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ORIGINAL PAPER

A boronic acid based glucose assay based on the suppression of the inner filter effect of gold nanoparticles on the orange fluorescence of graphene oxide quantum dots

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Abstract The authors describe a non-enzymatioc glucose assay that has three features: (a) The use of a boronic acid as the recognition element; (b) the aggregation of gold nanoparticles (AuNPs), and (c) the use of graphene oxide quantum dots (GOQD) whose fluorescence matches the absorption of the AuNPs and thereby results in an inner filter effect (IFE). The GOQD display an orange colored fluorescence that is filtered off by the AuNPs due to an IFE. In the presence of 3-aminobenzeneboronic acid, glucose is bound to form a cationic species that causes the aggregation of AuNPs to form large assemblies. This is accompanied by a color change from red to blue, and the IFE no longer does occur so that the orange fluorescence of the GOQD pops up again. These findings were used to design an assay witha linear response in the 2.5 to 75 μmol L^{-1} glucose concentration range, with a detection limit of 0.65 μmol L^{-1}. The method was applied to the determination of glucose in spiked diluted serum and gave satisfactory results.

Keywords Carbonaceous nanomaterial · Fluorescence · Aggregation assay · Glucose · Molecular recognition · Serum analysis

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Introduction

Glucose is a key nutrient for biological metabolism and is also an essential compound for medical, biotechnological, nutritional, and environmental applications [1]. As a result, its measurement is of important significance in clinical diagnosis, health protection and control of diabetes or hypoglycemia [2, 3]. Despite the enormous progress achieved in the field of glucose assay during the last decade [4], most of the glucose assay employ electrochemical or photoelectrochemical [5, 6] type and these methods are generally based on the oxidation of glucose by the enzyme glucose oxidase or glucose dehydrogenase [7, 8]. This is due to their high sensitivity, reproducibility, and ease of handling as well as their low production and running cost [9]. However, the catalytic of activity enzyme can be easily affected by environmental conditions such as acidity, temperature and inhibitors [10]. Selective recognition is a prerequisite for selective detection of glucose. This can be accomplished by various means such as relying on unique peroxidase-like activity of some nanomaterials instead of enzymes or the capability of organic boronic acids to act as molecular receptors for glucose [11]. Fluorescence methods show great promise for the detection of trace amounts of analytes owing to their sensitivity, simplicity, fast response, and cost-effective instrumentation [12]. Thus, it is of great significance to develop a sensitive and selective non-enzymatic fluorescent method as alternative for the determination of glucose.

Graphene oxide (GO), as a direct derivative of graphene, consists of small graphene domains surrounded by carboxyl, epoxyl and hydroxyl groups. When the sheets are less than 100 nm lateral size and between 3 and 20 nm diameter size, they are referred to as graphene oxide quantum dots (GOQD) [13]. Quantum confinement and edge effect make them exhibit interesting properties such as fluorescent activity, robust

chemical inertness, excellent photostability, high biocompatibility and low toxicity [14–16]. These features make GOQD especially useful for optical sensing and imaging and to be a potential candidate to replace traditional quantum dots. Tremendous attention has been paid to the covalent or noncovalent modification of GOQD with functional molecules or nanoparticles to facilitate target analyte sensing through energy or charge transfer from GOQD to the targets, which is often marked by fluorescence quenching of the GOQD [17]. However, the "turn off" sensing principle usually suffers from relatively low sensitivity and might be interfered with a variety of ligands or solvents, leading to false positives [18]. Moreover, the development and application of GOQD is still in its initial stage, and very little work has been done in the sensing system with "turn-on" model. To develop "turn on" fluorescence sensors, new approaches based on new GOQD architectures need to be established.

Gold nanoparticles (AuNP) have been broadly used in biochemical assays, owing to their straightforward synthetic/modification protocols and excellent properties such as high extinction coefficient for bare eye readout [19, 20] Moreover, AuNP can quench the fluorescence of organic dyes and QDs through the fluorescence resonance energy transfer (FRET) or the efficient inner filter effect (IFE). In particular, the IFE method does not require the intermolecular connection of fluorophores and absorbers at a particular distance, which provides a comparatively simple and facile approach for the analytical detection [21].

Considering the unique optical properties of GOQD and the high quenching efficiency of dispersed AuNP on the fluorescence of GOQD through the IFE, we develop a method for fluorescent detection of glucose. The detection strategy is shown in Scheme 1. An efficient IFE would occur between GOQD and AuNP, with GOQD acting as the donors and AuNP as the acceptors. So the fluorescence of GOQD can be significantly quenched by AuNP. The APBA functional groups react with the glucose molecule containing two pairs of cis-diols to form a new positively charged molecule named AGA. We find that AGA can induce the aggregation and color change of AuNP, whereas the formation of AGA prevents AuNP-triggered GOQD fluorescence quenching and restore the fluorescence. The specific interaction between AGA and AuNP can be exploited in the development of a simple and selective assay for glucose detection.

Experimental section

Materials

The water used in all experiments had a resistivity higher than 18 MΩ·cm. Graphite powder (100 mesh), H_2SO_4 (98%), H_2O_2 (30%) and $KMnO_4$ were purchased from HuaCheng Biological Co., Ltd. (http://www.cchcsw.com). $HAuCl_4$ was purchased from Acros Organics (http://www.acros.com). Glucose, 3-aminophenyl boronic acid (APBA) and some other chemicals used were purchased from Beijing Dingguo Changsheng Biotechnology Company (http://www.dingguo.com). Sodium dehydrogen phosphate (NaH_2PO_4) and disodium hydrogen phosphate (Na_2HPO_4) were purchased from Beijing Chemical Works (www.vvchem.com). All other chemicals were of analytical reagent grade. The 0.1 mol L^{-1} phosphate buffer (pH 6.2) was used as the medium for detection process.

Apparatus

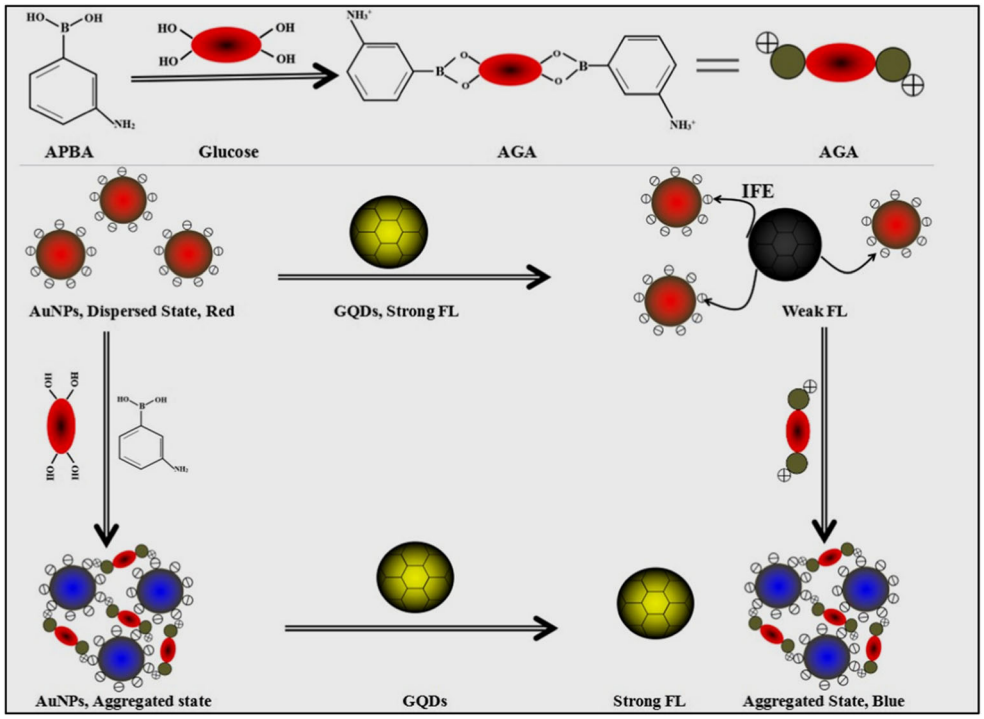
The fluorescence spectra were obtained by using a Shimadzu RF-5301 PC spectrofluorophotometer (Japan, http://www.shimadzu.com) equipped with a xenon lamp using right-angle geometry. UV-vis absorption spectra were obtained by a Varian GBC Cintra 10e UV-vis spectrometer (Japan, http://www.shimadzu.com). In both experiments, a 1 cm path-length quartz cuvette was used. FT-IR spectra were recorded with a Bruker IFS66V FT-IR spectrometer equipped with a DGTS detector. All pH measurements were made with a PHS-3C pH meter (China, http://www.lei-ci.com).

The preparation of GO by the modified hummers method

Graphene oxide (GO) was prepared from graphite powder by the modified Hummers method. Typically, 1.0 g of graphite powder was added to 25 mL H_2SO_4 (98%) and stirred 30 min. Afterwards, 3.5 g $KMnO_4$ was added and the mixture was stirred for 30 min in an ice bath, and then stirred at 35 °C for 1 h. Next, the mixture was diluted by 90 mL distilled water and the temperature was increased to 90 °C stirred for another 30 min. Subsequently, another 90 mL diluted water was added and then 10 mL of 30% H_2O_2 solution was added. The color of the mixture changed to bright yellow quickly. The resulting mixture was washed with distilled water several times and purified in a dialysis bag with a molecular weight cutoff of 10,000 Da against deionized water until the pH of the solution became neutral. After that, the solution was dried under vacuum to remove water. Finally, some black GO powder was obtained.

The preparation of GOQD by the chemical oxidation of GO

1.0 g GO was dissolved in 30 mL H_2SO_4 (98%) and stirred 15 min, Afterwards, 5.0 g $KMnO_4$ was added and the mixture was stirred for 30 min in an ice bath, and then stirred at 40 °C for 1 h, Next, the mixture was diluted by slowly dropwise adding 120 mL distilled water, afterward, 10 mL of 30%



Scheme 1 Schematic illustration for the detection of glucose based on inner filter effect between AuNP and GOQD

H_2O_2 solution was added. The solution became transparent and color of the solution changed to bright yellow quickly. Finally, the solution was purified in a dialysis bag with a molecular weight cutoff of 1000 Da against deionized water to obtain a pure GOQD solution. Finally, the brightly orange GOQD solution was obtained. 300 μL GOQD was diluted to 1.6 mL with deionized water. The fluorescence spectra were recorded from 490 nm to 700 nm with the excitation wavelength of 470 nm. The slit widths of excitation and emission were both 10 nm.

Synthesis of AuNP

The AuNP were synthesized by the reduction of $HAuCl_4$ with sodium citrate according to the previous reports [22]. In a typical experiment, 1 mL $HAuCl_4$ solution (1%, *V*/V) and 99 mL deionized water were added into a 250 mL round-bottom three-necked flask. Then, the solution was heated to a boiling state under reflux condenser conditions with vigorous stirring. Subsequently, 5 mL trisodium citrate solution (1%) was quickly injected to the flask. When the color of the solution changed from pale yellow to deep red, the reaction was finished. The solution was cooled down to room temperature and then stored at 4 °C in the refrigerator for further use. The molar extinction coefficient (ε) around 520 nm for the AuNP is about $2.7*10^8$ mol^{-1} cm^{-1} [23], thus the molar concentration of the AuNP was calculated to be nearly 4 nmol L^{-1} according to Lambert Beer's law.

Glucose detection

A typical glucose detection process was performed as follow. 0.1 mol L^{-1} phosphate buffer (pH 6.2, 160 μL), 150 μmol L^{-1} APBA solution, different amounts of glucose and 1.50 nmol L^{-1} AuNP were added to a series of 2.0 mL calibrated test tubes followed by the thoroughly shaking and equilibrated for 40 min. Subsequently, 300 μL purified GOQD solution were placed in the above calibrated test tubes. Then, the mixtures were diluted to 1.6 mL with deionized water and mixed thoroughly. At last, the fluorescence spectra were recorded from 490 nm to 700 nm with the excitation wavelength of 470 nm. The slit widths of excitation and emission were both 10 nm.

Detection of glucose in serum samples

The fresh human blood samples were supplied by the local hospital and all the blood samples were obtained through venipuncture. Some necessary processes were conducted to remove large molecules and proteins to get the serum samples. The blood samples were segregated by adding acetonitrile (the volume of acetonitrile and blood was 1.5:1) and at 5364 g centrifugational force 5 min after stored for 2 h at room temperature. Then, all supernatant serum samples were subjected to a 200-fold dilution before analysis, and a certain concentration of glucose was added to prepare the spiked samples. These samples were detected with the fluorescence measurements under the optimal conditions.

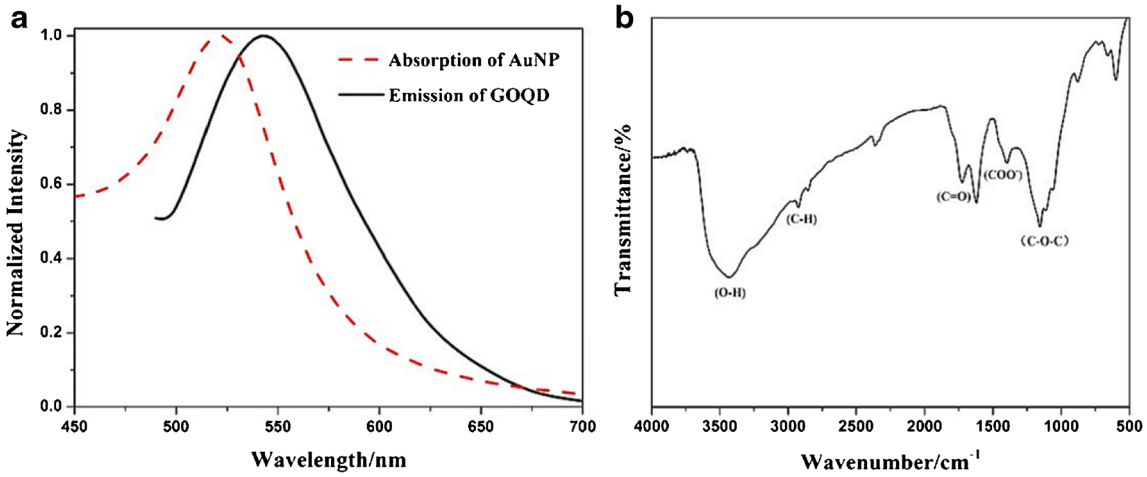
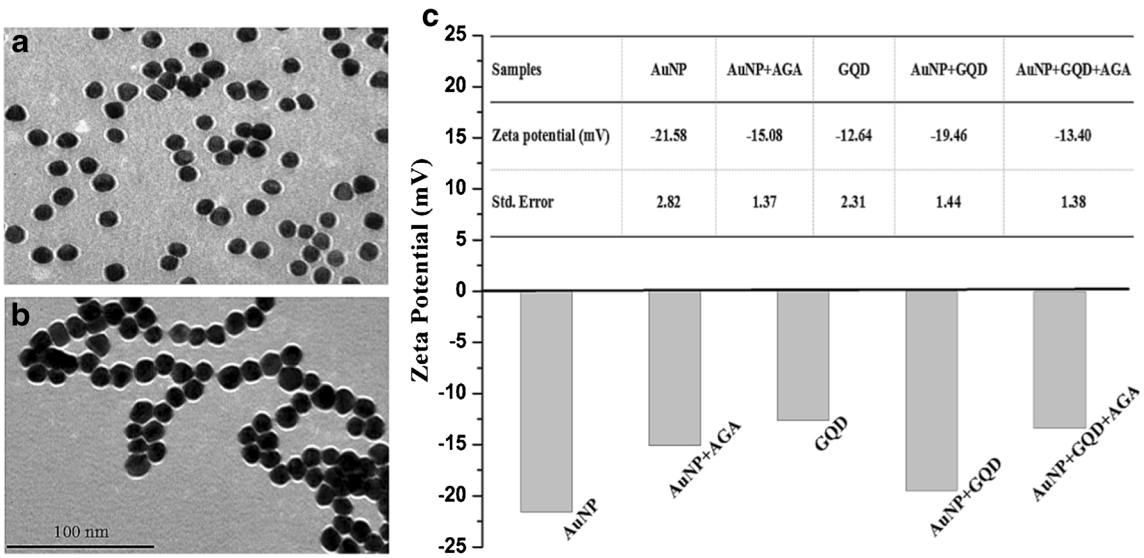


Fig. 1 **a** The absorption spectrum of AuNP (*red dash line*) and fluorescence spectrum of GOQD (*black solid line*). **b** The FT-IR spectra of GOQD

Results and discussion

The inner filter effect between GOQD and non-aggregated gold nanoparticles

The GOQD was synthesized by a facile chemical oxidized method. The morphology and size of GOQD was recorded by TEM (Fig. S1). It reveals that GOQD are spherical with an average size of about 16 nm. The assay system consisted of AuNP and GOQD, where GOQD acted as fluorometric reporter, and AuNP served as fluorescence quencher. Compared to the fluorescence resonance energy transfer, IFE does not require chemical linkage between absorber and fluorophore. As shown in Fig. 1(a), the green emissive GOQD (black solid line) emitted strong fluorescence with the maximal emission wavelength at 544 nm. The elemental analysis of GOQD was performed and the data summed up in Table S1, we can see the oxygen ratio was 37.21 which indicated numerous oxygen functional group existed on GOQD. Figure 1(a) shows the absorption spectra of AuNP (red dash line) and the maximum absorption at 522 nm. The remarkable overlap between the fluorescence emission spectrum of GOQD and the absorption spectrum of the AuNP is an indispensable factor for IFE. The existence of surface functional groups of GOQD is studied using FT-IR spectra, which is shown in Fig. 1(b). Peaks at 3200–3550 cm^{-1} and 2800–2950 cm^{-1} are attributed to the C–OH and C–H stretching vibrations, respectively [24]. Peak at about 1600 cm^{-1} indicate the presence of C = O and the band at around 1080 cm^{-1} present the existence of C–O (hydroxyl, ester, epoxide or ether) groups [25]. Generally, the existence of these functional groups represent excellent water solubility of these nanomaterials without further surface modification. Furthermore, both GOQD and AuNP possess negative charges,



Samples	AuNP	AuNP+AGA	GQD	AuNP+GQD	AuNP+GQD+AGA
Zeta potential (mV)	-21.58	-15.08	-12.64	-19.46	-13.40
Std. Error	2.82	1.37	2.31	1.44	1.38

Fig. 2 **a** TEM image of AuNP in dispersed form. **b** TEM image of AuNP in aggregated form. **c** The zeta potentials of AuNP, AuNP-AGA, GOQD, AuNP-GOQD and AuNP-GOQD-AGA in the 10 mmol L^{-1} phosphate buffer (pH 6.2)

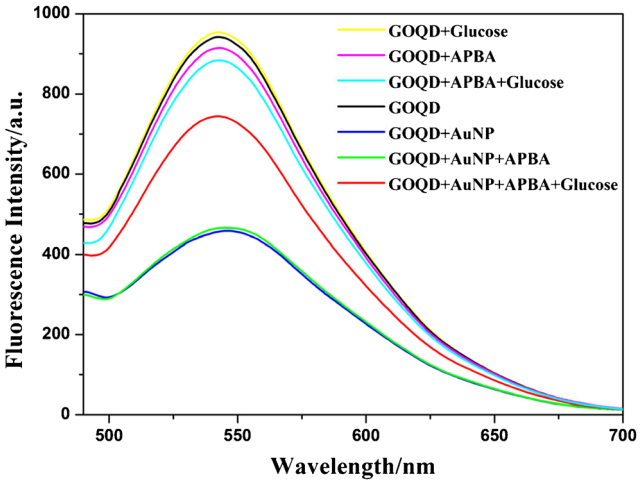


Fig. 3 Fluorescence spectra of GOQD, GOQD/Glucose, GOQD/APBA, GOQD/APBA/Glucose, GOQD/AuNP, GOQD/AuNP/APBA and GOQD/AuNP/APBA/Glucose system

there is no electrostatic attraction between the GOQD and AuNP. We conclude that quenching by AuNPs occurs via an IFE, not by FRET.

The mechanism for glucose assay

Boronic acid and various molecules containing the boronic acid have drawn an immense interest in the fabrication of monosaccharide sensors based on UV–vis absorption, fluorescence and surface plasmon resonance, due to the ability of forming five or six membered boronate esters through reversible covalent bonds with cis-1,2- or 1,3-diols [26, 27]. In this assay, APBA can react with glucose in the molar ratio 2:1 to produce a AGA, a five-ring boronate ester that carries two amino groups. AGA induces destabilization and aggregation of AuNP, phenomenon that can be ascribed to the electrostatic interaction between the positively charged AGA and the negatively charged AuNP. Consequently, as shown in Fig. S2, the optical properties of AuNP changed and the corresponding surface plasmon resonance induced absorption peak was shifted from 520 to 680 nm after the addition of AGA [28]. Moreover, AGA can trigger the color of AuNP solution change from wine-red to blue which depicted in Fig. S3. From the color of AuNP we can estimate the level of glucose via bare eye. More direct evidence for the AuNP aggregation comes from the TEM images (Fig. 2), we can see the AuNP is well dispersed while become aggregated after the addition of AGA molecule. Figure 2(c) shows the zeta potentials of AuNP, AuNP-AGA, GOQD, AuNP-GOQD and AuNP-GOQD-AGA system. The zata potential of AuNP-AGA is higher than that of AuNP, proves the AGA indeed absorb to the surface of AuNP via electrostatic interactions. The zeta potentials of AuNP (−21.58) and GOQD (−12.64) indicate that the former is more competitive to interact with AGA. The potential of the detection system become more positive than AuNP-GOQD and is near to GOQD after the addition of AGA, which indicates the AuNP aggregation formed while the GOQD still keep dispersed state.

Detection strategy for glucose

To study the detection mechanism of the GOQD based assay, the fluorescence emission spectra of GOQD, GOQD/Glucose, GOQD/APBA, GOQD/APBA/Glucose, GOQD/AuNP, GOQD/AuNP/APBA and GOQD/AuNP/APBA/Glucose system were studied and showed in Fig. 3. The fluorescence of the GOQD is obviously quenched with the addition of AuNP, which is due to the efficiently IFE between GOQD and AuNP. Subsequently, when introduction of APBA to the GOQD/AuNP system, it didn't display a remarkable influence on the fluorescence of GOQD/AuNP system. However, a great enhancement in the fluorescence intensity can be observed by adding the

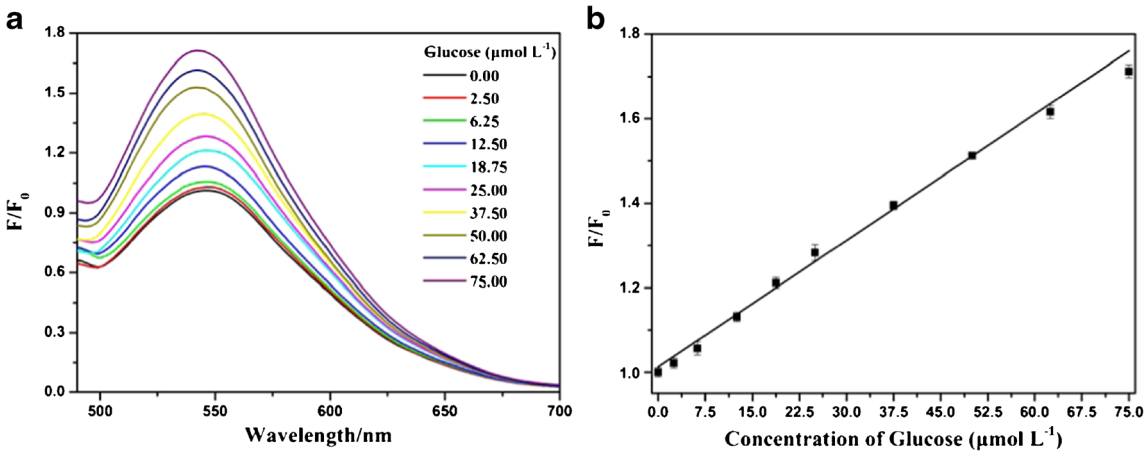


Fig. 4 **a** The fluorescence spectrum of GOQD in the presence of 1.50 nmol L^{-1} AuNP and 150 μmol L^{-1} APBA upon the addition of glucose at different concentrations from 0 to 75 μmol L^{-1}. The concentrations of glucose were 0, 2.5, 6.25, 18.75, 25, 37.5, 50, 62.5 and 75 μmol L^{-1}, respectively. **b** The linear plot of F/F_0 versus the concentration of glucose. F and F_0 were the fluorescence intensity of GOQD/AuNP/APBA system in the presence and absence of glucose, respectively

Table 1 An overview on the reported boronic acid-based methods for determination of glucose

Detection method	Material used	LOD	Linear range	Ref
Electrochemistry	Glassy carbon electrode modified with 3-aminophenylboronic acid	0.25 mM	0.5–50 mM	11
Electrochemistry	3-aminophenylboronic acid functionalized reduced graphene oxide	0.1 μM	0.1 μM-5 mM	26
Field effect transistors	Carbon nanotube functionalized with pyrene-1-boronic acid	0.3 μM	1 μM-100 mM	34
Electrochemistry	Au/p-aminothiophenol/4-formylphenylboronic acid electrode	8.4 mM	0.1–50 mM	35
Electrochemistry	Poly (3-aminophenylboronic acid) functionalized carbon nanotubes	3.46 mM	0–10 mM	36
Fluorometry	GOQD/gold nanoparticles/APBA	0.65 μM	2.5–75 μM	This work

glucose to the GOQD/AuNP/APBA system. Therefore, the observed fluorescence recovery of the GOQD/AuNP can be only due to the aggregation of AuNP, which is induced by AGA, the reactants of APBA and glucose. Based on the fluorescent signal changes of GOQD/AuNP/APBA/Glucose system, the detection of glucose is achieved. The fluorescence of GOQD can be partially quenched by the introduction of AGA or APBA, this phenomenon is caused by the weakly electrostatic interactions and hydrogen bond interaction between GOQD and AGA/APBA. It also can be seen that the fluorescence intensity of GOQD is not influenced by the addition glucose, which indicated that the interaction between glucose and GOQD is negligible.

Optimization of method

The following parameters were optimized: (a) concentration of gold nanoparticles; (b) concentration of APBA; (c); Sample pH value; (d) incubation time; Respective data and Figures are given in the Electronic Supporting Material. We found the following experimental conditions to give best results: (a) 1.5 nmol L^{-1} concentration of AuNP (Fig. S4, ESM); (b) 150 μmol L^{-1} concentration of APBA (Fig. S5, ESM); (c) A sample pH value of 6.2 (Fig. S6, ESM); (d) a sample reaction time of 40 min (Fig. S7, ESM).

Glucose detection

Under the optimized conditions, we further characterized the detection range of this sensing strategy. Figure 4(a) showed the fluorescence spectra of GOQD/AuNP/APBA system in the presence of different concentrations of glucose from 0 to 75 μmol L^{-1}. It can be seen that the fluorescence intensity increased dramatically with the increase of glucose concentration from 2.5 to 75 μmol L^{-1}. Figure 4(b) shows the calibration curve for the glucose detection and the linear range was found to be from 2.5 to 75 μmol L^{-1} with a linear equation of $F/F_0 = 1.01277 + 0.00997$ [Glucose] (μmol L^{-1}), where F and F_0 is the fluorescence intensity of GOQD/AuNP/APBA system in the presence and absence of glucose, respectively. The corresponding regression coefficient is 0.995, and the limit of detection (LOD) for glucose is 0.65 μmol L^{-1}. In addition, a comparison between the method and other reported methods for glucose detection in linear range and LOD were summed up in Table S2 [29–33]. Compared with other methods, our method shows a comparable or super quantification range and LOD for glucose detection. We also make a comparison between our method and other repoerted methods which used boronic acid as the recognition molecule (Table 1) [11, 16, 34–36]. It can be seen that other methods used various boronic acid as recognition molecule are almost all based on the electrochemistry assay mode. Moreover, our method based on fluorometry assay mode can offer a comparable or supper detection limit for glucose assay. So this method offer an alternative for the selective detection of glucose.

Interference study

Selectivity is a very important parameter to evaluate the performance of a new detection method, especially for ones with potential applications in biomedical samples, a highly selective response to the target over other potentially competing species is necessary. Therefore, we further evaluated the

Table 2 Detection of glucose in human serum samples

Sample	Glucose added (μmol L^{-1})	Glucose found (μmol L^{-1})	Recovery (%)	RSD (%, $n = 3$)
Sample 1	0.0	31.9 ± 0.1	—	2.1
Sample 2	5.0	35.3 ± 0.3	95.6	3.8
Sample 3	15.0	45.8 ± 0.2	97.6	3.7
Sample 4	30.0	61.6 ± 0.1	99.5	1.9

selectivity of our assay system with various coexistence substances added. Table S3 shows the interference effect of some biological molecules and common inorganic ions on the determination of glucose, a relative error of 5.0% was considered to be tolerable. Tolerable concentration was defined as the concentrations of coexisting substances causing less than 5.0% relative error. As shown in Table S3, the tolerable concentration of lysozyme (lys), human serum albumin (HSA) is 1 μmol L^{-1} and GSH is 100 μmol L^{-1}. The tolerable concentration of Na^+ and K^+ is 0.25 mmol L^{-1} while the concentration of Zn^{2+}, Mg^{2+} and Ca^{2+} is 0.1 mmol L^{-1}. The concentration of Fe^{2+} is 0.05 mmol L^{-1} and ATP is 10^3 μU mL^{-1}. When the concentration of fructose and saccharose was 50 μmol L^{-1}, the assay system does not obviously response to them. The results show that there is little interference from commonly existing substances. As the concentration of glucose in human serum is in mM levels [37], which is much higher than the coexistence substances. Thus, the present method is suitable for selective detection of glucose.

In order to demonstrate the feasibility of the present method, it was applied to the determination of glucose in human serum samples. Serum is what remains from whole blood after coagulation, the chemical composition is similar to plasma but does not contain coagulation protein. Since the glucose in human serum samples is at several mM level, we diluted the samples 200-fold. In this way, the concentrations of glucose in diluted samples are well within the linear detection range of our assay. All data were collected from three independent measurements. From Table 2, it can be seen that the recoveries based on our method in the real samples are between 95.6 and 99.5%. The relative standard deviations (RSD) are not higher than 3.8%, indicating that the accuracy and precision of the method are satisfactory.

Conclusion

In summary, a fluorescent glucose assay system have been constructed based on the efficiently IFE of AuNP on GOQD for the first time. AuNP serve as a dual function of fluorescence quencher and colorimetric reporter in the assay system. The presence of glucose can be observed via the color change of AuNP, and quantitated by the fluorescence of GOQD. Furthermore, the fluorescent assay system performs well in glucose sensing with a wide linear relationship and a low detection limit. The application of this glucose assay in real serum sample analysis shows satisfactory results.

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Compliance with ethical standards The author(s) declare that they have no competing interests.

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