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ScienceDirect

Procedia Technology 27 (2017) 208 – 209

Procedia Technology

Biosensors 2016

Minimally invasive microneedle array electrodes employing direct electron transfer type glucose dehydrogenase for the development of continuous glucose monitoring sensors

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Abstract

Closed loop systems hinge on the accuracy and precision of the continuous glucose monitoring sensors. Most of the commercially available continuous glucose monitoring sensors is implanted subcutaneously for a period of 7-14 days. The subsequent biofouling effects have implications on the performance of the sensors over time especially at low glucose concentrations. In addition, the commercially available sensors are sensitive to the presence of interfering species such as acetaminophen in the skin compartment. We report here on the marriage of minimally invasive, continuous glucose sensors and a direct electron transfer type glucose dehydrogenase enzymatic system. Whilst the microneedles here are designed to sit in the dermal interstitial fluid over a 24-48 hour period to minimize the biofouling effect, the direct electron transfer enzyme allows operation of the electrochemical sensor at lower potentials to minimize the effect of interference. The microneedle structure design also enables the use of compensation electrodes for background subtraction to further nullify the effects of interference.
Keywords: continuous glucose monitoring; minimally invasive sensors; direct electron transfer; microneedles

1. Introduction:

Closed loop systems comprising a continuous glucose monitoring (CGM) sensor and an insulin pump interfaced via suitable control software, continue to be the most effective solution for management of Type 1 Diabetes. The effectiveness of the closed loop system is highly dependent on the accuracy of the CGM sensors. Although decades of sensor technology development have improved the mean average relative deviation of the CGM devices there are still issues with accuracy of CGM sensors in the low concentration regime. In addition, interferences due to common substances such as acetaminophen, ascorbic and uric acid remain a challenge. We address these issues through the use of minimally invasive microneedle array electrodes (Trzebinski et al., 2012; El-Laboudi et al. 2013) coupled to a glucose dehydrogenase based direct electron transfer system and is therefore less likely to be subject to interference as has been reported recently (Sekimoto et al. 2016)

Peer-review under responsibility of the organizing committee of Biosensors 2016
doi:10.1016/j.protcy.2017.04.087

Method: The microneedle array electrodes are used over 24-48 hours to minimise the biofouling effect. The design of the microprobe arrays electrodes are such that the arrays are partitioned into working, reference and background compensation electrodes to enable parallel measurements of glucose and the background currents respectively.

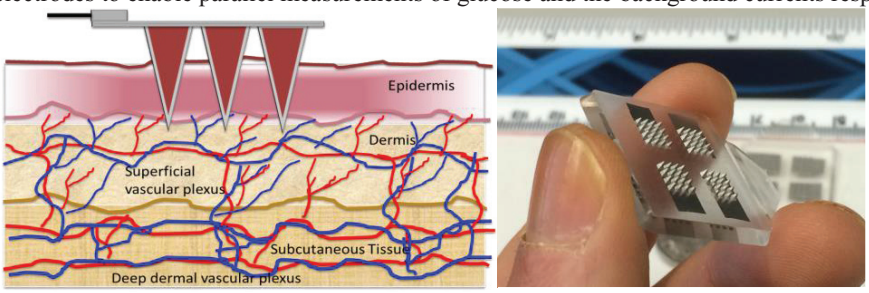

Figure 1a (left): Schematic showing the location of the minimally invasive continuous monitoring sensor in the skin compartment **1b (right)** shows Pt microprobe array electrodes on a polycarbonate substrate.

Two protocols reported earlier (Hanashi et al. 2011; Yamashita et al. 2013) for conventional disc electrodes were used for functionalisation of the Pt electrodes to FADGDH/Pt electrodes. These included preparation of FADGDHϒαβ electrode using Ketjen Black (KB) with TritonX-100 and Ketjen Black dispersed in ethanol.

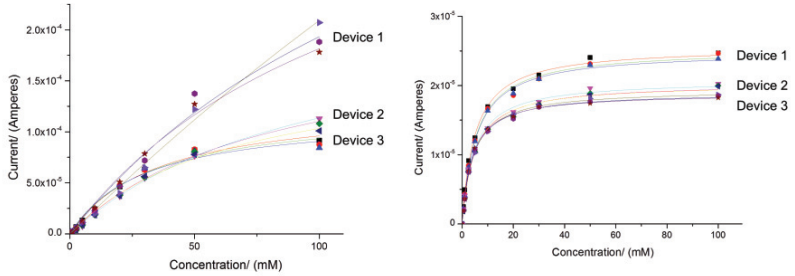

Figure 4: Dose response curves obtained from FADGDH/Pt electrodes functionalised by protocols described above.

Results: Functionalisation of the microprobe arrays with glucose dehydrogenase entrapped in polyphenols yield a third generation biosensor that operates at a lower potential (400mV) than those reliant on hydrogen peroxide detection (700mV). The use of compensation electrodes and a direct electron transfer are expected to drastically reduce the effects of interference due to electro-active species.

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Acknowldgement(s):
The authors wish to acknowldge the NIHR (i4i), UK and the JSPS, Japan for support.