Video Article

Fabrication and Characterization of a Conformal Skin-like Electronic System for Quantitative, Cutaneous Wound Management

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Abstract

Recent advances in the development of electronic technologies and biomedical devices offer opportunities for non-invasive, quantitative assessment of cutaneous wound healing on the skin. Existing methods, however, still rely on visual inspections through various microscopic tools and devices that normally include high-cost, sophisticated systems and require well trained personnel for operation and data analysis. Here, we describe methods and protocols to fabricate a conformal, skin-like electronics system that enables conformal lamination to the skin surface near the wound tissues, which provides recording of high fidelity electrical signals such as skin temperature and thermal conductivity. The methods of device fabrication provide details of step-by-step preparation of the microelectronic system that is completely enclosed with elastomeric silicone materials to offer electrical isolation. The experimental study presents multifunctional, biocompatible, waterproof, reusable, and flexible/stretchable characteristics of the device for clinical applications. Protocols of clinical testing provide an overview and sequential process of cleaning, testing setup, system operation, and data acquisition with the skin-like electronics, gently mounted on hypersensitive, cutaneous wound and contralateral tissues on patients.

Video Link

The video component of this article can be found at https://www.jove.com/video/53037/

Introduction

In clinical study and biomedical research, monitoring of wound healing has focused on an invasive method that is based on the histological evaluation of tissue morphologic change in wounds[1,2]. Recently, rapid advancements in electronic technologies enable the development of high-precision imaging and analysis tools that can visually inspect the wound healing process via digital imaging[3,4] or confocal scanning microscopy and spectroscopy[4,5]. However, those imaging approaches require high cost, complicated optical tools and operations, and more importantly, patients need to be immobilized during testing. Therefore, there exists a need for new devices and systems that are quantitative, non-invasive, easy-to-use, inexpensive, and multifunctional to offer more accurate wound management.

Here, we introduce a skin-like electronic system that provides precise, real-time mapping of temperature and thermal conductivity and delivers a precise level of heating at wound sites via conformal lamination of the device non-invasively. This device presents a class of technology, skin-mounted epidermal electronic systems that are designed to match to mechanical and material properties (total thickness, bending stiffness, effective moduli, and mass density) of the epidermis[6-9].

The device is designed in a biocompatible, skin-friendly, water-proof, and reusable form that can be washed and disinfected for clinical applications on patients[10]. The conformal electronic device mounted near the wound tissues captures the inflammation phase (one of wound healing process), caused by increased blood flow and enzymatic reactions to the wound[11,12], through quantitative recording of temperature[8] and thermal conductivity[13], correlated to hydration. Experimental and computational studies determine an optimal mechanics design to accommodate natural motions and applied strains without mechanical fracture and capture the underlying physics of stretching mechanics of the skin-like electronics that laminates conformally on the skin surface, which offers acquisition of high fidelity signals.

The protocols described in this article present the methods of microfabrication for skin-like electronic systems, testing preparation including device cleaning, equipment setup in a clinical setting, and clinical applications for quantitative monitoring of temperature and thermal conductivity on cutaneous wounds.

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Protocol

The experiments for device fabrication, skin lamination, and characterization shown in **Figures 1, 2**, and **4** involved two volunteers, all performed in the Bio-interfaced NanoEngineering Laboratory at Virginia Commonwealth University (VCU), Richmond, VA, USA. This study was approved by the VCU Institutional Review Board (protocol number: HM20001454) and followed the research guidelines from the VCU Human Research. The device and clinical data shown in **Figures 3 and 5** were acquired from the published article[10] where the experiments on patients were conducted under the protocol (number: STU69718) approved by the Institutional Review Board, Northwestern University, Chicago, IL, USA.

1. Device Fabrication

NOTE: **Figure 2** presents schematic illustrations for the overall fabrication process.

1. Prepare a carrier substrate
    1. Cut a bare 3 in silicon (Si) wafer into the desired size of the electronics by using a diamond blade.
    NOTE: About half Si wafer gives an ideal size for the wound device.
    2. Degrease Si wafer with acetone and isopropyl alcohol (IPA). Rinse the wafer with deionized (DI) water and then dry with nitrogen and dehydrate on a hotplate at 110 °C for 3 min.
    3. Prepare 11 g of polydimethylsiloxane (PDMS) mixture with 10:1 volume ratio of base and curing agent and degas the mixture in a vacuum chamber for an hour.
    NOTE: PDMS is used for a dry pattern retrieval and transfer printing after the microfabrication, which is preferable to the wet chemical (acetone)-based approach from the previous study[7].
    4. Spin coat 5 g of mixed PDMS solution on the wafer at 3,000 rpm for 1 min and fully cure on a hotplate at 150 °C for 30 min.

2. Deposit materials and pattern electronics
    1. Treat the PDMS-coated wafer with ultraviolet (UV)/ozone by using a UV lamp (8.9 mW/cm^2) for 3 min to make the surface hydrophilic.
    NOTE: The hydrophilic surface offers uniform coating of additional layers on the PDMS.
    2. Spincoat polyimide (PI; 2 ml) on the PDMS coated wafer, by pipetting, at 4,000 rpm for 1 min to form a 1.2-μm-thick layer, pre-bake on a hotplate at 150 °C for 5 min, and post-bake at 250 °C for 2 hr.
    3. Deposit chromium (Cr) to form a 20 nm-thick layer and then deposit copper (Cu) to form a 3 μm-thick layer by using electron-beam (e-beam) evaporation (base pressure: ~1×10^{-7} Torr, deposition pressure: ~1×10^{-6} Torr, deposition rate: 1 – 5 Å/s). Monitor the film thickness by the deposition controller interface embedded in the evaporator.
    NOTE: The thick layer of Cu provides enough levels of electrical conductivity on the microscale resistors of the device and thin Cr layer is used to promote adhesion between PI and Cu.
    4. Spincoat a photoresist (2 ml) with three steps at 900 rpm for 10 sec, 1,100 rpm for 60 sec, and 4,000 rpm for 20 sec and then cure it on a hotplate at 75 °C for 30 min.
    NOTE: The sequential steps described above were used to deposit a thick (> 10 μm) photoresist.
    5. Align Cu electronic patterns (sensors; fractal 'Peano' design with 35 μm in width and interconnects; serpentine open mesh design with 50 μm in width) at the center of the Si wafer by using a UV aligner (power: 10 mW/sec) with exposure time 25 s.
    NOTE: The fractal structures are used to provide superior mechanical stretchability, compared to merely meandering features[14].
    6. Develop the photoresist in a diluted base developer (1:2 ratio of developer and DI water) for a minute, rinse with DI water, and dry with nitrogen. Inspect the patterns (Cu fractals and interconnects) using a microscope to confirm the feature size and find any defects from particulates.
    NOTE: If there are any unwanted defects, then remove photoresist by rinsing with acetone/IPA/DI water. After drying with nitrogen, repeat the steps from 1.2.4 to 1.2.6.
    7. Etch the Cu layer on the Si wafer by immersing in a wet chemical etchant for ~6 min (10 ml; mixture of ammonium persulfate and water in ratio of 1:4; etch rate of 8 nm/sec in 40 °C), rinse with DI water, and dry with nitrogen. Inspect the patterns using a microscope for any over-etched patterns.
    NOTE: If the patterns are over-etched, it may cause unwanted sharp edges of the features, which could lead to mechanical fracture during device handling and washing process. The prior testing results showed that more than ~20% over-etching of the original patterns caused the aforementioned issues.
    8. Etch the Cr layer with reactive ion etching (RIE; pressure: 300 mTorr, power: 200 W, CF_4 gas: 5 sccm, O_2 gas: 10 sccm) for 5 min. Inspect the patterns.
    NOTE: For etching of the Cr layer, the RIE process is preferable to wet chemical etching that causes unfavorable reaction with the Cu layer.
    9. Remove the remained photoresist on the metal layers by immersing the wafer in acetone (10 ml), IPA (10 ml), and DI water (20 ml), respectively. Then, dry it with nitrogen.
    10. Spincoat PI (2 ml) on the metal deposited wafer, by pipetting, at 4000 rpm for 1 min to form a 1.2-μm-thick layer, pre-bake on a hotplate at 150 °C for 5 min, and post-bake at 250 °C for 2 hr.
    11. Spincoat a photoresist (2 ml) with three steps at 900 rpm for 10 sec, 1,100 rpm for 60 sec, and 4,000 rpm for 20 sec and then cure it on a hotplate at 75 °C for 30 min.
    12. Align PI patterns to encapsulate the Cu electronics (sensors; fractal 'Peano' design with 35 μm in width and interconnects; serpentine open mesh design with 250 μm in width) with the pre-defined Cu fractals and interconnects by using a UV aligner (power: 10 mW/sec) with exposure time 25 sec.
    13. Develop the photoresist with a diluted developer (1:2 ratio of developer and DI water) for a minute, rinse with DI water, and dry with nitrogen. Inspect the patterns using a microscope to confirm the feature size and find any defects from particulates.
    NOTE: If there are any unwanted defects, then remove photoresist by rinsing with acetone/IPA/DI water. After drying with nitrogen, repeat the steps from 1.2.10 to 1.2.13.
    14. Etch the PI layer with RIE (pressure: 170 mTorr, power: 150 W, O_2 gas: 20 sccm) for 25 min. Inspect the patterns.

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15. Remove the remained photoresist by immersing the wafer in acetone (10 ml), IPA (10 ml), and DI water (20 ml), respectively. Then, dry it with nitrogen.

3. Prepare an elastomeric membrane
    1. Prepare a 10 g of encapsulating silicone mixture (1:1 volume ratio of base and curing agent) and add a black ink[15] with one to one volume ratio, which is to facilitate control measurements of temperature variation on the skin using an infrared camera.
    NOTE: The utilized silicone (clear encapsulating rubber) provides unique characteristics of low viscosity, optical clarity, and electrical isolation/protection to the device[16].
    2. Spincoat 8 g of the mixture in a petri dish at 150 rpm for 1 min to form a 500 µm thick elastomeric membrane and cure at RT for O/N.
    NOTE: The material needs to be placed on a flat surface for uniform thickness.
    3. Cut the membrane into the desired size of 70 mm x 30 mm by using a sharp razor blade and gently detach it from the petri dish.

4. Retrieve and transfer electronics
    1. Cut a water soluble tape (25 mm x 80 mm) and gently laminate onto the fabricated electronic patterns and place them on a hotplate at 130 °C for 3 min.
    NOTE: Temperature elevation expands the PDMS layer on the Si wafer to help dissociation of the electronic patterns from the surface.
    2. Detach the tape rapidly from the PDMS/Si wafer to retrieve the electronic patterns.
    3. Deposit a 20 nm thick Cr (for adhesion) followed by a 50 nm thick silicon dioxide (SiO_2) on retrieved patterns by e-beam evaporation.
    4. Treat UV/ozone by using UV lamp (365 nm, 8.9 mW/cm^2) on the targeted silicone membrane for 2 min to activate the surface.
    5. Transfer the patterns to the silicone membrane by placing the retrieved patterns on the tape to the desired location and evenly adding pressure from top side of the patterns down to the substrate. Apply water to dissolve the tape for 5 min.
    NOTE: The described process of materials transfer is facilitated by covalent bonding (Si-O-Si) between the deposited silicon dioxide and the UV-activated silicone substrate[17].
    6. Peel off the tape, rinse with DI water, and dry on a hotplate at 90 °C for 1 min.

5. Encapsulate the device using a silicone membrane
    1. Prepare an 10 g of encapsulating silicone mixture (1:1 volume ratio of base and curing agent).
    2. Cover the cable contact pads with a rectangular PDMS piece (22 × 6 × 1 mm^3) by van der Waals bonding with the bottom silicone membrane, to avoid silicone coating the pads.
    3. Spincoat the 5 g of silicone mixture at 4,000 rpm for 1 min to form a 5 µm thick layer on the transferred electronics and then cure at RT for O/N.

6. Connect a flexible ribbon cable for data acquisition
    1. Apply liquid steel flux (0.5 ml), by pipetting, on the connector pads for 3 sec to make clean surface.
    2. Bond a thin, flexible ribbon cable on the contact points with pressure at high temperature (> 60 °C). A typical hair straightener offers easy handling and bonding.
    NOTE: The micro-film cable is preferable to the conventional hard-wire soldering to avoid any mechanical fracture of the transferred metal membranes on a silicone.
    3. Check the electrical connection using a digital multimeter. The resistance value is expected less than 1 Ohm between the sensor pad with one end and the other end of the film cable (distance: ~1 cm apart).
    4. Bond the other end of the ribbon cable to a customized printed circuit board with the same strategy described in the step 1.6.2.
    5. Check the electrical connection using a digital multimeter.
    6. Connect the device with the data acquisition hardware by soldering conventional wires on PCB.

2. Clinical Testing

1. Clean the device using a disinfectant solution
    1. Prepare 205 g of a diluted disinfectant solution (40:1 volume ratio of water and solution).
    2. Spray the solution (10 g) on the device and soak it for 10 min.
    NOTE: The diluted disinfectant cleaner can be stored at RT.
    3. Rinse with water three times and dry it with clean tissues.

2. Set up a series of equipment for device testing
    1. Prepare and connect a lock-in amplifier with a current source, a multiplexer, and the custom software installed on a laptop computer for data recording.
    2. Place an infrared camera on a tripod and focus on a target object for thermography as a reference.
    3. Set up system parameters of a lock-in amplifier to measure thermal conductivity (frequency: 1 & 3 Hz; time constant: 3 and 1 sec; sensitivity: 1 mV; dynamic reserve: high reserve) and temperature (frequency: 997 Hz; time constant: 300 msec; sensitivity: 2 mV; dynamic reserve: low noise) with the applied constant current (2 mA).
    4. Connect two wound devices, prepared by microfabrication and transfer printing and mounted on wound and contralateral sites, to the multiplexer right before recording data from a patient.

3. Record temperature and thermal conductivity
    NOTE: The data acquisition software is custom-made, which can remote control the lock-in amplifier for real-time data monitoring and saving. In the temperature measurement, each data point is measured every 300 msec for 20 sec. The set of data for the first 10 sec and next 10 sec are used to calculate the average temperature value and standard deviation, respectively. The recorded data are then saved as a comma-separated value file, which is used to plot a graph for comparison with data from infrared thermography. In the measurement of thermal conductivity, the 3Ω signals are directly read from the hardware screen (amplifier), which is then utilized to calculate the thermal conductivity analytically.

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1. Gently rub the device application sites on the skin using antiseptic alcohol wipes[10].
2. 2.3.2) Laminate two devices on the desired skin locations by gently pressing the device to the skin with fingers to facilitate the soft bonding: one on the surgical wound site and the other on the contralateral location as a reference.
3. Measure the electrical voltage (3Ω), related to thermal conductivity, of the device by starting the data acquisition.
4. Evaluate the obtained data to verify the conformal contact of the device to the skin; abnormal value (< 0.1 W/mK) shows bad contact of the device.
5. Measure the electrical resistance to determine temperature distribution and record data through the custom software.
6. Take optical and IR images of two devices on the skin.
7. Compare temperature values from the IR images with the data recorded from the wound device (2.3.5). Add both values to separate columns in a customized spreadsheet.

4. Analyze the recorded data
    1. Export the recorded data to the customized template to automatically calculate temperature and thermal conductivity from an array of sensors in the device.
    2. Plot the data (temperature and thermal conductivity according to the sensor location on a different time scale) for comparison over the course of one month (four sets of data on day 1, 3, 15, and 30).
    3. Analyze the data by comparing a series of temperature and thermal conductivity data according to time; Values with sudden elevation or drop tell the change of wound healing phase and/or unexpected abnormality on wound sites.

Representative Results

Figure 1 presents an overview of the characteristics of the conformal, skin-like electronic system, designed for quantitative, cutaneous wound management on patients. The multifunctional electronic device consists of microscale fractal structures[3,14] and filamentary serpentine traces[9,17] on a thin elastomeric membrane that offers exceptional mechanical stretchability and bendability. The compliant device that is completely enclosed by silicone layers enables gentle, reversible lamination on the skin through van der Waals interactions alone. The unique characteristics of the device include biocompatibility, waterproofness, ease-of-use, and mechanical flexibility for the use in realistic clinical settings.

The integration of hybrid materials such as polymers and a metal (silicone, polyimide, and copper) yields an electrically safe, waterproof, and biocompatible device (**Figure 2A**). An array of fractal (copper; Cu) resistors (35 μm in width and 3 μm in thickness) is placed at the neutral mechanical plane, by enclosed polyimide (PI, 1.2 μm in thickness) layers, to minimize applied bending strains on the core material (Cu) in clinical applications.

The total thickness of the device on a silicone membrane is only ~600 μm by offering extreme bendability. The schematic illustrations in **Figure 2B** describe the microfabrication process of the skin-like electronic system. The fabrication method combines the conventional microfabrication techniques (metallization, photolithography, and etching) with the newly developed transfer-printing techniques (retrieval, transfer, and bonding)[9,14,18,19]. This type of a device can be scaled up by using large scale transfer printing with an automated printing equipment[20,21].

Figure 3 summarizes the mechanical stretchability and electrical functionality of the skin-like electronics, reported in the prior work[10]. Mechanics and materials study by the finite element method (FEM) offers the optimal system design to accommodate natural motions and applied strains, involved in the clinical use, without mechanical fracture (**Figure 3A**, top). The experimental study that presents mechanical behavior of the fractal structure with tensile strains up to 30% (**Figure 3Aa**, bottom) shows a good agreement with the FEM results. The device with microscale resistors is used for quantitative measurement of temperature and thermal conductivity and delivering precise, localized heating (**Figures 3B – 3D**). The calibration curve of electrical resistance according to temperature change was obtained by using an infrared camera and a high-sensitivity hot plate (**Figure 3B**). The evaluation method of the measured thermal conductivity was adapted from the 3 omega technique[13] that uses 3 omega voltage signals at two different alternating current frequencies (**Figure 3c**). Applied electrical current (35 mA with 10 mW) to the fractal resistors occurs Joule heating, which offers controllable temperature actuation in a therapeutic mode (**Figure 3D**).

For practical, clinical applications, the suggested cleaning process of the hand-held device involves disinfection prior to use on patients. Spraying of a disinfectant solution on the waterproof device and following rinsing in water three times prepares the device for clinical testing (**Figures 4A and 4B**). The assessment of qualitative biocompatibility of the device utilizes a digital contact microscope to visually inspect the skin surface (**Figure 4C**), which investigates the change of the skin color and texture over multiple cycles of use on patients. An infrared (IR) thermography can make a quantitative assessment of the skin conditions for about two weeks (**Figure 4D**) since the side effects such as erythema causes temperature elevation[22]. The examined devices are laminated near the wound tissues and the contralateral location (as a reference). Recording of relevant parameters of temperature and thermal conductivity is conducted using a data acquisition system and IR imaging in an exam room (**Figures 4E and 4F**).

Figure 5 presents representative data of quantitative measurement of cutaneous wound healing on a patient from a prior study[10]. A series of photos in **Figure 5A** shows the monitoring process of wound healing with the skin-mounted device over the course of one month. The wound device dyed with a black ink was laminated near the surgical wound. Pen marks on the skin guided the mounting of the device on the same location for quantitative data comparison from day 1 to day 30. Measurement of temperature and thermal conductivity variation using an array of sensors in the device and comparison between the wound and reference sites captures the wound healing phase, inflammation (**Figures 5B – 5E**). The highly sensitive, six sensors in the wound device were able to capture minimal change of the body temperature and point intense inflammation on Day 3 (**Figures 5B – 5C**) and record variation of thermal conductivity (**Figures 5D – 5E**). A set of reference data was measured from the contralateral side as a control.

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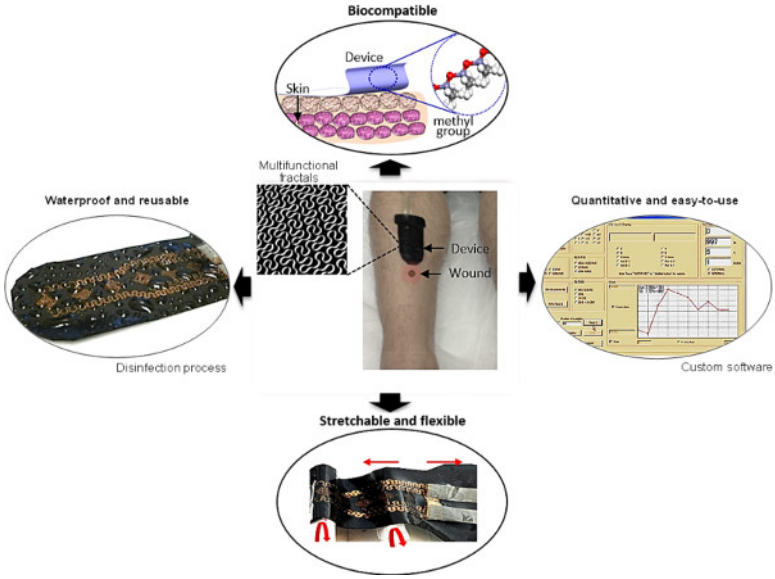

Figure 1. Overview of characteristics of the skin-like, wound monitoring device on a patient. Please click here to view a larger version of this figure.

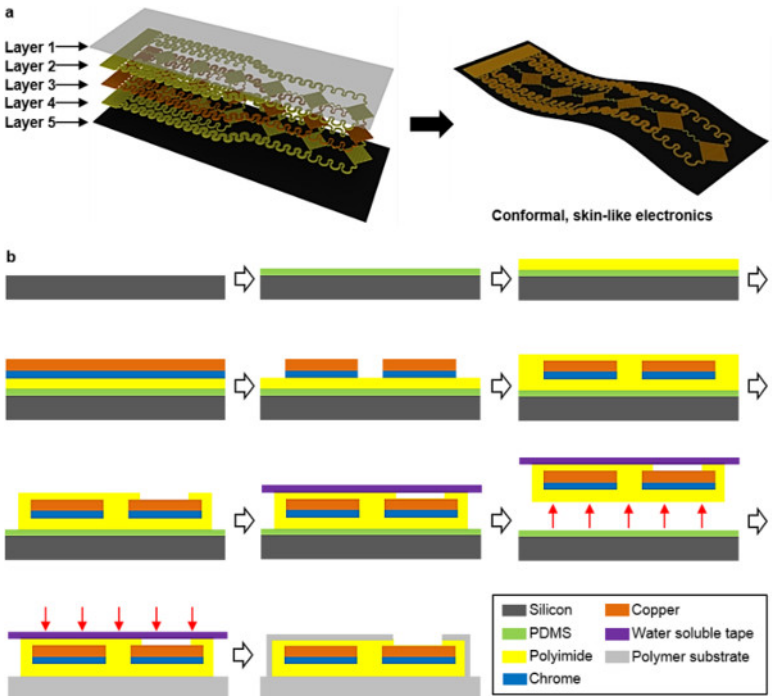

Figure 2. Device fabrication. (A) Schematic illustration of the device layouts (left; layer 1: transparent silicone at the top, layer 2: PI, layer 3: Cu, layer 4: PI, and layer 5: black silicone at the bottom) and the completed, flexible/stretchable electronics (right). **(B)** Illustration of the step-by-step fabrication process (cross-sectional view). Please click here to view a larger version of this figure.

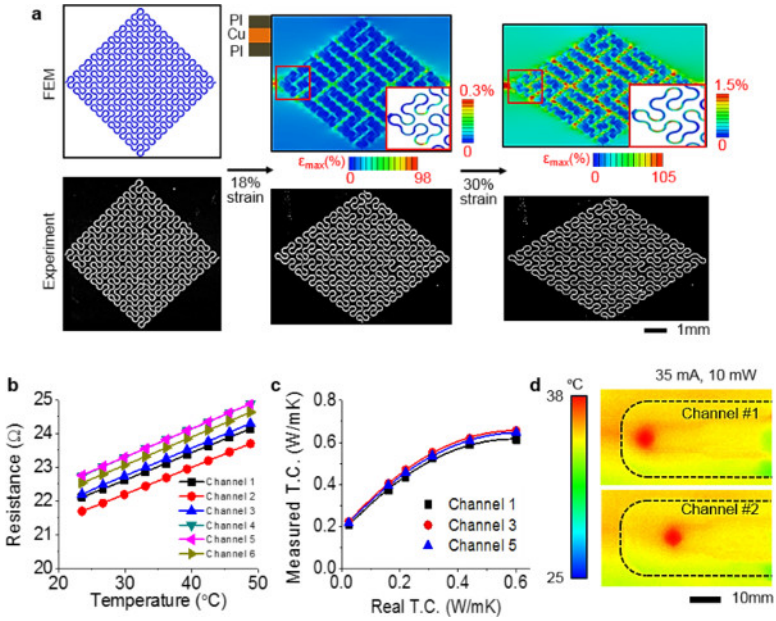

Figure 3. Device characteristics (reproduced with permission from *Advanced Healthcare Materials*, 3 (10), 1597-1607, 2014)[10]. (A) Finite element method (FEM) results (top) and the corresponding experimental results (bottom) of a fractal structure under uniaxial tensile strains up to 30 %. **(B)** Measurement of temperature using six sensors for device calibration. **(C)** Measurement of thermal conductivity using three sensors for device calibration. **(D)** Infrared thermography of the device that was used as a micro-heater with localized Joule heating. Please click here to view a larger version of this figure.

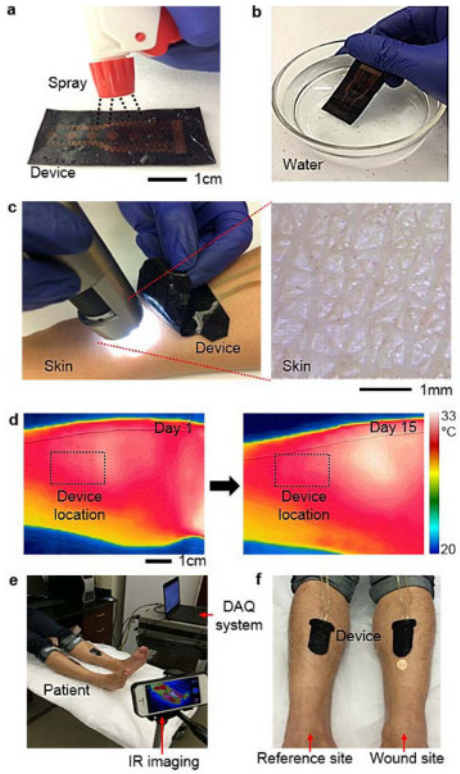

Figure 4. Clinical testing process. (A) Disinfection of the device using a cleaning solution. **(B)** Rinsing with water to clean the surface for clinical testing. **(C)** Skin assessment using a digital contact microscope (left) and magnified view of the skin (right). **(D)** Infrared thermography of the skin for quantitative assessment of temperature variation. **(E)** Clinical setting for wound management in an exam room. **(F)** Magnified photo of the laminated devices near the wound (right leg) and contralateral site (left leg) tissues. Please click here to view a larger version of this figure.

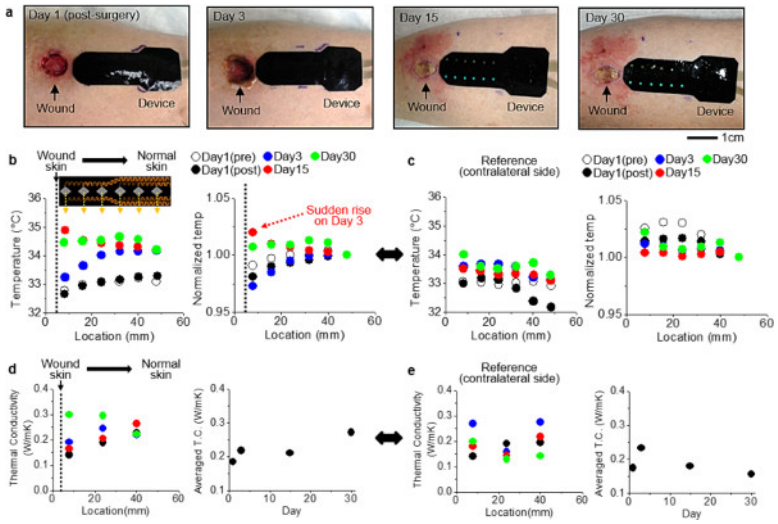

Figure 5. Representative data of quantitative management of wound healing with the device (reproduced with permission from *Advanced Healthcare Materials*, 3 (10), 1597-1607, 2014)[10]. (A) Photos of the wound with the device over the course of a month. **(B)** Recording of temperature distribution near the wound for one month with six sensors in the device (inset). **(C)** Recording of temperature distribution on a contralateral location as a reference. **(D)** Recording of thermal conductivity near the wound for one month with three sensors in the device (inset). **(E)** Recording of thermal conductivity on a contralateral location as a reference. Please click here to view a larger version of this figure.

Discussion

This article highlights the methods and protocols to fabricate a conformal, skin-like electronics system that enables conformal lamination near the wound tissues, which offers quantitative measurement of skin temperature and thermal conductivity mapping on the skin.

The key features include the utilization of novel techniques of materials transfer printing and hard-soft materials integration to design and develop the flexible/stretchable, soft electronic device. The use of biocompatible, electrically safe, silicone layers that completely enclose the device allows the electronics to be used for the first time in a realistic clinical setting, cutaneous wound management on patients.

In the protocol of device preparation, the following steps are critical to enhance the fabrication yield. Wet chemical etching of the metal layer (Cu) in the device should involve extreme time control since the etching rate is faster than other metals. The major drawback of Cu over-etching is the change of the combined electrical resistance of the device, which requires additional optimization and adjustment of equipment parameters in the data acquisition system. It should be noted that multiple layers of a water soluble tape needs to be used to avoid fracture during retrieval process of the electronics dissociated from a carrying PDMS. After the transfer printing of electronics with a water soluble tape, it is very important to completely remove any residue from the dissolvable material (polyvinyl alcohol) using multiple rinsing with DI water. In the process of cable bonding to the device, extra caution is required since the device is on a highly compliant and bendable material (low-modulus silicone), while the cable is thin plastic. Thus, careless handling of the device may lead to cause fracture or plastic deformation of metal resistors.

The device characterization and evaluation reveals some limitations in the clinical use. The data acquisition process using a thin cable still requires the connection with a series of equipment, which hinders continuous, long-term recording of skin parameters, relevant to wound management. The measured electrical signals accompany the downstream analysis for diagnosis, which limits on-site/point-of-care use of the device and system.

Further improvements of the electronic system include the development of the integration of a wireless power supply and telecommunication system with the device and smart-app interface that monitors the skin parameters, collects the data, and diagnoses automatically for alerting to medical personnel.

In conclusion, new strategies and methods of mechanical analysis and materials processing present a class of technology to develop a conformal, skin-like electronic system for quantitative, cutaneous wound management on patients. The biocompatible, waterproof, easy-to-use, mechanically compliant device provides the functions and characteristics for the use in the clinical settings. This type of electronic system has a potential to address important issues in chronic wound management.

Disclosures

The authors declare that they have no competing financial interests.

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contributions for the device and clinical data (**Figures 3 and 5** in this paper), acquired from the published article[10]. W.-H.Y thanks Yoshiaki Hattori for the custom-made, data recording software.

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