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Spectral Interrogation based SPR Sensor for Blood Glucose Detection with Improved Sensitivity and Stability

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Abstract

A sensor chip for specific detection of blood glucose was developed. The sensor utilized a surface-plasmon-resonance (SPR) setup on a prism based Kretschmann configuration utilizing spectral interrogation scheme. Self-assembled monolayers (SAMs) based preparation provided the chip stability due to covalent bonds and hence it can be reused for multiple times. Such a scheme can be advantageous in continuous monitoring of blood glucose, without changing the chip. Control experiments were performed without molecular recognition layer to confirm the performance of the sensor. Furthermore, the measurements were performed on blood serums and compared with that of a conventional glucometer. The present sensor has the advantages of improved sensitivity (0.14 nm/(mg/dl)) and stable response for 3 months, which are better compared to existing reports.

Keywords: Surface plasmon resonance; Blood glucose; Biosensor; Self assembled monolayers

Introduction

The phenomenon of surface plasmon resonance (SPR) has paved a way for highly sensitive and specific biological sensors along with biocompatibility [1,2]. During the past two decades, a number of sensors utilizing SPR have been reported for the detection of various chemical and biochemical analytes. SPR sensors have been reported for the detection of various analytes of blood, such as glucose, cholesterol, urea, etc. [3-5]. SPR is the phenomenon of excitation of collective oscillations of electrons with electromagnetic field at the interface of a metal and dielectric medium. As a result, a surface wave called surface plasmon wave is generated which travels along the interface and its field decays exponentially in both the media. Though such a wave can be supported by many metal-dielectric interfaces, it is not generally possible to excite it with light as the wave vector of surface plasmons is greater than that of the light in the dielectric medium. To excite surface plasmons, the wave vector of the incident light must be matched to that of the SP waves, known as the phase matching condition. In practice, most generally, Kretschmann configuration is utilized for the excitation of surface plasmons, where the base of a high index prism is coated with a thin layer of metal which is further surrounded by the dielectric medium, on whose interface the surface plasmons are to be excited. TM polarized light is incident on the interface from one face of the prism which excites surface plasmons on the interface. The light reflected back from the other face of the prism is measured. As a result of the SPR, a dip in the reflected optical power is obtained, when plotted versus angle or wavelength. With the development of miniature parallel spectrometers, spectral interrogation scheme becomes attractive and the system is compact, fast and benefitting from the high spectral sensitivity (typically few thousands of nm per RIU) of the SPR phenomenon. In such a case, the collimated polychromatic light is incident at a fixed angle and the reflected spectrum is recorded with a spectrometer. The resonance wavelength is a characteristic of the dielectric medium and the metal interface and gets changed if any change in refractive index of any of these two media occurs. When the refractive index of the dielectric medium around the metal film increases, a red shift in the resonance wavelength is observed.

Glucose sensing in blood has been a matter of interest to researchers from both the academia and the industry because it is quite critical and essential as high levels of glucose in blood may result in diabetes. For diabetic persons it also important to monitor their blood glucose levels frequently. Most of the sensors for glucose detection utilize glucose oxidase (GOx) as a molecular recognition element due to its specific selectivity towards glucose, stability and reliability [6-10]. In a number of studies, GOx was entrapped in a gel or polymer matrix [11,12]. Researchers have used molecular imprinted gels as well for molecular recognition [12]. Though the sensors based on these techniques are quite specific, they suffer from the issues of long term stability, repeatability and are more prone to false signals. Further, the gel matrix/polymer provides possibilities of non-specific interactions as well. Additionally, the gel matrix itself is not very stable, as no adhesive is generally used in between the metal film and the gel layer. Also, the electromagnetic field of the surface plasmon wave falls mostly in the gel/polymer layer and interacts less with the analyte. Hence, apparently, it does not specifically detect the change in refractive index due to the interaction of the analyte with the molecular recognition element; but an average change in the actual response plus that of the polymer in which the molecules are embedded [13]. In practice, the polymer/gel matrix can swell/shrink in the aqueous media and that is also counted in the response of such sensors. That's why, rather following the response curve as reported by Jorgenson and Yee [14], such sensors follow an opposite trend, which is due to the sensing of aggregate change in the refractive index of the polymer matrix containing the molecular recognition elements [11,12]. The sensors utilizing polymer/gel matrix further suffer from slow diffusion rate and hence large response time [15].

In the present article, we report a glucose sensor utilizing covalent

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bonding technique by making layer by layer self assembled monolayer structures to attach GOx on Silver coated SF11 glass slides. Covalent binding makes our sensor more stable and reliable. The response of the sensor was recorded with varying glucose concentrations in water. Control experiments with a sensor chip without the GOx attachment were performed to demonstrate the advantage of the molecular recognition layer. Since the specificity of GOx towards glucose is already well established, no further tests on specificity were performed. However, the performance of the sensor was tested on human and foetal bovine serums (HS and FBS) and the results were compared to the measurements with a conventional glucometer.

We have plotted the recorded SPR spectra for different concentrations of glucose in water in Figure 1. For each sample solution, a dip in the reflected optical power is observed. The wavelength corresponding to the minimum reflectance is referred as the surface plasmon resonance wavelength (λres). This resonance wavelength is a characteristic of the sample solution and is different for different sample solutions, as observed in the same figure. Further, it is observed that with an increase of glucose concentration from 0 to 200 mg/dl, a red shift in the SPR curves is observed. This red shift is due to the change in the local refractive index near the interface due to the following interaction of glucose with GOx:

$$\text{Glucose}+O_2 \longrightarrow \text{Gluconic Acid}+H_2O_2$$

However, one may claim that the shift in resonance wavelength might be due to the change in the refractive index by increase in glucose concentration in water. It was already reported elsewhere that there is negligible change (up to third decimal place) in the refractive index of glucose solution in water for the concentration range considered in the present study [16]. Further, a control experiment (control experiment 1) was carried out by recording SPR spectra for sensor chips without immobilizing GOx. The corresponding SPR curves have been plotted in Figure 2. It is observed that similar to the previous case, a dip in the reflection spectrum is observed for each sample solution. However, negligible shift in SPR curves was obtained with a change in the glucose concentration. Hence the substantial shift in SPR curves in the present sensor is due to the GOx layer and not merely due to a refractive index change with increase in the glucose concentration. Further, to quantify the response, we have plotted the variation of resonance wavelength (λres) with change in glucose concentration for both the cases: with and without GOx in Figure 3. A total shift of about 28 nm was measured for the change of glucose concentration from 0 to 200 mg/dl for the sensor chip immobilized with GOx. There is negligible shift in the resonance wavelength with varying concentration of glucose for the case where

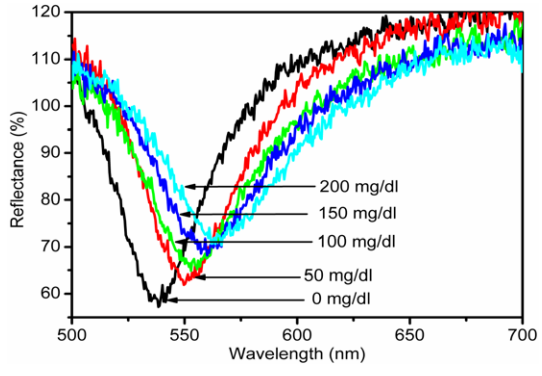

Figure 1: SPR spectra for varying concentration of glucose over GOx immobilized sensor chip.

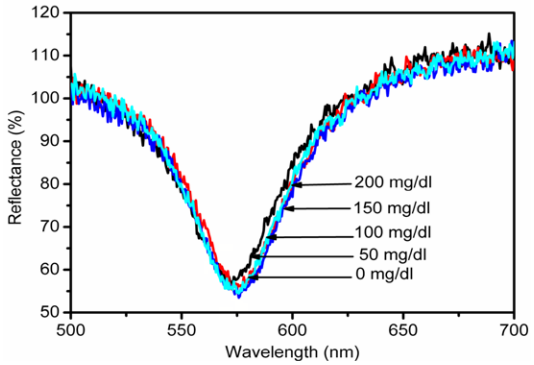

Figure 2: Control experiment 1: SPR spectra for varying concentrations of glucose in water for sensor chip without GOx.

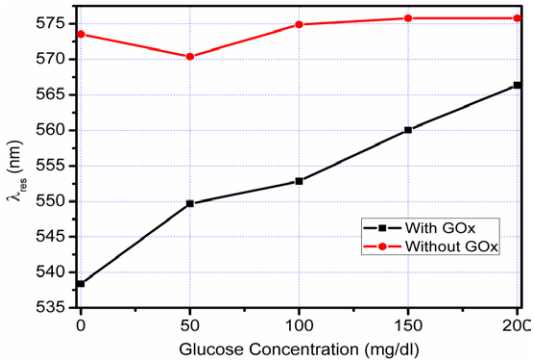

Figure 3: Response curves for SPR sensor chips with and without GOx.

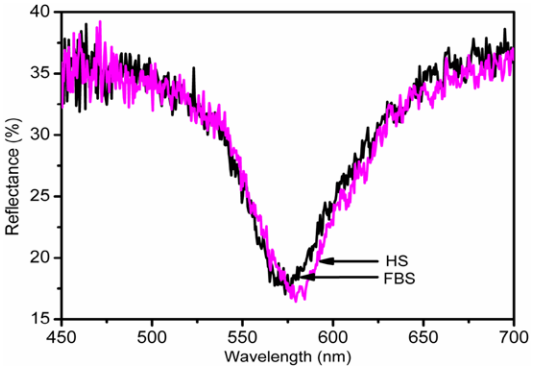

Figure 4: Control experiment 2: SPR spectra for two blood serums (FBS and HS).

no GOx was immobilized on the SPR chip. It is also observed that the resonance wavelengths for both the cases fall in different regimes of the electromagnetic spectrum. This is because of immobilization of GOx on the SPR chip which already shifted the starting resonance wavelength. Further, the response curve of the sensor is almost linear in the physiological range of the glucose concentration. The sensitivity of the sensor was calculated from the curve in Figure 3 and was found to be 0.14 nm/(mg/dl), which is more than twice to what was reported recently [11]. Hence, with standard off the shelf spectrometers with resolution of 1 nm, the detection limit is 1/0.14~7 mg/dl which is acceptable and can be improved further by using a spectrometer with

higher resolution. The performance of the sensor was checked for real applications. It is crucial to check whether there is some interference from other analytes in blood. The SPR spectra were recorded on the sensor chip for human and foetal bovine serums (HS and FBS) which were obtained commercially. The values of the glucose concentration were cross checked with a commercial glucometer. Figure 4 shows the SPR spectra for two blood serums. The SPR curve for HS is found to show a red shift to that for FBS. It was observed that there is a shift of 5.84 nm in the resonance wavelengths of both the curves. The glucose levels measured with conventional.

In conclusion, we have fabricated and characterized a SPR based blood glucose sensor with enhanced sensitivity and stability and repeatability. The sensor works in spectral interrogation scheme. The sensitivity of the sensor is 0.14 nm/(mg/dl). Control experiments were performed to demonstrate the significance of molecular recognition layer. The sensing capability in real samples was demonstrated.

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