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Continuous Non-Invasive Ophthalmic Glucose Sensor for Diabetics

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Dedicated to Professor Daniel Belluš on the occasion of his 70th birthday

Abstract: A contact lens with an embedded glucose sensor hologram has been developed for continuous non-invasive monitoring of glucose levels in diabetics. This article describes the development and initial clinical testing of this ophthalmic glucose sensor and provides a comparison to current continuous glucose monitors.

Keywords: Contact lens · Continuous glucose monitoring · Diabetes · Reflection hologram

1. Introduction

Diabetes presents one of the largest health concerns of the 21st century. However, the most common method of glucose level monitoring, the fingerstick method can be as problematic as the disease itself. Diabetics are required to obtain blood samples up to five times per day. This procedure is painful and inconvenient. As a result, patients tend to test themselves less frequently, which means less effective glycemic control. A new non-invasive, continuous glucose monitor [CGM] could increase patient usage and would significantly improve the lives and health of diabetes patients.[1,2]

Daily-wear disposable contact lenses have been shown to be safe for patients with diabetes.[3] Good correlation between tear and blood glucose levels and no significant differences in glucose concentration between normal and reflex tears were reported.[4] A contact lens glucose sensor was therefore thought of as a safe and non-invasive alternative to the fingerstick method. A technique suitable for a contact lens application combines a simple reflection hologram[5] recorded within a hydrogel matrix with covalently bound 3-acrylamidophenylboronic acid (3-APB) as the glucose binding ligand. The construction of such a holographic reflection grating is depicted in Fig. 1. When holographic reflection gratings are illuminated by white light they act as sensitive wavelength filters, reflecting only a specific narrow band of wavelength (λ) governed by the Bragg equation: $\lambda max = 2nd\cos\theta$ (I), where n is the average refractive index, θ is the angle of illumination to the normal and d is the fringe distance of the grating. Changes in the swelling state of the hydrogel in which the grating is recorded will alter the fringe distance and hence the reflected color that can be detected by a spectrometer. Hydrogels constructed with 3-acrylamidophenylboronic acid (3-APB) are capable of forming reversible covalent bonds with glucose.[6] Binding of glucose to 3-APB moieties causes the hydrogel to swell, which in turn alters the fringe distances and can be used to quantify the glucose concentration.[7,8]

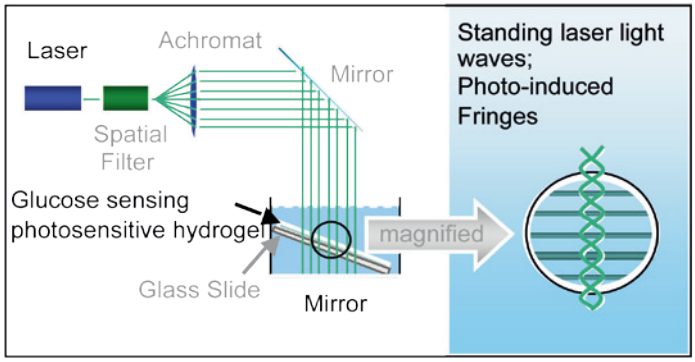

Fig. 1. The hologram is fabricated by passing a single collimated laser beam through the photosensitive hydrogel, backed by a mirror. Interference between the incident and reflected beams creates a permanent modulated refractive index in the form of fringes.

In previous papers we demonstrated the capability of holographic glucose sensors based on 3-APB and other derivatives to reversibly and continuously function in complex biological media at physiological pH, ionic strength and glucose levels.[9,10] This article describes the use of the reflection hologram technique in a contact lens, initial clinical testing, and a comparison of this technique to current other continuous glucose monitors.

2. Experimental

2.1 *Materials, Synthesis and Preparation of Contact Lens Sensor*

3-APB was synthesized and co-polymerized with acrylamide to yield a glucose sensitive hydrogel matrix. A reflection hologram was recorded into the hydrogel matrix as described previously.[10] Base material for the sensor contact lens is Nelfilcon A (CIBA VISION Corp., Duluth, GA), a poly(vinyl alcohol) derivative that polymerizes in the presence of a photo-initiator under UV irradiation. A 7 μm thick, 3 mm diameter holographic glucose sensor wafer was incorporated into the Nelfilcon A contact lens during the polymerization process (Fig. 2). The contact lens was then extracted and autoclaved to render it non-toxic and sterile. The function of the glucose sensor was then verified *in vitro*. Fig. 3 shows the *in vitro* glucose response.

2.2 *Equipment, Instrumentation and Methods*

Detection of the holographic signal was performed with an Avantes AvaSpec-***2048*** Fiber Optic or AVS MC-2000 Spectrometer, AvaSoft software and an optical fiber bundle detector (Quantel). One fasting subject was given an oral challenge consisting of 44 g of glucose. Glucose measurements

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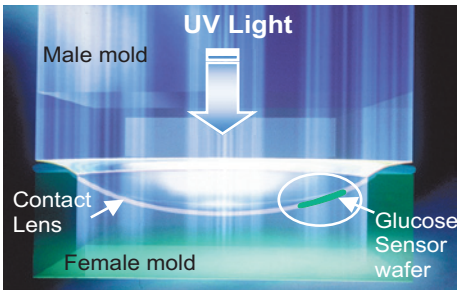

Fig. 2. Fabrication of a contact lens with embedded holographic glucose sensor wafer by UV polymerization of a Nelfilcon A formulation between male and female molds.

were performed with MediSense Precision Xtra® (Abbott). The contact lens hologram signal and fingerstick blood glucose were measured for about 30 minutes.

3. Results and Discussion

Fig. 4 shows the actual holographic contact lens in a normal patient's eye (subject A), a plot of blood glucose concentration against time after glucose administration in subject A, and the response of the holographic sensor for the same period in the same subject. There appears to be a slight delay in time between blood glucose increase and contact lens sensor response. A polynominal can be derived for each individual patient that can partially correct for this delay as previously described.[11] The bathochromic peak wavelength shift of *in vivo* responses, if compared to *in vitro* responses, is not yet understood. Although this ophthalmic sensor tracked glucose levels for about 30 minutes, longer term studies of comfort and function need to be performed before such a lens can be available for general use. The advantage of this technique is that the patient may take multiple readings of the contact lens holographic signal simply, non-invasively and without pain. This continuous monitoring gives the patient an idea of the rate of rise and fall of glucose, which might be as important as the absolute value of glucose.

Several CGMs are currently available: Guardian® REAL-Time (Medtronic), SEVEN® PLUS (Dexcom), Paradigm® REAL-Time and insulin pump (Mini-Med), FreeStyle Navigator® (Abbott), GlucoDay® S (Menarini Diagnostics microdialysis system for clinical use). These monitors consist of a disposable needle sensor wire, a transmitter and a receiver. The sensor wire is inserted by the patient or injected clinically under the skin with replacement times from 2–7 days. The availability of the complete glucose profile, provided by these methods, was proven to be beneficial for glycemic control.[12] However, for a variety of reasons, large-scale application of these monitoring devices in diabetic care still awaits breakthrough. For example, the method of sensor insertion is painful, frequent replacement increases risk of inflammation, they are often noticeable and in some cases have limited water resistance. They are also very expensive (between $2,100 and $5,400 per year[2]) and insurance coverage is approved on a case-by-case basis only.

The ophthalmic glucose sensor offers a less invasive and more convenient means of continuous monitoring. Tear fluid is in constant contact with the contact lenses, the spectrometer can be miniaturized into inconspicuous shapes such as a make-up compact and reflection holographic sensors can be produced cost effectively.

4. Conclusion

An ophthalmic glucose sensor based on a simple and mass producible reflection hologram was developed that showed in initial clinical studies the ability to track glucose response for about 30 minutes. While further long-term testing is needed to fully develop such a sensor, the method shows promise over current continuous monitoring systems because it is less invasive and can be mass produced more cost efficiently.

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[1] I. B. Hirsch, *J. Clin. Endocrinol. Metab.* **2009**, *94*, 2232.
[2] S. K. Garg, J. Smith, C. Beatson, B. Lopez-Baca, M. Voelmle, P. Gottlieb, *Diabetes Technol. Ther.* **2009**, *11*, 65.
[3] W. F. March, *Diabetes Technol. Ther.* **2004**, *6*, 49.
[4] G. R. Srivastav, B. K. Jain, R. Sahai, A. Sharma, S. Verma, in AIOC Proceedings, **2006**.
[5] Y. N. Denisyuk, *Opt. Spectrosc.* **1963**, *18*, 152.
[6] I. Hisamitsu, K. Kataoka, T. Okano, Y. Sakurai, *Pharm. Res.* **1997**, *14*, 289.
[7] M. C. Lee, S. Kabilan, A. Hussain, X. Yang. J. Blyth, C. R. Lowe, *Anal. Chem.* **2004**, *76*, 5748.
[8] S. Kabilan, J. Blyth, M. C. Lee, A. Hussain, X. Yang. C. R. Lowe, *J. Mol. Recognit.* **2004**, *17*, 162.
[9] A. Domschke, W. F. March, S. Kabilan, C.R. Lowe, *Diabetes Technol. Ther.* **2002**, *4*, 49.
[10] S. Kabilan, A. Marshall, F. Sartain, M. C. Lee, A. Hussain, X. Yang, J. Blyth, N. Karangu, K. James, J. Zeng, D. Smith, A. Domschke, C. R. Lowe, *Biosensors Bioelectron.* **2005**, *20*, 1602.
[11] W. F. March, *Diabetes Technol. Ther.* **2002**, *4*, 49.
[12] S. V. Edelman, T. S. Bailey, *Diabetes Technol. Ther.* **2009**, *11*, 68.

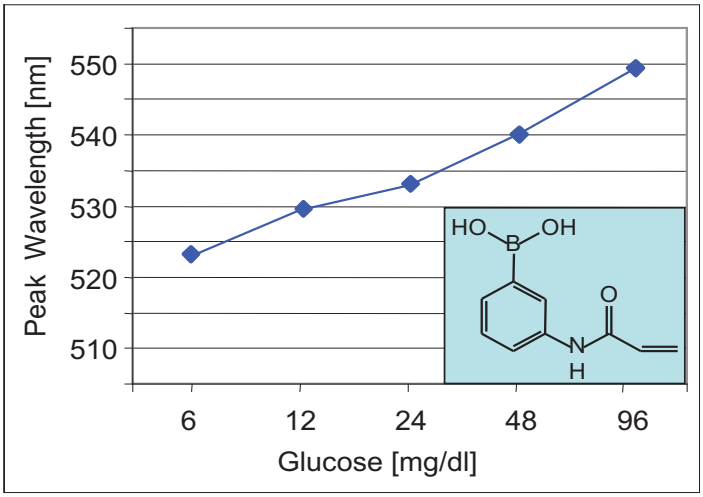

Fig. 3. *In vitro* tear glucose response of a sensor contact lens with 3-APB in saline at pH 7.4. (Fastening tear glucose value 10 mg/dl[4]); Inset: Chemical structure of 3-APB

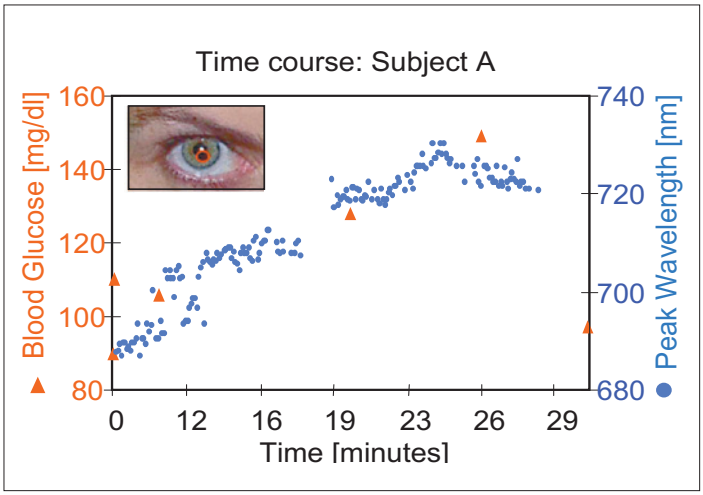

Fig. 4. Plot of blood glucose and holographic signal against time from glucose ingestion; Right eye of subject with contact lens and holographic sensor just beneath the pupil.