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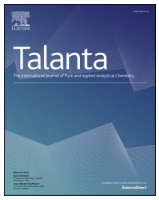

Spectroscopic ellipsometry-based aptasensor platform for bisphenol a detection

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ABSTRACT

Endocrine-disrupting chemicals (EDC) are pollutants that alter the function of the endocrine system by interfering with hormone biosynthesis, metabolism, or action. In this study, a spectroscopic ellipsometry platform is proposed using aptamers for the sensitive and selective detection of an EDC, 2,2-Bis(4-hydroxyphenyl)propane (Bisphenol A, BPA). Two different BPA-specific aptamers (Anti-BPA1 and Anti-BPA2) were immobilized to silicon wafer chips by the layer-by-layer self-assembly, a detection limit of 215 pM and 36 pM was obtained using the ellipsometric method for Anti-BPA1 and Anti-BPA2, respectively. Sensor specificity was tested with 2,2-Bis(4-hydroxyphenyl)butane and a maximum RSD of 3.8% was obtained. It has been reported that both aptasensors based on spectroscopic ellipsometry exhibit adequate analytical performance.

1. Introduction

Low molecular weight pollutants in water cause adverse effects on human health and animal life, even at trace concentrations in water sources [1–3]. Among these pollutants, endocrine-disrupting chemicals (EDC) are quite harmful because they can disrupt the functioning of the endocrine system and form a group containing approximately 800 chemicals, [4–6]. Bisphenol A (2,2-bis(4-hydroxyphenyl) propane, BPA) is an EDC and can be used as a plasticizer in the production of polycarbonate, epoxy resins and other polymeric materials [7,8]. BPA residues up to 160 ng/L were detected even in surface and ground waters due to the very high production of polymers with BPA added as plasticizers [9,10]. In addition, BPA is a lipophilic compound, therefore, it can be transferred to food in contact with the effect of heat in polymeric storage containers. BPA is structurally similar to endogenous estrogen and binds to estrogen receptors [11]. BPA has been reported to have the potential to produce reproductive disorders, chronic diseases, and susceptibility to various types of cancer, even at low concentrations [12–15] and it also induces apoptosis of germ cells [16]. In studies with rats, the median lethal dose was reported to be 3250 mg/kg and 0.02% at inhalation exposure [17]. For this reason, the use of BPA as a plasticizer was limited and residue limits were reduced to 50 μg/kg [18]. It is important to monitor these chemical residues in the receiving media and polymeric materials [19,20].

Conventional techniques for BPA detection are chromatographic techniques such as high-performance liquid chromatography (HPLC), HPLC-mass spectrometry (HPLC-MS), gas chromatography (GC) and GC-MS [21–27]. Although these methods offer sufficient analytical performance in terms of sensitivity and selectivity, the complexity of the sample preparation procedures, as well as the sophisticated and large equipment, the on-site analysis possibilities are limited [28–32]. Therefore, researchers tend to develop biosensor platforms for BPA detection [33,34]. There are extensive review articles on sensor platforms used in BPA detection [35], molecularly imprinted [36] and aptamer-based electrochemical sensors [37], and other sensor platforms [38].

In recent years, the applications of aptamers in environmental monitoring systems have been studied frequently [39,40]. Aptamer selection can be easily accomplished for targets such as chemicals that are difficult to elicit an immune response [41–43]. In addition, aptamers have high stability and can be easily modified for immobilization to the sensor surface [44,45]. The BPA specific aptamer used in this study was selected in 2011 and its K_d value was reported as 8.3 nM [46]. Different BPA aptamers have also been developed and reported [47–50]. Table 1 gives selected examples of aptasensor applications published in the literature, most of which have been successfully applied for BPA detection. Among these methods, such as electrochemical, fluorescent and surface-enhanced Raman scattering (SERS) have been tried.

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However, to the best of the authors' knowledge, a sensor for the detection of BPA using spectroscopic ellipsometry (SE) has not yet been proposed in the literature.

SE method is a measurement of the change in polarization of an electromagnetic wave when reflected from an interface. The film thickness, composition, optical properties and surface structure can be examined with this method [51]. The dielectric function of Delta (Δ) measured by the SE method is an average dielectric function along the region where the incident light penetrates into the material [52]. This function is very sensitive to the change in dielectric constants in any thin film. Ellipsometric methods, especially SE, have also been used successfully by our group in the detection of different analytes before [53]. Brevetoxin, a marine neurotoxin, was detected using SE with a detection limit (LOD) of 1.5 nM [54]. Using aptamer and SE, vascular endothelial growth factor 5 pM LOD has been reported [55]. Another marine neurotoxin, saxitoxin, has also been detected using SE in comparison with another ellipsometric technique [56]. Aminoglycoside group antibiotics have also been detected in milk with a LOD of 1.6 ng/mL [57]. The results of these previous studies have provided evidence that small molecules such as BPA can also be detected by SE. This study aimed to determine the appropriate aptamer immobilization conditions and detect BPA on simple biochips using a very sensitive SE technique.

2. Materials and methods

All chemicals are of analytical grade and were sourced from Sigma-Aldrich's local representative and used as received without further processing unless otherwise stated. Ultrapure water was used for final cleaning and buffer preparation. Si-wafer chips were cut to approximately 1 cm × 1 cm and then washed in the order of nitric acid/hydrogen peroxide/ethyl alcohol/acetone/water. Oxygen plasma was used for radical generation in the washed Si-wafer chips (Diener, Germany, @100 W–30 min) [74].

The spectroscopic ellipsometer includes a manually adjusted goniometer (Optosense, S6000, Turkey). The experimental setup is represented schematically in Fig. 1. The molecular layer thickness deposited on the surface of each sensor chip was calculated using both Δ and Ψ values. In this calculation, the ellipsometric thicknesses were determined using Si substrate/SiO_2 oxide layer/organic layer modeling (recalled from the instrument library). All thickness measurements were performed on 10 different randomly selected measurement points on 3 different test specimens and reported as the mean value (±1σ). Surface roughness measurements were determined using atomic force microscopy (AFM, Park Systems XE100, Korea). Roughness analyses were performed on 3 different test samples using the software of this device at 10 different and randomly selected measurement points. Roughness values were reported as mean values (±1σ). All measurements were repeated 3 times, unless otherwise stated, to meet analytical requirements. Results were reported as the mean and standard deviation (±1σ) of these measurements.

2.1. Immobilization of BPA-specific aptamers and improvement of immobilization conditions

Anti-BPA aptamers were supplied amine-functionalized from the 5′ end for surface immobilization on Si-wafers. Table 2 shows the aptamers used in this study and their structures modeled with the DNAFold open-source software [75]. Anti-BPA1, Anti-BPA2, and control (CTRL) aptamers were immobilized on the –COOH terminated Si-wafer surface. For this purpose, mercaptopropyl triethoxysilane (MPTES), which was first prepared in absolute ethyl alcohol after cleaning and radical formation on Si-wafer, was used to obtain –SH terminated functional surface on the Si-wafer surface. Then, –COOH functional ends were formed on the Si-wafer surface with mercapto undecanoic acid (MUA) using the disulfide reaction. Then, aptamers with NH_2-functional group were immobilized to the –COOH functionalized Si-wafer surface by 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDAC) reaction. Aptamers were prepared in 100 mM phosphate buffer solution (PBS, pH 7) and stored at 4 °C. The layer-by-layer self-assembly functional surface construction phase was optimized using response surface methodology

Table 1
Aptasensor studies in the literature and their analytical performances for the detection of BPA.

Analytical method	Modifier/Approach	Detection limit	Linear range	Recovery	Real Sample	Reference
Colorimetric	Cationic polymer-induced aggregation of gold nanoparticles (AuNPs)/aptamer	1.50 nM	1.50–500 nM	100.9–112.7	Tap and river water	[58]
DNA amplification	Aptamer coated well and real-time quantitative polymerase chain reaction	0.7 nM	1–500 nM	96.8–104.0	Tap water	[59]
Electrochemical	Au-NPs coated boron-doped diamond modified with aptamers, and 6-mercapto-1-hexanol (MCH)	7.2 fM	10 fM- 1 nM	92–108	Milk	[60]
Electrochemical	AuNPs/multi-walled carbon nanotubes (MWCNTs) and thiol-functionalized magnetic nanoparticles (Fe_3O_4-SH)/aptamer	0.03 nM	0.1–8 nM	97.5–120.5	Water, milk, juice	[61]
Electrochemical	Au–Pt nanoparticles on glassy carbon (GC)/carbon nanotubes (CNTs)/aptamer	0.035 pM	0.1–700 pM	94.5–103.6	Tap water	[62]
Electrochemical	Target-induced chain release, dendritic AuNPs, methylene blue (MB)/aptamer	0.98 nM	1.0–500 nM	93.8–104.9	Water, milk	[63]
Electrochemical	Screen-printed carbon electrode (SPCE) modified by AuNPs/aptamer	0.113 pM	1 pM - 10 nM	93.8–97.3	Serum	[64]
Electrochemical	Au-coated MWCNTs/single-stranded DNA-dye complex/aptamer	8 fM	10 fM - 1 nM	88.0–106.2	Water, milk, bottle	[65]
Electrochemiluminescent	Carboxylated graphitic carbon nitride/aptamer	30 fM	0.1 pM- 1 nM	97.1–104.2	Water, juice	[66]
Field-effect transistor	Aptamer-modified multichannel carbon nanofibers	1 fM	0.001–10 pM	–	–	[67]
Fluorescence	Graphene oxide/aptamer	210 pM	0.43–43 nM	96.0–104.5	Water	[68]
Fluorescence	Aptamer conjugated magnetic silica-coated Fe_3O_4 microspheres	0.22 nM	0.44–438 nM	78–113	Milk	[69]
HPLC/magnetic separation	Fe_3O_4@SiO_2 magnetic nanoparticles/aptamer	4.4 nM	21.9 nM–44 μM	90.8 with 7.3% RSD	Serum, urine	[70]
Optical spectroscopy	Plasmonic chirality/aptamer	35 pM	88 pM- 21.9 nM	93–98.4	Tap water	[71]
Photoelectrochemical	TiO_2 nanoparticles embedded in borocarbonitride nanosheets/aptamer	0.03 fM	0.1 fM- 5 nM	88.0–104.2	Water	[72]
SERS	Ag@Fe_2O_3 and Ag@Fe_2CoO_4 particles, optofluidic chips patterned with magnetically activated nickel pads/aptamer	1 nM	~1–100 nM	–	–	[73]
Spectroscopic ellipsometry	Layer-by-layer self-assembly on Si-wafer chips/aptamer	215 pM 36 pM	100 pM- 250 nM	Maximum 3.8% RSD	BPB specificity	This study

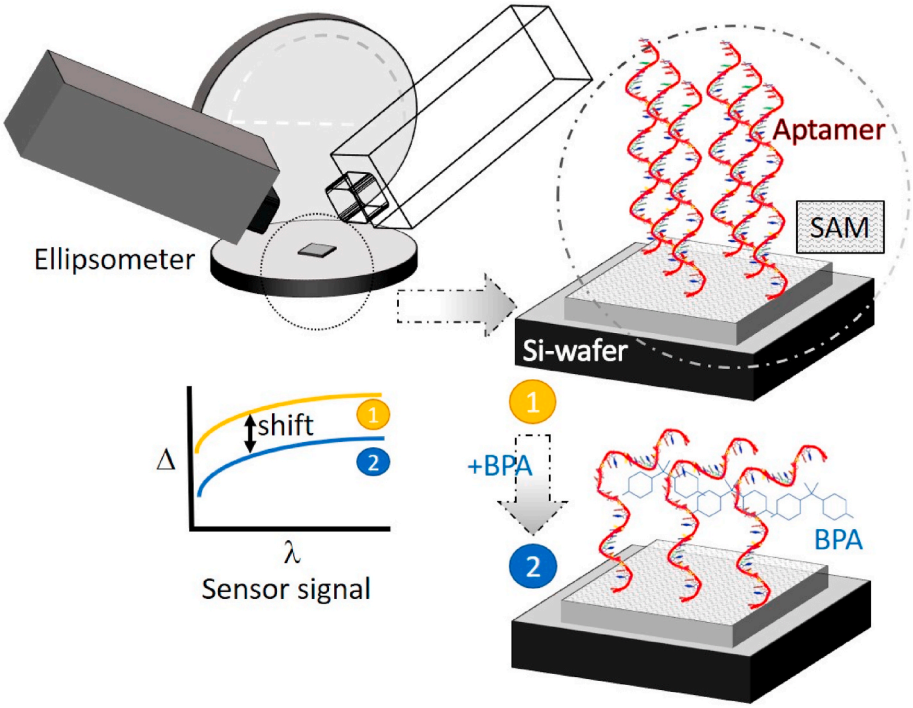


Fig. 1. – Schematic representation of the spectroscopic ellipsometry analysis method. 1) Before BPA, 2) After BPA, and sensor signal after recognition.

(RSM). For this purpose, the ellipsometric thickness and root mean square (RmS) roughness results of the concentration and reaction time optimization used in the formation of the layer were taken as the responses. Optimum values were determined with RSM historical data approach using a total of 60 experimental data for the immobilization of aptamer on Si-wafer, each of which was three repetitions. The RSM model and optimization studies are found in the Supplementary Document.

2.2. Determination of the analytical performance of the aptasensor

The analytical performance of the aptamers and the control aptamer in the determination of BPA was evaluated using a solution of 0.1–250 nM BPA in a buffer. BPA solutions were prepared in 100 mM PBS buffer (pH 7) according to the aptamer development step reported elsewhere [76,77]. Since BPA is an environmental pollutant, the effect of pH and solution type on sensor analytical performance was not included in the scope of this study. Si-wafers (sensor chips), which were interacted with BPA solution for 30 min, were then washed using buffer solution. Dried sensor chips were analyzed using a spectroscopic ellipsometer at 60° and 70° light incidence angles using light in the 400–1700 nm range. The ellipsometric parameters delta (Δ) and psi (Ψ) values were obtained and from these values, the delta (Δ) angle, in other words, the phase shift between the polarized incident light and the reflected light, was preferred as the sensor response since it is more sensitive to the molecular accumulation on the surface. The Δ spectrum obtained around 450–600 nm wavelength shows a nearly linear variation (Table 3). It also shifts towards lower degrees with the molecular accumulation on the surface. Based on this phenomenon, the Δ value at this wavelength was chosen as the main parameter in obtaining the sensor calibration graphs. Sensitivity and limit of detection (LOD) were calculated using the dependence graph of Δ variation on BPA concentration. To check the specificity of the sensor, analysis was performed by adding the analyte to the bottled drinking water. In addition, bisphenol B was spiked on the same sample and tested.

3. Results and dicsussion

3.1. Immobilization of BPA aptamers and improvement of immobilization conditions

RSM optimization was used in the immobilization stage of the BPA aptamer to the sensor chips. The optimum conditions were obtained from the meaningful model and determined by including the desirability function as a result of this optimization study, in which the surface molecular thickness and roughness were considered as the response. These conditions are as follows: MPTES immobilization time 176 min, MUA immobilization time 2 h, anti-BPA aptamer concentration 1500 nM, and anti-BPA aptamer immobilization time was 280 min. Considering the optimum conditions stated on the sensor chip surfaces, a mercapto functionalized surface was obtained for 180 min using 1 μM MPTES solution. Then, using 1 μM MUA (in ethyl alcohol) interaction was carried out for 2 h in the dark, and then –COOH terminated surface was obtained. Finally, an interaction time of 240 min with 1500 nM buffered aptamer solution was used for aptamer immobilization with the EDAC route. Since the specified route was also used in our previous studies, no chemical characterization was made regarding the modification, and only the ellipsometric thickness change was considered sufficient. The results regarding RSM optimization are given in the Supplementary Document.

3.2. Spectroscopic ellipsometry sensor performance evaluation

The interaction between the BPA solution in the buffer and the anti-BPA1, anti-BPA2, and CTRL aptamers was investigated using spectroscopic ellipsometry. For this purpose, the incident light angle was set to 60° and the Δ variation between 400 nm and 1700 nm was examined. The sensor response obtained as a result of the interaction of the BPA solution prepared in the buffer at different concentrations with the sensor chip is given in Fig. 2. The sensor response obtained from each sensor chip is similar to each other (since the base material is Si-plate and the top layer is organic material) and shifts to lower Δ degrees with increasing BPA concentration. When this change was examined for

Table 2
Anti-BPA aptamers and a control aptamer used in this study.

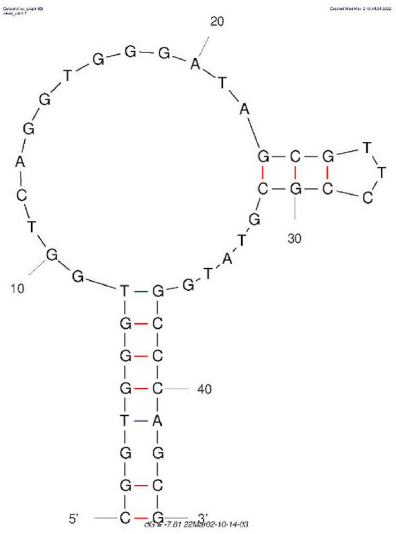
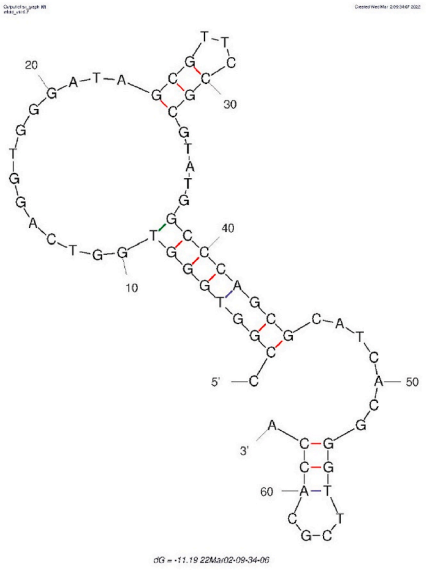
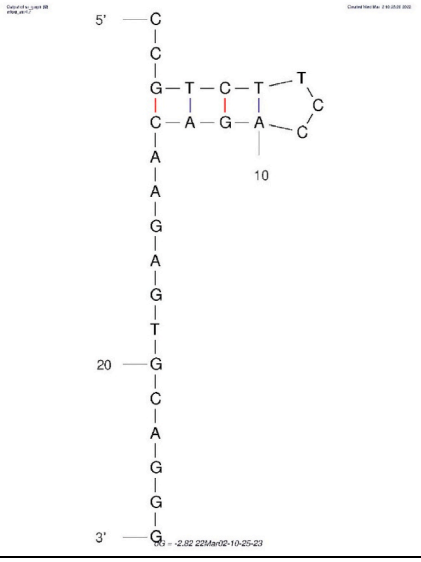
Aptamer	Sequence	Model
Anti-BPA1 [76]	5′-CGG TGG GTG GTC AGG TGG GAT AGC GTT CCG CGT ATG GCC CAG CG-3′	
Anti-BPA2 [77]	5′-CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA-3′	
Control (CTRL)	5′- CCG TCT TCC AGA CAA GAG TGC AGG G – 3′	

Table 3
Fitting data results for the region (450–600 nm) where the sensor response of AntiBPA-1 and AntiBPA-2 aptamer is linear.

AntiBPA1					
BPA concentration (nM)	Intercept		Slope		Statistics
	Value	Standard error	Value	Standard error	R^2
0	161.584	0.228	0.018	$4.326x10^{-4}$	0.97
0.1	161.109	0.259	0.018	$4.902x10^{-4}$	0.96
1	160.399	0.244	0.018	$4.615x10^{-4}$	0.97
10	158.761	0.273	0.020	$5.175x10^{-4}$	0.97
100	158.420	0.277	0.021	$5.247x10^{-4}$	0.97
250	157.940	0.264	0.021	$4.992x10^{-4}$	0.97
AntiBPA2					
BPA concentration (nM)	**Intercept**		**Slope**		**Statistics**
	Value	**Standard error**	**Value**	**Value**	**R^2**
0	163.069	0.281	0.017	$5.329x10^{-4}$	0.95
0.1	162.065	0.261	0.017	$4.942x10^{-4}$	0.96
1	159.805	0.244	0.020	$4.614x10^{-4}$	0.97
10	158.789	0.283	0.020	$5.354x10^{-4}$	0.97
100	158.173	0.244	0.021	$4.631x10^{-4}$	0.98
250	156.717	0.259	0.026	$4.900x10^{-4}$	0.98

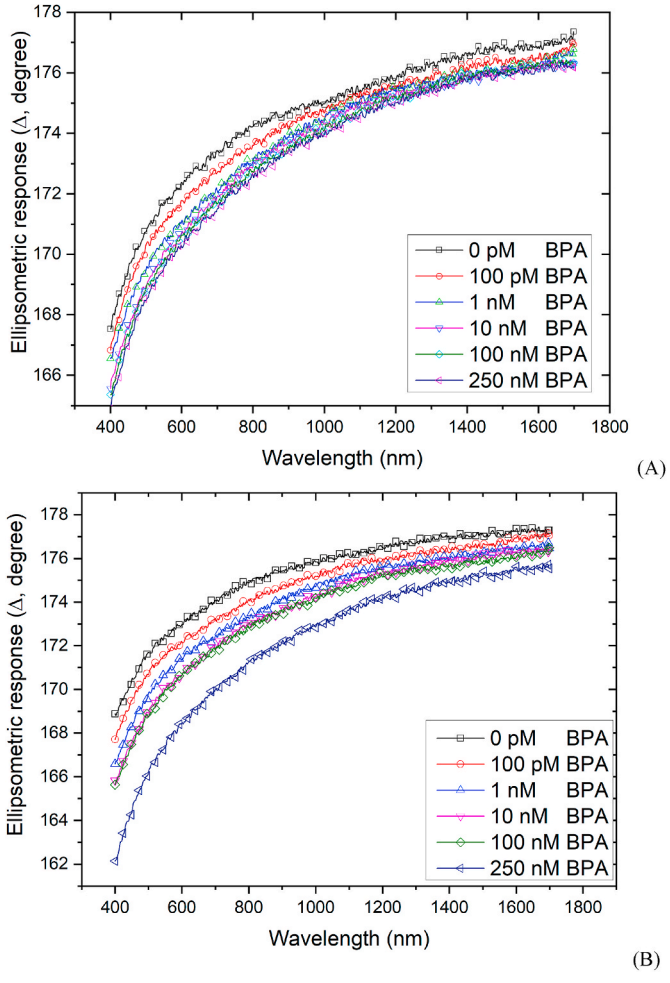


Fig. 2. Anti-BPA1 (A) and anti-BPA2 (B) aptamer sensor response obtained with 100 pM–250 nM BPA.

the BPA solution prepared between 100 pM and 250 nM, the Δ-λ change around 450–600 nm wavelength was linear with a determination coefficient (CoD) of 0.95–0.98 (Table 3). Considering the linear region in this range, the relative sensor response (based on 0 BPA value measured in the absence of BPA) was calculated and the sensor calibration graph

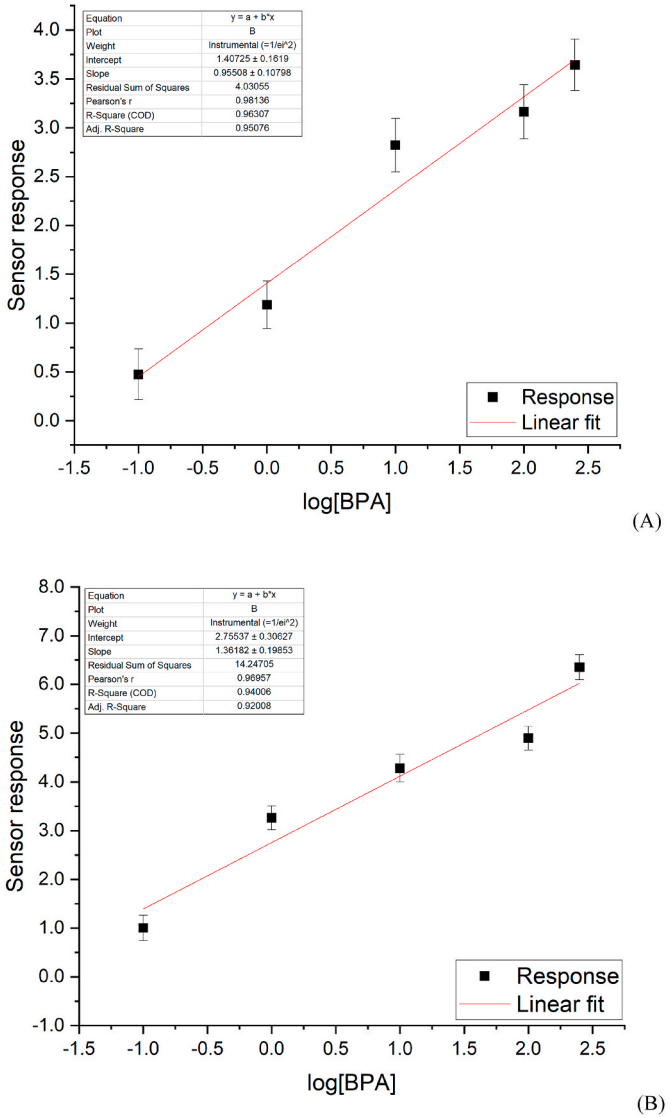


Fig. 3. Calibration curve of anti-BPA1 (A) and anti-BPA2 (B) aptamer.

was drawn (Fig. 3).

The calibration curve (Fig. 3) shows a line consistent with $\Delta = 0.955\log[BPA]+1.407$ with a CoD of 0.96. The sensitivity of the anti-BPA1 sensor by spectroscopic ellipsometry was 0.955 Δ/log[BPA]. Similarly, the sensor response for anti-BPA2 fits the line $\Delta = 1.362\log[BPA]+2.755$ with a CoD of 0.94 from 100 pM to 250 nM. The spectroscopic ellipsometry sensitivity of the anti-BPA2 sensor was 1.362 Δ/log[BPA].

The calibration curve parameters of anti-BPA1 and anti-BPA2 aptamers and the detection limit values calculated with 3σ by taking 3 times the average of the standard deviation obtained in the entire BPA concentration range (with S/N ratio of 3) are given in Table 4 and compared. A sensor signal of, 0.46 ± 0.22 Δ when 100 pM BPA, 0.51 ± 0.24 Δ when 1 nM BPA, and 0.58 ± 0.28 Δ when 500 nM BPA was used, resulted from CTRL aptamer. This shows the selectivity of the aptamers and that a very low amount of BPA could not be removed from the sensor surface during the washing steps.

The sensitivity of the anti-BPA2 sensor was (approximately 42%) higher than the anti-BPA1 sensor. In addition, a 5-fold difference was obtained in LOD values. This may occur because the two aptamers have a particularly dimensional difference. The aptamer with 63 bases instead of 44 bases was found to provide higher analytical performance in terms of both sensitivity and LOD. Considering that the ellipsometry measures the optical properties of the film formed on the surface, it is thought that these different results are obtained as a result of obtaining a much denser film with the antiBPA2 aptamer, on the sensor chip surface.

3.3. Evaluation of the specificity of the spectroscopic ellipsometry aptasensor using bottled water

Anti-BPA sensor chips were interacted with 100 pM and 1000 pM bisphenol B (2,2-Bis(4-hydroxyphenyl) butane, BPB) solution to test the specificity of the sensor. Although the selectivity of the aptamers was determined at the time of aptamer selection, it was tested whether an interference signal could be received at the sensor after modification. In addition, the final concentration of 100 pM and 1000 pM was added to the BPA solution, and analysis was carried out simultaneously with the same BPA solution. The results of the specificity test are given in Table 5.

Table 5 shows the sensor response obtained for anti-BPA1 at low and high BPB concentrations was approximately 3 times the noise obtained for BPA at that concentration and remained within the limits of 3σ. Similarly, while the sensor response obtained for anti-BPA2 was around 3σ at low concentrations, it increased slightly at high BPB concentration, up to 4 times the noise ratio. However, the response of the sensor falls within the noise limits in the analysis of BPA alone for both of the cases. The deviation in the sensor response obtained by applying the BPA and BPB solution mixture to the sensor at the same time was less than 3%. This shows that both of the aptamers used in this study are highly specific to BPA.

4. Conclusion

Herein, a BPA aptasensor was developed using two different aptamers based on spectroscopic ellipsometry. The analytical performance of a biosensor includes numerous requirements such as sensitivity, selectivity, detection range, repeatability, reliability, analysis time, and analysis cost. The detection sensitivity and selectivity of the BPA sensor were increased by developing a spectroscopic ellipsometry-based sensor and using aptamers with proven selectivity. The ellipsometric determination of 100 pM–250 nM BPA solutions was performed using two different aptamers with a LOD value of 215 pM and 36 pM for AntiBPA1 and AntiBPA2, respectively, which is quite promising and comparable to the reported values in the literature. Aptasensor response to BPB was compared with BPA for specificity tests and the results show negligible aptasensor response to BPB. Furthermore, recovery values between 98.6% and 96.2% were also obtained with BPA spiked in bottled water samples. It has been reported that both aptasensors based on spectroscopic ellipsometry exhibit adequate analytical performance.

Table 4
Comparison of BPA determination performances of spectroscopic ellipsometry aptasensors.

Aptamer	Parameters	CoD (R^2)	3σ	LOD (S/N = 3)
Anti-BPA1	Slope = 0.955 Intercept = 1.407	0.96	0.77	215 pM
Anti-BPA2	Slope = 1.362 Intercept = 2.755	0.94	0.79	36 pM

Table 5
Specificity test results of aptasensors with BPB only and BPB + BPA solution.

Aptamer	BPB added (pM)	BPA added (pM)	Sensor response Δ (degree)	S/N ratio for BPA only analysis (3σ)
Anti-BPA1	100	0	0.47 ± 0.21	0.77
	1000	0	0.84 ± 0.29	
Anti-BPA2	100	0	0.38 ± 0.19	0.79
	1000	0	0.56 ± 0.21	
Aptamer	**BPB added (pM)**	**BPA added (pM)**	**BPA Found (pM)**	**% Recovery**
Anti-BPA1	1000	100	102.4 ± 1.9	97.6
	1000	1000	1035 ± 15	96.5
Anti-BPA2	1000	100	101.4 ± 1.6	98.6
	1000	1000	1038 ± 18	96.2

Credit author statement

Samet Şahin: Conceptualization, Writing- Original draft, Writing - Review & Editing; **Zafer Üstündağ:** Writing- Original draft, Supervision; **Mustafa Oguzhan Caglayan:** Conceptualization, Investigation, Methodology, Writing- Original draft, Funding acquisition, Project administration.

Declaration of competing interest

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

Data availability

The authors are unable or have chosen not to specify which data has been used.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.talanta.2022.123885.

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