Sensitive Glucose Sensors to Manage Diabetes. Diabetes

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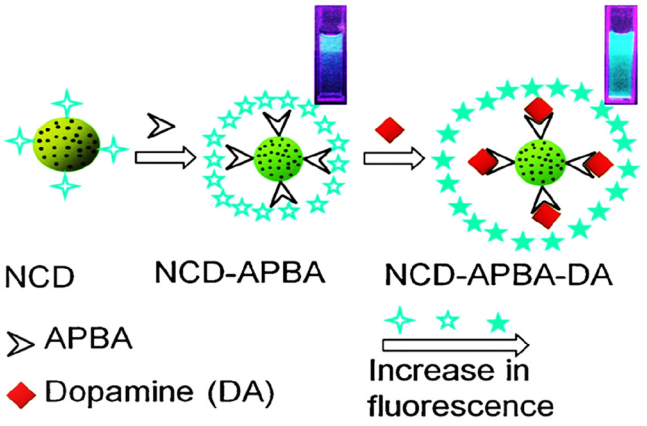

Figure 11. Schematic diagram of the dopamine detection mechanism. Reproduced with permission from ref 18. Copyright 2017 Springer Nature.

mellitus, commonly known as diabetes, is one of the chronic diseases that, if not controlled properly, may cause serious health problems including eye, kidney, nerve, and heart disorders in our body. The high glucose levels in the blood are a quantification of glucose levels in physiological bloody fluid including blood, urine, etc., and they are essential to improving diabetes diagnosis and treatment. In 1962, Lelard C. Clark presented the first glucose enzyme electrode-like glucose sensor to determine glucose concentration in the management of diabetes.[19] As shown in Table S4 (Supporting Information), some of the important sensing performances influence the detection of glucose. The glucose-sensing-based CDs exhibited tunable photoluminescence, biocompatibility, photostability, low toxicity, high sensitivity to target analyses, and high quantum yield; therefore, the glucose concentration in the serum sample solution has been widely adopted.

Furthermore, functionalization of CDs with boronic acid enhanced the diagnostic ability of nonenzymatic glucose by covalent bonding formation with the monosaccharide compounds at normal conditions. Therefore, boronic acid is extensively applied for the improvement of fluorescent sensors, carbohydrate transporters, and color sensors. On fluorescent-based sensors, the frequencies of light are correlated with glucose amount because chemical attraction of the active fluorophores is glucose-concentration dependent.

More recently, the glucose sensor based on CDs with high quantum yield (46%) was improved to determine the concentration of glucose in samples of blood serum via an aggregation-induced emission (AIE) effect and monitored by a smartphone-based method as shown in Table S4 (Supporting Information). In the field of glucose sensors, the fluorescence emission of BCNP effectively improved with increasing concentration of glucose. BCNPs found a good linear correlation (R^2 = 0.9931) in the 32 μM to 2 mM concentration range with a LOD of 8 μM. As reported above, the result of BCNPs for the glucose detection was better than the normal glucose amount in the blood sample (the level of glucose in normal blood is 3.6−6.6 mM).

3.4.1. Boronic-Acid-Modified Quantum Dots for Glucose Sensing. In addition, QDs also used numerous applications for sensing and biosensing because they have high fluorescence. As an example, the phenylboronic-acid-modified CdTe/ZnTe/ZnS quantum dots (PBA-QDs) were studied for intracellular glucose probing by Wu et al.[20] The functionalized PBA on the surface of QDs prepared linkers, which interacted with *cis*-diols to form a stable boronate compound and improved for continuous glucose sensing. At optimum conditions, the QDs performed linear corrections of PBA-QDs up to 0.9975 on a glucose concentration range of 0.4 mM to 20.0 mM and an LOD of about 0.3 mM. Therefore, physicochemical properties of QDs such as emission, wavelength, and collection efficiency also had an influence on the determination of glucose as a glucose probe in the living cells. In addition, the fluorescent QDs were prepared with inorganic semiconductor materials such as CdTe, CdSe, and ZnS, which can be developed in the two-component system for sensing transfers in the glucose aqueous solution. Thus, QDs were strongly performed as a dual-function probe with a two-component sensing system for the investigation of glucose and saccharide compounds simultaneously.

3.4.2. Boronic-Acid-Modified Graphene Quantum Dots and Graphene Oxide for Glucose Sensing. As shown in Table S4 (Supporting Information), the boron-doped graphene quantum dots (BGQDs) were reported from the boron-doped graphene (BG) using a hydrothermal approach for selective glucose sensing. The boronic acid sites on the BGQD surface facilitated their utility as a novel photoluminescence (PL) probe to label glucose sensors. It is proposed that due to the properties of boronic acid with glucose GQDs created the stiff structure of BGQD glucose aggregates, inhibiting the intramolecular reaction, thus ensuring in an outstanding excessive boost inside the PL intensity. As previously explained, adding glucose into the BGQD solution (PBS solution at pH = 7.4) leads to the aggregation-induced emission of the QDs according to the covalent binding among the boronic acid moieties. Therefore, QDs have efficiently improved the quenching of their fluorescence. From these results, the PL intensity of BGQDs was strongly increased with the glucose concentration range (0.1−10 mM) with a LOD up to 0.03 mM. On the other hand, synthesizing the biosensor as a glucose sensor with highly fluorescent quenching has also improved the beneficial nanoparticles by graphene-oxide-like carbon nanomaterials.

3.4.3. Boronic-Acid-Modified Carbon Dots for Glucose Sensing. In comparison with the other carbon-based materials, there are few applications of carbon dots as nanosensors, even though they can easily be functionalized and immobilized with polymers for biochemical analysis. It was notable that Wang et al. reported the immobilization of fluorescent carbon dot microgels (NIPAM-AAm-VPBA) from three functional comonomers (*N*-isopropylacylamide (NIPAM), acrylamide (AAM), and 4-vinylphenyl boronic acid (VPBA)), as well as fluorescent CDs (Figure 12).[21] The as-prepared glucose-imprinted poly-(NIPAM-AAm-VPBA)-CDs were able to be reversibly quenched, and the fluorescent gestures of the inserted CDs in the different glucose concentrations were recovered, which resulted in superior gesture reproducibility. The glucose-imprinted CD hybrid microgels also showed good sensitivity and selectivity for detecting glucose, which ranged between 0 mM and 30 mM at a pH value of 7.4. In these conditions, the CDs exhibited nontoxic concentration ranging from 25 to 100 μg/mL. The phenomenon of glucose-interconnected aggregation with carbon dots was applied to adjust the selective radiometric response to glucose and its effect on the quenching of carbon dot fluorescence. Interestingly, the intensity of carbon dot fluorescence significantly decreased with the rise of glucose concentration. Furthermore, the effect of pH was important to

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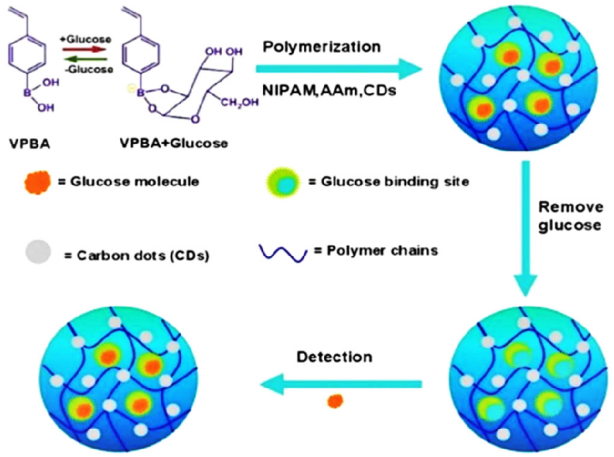

Figure 12. Schematic synthesis representation of the glucose-imprinted poly(NIPAM-AAm-VPBA)-CD hybrid microgels with certain binding sites on glucose for truly sensitive and selective glucose detection, which was based on the one-step free radical precipitation polymerization in water. Reproduced with permission from ref 21. Copyright 2015 American Chemical Society.

determine the stability of PL through the protonation and deprotonation of the molecules on the carbon dots. Therefore, the intensity of carbon dot fluorescence demonstrated a great dynamic response to the various glucose concentration ranges (1−100 mM) with linear coefficient R^2 = 0.996 (Table S4 (Supporting Information)).

For another case, Das's group published the preparation of CDs from sulfated polysaccharides k-carrageenan and phenylboronic acid for glucose determination (nonenzymatic monosaccharide) and their antidiabetes drug release properties via one-step hydrothermal treatment (Figure 13a).[22] The quenching capability of the boron, sulfur-doped carbon dots (BSC-dots) on above the pH conditions (maximum is pH 7.5) formed the boronate complex due to their proton donation reaction. The aggregation of BSC dots with glucose molecules was served through electrostatic interactions at pH 7−8.

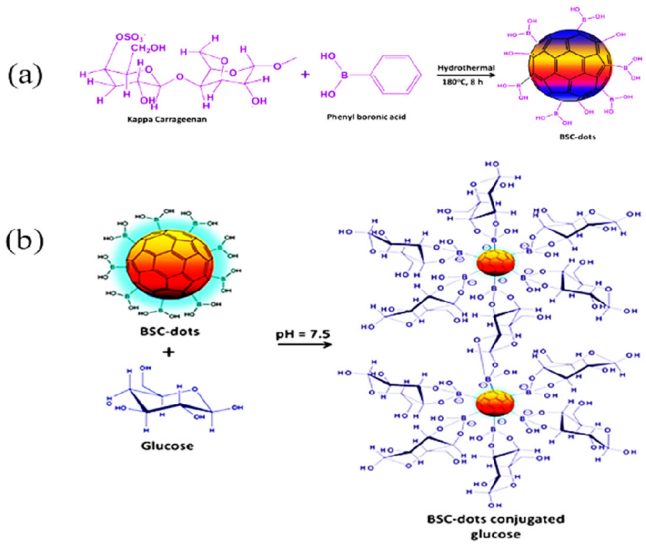

Figure 13. (a) Synthesis method of BSC dots. (b) Proposed representation process of BSC dots with the glucose molecule. Reproduced with permission from ref 22. Copyright 2019 Elsevier B.V.

Therefore, pH 7.5 was selected for the proposed mechanism of combining BSC dots with the glucose (Figure 13b). The CDs can be bound with various glucose concentrations (0−210 μM) on the blood sample. The good linear response had a concentration range from 0 to 210 μM (R^2 = 0.987) with an LOD of 1.7 μM. They suggested that the BSC dots were further applied as antidiabetes chemosensors because of their excellent biocompatibility.

3.5. Boronic-Acid-Modified Nanomaterials for Antiviral Inhibitor. The human immunodeficiency virus (HIV) is a global pandemic virus that causes acquired immunodeficiency syndrome (AIDS). Currently, HIV-1 infection can be efficiently instructed using multiple antiviral inhibitions, which are designated as a combination of antiretroviral therapy (cART) and a new ART drug. However, they have only limited or transient clinical benefits and are still highly desirable due to their major side effects (e.g., long-term toxicity) along with the rapidly developed virus drug resistance. Up to now, many researchers have still discovered no possible diagnostic interaction between the human immunodeficiency virus (HIV) and various drug materials. Particularly, the boron-containing materials are further attracting considerable interest for biomedical and biological applications. Previous authors have reviewed the new biological activity of drug design for pharmaceutical drugs using the boron element.[23] We have summarized the boron-containing materials including an organic compound, polymer, and nanoparticles for antiviral inhibition in Table S5 (Supporting Information) and boromycin that has an inhibitory effect, which highly blocks the replication step of cultured strain on the HIV life cycle. Boronic acid, as mentioned before, initiates essential binding with *cis*-diols for saccharide identification. There are as many hydroxyl moieties on the organic macromolecule as on the T cell surface. These phenomena open alternative ways for inhibition of HIV and antiretroviral infection using boronic-acid-motivated materials, including CDs. It was well noted that nanomaterials have interesting aspects for materials as small as a virus, the aspect ratio being closely related with the size of the nanoparticle that is smaller than that of the virus and thus easily disturbing the virus metabolism. Moreover, Table S5 (Supporting Information) shows that most applications of boronic acid nanomaterials on HIV therapy will relate to diol functional groups on gp120 overexpressed on the HIV surface. This shows the importance of boronic acid moiety applications on HIV therapy.

3.5.1. HIV-1 Barrier. One of the initial strains of HIV transmission in heterosexual sex is through moving of the biological fluids (from the seminal fluid to the vaginal fluid). Hence, the development of materials used to prevent the transition of the virions from the semen to the vaginal cell wall becomes a crucial aspect, which also depends upon the pH of the biofluids. The pH range of vaginal fluid is 4 to 5 which can be changed due to the kind of buffer, volume of buffer, the basicity of the pH, and semen capacity. Nevertheless, efficient transmission of HIV virions is through an impermeable gel type to the cell as well as through associated cells of virions with the neutral pH of seminal fluid. For example, Mahalingam et al. constructed a polymer similar to mucin with PBA (phenylboronic acid) and salicylghdroxamic acid (SHA), each separately polymerized with a 2-hydroxypropylmethacrylamide (PHPMA).[24] The interaction of the phenylboronic acid (PBA) and salicylgydroxamic acid (SHA) has exhibited a weak

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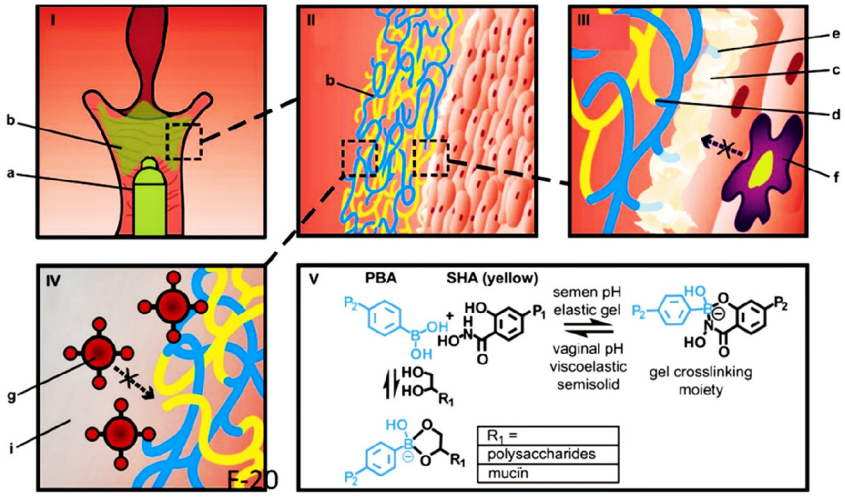

Figure 14. (I) An applicator (a) is formed for applying a weakly cross-linked viscoelastic fluid between the two-polymer solution (b). (II) The gel forms as a barrier in the middle of the vaginal mucosa and an environment. (III) The gel includes the cross-links joining the PBA (blue) and SHA (yellow) of the two polymers (d) and the bioadhesive interaction between PBA and diol moieties (e) within cervical mucus (c) and on the epithelial surface. (IV) At neutral pH, the densely cross-linked elastic network of hydrogel inhibited the virion diffusion (g) to the vaginal mucosa. (V) The pH-dependent conjugation between free and boronate-cross-linked hydrogel with salicylgydroxamic acid. Reproduced with permission from ref 24. Copyright 2011 Elsevier Ltd.

interaction under acidic pH conditions; it even has a larger combination constant at neutral pH conditions (Figure 14).

The viscoelastic nature of the covalently cross-linked PBA-SHA could be connected with mucous that prohibits the transfer of virions into cells in response to pH conditions. The benzoborozole moieties containing polymer can be combined with the group of mannoses on gp120, which could delay the HIV-1 activity before interacting with the CD4+ receptor in the cell (Figure S4). Due to the above-mentioned results, these polymers disturbed the transmission of HIV-1 entry into the cell.

3.5.2. HIV-1 Inhibition. The ongoing research on polymer modification with boronic acid has led some researchers to make improvements by modifying CDs with boronic acid and further applying them for HIV detection. As an example, Fahmi et al. have focused the antiviral drugs on the gp120 target entry inhibition concept using boronic-acid-modified carbon dots.[25] Indeed, the initial step of the life cycle of HIV virions was the gp120 interaction with the CD4 receptor on the target cell, gp120 mostly contains oligosaccharides and mannose sites with many hydroxyl groups. In this study, the noble CDs were prepared from citric acid (CA) as a carbon source and 4-carboxy-3-chlorobenzene boronic acid (CBBA) as a specific targeting agent for inhibition of HIV-1 entry. For experimental work, the inhibition ability of CBBA-CDs was examined by the infection in the cell-to-cell process, and the production of syncytia numbers was counted after incubation for 24 h using the cultured MT4/HIV-1 and MOLT-4 cells. After incubation with 300 μg/mL concentration of CBBA-CDs, the formation of syncytia was effectively prevented due to the combination with gp120 on the virus surface. According to the results, the high concentration of CBBA-CDs (75−600 μg/mL) more significantly inhibited the HIV-1 entry than the low concentration (4.69−37.5 μg/mL). Therefore, Fahmi's group found that the CDs successfully inhibited the connection of virions with MOLT-4 cells and blocked the virion activities. The as-reported GQDs could be developed to envision HIV DNA's dynamic invasions into the HeLa cells. Particularly, boron and nitrogen doping on GQDs supported the conjugation of this nanomaterial with HIV's DNA. Interestingly, the platform of sense usually coordinates a fluorophore and also a quencher that is attached by a single-stranded DNA probe molecule using fluorescence resonance energy transfer (FRET). Creating noncovalent bonds between probes and target HIV DNA is also important to reach high affinity and encourage the sensing platform. From the discussion above, the active boronic acid moiety strongly blocked the initial step of viral infection by cyclic ester formation through both chemical interaction and physical interaction. Also, the boromycin compounds have anti-HIV activity, which depends on the effect of the maturity stage for HIV replication. Thus, these biocompatible boron-modified nanomaterials were used for long interaction with glycoprotein and polysaccharide compounds and their intracellular distribution on the living cell membrane. On the other hand, most of the CDs exhibited fluorescent ability in the short-wavelength region (blue or green).[13] However, a study revealed that the red florescence of boronic-acid-modified CDs had an emission range of 620 nm, which could be deeply penetrated on the cell surface through the endocytic pathways with SA groups.[12]

4. CONCLUSION

In the research field of nanoparticles, CDs (CQDs, GQDs, PDs) have achieved tremendous importance in the last 10 years owing to their effectiveness, good biosafety, optical properties, and excellent biocompatibility. Herein, we have highlighted the boronic-acid-functionalized CDs in terms of their synthesis, properties, and biomedical applications. Although diverse synthetic methods have been demonstrated for CDs, one of the main synthesis processes for carbon dots is the hydrothermal/solvothermal method due to their low cost, stable luminescence, high QY, and ease of modification with starting materials (Table S1). For instance, the red emitted CDs (QY: 64.95%) are efficiently used for in vivo imaging. However, the QY of CDs depends on the solvent used. Additionally, the red-emission CDs were effectively used for selective determination of Fe^{3+}, sialic acid, cancer therapy, and bioimaging, respectively. Therefore, the functionalization/passivation of CDs with boron doping atoms was a crucial aspect not only to enhance desired

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optical properties but also to drive the material specific to its target. As Table S3 describes, the boronic-acid-modified CDs have been well controlled with the fluorescence at blue, green, yellow, and red wavelengths. Particularly, the multivalent interaction between boronic acid and *cis*-diol groups, producing reversible molecular assembly reactions on the biomolecule target, becomes the most important part of bioapplications for boronic-acid-containing nanomaterials. Therefore, the boronic-acid-modified CDs well demonstrated various potential in bioimaging, sensing, drug delivery, and inhibition.

5. CHALLENGES AND PERSPECTIVES

In this mini-review, boron derivative compounds including the synthesis of boronic-acid-modified carbon dots (GQDs, CQDs, PDs) and their properties were explained. The improvement of CDs for application in biomedical fields has been extensively updated within the research realm. Nevertheless, further challenging research still needs to be done for clarification. Tremendous efforts by researchers worldwide on improving the synthesis, mechanism, and performance of CDs are being devoted to these nanomaterials as promising luminescent materials, using diverse methods and sometimes inventing the selectivity and drug delivery inhibition that is still challenging. The limitations on larger size distribution, poor control of uniform size, and complex and unclear photoluminescence of prepared CDs are also important aspects for improvement.

In the case of boronic-acid-modified CDs, there are still many challenges that need to be solved, including toxicity, QY enhancement, multiinteraction system, surface passivation, and functionalization of the synthesis process that needs to be efficiently developed for the photostability and biocompatibility of CDs. Therefore, the advantages of the synthesis process should be studied more to achieve high QY, small particle size, and excellent biocompatibility. Furthermore, new boronic-acid-modified materials are formed by imprinting the multi-interaction of glucose moieties in this application area. In this mini-review, despite the above-reported challenges, the boronic-acid-modified nanomaterials have become excellent promising research materials for the future for various biological applications such as bioimaging, biosensing, and antiretroviral therapy. On the other hand, boronic-acid-modified carbon dots could inhibit viral HIV infection due to the chemical interaction effect. Also, the host genomic factors of the Covid-19 (SARS-CoV-2) virus are similar to the construction of the HIV-1 virus. Based on this phenomenon, research on boronic-acid-modified nanomaterials can be expanded to modern diseases like SARS-CoV-2, MERS-CoV, and other virus-based diseases coming in the future. The combination of experimental and theoretical studies will provide more worthy information and interesting aspects. We hope the information from this mini-review can provide guidance to the further use of boronic-acid-modified nanoparticles for many applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c01352.

Several data such as advantages and disadvantages of different synthesis methods (Table S1); the hydrothermal method for boron-modified carbon dots (Table S2); boronic-acid-modified CDs for cell imaging and cancer cell treatment (Table S3); sensing performance for glucose detection (Table S4); the summarization of the boron-containing materials for antiviral inhibition (Table S5); images of fluorescence microscopy and bright-field transmission of HeLa cells (Figure S1); confocal fluorescent images of HeLa cells without BCQDs and incubated with BCQDs (Figure S2); confocal laser scanning bright-field and fluorescence images of cells (HeLa, B16F10, NIH3T3) (Figure S3) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Mochamad Zakki Fahmi − *Department of Chemistry and Supramodification Nano-Micro Engineering Research Group, Airlangga University, Surabaya 60115, Indonesia;* orcid.org/0000-0001-5430-9992; Email: m.zakki.fahmi@fst.unair.ac.id

Authors

Yu-Yu Aung − *Department of Chemistry, Airlangga University, Surabaya 60115, Indonesia;* orcid.org/0000-0002-2169-4983

Alfinda Novi Kristanti − *Department of Chemistry, Airlangga University, Surabaya 60115, Indonesia*

Hwei Voon Lee − *Nanotechnology & Catalysis Research Centre (NANOCAT), Institute of Advance Studies, University of Malaya, 50603 Kuala Lumpur, Malaysia;* orcid.org/0000-0002-2997-5675

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c01352

Author Contributions

Yu Yu Aung studied the literature; Alfinda Novi Kristanti proofread; Hwei Voon Lee proofread; and Mochamad Zakki Fahmi proofread, studied the literature, and was editor of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

Yu Yu Aung received her master's degree (2009) in chemistry at Myitkyina University, Myanmar. Presently, she is studying as a Ph.D. researcher under the supervision of Associate Professor Dr. Mochamad Zakki Fahmi and Associate Professor Dr. Alfinda Novi Khristanti at Universitas Airlangga, Indonesia. Her research interest is based on boronic acid modified carbon dots for HIV-1 inhibition and cancer cell staining.

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Alfinda Novi Kristanti obtained her Doctorate in Organic Chemistry from Universite de Haute-Alsace, France, in 1997, under the supervision of Prof. Bernard Muckensturm. At this time, she is an associate professor at the Department of Chemistry, Faculty of Science and Technology, Universitas Airlangga, Indonesia. Her research interests are on Natural Product Chemistry and Organic Synthesis.

Dr. Hwei Voon Lee is a senior lecturer at the Nanotechnology and Catalysis Research Center (NANOCAT), University of Malaya, Malaysia. She received her Ph.D. in Catalysis (2013) and B.Sc. (Hons) in Industrial Chemistry (2008) from the Universiti Putra Malaysia. Her major research interests are energy and fuels (biodiesel, renewable diesel, biofuels), biomass conversion technology (catalytic conversion of biomass), oleochemical technology (methyl ester, polyol ester), catalysis (heterogeneous catalyst, mixed metal oxides, acid–base catalyst), and nanomaterials (biomass-derived nanocrystalline cellulose and application).

Mochamad Zakki Fahmi got his Ph.D. in Chemical Engineering in 2014 from the National Taiwan University of Science and Technology. Currently, he works as an Associate Professor at the Department of Chemistry Universitas Airlangga. His focus is on the study of medical purposed nanomaterials used mainly for theranostics of cancer and HIV.

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■ ABBREVIATIONS

CDs, carbon dots; QDs, quantum dots; GQDs, graphene quantum dots; CQDs, carbon quantum dots; PDs, polymer dots; GO, graphene oxide; HIV, human immunodeficiency virus; pH, power of hydrogen; PL, photoliminescent; gp 120, glycoprotein 120; QY, quantum yield; ORR, oxygen reduction reaction; BGQDs, boron-doped graphene quantum dots; BCQDs, boron-doped carbon quantum dots; LOD, limit of detection; LOQ, limit of quantification; DA, dopamine; rBA-CDs, reactive boronic-acid-functionalized carbon dots; N-B-CQDs, boron and nitrogen codoped carbon dots; PCQDs, 3-aminophenylboronic-acid-functionalized graphitic carbon nitride quantum dots; SA, sialic acid; BNS-CDs, boron, nitrogen, sulfur-codoped carbon dots; g-CNQDs/3APBA, aminoboronic-acid-functionalized graphitic carbon nitride quantum dots; B-CNPs, boron-doped carbon nanoparticles; MR, magnetic resonance; RCDs1s, photoselitizer(riboflavin)-tailed surface-functionalized carbon dots; ROS, reactive oxygen species; H16F10, melanoma cell; NIH3T3, noncancerous cell; DDS, drug delivery system; Dox, doxorubicin; NPs, nanoparticles; CCM, magnetic nanoparticles; DCCM, doxorubicin–carbon combined magnetic nanoparticles; CLSM, confocal laser scanning microscope; PB-AuNCs, phenylboronic acid template gold nanoclusters; CLO^-, hypochlorite; ARS, alizarin red S; B-MoS_2QDs, boronic-acid-functionalized molybdenum disulfide quantum dots; FRET, fluorescent energy transfer; IFE, inner filter effect; RLS, resonance light scattering; APBA-GQDs, boronic-acid-functionalized graphene quantum dots; DAPEG, diacrylate polyethylene glycol; AIE, aggregation-induced emission; BCNP, boronic-acid-doped carbon nanoparticles; PBA-QDs, phenylboronic-acid-functionalized graphitic carbon nitride quantum dots; HS, horse serum; rGO-PBA, phenylboronic acid functionalized with reduced graphene oxide; NIPAM-AAm-VPBA, immobilization fluorescent carbon dot microgel; BSC-dots, boron, sulfur-doped carbon dots; (VPBA-AAM)-CDs, carbon-dot-immobilized hybride microgel poly; cART, combination antiretroviral therapy; HCV, hepatitis C virus; HSV-1, herpes simplex type 1

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