Enhanced Skin Adhesive Property of Hydrophobically Modified Poly(vinyl alcohol) Films

Xi Chen†,‡ and Tetsushi Taguchi*†,‡

†Graduate School of Pure and Applied Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8577, Japan
‡Biomaterials Field, Research Center for Functional Materials, National Institute for Materials Science, 1-1 Namiki, Tsukuba, Ibaraki 305-0044, Japan

ABSTRACT: Hydrophobically modified poly(vinyl alcohol) (hm-PVA) films with various alkyl chain lengths were prepared. Their surface/ mechanical properties, cytocompatibility, and porcine skin adhesion strength were evaluated. hm-PVAs had 10 °C higher glass transition temperature than poly(vinyl alcohol) (PVA) (33.4 ± 2.5 °C). The water contact angle of the hm-PVA films increased with alkyl chain length and/or hydrophobic group modification ratio. The tensile strength of the hm-PVA films decreased with increasing alkyl chain length and/or hydrophobic group modification ratio. hm-PVA with short chain lengths (4 mol % propanal-modified PVA; 4C3-PVA) had low cytotoxicity compared with long alkyl chain length hm-PVAs (4 mol % hexanal and nonanal-modified PVA; 4C6-PVA and 4C9-PVA). The 4C3-PVA film had the highest porcine skin adhesion strength. Thus, the 4C3-PVA film is promising as an adhesive for wearable medical devices.

1. INTRODUCTION

Wearable sensors are integrated into soft materials. They directly contact the body to monitor the health condition and provide clinically relevant data. Most research in this field has involved testing rigid electronic devices developed by the semiconductor industry. Recently, the research focus has shifted toward wearable sensing platforms with stretchable and flexible electronics and excellent mechanical properties. A typical method of fabricating soft sensors consisted of integrating conducting material patterns into a stretchable substrate. However, these materials do not adhere to skin and must be affixed with commercially available adhesives.

Commercially available acrylic-based medical bandages are currently used to affix wearable sensors. Acrylic-based adhesives have high adhesion strength. Nevertheless, they may cause massive exfoliation of the stratum corneum and severe pain. Moreover, the chemical residues they leave on the skin surface may induce allergic and inflammatory reactions. Pressure-sensitive silicone-based adhesives were also developed. They have a low propensity for inducing exfoliation of the stratum corneum.

On the other hand, their skin retention is weak and they shift easily. Furthermore, they are relatively expensive. Bioinspired skin adhesives with various multiscale architectures were recently reported. They include patches simulating gecko feet,14,15 microneedles,16 octopus suckers,17 and mussel. However, their fabrication processes are complex and impractical for mass production.

Poly(vinyl alcohol) (PVA) is a hydrophilic, biodegradable, and biocompatible polymer. It has been widely used in biotechnology and biomedicine as it has excellent physico-chemical properties, is easy to process, and is highly cytocompatible. PVA has been used to fabricate contact lenses, wound dressings, and suture and catheter coatings. It has excellent film-forming and adhesive properties on soft tissues. It is, therefore, biocompatible and non-irritating to skin. However, the skin adhesion strength of the PVA film is low relative to commercial adhesives as it is highly hydrophilic and water soluble. Various techniques for insolubilizing PVA have been reported. One method is applying a cross-linking agent to the hydroxyl groups in PVA. Another involves serially freeze-thawing the PVA to form hydrogels with strong hydrogen bonds. An insoluble PVA film was also produced by modifying a hydrophobic functional group.

In our previous studies, we used hydrophobically modified biopolymers to prepare surgical sealants, films, porous membranes, and nanoparticles for adhesion to soft biological tissues. Hydrophobic modification enhances bonding strength even to wet soft tissues. The most important factors increasing the interfacial strength are the anchoring effect of the hydrophobic groups to phospholipid membranes and enhancement of the interactions between amphiphilic polymers and extracellular proteins. We hypothesized that the hydrophobic modification of PVA should strengthen its adhesion to soft tissue such as skin. The hydrophobic group...
could anchor phospholipid membranes of corneocytes on stratum corneum and enhance the interactions with keratinocyte lipids (ceramide, fatty acid, and cholesterol).

Here, we synthesized hydrophobically modified PVA (hm-PVA) with various alkyl chain lengths (3, 6, and 9 methylene carbons). We tested the theory that PVA with alkyl groups will be adhesive. Bonding, shearing, and peeling of hm-PVA films were also evaluated.

2. RESULTS AND DISCUSSION

2.1. Synthesis and Characterization of hm-PVAs. The chemical structures of hm-PVAs with various alkyl chain lengths (C3, C6, and C9) are shown in Figure 1a. From the scanning electron microscopy (SEM) images, it was indicated that the light transmissive hm-PVA films were flat (Figure S1). The hm-PVAs were prepared via the reaction between the hydroxy groups of PVA and aldehydes (Figure 1b) according to a previously reported procedure. Under acidic conditions, aldehydes react with hydroxyl groups by nucleophilic substitution and rapidly form stable hexagonal ring structures. Figure 1c shows the 1H NMR spectra for hm-PVAs with different numbers of methylene carbons. The chemical shifts at 0.85 and 1.26 ppm were assigned to the CH3 and αCH2 protons, respectively, in the hydrophobic groups of the hm-PVAs. Thus, the aldehyde groups were successfully introduced into the PVA molecules. The hm-PVA structure was also analyzed by Fourier transform infrared (FT-IR) spectra (Figure 1d). The peak at 2930 cm⁻¹ was attributed to the C–H stretching vibration of αCH3 in the acetal groups of the hm-PVAs. Therefore, hm-PVAs with different numbers of methylene carbons were successfully synthesized. The modification ratios of the hydrophobic groups (Table 1) were calculated from the 1H NMR data.

| Table 1. Modification Ratios of the hm-PVAs |
|--------------------------------------------|
| abbreviation | hydrophobic group reagent | hydrophobic group reagent addition (mol %) | hydrophobic group modification (mol %) |
|-------------|---------------------------|-------------------------------------------|----------------------------------------|
| 4C3-PVA     | propanal                  | 10                                        | 4                                      |
| 12C3-PVA    | propanal                  | 25                                        | 12                                     |
| 23C3-PVA    | propanal                  | 50                                        | 23                                     |
| 4C6-PVA     | hexanal                   | 10                                        | 4                                      |
| 4C9-PVA     | nonanal                   | 10                                        | 4                                      |

2.2. Glass Transition Temperature of hm-PVAs. The glass transition temperatures (Tg) of the hm-PVAs were determined by differential scanning calorimetry (DSC) as previously reported. The results shown in Figure 2b,d were obtained from the thermal analysis curve (Figure 2a,c). In Figure 2a, Tg is represented by the intersection of the two dotted lines. In general, Tg of the polymer increases with an increase of molecular weight. The Tg of PVA (Mw = 89 000–98 000; saponification degree = 99%) is 28.9 °C. This result is close to the Tg (33.4 ± 2.5 °C) of unmodified PVA (Mw = 88 000; saponification degree > 98.5%) measured in this study. However, the Tg of PVA (Mw = 115 000; saponification degree = 100%) increases to 80 °C due to higher molecular weight. Interestingly, the unmodified PVA had the lowest Tg, whereas the Tg for 4C3-PVA, 4C6-PVA, and 4C9-PVA rose to 47.1 ± 0.3, 45.7 ± 2.2, and 44.5 ± 3 °C, respectively (Figure 2b).
However, there were no significant differences among the hm-PVAs of varying alkyl chain lengths in terms of $T_g$. In contrast, the $T_g$ of 12C3-PVA and 23C3-PVA were 43.8 $\pm$ 0.6 and 51.3 $\pm$ 0.7 °C (Figure 2d). The $T_g$ of the hm-PVAs was 10 °C higher than that of PVA as a consequence of hydrophobic modification resulting from alkyl chain (C3, C6, and C9) aggregation. These findings also confirmed the successful integration of the alkyl groups into the PVA molecules. 

### 2.3. Tensile Strength of hm-PVA Films

Figure 3a shows the tensile strengths of hm-PVA films with various alkyl chain lengths. The tensile strengths decreased with increasing alkyl chain length. The stretching strength of the original PVA film was 105.5 $\pm$ 6.7 MPa. The tensile strength of the pure PVA film is reported to be 40–90 MPa. $\Delta$ These values are lower than the PVA film used in this study. The reason for this phenomenon is that PVA (saponification degree $> 98.5\%$) used in this study has a higher saponification degree compared with previous reports (88–98%). For the 4C3-PVA film, it was 96.9 $\pm$ 4.3 MPa, and the values for the 4C6-PVA and 4C9-PVA films were 66.0 $\pm$ 7.7 and 51.5 $\pm$ 9.8 MPa, respectively. A similar trend was observed for the Young’s moduli of various films. For the PVA and 4C3-PVA films, the Young’s moduli were 4.5 $\pm$ 0.22 and 4.6 $\pm$ 0.56 GPa, respectively. In contrast, they were 3.7 $\pm$ 0.08 and 2.0 $\pm$ 0.24 GPa for the 4C6-PVA and 4C9-PVA films, respectively. Long alkyl chains in the PVA molecule inhibit intermolecular hydrogen bonding. Figure 3b shows the ratios of hydrophobic modification to tensile strength. Here, C3-PVA with various modification ratios were used as typical hm-PVA films. The tensile strengths of the C3-PVA films decreased with increasing hydrophobic modification ratio. Relative to the 4C3-PVA film, the tensile strengths of the 12C3-PVA and 23C3-PVA films were much lower (47.4 $\pm$ 1.6 and 24.3 $\pm$ 2.1 MPa, respectively). A similar trend was observed for the Young’s moduli of the C3-PVA films with various hydrophobic modification ratios. The Young’s moduli for 4C3-PVA, 12C3-PVA, and 23C3-PVA were 4.6 $\pm$ 0.56, 2.5 $\pm$ 0.09, and 1.8 $\pm$ 0.04 GPa, respectively. Higher hydrophobic modification ratios inhibit intermolecular hydrogen bonding in C3-PVA.

### 2.4. Surface Wettability of hm-PVA Films

The surface wettability of the films differs between the side exposed to air and that in contact with the substrate. Here, we measured the WCA of hm-PVA films exposed to the air. Figure 3c shows the WCA of hm-PVA films with various alkyl chain lengths and modification ratios. The WCA for the original PVA film was lower (59.4 $\pm$ 6.8°) than those of the hm-PVA films with different alkyl chain lengths (62.8 $\pm$ 4.9–83.3 $\pm$ 0.6°). The WCA of the hm-PVA films increased with alkyl chain length. The longer alkyl chains incorporated in the PVA molecule integrated on the surfaces of the hm-PVA films. Figure 3d shows that the WCA of the hm-PVA films increased with the hydrophobic modification ratio. Film surface hydrophobicity increases with the number of alkyl groups introduced into the PVA molecule.

### 2.5. Cytocompatibility of hm-PVAs

To evaluate hm-PVA cytocompatibility, NHDF cells were cultured under various concentrations of hm-PVAs. Figure 4 shows cell viability and conditions after 24 h incubation. Figure 4a indicates that the NHDF cells spread over the tissue culture polystyrene surfaces. Cell density decreased with increasing hm-PVA concentration. However, the morphology of the surviving cells did not change. Figure 4b shows cell viability at various hm-PVA concentrations. NHDF cell viability was over 80% in medium with low (0.1 mg mL$^{-1}$) concentrations of all hm-PVAs except 4C3-PVA. Cell viability decreased with increasing hm-PVA concentration. In contrast, NHDF viability was highest at all 4C3-PVA concentrations (0.1–10 mg mL$^{-1}$). The hm-PVAs with comparatively longer side chains (4C6-
PVA and 4C9-PVA were more toxic than that of other PVA and 4C3-PVA. Thus, 4C3-PVA is relatively nontoxic to skin cells.

2.6. Adhesion Test of hm-PVAs on Porcine Skin. We determined the adhesive properties of hm-PVAs, by measuring bonding, lap-shear, and T-peel strength. Bonding strength was evaluated according to ASTM F2258-05 (Figure 5a). Figure 5b shows the force–distance curve used to calculate bonding strength. Bonding energy of the hm-PVA films on porcine skin was calculated from the area under the force–distance curve (Figure 5b). The bonding energy of the 4C3-PVA film was 5.50 ± 1.45 J m⁻² was nearly five times higher than that of the original PVA film (1.10 ± 0.23 J m⁻²) (Figure 5c). The 4C6-PVA and 4C9-PVA have longer side chains than those of 4C3-PVA. Nevertheless, the bonding energies of the 4C6-PVA and 4C9-PVA films were 1.94 ± 0.46 and 1.09 ± 0.15 J m⁻², respectively, which were closer to that for PVA. The 4C3-PVA film had high wettability and penetrated the gap on the skin surface. Moreover, the tensile strength of the 4C3-PVA film was as strong as that of the original PVA film. Thus, the 4C3-PVA film also had high bulk strength. This property substantially enhances the adhesion of the film to the surface. The modified alkyl groups (C3) readily anchored to the skin cell membranes and had strong interfacial adhesion. However, interfacial peeling occurred between the porcine skin surface and the PVA film as the latter has no alkyl side chains. The 4C6-PVA and 4C9-PVA films were anchored by their alkyl groups to the surfaces. Nevertheless, they had low adhesion strength as their wettability was weak and their skin surface gap penetration was poor.

Figure 5d–f shows the effects of alkyl chain length on hm-PVA lap-shear strength. This parameter was measured according to ASTM F2255-05 (Figure 5d). Figure 6e shows the force–distance curve for the lap-shear strength measurement. Figure 5f shows the lap-shear strengths of the hm-PVA films on porcine skin. These values were calculated from the force–distance curve (Figure 5e). The results indicated that hydrophobic modification enhanced lap-shear strength. The lap-shear strength of the 4C3-PVA film was 2.53 ± 0.71 kPa which was over two times higher than that of the original PVA film (1.12 ± 0.10 kPa). However, the lap-shear strengths of the 4C6- and 4C9-PVA films were comparatively lower than that of 4C3-PVA (2.24 ± 0.17 and 1.72 ± 0.21 kPa, respectively). The anchoring effect of the alkyl groups (C3, C6, and C9) drew the hm-PVA films into close contact with the porcine skin surface. Thus, the hm-PVA films had significantly greater resistance to transverse stress than the original PVA film.

Figure 5g–i shows the T-peel strength of hm-PVAs after adhesion to porcine skin according to ASTM F2256-05. Figure 5h shows the force–displacement curve for the T-peel strength measurement. The T-peel strengths of the hm-PVA films on porcine skin were calculated from this curve (Figure 5h). The T-peel strength of 4C3-PVA film was 10.4 ± 1.4 N m⁻¹ which was nearly twice that of the original PVA (5.6 ± 1.5 N m⁻¹). However, the peeling force decreased with increasing alkyl chain length. The values for the C6-PVA and the C9-PVA were 9.1 ± 0.7 and 8.4 ± 1.9 N m⁻¹; respectively. Figure 5c indicates that film surface wettability increases with decreasing alkyl chain length. Enhancement of the peeling strength is determined by the balance between surface wettability and alkyl chain anchoring.

Figure 5j–l shows the influences of the hydrophobic modification ratio on the bonding and lap-shear strength. Bonding strength decreased with the increasing hydrophobic modification ratio because of low wettability (Figure 5k). Moreover, shearing strength decreased with the increasing hydrophobic modification ratio because of weak hydrogen interactions among hm-PVA molecules (Figure 5i).

Debonding occurred after the hm-PVA films were applied to porcine skin. Figure 6a shows that the PVA film peeled off the entire porcine skin surface. Therefore, interfacial adhesion between the original PVA film and the skin tissue is weak. In contrast, the 4C3-PVA film strongly adhered to the upper and lower skin surfaces. Thus, the alkyl groups (C3) of 4C3-PVA were well anchored to the stratum corneum of the porcine skin. Peeling of the 4C6-PVA and 4C9-PVA films from the film–skin interfaces increased with the hydrophobic modification ratio. The 4C6-PVA and 4C9-PVA films had low wettability and, by extension, poor affinity for the porcine skin. Figure 6b shows the histology of the hm-PVA film–porcine skin interface after bonding strength measurement. No stratum corneum exfoliation was observed on either tissue surface when the original PVA film was applied. Thus, interfacial adhesion between the PVA film and the skin was quite weak. High stratum corneum exfoliation rates were confirmed for both skin surfaces when the 4C3-PVA film was applied to them. Therefore, this type of film adhered strongly to porcine skin. This finding was consistent with Figures 6c and 7. For the 4C6-PVA and 4C9-PVA films, there was partial stratum corneum exfoliation. For this reason, adhesion and penetration of these materials on porcine skin were lower than those for 4C3-PVA. These findings are consistent with those shown in Figure 6a.

Based on the foregoing results, we proposed a bonding mechanism for hm-PVAs films on porcine skin and illustrated it in Figure 7. During bonding, the PVA and 4C3-PVA films readily penetrate the gap on the skin surface. However, the 4C6-PVA and 4C9-PVA films have low wettability and their penetration in the skin surface is weak. The alkyl groups (C3, C6, and C9) easily anchor to the stratum corneum. The 4C3-
PVA film has a large contact surface and numerous alkyl group anchor points. After measuring the bonding strengths, we determined that the PVA film readily peels off the skin surface and causes no stratum corneum exfoliation as it lacks an anchor effect. In contrast, the 4C3-PVA film tightly adheres to the skin surface and induces stratum corneum exfoliation as it has a strong alkyl group anchor effect. However, the 4C6-PVA and 4C9-PVA films partially peel off the skin surface and promote relatively little stratum corneum exfoliation as they have low wettability.

3. CONCLUSIONS
We prepared hm-PVA films and evaluated their surface properties, mechanical strength, and adhesion to porcine skin by measuring their bonding, lap-shear, and T-peel strengths according to ASTM methods. We assessed the cytocompatibility of hm-PVAs in physical contact with skin cells. The water contact angles (WCAs) of the hm-PVA films increased with alkyl chain length and/or alkyl group modification ratio. The tensile strengths of the hm-PVA films decreased with increasing alkyl chain length and/or alkyl group modification ratio. The 4C3-PVA film showed excellent cytocompatibility compared to other hm-PVAs with long alkyl chain lengths (4C6-PVA and 4C9-PVA). When it was applied to porcine skin, it exhibited the highest bonding/lap-shear/T-peel strengths. Therefore, 4C3-PVA film may be an effective adhesive or bonding material for wearable medical devices.

4. MATERIALS AND METHODS
4.1. Materials. Ethanol (EtOH, 99.5%), dimethyl sulfoxide (DMSO), 6 N hydrochloric acid (HCl), 10% (v/v) formalin in neutral buffer solution, Dulbecco’s phosphate-buffered saline
PBS, and 99.9% DMSO-d_{6} with 0.05% (w/v) tetramethylsilane were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Otsuka normal saline 2-port was acquired from Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan). PVA (MW = 88 000; saponification degree > 98.5%) was procured from Nacalai Tesque, Inc. (Kyoto, Japan). Normal human dermal fibroblasts (NHDFs) were purchased from Lonza Biologics (St. Louis, MO, USA). Triton X-100 stock solution (Thermo Fisher Scientific (Tokyo, Japan)). Low-serum growth supplement (LSGS), penicillin/streptomycin solution, and phalloidin–tetramethyl rhodamine B isothiocyanate peptide from Amanita phalloides were purchased from Sigma-Aldrich Corp. (St. Louis, MO, USA). Porcine skin was acquired from Tokyo Shibaura Organ Co. Ltd. (Tokyo, Japan). Porcine skin was washed and shaved with a clipper (Thrive model 515R, Daito Electric Industry, Osaka, Japan).

4.2. Synthesis of hm-PVA. The hm-PVAs were prepared by nucleophilic substitution reaction between aldehydes and the PVA hydroxyl groups following a previously reported procedure.\(^{5,9}\) PVA (10 g) was dissolved in 98 mL H_{2}O at 80 °C for 60 min. Then, 100 mL DMSO and 2 mL of 1 N HCl were added to the solution to form a 200 mL solution comprising 5% (w/v) PVA and 1% (v/v) 1 N HCl. Various amounts of aldehyde groups (C{3}, C{6}, and C{9}) were added to the solution, and the mixtures were stirred at 50 °C for 1 h. A reflux condenser was used in all processes. The hm-PVA [H_{2}O/DMSO = 50/50 (v/v)] product was added to 600 mL cold ethanol, and the mixture was stirred for 1 h. The precipitated hm-PVAs were washed at least thrice with 300 mL EtOH to remove any unreacted aldehyde and DMSO. The solvent was evaporated under vacuum to obtain purified white hm-PVAs crystals which were then finely ground in a mill (Wonder Crusher WC-3; Osaka Chemical, Osaka, Japan).

4.3. Characterization of hm-PVAs. The chemical structures of the hm-PVAs were analyzed by nuclear magnetic resonance (\(^{1}H\) NMR) spectroscopy (AL300; JEOL Ltd., Tokyo, Japan) using a 0.5% (w/v) hm-PVA/DMSO-d_{6} solution at 25 °C. Each sample was scanned eight times. Fourier transform infrared spectroscopy (FT-IR; 8400S, Shimadzu Corp., Kyoto, Japan) was conducted to confirm the presence of acetal groups in the hm-PVAs. The scan range was 700–4000 cm\(^{-1}\), and each sample was scanned 64 times. The hydrophobic group modification ratios of the hm-PVAs were determined by \(^{1}H\) NMR spectroscopy. The modification ratios were calculated as follows

\[
\text{modification ratio (mol %)} = \left[ \frac{\text{integral area (CH proton)}}{3} \right] \times 100
\]

where the integral area (CH proton) is the area of the peak at 3.87 ppm, corresponding to the CH proton in the PVA and hm-PVA backbones, and the integral area (CH proton) is the area of the peak at 0.85 ppm assigned to the CH_{3} proton in the hydrophobic groups of the hm-PVAs.

4.4. Glass Transition Temperature of hm-PVAs. In this study, PVA and hm-PVAs powders were dried at 40 °C under vacuum for 24 h before DSC measurement. The glass transition temperatures (\(T_{\text{g}}\)) of the hm-PVAs were determined by DSC based on the technical standards established by the American Society for Testing and Materials (ASTM) E1356-03.\(^{40}\) Briefly, approximately 15 mg of each hm-PVA was placed in an aluminum pan and sealed with an autosampler. Thermograms were recorded in the range of −50 to 100 °C by DSC (Thermo Plus EVO 8230; Rigaku Corporation, Tokyo, Japan) at a heating rate of 10 °C min\(^{-1}\) under a N\(_{2}\) atmosphere.

4.5. Preparation of hm-PVA Films. hm-PVAs were dissolved in 40% (v/v) aqueous EtOH to obtain a 1% (w/v) solution. The hm-PVA solutions were then poured into silicone molds of 1 mm thick. These were dried on a clean bench (As One, Osaka, Japan) at 25 °C overnight. The dry

**Figure 6.** (a) Bonding strength measurements for hm-PVA films (scale bar = 5 mm). (b) Histology of the hm-PVA film–porcine skin interface after bonding strength measurement. The yellow arrow indicates stratum corneum exfoliation site (scale bar = 100 μm).

**Figure 7.** Bonding strength mechanism of hm-PVA films adhering to porcine skin.
hm-PVA films were peeled off from the silicone sheets. Surface morphology was observed by SEM (S4800, Hitachi Co., Tokyo, Japan). The thickness of hm-PVA films was measured with a coolant proof micrometer (MDC-MX, Mitutoyo Corporation, Kanagawa, Japan). The average thickness of each film was shown in Table 2.

### Table 2. Thickness of hm-PVA Films

| abbreviation | thickness (μm) |
|--------------|---------------|
| PVA          | 12.9 ± 0.9    |
| 4C3-PVA      | 13.1 ± 1.1    |
| 12C3-PVA     | 13.2 ± 1.1    |
| 23C3-PVA     | 13.6 ± 1.3    |
| 4C6-PVA      | 13.4 ± 1.3    |
| 4C9-PVA      | 13.6 ± 1.9    |

#### 4.6. Tensile Strength of hm-PVA Films

The tensile strengths of the hm-PVA films were determined according to the Japanese Industrial Standard (JIS) K 7161. Briefly, hm-PVA films (thickness was mentioned in Table 2) were cut into standard rectangles 150 mm long and 15 mm wide. The tensile strengths of the hm-PVA films were measured with a texture analyzer (TA-XT2i; Stable Micro Systems, Godalming, UK) at a tracking speed of 5 mm min⁻¹.

#### 4.7. Surface Wettability Measurement of hm-PVA Films

The WCAs of the hm-PVA films were measured with a contact angle meter (sessile drop method) (CAM; DM700; Kyowa Interface Science, Saitama, Japan). The hm-PVA films were placed on a glass sheet and deionized water was added to them dropwise to evaluate their water wettability.

#### 4.8. Cytocompatibility Test of hm-PVAs

NHDFs were cultured in Medium 106 (Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% (w/v) LSGS (Sigma-Aldrich Corp., St. Louis, MO, USA) under standard cell culture conditions (sterility; 37 °C; humidified 5% CO₂ atmosphere). One hundred microliter culture medium containing 5 × 10⁴ NHDF cells was placed in each well of 96-well plates and incubated for 24 h to ensure cell adhesion to the polystyrene surface. The culture medium in each well was then removed. Then, 100 μL culture medium aliquots containing various hm-PVA concentrations were added to each well. After incubation for an additional 24 h, 10 μL cell count reagent (WST-8) was added to each well followed by incubation for 2 h. The absorbances of the well contents were measured at 450 nm in a microplate reader (Spark10M; Tecan, Osaka, Japan). All operations were conducted on a clean bench (As One, Osaka, Japan). The actin cytoskeletons of the NHDF cells were stained with phalloidin–tetramethyl rhodamine B isothiocyanate peptide, and their nuclei were stained with DAPI. Briefly, the media was removed and the wells were washed with PBS solution. Then, 100 μL of fresh fixative solution (4% (v/v) paraformaldehyde in PBS) was added to each well and the cells were fixed at room temperature for 15 min. The fixative solution was then removed, and the wells were washed with PBS. Then, 0.2% (v/v) Triton X-100 solution was added to each well and left for 10 min at room temperature. The Triton X-100 was then removed by washing thrice with PBS. Blocking solution [1% (v/v) bovine serum albumin (BSA) in PBS] was added to each well and left for 1 h. After removing the blocking solution, 400 μL of phalloidin–tetramethyl rhodamine B isothiocyanate peptide in 1% (v/v) BSA (1:100 dilution) was added to each well and left for 1 h.

Each well was then washed at least thrice with PBS. DAPI in PBS (1:100 dilution) was added to each well, left for 10 min, and washed thrice with PBS. The stained cells were then observed under an inverted fluorescence phase contrast microscope (BX-ZX700; Keyence Co., Tokyo, Japan).

#### 4.9. Bonding Strength Measurement of the hm-PVA Films

Bonding strengths of the hm-PVA films on porcine skin were determined according to ASTM F2258-05. Briefly, porcine skin was cut into 25 mm × 25 mm squares and placed on the surface of a heater set to 37 °C. A sterile cotton surgical gauze was used to remove excess moisture from the skin surfaces. The hm-PVA films (thickness was mentioned in Table 2, 25 mm × 25 mm) were applied to the skin, and 50 μL of 40% (v/v) EtOH was dropped on the film surfaces to induce them to swell. The bonding energy of hm-PVA films was measured by the texture analyzer (TA-XT2i; Stable Micro Systems, Godalming, UK) at 2 N applied force, 3 min waiting time, and 10 mm min⁻¹ tracking speed.

To elucidate the adhesion mechanism, a cross-section of the porcine skin was observed after the bonding test. It was fixed in 10% (v/v) formalin neutral buffer solution, stained with hematoxylin and eosin, and examined under an inverted fluorescence phase contrast microscope (BX-ZX700; Keyence Co., Tokyo, Japan).

#### 4.10. Lap-Shear Strength Measurement of hm-PVA Films

The lap-shear strengths of the hm-PVA films were evaluated according to ASTM F2255-05. Briefly, porcine skin was cut into 50 mm × 25 mm rectangles and placed on the surface of the heater set to 37 °C. A sterile cotton surgical gauze was used to remove excess moisture from the skin surfaces. The hm-PVA films (thickness was mentioned in Table 2, length is 25 mm, and width is 10 mm) were applied to skin rectangles. Then, 20 μL of 40% (v/v) EtOH was dropped on the film surface and other pieces of skin were superimposed on them. A 200 g weight was placed on each composition and left there at 37 °C for 3 min. The lap-shear strengths of the hm-PVA films were measured by the texture analyzer at 5 mm min⁻¹ tracking speed.

#### 4.11. T-Peel Strength Measurement

The T-peel strengths of the hm-PVA films on porcine skin were determined according to ASTM F2256-05. Briefly, porcine skin was cut into 150 mm × 15 mm rectangles and excess moisture was removed from them with a mesh. The hm-PVA films were applied to the skin rectangles, and 40% (v/v) EtOH was sprayed onto them. After drying at 25 °C for 1 h, the peeling strengths of the hm-PVA films (thickness was mentioned in Table 2, 150 mm × 15 mm) were established by the texture analyzer at 200 mm min⁻¹ tracking speed. The average values of the peeling force were calculated over a 40–100 mm displacement range.

#### 4.12. Statistical Analysis

Statistical analysis was carried out using the Tukey–Kramer test with KyPlot software. Statistically significant differences were accepted when p < 0.05. Data are presented as means ± standard deviations (SD).

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b03305.

SEM images of the surface of PVA and hm-PVA films (PDF)
ACKNOWLEDGMENTS

The authors thank Dr. A. Nishiguchi, M. Katano, S. Watanabe, and Y. Kurihara of the Polymeric Biomaterials Group at the National Institute for Materials Science (NIMS) for their technical support. This research was partially supported by the Project for Japan Translational and Clinical Research Core Centers from the Japan Agency for Medical Research and Development (AMED), “Innovation inspired by Nature” Research Support Program, SEKISUI CHEMICAL CO. LTD, and Uehara Memorial Foundation.

REFERENCES

(1) Custodio, V.; Herrera, F.; López, G.; Moreno, J. A Review on Architectures and Communications Technologies for Wearable Health-Monitoring Systems. Sensors 2012, 12, 13907–13946.
(2) An, B. W.; Shin, J. H.; Kim, S.-Y.; Kim, J.; Ji, S.; Park, J.; Lee, Y.; Jang, J.; Park, Y.-G.; Cho, E.; Jo, S.; Park, J.-U. Smart Sensor Systems for Wearable Electronic Devices. Polymers 2017, 9, 303.
(3) Luo, C.; Liu, N.; Zhang, H.; Liu, W.; Yue, Y.; Wang, S.; Rao, J.; Yang, C.; Su, J.; Jiang, X.; Gao, Y. A new approach for ultrahigh-performance piezoresistive sensor based on wrinkled PPY film with electropun PVA nanowires as spacer. Nano Energy 2017, 41, 527–534.
(4) Hu, C.; Zhang, Y.; Wang, X.; Xing, L.; Shi, L.; Ran, R. Stable, Strain-Sensitive Conductive Hydrogel with Antifreezing Capability, Remoldability, and Reusability. ACS Appl. Mater. Interfaces 2018, 10, 40400–40410.
(5) Liu, W.; Liu, N. S.; Yue, Y.; Rao, J. Y.; Cheng, F.; Su, J.; Liu, Z. T.; Gao, Y. H. Piezoresistive Pressure Sensor Based on Synergistical Innerconnected Polyvinyl Alcohol Nanowires/Wrinkled Graphene Film. Small 2018, 14, 1704149.
(6) Park, S.; Heo, S. W.; Lee, W.; Inoue, D.; Jiang, Z.; Yu, K.; Jinno, H.; Hashizume, D.; Sekino, M.; Yokota, T.; Fukuda, K.; Tajima, K.; Someya, T. Self-powered ultra-flexible electronics via nano-grating-patterned organic photovoltaics. Nature 2018, 561, 516–521.
(7) Kwak, M. K.; Jeong, H.-E.; Suh, K. Y. Rational Design and Enhanced Biocompatibility of a Dry Adhesive Medical Skin Patch. Adv. Mater. 2011, 23, 3949–3953.
(8) Singer, A. J.; Quinn, J. V.; Hollander, J. E. The cyanoacrylate topical skin adhesives. Am. J. Emerg. Med. 2008, 26, 490–496.
(9) Kim, D. W.; Baik, S.; Min, H.; Chun, S.; Lee, H. J.; Kim, K. H.; Lee, J. Y.; Pang, C. Highly Permeable Skin Patch with Conductive Hierarchical Architectures Inspired by Amphibians and Octopi for Omnidirectionally Enhanced Wet Adhesion. Adv. Funct. Mater. 2019, 29, 1970080.
(10) Canipa, S. J.; Chilton, M. L.; Hemingway, R.; Macmillan, D. S.; Myden, A.; Plante, J. P.; Tennant, R. E.; Vessey, J. D.; Steger-Hartmann, T.; Gould, J.; Hillegass, J.; Etter, S.; Smith, B. P. C.; White, A.; Sterchele, P.; De Smidt, A.; O’Brien, D.; Parakhia, R. A quantitative in silico model for predicting skin sensitization using a nearest neighbours approach within expert-derived structure-activity alert spaces. J. Appl. Toxicol. 2017, 37, 985–995.
(11) He, M.; Zhang, Q. Y.; Guo, J. Y. Synthesis and characterization of silicone based Pressure sensitive adhesive. In Emerging Focus on Advanced Materials, Parts 1 and 2; Liu, S. Q., Zuo, M., Eds.; Trans Tech Publications, 2011; Vol. 306–307, pp 1773–1778.
(12) Antosik, A. K.; Bednarczyk, P.; Czech, Z. Aging of silicone pressure-sensitive adhesives. Polym. Bull. 2018, 75, 1141–1147.
(13) Matsumura, H.; Imai, R.; Ahmatjan, N.; Ida, Y.; Gondo, M.; Shibata, D.; Wanatabe, K. Removal of adhesive wound dressing and its effects on the stratum corneum of the skin: comparison of eight different adhesive wound dressings. Int. Wound J. 2014, 11, 50–54.
(14) Bae, W. G.; Kim, D.; Kwak, M. K.; Ha, L.; Kang, S. M.; Suh, K. Y. Enhanced skin adhesive patch with modulus-tunable composite micropillars. Adv. Healthcare Mater. 2013, 2, 109–113.
(15) Chen, X.; Mizuta, R.; Fukuta, N.; Taguchi, T. Design of bio-inspired adhesive surface composed of hexagonal group-modified gelatin and silicon nanowire. Colloids Surf., B 2019, 178, 111–119.
(16) Yang, S. Y.; O’Cearbhaill, E. D.; Sisk, G. C.; Park, K. M.; Cho, W. K.; Villiger, M.; Bouna, B. E.; Pomahac, B.; Karp, J. M. A bio-inspired swellable microneedle adhesive for mechanical interlocking with tissue. Nat. Commun. 2013, 4, 1702.
(17) Baik, S.; Kim, D. W.; Park, Y.; Lee, T.-J.; Ho Bang, S.; Pang, C. A wet-tolerant adhesive patch inspired by protuberances in suction cups of octopi. Nature 2017, 546, 390–400.
(18) Yamagishi, K.; Kirino, I.; Takahashi, I.; Amano, H.; Takeoaka, S.; Morimoto, Y.; Fujise, T. Tissue-adhesive wireless powered optoelectronic device for metronomic photodynamic cancer therapy. Nat. Biomed. Eng. 2019, 3, 27–36.
(19) Georgieva, N.; Bryskova, R.; Tzoneva, R. New Polyvinyl alcohol-based hybrid materials for biomedical application. Mater. Lett. 2012, 88, 19–22.
(20) Sulaiman, N. H.; Ghazali, M. J.; Majlis, B. Y.; Yunas, J.; Razali, M. Influence of Polyvinylalcohol on the Size of Calcium Ferrite Nanoparticles Synthesized Using a Sol-gel Technique. In International Conference for Innovation in Biomedical Engineering and Life Sciences, ICIBEL2015; Ibrahim, F., Usman, J., Mohiktar, M. S., Ahmad, M. Y., Eds.; Springer: New York, 2016; Vol. 56, pp 198–202.
(21) Chen, X.; Taguchi, T. Hydrophobically modified poly(vinyl alcohol) as antiatherogenic coating materials. Mater. Sci. Eng., C 2019, 102, 289–298.
(22) Gazaz, T.; Sulong, A.; Akhtar, M.; Kadhum, A.; Mohamad, A.; Al-Amieri, A. Properties and Applications of Polyvinyl Alcohol, Halloysite Nanotubes and Their Nanocomposites. Molecules 2015, 20, 22833–22847.
(23) Chonat, M.; Le Visage, C.; Baillie, W. E.; Escoubet, B.; Chaubet, F.; Mateescu, M. A.; Letourneur, D. A Novel Cross-linked Poly(vinyl alcohol) (PVA) for Vascular Grafts. Adv. Funct. Mater. 2008, 18, 2855–2861.
(24) Miyamoto, A.; Lee, S.; Cooray, N. F.; Lee, S.; Mori, M.; Matsuhashi, N.; Jin, H.; Yoda, L.; Yokota, T.; Itoh, A.; Sekino, M.; Kawasaki, H.; Ebihara, T.; Amagai, M.; Someya, T. Inflammation-free, gas-permeable, lightweight, stretchable on-skin electronics with nanomeshes. Nat. Nanotechnol. 2017, 12, 907–913.
(25) Mansur, H. S.; Saddahira, C. M.; Souza, A. N.; Mansur, A. A. P. FTIR spectroscopy characterization of poly (vinyl alcohol) hydrogel with different hydrogel degree and chemically crosslinked with glutaraldehyde. Mater. Sci. Eng., C: Biomimetic Supramol. Syst. 2008, 28, 539–548.
(26) Zhang, Y.; Zhu, P. C.; Edgred, D. Crosslinking reaction of poly(vinyl alcohol) with glyoxal. J. Polym. Res. 2010, 17, 725–730.
(27) Hassan, C. M.; Peppas, N. A. Structure and applications of poly(vinyl alcohol) hydrogels produced by conventional crosslinking or by freezing/thawing methods. In Biopolymers/Pva Hydrogels/ Anionic Polymerisation Nanocomposites; Abe, A., Ed.; Springer, 2000; Vol. 153, pp 37–65.
(28) Hassan, C. M.; Peppas, N. A. Structure and morphology of freeze/thawed PVA hydrogels. Macromolecules 2000, 33, 2472–2479.
(29) Ricciardi, R.; Auriemma, F.; De Rosa, C.; Laupre, F. X-ray diffraction analysis of poly(vinyl alcohol) hydrogels, obtained by freezing and thawing techniques. Macromolecules 2004, 37, 1921–1927.
(30) Gao, H. F.; Yang, H. Characteristics of poly(vinyl alcohol) films crosslinked by cinnamaldehyde with improved transparency and water resistance. J. Appl. Polym. Sci. 2017, 134, 45324.
(31) Mizuta, R.; Ito, T.; Taguchi, T. Effect of alkyl chain length on the interfacial strength of surgical sealants composed of hydrophobically-modified Alaska-pollock-derived gelatins and poly(ethylene)-glycol-based four-armed crosslinker. *Colloids Surf., B* 2016, 146, 212–220.

(32) Mizuno, Y.; Mizuta, R.; Hashizume, M.; Taguchi, T. Enhanced sealing strength of a hydrophobically-modified Alaska pollock gelatin-based sealant. *Biomater. Sci.* 2017, 5, 982–989.

(33) Mizuta, R.; Taguchi, T. Enhanced Sealing by Hydrophobic Modification of Alaska Pollock-Derived Gelatin-Based Surgical Sealants for the Treatment of Pulmonary Air Leaks. *Macromol. Biosci.* 2017, 17, 1600349.

(34) Yoshizawa, K.; Taguchi, T. Enhanced bonding strength of hydrophobically modified gelatin films on wet blood vessels. *Int. J. Mol. Sci.* 2014, 15, 2142–2156.

(35) Yoshizawa, K.; Taguchi, T. Bonding behavior of hydrophobically modified gelatin films on the intestinal surface. *J. Bioact. Comput. Polym.* 2014, 29, 560–571.

(36) Yoshizawa, K.; Mizuta, R.; Taguchi, T. Enhanced angiogenesis of growth factor-free porous biodegradable adhesive made with hexanoyl group-modified gelatin. *Biomaterials* 2015, 63, 14–23.

(37) Nishiguchi, A.; Sasaki, F.; Maeda, H.; Kabayama, M.; Ido, A.; Taguchi, T. Multifunctional Hydrophobized Microparticles for Accelerated Wound Healing after Endoscopic Submucosal Dissection. *Small* 2019, 15, 1901566.

(38) Ito, M.; Taguchi, T. Enhanced insulin secretion of physically crosslinked pancreatic beta-cells by using a poly(ethylene glycol) derivative with oleyl groups. *Acta Biomater.* 2009, 5, 2945–2952.

(39) Rault, J.; Gref, R.; Ping, Z. H.; Nguyen, Q. T.; Neel, J. Glass transition temperature regulation effect in a poly(vinyl alcohol)-water system. *Polymer* 1995, 36, 1655–1661.

(40) Peng, C.; Chen, G. Preparation and Assessment of Heat-Treated alpha-Chitin Nanowhiskers Reinforced Poly(vinyl alcohol) Film for Packaging Application. *Materials* 2018, 11, 1883.

(41) Liang, Y.; Shi, J.; Xiao, P.; He, J.; Ni, F.; Zhang, J.; Huang, Y.; Huang, C.-F.; Chen, T. A lotus-inspired Janus hybrid film enabled by interface self-assembly and in situ asymmetric modification. *Chem. Commun.* 2018, 54, 12804–12807.