Calcium-Modified Silk as a Biocompatible and Strong Adhesive for Epidermal Electronics

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With the increasing interest and demand for epidermal electronics, a strong interface between a sensor and a biological surface is essential, yet achieving such interface is still a challenge. Here, a calcium (Ca)-modified biocompatible silk fibroin as a strong adhesive for epidermal electronics is proposed and the physical principles behind its interfacial and adhesive properties are reported. A strong adhesive characteristic (>800 N m\(^{-1}\)) is observed because of the increase in both viscoelastic property and mechanical interlocking through the incorporation of Ca ions. Furthermore, additional key characteristics of the Ca-modified silk: reusability, stretchability, biocompatibility, and conductivity, are reported. These characteristics enable a wide range of applications as demonstrated in four epidermal electronic systems: capacitive touch sensor, resistive strain sensor, hydrogel-based drug delivery, and electrocardiogram monitoring sensor. As a reusable, biocompatible, conductive, and strong adhesive with water-degradability, the Ca-modified silk adhesive is a promising candidate for the next-generation adhesive for epidermal biomedical sensors.

1. Introduction

Epidermal systems based on ultrathin and flexible electronics are promising next-generation wearable platforms that enable close monitoring of physiological and physical signals in real time. Because of the conformal contact with the skin, the epidermal systems offer competitive advantages over conventional wearable sensors including enhanced user comfort, access to diverse physiological signals, and on-demand therapeutic intervention directly through the skin. With the advancement of the stretchable and foldable electronics and wireless systems,[1–3] epidermal systems have been successfully demonstrated on various active devices such as thin film transistors (TFT),[4,5] touch sensors,[6–8] and biosensors.[9–11] For these systems, establishing a stable yet nonallergic contact with high adhesion to the skin surface is essential to ensure reliable measurements with high signal-to-noise ratio against inevitable physical interaction with the environment.

Several approaches have been proposed to provide a stable interface for epidermal systems including chemical modification of the surface and development of biocompatible adhesives. Although the surface modifications of freestanding substrates such as glass, silicon, and elastomer improve the adhesion between electronics and substrates,[12,13] the chemical treatment is not suitable for epidermal systems that directly interface with the skin. Consequently, biocompatible adhesives have been actively explored. Few examples include modified polydimethylsiloxane (PDMS) elastomers,[14] poly(vinyl alcohol)-based gel,[15] commercial spray bandage,[16] and silica nanoparticles solution.[17] However, the reported peel strengths are relatively low to robustly secure the epidermal systems on the skin without any delamination. Another promising method is to use ultrathin and flexible substrates[18–20] that directly interface with the skin without any adhesive. Although such substrates offer highly conformal contacts, it is still challenging to achieve a mechanical stability with zero slippage or delamination because the epidermal systems are subject to frequent body movement.

The silk fibroin, a natural protein with high biocompatibility and biodegradability, has been widely explored as biocompatible polymer substrates, colorimetric films, dielectric layers, and water-soluble sacrificial layers for biomedical, optical, and electrical devices.[21–28] Because of these competitive advantages, silk is an attractive biomaterial for modification to endow additional functionalities. For example, a Ca-modified silk fabricated by dissolving silk fibroin and calcium chloride (CaCl\(_2\)) in formic acid was demonstrated as a highly stretchable substrate, but the interesting adhesive property of silk was not reported nor examined.[29–31] In addition, there is a brief report on an unmodified silk as a glue for resonant food sensor, but no details were provided such as peel strength or mechanical properties.[32] Moreover, a silk fibroin functionalized with mussel adhesive proteins was recently reported as a biocompatible adhesive with water solubility.[33] This silk adhesive is crystalline in nature and thus is limited to high Young’s modulus.

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and the catechol-functionalization renders the transparent silk opaque. Comparison of previously reported functionalized silk relevant to this work is summarized in Table S1 (Supporting Information).

In this work, we report a transparent, calcium (Ca)-modified silk fibroin as a strong and biocompatible adhesive for epidermal electronic, which offers multifunctional characteristics, such as reusability, stretchability, and conductivity, suitable for practical epidermal applications. We experimentally demonstrate the physical principles of adhesive characteristics including enhanced viscoelasticity of modified silk via a metal–chelate bonding and water-capturing of Ca ions and increased mechanical interlocking at the silk/substrate interface.[34,35] Furthermore, we show that the proposed silk adhesive is reusable, water-degradable, biocompatible, and conductive. The epidermal electronics interfaced with the silk adhesive readily detach and reattach on the skin, remain on the skin over a long period of time without lesions, and allow reliable measurement of physiological signals with high signal-to-noise ratio. Finally, we demonstrate the operation of four custom-designed epidermal systems (i.e., capacitive touch sensor, resistive strain sensor, dye-containing hydrogel drug delivery system, and electrocardiogram (ECG) sensor) which robustly adhered to the biological skins through the silk adhesive interface.

2. Results and Discussion

2.1. Adhesive Mechanism of the Ca-Modified Silk

The Ca-modified silk exhibits physical adhesive characteristics because Ca ions act as both cross-links for random coil chains of silk via metal–chelate complexes and water-capturing points. Using undamaged silk cocoons, degummed silk fibers were fabricated and dissolved in formic acid to make a silk solution (Figure 1a). The silk, a biocompatible polymer consisting of various functional groups such as serine, tyrosine, glycine (Gly), and alanine (Ala) (Figure S1 and Section S1, Supporting Information), is innately nonadhesive.[33] In addition, carboxylic acids, represented by formic acid, have a potential for

**Figure 1.** Adhesive mechanism of Ca-modified silk induced by calcium chelate reaction. Schematic illustration of a) fabrication process and structural changes of b) solution and c) film in the bare silk and Ca-modified silk. d) Schematic illustration of the bare silk and the Ca-modified silk at the interface. e) Average peel strengths of the bare silk and the Ca-modified silk (70:30 silk:Ca^{2+} weight ratio) from the PI film at 0 and 20% RH (12 h attaching time) with standard deviation (n = 3). f) FTIR spectra and g) shear modulus at different shear frequencies of the bare silk and Ca-modified silk.
interacting with hydrophilic parts of silk fibroin chain such as C=O, OH, and NH\(^+\) groups.\(^{36}\) As a result, in the case of a bare silk solution dissolved in formic acid, hydrophobic parts of silk fibroin chain become closer and form hydrophobic cores in polar formic acid solvent. This implies that hydrodynamic radius of silk fibroin chain is reduced (Figure 1b and Figure S2, Supporting Information). Thus, when silk fibroin solution is dried, especially the nonpolar amino acid parts such as Gly and Ala form \(\beta\)-sheet crystalline structure more readily, which results in high \(\beta\)-sheet crystalline contents of bare silk film (Figure 1c).\(^{36–38}\) By contrast, when Ca ions are introduced by dissolving CaCl\(_2\) in the silk fibroin solution, the Ca-modified silk film becomes rich in random coil contents as the crystalline structures are disrupted during the drying process due to the metal chelation and water-capturing of Ca ions (Section S2, Supporting Information).\(^{30,39–41}\) The detailed preparation process of Ca-modified silk is described in the Experimental Section (Figure S3 and Section S3, Supporting Information). The fabricated Ca-modified silk maintained a transparency over 95%, which is similar to that of a bare silk (Figure S4, Supporting Information). Moreover, unlike the bare silk film, Ca ions in a Ca-modified silk film can capture water molecules from atmosphere and result in a much softer and more fluidic film (Figure 1c-i).\(^{30}\) The high flowability allows the good contact at the adhesive/substrate interface of Ca-modified silk and the attached substrate.\(^{42,43}\) Furthermore, the metal chelation for random coil chains offers suitable cohesion (Figure 1c-ii), which endows the viscoelastic property to the film. In addition, the metal chelation allows for large energy dissipation at the interface with proper flowability (Figure 1c-iii).\(^{34,44–46}\) Therefore, the high adhesion by large energy dissipation with the good contact at the interface and appropriate cohesion enhances the peel strength of the Ca-modified silk.\(^{47}\) Therefore, the Ca-modified silk exhibits physical adhesive characteristic and shows a thread-like morphology at the interface (Figure 1d).

In order to evaluate the effects of the metal–chelate reaction and water-capturing of Ca ions on the peel strength, 90° peel test was conducted on a polyimide (PI) film, which was attached to a glass slide through the Ca-modified silk (Figure 1e). For 0% relative humidity (RH), the fabricated film was placed in vacuum for 1 d and subsequently attached on the PI film. At 0% RH, no adhesive characteristics were observed for both bare silk and Ca-modified silk (\(\approx 0.1 \, \text{N} \, \text{m}^{-1}\)) due to the absence of water in silk that causes no flowability and a weak mechanical interlocking at interface. This result shows that the water-capturing plays an important role in adhesive mechanism. Moreover, almost no peel strength was observed for the bare silk with the peel strength of \(\approx 0.1 \, \text{N} \, \text{m}^{-1}\) at 20% RH. In the bare silk, there is no metal chelation due to the absence of Ca ions, which results in weak mechanical interlocking at the interface. By contrast, the Ca-modified silk showed a high peel strength of \(429 \pm 18 \, \text{N} \, \text{m}^{-1}\) at 20% RH. The enhanced peel strength is attributed first to the increase in flowability due to the water-capturing which enables the Ca-modified silk to flow along the surface of the attached substrate. This implies that the mechanical interlocking at the interface enhanced the adhesion of Ca-modified silk. Moreover, to evaluate the effect of metal chelation, we measured the peel strength of bare silk and Ca-modified silk while maintaining the same amount of water contents for both films (Figure S5a, Supporting Information). We observed an increase in the peel strength due to the addition of Ca ions. These results show that the Ca ions play an important role in the adhesive mechanism; they act as the cross-linkers for random coil chains of silk via metal–chelate complexes and contribute to the high cohesion and large energy dissipation although water-capturing decreases both cohesion and energy dissipation. Therefore, the Ca-modified silk is now adhesive and clearly shows a thread-like morphology at the interface due to the high peel strength (Figure S5b,c, Supporting Information).

The metal–chelate reaction and water-capturing property of Ca ions in the Ca-modified silk in comparison with the bare silk were examined using the Fourier transform infrared (FTIR) spectra (Figure 1f). The bare silk film, which is much stiffer than the Ca-modified silk, consists mainly of crystalline \(\beta\)-sheets with characteristic amide I (1618 cm\(^{-1}\)) and amide II peaks (1508 cm\(^{-1}\)) that represent the C=O stretching group and the N–H bending group, respectively.\(^{48–50}\) The amide I and II peaks are related to the backbone conformation of polymer chain structure and imply the presence and degree of crystalline \(\beta\)-sheets. In comparison to the bare silk, the amide I and II peaks of the Ca-modified silk were blueshifted to 1637 and 1540 cm\(^{-1}\), respectively, because Ca ions intercalated in Ca-modified silk reacted with the carboxyl (\(\approx \text{COO}^-\)), amino (\(\approx \text{NH}_2\)), and imino (\(\approx \text{NH}\)) groups of peptide in silk fibroin for chelate reaction.\(^{51,52}\) In addition, water molecules captured by Ca ions enlarge the hydrodynamic radius of silk fibroin (Figure S2, Supporting Information). These roles of Ca ions hinder the formation of crystalline \(\beta\)-sheets and results in high amount of amorphous random coil structures.\(^{30,36,51–53}\) Moreover, the amide-A peak (3276 cm\(^{-1}\)) of the Ca-modified silk representing the N–H stretching groups of the silk film was redshifted to 3250 cm\(^{-1}\) because \(\approx \text{NH}_2\) and \(\approx \text{NH}\) bonds are coordinated to Ca–N bonds which are replaced from hydrogen bond through chelate reaction.\(^{34,53}\) Additionally, the newly observed 3350 cm\(^{-1}\) peak representing the O–H stretching group of water molecules showed that Ca ions can capture water molecules from the atmosphere.\(^{56–58}\)

The metal–chelate reaction and water-capturing property of Ca ions in the Ca-modified silk were also examined through ultraviolet–visible (UV–vis) absorbance spectra (Figure S6a, Supporting Information). A silk fibroin consists of carboxyl and tyrosine groups that absorb maximally at 240 and 280 nm, respectively. When Ca ions intercalated in Ca-modified silk reacted with the carboxyl (\(\approx \text{COO}^-\)), amino (\(\approx \text{NH}_2\)), and imino (\(\approx \text{NH}\)) groups of peptide in silk fibroin for chelate reaction,\(^{34,44–46}\) the absorbance intensity of the Ca-modified silk is higher than that of the bare silk at 280 nm due to the hyperchromic effect.\(^{59}\) The difference in flowability and energy dissipation of the bare silk and the Ca-modified silk was also examined through shear modulus measurements using a rheometer. Figure 1g and Figure S6b (Supporting Information) show the storage (\(\text{G}'\)) and loss modulus (\(\text{G}''\)), and loss tangent (\(\tan \delta\)) of the two films. A polymer film with \(\text{G}'\) below \(1 \times 10^9\) Pa and high \(\tan \delta\) is considered
to exhibit high flowability and large energy dissipation, and thus can readily flow on the surface of other attached substrate.[15] The $G'$ of the bare silk was over $10^3$ Pa with low tan$\delta$ of 0.3, which was too high for the silk film to flow on the surface of the attached substrate and to induce mechanical interlocking at the interface. However, $G'$ of the Ca-modified silk film was below $10^3$ Pa with high tan$\delta$ of 2, which is sufficiently low for the Ca-modified silk to flow on the surface of the attached substrate and to enhance the energy dissipation with mechanical interlocking at the interface.

Next, in order to estimate the effects of humidity on the peel strength, we measured peel strength of the Ca-modified silk (70:30) at different humidity (0–70% RH) (Figure S7, Supporting Information). The time of attachment between the hydrogel and the Ca-modified silk was fixed at 12 h. At 0% RH, the Ca-modified silk did not show adhesive characteristics because of absence of adhesion. At 20% RH, the peel strength of 182.6 ± 19 N m$^{-1}$ was measured because of the sufficient adhesion at the adhesive/substrate interface by increased water contents (11 wt%). At RH higher than 20%, the increased water contents resulted in a decrease in the cohesion, and thus a decrease in the peel strength (44.8 ± 3.2 N m$^{-1}$). However, despite the decrease in peel strength at higher humidity, the peel strength of Ca-modified silk was still comparable to that of commercial 3M tape (40 ± 2 N m$^{-1}$) and we observed sufficiently strong peel strength between hydrogel and Ca-modified silk (Figure S7a, Supporting Information).[15] Moreover, the same experiment was conducted on the 85:15 silk:Ca$^{2+}$ film. Similar to that of the 70:30 silk:Ca$^{2+}$ film, a decrease in the peel strength was observed as the humidity increased (Figure S7b, Supporting Information).

For a practical epidermal application, it is also important to observe the effect of sweat on the adhesive force. For the case, when the device was subject to a relatively short sweating condition, the water content in the adhesive would reach equilibrium through evaporation into the atmosphere. According to the experiment where the peel strength was observed over the attaching time, the water content of the adhesive should reach equilibrium to that of environment humidity within 30 min. For the case, when the device is subject to a continuous sweating condition, the water content of the adhesive would exceed that of environment humidity due to slow evaporation. Thus, to observe the stability of the Ca-modified silk during the continuous sweating condition, we conducted a peel test before and after a 30 min exercise (Section S4, Supporting Information). After the 30 min exercise, the PI film was stably attached on the skin without slippage, and sufficiently strong peel strength was observed for both before and after the exercise (Figure S8 and Movie S1, Supporting Information) with thread-like morphology.

2.2. Relationship between the Adhesive and the Viscoelasticity of the Ca-Modified Silk

In order to analyze the relationship between the adhesive force and the viscoelasticity of the Ca-modified silk and thus optimize the adhesive force, we measured and examined the peel strength of the Ca-modified silk from the hydrogel as a function of Ca$^{2+}$ concentration (Figure 2a). We observed that the peel strength increased as the Ca ions in the composition increased to 70:30 silk:Ca$^{2+}$ weight ratio. As the Ca ion concentration increased, the intensity of the amide II peak (1540 cm$^{-1}$) decreased due to the increase in a coordinate covalent bond between Ca ions and ligands of silk fibroin chain that represent amide II vibration (Figure 2b). This decrease in the intensity implies a potential increase in the crosslinking of silk fibroins via metal–chelate complexes. Moreover, when Ca ion concentration (<70:30) in the Ca-modified silk films is small, amino acid groups prefer to be bonded with Ca ions rather than with the water molecules and form chelate complex. Therefore, the chelate complex peak (3250 cm$^{-1}$) is more dominant than the water molecule peak (3350 cm$^{-1}$).[56] Therefore, from 85:15 to 70:30 weight ratio, the increase in metal–chelate complexes and water molecules endowed the Ca-modified silk with the suitable viscoelasticity to retain high energy dissipation and mechanical interlocking and thus led to high peel strength. However, for films with a large Ca ion concentration (>70:30), too many water molecules in Ca-modified silk screen the Ca ions and hinder the Ca ions to coordinate with amino acid group. Thus, water molecule peak (3350 cm$^{-1}$) is more dominant than the chelate complex peak (3250 cm$^{-1}$). Too many water molecules would deform the silk fibroin structure, decrease the cohesion, and decrease the peel strength of Ca-modified silk.

To support our hypothesis on the adhesive mechanism, we measured the water contents of Ca-modified silk films with different Ca$^{2+}$ concentrations across various humidity conditions (Figure S9, Supporting Information). When increasing Ca$^{2+}$ weight ratio under the same humidity condition, our measurement showed a continuous increase in the water content, which facilitates the high mechanical interlocking at interface.

Moreover, we measured the shear modulus as a function of Ca ion concentration. At a low shear frequency of 0.5 Hz, the bonding frequency related to the attachment of an adhesive on a substrate,[60] the $G'$ decreased while tan$\delta$ increased for the films with higher Ca ion concentration. These changes in the shear modulus imply high flowability of the Ca-modified silk at higher Ca ion concentration, which agrees with the enhanced mechanical interlocking and the measured peel strengths (Figure 2c).[34,44] Moreover, very low $G'$ and $G''$ were observed for the film with 50:50 weight ratio due to the too many amorphous and water contents in Ca-modified silk film, which implies a weak cohesion of silk fibroins. These results again match with the observed collapse and slippage of the film during the peel test (Figure S10 and Section S5, Supporting Information).

The change in the flowability as a function of the Ca ion concentration was observed in the cross-sectional images of scanning electron microscope (SEM) (Figure 2e). The Ca-modified silk was placed on a polymethyl methacrylate (PMMA) mold with V-groove line patterns for 12 h in the ambient environment. The Ca-modified silk with 85:15 weight ratio did not deform along the patterned surface of the mold due to the low flowability, which was predicted from shear modulus measurement (high $G'$ and low tan$\delta$). Thus, low mechanical interlocking at the interface was observed.[34,44] For the film with 80:20 weight ratio, although the Ca-modified silk deformed along the V-grooves, small gaps between the Ca-modified silk and the mold were still presented. Therefore, the flowability was still low. However, for the films with 70:30 to 50:50 weight...
ratio, the Ca-modified silk completely filled the grooves with no gap. These films exhibited sufficiently high flowability and mechanical interlocking as predicted from the shear modulus measurement.

Next, at a high shear frequency of 100 Hz, the debonding frequency related to the peeling of adhesive from the attached substrate,[60,61] a high tanδ implies that the process of energy dissipation is more preferred than energy storing during peeling and thus requires higher peel strength to delaminate an adhesive from a substrate.[44,62] As the Ca ion concentration increased, we observed a maximum tanδ for the film with 70:30 weight ratio with sufficiently high $G''$ over $5 \times 10^4$ Pa (Figure 2d). Consequently, through a high energy dissipation process, the 70:30 weight ratio film exhibited the maximum adhesion. The increased tanδ was due to the interplay between the increase in water contents and crosslinking of metal chelation. Moreover, the chelation enhanced the cohesion while water decreased elastic modulus.[63–65] Because of this chelation of Ca ions, our adhesive could maintain appropriate rheological properties for high enough energy dissipation and high enough elastic modulus although water as a plasticizer keeps decreasing both. The additional demonstration of the cohesion of Ca-modified silk films by metal chelation is presented in Table S2 and Section S6 (Supporting Information).

For optimizing the mechanical interlocking and thus achieving a high peel strength, we varied the initial time of attachment and measured the peel strength of the Ca-modified silk from the PI film (Figure 2f). Immediately after the PI film was attached to the Ca-modified silk, the peel strength of 143 N m$^{-1}$ was observed. This strength was comparable to that of commercial spray bandage[16] and was sufficiently strong to prevent delamination of the PI film from the Ca-modified silk.[15] However, the viscoelasticity of the Ca-modified silk implies that a contact area between the PI film and the Ca-modified silk would increase as the time of attachment increased. In fact, the Ca-modified silk was deformed into the surface of the PI film over time and resulted in an increase in the contact area between two layers. This increase in the contact area enhanced a mechanical interlocking at the interface.

Figure 2. Relationship between the peel strength and the viscoelasticity of Ca-modified silk. a) Peel strengths of the Ca-modified silk from the hydrogel (12 h attaching time) and b) corresponding FTIR spectra of the Ca-modified silk with varying silk:Ca$^{2+}$ weight ratio from 85:15 to 50:50. The shear modulus of the Ca-modified silk at different silk:Ca$^{2+}$ weight ratio from 85:15 to 50:50 at c) low shear frequency (0.5 Hz) and d) high shear frequency (100 Hz). e) Cross-sectional scanning electron microscope (SEM) images of the various Ca-modified silk films (silk:Ca$^{2+}$ weight ratio: 85:15 to 50:50) placed on top of PMMA polymer mold for 12 h. The Ca-modified silk film is colored. Scale bar, 50 µm. f) Peel strengths of the Ca-modified silk (70:30) as a function of the attaching time from the PI film. The humidity of all experiments was 20% RH.
After 6 h, the mechanical interlocking at the interface reached equilibrium at which the peel strength was 425 N m⁻¹. This peel strength remained over 24 h.

2.3. Characterization of the Silk Adhesive

For the epidermal application, it is essential that we demonstrate that the silk adhesive (Ca-modified silk) provides a mechanically stable interface between the human skin and the hydrogel which suits the epidermal electronics due to the biocompatibility (Figure 3a). Thus, a hydrogel patch was fabricated and attached to the skin through the silk adhesive intermediate layer. The silk adhesive was stained using a methylene blue dye to visually distinguish the adhesive layer from the transparent hydrogel and the silk adhesive. Since the silk adhesive exhibited a high adhesion for both the hydrogel and the skin, it shows a thread-like morphology at the interface. Next, another hydrogel patch was placed on the back of a hand using a transparent silk adhesive. We observed a conformal contact of the hydrogel on the skin along the highly curved contour of the knuckles with the radius of curvature (ROC) of ≈5.5 mm. Neither transformation nor delamination was observed during a set of movements (Figure 3b). Moreover, another hydrogel patch was attached on the forearm using a stained silk adhesive. The hydrogel patch retained its position without delamination nor tear despite various external forces such as stretching, compressing, and twisting (Figure 3c). Thereafter, the peel strengths of the silk adhesive for common flexible substrates such as polyethylene (PE), polyethylene terephthalate (PET), hydrogel, and PI film as well as pig skin were measured (Figure 3d and Section S7, Supporting Information). The silk adhesive physically adhered to all substrates under test. The highest adhesive force of 788 ± 56 N m⁻¹ was observed on the hydrogel. Therefore, as long as the substrates have a sufficiently high surface energy to allow high mechanical interlocking at the adhesive/substrate interface, a high adhesive force is achievable on a diverse set of substrates using the proposed Ca-modified silk adhesive.

However, too high peel strength can cause the epidermolysis when we detach a film that was strongly attached to the skin with an adhesive. Due to the water-degradability of the silk fibroin, the film attached to the skin through the silk adhesive can readily detach without incurring epidermolysis when

Figure 3. Characterization of silk adhesive. a) Schematic and photograph of a hydrogel patch adhered on the human skin through the silk adhesive (70:30). Scale bar, 5 mm. b) Photographs of the hydrogel patch attached to a highly curved part of the hand, the knuckle region with a radius of curvature of ≈5.5 mm. Scale bar, 30 mm. c) Photographs of the hydrogel patch strongly attached to the forearm using the silk adhesive (70:30) when subject to stretching, compressive, and twisting force. Scale bar, 15 mm. d) Average peel strengths of the silk adhesive (70:30) when interfaced with PE, PET, PI, hydrogel, and pig skin (24 h attaching time) with standard deviation (n = 3). The humidity was 20% RH. e) Photographs showing easy detachment of the hydrogel from the skin with the silk adhesive through soaking in water. Scale bar, 30 mm. f) Changes in the peel strengths of the bare silk and the silk adhesive from hydrogel during soaking in water.
soaked under water. When the hydrogel film was attached to a human hand using the silk adhesive and was soaked in water, the peel strength sharply decreased from 200 to 19.3 N m⁻¹ within 2 min. After 2 min in water, the hydrogel film was detached from the skin (Figure 3e). The residue of silk adhesive that remained on the hand was readily removed by weak rubbing. Moreover, within 30 min, the peel strength dropped to 1.2 N m⁻¹ due to the weak cohesion (Figure 3f). The water-degradability of the silk adhesive facilitated easy switching between attachment and detachment (Movie S2, Supporting Information).

2.4. Reusable Silk Adhesive on a Capacitive Touch Epidermal Sensor

We custom-designed and fabricated four epidermal sensor systems to explore and illustrate key additional properties of the proposed silk adhesive: capacitive touch sensor on human skin, resistive strain sensor on pig bladder tissue, drug delivery systems on mouse skin, and ECG sensor on human skin. For these epidermal systems, we used the optimal silk:Ca²⁺ weight ratio (70:30) with the maximum adhesive force. First, an epidermal capacitive touch sensor was fabricated and evaluated by attaching it to the human skin using the silk adhesive. The physical adhesion of the silk adhesive by mechanical interlocking at the interface facilitates its reusability as well as high peel strength, which is not possible for chemically bonded peel strength. To verify the reusability, a repeated attachment/detachment test was performed. First, a PI film was attached to glass using silk adhesive for 6 h and was detached to perform the repeatability test. For the first five cycles, the PI film was attached and immediately detached from the silk adhesive. The peel strength gradually decreased and dropped to 60% of the initial value after five cycles because of the immediate detachment; the mechanical interlocking was insufficient due to the short attaching time (Figure 4a). However, when the detached PI film was reattached and detached after 6 h, the silk adhesive showed high peel strengths over multiple cycles with values similar to that at the first attachment. The sufficient attaching time facilitated the recovery of peel strength and thus led to the reusability of silk adhesive. This used silk adhesive was kept in the atmosphere and after a week, a new PI film was attached. After 6 h, the peel test was performed again and we confirmed that the peel strength of the silk adhesive was still high.

Using the reusability and high peel strength of silk adhesive, we fabricated the reusable epidermal capacitive touch sensor consisting of a hydrogel-PDMS-hydrogel stack (Figure 4b). The silk adhesive was used not only between the skin and the PE film, but also between the PE film and the hydrogel to provide a mechanically stable contact. A thin PE film was used as an insulation layer between the hydrogel sensor and the skin. As
expected, the sensor placed on the human arm without any adhesive was readily detached. However, the sensor attached by the silk adhesive showed high peel strength on the arm without delamination nor tear during pulling (inset of Figure 4d). When we reattached the detached sensor after 2 d, the adhesion between the sensor and the skin was still high because of the reusability of the silk adhesive. Distinctive changes in the capacitance were observed for both the as-attached and reattached devices when touched gently using a finger. This demonstrates the feasibility of the on/off touch epidermal sensor and the reusability of the silk adhesive (Figure 4c,d).

2.5. Stretchable Silk Adhesive on a Resistive Strain Epidermal Sensor

Next, a resistive strain sensor was fabricated and placed on an extracted pig bladder to show the stretchability of the silk adhesive. Although a bladder tissue is not an epidermal skin, we chose the bladder tissue because of its high stretchability (>100%) to measure the resistance–strain characteristic of silk adhesive. For strain sensors, it is important that intermediate layers such as an adhesive must comply to a large strain of highly stretchable sensor materials such as PDMS (Young’s modulus: 0.519 MPa) and hydrogel (0.21 MPa). As illustrated in Figure 4e, the bare silk showed a high Young’s modulus of 479 MPa (i.e., stiff). However, after Ca modification, the silk adhesive showed a much smaller Young’s modulus of 0.16 MPa, which is sufficiently low to withstand the large strain incurred on soft substrates such as hydrogel and biological tissues (Figure S12, Table S3, and Section S8, Supporting Information). Therefore, when the bladder tissue was stretched from 0 to 50%, the conductive hydrogel electrode on the bladder tissue with the silk adhesive closely corresponded to the tensile strain without slippage or delamination (Figure 4f). The hydrogel was stained using a dye to visually distinguish the transparent hydrogel from the bladder. Consequently, the change of resistance of the conductive hydrogel attached to the bladder tissue with the silk adhesive closely matched that of a bare conductive hydrogel. By contrast, the hydrogel placed on the bladder tissue without any adhesive did not respond to the movement of the attached substrate and thus the resistance did not change (Figure 4g). Thus, by using the soft yet highly adhesive silk, a strain sensor based on hydrogel was implemented on the biological tissue and the applied strain as large as 50% was successfully measured.

2.6. Biocompatible Silk Adhesive and Its Application on a Drug Delivery Epidermal System

In addition to biodegradable, stretchable, and reusable properties of the silk adhesive, the silk adhesive is highly biocompatible and suitable for interfacing with the human skin for a long time. Although the silk adhesive absorbs moisture from the skin as well as from the atmosphere, the water-capturing of the silk adhesive did not cause any dehydration of the skin when the silk adhesive was attached on the skin for 12 h (Figure S13 and Section S9, Supporting Information). We fabricated a hydrogel:rhodamine B matrix as an epidermal dye delivery system (Figure 5a). The matrix was attached at the back of a mouse with and without the silk adhesive, respectively (Figure 5b). After 2 d of attachment on the freely moving mouse, the hydrogel matrix with silk adhesive remained at its original position without any change in the shape. In contrary, the one without silk adhesive was delaminated after 1 min of attachment from the back of the mouse due to the active movement (Figure 5c,d and Movie S3, Supporting Information). After the hydrogel was removed, the rhodamine B dye permeated into the skin (Figure 5e). Although the drug release rate and the penetration depth across the epidermis and dermis layers were not examined, this experiment showed the potential of a drug-loaded hydrogel as a chronic epidermal drug delivery system. The silk adhesive enables a long-term and secure attachment of a drug-loaded patch on a biological skin.

In order to confirm biocompatibility of the silk adhesives, histology was performed on the skin at the back of the mouse with and without the silk adhesive (Figure 5f,g). A 15 mm × 15 mm silk adhesive film was attached to the dorsal skin of the shaved mouse for 5 d. After removing the silk adhesive film from the dorsal skin, the skin tissue was stained with hematoxylin and eosin (H&E) and was observed using an optical microscope. In comparison to the region without the silk adhesive, the tissue structures of the region with the silk adhesive were intact without specific lesions such as erythema, infiltration, and immune response at stratum corneum and epidermis. This implies that even if the silk adhesive solution consisted of the formic acid solvent, it evaporated during the fabrication of the silk adhesive and did not adversely affect the biocompatibility of silk.

2.7. Conductive Silk Adhesive for an ECG Epidermal Sensor

While the bare silk is a dielectric (Figure 6a and inset), the impedance of the silk adhesive shows a strong frequency dependency, which indicates ionic conductive behavior. An ionic conductor forms an electrical double layer at the electrode and has a low ion mobility compared to the electron mobility, which results in a strong dependence on the frequency.\(^{[66,67]}\)

The ionic conductivity of the silk adhesive is attributed to both the charged Ca ions and the water capturing. Therefore, as the Ca\(^{2+}\) concentration increased, the conductivity of silk adhesive increased from 0.005 to 5.99 mS cm\(^{-1}\) (Figure 6b). Moreover, when the silk adhesive is placed between the metal electrode and the biological tissue, the impedance decreased (Figure 6c). While a high impedance of 6.2 kΩ at 1 MHz was observed between the Ag/AgCl electrode and the bladder tissue because of the dry interface,\(^{[68]}\) a low impedance of 1.5 kΩ was measured when the silk adhesive was used. This impedance value is comparable to that measured between the Ag/AgCl with commercial hydrogel electrode and the tissue (=1.3 kΩ).\(^{[69]}\)

However, due to the volatility of the commercial hydrogel electrodes, after 1 h, the impedance increased to 2.0 kΩ while the impedance using the silk adhesive remained low.

Since the silk adhesive exhibits ionic conductivity, we explored the use of the silk adhesive as the conductive gel for the measurement of ECG signals. Accurate monitoring of the
ECG signals is important as the abnormalities of these signals are signs for various medical conditions such as heart diseases and seizures. For reference, we first used three commercial ECG metal electrodes (Ag/AgCl) without attached commercial hydrogel that were originally accompanied with 3M adhesive because of clear comparison between bare metal electrode and silk adhesive on metal. These electrodes were attached to both forearms and a left leg to measure the electrophysiological signals of the heart and the measured signals showed the P wave, QRS complex, and T wave (Figure 6d). However, due to the weak contact and the high impedance between the metal electrodes and the skin, a fluctuation of the baseline, a higher noise level, and low amplitudes of signals were observed. In contrast, the electrophysiological signals measured by ECG metal electrodes interfaced with the silk adhesive showed clear signals with a low noise level and negligible baseline fluctuation. The silk adhesive enhanced the conformal contact and decreased the impedance between metal electrodes and skins (Figure 6e).

In addition, use of silk adhesive is advantageous when measuring the ECG signals under motion due to the strong peel strength and ionic conductivity. To evaluate the effect of motion, both wrists were repeatedly bent and relaxed during the ECG measurements. The electrophysiological signals measured without the silk adhesive showed a large fluctuation in the baseline and distorted signals during the bending due to the partially detached pad on the skin (Figure 6f). The 3M adhesive could not cover the entire region of metal electrode because of its electrical insulation. Moreover, the metal electrodes with commercial hydrogel also showed the fluctuation of ECG signals when it was bended and relaxed because of the low peel strength of commercial hydrogel (0.2 N m⁻¹) although the ECG signal in static state was clear with low impedance compared to the that of bare Ag/AgCl electrodes (Figure S14, Supporting Information). However, due to the conductive characteristics, the silk adhesive was applied over the entire ECG pad and a larger area of the electrode was conformably contacted to the body (Figure 6e). The measured signals at the pad with the silk adhesive were not distorted even under a repeated bending and remained robustly on the arm without detachment over multiple cycles of movements (Figure 6g). Therefore, the silk adhesive serves not only as an adhesive but also a conductive gel which enables accurate measurement of ECG signals and real-time electrophysiological signals without motion artifact.

3. Conclusion

With a rapid development of epidermal and implantable electronics, achieving a strong interface between electronics and biological surfaces is important, yet developing an adhesive that provides such interface is challenging. Here, we developed a biocompatible, reusable, conductive, and strong silk adhesive.
and discussed the mechanism of adhesive. The intercalated Ca ions played an important role in the adhesive mechanism. The metal–chelate bonding and water-capturing of Ca ions enhanced the viscoelasticity and thus the mechanical interlocking of the silk film. This enhanced mechanical interlocking at the interface with the biological surfaces and resulted in the adhesive characteristics.

Based on this mechanism, the Ca$^{2+}$ concentration was adjusted to control the viscoelasticity and hence the adhesive force. Through the optimization, we demonstrated the maximum peel strength of $\approx 800$ N m$^{-1}$ at 70:30 silk:Ca$^{2+}$ weight ratio. Moreover, the ionic conductivity of the silk adhesive allowed accurate monitoring of the electrophysiological signals. Finally, utilizing the high peel strength of the silk adhesive, we demonstrated four robustly adhered epidermal electronics on both human and animal skins. This study not only broadens the spectrum of application of the biocompatible silk materials to epidermal electronics, but also expands the functionality of adhesives, such as conductivity and stretchability, to enhance the performance of the epidermal systems.

### 4. Experimental Section

**Preparation of Degummed Silk Fibers:** 5 g of *Bombyx mori* silk cocoons was immersed in 2 L of 0.02 m Na$_2$CO$_3$ (Alfa Aesar, Korea) solution, which was then boiled at 100 °C for 30 min. The degummed silk fibers were rinsed with deionized (DI) water to remove the residue of the Na$_2$CO$_3$ solution.

**Synthesis of the Silk Adhesive:** A silk adhesive with a silk:Ca$^{2+}$ weight ratio was formed from a solution that consists of silk, CaCl$_2$ (Alfa Aesar, Korea), and formic acid (Sigma Aldrich, Korea). Here, silk:Ca$^{2+}$ weight ratio is defined as the weight ratio between silk fibroin and calcium ions.
in the final adhesive. For the synthesis, the weight of the degummed silk fiber and formic acid was first fixed to 0.6 and 10 g, respectively. Then, the amount of CaCl₂ required to satisfy the ratio between silk and Ca²⁺ was calculated. The required amount of CaCl₂ and the degummed silk fiber were mixed with the formic acid. Finally, after stirring the solution at room temperature, the solution was degassed in a vacuum desiccator. For example, to synthesize a 70:30 weight ratio of silk adhesive film, 0.6 g of silk fiber, 0.257 g of CaCl₂, and 10 g of formic acid are required. To add 0.257 g of CaCl₂, 0.712 g of CaCl₂ powder is required. 200 µL of this degassed solution was then cast on a glass slide with a 10 × 10 mm square-shaped patterned PDMS mask and the solvent was evaporated at 65 °C and 20% RH to form the silk adhesive. The stained silk adhesive was fabricated by dispersing a methylene blue dye (Alfa Aesar, Korea) in the prepared hydrogel solution.

Synthesis of the Conductive Bare Hydrogel: The conductive bare hydrogel was synthesized based on the ion-containing polyacrylamide hydrogel fabrication described previously. [7] 2.17 m acrylamide (AAm; Sigma-Aldrich, Korea) and 4 µL lithium chloride (LiCl; Sigma-Aldrich, Korea) were dissolved in deionized water. Thereafter, N,N-methylenebisacrylamide (MBAA; Sigma-Aldrich, Korea) and ammonium persulfate (AP; Sigma-Aldrich, Korea) were added with 0.06 and 0.17 wt% of AAm, respectively. After stirring and degassing the solution, 0.25 wt% (of AAm) N,N,N,N′-tetramethylethylenediamine (TEMED; Sigma-Aldrich, Korea) was added. A hydrogel patch was then formed by pouring the solution into a glass mold and drying it at 60 °C for 20 min. The stained hydrogel was fabricated by dispersing a tartrazine dye (Alfa Aesar, Korea) and a rhodamine B dye (Sigma-Aldrich, Korea) in the prepared hydrogel solution.

Peeling Test: The peel strength of the silk adhesive was measured through a 90° peel test using a mechanical testing machine (MCT-2150, AND KOREA, Korea) composed of two linear moving stages along y-axis and z-axis. The silk adhesive film was coated on a glass slide (25 × 75 mm) and dried. Next, various materials such as hydrogel, pig skin, PE, PET, and PI film were attached to the silk adhesive. The size (width and height) of silk adhesive was 35 mm × 20 mm and that of hydrogel and PI film was 10 mm × 40 mm (Figure S15, Supporting Information). The water contents of silk adhesive at 30% RH for 12 h with and without attaching PI film were approximately the same. In case of the hydrogel, 3M adhesive tape (810DD, 3M, Korea) was attached on top of the hydrogel matrix to prevent the stretching of hydrogel during peel test. The edge of various materials was fixed in upper z-axis stage and detached at 90° angle with a peeling speed of 50 mm min⁻¹. The sample moved along the y-axis while the fixed edges of materials were detached from the z-axis with the same speed. Because of the high peel strength between the silk adhesive and the glass, detachment occurred at the interface of silk adhesive and the attached substrates. The peel strength was measured by dividing the measured peeling force by the tape width.

Characterization of the Silk Adhesive: The structures of the silk adhesive and calcium–chelate complex were monitored by spectrophotometers. The thin film samples (2 × 2 cm), at room temperature, were monitored by an attenuated total reflectance (ATR)-FTIR (Nicolet iS50, Thermo Fisher Scientific Instrument, USA) from 4000 to 400 cm⁻¹ or UV–vis spectrophotometer (UV3600plus, Shimadzu, Japan) from 1200 to 300 nm. To analyze the flowability of the silk adhesive as a function of calcium concentration, the SEM images were acquired by a field-emission scanning electron microscopy (FESEM; Nova230, FEI Co., USA). For measuring the impedance and conductivity, the silk adhesive film was sandwiched between a gold electrode and a copper electrode. The two electrodes were connected to the Impedance Analyzer (E4990A, Keysight Tech., USA) and the impedance of the silk adhesive was measured across a frequency span from 20 Hz to 1 MHz at an AC bias of 20 mV. The measured area was 2 mm × 2 mm and thickness was 0.5 mm. For measuring the impedance between a metal electrode and a bladder tissue, the bladder tissue was placed on two Ag/AgCl electrodes patterned glass. The silk adhesive can be coated on Ag/AgCl electrodes before placing the bladder tissue. The electrodes were then connected to the Impedance Analyzer. Moreover, the Ag/AgCl electrodes with and without commercial hydrogel were also measured.

Rheology Measurement: The viscoelasticity of the silk adhesive was measured using a rheometer (MCR 302, Anton Paar, Graz, Austria) equipped with two parallel metal plates (25 mm diameter). The sample (1 × 1 in.) was loaded on the bottom metal plate and sandwiched by the top plate. The frequency-dependent storage, loss shear modulus, and loss tangent (G', G'', tanδ) were measured at a shear frequency from 100 to 0.5 Hz at fixed strain amplitude of 1%.

Dehydration Measurement of Skin: The moisture value on the skin surface was measured using a commercially available skin hydration measurement instrument (Corneometer CM 825, Courage-Khazaka Electronic, Germany). The unit of Corneometer measurement is arbitrary which ranges from 0 (no water at all) to 120 (on water). Measurements were conducted on three subjects under 40% RH and 20 °C. Before attaching the silk adhesive on the skin, the moisture value of bare skin was measured. A 70:30 silk adhesive sample (30 mm × 40 mm) was attached to the forearm for 12 h. After detaching the silk adhesive, the moisture value on the skin was measured again.

Measurement of Water Contents in the Film: The water contents in the bare silk and silk adhesive were measured using a gravimetric analysis. [7] First, the sample was dried in 20% RH for 12 h and placed in a vacuum chamber for 1 d. The dried sample was then weighed. The water contents of film under various humidity conditions were then estimated by placing the sample in the environmental chamber (TH-ME-025, JEIO Tech., Korea) at specific humidity for 12 h and weighing the sample again.

Preparation of the Epidermal Strain Sensor: Two 2-mm-thick, 3 mm × 10 mm conductive hydrogel electrodes were attached onto 3-mm-thick, 10 mm × 30 mm bladder tissues with and without the silk adhesive. The bladder tissue was prepared by cutting an extracted pig bladder. The bladder tissues were gradually stretched using a lab-built stretching rig. The gold-probe tips connected to the LCR meter (E4980A, Agilent, USA) were in contact with both the hydrogel to measure the change in the resistance.

Preparation of the Epidermal Capacitive Touch Sensor: The epidermal touch sensor consists of the following layers, listed from bottom to top: silk adhesive (300 µm), PE film (10 µm), silk adhesive (300 µm), hydrogel (1 mm), PDMS (500 µm), hydrogel (1 mm), and PDMS (500 µm). The capacitive touch sensor consists of two 30 mm × 45 mm hydrogel sheets that serve as the top and bottom electrodes, which encloses the PDMS dielectric layer. The order of assembly is as follows. On the PE substrate, the silk adhesive was coated and the bottom hydrogel electrode was attached. Next, on this bottom hydrogel electrode, PDMS, top hydrogel electrode, and PDMS film were sequentially attached. A Cu tape was connected on both top and bottom hydrogel electrodes to provide an electrical interface. The fully fabricated capacitive touch sensor was placed on the forearm with a silk adhesive layer. The Cu tapes on the bottom and top hydrogel were connected to an LCR meter, which measured the capacitance using a 1 Vrms AC signal at 1 kHz.

Preparation of the Epidermal Dye-Containing Hydrogel Matrix System: 0.01% w/v rhodamine B solution was prepared in DI and 10 vol% rhodamine B solution was dispersed in a hydrogel solution. The hydrogel-rhodamine B solution was dried at 60 °C for 20 min and the hydrogel matrix was attached to the back of a mouse using the 70:30 silk adhesive. The skin tissue was stained with H&E and was observed using an optical microscope for histology.

ECG Signal Measurement: The silk adhesive or commercial hydrogel was placed on the commercial ECG electrodes (Ag/AgCl) with 3M adhesives. The ECG electrodes were attached to the two forearms and the left leg of a volunteer and the ECG signals were measured using the ECG module (ADS1x9x ECGFE, Texas Instruments, USA). To eliminate any low-frequency motion artifacts incurred due to skin stretching during the bending and relaxing motion, a band-pass filter during the recording was applied. [71] Specifically, the measured ECG signals were filtered using an eighth-order low-pass filter with a cutoff frequency of 40 Hz, a three-order high-pass filter with a cutoff frequency of 0.3 Hz, and 60 Hz notch filtering.

Experiments on Animal Subjects: All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Korea.
Advanced Institute of Science and Technology (KAIST). All experiments were performed according to IACUC guidelines.

Experiments on Human Subjects: All experiments on human skin were conducted under approval from Institutional Review Board (IRB) at the KAIST (IRB No. KH2017-108). There were two subjects (age: 29 years, male). All work involved informed consent from the subjects.

Supporting Information
Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest
The authors declare no conflict of interest.

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