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Non-enzymatic sensing of glucose using a glassy carbon electrode modified with gold nanoparticles coated with polyethyleneimine and 3-aminophenylboronic acid

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Abstract A non-enzymatic electrochemical method was developed for sensing glucose by using a glassy carbon electrode modified with 3-aminophenylboronic acid (APBA) immobilized on polyethyleneimine (PEI)-coated gold nanoparticles. The modified electrode was characterized by TEM, zeta potential measurements and UV-Vis spectroscopy. Its analytical performance was evaluated in pH 9 solution by potentiometry. The respective calibration plot, established at open circuit potential (vs. Ag/AgCl) covers the 0.5–50 mM glucose concentration range, which makes it suitable for blood glucose assays. The detection limit is 0.025 mM, and no interference is caused by ascorbic acid, dopamine, and uric acid. Effects of other carbohydrates such as fructose, galactose and saccharose were also investigated. The electrode was used to determine glucose in human serum samples and the results agreed well with those obtained with commercial amperometric enzymatic sensors.

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Introduction

Numerous approaches have been reported for determination of glucose. Most of the traditional methods employ electrochemical or colorimetric readout systems and these methods are generally based on the oxidation of glucose by the enzyme glucose oxidase (GOx) or glucose dehydrogenase (GDH) [1].

Although there is a good selection of high sensitivity of enzymatic sensors, they have a number of limitations including: (1) the catalytic activity of GOx is sensitive to environmental aspects such as temperature, humidity, pH and chemical reagents due to the intrinsic nature of the enzyme [2] (2) the storage of an enzyme is difficult because it can be easily denatured in its environment and (3) the production of enzymes is very troublesome [1]. Therefore, researchers have focused to non-enzymatic glucose detection, based on the direct oxidation of glucose on the electrode surface without using the immobilized enzyme [2, 3]. Compared with enzymatic biosensors, the non-enzymatic sensors have some attractive advantages in terms of their simplicity, portability, manufacturability, low cost, stability, sensitivity and their high selectivity [4]. At the same time, the advance of nanomaterials caused a progress to occur in non-enzymatic systems [5]. Various nanomaterials such as Au, Pt, Cu nanoparticles, graphene, carbon nanotubes and nanocomposites have been used in the manufacturing of non-enzymatic glucose sensors in order to overcome some of their drawbacks [6].

Molecular recognition systems have been widely used for selective binding of a target molecule. A molecular recognition agent mimics natural receptors such as enzymes and antibodies for selective and affinity binding of a target molecule [7, 8]. Boronic acids have been extensively used as affinity ligands for carbohydrates, glycoproteins and nucleotides [9]. Boronic acids and derivatives form five-and six membered cyclic esters with cis-1,2 and cis-1,3 diols, respectively, in aqueous basic media. The binding process is rapid and reversible. For saccharides, they have a convenient structural framework to bind the hydroxyl groups of boronic acids. Also, while enzyme based sensors can not suitable directly monitor the detection of bound sugars, the direct detection both free and bound sugars with molecular recognition systems is possible, due to the detection principle of their bases on a reversible, equilibrium reaction without the consumption of the analyte (Scheme 1) [10]. Several boronic acid derivatives have been used for selective binding of carbohydrates, such as glucose, maltose or fructose [11]. In the study by Tsukagoshi et al., they used *p*-iodophenylboronic acid as a recognition ligand in the capillary electrophoresis system for detection of several mono- and disaccharides [12]. Torun et al. reported that the interaction of a 3-aminophenylboronic acid with different monosaccharides that were using isothermal titration calorimetry (ITC) [7]. In our previous study, an enzyme free potentiometric glucose sensor based on (3-aminophenylboronic acid-co-3-octylthiophene was developed [8].

We demonstrate a method to fabricate a glucose sensor using gold nanoparticles synthesized with branched polyethyleneimine (PEI). Here, PEI acted as a reducing/−stabilizing agent and PEI coated AuNPs were immobilized on a glassy carbon electrode via simply dropping and drying method to construct a glucose sensor. Then, PEI covered AuNPs were modified with glutaraldehyde (GA) and 3-aminophenylboronic acid (APBA). The resulting electrode surfaces with AuNP/GA/APBA were used as non-enzymatic potentiometric glucose sensor.

Experimental

Materials

The polyethyleneimine (PEI, Mw: 65.000) and hydrogen tetrachloroaurate ($HAuCl_4$) were obtained from Sigma-Aldrich (Taufkirchen, Germany, https://www.sigmaaldrich.com/). A 3-aminophenylboronic acid (APBA) was used as received from Aldrich (Steinheim, Germany). All other chemicals were of analytical grade and were purchased from MerckAG (Darmstadt, Germany, http://www.merckgroup.com/en/index.html). All solutions were prepared using deionized water, 18.2 MΩ cm free from organic matter, which was obtained from a Millipore purification system.
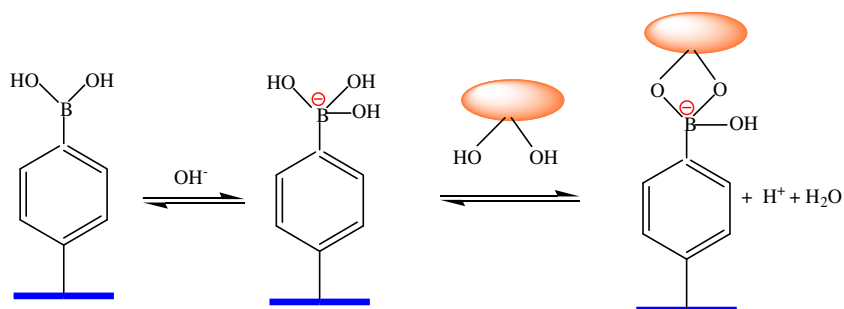
Instrumentation

The electrochemical experiments were performed with a Gamry potentiostat (model Reference 600, USA). Potentiometric measurements were carried out in a two-electrode cell configuration. A glassy carbon electrode (GC) was modified with the AuNP/GA/APBA film as described below and then used as the working electrode. An Ag/AgCl electrode served as the reference. Before modification, the surface of the glassy carbon electrode was hand-polished with alumina–water slurries (1.0, 0.3 and 0.05 μm, respectively) using a polishing cloth. Then, the electrode was washed and sonicated in pure water for 10 min to remove impurities. All electrochemical measurements were conducted at room temperature (25 °C).

A UV–Visible absorption spectroscopy was also used to monitor the plasmon absorption of the AuNPs, and spectra were collected using a Perkin Elmer Lambda 25 UV-Vis spectrophotometer at wavelengths of 400–800 nm.

Zeta potential measurements were made in a dynamic light-scattering apparatus (Zeta Sizer-Nano series Malvern Instruments) to examine the colloidal stability and charge of the AuNPs. The morphology of the AuNPs was examined by TEM using a JEOL 2100 HRTEM (JEOL Ltd., Tokyo, Japan) transmission electron microscope. FT-IR spectrum was obtained on a Bruker, Vartex 70 V FT-IR spectrometer using KBr pellets.

Scheme 1 Binding process between phenylboronic acid and a diol

Synthesis of AuNP/GA/APBA

The PEI covered AuNPs was prepared by reducing HAuCl$_4$ in the presence of the PEI in an aqueous solution according to the previously reported procedure in the literature [13]. Briefly, 1 mL of 1×10^{-2} M concentrated aqueous solution of HAuCl$_4$, 2 mL PEI and 7 mL deionized water were mixed and heated at 90 °C for 10 min to yield a wine red solution. The resulting solution was centrifuged and gold nanoparticles were separated from unreacted PEI solution. Before the attachment of the APBA, the PEI covered AuNPs was modified with glutaraldehyde (GA). The glutaraldehyde reaction experiments were performed in a phosphate buffer (pH 7.4). Firstly, the AuNPs was equilibrated into the buffer. Next, it was transferred into the GA solution (5 % v/v) and treated with shaking at room temperature for 12 h. After reaction, the AuNPs was then washed several times with acetic acid solution (100 mM) and phosphate buffer (pH 7.0) until removal of the excess GA. Finally, the resulting particles were dispersed in a 2 mL ethanol solution containing 10 mM APBA for overnight under constant stirring and then it was cleaned three times with an ethanol solution to remove the excess APBA. The AuNP/GA/APBA was stored at 4 °C before use (Fig. 1).

Preparation of AuNP/GA/APBA electrode

All of the steps represented in this section were performed before the usage of working electrodes in electrochemical experiments in order to avoid contamination by the oxidation products and to obtain a clean renewed electrode surface. In order to prepare an AuNP/GA/APBA modified GC electrode, a 5.0 μL solution of AuNP/GA/APBA was dropped on the polished and cleaned glassy carbon (GC) electrode surface, and then it was dried at room temperature.

Electrochemical measurements

The potentiometric measurements were carried out using a two electrodes cell configuration. The AuNP/GA/APBA electrode was used as the working electrode, and an Ag/AgCl electrode was employed as the reference electrode. Unless otherwise stated, all of the open circuit experiments were conducted in a stirred boric acid/borate buffer solution at pH 9. The electrode potential was allowed to settle in the buffer solution prior to performing all of the open circuit measurements. After the AuNP/GA/APBA electrode settled the change in open circuit potential (E_{oc}) was monitored before and after the addition of glucose. The durability of the AuNP/GA/APBA electrodes was examined within 10 days by storing the electrodes at 4 °C in the closed vessel over the buffer solution, pH 9.0.

Determination of glucose in human blood serum

Serum samples were collected from normoglycemic individuals from Kırıkkale University Hospital. 100 μL of the serum samples were injected to 2.5 mL of constantly stirred solution of pH 9, and the potentiometric response was recorded.

Fig. 1 Schematic of the preparation of gold nanoparticles modified with glutaraldehyde and 3-aminophenylboronic acid (AuNP/GA/APBA)

(HAuCl$_4$)

AuNP

AuNP/GA/APBA

Polyethyleneimine (PEI)

: PEI covered AuNP

:3-aminophenylboronic acid

:Glutaraldehyde

Results and discussion

The synthesis and application of metal nanoparticles have recently attracted great interest; because of their unique electronic, optical, magnetic and catalytic properties that differ greatly from those of corresponding bulk material due to a function of their size and shape [14]. During the synthesis of nanoparticles, metal ions should be reduced in a colloid form against precipitation. However, stable dispersions of nanoparticles are generally short-lived in aqueous media since they agglomerate to form larger clusters. On the other hand, precipitation and agglomeration are overcome through spontaneous adsorption of polymeric stabilizers on the particle surface [13, 15]. As an example, poly(ethyleneimine)(PEI) which is a cationic polymer with a high charge density in the synthesis of colloidal gold can simultaneously act as both Au(III) reducing agent and stabilizer of AuNPs [16–18]. The PEI-stabilized AuNPs are biocompatible [19] and can be incorporated into supramolecular assemblies for electrostatic interactions with polyanions owing to the ability of protonated PEI. In addition to this, its fragments containing amino groups can provide nanoparticles with a positive charge and stability against agglomeration also together with further modification of nanoparticle surface. The PEI-stabilized AuNPs can form complexes with Au(III) and reduce Au(III) to Au(0). Therefore it can be used as seed for size-controlled hydrothermal growth of larger AuNPs [20] or anisotropic Au crystals such as nanorods [21]. Kim et al. have reported that AuNPs formed clusters in different ways when different polymeric stabilizers were used. The AuNPs, synthesized in the aqueous solution of PEI without NaBH$_4$ have formed the smallest nanoclusters (67.4 nm). The PEI-stabilized AuNPs synthesized with NaBH$_4$ has been irregular in size and has formed clusters approx. in hydrodynamic size of 98.7 nm. As a result, they have explained that PEI did not play an effective role in the stabilization when it was used with NaBH$_4$ due to the rapid formation of AuNPs [22]. Furthermore, other metal nanoparticles such as silver naoparticles cannot be synthesised

without NaBH$_4$ as known in the literature. Due to this reasons, we synthesized gold nanoparticles without NaBH$_4$ with using PEI for sensor construction.

We synthesized gold nanoparticles in the presence of PEI and the resulting PEI capped AuNPs are stable over 4 months due to the positively charged PEI onto the particle surfaces. The zeta potential value was a positive 36.6 mV with 0.373 PDI. The measured hydrodynamic diameter of the PEI reduced AuNPs was found to be 60.98 nm as shown in (Fig. 2(a)).

To confirm the size of the resulting nanoparticle, TEM measurement was carried out. The TEM result indicated that the AuNPs has a spherical shape and particle aggregation was not observed due to the presence of positively charged the AuNPs as shown in (Fig. 2(b)).

To verify and confirmation of chemical immobilization, FT-IR measurements was carried out using AuNP/GA/APBA electrode surface. In FT-IR spectrum, some peaks related to boronic acid groups were seen and these findings showed that modification was made successfully (Fig. S1).

The effect of particle synthesis time on glucose response

To optimize the particle synthesis condition, we tested different duration time for the reduction of gold ions in the presence of PEI to synthesize nanoparticles and the obtained gold nanoparticles were characterized using UV-Vis spectra (Fig. S2). The optical absorption spectrum of gold nanoparticles is a good indicator of their size and shape [23]. The UV–Vis absorption spectra of the synthesized nanoparticles show a sharp peak centered at 520 and 530 nm at 10 and 15 min, respectively. This is a typical plasmon resonance band for the AuNPs, suggesting the formation of AuNPs and it is the standard optical signature for the formation of gold nanospheres in a solution. For 20 min duration time, the UV–Vis absorption spectrum of the synthesized gold nanoparticles shows a broad peak that was shifted to a red region.

Fig. 2 **a** Size distribution measurements of AuNPs prepared by PEI, **b** TEM image of AuNPs prepared by PEI
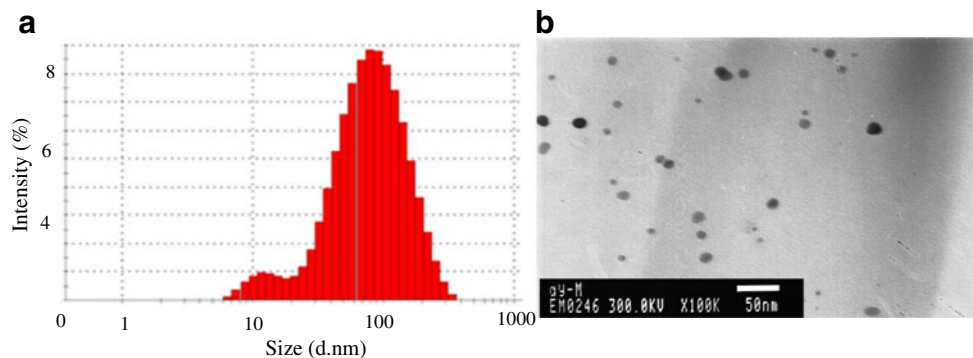
The potentiometric glucose responses were studied with the obtained gold nanoparticles at three different times and the optimum glucose response were obtained at 15 min (Fig. S2).

Potentiometric measurements at AuNP/GA/APBA modified glassy carbon electrode

The AuNP/GA/APBA-GC electrode was used for the determination of glucose by potentiometric methods. For a comparison, unmodified GC electrode, a PEI covered AuNPs and the AuNP/GA/APBA modified GC electrodes were also used for the determination of glucose by a successive addition of 5 mM glucose. As seen in Fig. 3, while a glucose response was not seen by using both unmodified GC and AuNP-GC electrode, the open circuit potential was increased by using the AuNP/GA/APBA electrode. This result indicates that the AuNP/GA/APBA electrode can be used as a sensor for enzyme free potentiometric glucose measurements.

The glucose calibration curve was obtained in the range of 0.5–50 mM using the standard addition method under optimized experimental conditions (Fig. 4). The calibration curve equation of glucose was found as E (mV) = 0.4107 C (mmol L^{-1}) + 1.5484 with R^2 = 0.9925. The detection limit was calculated on the basis of a signal to noise ratio of 3, which was 0.025 mM and the repeatability of the method was checked by three consecutive measurements. The relative standard deviation (RSD) was calculated as 7.68 %. The reproducibility of the AuNP/GA/APBA electrode was also investigated and RSD was calculated as 7.25 %. The durability of the non-enzymatic sensor based on the AuNP/GA/APBA electrode was investigated. After 10 days, 96.6 % of initial response of the AuNP/GA/APBA electrode was observed.
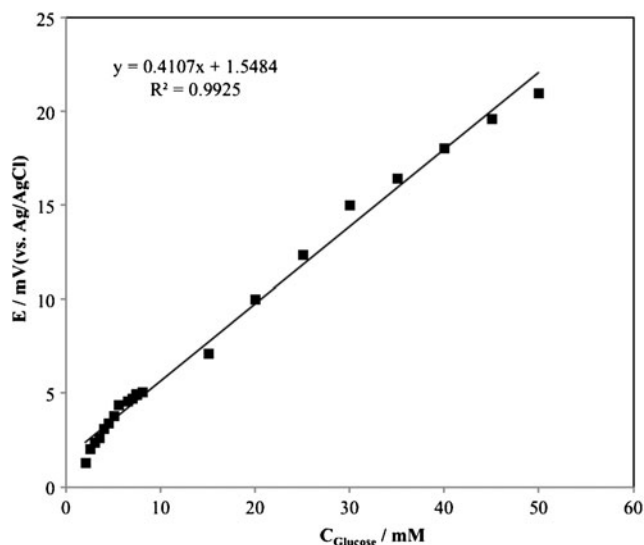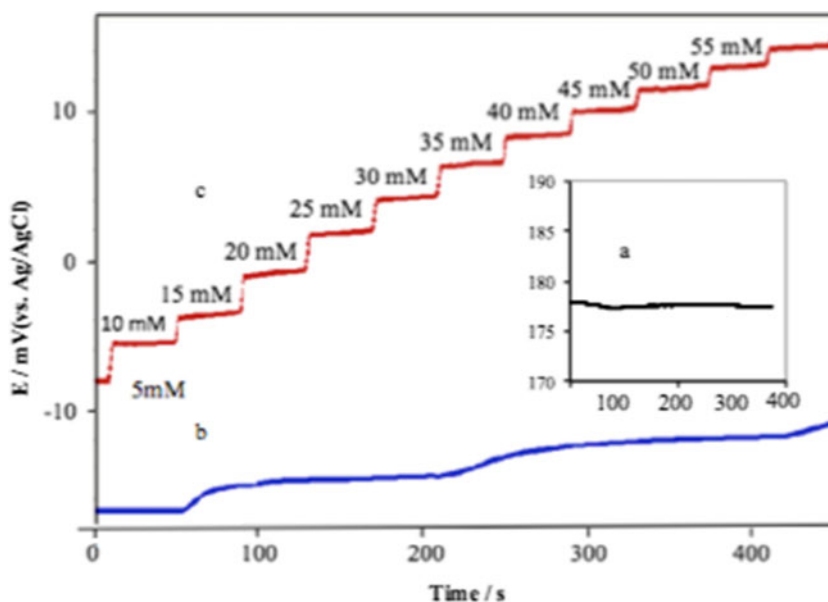

Fig. 4 Calibration curve of glucose sensors based on AuNP/GA/APBA

A comparison of the linear range and detection limit for the AuNP/GA/APBA non-enzymatic sensor with other reported non-enzymatic glucose sensors is given in Table 1. The measured glucose concentration is a significantly wider range when compared with other non-enzymatic sensors.

Interference studies

The presence of interferences, such as ascorbic acid (AA), uric acid (UA), and dopamine (DA) in the biological sample can prevent the signal of glucose. Therefore, these potentially interfering materials were used to conduct the interference test. The physiological level of glucose is about 50 times higher than that of interfering species. Therefore, adding 5 mM

Fig. 3 The response curves of **a** GC, **b** AuNP-GC, **c** AuNP/GA/APBA-GC electrode as a function time upon the addition of 5 mM glucose

Table 1 A comparison of our developed AuNP/GA/APBA-GC sensor with other non-enzymatic glucose sensors

Electrode modifier	Method	Linear range	Detection limit (LOD)	Working potential	Medium	Ref.
Au/DLC/P[a]	Amperometry	0.5–25 mM	0.3 mM	0.4 V	pH 13 (0.1 MNaOH)	[24]
PAPBAOT[b]	Potentiometry	5.0–50 mM	0.5 mM	OCP	pH 9 (0.1 M H_3BO_3/BO_3^{-3})	[8]
Chitosan/AuNPs[c]	Amperometry	0.4–10.7 mM	0.37 mM	0.4 V	pH 13 (0.1 M NaOH)	[25]
(POT/AuNPS/MPB)[d]	Potentiometry	5.0–30 mM	0.2 mM	OCP	pH 9(0.1 M H_3BO_3/BO_3^{-3})	[26]
Pt/Pd/MCV[e]/NA[f]	Amperometry	1.5–12 mM	120 μM	0.55 V	pH 7.4 (0.1MPBS)	[27]
Pt/MWCNTs[g]	Amperometry	1–23 mM	50 μM	−0.35 V	pH 7.4 (0.1MPBS)	[28]
NiO/Pt/ERGO[h]	Amperometry	2 μM-5.66 mM	0.2 μM	0.6 V	0.05 M NaOH	[29]
NA/NiONF[i]-rGO[j]	Amperometry	2 μM-0.6 mM	0.77 μM	0.6 V	pH 13 (0.1 M NaOH)	[30]
PABA[k] nanotubes	Potentiometry	2-14 mM	0.5 mM	OCP	pH 9.2(optimum) pH 7.4(worked)	[31]
(AuNP/GA/APBA)[l]	Potentiometry	0.5–50 mM	0.025 mM	OCP	pH 9(0.1 M H_3BO_3/BO_3^{-3})	This study

OCP open circuit potential

[a] DLC/P: phosphorus doped diamond-like carbon

[b] PAPBAOT: poly (3-aminophenyl boronic acid-co-3-octylthiophene)

[c] AuNPs: gold nanoparticles

[d] POT/AuNPS/MPB: Poly(3octylthiophene)–AuNPs-(3-mercaptophenyl boronic acid)

[e] MCV: Mesoporous carbon vesicle

[f] NA: Nafion

[g] MWCNTs: Multiwalled carbon nanotubes

[h] ERGO: electrochemicallyreduced graphene oxide

[i] NiONF: NiO nanofibers

[j] rGO: reduced graphene oxide

[k] PAPBA: poly (2-aminophenyl boronic acid)

[l] (AuNP/GA/APBA): gold nanoparticles/glutaraldehyde/3-aminophenylboronic acid

glucose solution, and then 0.1 mM interfering agents tested the interference of these molecules. There are no potentiometric responses of the UA, DA, and AA for glucose determination as seen in Fig. 5.
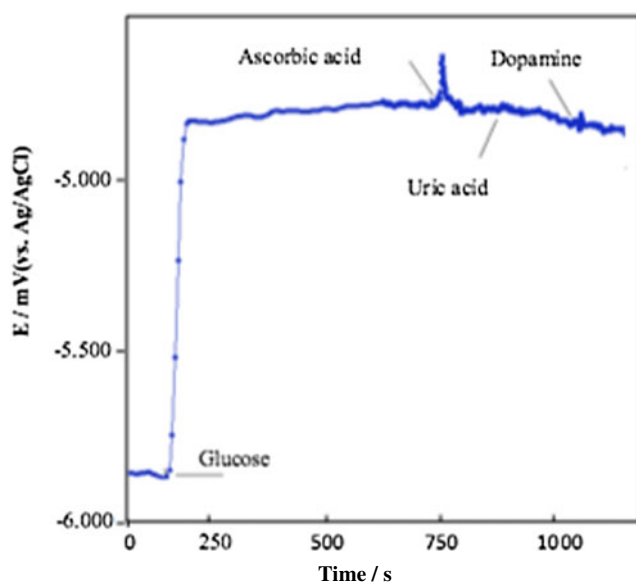
The performance of the AuNP/GA/APBA film electrode was also evaluated in the presence of the AA, DA and UA. As can be seen in Fig. 6, the response was linear between 5 and 30 mM glucose concentration.

Results indicate that the electrode can be used to determine glucose in the presence of such interferences. In addition, the glucose sensitivity decreased in the presence of these
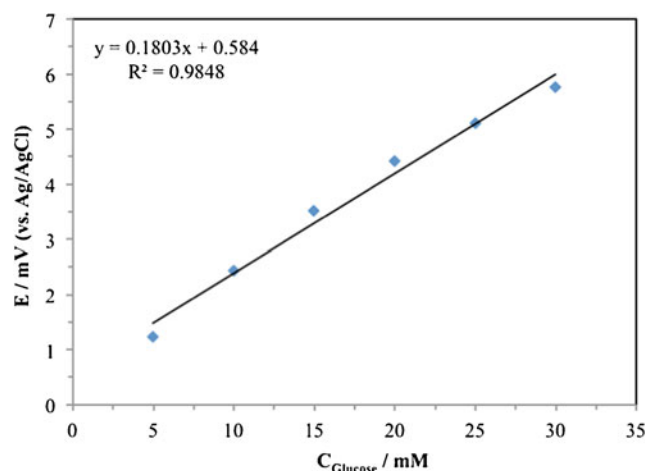

Fig. 5 Potentiometric response of glucose, AA UA and DA

Fig. 6 Calibration plots of AuNP/GA/APBA modified GC electrode in the presence of interferences

interfering agents. It may be due to the adsorption of the interfering molecules on the AuNP/GA/APBA film electrode surface and sterically hindering glucose binding. There can be differences in the binding ability between the various carbohydrates having vicinal diols and boronic acid groups. This is why, other carbohydrates having diols such as fructose, galactose would also affect the determination of glucose.

Li et al. reported that potentiometric detection of saccharides based on poly(aniline boronic acid) nanotubes. They found optimum pH 9.2 for glucose determination. Furthermore, they observed that fructose sensitivity (3.5 mV/mM) of poly(anilineboronicacid) nanotubes was more than glucose sensitivity (1.5 mV/mM) [31]. Manesh et al. studied non-enzymatic amperometric glucose determination at 0.004 V based on boronic acid recognition group. They also used crown ether to eliminate response of other diols. For a mixture of glucose and maltose having milli mole concentration each, maltose showed a 72.35 % current response with respect to glucose. However, when the current response was normalized with regard to the current response of maltose to glucose in the real blood sample, the current response of maltose (0.04 μA) was 2.08 % in comparison to the current response of glucose (2.12 μA) [32]. Alexeev et al. reported that boronic acid in the presence of crown ether consisting of a 4-acryl- oylamidobenzo-15-crown 5 functional group selectively binds glucose over the other carbohydrates, galactose, mannose, and fructose [33]. Mei et al. reported non-enzymatic sensing of glucose at neutral pH values using Co@Pt core-shell nanoparticles. According to their results, there were no interfering effect of UA (0.1 mM), AA (0.1 mM) and fructose (0.1 mM) for amperometric glucose (5 mM) determination at −0.05 V [34].

We also investigated interference effect of saccharose, galactose and fructose for potentiometric glucose determination. When each of galactose, fructose and saccharose was 0.1 mM, which is in the amount of real blood sample, potential increasing was 5.0 %, 12.25 % and 8.25 % with respect to glucose response (5 mM), respectively (Fig. S3). On the other hand glucose and fructose were prepared with the same concentration (1 mM), interference effect of fructose was obtained 56.32 % (data not shown). The complexation of saccharides

with aromatic boronic acids produces a stable ester, where the binding constant is dependent on the pH, electrolyte concentration and pKa of the aromatic boronic acid. The selective binding of boronic acid to glucose can be achieved with using appropriate pH. Torun et al. showed that fructose has higher affinity than glucose and galactose at pH 11 [7].

Application in serum sample

The AuNP/GA/APBA non-enzymatic glucose sensor was applied in to the human blood serum. The concentration of glucose in the human blood serum was obtained using the standard additions method. The glucose measurements in the serum samples were compared with commercial sensor results as seen in Table 2. The compatibility between the commercial sensor results and the AuNP/GA/APBA sensor results proves the reliability of this sensor in determination of glucose in real samples. The results show that this sensor can be used for glucose determination in a real sample.

Conclusion

A non-enzymatic glucose sensor for determination of glucose on the GC electrode modified with AuNP/GA/ APBA was developed. The AuNP/GA/APBA sensor displays good electrochemical behavior in a wide linear range (0.5–50 mM) for determination of glucose. The detection limit was determined as 0.25 mM. We also show that this electrode can be used to determine glucose in human serum. We believe that our modified electrode can be an alternative for non-enzymatic glucose determination with both a low detection limit and easy preparation.

AuNP/GA/APBA potentiometric non-enzymatic sensor has some advantages such as preparation of AuNPs and PEI composite is a simple and green technique, potentiometry needs very simple operating circuit. Therefore, potentiometric non-enzymatic glucose sensors are attractive in point of integrating with conventional ion-selective electrodes like pH meter. Despite all these, non-enzymatic glucose sensors up to now are still using in the laboratory because of the biological matrices is very complex and it requires more academic studies for take place in medical market instead of enzymatic sensors.

Table 2 Assay of glucose in human blood sample

Sample number	Commercial sensor (n = 3)	AuNP/GA/APBA sensor (n = 3)
1	5.49 ± 0.029 mM	4.23 ± 0.162 mM
2	5.56 ± 0.035 mM	4.63 ± 0.127 mM

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