Non-invasive glucose measurement by enzymatic reaction in tear fluid

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An enzymatic reaction is used to amperometrically measure the glucose concentration in tear fluid with a miniaturized electrochemical cell. The miniaturized system consists of a coil of six wires. Three of these wires are used as electrodes. The other three wires serve to stabilize the coil and at the same time as antennas for wireless communication with a reader. The measurement data are processed on a CMOS potentiostat, the transmission by a transponder ASIC. Due to the coil form and a flexible connection of the sensors, the whole assembly remains bendable and can adapt optimally to the curvature of the eye when used in the lower eyelid.

Diagnostically, the tear fluid is very interesting for the use of in vitro systems due to the large number of biomarkers involved [1]. Since the tear fluid, and thus also the contained biomarkers, is constantly being renewed, it provides the possibility of real-time monitoring of biomarkers, e.g. Glucose.

The normal glucose concentration in tear fluid is in the range of 0.2-0.33 mmol/l. Comparing this course with that in blood (norm values between 4.2 and 6.0 mmol/l) it is noticeable that this is 20 times smaller and has a delay of about 10 minutes (see Fig. 1) .

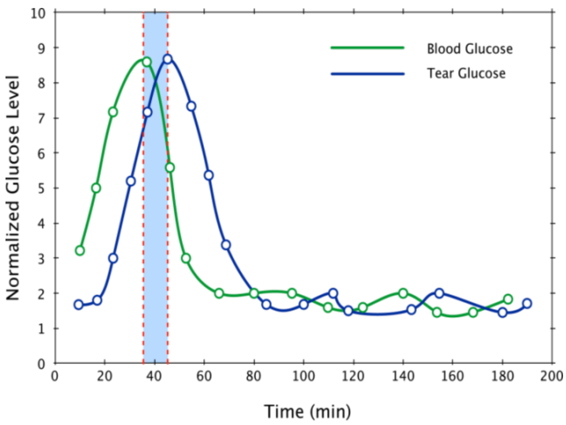

Fig. 1: *Measurement of glucose concentration in tear fluid compared to that in blood at different times [2]*

A large number of different sensor systems exist for the detection of glucose in tear fluid [3] [4]. By using a microsystem, which is placed behind the lower eyelid, the tear fluid can be analyzed and used for continuous, non-invasive measurement of glucose concentration. The location close to the lower tear duct offers the advantage that the flow of tears is almost constant [5].

The development of such a microsystem involves various challenges: a robust enzymatic detection of glucose, the measurement data has to be telemetrically readable, a certain flexibility of the system is present so that it can adapt to the contour of the eye or eyelid and the miniaturization of the system has to be possible to avoid irritation and thus a poor wearing comfort.
On these foundations, a microsystem was developed which consists of six wires wound into a coil and a miniaturized electrochemical cell (see Fig. 2).

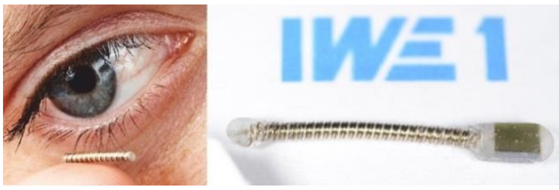

Fig. 2: *Left: Proper dimensions of the sensor system; Right: Demonstrator of the glucose sensor system with silicone-molded ends*

The coiled form and the choice of the materials of the individual wires mean that the sensor remains flexible and the stability of the system is ensured. For measuring the glucose concentration, a potentiostat ASIC is used, which is read out wirelessly using a transponder ASIC. The inductive coupling is used simultaneously for the energy supply of the sensor system. The connection between the coil and the ASICs is made by a flexible substrate made with thin-film technology (see Fig. 3).

Fig. 3: *Functional design with SMD components and casting compound with transparent GlobTop*

The measuring coil works like a micro electrochemical cell. This cell consists of three measuring wires:

a working electrode, a counter electrode and a reference electrode (see Fig. 4). The counter and reference electrodes consist of a stainless steel wire coated with Ag/AgCl, the working electrode is made of a Pt/Ir wire.

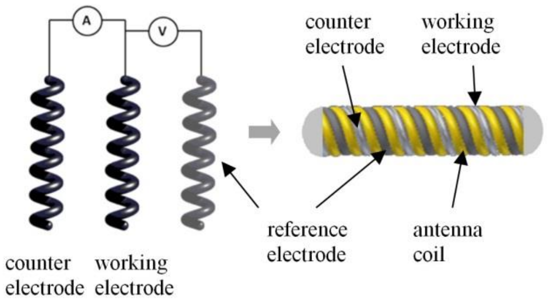

Fig. 4: *Concept and construction of the electrochemical measuring cell as measuring coil*

The working electrode is functionalized with the enzyme glucose oxidase. This oxidase converts the glucose of the tear fluid into gluconic acid and hydrogen peroxide. The hydrogen peroxide produced by the enzyme activity is reacted on the working electrode to release electrons. At the counter electrode, water is produced with the release of electrons. This electron current is measured and is proportional to the glucose concentration of the tear fluid. As waste product water is produced (see Fig. 5).

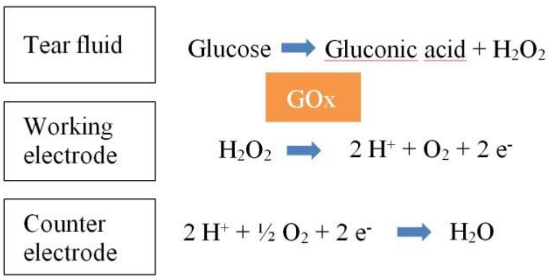

Fig. 5: *Partial reactions on the electrodes*

Measurements were carried out for data transmission of the transponder to the hand-held device. With these, the functionality of potentiostat and transponders could be shown in conjunction with the other components. Tests with the coil showed that a maximum transmission distance of 30 mm can be achieved with the present configuration (winding number, material of the antenna wires and winding diameter). In order to test the functionality of the sensor system, it was placed in artificial tear fluid and the measurement data were read out (see Fig. 6).

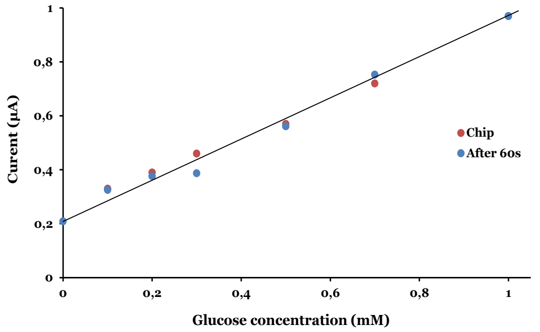

Fig. 6: *Proportional correlation of electron current to glucose concentration in tear fluid*

Project Partners

- Fraunhofer IMS Duisburg
  www.ims.fraunhofer.de
- NovioSense
  www.noviosense.com

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