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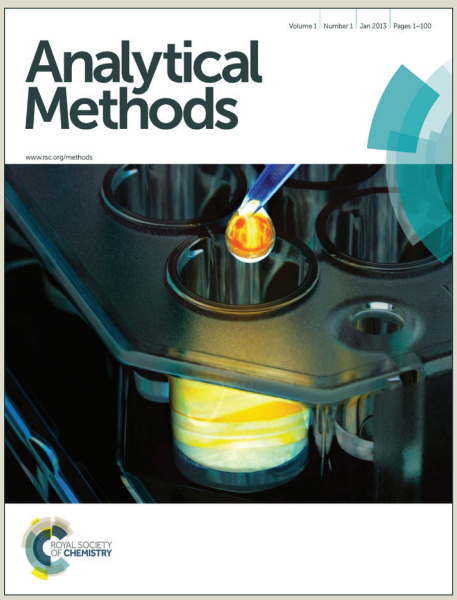

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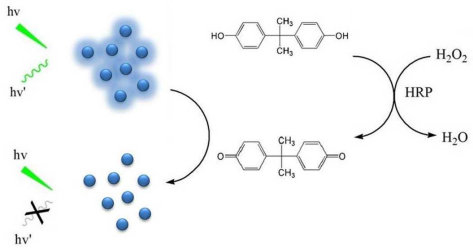
Graphical Abstract



A novel sensing strategy for bisphenol A was designed based on graphene quantum dots and peroxidase.

Highly sensitive detection of bisphenol A in food packaging based on graphene quantum dots and peroxidase

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Abstract

A novel sensing strategy for bisphenol A (BPA) was designed based on graphene quantum dots (GQDs) and peroxidase. In the presence of H_2O_2 and HRP, BPA was oxidized and the oxidation produce of BPA could effectively quench the fluorescence of GQDs. The quenching PL intensity of GQDs (I_0/I) was proportional to the concentration of BPA in the range of 1 - 1000 nM, and the detection limit was as low as 0.4 nM. The proposed method could be applied to detect BPA in real food packaging samples with satisfactory results.

Keywords: Bisphenol A; Food packaging; Graphene quantum dots; Fluorescence

1. Introduction

Graphene quantum dots (GQDs), a new kind of fluorescent nanomaterial, has drawn plenty of attention recently [1]. Lots of efforts have been spared to develop various GQDs preparing methods and explore their properties [2-5]. Compared with conventional semiconductor quantum dots, GQDs are superior in chemical inertness, ease of production, low cytotoxicity, resistance to photobleaching and excellent biocompatibility, which all make GQDs promising in sensors, bioimaging, optoelectronic devices and so on [3,4]. In addition, GQDs are highly luminescent because of the quantum confinement and edge effects [4,5]. It has been used to develop many analytic methods, such as the detection of glucose [6,7], metal ions [8-13], protein kinase [14], biothiols [15], adenosine triphosphate [16], and paranitrophenol [17].

Bisphenol A (2,2-bis(4-hydroxyphenyl)propane, BPA), is an indispensable monomer in the production of polyesters, polysulfones, polycarbonate plastic, and epoxy [18], and it has been widely used as plastic food containers, food can linings and water bottles [19]. Since BPA could make products with colorless, transparent, durable, lightweight and prominent anti-impact properties, it is also added in plastics manufacturing process as an additive [20]. Researcher has shown that being exposed to heat, acid or base, ester bonds that link the BPA monomers in these plastic or resin materials will be hydrolyzed, leading to the release of BPA into environment [21]. Meanwhile, humans may routinely ingest trace amounts of BPA because it can also inevitably migrate into foodstuffs and beverages from packing of product. Actually,

low levels of BPA had already been detected in a diverse range of products such as canned vegetables, desserts, seafood, meat products, environmental water, artificial teeth, food pack-aging materials etc [22,23]. However, even such low levels of BPA can still be a tremendous threat to human's health. Recently, several reports have demonstrated that BPA may cause several adverse health effects, such as disrupt normal cell function by acting as an estrogen agonist as well as an androgen antagonist [24,25] and influence the development of reproductive tracts inutero [26,27]. Moreover, there is a strong relationship between BPA and cancer in the hematopoietic system since BPA can alter microtubule function and induce aneuploidy in some cells and tissues [28]. Additionally, BPA may also increase endpoints which are considered as markers of breast cancer risk in human if infants are exposed to diverse and environmentally relevant doses of BPA during prenatal period [27]. Thus, it is essential to develop rapid, reliable and sensitive methods for the determination of BPA.

Up to now, various methods have been established to detect BPA, such as liquid chromatography [29-31], and gas chromatography coupled with mass spectrometry (GC-MS) [32]. Although these methods exhibit high sensitivity and good precision, they all need time-consuming pretreatment steps and skilled operators due to the complex procedures of preconcentration for trace BPA from samples such as liquid-liquid extraction, solid-phase extraction and solid-phase microextraction [33-35]. In addition, immunoassay-based methods have also attracted considerable attention for BPA detection due to its high sensitivity and relative low costs compared

with the former techniques [36-39]. However, determinations with immunoassay-based methods depend on the quality of the prepared antibody a lot [40, 41]. Therefore, it is of great significance and necessary to develop a high sensitive analytical method with the process of a relatively simple, rapid, and organic solvent-free pretreatment to detect BPA.

It is reported that phenol compounds could be converted to quinone and quench the fluorescence of semiconductor quantum dots [42-43]. In this work, we found that the fluorescence of GQDs could be quenched by BPA in the presence of oxidant (H_2O_2) and catalyst (horseradish peroxidase, HRP). And a highly sensitive BPA detection technic was thus established based on the fluorescent GQDs and peroxidase (Scheme 1). BPA was oxidized to its benzoquinone structure in the presence of H_2O_2 and HRP and resulted in the fluorescence quenching of GQDs. Due to the excellent optical property of GQDs, the limit of detection were much lower than the published BPA detecting methods. The proposed method could also be applied for the sensing of BPA in real food packaging samples with satisfactory results.

2. Experimental

2.1 Reagents

BPA was bought from Tianjin Guangfu Institute of elaborate chemical industry. Horseradish peroxidase was purchased from Beijing Dingguo Biotechnology. Sodium chloride and hydrogen peroxide were obtained from Shanghai Institute of Biochemistry, Chinese Academy of Sciences. All the other chemicals used in this experiment were of analytical grade without further purification. All the solutions

were prepared with deionized water and all experiments were carried out at room temperature (4 ºC).

2.2 Apparatus

Fluorescence measurements were performed on a Shimadzu RF-5301 PC spectrofluorophotometer (Shimadzu Co., Kyoto, Japan), and a 1 cm path-length quartz cuvette was used in experiments. UV-vis absorption spectra were obtained with a Cary 50 Bio spectrophotometer (Varian, USA). All pH measurements were taken with a PHS-3C pH meter (Tuopu Co., Hangzhou, China). All the optical measurements were carried out at room temperature under ambient conditions.

2.3 Synthesis of GQDs

Synthesis of GQDs was carried out according to our previous report [44]. 10 mL beaker with 0.5 g citric acid was heated to 260 ºC for 50 min. The liquefied citric acid was changed to orange and it was quickly added to 10 mL of NaOH aqueous solution (10 mg mL^{-1}) with continuous stirring. Then mixed liquor was neutralized to pH 7.0 with NaOH. The GQDs aqueous solution was stored at 4 ºC before use.

2.4 Detection of BPA using GQDs and HRP

For optimization parameters experiment, certain amounts of BPA were added to microcentrifuge tubes with different concentrations of HRP, H_2O_2, NaCl and different pH and time. For BPA detection, under the optimal conditions, different concentrations of BPA solutions with 1.0 μg mL^{-1} HRP, 0.5 mM H_2O_2, and 10 mM NaCl followed by 10% GQDs were diluted to 1 mL with PBS (pH 7.4) buffer, thus a series of BPA solutions with different concentrations was obtained for detection of

BPA. Finally, the resulting solution (1.0 mL) was shaken evenly and kept at room temperature for 20 min before recording the spectral information by luminescence spectrometer.

2.5 Detection of food packaging samples

Six food packaging samples used in this study were plastic lunch-box, purified water bottle, plastic juice box, plastic yogurt bottle, plastic wrap and meat tin. All the samples were pretreated as the method described in early report [45]. In briefly, the samples were cut into small fragments about 5 mm × 5 mm size, respectively, and then an accurately weighed sample. Then the small fragments were brought to a round-bottom flask fitted with a reflux condenser. Then certain amount of deionized water was added into the flask. After that, the mixture was heated to 90℃ for 2h. After the solution was cooled to room temperature, the supernate fluid was filtered with a 0.45μm-filter. Then the concentration of BPA was determined by the proposed method.

3. Results and discussion

3.1 Spectral characteration of GQDs

The PL emission and UV-vis absorption spectra GQDs are shown in Fig. 1. It could be seen that the fluorescence emission peak of the GQDs around 460 nm, and the UV-vis absorption peak was around 360 nm, which were consistent with our previous report [44]. The maximum absorption wavelength of 460 nm was chosen as the excitation wavelength in the following experiments. The small peak at around 415 nm was the water Raman peak.

3.2 Quenching of GQDs by BPA in the presence of HRP and H_2O_2

GQDs solution mixed with H_2O_2, HRP and BPA separately and the mixtures of two or three were investigated and the results were shown in Fig.2. When GQDs mixed with H_2O_2, BPA or HRP separately, the decrease of the PL intensity of GQDs was no more than 5%, which indicates that none of three agents could act as a PL quencher solely. However, the PL intensity of GQDs was quenched by BPA obviously in the presence of H_2O_2 and HRP and the PL intensity decreased with increasing BPA concentration from 20 nM to 500 nM. The above results suggest that BPA can be oxidized by H_2O_2 in the presence of HRP and the oxidation product of BPA as an effective quencher can highly quench the PL intensity of GQDs (scheme 1). Thus, a sensing method for BPA is proposed according to the quenching effect of GQDs in the presence of HRP and H_2O_2.

The quenching mechanism was investigated by the lifetime study (Fig. 3). The fluorescence lifetime remained almost the same (around 1.6 ns) in the absence and the presence of H_2O_2, HRP and BPA. The results suggest that the mechanism of the quenching process involves static quenching rather than dynamic quenching.

3.3 Optimization of experimental parameters for BPA detection

To fabricate the GQDs based sensor for BPA detection, experimental parameters were optimized in Fig.4. The relationship between the PL intensity and the incubation time was studied firstly in Fig. 4A. The PL intensity of GQDs and GQDs/HRP/H_2O_2 almost stayed as the same level with the increasing of incubation time. When BPA was added, the PL intensity of GQDs decreased at the beginning. Then PL intensity

reached a plateau after 20 min, which means the quenching process is finished. Thus, 20 min was chosen as the optimal incubation time for the following experiments.

H_2O_2 is the oxidizing agent to convert BPA to its benzoquinone structure which quenched the PL of GQDs. The effect of H_2O_2 concentration on the GQDs PL intensity was investigated at BPA concentrations of 20, 100 and 500 nM (Fig. 4B). The PL quenching extent was enhanced with increasing the concentration of H_2O_2, which means that increasing amount of BPA was oxidized. When the concentration of H_2O_2 reached 0.5 mM, the PL intensity of GQDs remained nearly unchanged with the further increase of H_2O_2 concentration. Therefore 0.5 mM of H_2O_2 was chosen in the following studies.

The effect of HRP concentration was carried out in Fig. 4C. HRP is the catalyst of the reaction. The PL intensity of GQDs decreased with the increasing concentration of HRP in the range of 0 - 3 μg mL^{-1}. When the HRP concentration was higher than 1 μg mL^{-1}, the PL intensity of GQDs remained the same. Further increasing HRP had no effect on the quenching of GQDs. Thus, the 1 μg mL^{-1} was chosen as the optimal HRP concentration.

Salt concentration has clear effect on many analytical systems. So the effect of NaCl concentration in our system was investigated. Fig. 4D showed that the addition NaCl from 10 nM to 10 mM caused no obvious PL quenching of GQDs. The results suggest that our system did good defense to NaCl. We chose 10 mM NaCl in the following experiments.

3.4 Quantitative detection of BPA

The quenching of GQDs PL intensity by BPA in the presence of HRP and H_2O_2 was further investigated under the optimized conditions. Fig. 5 shows the fluorescence spectra of GQDs in the presence of 0.5 mM H_2O_2, 1 μg mL^{-1} and a series of different BPA concentrations. The PL intensity of GQDs decreased with the increasing BPA concentration and a linear relationship between I/I_0 and the logarithm of the concentration of added BPA was found as the following form:

$$I/I_0 = 0.96 - 0.24 \log C_{BPA} \text{ (nM)}$$

where I and I_0 are the PL intensity of the GQDs in the presence and absence of BPA, respectively. C_{BPA} is the concentration of BPA. The range is from 1 to 1000 nM with a correlation coefficient R^2=0.998. The detection limit for BPA was 4×10^{-10} mol L^{-1}, calculated following the 3σ IUPAC criterion. Compared with the previous reports about BPA detection (table 1), the proposed method has a superior detection limit and a wide dynamic range.

3.5 Interference study

In Fig. 6, we studied the effect of a series of ions and some other substances which may existing in food, such as K^+, Mg^{2+}, Ca^{2+}, Fe^{2+}, Fe^{3+}, Ba^{2+}, Pb^{2+}, ascorbic acid, L-Glycine, L-Tyrosine, L-Proline, L-Tryptophan, L-Isoleucine, L-Cysteine, citric acid and glucose. Among a series of potentially interfering molecules and ions, only BPA could effectively quench the PL intensity of GQD, and the other molecule or ions nearly had no effect on the fluorescence of the quenched GQDs. These results indicated that the proposed detection method for BPA is acceptable and reliability.

3.6 Detection of BPA in food packaging

In order to evaluate the feasibility of the method in the determination of BPA in real samples, the proposed BPA detection method was applied to detect BPA in six real samples, plastic lunch-box, purified water bottle, plastic juice box, plastic yogurt bottle, plastic wrap and meat tin. The results obtained by standard addition method were showed in Table 2. It can be seen that the average recoveries in the real samples were between 95.2% and 108.3% and the RSD was lower than 3.9%. The above results demonstrated the potential applicability of the GQDs and HRP system for the detection of BPA content in food packaging samples.

4. Conclusion

In this work, a novel simple, sensitive, selective and reliable BPA sensor based on GQDs and enzyme was developed. With HRP as catalyst, the oxidation product of BPA oxidized could quench GQDs PL intensity obviously. Under the optimal conditions, a linear correlation between I/I_0 and logarithm of BPA concentrations was obtained from 1 nM to 1000 nM with a detection limit of 0.4 nM. Due to the excellent optical property and nanometer size effect of GQDs, the detection limits were lower than the published methods. Little interference was observed when a number of common ions and amino acids were tested. Furthermore, the proposed BPA detection method was applied to BPA detection in six food packaging samples with satisfactory results. The proposed method provides a new pathway for BPA detection which has great potential practical application in food analysis filed in the future.

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Captions

Scheme 1 The schematic illustration of BPA detection principle.

Fig.1 The UV-vis absorption spectra (A) and fluorescence emission (B) of the GQDs solution.

Fig. 2 Effect of components of BPA sensor on the PL intensity of GQDs. a: GQDs; b: GQDs with 0.5 mM H_2O_2; c: GQDs with 1 μg mL^{-1} HRP; d: GQDs with 0.5 mM H_2O_2 and 1 μg mL^{-1} HRP; e: GQDs with 500 nM BPA; f: GQDs with 0.5 mM H_2O_2, 1 μg mL^{-1} HRP and 20 nM BPA; g: GQDs with 0.5 mM H_2O_2, 1 μg mL^{-1} HRP and 100 nM BPA; h: GQDs with 0.5 mM H_2O_2, 1 μg mL^{-1} HRP and 500 nM BPA.

Fig. 3 Fluorescence decay curves of GQDs by TCSPC in the absence and the presence of H_2O_2, HRP and BPA.

Fig. 4 The optimization of experimental parameters. (A) Effect of the incubation time on the PL intensity of GQDs without any addition (a), with the addition of 0.5 mM H_2O_2, 1 μg mL^{-1} HRP and 0 nM (b), 20 nM (c), 100 nM (d), 500 nM (e) BPA, respectively; (B) Effect of H_2O_2 concentrations on the PL intensity of GQDs without any addition (a), with the addition of 1 μg mL^{-1} HRP and 0 nM (b), 20 nM (c), 100 nM (d), 500 nM (e) BPA, respectively; (C) Effect of different HRP concentrations on the PL intensity of GQDs without any addition (a), with the addition of 0.5 mM H_2O_2

and 0 nM (b), 20 nM (c), 100 nM (d), 500 nM (e) BPA, respectively; (D) Effect of NaCl concentrations on the PL quenching GQDs by BPA, without any addition (a), with the addition of 0.5 mM H_2O_2, 1 μg mL^{-1} HRP and 0 nM (b), 20 nM (c), 100 nM (d), 500 nM (e) BPA, respectively.

Fig. 5 Effect of BPA concentration on the PL intensity of GQDs in the presence of 0.5 mM H_2O_2, 1 μg mL^{-1} HRP; (A) a-p represents the concentration of BPA of 0, 1, 2, 5, 10, 20, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 nM respectively. (B) the linear relationship between the PL intensity ratio of I/I_0 and the logarithm of BPA concentration in the range of 1-1000 nM.

Fig. 6 Effect of a series of 500 nM coexist substances on the PL intensity of detection of system. 1: GQDs, 0.5 mM H_2O_2, 1 μg mL^{-1} HRP with no addition; with 2: Na^+; 3: K^+; 4: Mg^{2+}; 5: Ca^{2+}; 6: Zn^{2+}; 7: Ba^{2+}; 8: Pb^{2+}; 9: Fe^{2+}; 10: Fe^{3+}; 11: L-Cysteine; 12: L-Glycine; 13: L-Isoleucine; 14: L-Proline; 15: L-Tryptophan; 16: L-Tyrosine; 17: Ascorbic Acid; 18: Benzoic Acid; 19: Citric Acid; 20: Glucose; 21: BPA.

Table 1 Comparison of different methods for the determination of BPA.

Table 2 Determination of BPA in food packaging samples.

Scheme 1

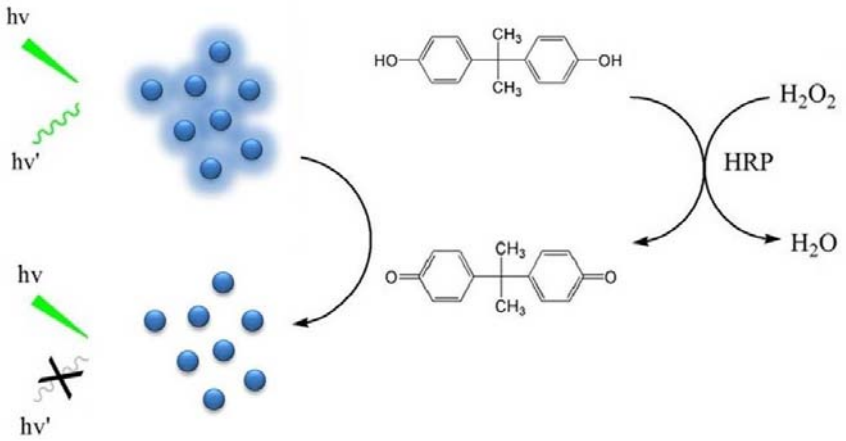

Figure 1

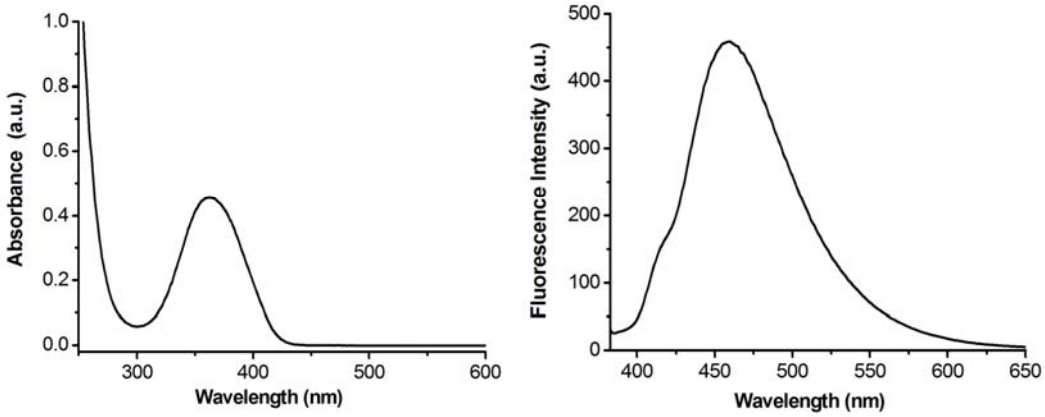

Figure 2

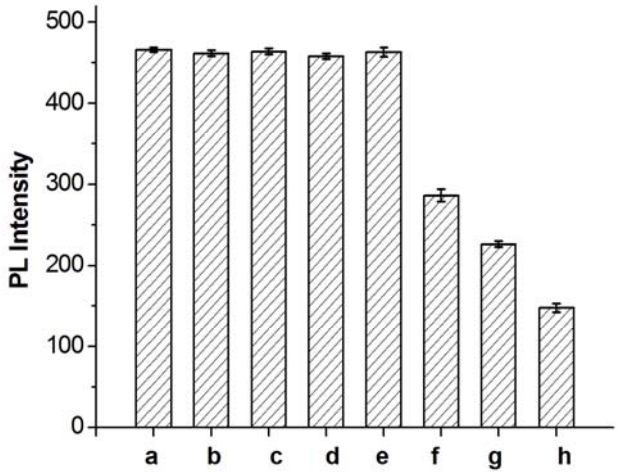

Figure 3

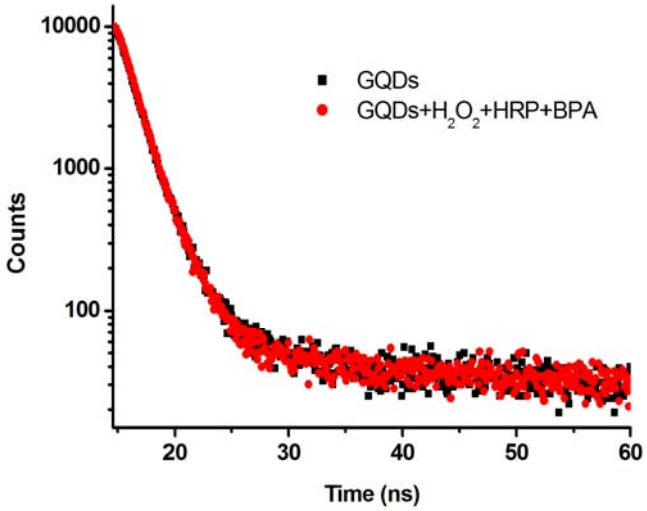

Figure 4

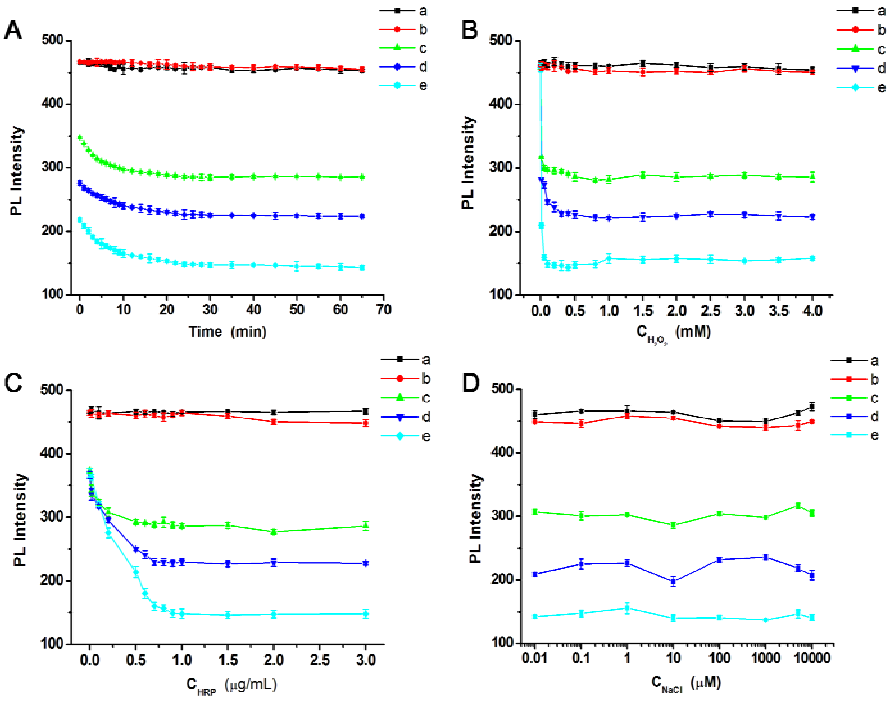

Figure 5

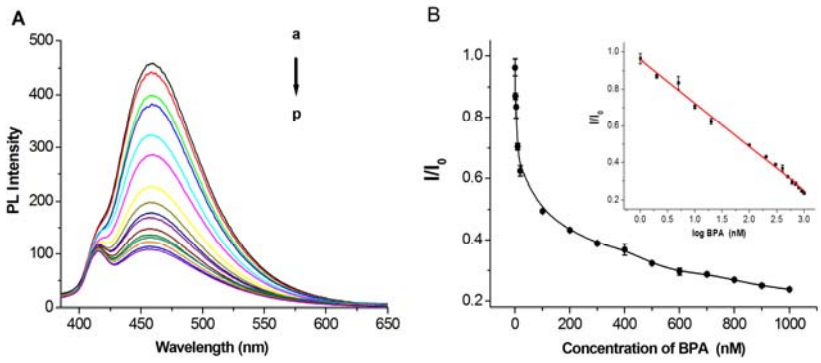

Figure 6

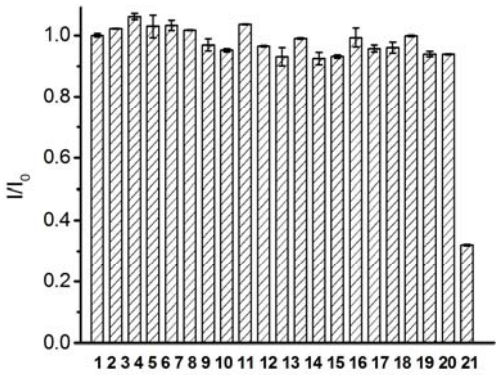

Table 1 Comparison of different methods for the determination of BPA.

System	Linear range (M)	Detection limit (M)	Ref.
UV-Vis detection	1.0×10^{-7}~1.0×10^{-4}	2.0×10^{-8}	[45]
SERS of core-shell Au nanoparticles	2.19×10^{-6}~1×10^{-4}	5.3×10^{-7}	[46]
Chemiluminescence from gold(III)-peroxymonocarbonate	3×10^{-7}~8×10^{-5}	8×10^{-8}	[47]
Direct irradiation method	-	7.5×10^{-8}	[48]
Cd-doped ZnO quantum dots	9.12×10^{-8}~1.45×10^{-6}	5.75×10^{-8}	[49]
Fenton-Like reaction	4.39×10^{-8}~2.19×10^{-6}	2.807×10^{-9}	[50]
Graphene quantum dots and peroxidase	1.0×10^{-9}~1.0×10^{-6}	4×10^{-10}	This work

Table 2 Determination of BPA in food packaging samples.

Samples	Original found by this method (nM)	Added (nM)	Found (nM)	Recovery (%)	RSD (n=3, %)
Plastic lunch-box[a]	-	100.0	106.6	106.6	2.1
Purified water bottle[b]	-	100.0	99.3	99.3	3.4
Plastic juice box[c]	7.2	100.0	115.5	108.3	2.6
Plastic yogurt bottle[d]	12.1	100.0	111.5	99.4	3.2
Plastic wrap[e]	140.1	100.0	238.2	98.1	3.9
Meat tin[f]	725.5	100.0	820.7	95.2	1.2

a 10 g plastic lunch-box added with 100 mL water;

b 10 g purified water bottle added with 100 mL water;

c 10 g plastic juice box added with 100 mL water;

d 10 g plastic yogurt bottle added with 100 mL water;

e 10 g plastic wrap added with 100 mL water;

f 35 g meat tin added with 100 mL water.