OSMOTIC GLUCOSE SENSOR FOR CONTINUOUS MEASUREMENTS IN VIVO

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ABSTRACT

Tracking blood glucose using osmotic pressure represents a revolutionary new sensor concept adaptable for long term continuous measurements in patients suffering from diabetes mellitus. This paper presents a state of the art osmotic sensor that will be miniaturized for insertion under the skin by injection.

KEYWORDS: Nanoporous, osmosis, glucose sensor, continuous, affinity assay

INTRODUCTION

The detection of blood glucose is currently based on Clark and Lyons enzyme sensor [1] in which subjects needs to sample blood from the finger several times a day. The procedure is quite painful especially for small children and the accuracy of the measurement relies on the number of samples performed. In contrast, continuous measurement of blood glucose presents a completely new standard in which the blood glucose can be automatically tracked and thereby allowing the subject to control their blood glucose in a manner comparable to healthy subjects.

THEORY

The osmotic principle of nature is implemented [2] as the basis of the sensor technology where a reversible competitive affinity assay performs glucose specific recognition from other dissolved constituents in blood. The sensor prototype of stainless steel is presented in figure 1 containing (1) a T-shaped holder (i), support plate (ii), front plate (iii), back plate (iv), o-ring (v), pressure transducer (vi) and support plate for pneumatic calibration (vii) from an external pneumatic source.

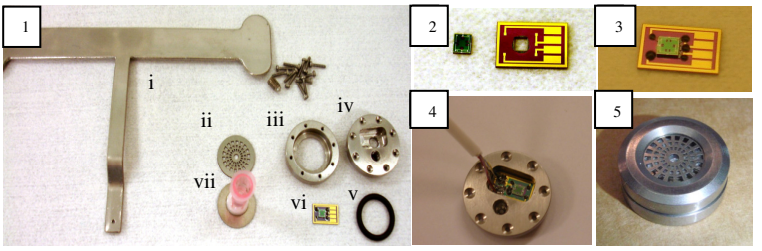

Figure 1. Prototype sensor components (1). MEMS pressure transducer and carrier (2,3); attachment of pressure transducer to sensor housing (4); reverse side showing the nanoporous membrane and support structure (5). Sensor diameter is 16 mm.

978-0-9798064-2-1/μTAS2009/$20

EXPERIMENTAL

The sensor is equipped with a polymeric nanoporous membrane (cellulose ester) offering a molecular weight cut off (MWCO) of 5000 Da. The membrane encloses an isovolumetric reference cavity in which the 2x2 mm^2 pressure transducer is located. The affinity assay is based on the reversible competitive bonding of glucose (0-40 mM) and dextran (4%) to the lectin concanavalin A (8%) dissolved in Trisma at pH 7.4. The concept is known from literature [3][4] where the principle has been explored detecting viscosity changes in response to changing glucose concentrations. The performance of the affinity assay was compared to direct osmotic measurements of glucose using a 100 Da membrane impermeable to glucose and in which the affinity assay in the sensor lumen was replaced with a 40 mM glucose solution. The sensor was calibrated from 0 – 1 bar by an external pneumatic source.

RESULTS AND DISCUSSION

The affinity assay generated an osmotic pressure change of 4.2, 7.7 and 16.5 mbar in response to the glucose concentration changing from 40 mM to 30, 20 and 10 mM respectively (figure 2) - thus spanning the dynamic range of conventional blood glucose readers.

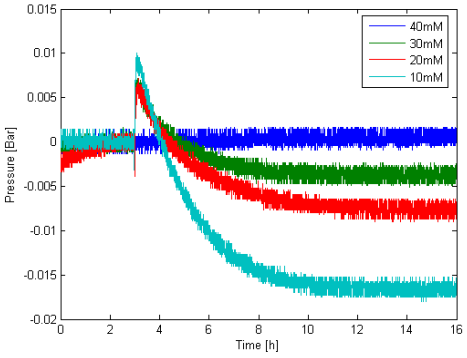

Figure 2. Pressure changes in response to changing glucose concentrations.

The results are comparable to direct glucose measurements shown in table 1. Note that the generated pressures are inverse due to the nature of the sensing mechanism. Concanavalin A and dextran are attached together and forms a large molecular complex in the absence of glucose. However, as the presence of glucose increases, glucose will compete with dextran and start bonding to the lectin resulting in more dextran molecules detaching. Thus, the net increase in dextran molecules will mirror the concentration increase of free glucose diffusing into the sensor. The process is fully reversible, and dextran will reattach to concanavalin A when the glucose concentration is reduced. In contrast, the 40 mM reference solution of the direct measurements sees the net pressure increase in response to a decreasing particle concentration (and hence osmotic strength) outside the sensor.

Table 1. Transmembrane pressures

Glucose [mM]	ΔP direct [mBar]	ΔP affinity assay [mBar]
40	2.0	0
30	7.6	- 4.2
20	10.9	- 7.7
10	14.8	- 16.5

CONCLUSIONS

Successful implementation of an affinity assay have been shown presenting means of identifying glucose from other molecular constituents in blood. The osmotic sensor will be further miniaturized for injection under the skin by integrating the pressure transducer and reference chamber into a 3x7 mm large autonomous inductive powered ceramic package of LTCC (figure 3). The simultaneous development of a nanoporous silicon membrane will seek to reduce the diffusion barriers and thus improve response times of the sensor.

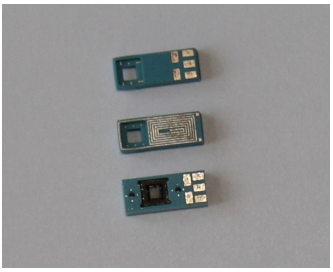

Figure 3. Microfabricated osmotic sensors with a silicon nanoporous membrane.

ACKNOWLEDGEMENTS

This work was funded by the Research Council of Norway and Lifecare AS.

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