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A transparent glucose-sensitive double polymerised holographic sensor

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ABSTRACT

This report describes a new approach for monitoring glucose levels for the management of diabetes, in which a metal nanoparticle-free, transparent holographic sensor was evaluated. Double-polymerised holographic gratings were fabricated using two copolymers with different densities of cross-linker. Preliminary results of the proposed sensor platform look promising although further research is required to optimise the response of the sensor.

1. Introduction

There have been numerous attempts to develop minimally invasive methods for glucose monitoring in readily accessible fluids such as tear fluid using strip-based wearable sensors [1,2] and embedded sensors in contact lenses [3–5]. Prototype holographic glucose-responsive contact lenses have been fabricated in polyacrylamide hydrogels functionalised with a non-toxic and fully reversible receptor, 3-acrylamido-phenylboronate (3-APB), and assessed in a human subject following an oral glucose tolerance test [6,7]. The contact lens sensor tracked the blood glucose concentration determined by conventional finger pricking. The holographic sensor described in this early work used silver nanoparticles to generate the holographic gratings within the "smart" hydrogel; however, there remain issues to address. Silver nanoparticles require a complex regulatory process according to the FDA [8] and are aesthetically unappealing in that they create a dark coloured visible spot in the contact lenses. Furthermore, additional manufacturing steps would increase the costs of production and thereby reduce the adoptability of this technology into existing contact lens production lines. This report assesses the viability of developing an alternative metal-free, transparent glucose-sensitive holographic grating using a double-polymerisation method.

In this approach, modulation of the refractive index occurs by polymerising a second more highly cross-linked polymer (P2) within the first baseline polymer (P1). The process of creating gratings is illustrated in Fig. 1 in a two-dimensional (2D) schematic. The polymerisation of P2 is a function of the standing wave, where, in the light regions, the exposure strongly promotes polymerisation. Consequently, a sinusoidal concentration profile [9] of P2 is formed that modulates the permittivity of the polymer material and generates a grating structure. For sensor applications, the P1 phase is functionalised with 3-APB to develop a glucose-responsive "smart" hydrogel. This double polymerisation approach is robust and generates a transparent final product which can be configured for use in daily-wear contact lenses.

This paper explores the development of glucose-sensitive double polymerised holographic sensors using 3-APB as the functional monomer [10,11]. Samples of the double-polymerised holographic sensors were developed and preliminary studies on the response to glucose performed.

2. Experimental

Reagents, materials, buffer preparation and silanisation are described in Appendix A (see the Supplementary Material).

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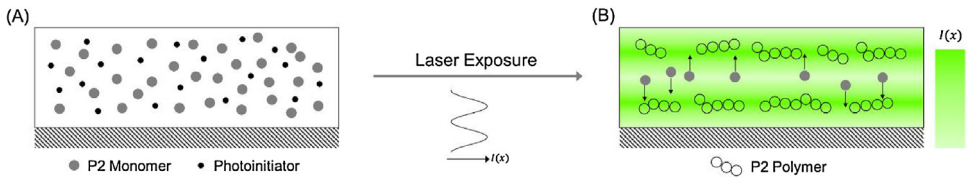

Fig. 1. The 2D schematic of developing double-polymerised holographic gratings. (A) The P1 film layer with the P2 monomers and photoinitiators; (B) The formation of P1-P2 polymer film during the laser exposure.

2.1. Baseline polymer synthesis (P1)

The P1 solution contained 76.7 mol% acrylamide, 11.8 mol% 3-APB, 2.9 mol% MBA and 8.6 mol% DMAPA. A 200 μl droplet of the P1 monomer solution was pipetted onto the polyester surface of an aluminised polymer film and placed face down on a silanised-glass slide. Polymerisation was initiated using UV light with an exposure time of 25 min. The polymerised films were slowly separated from the support by submerging in a deionised water bath at room temperature and the excess polymer films on the edges removed using a blade. The slides were rinsed briefly with deionised water and then washed in a deionised water bath (1L per slide) for 3 h on a gentle stir.

2.2. Development of double-polymerised holographic sensor

The highly cross-linked monomer solution, P2, was prepared using 63.4 mol% acrylamide and 36.6 mol% MBA. The solvent contained 64% (*v*/*v*) DMSO, 10.7% (*v*/*v*) EG, 21.2% deionised water, 3.2% (*v*/*v*) MeOH with the dye, 2% (*w*/*v*) Safranin O, and 0.9% (*v*/*v*) TEOL. The laser settings were adjusted at 532 nm, 10 Hz, 400 μs for10 s exposures. The penetration of the P2 monomer solution into the P1 polymer film requires soaking the P1 in a deionized water bath for 3 min to stimulate the swelling phase and then cold blow drying for 1 min prior to applying the P2 solution. The P2 solution (200 μl) was aerated before applying to the glass slide because the oxygen molecules inhibit the free radicals and control the P2 polymerisation upon laser exposure to maintain the required difference in the refractive indices of light (P1 + P2) and dark (P1) fringes to develop a viewable grating. Subsequently, the glass slide was sandwiched with a clean glass slide for 5 min. Afterwards, the excess solution was wiped off with a rubber wiper blade. After laser exposure, the gels were washed in 1:1 (*v*/*v*) ethanol:5% (*w*/*v*) sodium bisulphate for 5 min to remove dye and unreacted P2 monomer. The "smart" hydrogel was immersed in PBS overnight.

2.3. Instrumentation and quantitative measurements

The response of the holographic sensors to test solutions was measured using a reflection spectrophotometer at room temperature. The "smart" hydrogel film (1.5 cm strip) was placed face up in a black anti-static weighing boat containing 5 ml of the buffer solution and a 2 × 5 mm magnet on gentle agitation to avoid overlaying of solutes on the surface of the hydrogel film which could act as a barrier for further glucose molecules to diffuse into the hydrogel. The change in diffraction wavelength was recorded using the spectrophotometer with an integration time of 200 ms. The holographic grating sensors were allowed to reach equilibrium in between changes in buffer solutions by monitoring the stability of the diffracted wavelength. Each sample data is the average of measurements on 5 samples in 0, 2, 4, 6 and 10 mM glucose concentrations.

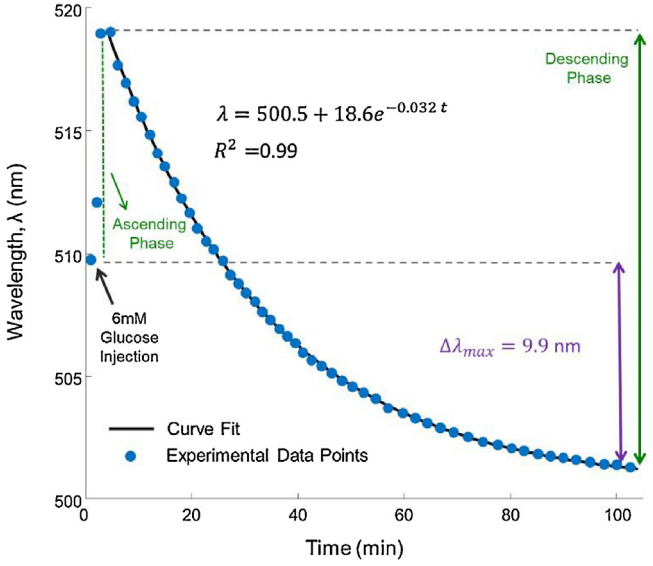

Fig. 2. A typical ascending-descending response of double polymerised 11.8 mol% 3-APB to a buffer solution containing 6 mM glucose and a three-parameter exponential curve fit ($\lambda = 500.5 + 18.6e^{-0.032t}$; $R^2 = 0.99$). The maximum wavelength shift ($\Delta\lambda_{max}$) is 9.9 nm and t is the elapsed time after glucose injection.

3. Results

This report describes the development of an all polymer 3-APB-based holographic sensor using a double polymerisation method. The lightly cross-linked copolymer, P1, was prepared by copolymerisation of acrylamide and DMAPA in the presence of 2.9 mol% MBA as a cross-linking agent and the functional monomer, 11.8 mol% 3-APB, whilst the fringes of the holographic grating comprised a highly cross-linked second polymer, P2, containing only acrylamide and 36.6 mol% MBA.

Fig. 2 shows that the response of the 3-APB-based double polymerised grating to glucose concentrations is biphasic. The initial rapid wavelength shift of expansion ($\Delta\lambda$) with respect to the initial replay wavelength (λ) was independent of the glucose concentration, whilst the magnitude of the slower response ($\Delta\lambda$) for the contraction was correlated to the glucose concentration. A plausible explanation is that the expansion phase could result from an initial 1:1 reaction between glucose and the boronate groups within the P1 phase, which creates a partial negative charge within the "smart" hydrogel lattice, and subsequently, diffusion of hydrated sodium ions, which in turn, leads to expansion of the hydrogel. This effect of charge generation and hence expansion of the hydrogel could be overcome in the contraction response due to additional slower interactions caused by a combination of the formation of 1:2 glucose-boronate complexes [12] as well as inter-chain hydrogen bonding interactions within the polymer lattice and/or π-π overlap with the aromatic phenylboronate groups. Hence, the biphasic profile could be attributable to competition between a fast charge-induced swelling resulting from the formation of 1:1 complexes and a slow contraction driven by 1:2 complex formation.