Totally organic electrical skin patch powered by flexible biobattery

Shotaro Yoshida¹, Hiroya Abe¹, Yuina Abe¹, Shinya Kusama¹, Kenichi Tsukada¹, Ryo Komatsubara¹ and Matsuhiko Nishizawa¹, ²

¹ Department of Finemechanics, Graduate School of Engineering, Tohoku University, 6-6-01 Aramaki-Aoba, Aoba-ku, Sendai 980-8579, Japan
² Frontier Research Institute for Interdisciplinary Sciences, Tohoku University, 6-3, Aramaki-aza Aoba, Aoba-ku, Sendai 980-8578, Japan
³ Niigata Factory, Sunarrow Limited, 5-1, Shinko-cho, Mitsuke-shi, Niigata 954-0076, Japan
⁴ Division for the Establishment of Frontier Sciences of the Organization for Advanced Studies, Tohoku University, 2-1-1 Katahira, Aoba-ku, Sendai 980-8577, Japan

E-mail: nishizawa@biomems.mech.tohoku.ac.jp

Abstract

An electrical skin patch that can be flexibly attached to the skin and activated in 30 s by adding water was developed by integrating a built-in flexible glucose/O₂ biobattery. The latter consisted of a glucose dehydrogenase (GDH)-modified anode and an iron(II) phthalocyanine (FePc)-modified cathode. The quick activation of the patch components by water addition deep inside the patch was achieved by using a flexible water-absorbing sponge containing glucose and buffer electrolyte. A patch current of about 10 µA was maintained for more than 12 h by optimizing the amount of glucose and electrolyte contained in the sponge tank. The entire patch was soft and highly flexible to conform to curved skin surfaces, owing to its thinness (<2 mm) and the flexibility of all the patch components, including the enzyme electrodes based on the carbon fabric.

1. Introduction

Skin patches have been widely studied for ubiquitous healthcare and personalized medicine applications [1–6]. Recent advances in skin patch technologies enable sensing vital information from sweat [7–13] and interstitial fluid [14–16]. In addition to diagnostic functions, medical and cosmetic treatments with electrical stimulation are important applications of skin patches. For example, wound healing of skin is accelerated by iontophoretic currents that can activate electromigration of keratinocytes [17, 18]. Iontophoretic drug delivery and wrinkle removal are also facilitated by electrical stimulation [19]. Conventional power sources for the electrical skin patches have been traditional metallic batteries that were generally heavy, rigid, and composed of hazardous materials, making them non-disposable [20, 21]. Recently, the development of wearable energy harvesters based on triboelectric, vibration-electric, photovoltaic and thermoelectric conversion have been remarkable [22–25]. As one of the options for such wearable power source, enzymatic biobatteries, which generate electricity via enzymatic oxidation of fuels such as sugars and reduction of ambient O₂ [26–53], have attracted particular attention aiming for construction of the metal-free, totally organic electrical skin patch. These biobatteries have been utilized in skin patches for wound healing [54] and iontophoretic drug dosing [55]. An organic electrochromic timer integrated with a biobattery is also useful for displaying elapsed time of the medical and cosmetic treatment [56].

Although the concept of a non-invasive biobattery-based skin patch has matured, technical issues still remain in the areas of shape conformability and quick on-site activation. The enzymatic batteries have required drying to maintain the enzyme activity during storage [44], and must be activated by moisturizing just prior to use by a simple procedure. In the present work, we describe the development of a flexible, organic skin patch that can be activated rapidly by a one-shot addition of water to generate transdermal current (figure 1). The integrated patch, dubbed the Bio-Iontophoresis Patch, is composed of a flexible biobattery and water-absorptive sponge tanks containing fuel and buffer electrolyte. A typical application is
transdermal drug delivery (figure S1 (available online at stacks.iop.org/JENERGY/2/044004/mmedia)). The patch is inactivated by freeze drying for storage, and can be re-activated simply by adding pure water. The patch design includes integrated water-sensitive paper that changes color with wetting, allowing users to verify that the patch is ready for use.

2. Methods

2.1. Fabrication and electrochemical characterization of the biobattery

Enzyme electrodes were fabricated using methods described previously [55, 57]. Briefly, 6.6 g of carbon nanotubes (CNT, Baytube) were heated at 400 °C in an oven for 11 h, cooled for more than 2 h, then sonicated in a mixture of distilled water, sulfuric acid (96%, FUJIFILM Wako Pure Chemical), and nitric acid (70%, FUJIFILM Wako Pure Chemical) (volume ratio 1:1:3) for 30 min. The CNTs in the solution were left at room temperature for 5 h, neutralized using sodium hydroxide (97%, FUJIFILM Wako Pure Chemical), and collected by a conventional suction filtration method using a φ10 μm filter, a funnel and an aspirator.

The CNTs were then frozen at −80 °C overnight and dried in a freeze-dryer. The processed CNTs were resuspended in 4 ml of a surfactant solution (1 wt% Triton-X) at a loading of 10 mg ml$^{-1}$, then sonicated using a probe sonicator to obtain a homogenous suspension. A small volume (50 μl) of the CNT suspension was dropped on to a piece of carbon fabric (CF, 1 × 1 cm$^2$, TCC-3250, Toho Tenax Co.) and dried in a vacuum oven at 70 °C, −0.1 MPa for 15 min. This was repeated two times on each side of the fabric. The CNT-modified CF (CF-CNT) was stirred in pure water under vacuum at −0.1 MPa for 1 h to remove excess CNTs and Triton-X.

The battery’s anode consisted of glucose dehydrogenase (GDH). To form the anode, 1-pyrenebutanoic acid succinimidyl ester (PBSE, FUJIFILM Wako Pure Chemical) was diluted in N,N-dimethylformamide at 5 mg ml$^{-1}$ concentration, and 80 μl of the solution was drop casted on the CF-CNT. The coated CF-CNT was dried overnight at 25 °C and put in 2 ml of a solution of 4 mg ml$^{-1}$ 4-isopropylaminodiphenylamine (IPPD, Sigma-Aldrich) in methanol for 1 h. The CF-CNT was then washed with water 3 times. Next, 40 μl of a 5.3 (for cyclic voltammetry) or 21.8 (for stability measurement) mg ml$^{-1}$ glucose dehydrogenase (GDH, Amano enzyme) solution in potassium phosphate (KP) buffer (50 mM, pH7, mixture of 26.8 mM K$_2$HPO$_4$ and 23.2 mM KH$_2$PO$_4$) was drop casted on the CF-CNT. The anode was immersed in a 1 M trehalose (FUJIFILM Wako Pure Chemical) solution for 10 min, flash frozen in liquid nitrogen for 3 min, and then freeze-dried at −50 °C under vacuum.

Modified iron(II) phthalocyanine (FePc, Tokyo Chemical Industry) was used as battery cathode. One mg of FePc was diluted in 80 μl ethanol, and the solution was drop casted on the CF-CNT (1 × 1 cm$^2$). The FePc-modified CF-CNT was dried for more than 2 h at 25 °C. To make the surface hydrophobic, the CF was additionally coated with 100 μl of a solution of 4 mg ml$^{-1}$ CNT and 12.5 mg ml$^{-1}$ polytetrafluoroethylene (PTFE, FUJIFILM Wako Pure Chemical) in 99% ethanol that was sonicated for 10 min. The coated CF was then dried in an oven at 35 °C for 15 min. The modification of CNT and PTFE was repeated twice.

The performance of the anode and the cathode was analyzed using a three-electrode system (BSA, 730C electrochemical analyzer or model 2325 potentiostat, BAS Japan), employing an Ag/AgCl reference (KCl-saturated, RE-1CP, BAS Japan) and a platinum counter electrode on a cotton sheet (0.5–1 mm thick) wetted by 300 μl of McIlvaine buffer (50 mM, pH 5.0) containing 200 mM glucose (FUJIFILM Wako Pure Chemical). Cyclic voltammetry (CV) measurements were carried out at a scanning speed of 10 mV s$^{-1}$. The performance of the biobattery was evaluated from the cell voltage upon connection with a variable external
resistance (0.022, 0.16, 0.3, 0.56, 0.75, 1.2, 2.7, 5.6, 10, 20, 47, 82, 100, 220, 330 kΩ). The current and power were derived from the cell voltage and the resistance. All measurements were carried out at room temperature, around 25 °C.

2.2. Evaluation of water absorption materials
Three kinds of sponge materials, water-absorptive polyurethane (PU) (Soflus N, aion), water-absorptive poly(vinyl) alcohol (PVA) (Belleater D, Aion), and a conventional PVA (Belleater A, Aion) were investigated. Water-sensitive paper (MN90609, Isis) 0.5 × 0.5 cm² in area was placed on top of each 1 × 1 cm², 0.1 cm-thick specimen and 100 µl of water was applied from the bottom. The time for water to be absorbed from the bottom to the top of the specimen was measured by observing the color change of the water-sensitive paper. In order to measure the water absorption speed, water was supplied to one end of the PU sponge sheet (0.5 × 14 cm², 0.1 cm-thick) with or without glucose (200 mM) and buffer (McIlvaine buffer, 200 mM).

2.3. Fabrication of the flexible patch
An outer patch covering of area 2 × 5 cm² (1.5 mm thick) with holes and a square port was fabricated by heat curing silicone pre-polymer solution in a custom-made mold (Sunarrow Ltd). Double-sided tape was applied to the back of the outer covering, and a small patch of cotton (Bemcot M-3 II, Asahi Kasei) was attached at the oxygen supply port, while two water-sensitive papers (MN90609, Isis) were placed at the water-sensing windows. The anode of area 15 × 10 mm² (0.3 mm thick) was attached under the water-sensitive paper, and the cathode (6 × 10 mm² in area and 0.3 mm thick) was attached under the cotton. The anode and cathode were connected with a lead made of PTFE-modified CF. In order to modify the fuel and buffer electrolyte, a PU tank (1 mm-thickness, Soflus N, Aion) was soaked with a mixture of fuel (glucose, 50, 200, 500, and 1000 mM, FUJIFILM Wako Pure Chemical) and buffer solution (McIlvaine buffer at 50, 200, and 500 mM, pH 5.0), then dried at 25 °C. Two PU tanks (10 × 24 mm² and 10 × 12 mm², respectively, both 1 mm thick) were placed under the anode and cathode electrodes. The perimeter of the PU tanks was covered with a flexible frame fabricated by molding silicone (Ecoflex 00-30®, Smooth-On) to ionically insulate the anode and cathode. Double-sided medical tape was put under the frame. The total thickness of the integrated patch was less than 2 mm. The bottom face of the patch was capped by PU sponge that blocks the leakage of CNT. Also the leakage of CNT from the cathode window is prevented by the immobilization with PVDF and the covering with a cotton.

2.4. Activation property and stability of the patch
Color change of the water-sensitive paper was observed from the water-sensing window during the addition of water from the bottom of the PU tank. The anode was placed on top of the tank (1 × 1 cm², 1 cm-thick) containing glucose (300 µmol) and buffer (60 µmol), and the cathode was placed on the PU tank (1 × 2.5 cm², 1 cm-thick) containing buffer (60 µmol). The integrated patch was placed on a cotton sheet, and 600 µl water was supplied through the cotton, while the trans-cotton current across a 10 kΩ load was measured using a potentiostat (BSA, 730C electrochemical analyzer).

To optimize the amount of glucose in the tank, the generated current was measured for 16 h with tanks containing various amounts of glucose (15, 60, and 150 µmol) and buffer electrolyte (60 µmol). To optimize the buffer amount modified in the tank, generated current was measured for 16 h with tanks containing various amounts of buffer electrolyte (15, 60, and 150 µmol) and glucose (60 µmol).

2.5. Generation of transdermal current
A 1 kΩ resistance was used as the external load for measurement of transdermal current. The patch containing 60 µmol glucose and 60 µmol buffer was previously activated by adding water, and was sequentially put on cotton containing an electrolyte solution (phosphate buffer saline, PBS, 50 mM, Sigma-Aldrich), as well as several spots on the skin of a human subject (on the inner and outer surfaces of an arm and on a face).

3. Results and discussion

3.1. Performance of the biobattery
Figure 2(a) shows the setup to measure the performance of the biobattery on a cotton sheet wetted with aqueous buffer solution containing 200 mM glucose. Although enzymatic batteries have been generally studied in a stirred solution of fuel in a beaker [55], the performance on cotton without stirring is practically important for application to skin patches. The hydrophilic anode was fully wetted by the solution from the
Figure 2. (a) Setup for evaluation of the biobattery on a wet cotton sheet to mimic the practical situation of a skin patch. (b), (c) Representative cyclic voltammograms at 10 mV s$^{-1}$ of the GDH-modified anode and the FePc-modified cathode on a cotton sheet wetted with a buffer containing 200 mM glucose. (d) Cyclic voltammograms of the cathode under ambient air or nitrogen. (e) A cyclic voltammogram of the cathode under nitrogen showing the redox potential of FePc. (f) Output performance of the glucose/O$_2$ biobattery on cotton, measured using load resistances of 22 Ω–300 kΩ. All data are typical results of three experiments.

cotton. The upper surface of the cathode was made hydrophobic and only the lower surface was wetted to form a three-phase boundary of a solution-electrode-air interface for O$_2$ reduction \[55, 58\].

Figure 2(b) shows a separately measured cyclic voltammogram of the GDH-modified anode at 10 mV s$^{-1}$. A maximum current density of as high as 1.5 mA cm$^{-2}$ at 0.6 V was obtained due to the large specific surface area of the CF-CNT \[55, 57\]. Figures 2(c) and (d) depict cyclic voltammograms of the FePc-modified cathode at 10 mV s$^{-1}$, showing the current of the FePc-catalyzed O$_2$ reduction reaction (ORR) that starts to increase at around 0.2 V and reached $-$1 mA cm$^{-2}$ at 0 V. By expanding the negative limit of potential scan to $-$0.2 V, the redox potential of FePc was found to be at 0.08 V (figure 2(e)), which is close to the reported value in neutral media \[59\]. The reduction of FePc started from around 0.2 V, which matches the start potential of the ORR. The capacitive property of the electrodes observed in figures 2(c)–(e) is due to the large specific surface area of the CNT-modified CF electrodes (ca. 20 mF cm$^{-2}$).

FePc is a promising cathode catalyst \[7, 60, 61\] that has recently attracted much attention among many non-precious metal-based O$_2$ reduction catalysts \[62–64\]. The low cost and high stability of FePc make it suitable for use in disposable skin patches, although its reduction potential is lower than that of the bilirubin oxidase (BOD) catalyst (0.6 to 0.2 V) that is frequently used for biobatteries \[55, 57, 58\]. An advantage of the FePc-modified electrode is that it can be stored without additional treatment such as freeze-drying with trehalose.

Figure 2(f) shows the performance of a biobattery consisting of the GDH anode (1 cm$^2$) and FePc cathode (1 cm$^2$) on cotton with a buffer containing 200 mM glucose. The open-circuit voltage of the cell was $\sim$0.3 V, which was similar to the difference between the potentials at which glucose oxidation ($-$0.1 V) and oxygen reduction (0.2 V) start to occur in cyclic voltammetry (figures 2(b), (c)). The maximum power density reached 6 $\mu$W cm$^{-2}$ at 0.2 V, which was determined by the cathode because of its comparatively inferior performance compared to the anode on the cotton.

3.2. Water absorption material for activation of patch

The enzymatic batteries need the storage in dry state and will be activated by moisturizing just prior to the use. The cotton material used in our previous patch \[58\] has problems in retaining enough fuel solution due to the larger internal voids (mm scale) and the smaller surface area of cotton fibers. In order to realize the all-in skin patch that can be activated by water in simple and quick manner, the patch requires a water adsorptive material that contains the dried-electrolyte in advance. Figure 3(a) shows the property of water absorption/retention was studied for three types of sponge materials made of a water absorptive
polyurethane (PU), a water absorbent poly(vinyl) alcohol (PVA), and a normal PVA, which have narrower internal vacancies (μm scale) and larger surface areas. A volume of water equal to that of the sponge (100 μl) was applied to the sponge from the bottom, and water absorption was detected by the water-sensitive paper placed on the top of the sponge. The time for water transfer from the bottom to the top of the sponge sheet was 2 min 30 s for the normal PVA and 15 s for a water-absorbing PVA, whereas that for a water-absorptive PU was more rapid at less than 1 s. From these results, the water absorbent PU was chosen as the optimal material for the sponge tank that can store the dried fuel and electrolytes, quickly adsorb water, and stably retain the resulting solution.

Figure 3(b) shows the water absorption speed of the PU sponge, quantified by measuring the time for the water absorption from one end to the other of a long (14 cm) sponge sheet. The sponge sheet was pre-filled with an aqueous solution of buffer and glucose, and then dried at room temperature to obtain a tank containing the powdery glucose and buffer electrolytes. During the feed of water to the dried tank, the buffer and glucose dissolve again, creating the inner solution of the biobattery. Although the water absorption speed of the glucose/buffer-modified tank (1.5 mm s⁻¹) was relatively slower than the blank tank (1.1 mm s⁻¹) due to the reduction of internal voids by the modification, these tests indicated that the PU sponge tank of 1 mm thickness integrated in the patch can absorb water within 1 s.

### 3.3. Fabrication of flexible patch

Figure 4(a) shows an exploded view of the patch. The outer covering has a square port for oxygen supply and circular windows for monitoring the color-changing water-sensitive paper. The GDH anode and the FePc cathode were coupled with the water-absorbent PU tanks, and were ionically isolated from each other by a hydrophobic flexible silicone frame. Oxygen in ambient air is supplied to the cathode through a cotton layer that physically protects the cathode from the outer environment. The upper surface of the cathode is hydrophobic for taking in gaseous oxygen, and only the lower surface is wetted to form a three-phase solution-electrode-air interface, allowing efficient ORR. The full wetting of the sponge tank of the cathode can be confirmed by observing a color change in the water-sensing window. The GDH anode was made hydrophilic so that both the top and bottom surfaces are fully wetted with the fuel/buffer solution, which can be confirmed at the window on the anode. The anode and cathode are electrically connected by a CF lead that was made water-repellent to prevent an ionic short-circuit of the anode and cathode through the lead.
Figure 4. (a) Illustrations of the patch showing its inner structure and components. (b) Photographs of the patch demonstrating high flexibility that allows conformable adherence on a human finger. (c) Illustration of the mechanism of checking the completion of water absorption via the water-sensing window. The photographs show the color change of the water-sensitive paper about 1 s after water addition.

The medical adhesive layer on the underside of the silicone frame allows tight adherence to the skin without irritation.

The outer patch covering, electrodes, tanks, and frames were all made as thin as possible to keep the total thickness of the integrated patch under 2 mm. Figure 4(b) shows pictures of the fabricated patch. The entire patch was soft and flexible enough to conform to curved skin surfaces, and adhered tightly to skin even around a finger, owing to patch’s thinness (<2 mm) and the sufficient flexibility of all components including the enzyme electrodes based on the carbon fabric modified with carbon nanotubes [55, 57, 65]. Figure 4(c) illustrates the operation of the patch. The water-sensitive paper is wetted by flow from the PU tanks, causing a color change within ~1 s. This result was consistent with the wetting speed estimated in figure 3(b).

3.4. Patch activation and stability

Figure 5(a) shows typical activation properties of the biobattery in response to supplying water from the tank. A dried patch was placed on a dry cotton sheet, and 600 µl of water was supplied through the cotton. The amount of glucose and buffer electrolyte stored in the tanks was 300 µmol (1 M) and 60 µmol (200 mM), respectively. The power generation with a load of 10 kΩ started at 10 ~ 15 s after the water addition (n = 3). The delay after water adsorption should be the time required for the dissolution of the powdered fuel and electrolytes in the tanks. After the complete dissolution (30 ~ 45 s), the internal ionic resistance of the patch became low (<200 Ω) enough for the expected performance generating a trans-cotton current of about 10 µA.

Figure 5(b) shows the stability of the output current over a longer period (16 h) measured for the activated patch on a cotton sheet filled with buffer solution. Owing to the optimized amount of glucose (60 µmol, 200 mM) and buffer electrolyte (60 µmol, 200 mM) in the PU tanks (figure S2), the current of more than 10 µA was maintained. The output current measured on a cotton without stirring initially
Figure 5. (a) Measurement of biobattery activation in response to the addition of water (600 µl) to the tanks containing glucose (300 µmol, 1 M) and buffer electrolyte (60 µmol, 200 mM). Time plot of generated current with 10 kΩ load after water addition. (b) Stability of the trans-cotton current for a longer period (up to 16 h) measured with a 10 kΩ load for the pre-activated patch containing 200 mM glucose and 200 mM buffer. Data are typical results of three experiments.

3.5. Transdermal current generation by the patch

Figure 6 shows generation of transdermal current by the patch with a 1 kΩ load. After applying water to dissolve the dry fuel and electrolytes, the patch was placed on a cotton sheet filled with an electrolyte solution for comparison, and then sequentially applied to a volunteer’s arms and face. A current of ~80 µA was observed on the wet cotton and ~10 µA on the human skin. The current of 80 µA with a 1 kΩ load is consistent with the power curve shown in figure 2(f). Then, the skin resistance in this case can be estimated to be around 20 kΩ from the current value of 10 µA. These results are the demonstrations of generating transdermal current by short term application of the patch (10 s). A longer operation will be required for the iontophoretic treatments in both cosmetic and medical purposes. For the longer operation of the pasted patch may require a countermeasure for the drying of the patch due to water evaporation especially from the oxygen supply port of the cathode, including the periodic refilling of water to the patch.

4. Conclusion

We have developed a glucose/oxygen biobattery-based skin patch that can generate transdermal current. The patch benefits from several practical improvements, including better shape conformability and quick activation times. By employing soft materials as the components of the patch and limiting the total thickness to 2 mm, the entire patch was soft and flexible enough to conform to curved skin surfaces. The quick activation with water was enabled by using a flexible water absorptive PU as the source for both fuel and electrolytes. Since this PU material can be configured three-dimensionally while maintaining its fast water absorption of ~1 mm s⁻¹ (figure S3), it will be possible to supply water to more complicated structures, e.g. the feeding of two or more series-connected higher-voltage biobatteries [57]. The water evaporation from
the oxygen supply port of the cathode can be a problem for longer-time application of the patch. Covering the port with O2 permeable thin films (e.g., PDMS) would be effective to minimize the water evaporation. Integration of the patch with porous microneedles that penetrate the stratum corneum layer of the skin [66, 67] will also increase the transdermal current by decreasing the skin resistance.

Acknowledgments

This work was partly supported by Tohoku University Frontier Research program (FRiD) and by Grand-in-Aid for Scientific Research A (18H04158) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The authors acknowledge Ryo Sato, Hideaki Ikeda, Yutaka Kuwabara, Kazuhisa Yahachi and Shuji Koga at Sunarrow Limited for helpful discussion.

Ethical statement

All procedures performed in studies involving human participants were in accordance with the standards of the Ethics Committee of the Graduate School of Engineering, Tohoku University (16A-4) and with the 1964 Helsinki declaration and its later amendments. Prior to the experiments, the purpose of this study was explained to subjects who signed the university institutional approved informed consent agreement.

ORCID iDs

Hiroya Abe https://orcid.org/0000-0002-8847-1581
Matsuhiko Nishizawa https://orcid.org/0000-0002-9423-0952

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