A TRANSDERMAL CONTINUOUS GLUCOSE MONITORING SYSTEM WITH AN IMPLANTABLE FLUORESCENT HYDROGEL FIBER AND A WEARABLE PHOTO-DETECTOR

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ABSTRACT

We developed a transdermal continuous glucose monitoring (CGM) system that consists of an implanted fluorescent-hydrogel fiber and a wearable photo-detector. While we showed the potential of the fluorescent-hydrogel fibers for applying to CGM in our previous study, we are still on the way to realize "true" CGM system. In our CGM system, the wearable detector reads the fluorescent signals through skin layers. The fluorescence signals showed a good correlation with the blood glucose concentrations measured by a conventional method. Therefore, our system has the great potential for a practically usable device to realize a CGM.

KEYWORDS

implantable glucose sensor, glucose-responsive fluorescence, wearable detection system, diabetes mellitus

INTRODUCTION

Diabetes is a global pandemic affecting over 366 million people in 2011 and this number is going to increase to 552 million within 20 years [1]. Diabetes causes several complications like cerebral vascular disturbance, retinopathy and nephropathy. To prevent these diabetic complications, diabetic patients need measuring blood glucose concentration and injecting insulin according to the measured blood glucose value [2]. Finger tip prick method and CGM system with enzyme-tipped catheters are well-known methods to measure and control blood glucose concentration. Although these methods are accepted by a lot of diabetic patients or medical fields, pricking finger tip is invasive and semi-implantable sensors for CGM have a risk of infection [3]. To overcome these problems, we proposed the fully implantable glucose sensor that maintains its function for 140 days in our previous study [4-6]. However, we have yet to realize a "true" CGM system mainly due to the lack of a light-weight, wearable detecting system and signal calibration with blood glucose concentrations.

In this paper, we propose a transdermal CGM system with implantable fluorescent-hydrogel fibers and wearable photo detectors (Fig.1). We created the detection device for implantable fluorescent-hydrogel fibers. Our device consists of two main parts: The first part is the detection device that consists of a light emitting diode (LED), a photo diode (PD) and an electrical circuit. Using the detection device, the fluorescent signals are automatically measured thorough skin layers. The second part is a microcontroller to control the detection device and communicate with computer-based, control software in MATLAB. We set this device to the rat's ear with the implanted fiber to read out fluorescence intensity. Therefore, our system is promising for the "true" transdermal CGM system.

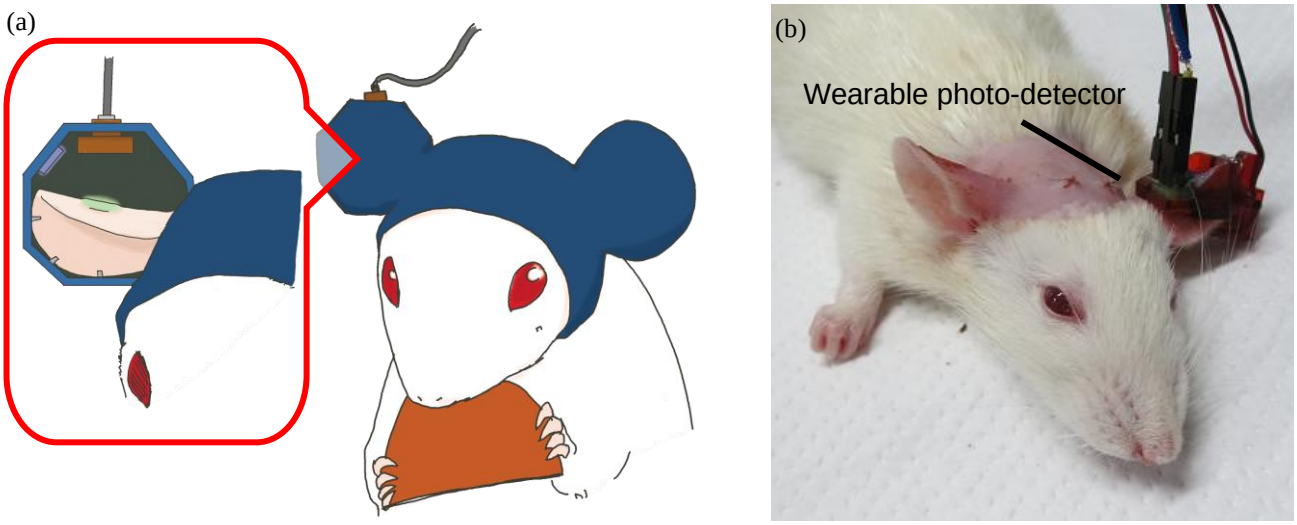

Fig.1 (a) Conceptual view of the continuous glucose monitoring system using glucose-responsive fluorescent hydrogel fiber implanted to rat's ear. UV LED is used as excitation light and fluorescence intensity is detected by a photo diode (PD). These two parts nip the fluorescent fiber under the skin. (b) Image of rat wearing the photo-detector.

MATERIALS ANS MEDOTHS

Fabrication process of fluorescent hydrogel fiber

We prepared the pre-gel solution containing 15 wt% acrylamide (AAm), 0.3 wt% *N, N'*-methylene bis (acrylamide) (Bis-AAm), 5 wt% polyethylene glycol (PEG), 0.9 wt% sodium peroxo disulphate (SPS) and *N,N,N',N'*-tetramethyl ethylene diamine (TEMED). Pre-gel solution was polymerized in a silicone rubber (Fig.2a). After gelation, the hydrogel fibers were washed with large amount of water for over 48 h to remove unpolymerized PEG and AAm monomers. A rat (Slc:SD) was in a deep sleep under anesthesia during surgery. We inserted the indwelling needle from the base to the tip of rat's ear to make space for the hydrogel fiber. The hydrogel fiber was implanted under the skin through the external cylinder. The fluorescence intensity is visible through skin layers (Fig. 2b).

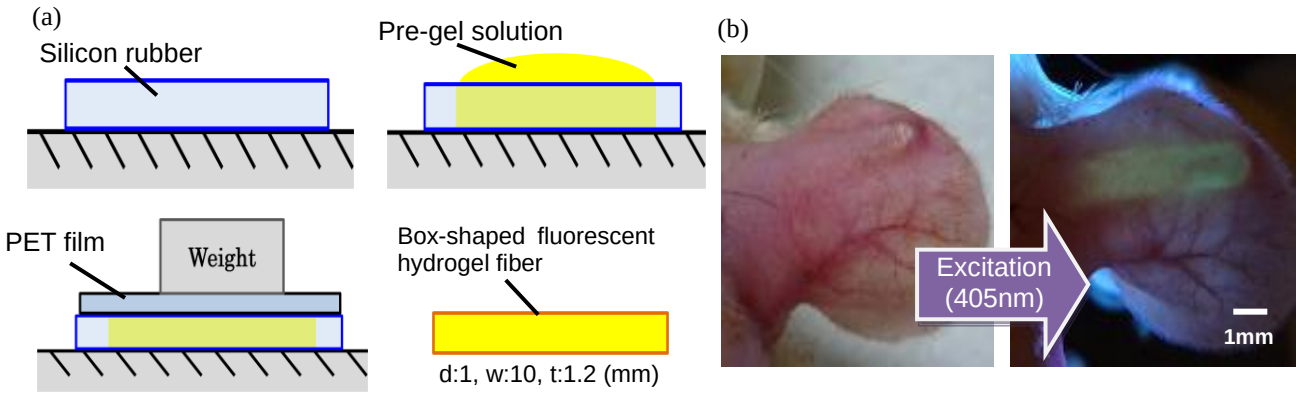

Fig.2 (a) Fabrication process of box-shaped fluorescent hydrogel fiber. (b) Images of the implanted fluorescent-hydrogel fiber in rat's ear. Fluorescence intensity is visible through skin layers.

Transdermal continuous glucose monitoring system

The detection device is composed of a commercial photodiode (PD, Hamamatsu Photonics, G6262) and a LED (BIVAR, 405 nm) as a fluorescent detector and an excitation light source, respectively, and covered by a housing fabricated by stereolithography (Fig.3a). The detection device has a clipping mechanism to hold on the ear of a rat implanted the fluorescence hydrogel-fiber between a PD and a LED (Fig.3b, c). The attached detection device transdermally reads fluorescent signals from the implanted fiber. Photodiode was connected to the amplification circuit and analog digital conversion was conducted on the microcontroller (Switch Science, Arduino Fio). The microcontroller communicates with the software written in MATLAB. The detection device is software-controlled through microcontroller to provide pulsed excitation light and read fluorescent signals. Measured fluorescence intensities are sent to the software and recoded on the PC.

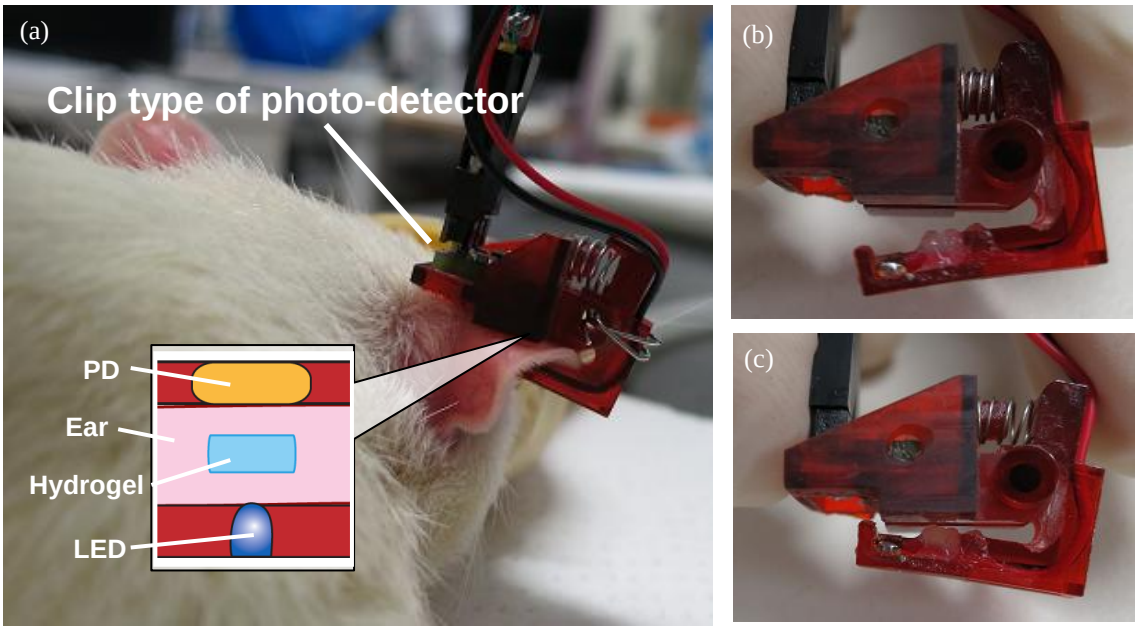

Fig.3 (a) Images of measurement devices clipping the ear implanted the fluorescent hydrogel fiber. Implanted hydrogel to the ear of a rat is placed between a PD and a LED. (b) Open state of the detection device. (c) Closed state of the detection device.

Results

We conducted the *in vivo* glucose fluctuation test to evaluate the transdermal, continuous monitoring performance of our system. In the glucose fluctuation test, we applied 50% glucose liquid or 0.25% insulin to abdominal cavity to increase or decrease blood glucose concentration (Fig.4). Blood glucose concentration was measured by commercial blood glucose meter (AccuChek, Roche) every 5 min as a reference blood glucose concentration. The fluorescence intensity measured by the system successfully tracked the fluctuation of reference blood glucose concentrations. Therefore, our system shows the potential for practical, "true", continuous glucose monitoring.

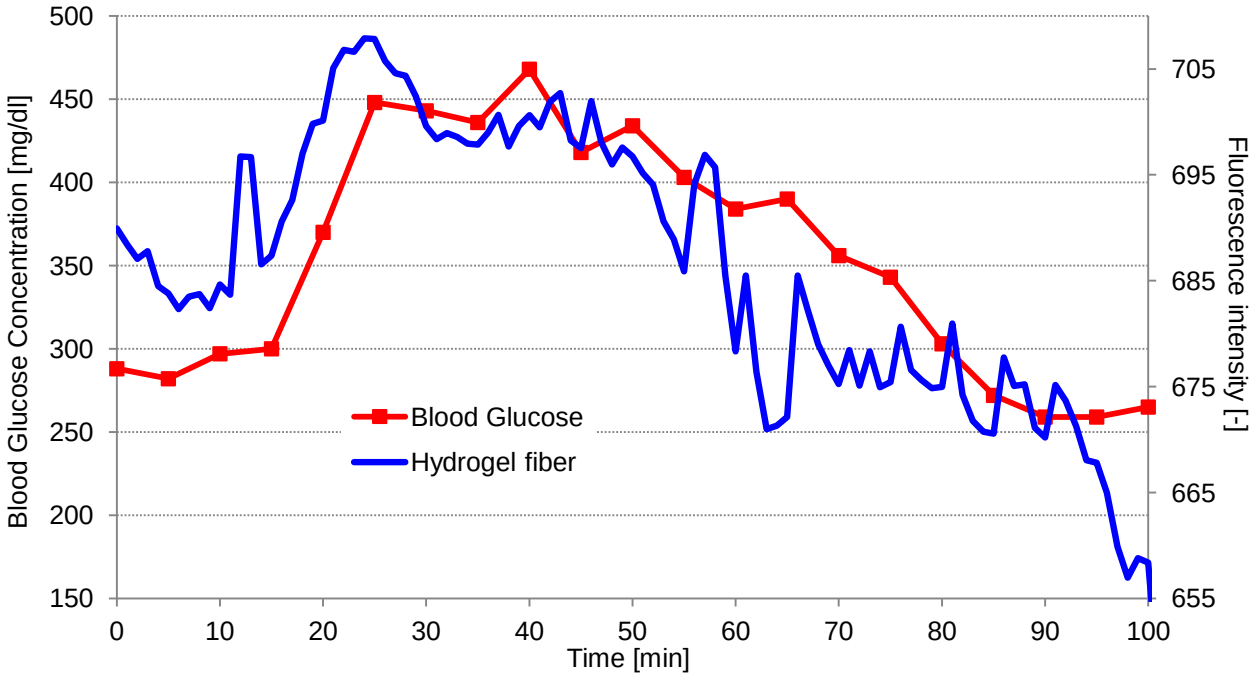

Fig. 4 Results of the *in vivo* glucose fluctuation test with our analysis system. Fluorescence intensities showed good correlation with the measured blood glucose concentrations.

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