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Importance of Skin Resistance in the Reverse Iontophoresis-based Non-invasive Glucose Monitoring System

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Abstract— **Utilization of the changes in skin resistance during reverse iontophoresis is proposed to detect severe perspiration as well as to correct the glucose estimation. Developed system consists of the amperometric biosensor unit, the electrode unit, a constant current driver circuit and a microcontroller-based control. Performance of the developed system was evaluated by the in-vitro skin model which was specially designed for resverse iontophoresis system.**

Keywords—**Skin Resistance, glucose monitoring system, Reverse Iontophoresis, Non-invasive**

I. Introduction

Diabetic patients typically measure their blood glucose level by pricking a finger to obtain blood sample(we call it as finger stick method). This finger stick method is accurate but it is also painful and inconvenient, particularly when it comes to need multiple measurements per day. Despite of the pain and inconvenience of finger stick method, the tight control of blood glucose level is known to be helpful for those diabetic patients to reduce the risk of hypoglycemia and the long term complications in diabetes[1].

Recently, researches have been focused on non-invasive continuous glucose monitoring system. These non-invasive techniques can provide painless and more convenient procedure of monitoring blood glucose level to the diabetic patients. Under developing non-invasive methods are mainly classified into two categories. One is an optical measurement and another is a reverse iontophoresis based measurement. The former could not be commercialized yet but the later already commercialized(Cygnus Inc, USA).

Reverse iontophoresis is a technique whereby a low-level DC current is conducted through the skin between an anode and cathode. Because skin carries a net negative charge at neutral pH, sodium ions in the interstitial fluid are major charge carrier through the skin. So the migration of these sodium ions makes a net convective solvent flow(call it as an electro-osmotic solvent flow) toward the cathode. Reverse iontophoresis uses this electro-osmotic solvent flow to extract uncharged molecules, such as glucose, across the skin[2-3]. Fig. 1 shows this reverse iontophoresis mechanism. The external amperometric bio-sensor system measures the extracted glucose which is closely correlated with the blood glucose levels[4].

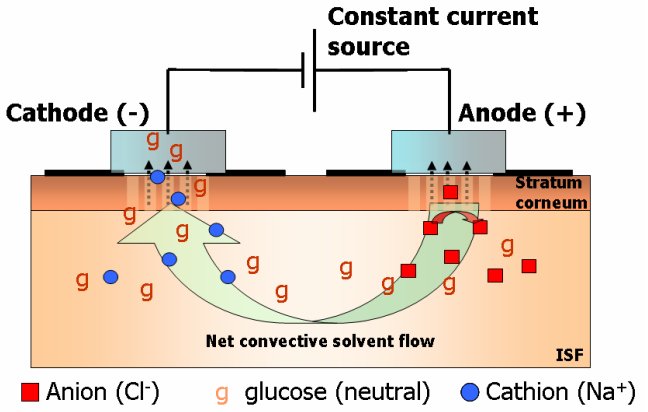

Fig. 1. The extraction of glucose by the net convective solvent flow of reverse iontophoresis

But there are two difficulties to overcome in the reverse iontophoresis based glucose monitoring system. One is reducing the effect of excessive perspiration[5] and another is applying proper glucose estimation algorithm. In this paper, utilization of changes in skin resistance during the reverse iontophoreiss can overcome the problems of reverse iontophoresis based glucose monitoring system.

II. Methodology

A. System Description

The developed system consists of four parts: the amperometric biosensor unit, the electrode unit, a constant current driver circuit and a microcontroller-based control unit.

1) *Amperometric biosensor unit*: This part consists of a hydrogel-based glucose sensor and a high-gain current measuring circuit with potentiostat driver. HPMA-DMA copolymer hydrogel which contains glucose oxydase(GOD) converts the extracted glucose into gluconic acid and hydrogen peroxide(H_2O_2). The produced H_2O_2 is then reduced at the anodic electrode to generate electronic current proportional to the glucose concentration.

2) *Electrode unit*: We used an in-house fabricated electrode unit which contains two sets of planar electrodes. One pair of Ag/AgCl electrode was used for reverse iontophoretic extraction and skin resistance measurement. For amperometric measurement, a working electrode was

made of platinum and carbon(50% to 50%) and two Ag/AgCl electrodes were used for a counter and a reference electrode. The geometrical shapes of each electrode were fully considered in order to increase the measurement and the extraction efficiency.

3) *Constant current driver*: The constant current circuit drives a low level DC current for reverse iontophoresis. Skin resistance was simultaneously obtained by measuring the potential drop between two electrodes. Electrical isolation between the current driver and the rest of circuitries(such as potentiostat, control, and communication units) was provided using PhotoMos relays(NAIS, Matsushita Electric, Japan) and isolated instrumentation amplifier(ISO102, Texas Instruments, USA) as shown in Fig. 2.

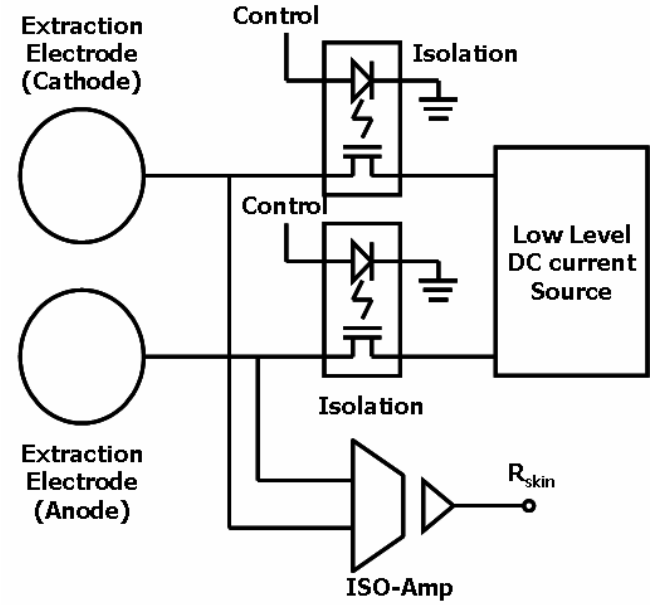

Fig. 2. Block diagram of the constant current driver with skin resistance measurement circuitry.

4) *Control units*: Analog outputs of the biosnesor and skin resistance measuring circuit were digitized by an analog-to-digital converter which was controlled by a microcontroller(AVR8515, Atmel, USA). Sampled data were then sent to a notebook PC(LIFEBOOK S6010, Fujitsu, Japan) real-time through Bluetooth® modules(Promi-ESD and Promi-SD, Initium co. Ltd, Korea). This wireless linkage allowed not only the electrically isolation between patients and AC power line, but also real-time communication.

B. Experiments

We designed an in-vitro skin model for performance evaluation of the developed system based on the modified model suggested by Patricia Connolly[6]. The skin model consist of two chambers seamlessly separated by a hairless mouse skin sample(Samtako co. Ltd, Korea).

Hydrogel discs of the amperometric biosensor unit coupled with the developed electrode unit were attached to the bottom side of the upper chamber. Contact between the mouse skin and the hydrogel disc was secured by a ring-shaped adhesion tape. The gap between the upper chamber and mouse skin was completely sealed by silicon glue(Fig. 3).

The lower chamber was filled with the solution(PBS and glucose) of the known concentration, which acted as the interstitial fluid. Then the upper chamber covered with the mouse skin was dimmed to the lower chamber.

The system was stabilized with only amperometric measurement for the first 30 minutes where capacitive currents dominated. One set of experiment was organized as a series of 3 minutes of extraction and 7 minutes of measurement where a reverse iontophoresis(with 100uA DC current) and the extracted glucose measurement were carried out, respectively. Total three sets of experiments were performed per one glucose concentration level. Three glucose concentration levels of 100mg/dL, 200mg/dL and 400mg/dL were tested sequentially.

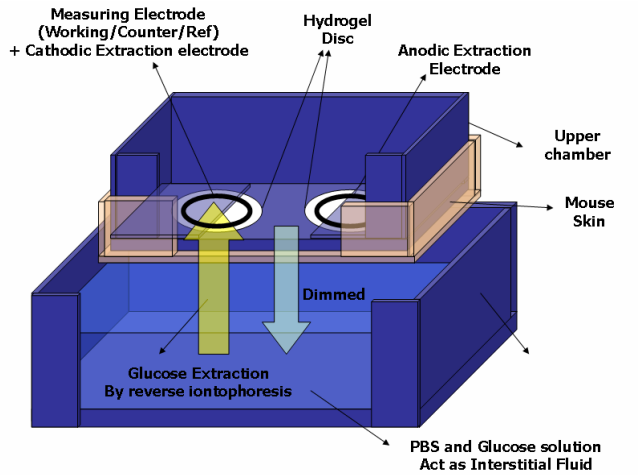

Fig. 3. Schematic drawing of the experimental chamber

III. RESULTS

The waveforms of current output at four different glucose concentration levels and the corresponding skin resistance changes are plotted in Fig. 4 and Fig. 5, respectively. The solution without glucose was used to find out the time for stabilization of the system. There was one hour time gap between experiments with no glucose solution and 100mg/dL solution. Remaining three experiments were performed without any time gap.

During the stabilization period, both the slowly changing current signal and the fast decrease in skin resistance represent that the system is being stabilized(Fig. 4 and Fig. 5).

Integration of the measured current waveform provides the total charge produced by the reaction of extracted glucose. As shown in Fig. 6, simple integration of current resulted in poor correlation to the real glucose concentration level.

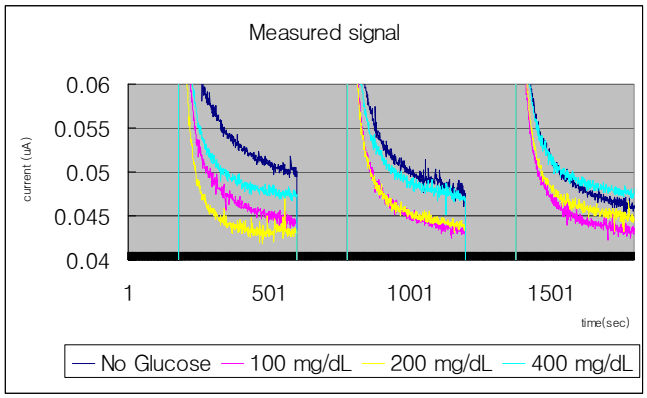

Fig. 4. The results of measured current waveforms at four different glucose concentration levels.

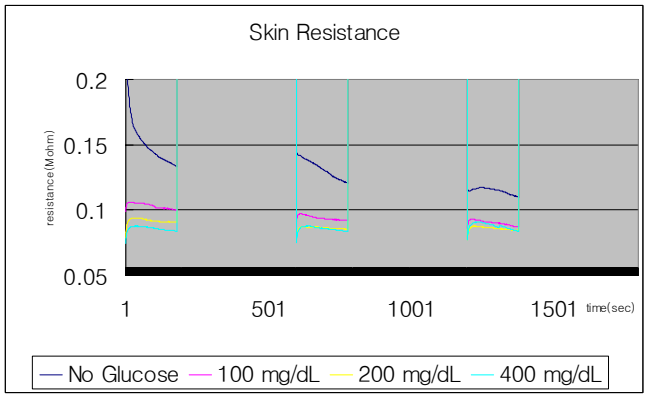

Fig. 5. Skin resistance changes during each experiment of Fig. 4.

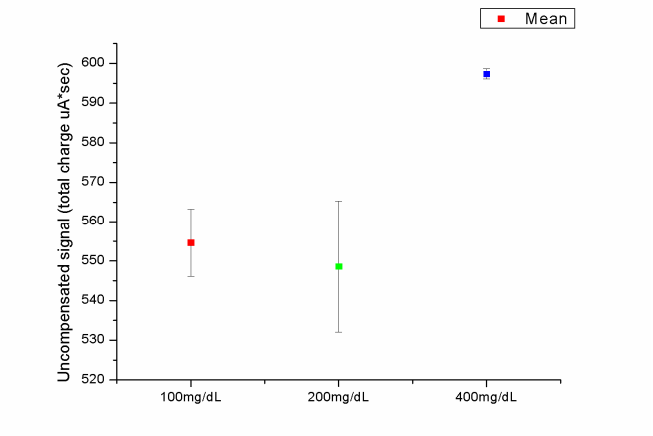

Fig. 6. Correlation between the measured charge and the real glucose concentration level.

From the skin resistance curve, we calculated a feature parameter which reflects the skin status as a whole[7]. We compensated the measured total charge value with the feature parameter. After the compensation, it shows noticeably higher correlation with the glucose concentration than uncompensated results(Fig. 7).

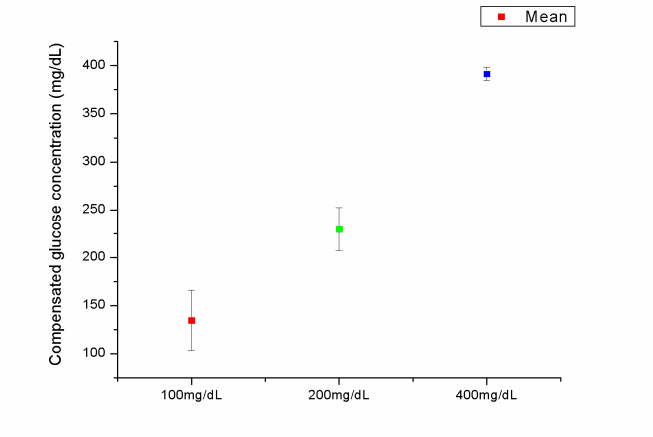

Fig. 7. Correlation between the measured charge and the real glucose concentration level after compensation by skin resistance.

IV. Discussion & Conclusion

In this experiment, we proposed that the skin resistance can be used as not only a compensation factor but also the representing parameter for skin status, such as severe perspiration or stabilization phase. Limited in vitro experiments verified this idea by providing better correlation results between compensated total charge values and the given glucose concentration than uncompensated case.

The skin resistance change implies many phenomena during the reverse iontophoresis, particularly the skin porosity. Therefore, it should be directly related to the amount of extracted glucose and it is reasonable to use the skin resistance as another feature for the estimation of the blood glucose level as well as a good index for the degree of skin stabilization in the reverse iontophoresis based glucose monitoring system. Moreover, the skin resistance can be measured easily during the reverse iontophoresis with minimal circuitry added. Future work includes further acquiring precise data and applying in vivo, in man. The result could be greatly helpful to improve the accuracy of reverse iontophoretic glucose monitoring system.

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