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A novel photoelectrochemical singal amplification assay for procalcitonin detection based on $Zn_xBi_2S_{3+x}$ sensitized $NiTiO_3$ matrix

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ABSTRACT

An original signal amplification photoelectrochemical (PEC) immunosensor for procalcitonin detection was fabricated based on $Zn_xBi_2S_{3+x}$ sensitized $NiTiO_3$ nanorods. Using ethylene glycol as medium, the $NiTiO_3$ nanorods were successfully manufactured after calcination in air atmosphere, the rod-like structure have rough surface that produced benefit to capture lots of functional $Zn_xBi_2S_{3+x}$, the sensitizer sensitized $NiTiO_3$ on ITO substrate by means of a sequential ionic layer adsorption reaction, and the obtained $Zn_xBi_2S_{3+x}/NiTiO_3$ composites showed an excellent absorption of visible light owing to the matched band gap. By the way, $Zn_xBi_2S_{3+x}/NiTiO_3$ composites as mimic enzyme of glucose oxidase, high sensitivity was achieved due to the generated H_2O_2 as holes scavenger when glucose added, that promote the photo electrons transfer quickly, further increased the PEC signal. The as prepared sensor showed a large linear range of 0.0001–50 ng·mL^{-1} with 0.04 pg·mL^{-1} detection limit. Simultaneously, the signal amplification strategy of this sensor provides applicable to other PEC immunosensors for detection of other targets.

1. Introduction

Procalcitonin (PCT) is a protein that reflects the activity of the systemic inflammatory response, the level will elevated in blood when severe bacterial, fungal or parasitic infections, as well as sepsis appears and organ failure [1–3], even in the absence of bacterial infections or bacterial lesions. PCT levels increase in the presence of severe shock, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome (MODS) [4–7]. PCT is a specific indicator of severe bacterial and fungal infections, and is a reliable indicator of multiple organ failure associated with sepsis and inflammatory activity, is not only an acute indicator for differential diagnosis, but also a parameter for monitoring inflammatory activity. The concentration in normal human serum is inferior to 0.1 ng mL^{-1} [8], hence, sensitive and efficient PCT detection it a critical matter. Up to this day, various means and tools have been developed in the past to exploited new measurements for PCT detection, such as electrochemical sensor [9], electrochemiluminescence sensor [10], fluorescence sensor [11], imaging ellipsometry [12], and flow immunoassay [13] et al. Satisfactory results have been obtained by means of these methods, relatively.

With the rising requirements for the future sensing, novel methods were claimed imminently for special signal strategies. Photoelectrochemical (PEC) sensing, a gradually advanced method of detecting biomolecules, possess the merits of high stability and great sensitivity, meanwhile it have low background signal because of the unique form of signal produced and changed [14,15]. As the basis of PEC immunosensor, photoactive materials played an important role in sensors fabrication process. There are various types of photosensitive materials, perovskite-like compounds have the merit of stable structure, and it could combine with many metal ions to form solid solutions. Titanium-based perovskite oxides are an important class of photocatalysis materials for hydrogen production and toxic pollutants, such as $CaTiO_3$ [16], $SrTiO_3$ [17], $BaTiO_3$ [18], and $NiTiO_3$ [19]. Owing to the great photocatalytic activity under ultraviolet visible (UV) irradiation, $NiTiO_3$ has attracted much attention [20]in recent years. However, the narrow band gap (~2.2 eV) making the photo generated electrons-holes recombined quickly lead to a poor PEC signal when using $NiTiO_3$ solely, thus, it is necessary to find a suitable material to sensitize $NiTiO_3$ in order to acquire a superb PEC response. CdS [21,22], CdSe [22,23], and Bi_2S_3 [24] were the commonly used

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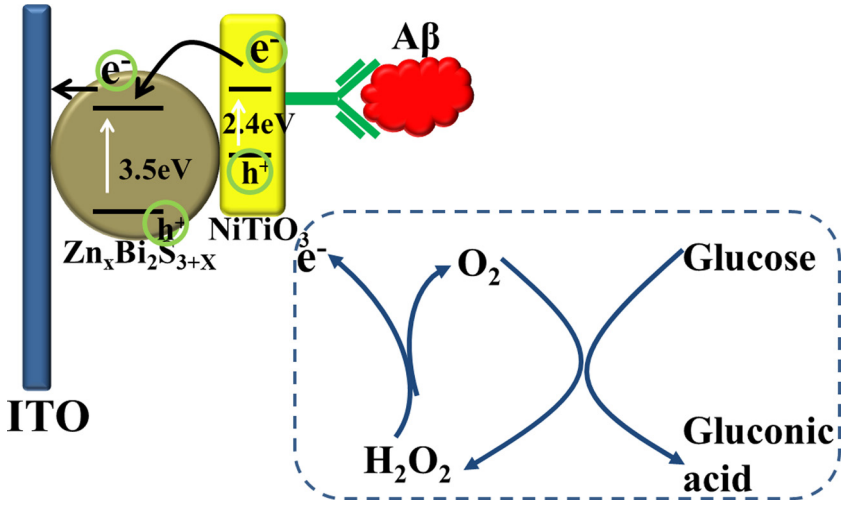


Scheme 1. The schematic description of the fabrication process of the PEC sensor.

sensitizer, but their narrow band gaps are not compatible with $NiTiO_3$, a new wide band gap sensitized material was urgent needed. Hence, $Zn_xBi_2S_{3+x}$ was designed and obtained by sequential ionic layer adsorption reaction (SILAR) process, the prepared $Zn_xBi_2S_{3+x}$ combined the advantages of ZnS and Bi_2S_3 [25], with suitable band gap [26] (Fig. S1) and super sensitization performance lead to increased PEC response and stability of the sensor.

According to the innovation thinking, a novel PEC detection platform was structured showed in Scheme 1, the functional $Zn_xBi_2S_{3+x}$ was successfully modified onto $NiTiO_3$/ITO surface by SILAR method to obtained a desire photocurrent. Then the embellished electrodes were immersed in 3 mmol·L^{-1} thioglycollic acid (TGA) solution for assembly of $-COOH$ on $Zn_xBi_2S_{3+x}$ surface, then procalcitonin antibody (Ab) was attached to the electrode with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and *N*-hydroxysuccinimide (NHS), which could activate $-COOH$ groups on the surface of $Zn_xBi_2S_{3+x}$ and link $-NH_2$ groups of the Ab, after BSA blocked non-specific active sites of Ab, procalcitonin antigen (Ag) was incubated onto the electrode, then washed the electrode, and got the finished PEC platform. The as preparation of $NiTiO_3$/ $Zn_xBi_2S_{3+x}$ has the catalytic function to catalyze the glucose, and the product acted as an hole scavenger to combine with photo generated holes in the valence band of $Zn_xBi_2S_{3+x}$ and $NiTiO_3$, thereby further accelerate the transmission of photo generated electrons hence obtain an increased photocurrent and enhancing the sensitivity of the sensor for detection of PCT. The proposed immunosensor also provided good stability and super reproducibility.

2. Experimental section

2.1. Reagents and apparatuses

The ITO glass electrode was gained from Zhuhai Kaivo Electronic Components Co. Ltd., China. Procalcitonin antigen and antibody were purchased from Shanghai Aladdin Biochemical Technology Co. Ltd., (Shanghai, China). Additional details were listed in Supplementary Materials.

2.2. Synthesized of $NiTiO_3$ nanorods

The $NiTiO_3$ nanorods were synthesized successfully adopt a hydrothermal process on the basis of the foregone report [20]. Firstly, 2.48 g nickel acetate was dispersed in 60 mL ethylene glycol at atmosphere temperature to form a green solution under stirring. Then, 3.4 mL tetrabutyl titanate was added into the solution, about 20 min later, the solution was turned to a light blue solution. After that, the solution was continued to stirring for another 3 h to ensure the reaction completed. After that, the blue precipitate was obtained and rinsed several times with ethanol and ultrapure water, and dried under vacuum at 60 °C overnight. Finally, the target product was obtained after calcined at 600 °C for 4 h in air.

2.3. Preparation of ITO/$NiTiO_3$/$Zn_xBi_2S_{3+x}$ electrode

The $Zn_xBi_2S_{3+x}$ was deposited onto $NiTiO_3$ rod-like structure by a SILAR method. First, 10 μL of $NiTiO_3$ (3 mg mL^{-1}) was added to ITO electrode, after dried at atmosphere temperature, the electrode was immersed in a methanol solution for 2 min which including 30 mM Bi $(NO_3)_3$ and 15 mM $Zn(NO_3)_3$ to achieve the adsorption of Bi^{3+} and Zn^{2+} onto the rod-like $NiTiO_3$ surface, followed by thoroughly washed with methanol. After airing, the electrode was immersed in methanol solution containing 20 mM of Na_2S for another 2 min, also thoroughly cleaned with methanol. Thus, the adsorbed S^{2-} would react with the previously adsorbed Zn^{2+} and Bi^{3+} to form $Zn_xBi_2S_{3+x}$. These two consecutive adsorption steps were repeated three times for obtain enough $Zn_xBi_2S_{3+x}$.

2.4. Fabrication of PEC immunosensor

Scheme 1 descripted the schematic of the fabrication process of the PEC sensor. Firstly, ITO slices (2.0 cm × 0.8 cm) were processed by ultrasound in turn for 30 min in acetone, ethanol and ultrapure water, separately. The ITO substrates were dried under nitrogen stream until dry out. The as prepared ITO/$NiTiO_3$/$Zn_xBi_2S_{3+x}$ electrode was firstly soaked in 3 mmol·L^{-1} TGA solution for 30 min, then decorated with 4 μL of EDC-NHS (5 mg mL^{-1}/1 mg mL^{-1}) for an hour, followed by modified 6 μL Ab after completely washed the electrode. After that, rinsed the electrode and modified 3 μL BSA (0.1%) for block the non-specific active sites of Ab. Finally, 6 μL of Ag was dispersed on the surface of the obtained electrode and incubated for 40 min, the finished electrode was inserted into 10 mL of PBS buffer solution containing a certain concentration of glucose at atmosphere, and the photocurrent was measured after 20 min later.

2.5. Photoelectrochemical measurements

The PEC measurement was operated at room atmosphere in 10 mL of PBS (pH 7.38) containing certain concentrations of glucose (0.2 M.) solution in a conventional electrochemical cell, saturated calomel electrode (SCE) as a reference electrode and platinum electrode as the counter electrode. The LED lamp (450 nm) was applied as an excitation

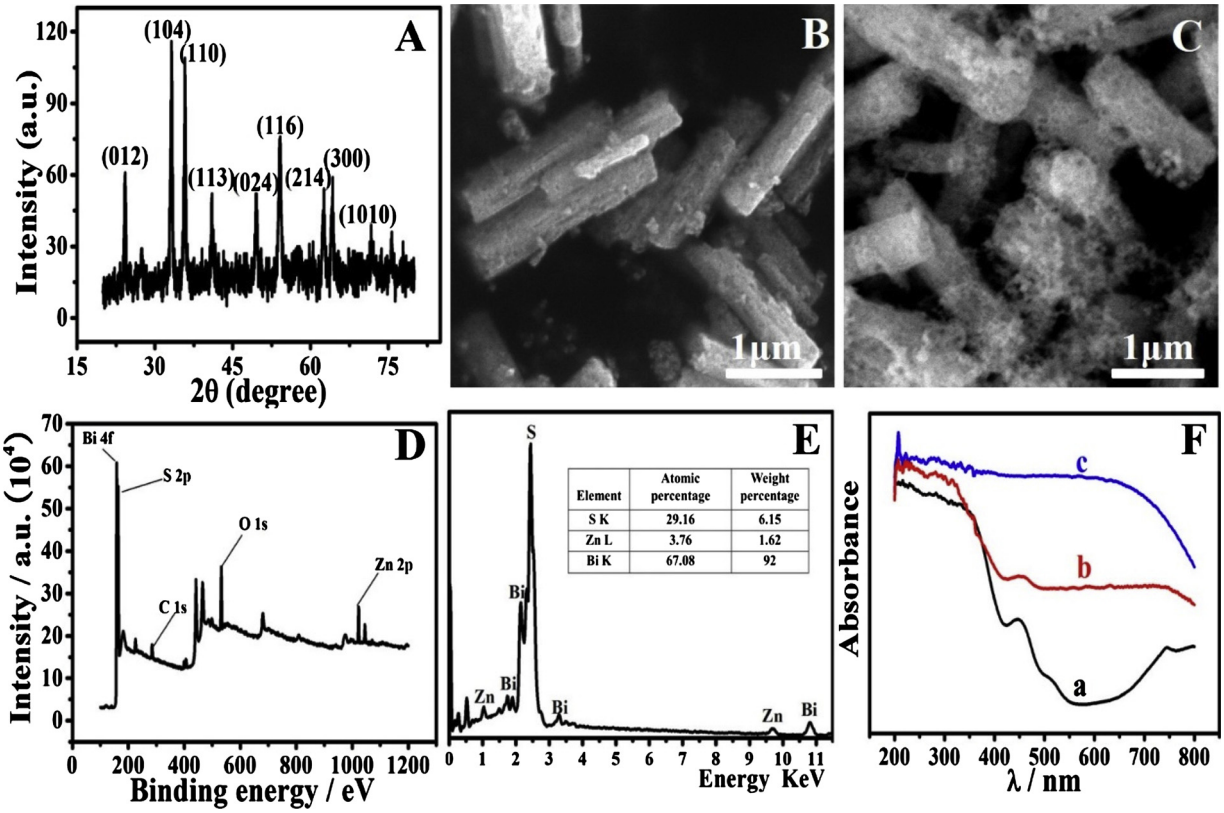
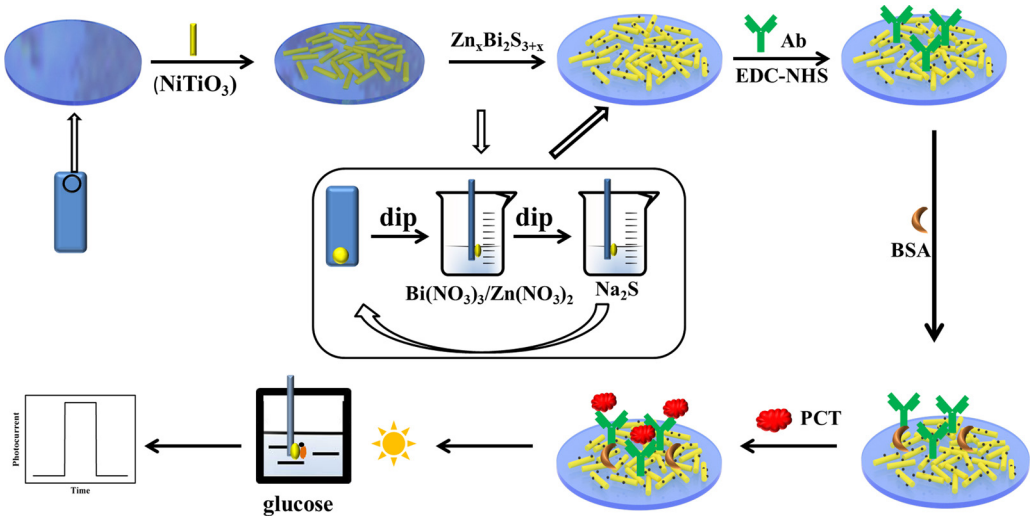


Fig. 1. XRD image (A) and SEM image (B) of $NiTiO_3$, SEM image of $NiTiO_3/Zn_xBi_2S_{3+x}$ (C), XPS image (D) and EDS image (E) of $Zn_xBi_2S_{3+x}$, and the UV–vis image (F) of $NiTiO_3$ (a), $Zn_xBi_2S_{3+x}$ (b), $NiTiO_3/Zn_xBi_2S_{3+x}$ (c).



Scheme 2. The possible mechanism of electron transfer.

signal and turned on and off every 20 s with no additional external bias.

3. Results and discussion

3.1. Characterization of synthesized materials

The crystal structure of $NiTiO_3$ was characterized by powder XRD, diffraction peaks from (012), (104), (110), (113), (024), (116) (214), (300) and (1010) crystal faces can be observed, and no other impurity peaks, indicating that pure crystalline $NiTiO_3$ was successfully prepared (Fig. 1A). Fig. 1B exhibited the typical SEM image of the $NiTiO_3$, the product was rod-like structure with a length of about 1.5 μm and a diameter of about 300 nm, the cylindrical structure provided a large specific surface area for adsorb more $Zn_xBi_2S_{3+x}$. It also facilitates the exchange of photo generated electrons, thereby obtaining a larger photocurrent. Fig. 1C showed the SEM image of the $NiTiO_3/Zn_xBi_2S_{3+x}$ electrode depicted that $Zn_xBi_2S_{3+x}$ was successfully adsorbed on $NiTiO_3$ surface. Fig. S2 shown the mapping image of the distribution of $Zn_xBi_2S_{3+x}$ on $NiTiO_3$ nanorods. The XPS image (Fig. 1D) showed the peaks of Zn, Bi and S element was existence consistent with, and the EDS image (Fig. 1E) proving the successful adsorption of $Zn_xBi_2S_{3+x}$. The detailed XPS peak structure of Bi, Zn, and S has been shown in Fig. S3, the peaks at 163.5 eV and 158.49 eV in Fig. S3A fit well with Bi $4f_{5/2}$ and Bi $4f_{7/2}$, respectively, indicating the +3 valence state of Bi, and the

peaks of S $2p_{1/2}$ (162.2 eV) and S $2p_{3/2}$ (160.7 eV) are assigned to S^{2-} in $Zn_xBi_3S_{3+x}$ [27,28]. The peaks at 1022.4 eV and 1045.5 eV in Fig. S3B fit well with Zn 2p, indicating the +2 valence state of Zn [29]. Fig. 1F showed the UV–vis spectra of $NiTiO_3$ (a), $Zn_xBi_2S_{3+x}$ (b) and $NiTiO_3/Zn_xBi_2S_{3+x}$ (c), it can be seen that the $Zn_xBi_2S_{3+x}$ enhanced the absorption of visible light because it sensibilization.

3.2. Possible PEC mechanism of assay

In Scheme 2, the possible light-induced electron transfer process of the sensor was shown. Under the illumination of a light with a wavelength of 450 nm, a tiny photocurrent was generated by $NiTiO_3$ nanorods due to the narrow band gap that photo electrons and holes were quickly recombined and had low light absorbance. Fortunately, the designed $Zn_xBi_2S_{3+x}$ as a splendid sensitizer has a matched band gap with $NiTiO_3$, which could make good use of visible light sources, and improve the photoelectric conversion efficiency (the photocurrent of bare $Zn_xBi_2S_{3+x}$ electrode was shown in Fig. S4). Meanwhile, the $Zn_xBi_2S_{3+x}$ /$NiTiO_3$ share the similar function of glucose oxidase (As shown in Fig. S5, the chronoamperometry test of the $Zn_xBi_2S_{3+x}$ /$NiTiO_3$ in glucose solution confirmed redox reaction occurred), which could catalyze the glucose to produce H_2O_2. Based on this advantage, the appropriate amount of glucose was added to the electrolyte solution (PBS) during the PEC measurement, when the PEC platform was exposed to PBS solution containing glucose, the glucose was catalyzed to produced H_2O_2 and gluconic acid, the former acted as an electron donor could combine with photo generated holes in the valence band of $Zn_xBi_2S_{3+x}$ and $NiTiO_3$, thereby decreased the combination of photogenerated electrons and holes, hence obtain an increased photocurrent. Meanwhile, enhancing the sensitivity of the sensor for PCT detection.

3.3. Optimization of experimental conditions

For the purpose of obtain the best performance of the PEC platform, the concentrations of $NiTiO_3$, the adsorption circulating cycles of $Zn_xBi_2S_{3+x}$, the pH values of electrolyte solution and the catalytic time were evaluated. As illustrated in Fig. 2A, the PEC response augment as the concentration of $NiTiO_3$ up to 3 mg mL^{-1}, demonstrating that too much $NiTiO_3$ was not suitable for light absorption. Fig. 2B showed the effect of the adsorption circulating cycles of $Zn_xBi_2S_{3+x}$, the photocurrent reached peak value with the number of cycles increasing until 3 cycles, the excessive $Zn_xBi_2S_{3+x}$ loading capacity may impeded the transfer of electrons. As one of the important factors for the sensor, the pH of the electrolyte has a great influence of the sensor, the photocurrent increased as the pH increased to 7.38, which was parallel to the physiological environment, and was suitable for active environments of proteins. Therefore, the pH of 7.38 was voted as the befitting value. $Zn_xBi_2S_{3+x}$ /$NiTiO_3$ Nano-composites as the simulated enzyme of glucose oxidase, the time to catalyze glucose in the electrolyte solution was also critical, as shown in Fig. 2D, as the catalytic time increased, the photocurrent gradually increased. When the catalytic time reached 20 min, the signal reached a maximum value, and no longer changed significantly with time. Hence, 20 min was selected as the optimum time.

3.4. Analytical performance of the PEC sensor

A time-based photocurrent curve for characterizing PEC behavior was obtained via detecting the photocurrent of the electrodes decorated with different materials. Obviously, as shown in Fig. 3A and B, there was almost no photocurrent of the bare ITO electrode (curve a), after modified with $NiTiO_3$, an increasing photocurrent (curve b) was observed. Then, the $Zn_xBi_2S_{3+x}$ was adsorbed to the electrode, owing to the matched energy level and the great sensitized ability, the best PEC signal was obtained (curve c). Following that, EDC-NHS (curve d), Ab (curve e), BSA (curve f), and Ag (curve g) was modified to the electrode, and due to the steric hindrance, the photocurrent gradually decreased. The aforementioned tests were all in the buffer solution of PBS, and when the ITO/$NiTiO_3$/$Zn_xBi_2S_{3+x}$/EDC-NHS/Ab/BSA/Ag electrode dipped to PBS (pH 7.38) containing glucose, the photocurrent increased

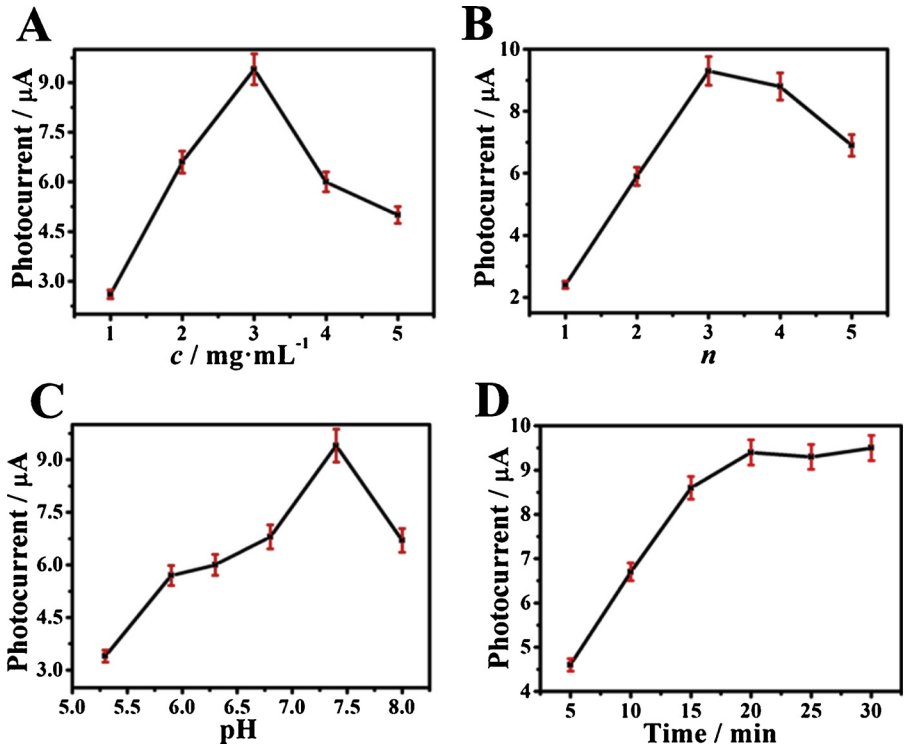


Fig. 2. Optimization of experimental parameters: (A) Influence of $NiTiO_3$ concentrations on the sensor, (B) Effect of circulating cycles of $Zn_xBi_2S_{3+x}$. (C) Effect of pH of the testing solution containing glucose (c_{PCT} = 0.005 ng mL^{-1}). Error bars = SD (n = 3).

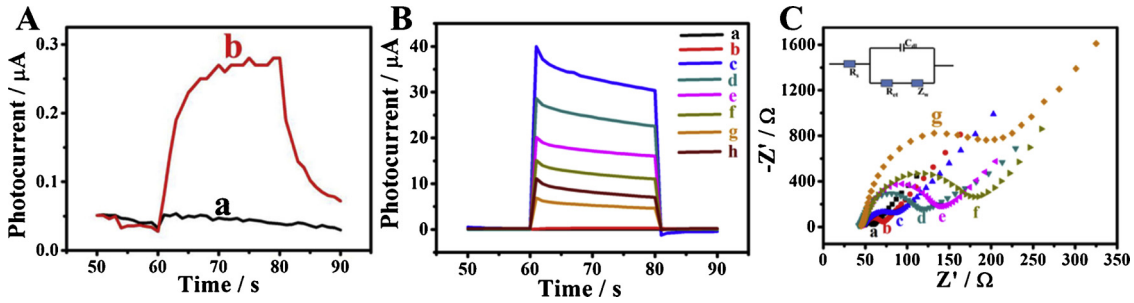


Fig. 3. (A), (B) Photocurrent responses and (C) Nyquist diagrams of (a) the bare ITO electrode, (b) $NiTiO_3$/ITO, (c) $Zn_xBi_2S_{3+x}$/$NiTiO_3$/ITO, (d) EDC-NHS/$Zn_xBi_2S_{3+x}$/ $NiTiO_3$/ITO, (e) Ab/EDC-NHS/$Zn_xBi_2S_{3+x}$/$NiTiO_3$/ITO, (f) BSA/Ab/EDC-NHS/ $Zn_xBi_2S_{3+x}$/$NiTiO_3$/ITO, (g) Ag/BSA/Ab_1/EDC-NHS/$Zn_xBi_2S_{3+x}$/ $NiTiO_3$/ITO (PBS solution), (h) Ag/BSA/Ab/EDC-NHS/$Zn_xBi_2S_{3+x}$/$NiTiO_3$/ITO (PBS solution containing glucose, c_{PCT} = 0.005 ng mL^{-1}). Inset of part C: the electrical equivalent circuit applied to fit the impedance spectra.

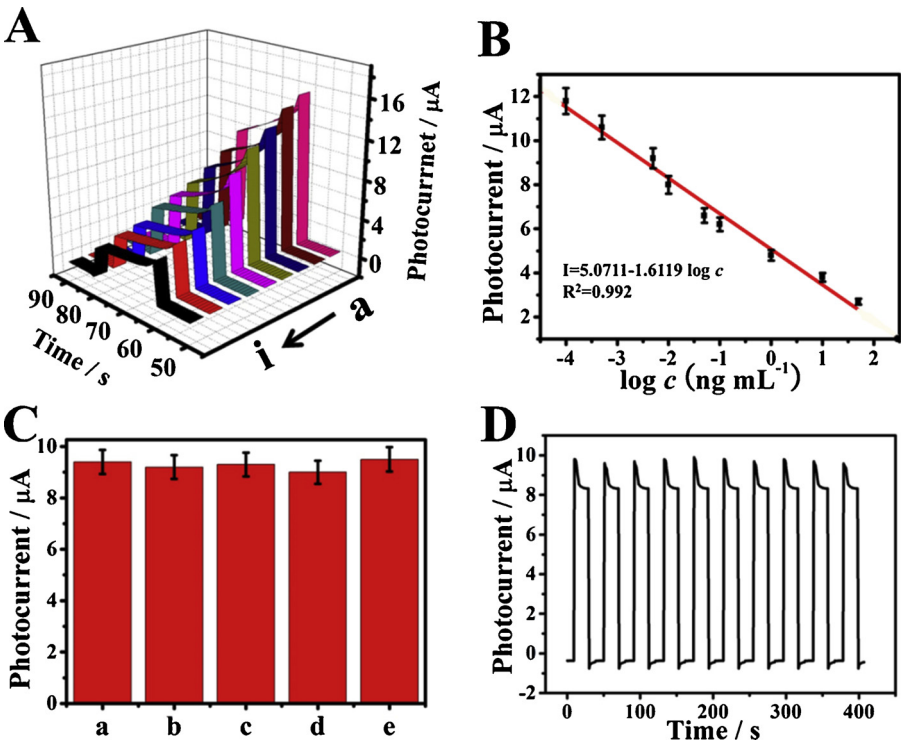


Fig. 4. (A) PEC response and (B) corresponding calibration curve of ITO/$NiTiO_3$/$Zn_xBi_2S_{3+x}$/EDC-NHS/Ab/BSA/Ag electrode in the presence of glucose solution with different concentration of PCT: (a–i) : 0.0001, 0.0005, 0.005, 0.01, 0.05, 0.1, 1, 10, 50 ng mL^{-1}. (C) Reproducibility test of the PEC immunosensor, (D) Signal stability of photocurrent intensity for detection 0.005 ng mL^{-1} PCT under for dozens of cycles. Error bars = SD (n = 3).

obviously (curve h), and the results showed that the sensor was successfully fabricated.

To further characterize the surface characteristics of the PEC sensor, using electrochemical impedance spectroscopy (EIS) to characterize the establishment process of the sensor. Fig. 3C showed that the bare ITO have a diminutive resistance (curve a), which manifested that the surface oxidation resistance of the conductive glass is very low. When $NiTiO_3$ (curve b) and $Zn_xBi_2S_{3+x}$ (curve c) was immobilized onto ITO electrode, the resistance was enlarged since the relatively poor conductivity of the semiconductor. Subsequently, along with the non-conductive protein of EDC-NHS (curve d), Ab (curve e), BSA (curve f) and Ag (curve g) layer by layer modification, the impedance value was gradually increased, indicated that the sensor was successfully constructed.

3.5. Photoelectrochemical determination of PCT

From Fig. 4A and B, with the increasing concentration of PCT, the photocurrent intensity gradually decreased, which confirmed the sensor was appropriated to the detection of PCT. Moreover, as the logarithm of PCT concentration increases, the range was from 0.0001 to 50 ng mL^{-1}, the photocurrent signal increased linearly. The linear equation was I = 5.0711-1.6119lg (c_{PCT}, ng·mL^{-1}) and the result of the detection limit calculation was 0.04 pg mL^{-1}. Comparing with other detection methods showed in Table S1, the proposed PEC immunosensor achieved much lower detection limit or wider detection linear range.

Reproducibility and stability were important factors in the performance of the sensor. Several electrodes were prepared to test the PEC response under the same modification conditions, to study the reproducibility of the immunosensor. The test obtained satisfactory results with a relative standard deviation of less than 4.14%. (Fig. 4C), proven that the prepared sensor has good reproducibility. The stability test of the sensor was based on placed the electrode under the light, through dozens of on/off light illuminations monitored, the resulting time-based photocurrent almost remain unchanged (Fig. 4D). The result indicated that the prepared PEC platform put up satisfied stability. The specificity of the sensor was exhibited in Fig. S6, the relative standard deviation (RSD) of photocurrent response was 4.12% and 3.05% after addition of a 100-fold excess of other interfering agents, compared to biosensors incubated with 0.005 ng·mL^{-1} PCT only. Demonstrated that the sensor has good specificity.

Table 1
The result of procalcitonin determination in blood samples (n = 5).

sample (ng mL^{-1})	PCT added (ng mL^{-1})	Average (ng mL^{-1})	RSD (%)	Recovery (%)
	0.001	0.37098	2.01	98
	0.005	0.37492	1.02	98.4
0.37	0.01	0.38	4.16	100
	0.1	0.466	4.44	96
	10	10.76	2.40	103.9

3.6. Application of the PEC sensor in human blood

Whether the prepared immunosensor can be used for the detection of real samples was tested by standard addition method. (Table 1). The real serum samples were obtained from the hospital of University of Jinan collected from normal human serum, the serum samples were centrifuged at 2800 rpm under 4 °C for 10 min to receive the supernatants, which were used as the detection samples. When the levels of serum PCT were found to be outside the calibration range, they were then appropriately diluted with 1/15 M PBS (pH 7.4). The recovery of the spiked samples varied from 96% to 103.9%, and the RSD were ranged from 2.01% to 4.44% for five independent tests. To further verify the accuracy of the analytical method, five different human serum samples was measured by the proposed PEC immunosensor, and compared with the accepted analytical method (ELISA). The results were revealed in Table S2. As a result, the relative deviation of the two methods was in the range from -1.57% to 4.30%, suggesting that the PEC immunosensor was reliable for PCT detection.

4. Conclusion

To sum up, $Zn_xBi_2S_{3+x}$ was successfully modified onto $NiTiO_3$ nanorods by SILAR procedure, the rod-like structure could adsorb much functional $Zn_xBi_2S_{3+x}$, the composites effectively accelerate the electron transfer, and enhanced the utilization rate of visible light to achieved superb PEC response and excellent sensitivity of the sensor. In addition, the simulated enzyme of glucose oxidase catalyze the glucose to produced H_2O_2 as electrons donor, eliminated the photo generated holes that further enhanced the photocurrent, increased the sensitivity of the immunosensor. In this procedure, the wide detection range (0.0001–50 ng·mL^{-1}) was obtained with low detection limit (0.04 pg·mL^{-1}), the sensor also displayed high stability, satisfactory selectivity, and great reproducibility. Furthermore, the signal amplification strategy of this sensor is also applicable to other PEC immunosensors to achieve signal amplification strategy.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.snb.2019.127099.

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