Sensors and Actuators A 222 (2015) 58–66

Contents lists available at ScienceDirect

Sensors and Actuators A: Physical

journal homepage: www.elsevier.com/locate/sna

Glucose affinity measurement by surface plasmon resonance with borate polymer binding

Dachao Li[a,*], Di Yang[a], Jia Yang[a], Yuan Lin[b], Yingjuan Sun[b], Haixia Yu[a], Kexin Xu[a]

[a] State Key Laboratory of Precision Measuring Technology and Instrument, Tianjin University, Tianjin, China
[b] State Key Laboratory of Polymer Physics and Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, China

ARTICLE INFO

Article history:
Received 29 June 2014
Received in revised form 29 October 2014
Accepted 30 October 2014
Available online 13 November 2014

Keywords:
Continuous glucose monitoring
Surface plasmon resonance
Affinity measurement
Borate polymer
Layer-by-layer self-assembly

ABSTRACT

A novel surface plasmon resonance (SPR) sensor bound to the borate polymer PAA-ran-PAAPBA through a layer-by-layer method was proposed for the determination of glucose concentration. In contrast to the enzyme electrode sensor, the use of optical refractive index sensing to detect glucose concentration eliminates the measurement drift caused by bioelectricity when the sensor is implanted into subcutaneous tissue; in addition, a borate polymer was used to replace the glucose oxidase (GOD) enzyme and it does not consume the glucose molecule during measurement through the affinity reaction between the polymer and glucose. In this study, the layer-by-layer self-assembly method was used to immobilize the borate polymer on the surface of the SPR sensor. The effects of the number of layers are discussed in the manuscript, and the regenerability, reproducibility, and stability of the SPR sensor were evaluated. Almost all of the studies are performed under specific alkaline conditions (usually close to or higher than the p*Ka* of PBA). And for the future application in vivo, we further investigated glucose detection at physiological conditions. The measurement resolution of the sensor bound to 12 polymer layers at physiological conditions was 1 mg/dL, and the R-squared value of the glucose concentration-ΔRU fitting curve within 1–1000 mg/dL was as high as 0.998, which indicates that this measurement may form the foundation of an implantable device for the continuous measurement of glucose concentration.

1. Introduction

Continuous blood glucose monitoring provides guidance for diagnosis and therapy [1]. The concentration of glucose in the blood is closely correlated to that in interstitial fluid [2–8]. Currently, the only technique available for continuous glucose monitoring in clinical applications involves the implantation of an enzyme electrode sensor under the skin to detect the concentration of glucose in interstitial fluid through an electrochemical method. However, since the enzyme electrode sensor detects the change of electric current caused by the reaction between the glucose oxidase (GOD) enzyme and the glucose, the bioelectricity of the human body may causes the drift during the measurement; thus, finger-prick blood collection is required to calibrate the sensor several times each day. In addition, the reaction between the enzyme electrode sensor and glucose is not reversible, which means that the consumption of glucose cannot be avoided during the measurement, and this effect cannot be ignored, particularly in cases of hypoglycemia [9].

A new glucose affinity measurement method based on a surface plasmon resonance (SPR) sensor with the borate polymer PAA-ran-PAAPBA [10] is proposed in this paper. The SPR sensor detects the differences in the refractive index of glucose solutions of different concentrations flowing over the surface of the sensor; therefore, this optical sensing method is not affected by the bioelectricity of the human body when the SPR sensor is implanted into subcutaneous tissue for continuous glucose monitoring. Moreover, the concentrations of any components in the interstitial fluid would affect the change in the refractive index, which means measurement result will be affected by all the components in the interstitial fluid. Therefore, the borate polymer PAA-ran-PAAPBA, which can specifically adsorb glucose molecules, is immobilized on the surface of the SPR sensor to replace GOD. The affinity reaction between the polymer and glucose molecules is reversible, which means that the molecules will bind to the polymer at high glucose concentrations and this bond will break at low glucose concentrations. This reversible binding to the borate polymer stands in contrast to the consumption of glucose observed during measurements with enzyme electrode sensors [11].

The binding materials that are most commonly used to specifically adsorb glucose to SPR sensors are concanavalin (Con A) [12,13]

* Corresponding author. Tel.: +86 022 27403916; fax: +86 022 27404209.
E-mail address: dchli@tju.edu.cn (D. Li).

http://dx.doi.org/10.1016/j.sna.2014.10.039
0924-4247/

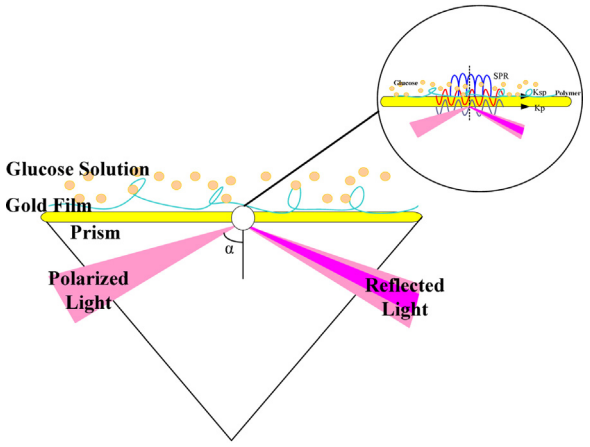

Fig. 1. Measurement principles underlying the use of the SPR sensor for the detection of glucose molecules.

and D-galactose/D-glucose binding protein (GGBP) [14–16]. Due to its immunogenicity and cytotoxicity, Con A is not suitable for implantable medical devices. The GGBP protein is inherently unstable, which makes it difficult for a sensor based on this protein to operate for a long time; furthermore, the binding of the protein via covalent bonds is complex. Indeed, the flow velocity, temperature, and preparation of the protein affect its binding properties [17,18] and only single layer of GGBP could be bound to the surface of the sensor. The borate polymer was introduced in the SPR sensing by our group, and this polymer has no immunogenicity or cytotoxicity, and its physical and chemical properties are stable [10], which extends the life of the SPR sensor based on this polymer. In this study, this borate polymer was bound to the surface of a sensor through layer-by-layer self-assembly method. This technology exhibits high reliability, making it possible to control the number of borate polymer layers and enabling the improvement of the measurement range and resolution of the SPR sensor.

2. Glucose measurement method by surface plasmon resonance

In this paper, the standard glucose solutions of different concentrations were used as standard to evaluate the accuracy and validation of the SPR sensor. Glucose solutions of known concentrations were sequentially injected through the surface of the SPR sensor without the borate polymer and the sensor bound with six or twelve layers of borate polymer. The effects of the number of layers are discussed in the manuscript, and the regenerability, reproducibility, and stability characteristics of the SPR sensor were evaluated. Almost all of the studies are performed under specific alkaline conditions (usually close to or higher than the p*Ka* of PBA). And for the future application in vivo, we further investigated glucose detection at physiological conditions.

2.1. Measurement principle of surface plasmon resonance

As shown in Fig. 1, the total internal reflection occurs when an incident beam of p-polarized light of a given wavelength strikes the interface between the prism and metal over the angle of total reflection through a prism. Under such conditions, part of the polarized light continues propagating in the form of an evanescent wave, which is parallel to the mental dielectric interface. When the wave vector of the evanescent wave (K_x) matches that of the surface plasmon wave (SPW) in the metallic film (K_{sp}), surface plasmon resonance occurs, and the associated optical electric field decays

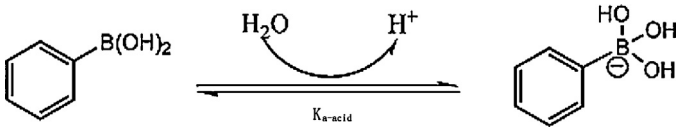

Fig. 2. Reaction of boric acid and water.

exponentially with distance from the surface. The incident angle at this moment is called the SPR angle (θ_{spr}).

The wave vector K_x of the horizontal component of the p-polarized light is

$$K_x = \frac{2\pi}{\lambda}\varepsilon_p \sin(\theta) \tag{1}$$

The wave vector K_{sp} of the surface plasmon resonance is

$$K_{sp} = \frac{2\pi}{\lambda}\sqrt{\frac{\varepsilon_n \varepsilon_o}{\varepsilon_m + \varepsilon_o}} \tag{2}$$

The SPR angle is

$$\theta_{spr} = \arcsin\left(Re\sqrt{\varepsilon_o\varepsilon_m/(\varepsilon_0 + \varepsilon_m)}/\sqrt{\varepsilon_p}\right) \tag{3}$$

where λ is the incident wavelength, and ε_p, ε_m, and ε_o represent the dielectric constants of the prism, gold film, and glucose solution, respectively [19,20].

According to the Maxwell equations, the velocity of light is

$$v = \frac{1}{\sqrt{\varepsilon\mu}} = \frac{1}{\sqrt{\varepsilon_0\mu_0}} \cdot \frac{1}{\sqrt{\varepsilon_r\mu_r}} = \frac{c}{\sqrt{\varepsilon_r\mu_r}} = \frac{c}{n} \tag{4}$$

Thus the relation between the refractive index and the dielectric constant is

$$n = \sqrt{\varepsilon_r\mu_r} \tag{5}$$

where c is the speed of light in vacuum, μ is the medium's permeability, ε is the medium's dielectric constant, μ_0 is the permeability in vacuum, ε_0 is the dielectric constant in vacuum, μ_r is the medium's relative permeability, and the ε_r is the medium's relative dielectric constant.

Based on the relationship between the refractive index and the glucose concentration, from Eq. (5) the glucose concentration can be obtained through the change in the dielectric constant, which can be calculated by the SPR angle [21]. In this study, 6 and 12 polymer layers were bound to a gold film, which could adsorb glucose molecules when a glucose solution was passed through the surface of the SPR sensor. Compared with the enzyme electrode sensor, which detects changes in electric current, the SPR sensor uses optical refractive index sensing to detect the glucose concentration, which eliminates the effects of bioelectricity when the sensor is implanted under the skin and results in high-precision measurements [19,20].

2.2. Affinity reaction between the borate polymer and glucose

As shown in Fig. 2, boric acid in aqueous exists in equilibrium between its uncharged normal state and its negatively charged dissociated state, and the percentage of the anionic state in the solution can be increased by increasing the solution pH because the p*Ka* of PBA is 8.8[22]. Fig. 3 shows the condensation reaction between the borate polymer and glucose. As shown, glucose will bind to the borate polymer to form boronate ester reversibly which depends on the concentration of glucose and the pH of the solution, because only tetrahedral anionic boric acid can form a stable complex with diols-containing targets [22]. Therefore, as the more glucose or the higher pH is present in the solution, the more PBA-glucose compounds form. In contrast, as the boronate ester bonding is reversible, PBA-glucose compounds disassociated