ACS APPLIED MATERIALS & INTERFACES

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Building An Aptamer/Graphene Oxide FRET Biosensor for One-Step Detection of Bisphenol A

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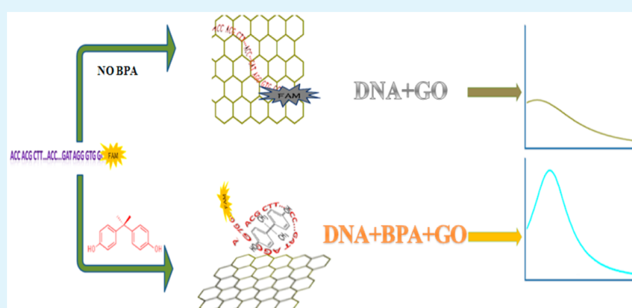
ABSTRACT: Bisphenol A (BPA) is an important industrial chemical for polycarbonate (PC) and epoxy resins in paper and plastic industries. In our work, a kind of new method for detection of BPA was designed based on graphene oxide and anti-BPA aptamer. The graphene oxide can specifically adsorb and quench the fluorescence of fluorescently modified ssDNA probes. Meanwhile, the BPA can combine with anti-BPA optamer and switch its configuration to prevent the aptamer from adsorbing on the surface of graphene oxide (GO). Under different concentrations of BPA, based on the target-induced conformational change of anti-BPA aptamer and the interactions between the fluorescently modified anti-BPA aptamer (FAM-ssDNA) and GO, the experimental results show that the intensity of the fluorescence signal was changed. A low limit of detection of 0.05 ng/mL was obtained in the range 0.1−10 ng/mL. In addition, the specificity was outstanding among analogues of BPA. The recovery rate in actual water samples spiked with BPA can be 96.0% to 104.5%. The developed method was successfully used to determine BPA in actual water samples.



KEYWORDS: *graphene oxide, bisphenol A, fluorescence, biosensor, FAM-ssDNA*

1. INTRODUCTION

Graphene oxide (GO) has potential applications in a variety of biological fields because of its unique characteristics, such as its large surface area, facile surface modification,[1−3] good water dispersibility,[4,5] and strong photoluminescence.[6] In addition, because of large absorption cross sections[7] and the non-radioactive electronic excitation energy transfer from a fluorophore to GO,[8−10] GO has been employed to construct fluorescence resonance energy transfer (FRET) biosensors. Recently, both Lu et al.[11] and He et al.[12] have demonstrated that GO could specifically adsorb and quench a dye-labeled single-stranded ssDNA probe, and the fluorescence could recover, while the probe formed a duplex with its complementary strand that resulted in the probe released from the surface of GO. Thus, GO may have applications in biosensors using ssDNA probes.

Bisphenol A (BPA), 2,2-bis (4-hydroxyphenyl) propane, has several applications in the production of food-storage components, packaging materials, tableware, and microwave ovenware. However, BPA is also a common pollutant that is hazardous to human and animal health and has been reported to be toxic.[13,14] The structure of BPA is analogous to that of endocrine hormones, which can bind to estrogen receptors because of the presence of phenol groups.[15] Research on benzene and its derivatives has attracted much attention because of the environmental hazards associated with these compounds.[16,17] Indeed, many research groups have reported a variety of techniques for the detection of benzene and its derivatives, including UV spectrometry,[18] CD spectrum analysis,[19] fluorescence analysis,[20,21] immunoassay-based methods,[22,23] electrochemical sensors,[24,25] and conventional instrument-based methods.[26−28] However, samples must be pretreated adequately to meet the requirements of such instrument-based methods. Additionally, the technicians performing such analyses must be proficient. Immunoassay-based methods depend largely on the quality of the prepared antibodies. Moreover, direct measurement of BPA is difficult because of the weak response given by conventional electrochemical sensors, and current optical analysis methods are susceptible to the influence of interfering substances.

Recently, the development of novel sensing and biosensing techniques has received substantial attention. In particular, owing to the superior attributes of aptamers, including increased specificity and sensitivity compared to antibodies, aptamer-based means have been widely used for the development of new detection methods.[29−31] Since the anti-BPA aptamer[32] was screened out for the first time in 2011, many related studies have been performed to detect BPA using

Received: September 24, 2014
Accepted: March 23, 2015
Published: March 23, 2015

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DOI: 10.1021/acsami.5b00199
ACS Appl. Mater. Interfaces 2015, 7, 7492−7496

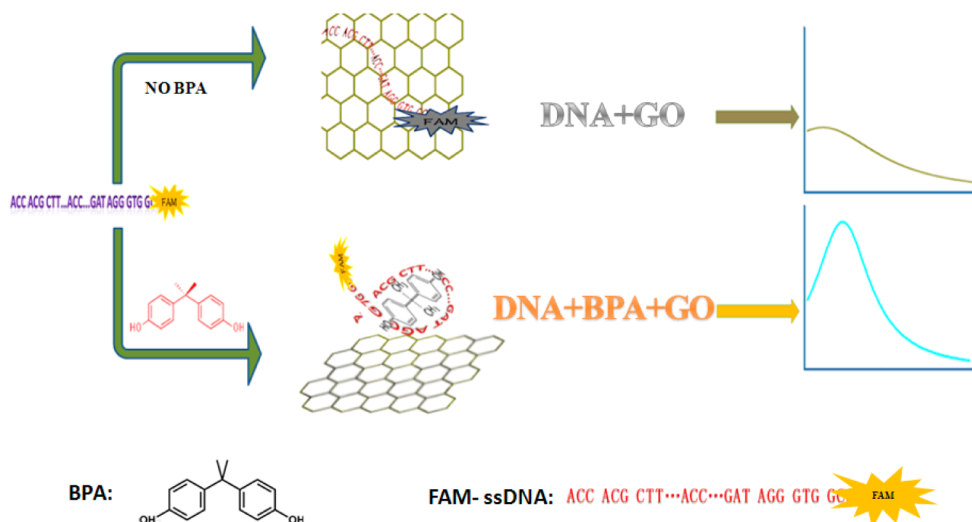

Figure 1. Schematic illustration of the biosensor for BPA based on the target-induced conformational change of the anti-BPA aptamer and the interactions between the FAM-ssDNA probe and GO.

aptamer-based technology.[33,34] Jo et al.[32] developed an aptamer-based sensor utilizing the selection of an aptamer targeting BPA with a dissociation constant of 8.3 nM; this method achieved much more sensitive results than detection with antibodies. Similarly, Kang et al.[35] also built a capacitive sensor based on aptamers using anodized aluminum oxide, and a 3% change in capacitance was achieved per 100 pM of BPA; this method was found to be suitable for analysis of actual samples.

Herein, a novel, rapid, sensitive fluorescence sensor was developed based on water-soluble and well-dispersed graphene oxide (GO), which was used as the fluorescence quenching agent, and a specific anti-BPA aptamer labeled by FAM. In the absence of BPA, FAM-ssDNA can be adsorbed onto the GO surface, leading to FRET between GO and FAM-ssDNA. Subsequently, the fluorescence can be quenched quickly. Conversely, BPA can interact with FAM-ssDNA and switch its conformation to prevent the adsorption of GO, resulting in fluorescence recovery in the sensing system. In our study, we aimed to develop a biosensor for BPA-based on the target-induced conformational change of fluorescently modified ssDNA and the interactions between the fluorescently modified ssDNA and GO.

2. EXPERIMENTAL SECTION

2.1. Reagents and Apparatus. Bisphenol A (BPA) was obtained from J&K Chemical Company, Shanghai. Graphene Oxide was purchased from Nanjing XFNANO Materials Tech Co. Ltd. Other common chemicals, including sodium chloride (NaCl), magnesium chloride ($MgCl_2$), potassium chloride (KCl) and trisbase, were all purchased from Shanghai Chemical Reagents Company (Shanghai, China). Anti-BPA aptamer was synthesized by Shengon Biotechnology Co. Ltd. (Shanghai, China). The sequence of the anti-BPA aptamer (FAM-ssDNA) was designed as 5′-FAM-CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA-3′.

Millipore Milli-Q ultrapure (>18 MΩ) water was used throughout the whole research. Actual blank water samples were taken from the tap water in our laboratory and the river water in Kuncheng Lake in Changshu City. The fluorescence spectra were measured using a Thermo Scientific Lumina fluorescence spectrometer that equipped with a xenon lamp excitation source. The excitation wavelength was λ = 494 nm, and the fluorescence measurements were carried out at room temperature.

2.2. General Procedure of Fluorescence Sensing of BPA. For BPA detection, 975 μL of 0.02 M Tris-HCl buffer (20 mM $MgCl_2$, 40 mM KCl, and 100 mM NaCl, pH 8.0) was added into a 1.5 mL plastic vial. Anti-BPA aptamer (10 nM) was initially added to form the BPA-aptamer complex. BPA standards were prepared with ultrapure water. A series of concentrations of BPA standard solution (0.1, 0.5, 0.8, 2, 5, 10, 50, and 100 ng/mL) was separately added and mixed well. This FAM-ssDNA solution was incubated for 15 min at room temperature, and 20 μL of GO (0.1 mg/mL) was then added to this mixture. The solution was mixed well and incubated for another 5 min at room temperature. Next, 1000 μL of the resulting solution was transferred to a 1 cm micro quartz cuvette, and then the fluorescence intensity of the biological sensing system was recorded to measure the effects of BPA on the fluorescence recovery degree. The mixture of GO with FAM-ssDNA was also analyzed for comparison.

2.3. Investigating the Specificity and Selectively of this Developed Sensor. The specificity and selectively of the developed method were tested using different analogs in the sensing system. Three types of BPA analogs (bisphenol B [BPB], bisphenol C [BPC], diethylstilbestrol [DES], and ethoxylated bisphenol A [BPE]) were tested at a concentration of 100 ng/mL, using the same procedure as that described above for BPA. These data were contrasted with data collected using 10 ng/mL BPA.

2.4. Determination of BPA in Actual Water Samples with Developed Sensor. The reliability of the method in practical applications was measured by determining the recovery rate in actual water samples. Tap and river water samples were spiked with different concentrations of BPA standard samples (0.5, 2, and 5 ng/mL). All procedures were identical to those mentioned above.

3. RESULTS AND DISCUSSION

3.1. Sensing Principle of the Biosensor for BPA Detection. A biological sensing system-based fluorescence aptamer-sensor for BPA was developed using BPA-induced fluorescent signal changes. In the presence of BPA, BPA preferentially binds to the aptamer because of strong affinity effects, including the electrostatic effect, hydrogen bond effect, and spatial matching effect,[36] which prevent the adsorption of GO. A schematic of the sensing principle is shown in Figure 1.

Specific biological sensors are expected to have improved biosensing performance based on the following three principles: (1) aptamers are a new type of ssDNA recognition probe that can be used to ensure the specificity of detection;

DOI: 10.1021/acsami.5b00199
ACS Appl. Mater. Interfaces 2015, 7, 7492−7496

(2) GO could selectively adsorb and quench a dye-labeled ssDNA probe due to FRET; and (3) upon addition of BPA, the anti-BPA aptamer can switch its configuration, preventing the aptamer from being adsorbed onto the surface of GO. Hence, at a certain concentration, BPA may couple with FAM-ssDNA, and upon BPA binding, the fluorescence value of FAM-ssDNA, which is very sensitive to the amount of FAM-ssDNA in the solution, would change accordingly compared to the solution without added BPA. Thus, we reasoned that a BPA-specific ssDNA probe could be combined with the ability of GO to specifically adsorb and quench the fluorescence of the FAM-ssDNA probe to develop a new type of fluorescent biosensor for BPA.

3.2. Optimization of the Experimental Conditions. Following the above-mentioned rules, the performance of the biosensor for BPA detection was determined based on the competitive reaction of target BPA and GO with limited ssDNA against BPA labeled with FAM. This reaction depended on relevant experimental factors, including GO concentration, temperature, pH value, and incubation time. First, various concentrations of GO (0.1, 0.5, 1. 2, 5, and 10 μg/mL) were added into a microcuvette containing 980 μL of 20 mM Tris-HCl buffer solution at a fixed concentration of 10 nM anti-BPA aptamer. The fluorescence values showed that 2 μg/mL GO was suitable for achieving the minimum fluorescence intensity (as shown in Figure 2A), indicating that this amount of GO could quench the fluorescence intensity of DNA. Therefore, in a later experiment, GO was added at a fixed concentration of 2 μg/mL, and subsequent experiments were performed for parameter optimization.

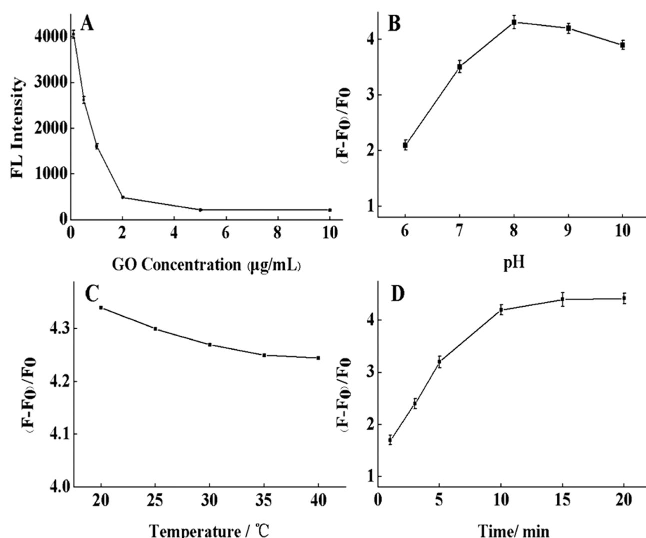

Figure 2. Influence of the relevant experimental factors on the fluorescence intensity of sensing system. (A) GO concentration, (B) pH values, (C) temperature, and (D) reaction time: FAM-ssDNA for A–D, 10 nM; BPA for B–D, 10 ng/mL; GO for B–D, 2 μg/mL.

The stable conformation of DNA and the fluorescence intensity of FAM were strongly affected by the pH of the buffer. Therefore, Tris-HCl buffer solutions with different pH values, ranging from 6.0 to 10.0, were used to evaluate the effects of pH on the responses of 10 ng/mL BPA. As observed in Figure 2B, the fluorescence signal increased from 6.0 to 8.0 and then decreased gradually when the pH exceeded 8.0. FAM-ssDNA has been shown to have better sensing efficiency at pH 8.0 approximately.[33,37] Thus, a Tris-HCl buffer solution at pH 8.0 was chosen for the experiments.

To evaluate the effects of temperature, the response to 10 ng/mL BPA was analyzed at temperatures ranging from 20 to 40 °C. As depicted in Figure 2C, the sensing signal remained about the same, although the response decreased gradually along with the increase in temperature. Considering the simplicity of the method, room temperature was thus selected for the experiments.

To examine the effects of incubation time, the sensing system was divided into two parts: (1) the specific conjugation of FAM-ssDNA and BPA and (2) the adsorption of FAM-ssDNA onto GO. Because of the strong absorption of GO, GO can quickly absorb ssDNA and quench its fluorescence. Hence, the first part of the sensing system was examined at different times in the presence of 10 ng/mL BPA, followed by the addition of 2 μg/mL GO. As displayed in Figure 2D, BPA reacted with FAM-ssDNA, achieving maximum response within 15 min. Therefore, 15 min was chosen as the incubation time.

3.3. Analytical Performance of the Biosensor. The optimized sensor was applied to the detection of BPA. A series of different concentrations of BPA were added, and their fluorescence spectra were recorded. From the results shown in Figure 3, we found that fluorescence recovery was obviously changed following addition of BPA, as compared with the blank sample. Further increases in the concentration of added BPA above10 ng/mL did not yield higher fluorescence values. The resulting calibration curve for BPA detection was obtained by determining the relationship between the ratio Y ($Y = [F - F_0]/F_0$) and BPA concentrations (iX). In the linear range of 0.1–10 ng/mL (Figure 4), the linear equation could be fitted as $Y = 0.016 + 0.43X$ with a linearity correlation coefficient of $R^2 = 0.9940$. Moreover, the limit of detection (LOD) of 0.05 ng/mL was obtained ($S/N = 3$). It should be noted that each experimental point in Figure 4 was the mean of five experiments carried out under identical conditions. Moreover, the developed method exhibited a lower LOD than did other detected methods for BPA. For example, Wu et al.[38] developed a nanographene-based tyrosinase biosensor for detection of BPA, with an LOD of 7.53 ng/mL, and Mei et al.[33] presented a method for rapid visual detection of BPA in water based on an

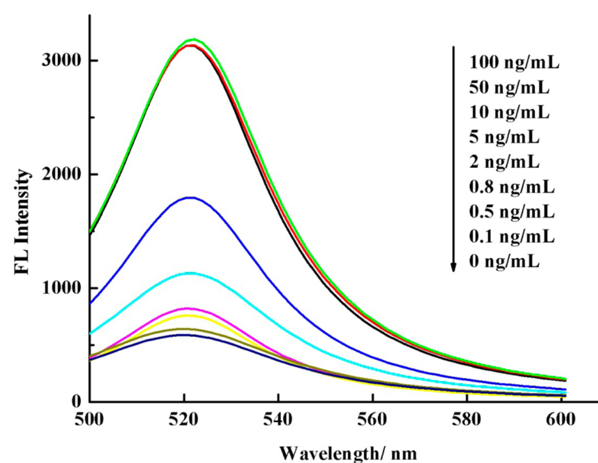

Figure 3. Fluorescence spectrum of developed system in the presence of 10 nM FAM-ssDNA and 2 μg/mL GO in 20 mM Tris–HCl buffer solution (pH 8.0) containing different concentrations of BPA (0.1–100 ng/mL).

DOI: 10.1021/acsami.5b00199
ACS Appl. Mater. Interfaces 2015, 7, 7492–7496

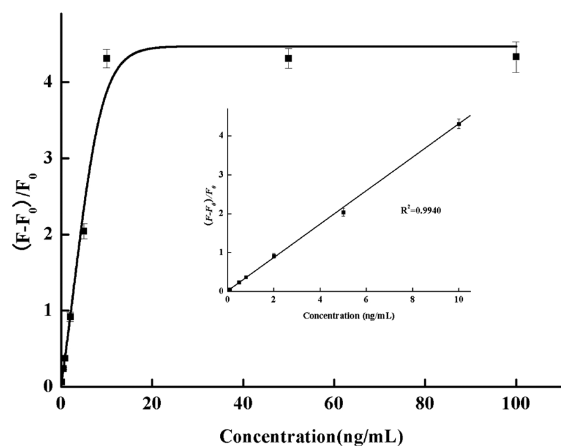

Figure 4. Peak fluorescence change ($(F - F_0)/F_0$) as a function of BPA concentration. Inset: Peak fluorescence of change is linear with BPA concentration over the range from 0.1 to 10 ng/mL. λ = 494 nm.

aptasensor and gold nanoparticles, with an LOD of 0.049 ng/mL. From these comparisons, the LOD of the method developed here was comparable to that of other newly developed methods and conventional immuno-based sensing systems and instrument-based methods.[39]

To determine the specificity and selectively of this method, the effects of BPA analogs on the fluorescence intensity were also assessed by evaluating its responses to interferences from other analogues. There was hardly any change in the fluorescence intensity of the developed sensors after adding analogs (Figure 5), suggesting that BPA can be easily differentiated when the other analogs are present at higher concentrations.

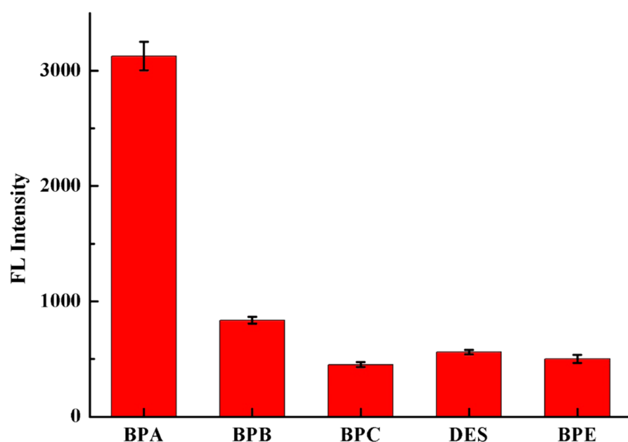

Figure 5. Specificity of the biosensor for BPA (10 ng/mL). The peak fluorescence for other analogues was measured at the same concentration of 100 ng/mL.

The application of this GO−DNA detection method was evaluated by testing spiked samples of actual water sample. A series of known quantities of BPA was added into the water samples and measured using the developed detection method. Additional experiments were also performed to compare the current sensing system by high performance liquid chromatography with fluorescence detection (HPLC-FLD). The concentration of samples without BPA was detected using HPLC-FLD. As shown in Table 1, the results indicate that the recovery was in the range of 96.0% to 104.5%, indicating that this sensor may be reliable in practical applications without the need for sample pretreatments.

Table 1. Determination of the Concentration of BPA of the Water Samples Using the Proposed Sensor

sample	FLD-HPLC (ng/mL) real value ± SD	spiked (ng/mL)	measured (ng/mL)^a mean^a ± SD^b	recovery (%)
tap water	0.2 ± 0.1	0.5	0.67 ± 0.013	96.0
		2	2.15 ± 0.070	97.5
		5	5.32 ± 0.23	102.4
river water	1.2 ± 0.2	0.5	1.71 ± 0.027	102.0
		2	3.29 ± 0.15	104.5
		5	6.06 ± 0.34	97.2

^{a}The mean of five experiments. ^{b}SD = standard deviation.

4. CONCLUSIONS

In summary, we developed a simple, novel method based on GO and anti-BPA aptamers to enable the rapid detection and risk assessment of BPA with high sensitivity and selectivity. A fluorescently modified anti-BPA aptamer was used to produce a detectable signal, and the added BPA competitively bound with the aptamer and prevented the adsorption of GO. The corresponding peak exhibited a linear relationship with the concentration of added BPA. Qualitative and quantitative detection of BPA were successfully realized with a LOD of 0.05 ng/mL, which was obtained in the range of 0.1 to 10 ng/mL by fluorescence spectrum analysis. Importantly, this method showed no cross-reaction with BPA analogs and could also be used for the analysis of real samples with excellent recovery. To the best of our knowledge, this is the first report demonstrating the application of a biosensor for BPA detection based on FAM-ssDNA and GO in real water samples. Because of its simple preparation, facile manipulation, and good detection performance, the results of this method meet the various detection requirements for BPA and are comparable to conventional immuno-based sensing systems and instrument-based methods.

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Author Contributions

Y.Z. and Y.C. contributed to this paper equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is financially supported by the Key Programs from MOST (2012AA06A303), National Natural Science Foundation of China (31401566), NSF of Jiangsu Province (BK20130379, 13KJB550001, BK20140416), and the Suzhou Science and Technology Committee Program (SS201335, SYN201210)

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