A multifunctional electronic suture for continuous strain monitoring and on-demand drug release

Surgical sutures are widely used to close wounds in the skin. However, monitoring of the wound integrity and promoting tissue regeneration at the same time still remain a challenge. To address this, we developed a drug-releasing electronic suture system (DRESS) to monitor the suture integrity in real-time and to enhance tissue regeneration by triggered drug release. We expect DRESS to provide an insight into multifunctional sutures which offer additional diagnostics and therapeutic options for clinical applications.
A multifunctional electronic suture for continuous strain monitoring and on-demand drug release†

Yeontaek Lee,‡a Hwajoong Kim,‡b Yeonju Kim,‡a Seungbeom Noh,b Beomsoo Chun,‡a Jinho Kim,b Charnmin Park,‡a Minyoung Choi,‡b Kijun Park,a Jaehong Lee*b and Jungmok Seo‡a

Surgical sutures are widely used for closing wounds in skin. However, the monitoring of wound integrity and promoting tissue regeneration at the same time still remains a challenge. To address this, we developed a drug-releasing electronic suture system (DRESS) to monitor the suture integrity in real-time and enhance tissue regeneration by triggered drug release. DRESS was fabricated by using a single fiber with a core–shell structure consisting of a stretchable conductive fiber core and a thermoresponsive polymer shell containing drugs. The highly conductive fiber core acts as a strain sensor that enables continuous monitoring of suture strain with high sensitivity (a gauge factor of ∼686) and mechanical durability (being able to endure more than 3000 stretching cycles). The thermoresponsive shell layer composed of flexible poly(vinyl alcohol) (PVA) grafted onto poly(N-isopropylacrylamide) (PNIPAm) facilitates on-demand drug release via Joule heating. The results of an in vitro scratch assay showed a 66% decrease in wound area upon heat-activation after 48 hours demonstrating the stimuli-responsive therapeutic efficacy of DRESS by promoting cell migration. Moreover, ex vivo testing on porcine skin demonstrated the applicability of DRESS as a electronic suture. The approach used for DRESS provides insight into multifunctional sutures and offers additional therapeutic and diagnostic options for clinical applications.

1. Introduction

A suture is one of the most common surgical instruments to facilitate wound healing by sealing the wound after incision or laceration. There are various types of sutures that are classified according to material (natural or synthetic), biodegradability (absorbable or non-absorbable), and structure (monofilament or multifilament). In particular, for wound closure of skin tissue, nonabsorbable sutures are preferred because byproducts of absorbable sutures during the degradation lead to additional scar tissue formation near the sutured area.1 In addition, acute wound failure frequently occurs on the sutured skin tissue due to dynamic tensile strength generated by the movements required for daily life. If excessive tensile strength is applied to the sutured wound site at an early stage of healing, the overall healing process can be significantly delayed, which can lead to wound failure and tissue necrosis.2 To minimize wound failure and scar tissue formation, it is essential to enhance tissue regeneration efficiency and to continuously monitor the suture integrity over time. However, this is not easy because the sutured site is usually covered with a dressing to prevent contact with air and infectious contaminants.3 In addition, frequent dressing changes for monitoring the wound healing process can cause tissue regeneration delay and peripheral skin problems.4

To address these limitations, there have been attempts to develop drug-eluting sutures that can enhance tissue regeneration or patchable electronics that can sense the physiological information (e.g., pH and tensile strain) at the wound site. Chen et al.5 developed a braided silk sutures with polycaprolactone (PCL) containing levofloxacin hydrochloride that showed excellent antimicrobial activity against both Escherichia coli and Staphylococcus aureus. Despite its excellent antimicrobial properties, the drug-eluting PCL coating layer is susceptible to the mechanical stress of suturing, which leads to delamination of the coating layer from the suture surface. Moreover, the drug-loaded PCL layer was designed to provide a sustained drug-release profile, and so additional drug doses were required at the early stage of wound healing or emergent clinical situations requiring high drug doses. Mostafalu et al.6 reported patchable microfluidic networks interconnected with electronic circuitry to monitor chemical markers (pH and glucose level) for the wound healing process. However, separating the bulky ele-
tronic circuits anchored near the wound site became problematic in practice. Similarly, Schachtrupp et al.\textsuperscript{7} fabricated an implantable force sensor that can monitor dynamic changes in the tension of sutures during the closure of a median laparotomy. However, the implantation of the sensor at the wound site posed a high risk of causing inflammation and the foreign body response that can worsen the healing process.\textsuperscript{8}

Inspired by spider silk and muscle, there have been recent attempts to integrate functional sensors and stimuli-responsive polymers into a single fiber.\textsuperscript{9–11} These fiber-type sensors show high conductivity and can be effectively anchored at the wound site to measure glucose level, pH, and various ion concentrations. Furthermore, polymers that can respond to changes in various stimuli (e.g., pH, temperature, mechanical force, and electric/magnetic fields) have been used for controlled drug release. However, these multifunctional fiber sensors are not suitable for measuring strain that directly indicates suture integrity. Moreover, releasing drugs in a controlled manner in response to spatial and temporal changes in the stimuli is challenging. Hence, wound healing treatment by integrating a real-time suture strain monitoring sensor and controlled drug-release system into a single suture fiber still remains a challenge.

In this study, we developed a multifunctional drug-releasing electronic suture system (DRESS) composed of a fiber strain sensor core and a thermoresponsive polymer shell containing drugs. DRESS continuously monitors the strain occurring at the suture site and releases drug molecules on-demand via Joule heating. The highly conductive core fiber was fabricated by repeated absorption and reduction steps with Ag precursors on commercialized multifilament fiber. The core fiber acts as a strain sensor that can monitor the strain of the sutures in real-time with ultrahigh sensitivity (a gauge factor (GF) of $\sim$686) and durability (more than 3000 stretching cycles). The thermoresponsive polymer was synthesized by grafting poly(N-isopropylacrylamide) (PNIPAm) to flexible poly(vinyl alcohol) (PVA) via esterification. PVA:PNIPAm ratio was optimized to maximize drug loading capacity and thermoresponsibility, resulting in 98.2 ± 19.5% enhanced drug release when the heat was applied via Joule heating. Moreover, to release the same level of the drug regardless of strain levels applied to DRESS, the core fiber can calibrate its heat flux using a closed-loop voltage control unit. Despite their multifunctionality, DRESS maintained a single fiber shape and shows high stretchability and tensile strength. As shown in Fig. S3, the fracture strain of DRESS clearly demonstrates a well-defined core–shell structure. DRESS has a multilayer structure consisting of the multifilament fiber strain sensor core (the gray-colored part) and two layers of the shell (blue: PDMS layer and red: PVA–PNIPAM). The diameter of the fiber strain sensor was relatively uniform with an average value of 300 μm and the overall diameter of DRESS was around 600 μm. Despite a series of coating processes, DRESS showed high stretchability and tensile strength. As shown in Fig. S3, the fracture strain and tensile strength were slightly decreased as Ag nanoparticles were incorporated. This can be attributed to the increase in the stiffness due to reducing agent and rigid Ag nanoparticle. However, tensile strength was increased again as PDMS and PVA–PNIPAM were coated. Also, the fracture strain of DRESS still remains over 450%, indicating the high stretchability of DRESS. Moreover, the surface of DRESS shows a smooth morphology, thereby suggesting its enhanced biocompatibility so that cells can grow around the suture site with high cell viability (Fig. S4†).

2. Results and discussion

2.1. The design and fabrication of DRESS

Fig. 1A shows a schematic of DRESS and its application. DRESS is composed of a multifunctional electronic suture that can be integrated with a flexible printed circuit board (FPCB) to continuously monitor the applied strain at the suture site with on-demand drug-release capability. A “core–shell” multilayered structure of DRESS allows multiple functionalities, including strain monitoring and on-demand drug release. As a core material, Ag nanoparticles were embedded into polyurethane multifilament fiber. Due to the percolated network and high conductivity of the Ag nanoparticles, the core fiber displays high electrical conductivity enabling continuous strain monitoring and heat flux control.\textsuperscript{12} Subsequently, the thermoresponsive polymer complex comprising poly(vinyl alcohol) (PVA)/poly(N-isopropylacrylamide) (PNIPAm) was coated onto the Ag-based core fiber. The PVA/PNIPAm coating shows excellent swelling and deswelling behavior upon temperature changes, thereby making it suitable for drug delivery systems. The swelling and deswelling behavior enabled the successful loading of regenerative drugs into DRESS for release on-demand.

The fabrication process of the electronic suture is shown in Fig. S1.\textsuperscript{†} First, a fiber strain sensor was fabricated by incorporating Ag nanoparticles into a commercial multifilament polyurethane fiber via repeated Ag precursor absorption and reduction processes. Second, the fiber strain sensor was encapsulated with biocompatible poly(dimethylsiloxane) (PDMS) to achieve high stability against external mechanical damage. Next, the encapsulated fiber strain sensor was functionalized with hydroxyl (–OH) groups via O$_2$ plasma treatment, followed by coating with a thermoresponsive PVA–PNIPAm layer. The classic freezethawing method was applied to enhance the mechanical stability of the hydrogel layer.\textsuperscript{13} Finally, the drug was loaded by swelling of lyophilized fiber strain sensor in the drug solution with the desired concentration when making DRESS. A photograph of DRESS with a suture needle is shown in Fig. 1B and Fig. S2.\textsuperscript{†} Just like a commercial suture, DRESS can be fabricated to be one meter long with excellent flexibility, which attributes to dip coating fabrication of PVA–PNIPAm and PDMS layers. In addition, the cross-sectional scanning electron microscopy (SEM) image in Fig. 1C of DRESS clearly demonstrates a well-defined core–shell structure. DRESS has a multilayer structure consisting of the multifilament fiber strain sensor core (the gray-colored part) and two layers of the shell (blue: PDMS layer and red: PVA–PNIPAm). The diameter of the fiber strain sensor was relatively uniform with an average value of 300 μm and the overall diameter of DRESS was around 600 μm. Despite a series of coating processes, DRESS showed high stretchability and tensile strength. As shown in Fig. S3, the fracture strain and tensile strength were slightly decreased as Ag nanoparticles were incorporated. This can be attributed to the increase in the stiffness due to reducing agent and rigid Ag nanoparticle. However, tensile strength was increased again as PDMS and PVA–PNIPAM were coated. Also, the fracture strain of DRESS still remains over 450%, indicating the high stretchability of DRESS. Moreover, the surface of DRESS shows a smooth morphology, thereby suggesting its enhanced biocompatibility so that cells can grow around the suture site with high cell viability (Fig. S4†).\textsuperscript{14}
2.2. The electrical performance of DRESS

The SEM images in Fig. 2A and Fig. S5† show that the Ag nanoparticles were uniformly coated and incorporated throughout the fiber strain sensor via in situ formation approach.\(^{15,16}\) In particular, the Ag nanoparticles were mainly concentrated along the edges of the fiber due to the inherent nature of the in situ formation process, thereby forming an active layer.\(^{17}\) Moreover, the uniformly distributed Ag nanoparticles enable the stable conduction of electrons. Fig. 2B indicates a decrease in the initial electrical resistance of the fiber strain sensor with each repeat of the in situ formation process of the stretchable fiber. This improvement in the electrical properties is attributed to the increased amount of Ag nanoparticles incorporated into the stretchable fiber producing a more efficient electrical conduction path.

When external tensile strain was applied to the fiber strain sensor, physical deformation of polymer chains is induced in the stretched sensor.\(^{18-20}\) Such deformation leads to the disconnections between the Ag nanoparticles incorporated in the fiber sensor, resulting in the continuous increase in the electrical resistance of the sensor (Fig. 2C). In particular, the Ag-based active layer in the fiber sensor is locally cracked into small pieces under external tensile strain, which induces the change in the electrical resistance of the fiber sensor (Fig. S6†). Thus, the fiber sensor can effectively detect the applied external tensile strain by leveraging the change in the electrical resistance. The GFs of the strain sensors were calculated as follows:

\[
GF = \frac{(R - R_0)}{R_0} \frac{R_0}{\Delta \varepsilon}.
\]

where \(R\) is the measured resistance at a certain strain, \(R_0\) is the initial resistance of the fiber strain sensor without strain, and \(\varepsilon\) is the applied strain. The fiber strain sensor exhibited a high GF of \(~155\) after two formation cycles, which gradually increased to \(~686\) in the same strain range after five cycles (40–50%). The increased GF of the sensor in accordance with the repeated in situ formation approach is due to the low initial electrical resistance of Ag nanoparticles densely incorporated in the active layer of the fiber sensor. Fig. 2D and E, and Fig. S7,† present evidence for the excellent electrical and mechanical stability of the fiber strain sensor via hysteresis and durability tests. The fiber strain sensor fabricated through a repeated formation process exhibited a negligible hysteresis, thereby demonstrating its high stability (Fig. 2D). Fig. S7† also demonstrates the hysteresis of the fiber strain sensor under external strain levels of up to 50%, which was still negligible even with a high level of stretching. In addition, the Ag-based active layer in the fiber sensor remained intact without any considerable damage after stretching-releasing deformation of the sensor, showing high stability of the active layer in the sensor during external tensile deformation (Fig. S6†). Based on the high stability, the stable response of the fiber strain sensor was maintained even after an intensive 3000-cycle test with 10% strain (Fig. 2E), thus showing its reliable durability.

2.3. Heat generation characterization of the fiber strain sensors

The fiber strain sensor with excellent electrical properties can act as a heat flux generator through Joule heating. To characterize the heat generation properties of the fiber strain sensor fabricated by 5 repeated cycles of the in situ formation process,
its surface temperature was measured with varying applied voltages (Fig. 3A). The surface temperature of the sensor increased with increasing applied voltage due to enhanced collisions between electrons and silver atoms.\textsuperscript{21,22} Therefore, the fiber strain sensor could generate sufficient heat required for the desired application by adjusting the applied input voltage.

For controllable drug release, it is important to maintain the temperature of DRESS under external tensile strain. However, the surface temperature of the sensor varied in response to different tensile strain levels when a fixed voltage of 130 mV was applied (Fig. 3B). As the applied strain was increased, the electrical resistance of the fiber sensor also increased, resulting in a decrease in heat generation. Similarly, the surface temperature of the fiber was continuously measured with varying applied voltages at a fixed tensile strain of 30\% (Fig. 3C). Despite the applied strain to the sensor, it showed a controllable thermal response to the varying input voltage due to the low hysteresis property of the fiber.

The thermal response of DRESS against applied input voltage can be mathematically described by considering its cross-sectional structure and thermodynamics (Fig. 3D).\textsuperscript{23–25} By assuming that the surface temperature of each layer represents the temperature of the layer, the increased temperature $T$ of the PVA–PNIPAm layer in DRESS under external input voltage $V$ can be calculated as follows:

$$T = \frac{V^2}{R} t + C_a m_a \left( T_0 - h \left( \frac{L_d}{k_d} + \frac{L_p}{k_p} \right) T_a \right) + C_p m_p \left( T_0 - h \frac{L_d}{k_d} T_a \right) + C_d m_d T_0 + h \Delta t T_a \left( 1 - \frac{L_d}{k_d} + \frac{L_p}{k_p} \right) + C_d m_d + h \Delta t T_a.$$

where $T_0$ and $T_a$ indicate the equilibrium temperature of the system in the initial state and ambient temperature, respectively; $h$ is the convection heat transfer coefficient of air; subscripts $a$, $p$, and $d$ indicate the Ag-based active layer, the PDMS layer, and PVA–PNIPam layer, respectively; $k$ is the thermal conductivity; $L$ denotes the thickness of each layer in DRESS; $C$ is the heat capacity of each layer; $m$ indicates the approximate mass of each layer; $t$ is the saturation time for the equilibrium temperature in the system; $R$ is the electrical resistance of the fiber strain sensor; and $A$ indicates the surface area of DRESS. The detailed calculation of the temperature is described in the ESI (Fig. S8). The analytical prediction on the temperature of the PVA–PNIPam layer was similar to the experimental result, as shown in Fig. 3E. In addition, finite element model (FEM) analysis of the steady-state thermal response was conducted.
Fig. 3  Thermal characterization of the fiber strain sensors. (A) Surface temperature of the fiber strain sensor according to various applied input voltages without external tensile strain. (B) Changes in the surface temperature of the fiber strain sensor under various applied tensile strain levels at a fixed input voltage of 130 mV. (C) Changes in the surface temperature of the fiber strain sensor under various applied input voltages with a fixed tensile strain of 30%. (D) A schematic illustration showing a cross-sectional view of the fiber strain sensor. (E) The thermal response of the fiber strain sensor in DRESS with increasing input voltage without external tensile strain. The solid and dashed lines show the expected response based on an analytical model and FEM simulations, respectively. (F) Numerical simulation of the heat distribution in DRESS under an input voltage of 100 mV. (G) Changes in surface temperature and electrical resistance of DRESS with a fixed input voltage upon repeated external tensile strain levels of 10%. (H) IR images of DRESS at a fixed input voltage under consecutive stretch-release deformation with 10% strain. (I) Changes in surface temperature and electrical resistance of DRESS with the closed-loop voltage control system upon repeated external tensile strain levels of 10%. (J) IR images of DRESS with the closed-loop voltage control system under consecutive stretch-release deformation with 10% strain.
The simulated temperature of the PVA–PNIPAm layer was in good agreement with the analytical prediction, thus demonstrating the validity of the analytical model (Fig. 3E). Therefore, the analytical model can be effectively used for DRESS.

For on-demand drug release by DRESS, the intended heat generated by the fiber strain sensor should be stable under any deformation of DRESS. However, the heat generated from the fiber strain sensor was instantly reduced according to the applied tensile strain due to the increase in the electrical resistance of the fiber strain sensor (Fig. 3G and H), which decreases the drug-releasing efficiency of DRESS. Hence, a closed-loop voltage control system that could successfully maintain the heat generation in DRESS was designed to achieve on-demand drug release regardless of external deformation (Fig. S9 and S10). In the voltage control system, the input voltage applied to DRESS was continuously adjusted to maintain its temperature. According to eqn (1), the external tensile strain applied to DRESS increases the electrical resistance of the fiber strain sensor, which leads to a decrease in the temperature of DRESS. To compensate for this, an analytical model was used to modulate the input voltage up to the required level. Therefore, the target temperature for drug release by DRESS could be successfully maintained during repeated stretching and releasing deformation (Fig. 3I and J, and Movie S1†). This voltage control system enabled DRESS to provide stable and accurate drug-releasing performance by maintaining its required temperature despite external tensile deformation.

2.5. Synthesis and characterization of thermoresponsive PVA–PNIPAm

The synthesis of PVA–PNIPAm polymer achieved via an esterification reaction between carboxylic acid-terminated PNIPAm and PVA is illustrated in Fig. 4A.26 PVA is a hydroxyl group-rich hydrophilic polymer having high biocompatibility and other useful properties, including mechanical flexibility, strength, and fluid uptake capability, which make it suitable for the development of drug delivery systems.27 PNIPAm is a thermostressive polymer that can swell to contain the drug below its lower critical solution temperature (LCST) and shrink to release its contents above the LCST.28,29 To obtain a thermoressive, flexible, and sufficient drug-containing shell layer, we grafted PNIPAm onto the PVA side chain via an esterification reaction. The PVA–PNIPAm polymer was then uniformly coated onto the fiber strain sensor by dip-coating. The coated PVA–PNIPAm shell on the conductive fiber strain sensor enabled excellent biocompatibility and thermoresponsive drug release properties without compromising its flexibility.

Fourier transform infrared (FT-IR) spectroscopy of PVA, PNIPAm–PVA, and PNIPAm-COOH was conducted to confirm the synthesis of PVA–PNIPAm (Fig. 4B). Characteristic bands in the PVA spectrum confirming hydroxyl (O–H stretching) and alkyl (C–H stretching and bending) groups were obtained in the 3200–3500, 2800–3000, and 1400–1500 cm⁻¹ regions, respectively. In the PNIPAm-COOH spectrum, specific bands for amine (N–H stretching), carboxylic acid (C=O stretching), and amide I (C=O stretching) groups were obtained in the 3300–3400, 1700–1800, and 1600–1700 cm⁻¹ regions, respectively. After the synthesis of PVA–PNIPAm, the spectrum revealed a decrease in the hydroxyl band (O–H stretching; 3200–3500 cm⁻¹) and increases in the amine band (N–H stretching; 3300–3400 cm⁻¹) and amide I band (C=O stretching; 1600–1700 cm⁻¹) compared to the levels in the PVA spectrum. In addition, the characteristic band for PNIPAm-COOH corresponding to carboxylic acid (C=O stretching; 1700–1800 cm⁻¹) was not obvious in the PVA–PNIPAm spectrum. These results confirm the synthesis of PVA–PNIPAm by forming ester bonds between PVA and PNIPAm.

2.6. Drug loading and release by DRESS

Fig. 4C illustrates the heat-triggered drug-release mechanism of PVA–PNIPAm. Below the LCST, hydrogen bonding between the hydrophilic solvent and amide groups in PNIPAm dominated, resulting in hydration of the amide groups.30,31 Therefore, the PVA–PNIPAm polymer network and the drugs are homogeneously mixed into a single phase. As the temperature is increased over LCST, the hydrogen bonding is weakened, which induces dehydration of the amide groups.32,33 Subsequently, a coil-to-globule phase transition occurs due to enhanced hydrophobic interaction among the nearby propyl groups.34 The shrunken volume of PVA–PNIPAm accelerates hydrophilic solvent exclusion, thereby leading to the release of the drug. Therefore, the on-demand drug release of DRESS is facilitated via the PVA–PNIPAm coating on the strain fiber sensor and electrical control of the heat flux by changing the temperature.

Both the passive and triggered drug-release rates should be precisely engineered to maximize the drug-release controllability of DRESS.35 As the PVA ratio increases, the LCST required for the phase transition is also increased, which minimizes the passive drug release.36 However, the skin is burned by temperatures above 45 °C, and so we compared the drug-release profile of PVA–PNIPAm polymer with different ratios of PVA/PNIPAm to optimize the maximum drug loading and release efficiency. First, the drug loading capacity of PVA and PVA–PNIPAm with different ratios (PVA : PNIPAm; 5 : 1, 10 : 1, or 20 : 1) were evaluated. The drug loading process of a lyophilized hydrogel includes preparing drug solution at desired concentration and hydration. Therefore, drug loading capacity is proportional to their swelling degree under the same drug concentration.37 As shown in Fig. 4D, PVA–PNIPAm with a 10 : 1 ratio showed the highest swelling degree overall. PVA–PNIPAm with higher ratio of PNIPAm showed increased swelling degree at early stage, but swelling degree of 5 : 1 PVA–PNIPAm decreased sharply with time. This is attributed to the accelerated mass loss due to the lower PVA crystallinity as the PNIPAm ratio increases.38 Then, the drug-release profile of PVA and PVA–PNIPAm was characterized at room temperature and 42 °C. In the experiments, rhodamine B was used as a model drug because of its positive charge, low molecular weight, and photoluminescence.39 Composite polymers with the same...
weight were used to eliminate drug-release variation due to the weight difference. As shown in Fig. S11 and S12,† the drug-release profiles at all ratios were accelerated, which is attributed to the increasing diffusion rate at high temperatures. Notably, PVA–PNIPAm with a 10 : 1 ratio showed 98.2 ± 19.5% enhanced drug-release efficiency upon heating (Fig. 4E). However, polymer composite with a high concentration of PNIPAm (5 : 1) had an even lower drug-release efficiency compared to that of 10 : 1 PVA–PNIPAm. This is attributed to a low LCST that increased drug release at room temperature and poor swelling ability. Based on the drug-release profiles, 10 : 1 PVA–PNIPAm was selected as the shell layer for DRESS. It offers optimal drug-release efficiency as well as stable control of its release with increasing temperature.

DRESS was then tested in vitro to demonstrate its triggered drug-release capability using a skin phantom. We chose an agarose-based skin phantom since its mechanical properties can be engineered to be similar to dermal tissue. In addition, its transparency enables real-time tracking of drug release. Fig. S13† shows optical images of drug diffusion in the skin phantom. The results illustrate that the drug diffused area of the voltage applied DRESS was twice larger than that of non-activated DRESS (Fig. 4F), which is attributed to the thermoresponsive properties of the drug-loaded shell layer in DRESS. Moreover, as shown in Fig. 4G, the drug-release profile increased linearly with the number of threads, which suggests that the drug dosage could be multiplied by integrating multiple threads while suturing.

2.7. The in vitro biocompatibility of DRESS

The healing process of a sutured wound is an enduring and complex process comprising multiple stages: inflammation,
cell proliferation, matrix deposition, and tissue remodeling. In the wound healing process, suturing plays an important role by closing wounds to prevent contact with air, contaminants, and infectious agents while directly interfacing with the skin tissue. Thus, the biocompatibility of the suture must be considered as infection or inflammation can retard wound healing while skin damage can cause excessive dermal collagen deposition, thereby resulting in a hypertrophic scar. Cell viability assays were conducted to confirm the biocompatibility of DRESS. NIH-3T3 cells were cultured with four types of thread: bare Ag fiber, PDMS-coated Ag fiber, DRESS, or commercial suture and after 72 hours, cellular attachment and viability of adjacent cells near the fibers were evaluated via the Live/Dead assay (Fig. 5A and S14†). The majority of cells adjacent to the bare Ag fiber were dead, which is attributed to the toxicity of Ag in the aqueous biological environment. In contrast, the majority of cells were alive adjacent to the both PDMS-coated Ag fiber and DRESS, with the cell viability increased from 68% to 85% after coating the Ag fiber with PDMS and PVA–PNIPAm (Fig. 5B). In addition, DRESS showed similar cell viability to that of commercial sutures (Fig. S15†). The results suggest that the PDMS and PVA–PNIPAm layers fully encapsulated the Ag fiber, thereby blocking the release of Ag nanoparticles.

2.8. The wound healing properties of DRESS in vitro

Migration of cells to the damaged area occurs during the initial phase of the wound healing process. Hence, a scratch assay was conducted in vitro to assess the efficacy of DRESS in wound healing. In this experiment, fibroblast was used as a skin model, and epidermal growth factor (EGF) which is known to enhance fibroblast migration and proliferation was used as a drug. Also, two groups of DRESS were used to assess the degrees of cell migration under controlled drug delivery: (1) non-activated DRESS (DRESS without applying a voltage) and (2) heat-activated DRESS (DRESS with an applied voltage of 130 mV). First, drug-eluted media was prepared by immersing those two groups of DRESS in media without cells to prevent heat from being directly applied to the cells. Then, the scratch was applied to a monolayer of confluent fibroblasts. After scratching, their media were changed to the prepared medium. As shown in Fig. 5C, both groups demonstrated a similar width of scratches at 0 hours. However, as cell migration and proliferation took place, the gap between the

---

Fig. 5  The biocompatibility and wound healing properties of DRESS in vitro. (A) Live/Dead staining images of NIH-3T3 cells cultured with Ag fiber, PDMS coated Ag fiber, or DRESS after 3 days (dead cells, red; live cells, green) and (B) quantitative cell viability data (scale bars, 400 µm). (C) Representative time-lapse microscopy images of wound closure with non-activated DRESS (upper) and heat-activated DRESS (lower) at 0, 24, and 48 h after scratching (scale bars, 1 mm). Quantification of the wound area with (D) non-activated DRESS and (E) heat-activated DRESS at 0, 24, and 48 h after scratching.
cell layers had shrunk by up to 11% for the heat-activated DRESS, while the non-activated DRESS remained on 31% of the wound area (Fig. 5D and E). This result suggests that the heat-triggered drug delivery by DRESS has the capability of accelerating the wound healing process by promoting cell migration.

2.9. An ex vivo demonstration of the applicability of DRESS
To test the applicability of DRESS on the skin, an ex vivo demonstration was performed by directly suturing DRESS onto injured porcine skin, which has structurally similar features to those of human skin (Fig. 6A). When external tensile strain was applied to the sutured wound site on the porcine skin, the sutured DRESS was stretched, thereby increasing the electrical resistance of the fiber strain sensor in DRESS (Fig. 6B and C). This showed a stable resistive response even during the repeated stretch-release deformation cycles applied to the sutured wound site. This result shows that the additional coating layers in DRESS do not negatively affect the strain-sensing performance of the fiber sensor based on the excellent flexibility and mechanical stability of the layers while being sutured ex vivo. Controllable heat generation by the sutured DRESS was also investigated to examine its drug-releasing capability. Fig. 6D and F show the temperature response of DRESS sutured onto the wound site without and with the closed-loop voltage control during repeated stretch-release deformation cycles on the injured pork skin, respectively. The target temperature of the sutured DRESS resulting from external strain can severely degrade the drug-release performance of DRESS. On the other hand, when closed-loop voltage control was applied to the sutured DRESS, its target temperature was successfully maintained despite repeated tensile strain cycles applied to the sutured wound (Fig. 6F and G, and Movie S2†). These results demonstrate that DRESS with closed-loop voltage control can be effectively used for on-demand drug release with high accuracy and controllability in practical applications.

3. Conclusions
DRESS addresses the existing challenges of a multifunctional suture integrated with a monitoring system that offers additional therapeutic benefits to the suturing process. Various characterization methods, including SEM, FT-IR, resistive response, heat generation, swelling degree, and thermoresponsive drug release profile measurements were conducted to optimize the fabrication conditions for DRESS. Especially, a core–shell structure enables multifunctionality integrated into a single fiber. The fiber strain sensor core of DRESS allows continuous strain monitoring of the suture. The Ag nanoparticles incorporated into the multifilament fiber bestow highly sensitive (a GF of ~686) and mechanically stable (over more than 3000 stretching cycles) strain-sensing properties. In addition, the theoretical results of the analytical model and FEM simulation have shown the suitability of DRESS as a microheater via Joule heating. Indeed, IR images of DRESS with an applied input voltage validated the simulation results. Moreover, in order to precisely control the temperature changes upon various strain levels, the heat flux of the core fiber was calibrated using a closed-loop voltage control unit. Then, the thermoresponsive drug release performance of DRESS was investigated. The results showed 98.2 ± 19.5% enhanced drug-release efficiency by controlling the release profile via Joule heating. Moreover, biocompatibility and capability as wound-healing therapeutics were examined in vitro. Cell viability assay demonstrated that adjacent cells near DRESS showed similar viability to that of commercial sutures due to their biocompatibility. Also, in vitro scratch assay showed a 66% smaller wound gap compared to that of the non-activated DRESS suture material after 48 hours. Last, the feasibility of DRESS as a suture was confirmed on porcine skin ex vivo.

Our DRESS has several advantages over conventional or previously developed functional sutures. First, DRESS is an active drug release system. Current drug eluting sutures have difficulty in controlling drug release timing and rate. However, DRESS could release drug on-demand by heating the thermoresponsive PVA–PNIPAm shell layer providing temporal control of therapeutic delivery. Second, both strain sensing and thermoresponsive drug release of DRESS were electrically driven. DRESS could measure tensile strain by leveraging the changes in the electrical resistance and control drug release via joule heating. Therefore, DRESS can be used not only on the skin but also inside the human body like Achilles tendon suturing. Despite the multifunctionalities of DRESS, the list of drugs that DRESS can load is limited to hydrophilic drugs which remains as a challenge. Thus, further research is required to develop an advanced thermo-responsive polymer that can load both hydrophilic and hydrophobic drugs while maintaining multi-functionalities. Also, investigation on in vivo feasibility is demanded for clinical application. Overall, we expect DRESS to provide a step forward in developing multifunctional suture capable of monitoring strain and promoting wound healing via on-demand drug release.

4. Experimental
4.1. Materials
Poly(vinyl alcohol) (PVA), carboxylic acid-terminated poly(N-isopropyl acrylamide) (PNIPAm-COOH), silver trifluoroacetate (AgCF3COO), ascorbic acid, and agarose were purchased from Sigma-Aldrich (St Louis, USA) and used without further purification. Dulbecco’s Modified Eagle Medium (DMEM), bovine calf serum (BCS), and phosphate-buffered saline (PBS) were acquired from Gibco (New York, USA). Penicillin–streptomycin (PS) was purchased from Welgene (Seoul, Korea). Animal-free recombinant human EGF was purchased from PeproTech Inc. (New
Jersey, USA). Live/Dead kits were obtained from Invitrogen (California, USA). PDMS was purchased from Dow Inc. (California, USA) and the stretchable fiber, Spandex, was purchased from Taekwang Industry Co. Ltd (Seoul, South Korea).

4.2. Fabrication of the fiber strain sensor

The fiber strain sensor was fabricated using a repeated formation approach that consists of repeated absorption and reduction processes of the Ag precursors in the stretchable fiber. A polyurethane-based stretchable fiber was submerged in AgCF₃COO solution in ethanol (30 wt%) for absorbing Ag ions into the fiber. After 30 min, the stretchable fiber was pulled out and dried in air. The stretchable fiber containing a large amount of Ag ions was immersed in an ascorbic acid solution in deionized (DI) water (2 wt%) to reduce the absorbed Ag ions into nanoparticles. After 20 min, the fiber was dried in air, and then PDMS was coated onto it to insulate and protect it.

4.3. Fabrication of DRESS

PVA solution was prepared by dissolving 2 g of PVA powder in 10 mL of DI water at 80 °C for 20 min. The prepared PVA solu-
tion and PNIPAm were mixed at a different weight ratio (PVA : PNIPAm; 5 : 1, 10 : 1, 20 : 1) at room temperature for 24 h. The fiber strain sensor was treated with oxygen plasma (100 W for 5 min) to enhance adhesion between PVA and PDMS. After the plasma treatment, the fiber strain sensor was coated with the homogeneous PVA–PNIPAm solution followed by freezing at −20 °C for 8 h. The frozen fiber was then thawed at room temperature for 1 h before use.

4.4. FT-IR spectroscopy

This was conducted to elucidate the chemical structures of the materials. Pristine PVA, pristine PNIPAm-COOH, or PVA–PNIPAm of different ratios (5 : 1, 10 : 1, or 20 : 1) was mixed with dry potassium bromide (KBr) and ground into a fine powder using an agate mortar. Afterward, the powder was compressed into a KBr disc. Each KBr disc was scanned at 4 mm s\(^{-1}\) with a resolution of 2 cm\(^{-1}\) over a wavenumber region of 400–4000 cm\(^{-1}\).

4.5. Swelling testing

To analyze the swelling properties of PVA–PNIPAm, the lyophilized PVA–PNIPAm was prepared in a rectangular shape (10 × 10 mm\(^2\), thickness <1 mm). After measuring the initial weight, the prepared block was immersed in release medium (PBS, pH = 7.4) at room temperature. The swollen samples were taken out and weighed at 1, 3, 6, 24, and 48 h after immersion.

The swelling degree was calculated as follows:

\[
\text{Swelling ratio(\%)} = \frac{M_s(t) - M_0}{M_0} \times 100, \tag{3}
\]

where \(M_0\) is the mass of the dried sample and \(M_s(t)\) is the weight of the swollen sample at time \(t\) after wiping with paper.

4.6. Characterization of DRESS

An LCR meter (Keysight-technologies Inc., E4980AL) was used to measure the resistive response of the fiber strain sensor. A customized one-dimensional x-stage was used to examine the stretching deformation of DRESS. Thermal images and the temperature measurements of DRESS were obtained by using simulation software (ANSYS, ANSYS R17.2) to conduct a steady-state thermal analysis of DRESS. Surface morphology and cross-sectional images were obtained by using field emission SEM (FE-SEM; JEOL, J-500HR). Before the SEM analysis, DRESS was frozen at −80 °C for 12 h and subsequently lyophilized for 12 h in a freeze dryer (Daihan, Korea). Afterward, the freeze-dried DRESS was fractured with a sharp blade and coated with Pt before analysis.

4.7. Measurement of the thermoresponsive drug-release profiles

The different weight ratios of PVA–PNIPAm (PVA : PNIPAm; 5 : 1, 10 : 1, or 20 : 1) and PVA (20 wt%) solution were cured into block samples of uniform weight (200 mg). The blocks were kept at −20 °C for 1 day and lyophilized for 2 days. The freeze-dried blocks were swollen in rhodamine B (0.5% w/v in DI water) solution for 1 day. The swollen blocks were washed with PBS (pH 7.4) 3 times and then submerged in 3 mL of fresh PBS. The samples were placed at two different temperatures (room temperature and 42 °C) and removed after 10 min intervals, at which point UV/VIS spectroscopy (V-650, JASCO Corporation, UK) was used to measure the absorbance of each sample for creating their drug-release profiles.

4.8. In vitro drug-release testing

Agarose powder was dissolved in DI water (2% w/w) and heated until the liquid became fully transparent. The agarose solution was poured into a cylinder-shaped dish and cooled down to form a gel. Suturing with the rhodamine-loaded DRESS was carried out at the center of the cylinder and voltage was applied. Images were taken every 10 min.

4.9. In vitro cell viability assay

DRESS was attached to the bottom of a 12 well plate. NIH-3T3 cells (0.4 × 10\(^5\) cells per mL) were cultured using DMEM cell culture medium supplemented with 10% BCS and 1% PS at 37 °C for 24 or 72 h. Cellular attachment and viability were observed by using a Live/Dead kit (L3224, Invitrogen, CA, USA) according to the manufacturer’s instructions. A laser scanning confocal microscope (LSM 980, Carl Zeiss, Oberkochen, Germany) with a 10× objective lens was used for tile-scan image acquisition of the stained samples under identical microscope settings.

4.10. In vitro wound scratch assay

3 cm long EGF-loaded DRESS samples were prepared and immersed in 1 mL of DMEM. Afterward, the samples were divided into two groups: group I was stored at room temperature and group II was heated by applying a voltage (\(n = 3\)). The two groups were removed after 1 h of drug release and the drug-eluted media were stored at 4 °C before use. Subsequently, NIH-3T3 cells were cultured in 12-well plates using new medium (seeding density: 0.5 × 10\(^5\) cells per mL). Cells were cultured for 3 days until reaching confluency (>90%). Once a confluent layer of cells had formed, a wound was created by scratching it with a 200 μl pipette tip. The damaged cells were then aspirated and drug-eluted media from the two groups were added to each well plate. Cell images were taken at 0, 24, and 48 h after scratching using an optical microscope (IX81, Olympus, Tokyo, Japan).

4.11. The ex vivo demonstration of DRESS

Fresh porcine skin obtained from the local market was prepared with a height of 15 mm, a width of at least 50 mm, and a length of at least 50 mm. Afterward, a 30 mm long and 5 mm deep wound was made using a knife. DRESS was directly sutured to close the wound on the porcine skin. Heat generation and closed-loop voltage control of the sutured DRESS were performed by using an Arduino Mega 2560 and a voltage divider circuit.
4.12. Statistical analysis

GraphPad Prism 8 software (Graphpad Software Inc., USA) and Origin 2018 (OriginLab Cooperation, Northampton, MA, USA) were used to assess statistical significance. Differences between groups were assessed via unpaired t-tests and one-way ANOVA tests. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001; NS: no significant difference.

Author contributions

All authors approved the final version of the manuscript. Y. L., H. K., J. L., and J. S. conceived the study and designed the experiments. Y. L. and H. K. performed most of the experiments, analyzed the data, prepared the figures, and wrote the manuscript. Y. L., Y. K., B. C., and C. P. fabricated DRESS and characterized its drug-releasing profile. H.K. fabricated the fiber strain sensors and conducted the electrical performance test, thermal performance test, ex vivo demonstration, and mathematical analysis. Y. L. and Y. K. performed the biocompatibility assay and wound scratch test in vitro. Y. K. and C. P. performed in vitro drug-release testing. B. C. designed and conducted a swelling test. S.N. described mathematical modeling and conducted FEM simulation. S.N. and J.K. designed and fabricated the circuits for the voltage control system. J.K. assisted in the experiments of thermal characterization. M.C. assisted in the fabrication of the fiber strain sensors. K. P. assisted in writing the manuscript. J.L. and J.S. supervised the project.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (NRF-2019R1C1C1006720, NRF-2021M3H4A1A03048658, and NRF-2021R1C1C1009271), the Korean Medical Device Development Fund grant funded by the Korean government (the Ministry of Science and ICT, the Ministry of Trade, Industry, and Energy, the Ministry of Health & Welfare, and the Ministry of Food and Drug Safety) (Project Numbers: 17111138242, KMDF_PR_20200901_0131), (Project Number: 17111138243, KMDF_PR_20200901_0131), (Project Number: 1711137994, KMDF_PR_20200901_0039). This work was also financed by the DGIST Start-up Fund Program of the Ministry of Science and ICT (2021010030).

References


21 M. T. B. Kashem and S. Subrina, ECS Trans., 2021, 102, 43.
22 N. S. Khashi, M. T. B. Kashem and S. Subrina, ECS Trans., 2021, 102, 43.