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A novel conductance glucose biosensor in ultra-low ionic strength solution triggered by the oxidation of Ag nanoparticles

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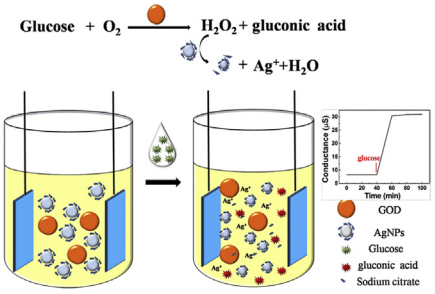
HIGHLIGHTS

- A novel sensitive conductance biosensing for glucose detection was achieved.
- The conductance biosensing achieved a significant breakthrough of glucose detection in ultra-low ion strength media.
- This proposed strategy described here could be expanded for detecting other substances.
- The nanosensor is also used to determine glucose in beverage samples.

GRAPHICAL ABSTRACT



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ABSTRACT

A simple, sensitive and effective method to detect glucose in ultra-low ionic strength solution containing citrate-capped silver nanoparticles (CCAgNPs) was developed by monitoring the change of solution conductance. Glucose was catalyzed into gluconic acid firstly by glucose oxidase in an O_2-saturated solution accompanied by the reduction of O_2 into hydrogen peroxide (H_2O_2). Then, CCAgNPs was oxidized by H_2O_2 into Ag^+ and the capping regent of citrate was released at the same time. All these resulted Ag^+, gluconic acid and the released citrate would contribute to the increase of solution ionic strength together, leading to a detectable increase of solution conductance. And a novel conductance glucose biosensor was developed with a routine linear range of 0.06–4.0 mM and a suitable detection limit of 18.0 μM. The novel glucose biosensor was further applied in energy drink sample and proven to be suitable for practical system with low ionic strength. The proposed conductance biosensor achieved a significant breakthrough of glucose detection in ultra-low ionic strength media.

1. Introduction

Electroanalytical chemistry has received extensive attention owing to its low-cost instrumentation, rapid response, high sensitivity, simplicity, etc [1–6]. Over the past few years, important advancements in electrochemical biosensing based on enzymatic catalysis have been achieved as a result of the development of related strategies to immobilize enzymes on electrode surface [7–12]. However, some inherent drawbacks resulted inevitably in low sensitivity, fragile stability, poor reproducibility and weak regeneration ability due to partial loss of enzyme bioactivity in contact with electrode and partial enzyme removal off from electrode surface [13–20]. Furthermore, sequential immobilization procedures are tedious, complicated and consuming [21–24].

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To solve this contradiction, a novel promising solution strategy is attracting more and more interests [25,26]. In this strategy, enzymes exist in a solution and their bioactivity could reach the maximum degree accordingly, which will enhance the sensitivity and selectivity of biosensors. Furthermore, bare electrodes or simply modified electrodes are used in this strategy, which will improve the reproducibility, regeneration and stability of biosensors. Simultaneously, the strategy is simple and low-cost. Up to now, there were only a few reports of electrode immobilization-free strategies [27,28]. For example, our group developed a simple chitosan-reduced graphene oxide/concanavalin modified electrode for assay of urea and glucose based on enzyme-catalyzed reaction in one sample. Free glucose oxidase (GOD) catalyzed the oxidation of glucose and urease catalyzed the hydrolyzation of urea to give different response toward $Fe(CN)_6^{3-}$ on the simply modified electrode [29]. Yang et al. reported a GOD label-based electrochemical immunosensor without incubation period. Their work proved that they could minimize the incubation period for enzyme label-based catalytic reactions effectively in the immunosensor by using GOD enzymatic redox cycling [30].

For amperometric methods, supporting electrolyte are generally needed to reduce electrical resistance of solution [31–37]. However, high ion concentration would cause high background which might result in low sensitivity. Furthermore, with the improvement of living standards and the growing concern for health, more and more food with low-sugar and low-salts have been provided so that it might be necessary to detect glucose in ultra-low ionic strength media [38]. Therefore, introducing electroanalytical chemistry to ultra-low ionic strength solution could not only expand new applications but also exploit new properties of electroanalytical chemistry. At present, only a few studies have been performed in ultra-low ionic strength solution. For example, Li et al. reported a novel biosensor for avian influenza virus detection in ultra-low ionic strength media [14]. The detection principle was based on the oxidation of glucose into gluconic acid catalyzed by free GOD to increase the ionic strength and accordingly caused the change of electrochemical impedance, which endowed the biosensor with better sensitivity and detection limit than traditional sensors.

Herein, a simple and sensitive conductivity method was developed to detect glucose in an ultra-low ionic strength solution. As illustrated in Fig. 1, firstly, glucose was oxidized into gluconic acid under the catalysis of GOD and hydrogen peroxide (H_2O_2) was generated at the same time. Then, the citrate-capped silver nanoparticles (CCAgNPs) in the solution were oxidized into Ag^+ by H_2O_2 and the capping reagent of citrate was released simultaneously. The produced Ag^+, gluconic acid and released citrate would contribute to the total ionic strength of the solution, leading to the increase of conductance in ultra-low ionic strength media. The change of solution conductance was used to develop a novel conductance glucose biosensor. Analytical parameters such as sensitivity, linear range and detection limit of the novel conductance method were explored in this work.

2. Experimental section

2.1. Materials

H_2O_2 (30%) was purchased from Beijing Chemical Reagent Factory (Beijing, China). Glucose oxidase (GOD, EC 1.1.3.4, 140 U mg^{-1}) and 6-mercapto-1-hexanol (MCH) were obtained from Sigma–Aldrich. Silver nitrate ($AgNO_3$) was purchased from Shanghai Shenbo Chemical Plant (Shanghai, China). Sodium citrate was purchased from Xilong Chemical Co. Ltd. (Guangdong, China). Sodium borohydride ($NaBH_4$), glucose and sucrose were purchased from Tianjing Fuchen Chemical Reagent Factory (Tianjing, China). The D-galactose, D-mannose and fructose were purchased from Siopharm Chemical Reagent Co. Ltd. All solutions were prepared with ultra-pure water purified by a Millipore-Q System ($\rho \geq 18.2$ MΩ cm).

2.2. Equipment and instrumentation

Conductance was determined by DDS-307 conductance meter (Shanghai Precision & Scientific Instrument Co., Ltd.). In order to avoid electrode contamination, the Pt electrode was immersed beforehand in 1.0 mM ethanol solution of MCH for 12 h to form MCH self-assembled monolayers. Then, the Pt electrode was rinsed by alcohol and ultrapure water to remove the un-immobilized mercaptan molecules for next use. Characterization of CCAgNPs was performed on AJ-III atomic force microscope (AFM) system (Shanghai Aijian Nanotechnology, China) using tapping mode. Standard silicon cantilevers (spring constant 0.6–6 N m^{-1}) were used under their resonance frequency (typically, 60–150 kHz). UV–vis absorption spectra were recorded on Lambda 35 UV–vis Spectrophotometer.

2.3. Synthesis of CCAgNPs

20 mL $AgNO_3$ aqueous solution (30 mM) were mixed with 2 mL sodium citrate (194 mM) as a coating agent. The mixture was kept stirring and then 20 μL $NaBH_4$ (5 mg/mL) as a reducing agent was added into the mixture every 30 s. After the mixture was turned into black brownish, the adding of $NaBH_4$ was stopped at once. Here 100 μL $NaBH_4$ has been added into the above mixture in total. After continuous stirring for 30 min, the mixture was centrifuged and the solid products were washed three times with ultra-pure water. The synthesis of CCAgNPs with different sizes was carried out by changing the ratio of $AgNO_3$ and sodium citrate ($n_{Ag}/n_{sodium\ citrate}$) according to the same procedure.

2.4. Determination of glucose based on conductance change

2.0 mL aqueous solution containing 0.2 mM CCAgNPs and 25 μg/mL GOD was prepared with ultra-pure water under oxygen saturation. The conductance was measured immediately as background value. A series of glucose solution with different concentration were added into the above solutions. 30 min later, the conductance of the series of solution were re-measured. The change in the conductance caused by glucose was recorded.

3. Results and discussion

3.1. Characterization of CCAgNPs

AFM was employed to characterize the morphology of CCAgNPs. As shown in Fig. 2, many small spherical CCAgNPs were uniformly distributed over the substrate. The size of CCAgNPs could be easily controlled by changing the molar ratio of $AgNO_3$ and sodium citrate ($n_{Ag}/n_{sodium\ citrate}$) as shown in Fig. 2A–C. The histograms (inset of Fig. 2A–C) indicated that the average size of CCAgNPs was 4 nm, 6 nm and 8 nm when the $n_{Ag}/n_{sodium\ citrate}$ was 3:2, 3:1 and 6:1, respectively. Fig. 2D showed UV–vis absorption spectra of above three kinds of CCAgNPs with different size (a: 4.0 nm, b: 6.0 nm, c: 8.0 nm). Obviously, the successful synthesis of CCAgNPs was confirmed by the appearance of strong characteristic absorption bands at about 380 nm [4].

3.2. The novel conductance sensing of H_2O_2

The conductivity is a basic electrochemical parameter which

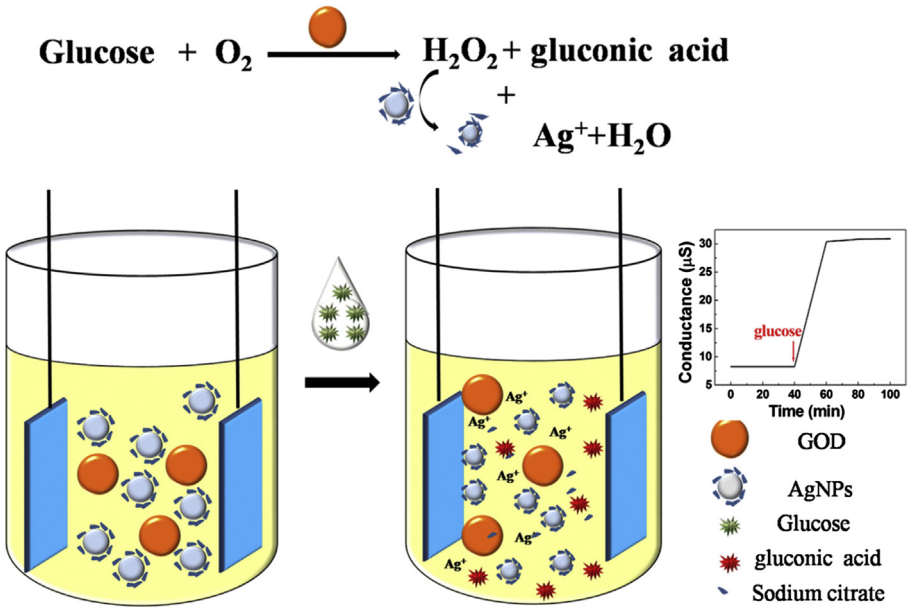

Fig. 1. Schematic illustration of the mechanism of the proposed conductance biosensor.

could be used to determine the water quality in power plants, metallurgy, chemical industry, medicine and other industries [39–42]. Conductivity meter could measure the tiny conductivity in a non-zero background accurately, and detect the changes of ion concentration via the variation of the conductivity [14,43]. Therefore, all of the conductance changes were measured by a conductivity meter in this work.

As shown in Fig. S1 (Supporting Information, SI), variations in

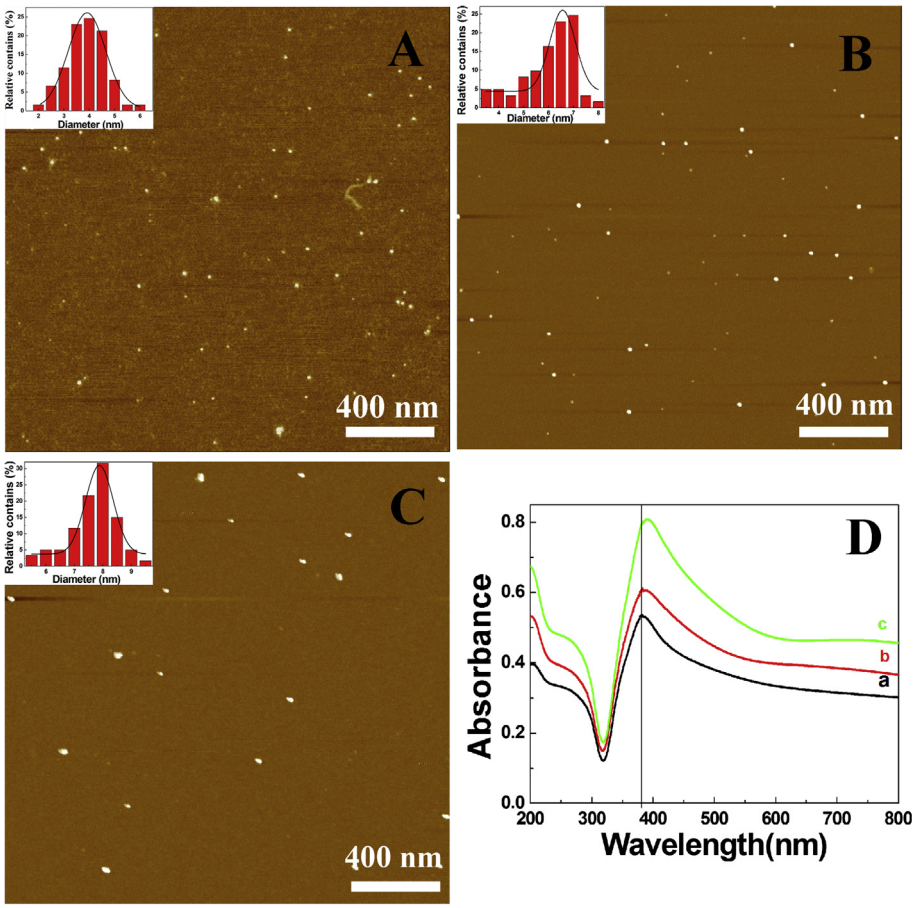

Fig. 2. (A–C) AFM images of CCAgNPs synthesized at various ratios of $AgNO_3$ and sodium citrate ($n_{Ag}/n_{sodium\ citrate}$): (A) 3:2, (B) 3:1 and (C) 6:1. The inserts showed the size histograms of these CCAgNPs. (D) UV–vis absorption spectra of CCAgNPs with different sizes: (a) 4 nm, (b) 6 nm and (c) 8 nm.

the conductivity because of changes in the peroxide concentration could be due to the reproducibility of the measurements because they are similar to the variations found in the ultrapure water. The effects of CCAgNPs concentration and reaction time on the performance of the novel conductance H_2O_2 sensor were investigated in Fig. 3A and B. After CCAgNPs with different concentrations were equivoluminally added into 30 μM H_2O_2 solutions for 30 min, it was found that the change in conductance was gradually increased as the concentration of CCAgNPs increased. The increased conductance could be ascribed to the fact that more CCAgNPs was oxidized into Ag^+ by H_2O_2 and more citrate was released simultaneously, which both resulted in the increase of ionic strength of the solution. The maximum conductance change appeared at 0.2 mM CCAgNPs (Fig. 3A). The slight decrease of conductance change with further increase of CCAgNPs concentration might result from the adsorption of Ag^+ on the CCAgNPs surface. The conductance change also increased with increasing reaction time as shown in Fig. 3B. After reaction for 30 min, the conductance change was maintained, suggesting the reaction of H_2O_2 with CCAgNPs was complete in this period. Thus, 0.2 mM and 30 min was chosen to be the optimum CCAgNPs concentration and reaction time in the following experiments, respectively.

Fig. 3C showed the UV–vis absorption spectra of CCAgNPs in the presence of various amount of H_2O_2. The absorbance intensity decreased with the increase of H_2O_2 concentration. It indicated that CCAgNPs has been oxidized into Ag^+ by H_2O_2 and resulted in the decrease of CCAgNPs. The conclusion was further confirmed by the obvious color fading of AgNPs solution with the increase of H_2O_2 concentration (Inset of Fig. 3C). Fig. 3D showed the plot of conductance change of the novel biosensor versus H_2O_2 concentrations. It was found that the addition of H_2O_2 into CCAgNPs solution could induce the increase in conductance with a good linear relationship. Thus the proposed novel conductance biosensor could be used to detect H_2O_2 with a linear range from 15 to 200 μM (R = 0.999, n = 15), a sensitivity of 0.035 S/M and a detection limit of 3.96 μM based on the criterion of signal-to-noise ratio of 3.

3.3. The novel conductance biosensing of glucose

It is well known that GOD could catalyze the oxidation of glucose specifically in the presence of oxygen to produce H_2O_2 and gluconic acid. Thus the novel conductance biosensor was further applied to detect glucose. The conductance change was triggered by adding glucose into a solution containing both GOD and CCAgNPs. The effects of CCAgNPs size and GOD concentration on the performance of the biosensor were investigated firstly (Fig. 4A and B). As shown in Fig. 4A, the change of conductance increased with the increase of CCAgNPs size (Fig. 4A), which could be ascribed to the large specific surface area of the small CCAgNPs that was easier to adsorb the produced Ag^+. The conductance change of 4.0 nm-sized CCAgNPs exhibited not only good sensitivity but also good linear relationship as compared with the other two kinds of CCAgNPs, which was beneficial to determine glucose concentration quantitatively. Thus, 4.0 nm-sized CCAgNPs were used in the following glucose detection. To optimize the concentration of GOD, GOD of different concentrations were added into 0.1 mM, 2 mM and 4 mM glucose solution in the presence of 4.0 nm-sized CCAgNPs, respectively. And the change of conductance was recorded after reaction for 30 min. As shown in Fig. 4B, the conductance had a quite obvious and regular change at 25 μg/mL GOD as compared with the other two concentrations of GOD (12.5 μg/mL and 37.5 μg/mL). The result indicated that the appropriate concentration ratio of GOD, glucose and CCAgNPs was very important for glucose

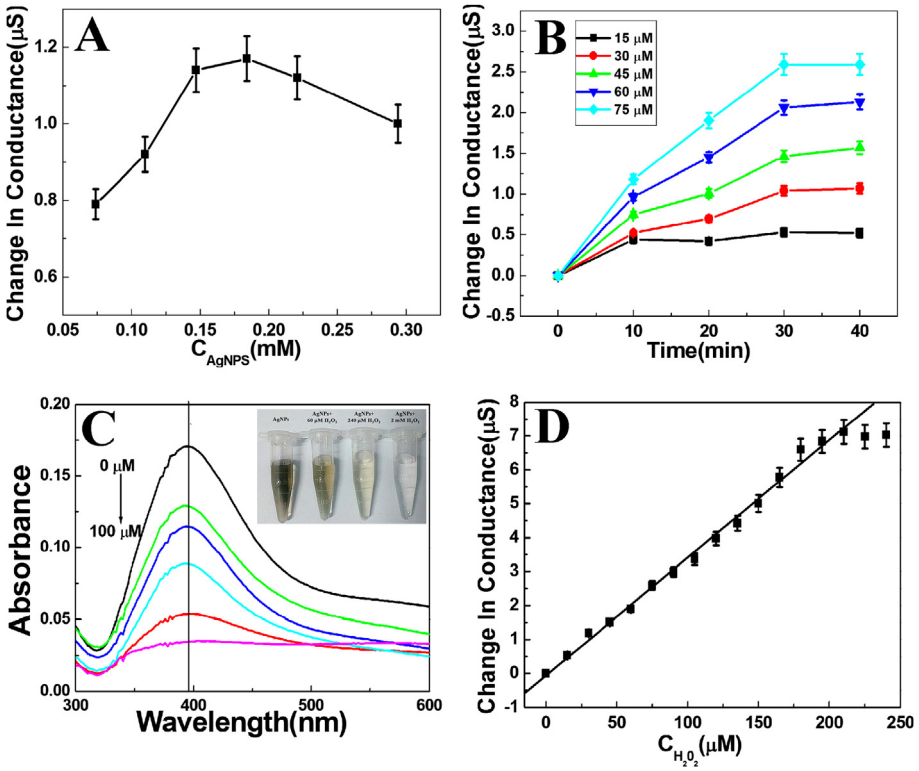

Fig. 3. (A) The conductance change of 30 μM H_2O_2 aqueous solutions after different concentrations of CCAgNPs was added for 30 min. (B) The conductance changes of 0.2 mM CCAgNPs aqueous solution after H_2O_2 with different concentration was added for different reaction time. (C) UV–vis absorption spectra of 0.2 mM CCAgNPs aqueous solution in the presence of H_2O_2 with different concentration; (D) The plot of conductance change versus concentration of H_2O_2 in the presence of 0.2 mM CCAgNPs.

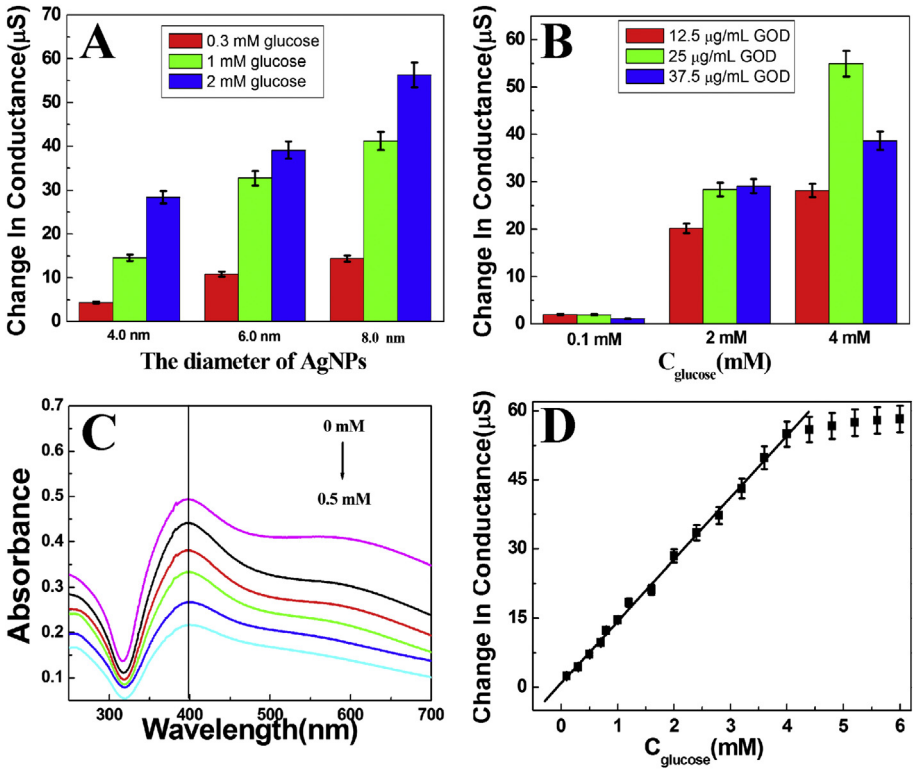

Fig. 4. (A) The conductance change of novel conductance biosensor versus different concentration of glucose in the presence of 0.2 mM CCAgNPs with different diameters and 0.2 mM H_2O_2 at 37 °C. (B) The conductance changes of novel conductance biosensor versus different concentrations of glucose and different concentrations of GOD in the presence of 0.2 mM CCAgNPs at 37 °C. (C) UV–vis absorption spectra of 0.2 mM CCAgNPs and 25 μg/L GOD in the presence of glucose with different concentrations. Inset: photographs of color change of CCAgNPs solution in the presence of 0, 60, 240 and 2000 μM H_2O_2. (D) The plot of conductance change versus different concentrations of glucose in the presence of 0.2 mM CCAgNPs and 25 μg/L GOD at 37.5 °C (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

detection. Thus, the 25 μg/mL GOD was used for the following glucose detection.

Fig. 4C showed the UV–vis absorption spectra of 0.2 mM 4.0 nm-sized CCAgNPs solution in the presence of 25 μg/mL GOD after various amount of glucose was added and reacted for 30 min. Similar to the result of H_2O_2 (Fig. 3C), the absorbance intensity decreased with the increase of glucose concentration [44]. As discussed above, the produced H_2O_2 further oxidized CCAgNPs into Ag^+ to result in the decrease of the absorbance intensity. A linear relationship was achieved by plotting the change of conductance versus glucose concentration. The linear range was estimated to be 0.06–4.0 mM with a sensitivity of 13.42 μS/M and a detection limit of 18.0 μM based on the criterion of a signal-to-noise ratio of 3 ($R = 0.999$, $n = 20$) (Fig. 4D). The good performance of novel conductance glucose biosensor might mainly be due to the generation of Ag^+ and gluconic acid and releasing of citrate via the oxidization of CCAgNPs triggered by H_2O_2. Fig. S2 (SI) showed the smaller conductance change induced by glucose in ultra-pure water. It indicated that CCAgNPs produced a more obvious change in conductance, which improved the sensitivity and the linear range of this method.

3.4. The selectivity and repeatability of the resulted conductance glucose biosensor

Some possibly coexisted materials including sucrose, fructose, D-galactose and D-mannose were chosen to test the selectivity. Fig. 5 showed the conductance change of CCAgNPs solution in the presence of glucose and some other carbohydrates. It indicated clearly that the novel conductance biosensor exhibited a specific response to glucose. To evaluate the repeatability, six experiments were performed to detect 2.0 mM glucose separately under the same conditions. The change of conductance was recorded as 28.4, 29.8, 27.0, 27.8, 28.9 and 28.6 μS, respectively, yielding a relative standard deviation (RSD) of 3.36%. The good repeatability of the results indicated the reliability of resulted conductance biosensor.

Up to now, many electrochemical glucose biosensors have been developed and their assay results have been listed in Table S1 (SI)

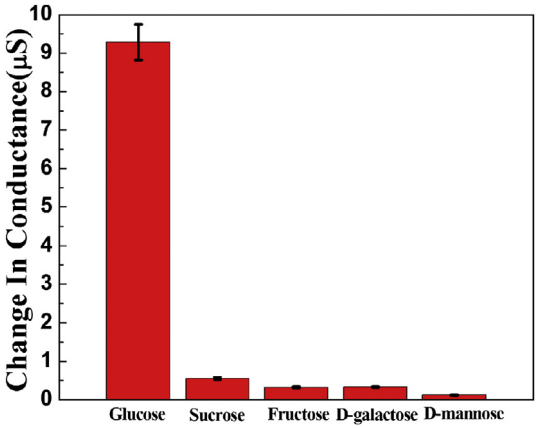

Fig. 5. The conductance change of novel conductance biosensor in response to glucose and interfering substances in the presence of 0.2 mM CCAgNPs and 25 μg/L GOD at 37.5 °C. The concentration of glucose was 1.0 mM and each interfering substance was 5.0 mM.

for comparison with our designed conductance biosensor. By comparing, it was obvious that our new method offered a reasonable linear range, sensitivity and detection limit. The new method also showed an excellent repeatability because CCAgNPs, GOD and glucose existed in the solution. What is more, it provided a possibility to detect glucose in an ultra-low ionic strength media. Furthermore, the simply modified Pt electrode was only exposed to CCAgNPs-GOD-glucose solution with citrate, gluconic acid and Ag^+, thus it was very easy to regenerate by simply rinsing with the ultrapure water.

3.5. Practical application of the novel conductance glucose biosensor

To verify the practical application of the novel biosensor, the conductance biosensor was employed to detect the glucose in energy drink (red bull) sample (commercial beverage) with a standard addition method which could eliminate the matrix effect. 40 μL original energy drinks was added directly into 2.0 mL aqueous solution containing 0.2 mM CCAgNPs and 25 μg/mL GOD under oxygen saturation. Then standard glucose solution with different concentration was injected into the above solution, and the measurements were carried out by the proposed method. Injections have been performed successively on the same solution for each glucose test. The glucose concentration in the original energy drink was calculated to be 104.5 mM and the results were shown in Table S2 (SI). To verify the validity of the proposed method, the glucose concentration in energy drink sample was further confirmed using colorimetric enzymatic method. Before detection, the energy drink sample was diluted 50 times with ultra-pure water to improve the sensitivity. The glucose concentration in the diluted energy drink was confirmed to be 2.01 mM and the glucose concentration in the original energy drink should be 100.05 mM. The result obtained by our conductance biosensor was similar to that obtained by colorimetric enzymatic method. The slightly bigger prediction value obtained by the novel conductance biosensor might result from some other coexisted substances which would increase the solution conductance. Both the consistent results with the standard method and the small RSD suggested that the novel conductance biosensor was possible for real samples detection. The proposed glucose biosensor based on the conductance change in ultra-low ionic strength media could simplify the complicated procedures for detecting glucose in real sample, as compared with previous glucose biosensors which often involve pre-treatment of sample, dilution, addition of salts, and adjustment of pH vale.

4. Conclusion

A novel conductance glucose biosensor in ultra-low ionic strength media was proposed. The glucose was firstly catalyzed by GOD to produce gluconic acid and H_2O_2, then CCAgNPs was oxidized into Ag^+ by the produced H_2O_2 in ultra-low ionic strength media to induce the increase of ionic strength. The biosensing of glucose with a low detection limit of 18.0 μM and a good repeatability was better than many other reported electrochemical biosensors. The novel conductance biosensor was proven to be suitable for glucose detection in real ultra-low ionic strength sample. This novel conductance glucose biosensor not only avoided the problems of complex electrode immobilization strategies but also achieved a significant breakthrough of glucose detection in ultra-low ionic strength media. It might also open up new possibilities for other substances detection in ultra-low ionic strength media.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.aca.2015.08.009.

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