Fabrication of a PVA-Based Hydrogel Microneedle Patch

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**ABSTRACT:** The degree of saponification, which is a dissolution characteristic of poly(vinyl alcohol) (PVA), is used to blend PVA to prepare a hydrogel microneedle (MN) patch. The MN patch was manufactured with an adjustable disassembly time using a molding process, and it was confirmed to have morphological stability and excellent needle formation. The permeability of the gelatin sheet, which is analogous to the skin elasticity coefficient of a real human, was confirmed. The penetration ratio had a very high value of 100% and sufficient physical properties to penetrate the skin. In the disassembly experiment, the MN patch was produced with ratios of lower:higher saponification of 6:4 (PVA6), 7:3 (PVA7), 8:2 (PVA8), 9:1 (PVA9), and 10:0 (PVA10). Degradation did not occur for PVA6 and PVA7 but occurred for PVA8, PVA9, and PVA10. A cytotoxicity test to investigate its suitability for use in the human body confirmed the cell viability of 80% or more and nontoxic properties. Therefore, sufficient cell viability was confirmed when compared to the existing products.

1. INTRODUCTION

Although oral administration accounts for the majority of drug delivery methods, it has limitations in cosmetology where immediate effects are desired, and it is questionable whether the drug is actually effective.1 A transdermal drug delivery system (TDDS) is the most notable and attractive method to compensate for such shortcomings by effectively conveying the active ingredient to the desired layer of the skin.2

However, the corneal layer is the main barrier to drug penetration, so substances that can be delivered via the transdermal route are limited to small (<500 Da) intermediate hydrophobic compounds.1,3 Microneedle (MN) arrays use tens to hundreds of micron-sized needles, providing a painless option to increase skin permeability and enhance transdermal transmission.2,4 This technique can be used to create micropores in which the drug diffuses into the microcirculation of the skin to provide a minimally invasive, comprehensive therapeutic polymer across the skin surface and epidermis.5 This microneedle array can be implemented in various applications, such as medical diagnosis, home diagnosis, beauty/clinic, medical treatment, and medical equipment.

MN patch manufacturing methods can be broadly divided into two types: micro-mold-free methods and micromolding methods.6−8 The distribution methods for MN patches include solid microneedles, hollow microneedles, coated microneedles, swellable microneedles, and dissolving microneedles.7,8 Among these methods, the following paper produced a biodegradable MN patch by preparing an MN patch via micromolding and solving microneedles using a poly(vinyl alcohol) (PVA)-based hydrogel. This system can be applied not only to functional substances but also to synthetic chemical drugs and biopharmaceuticals in polymer materials, with the possibility of expanding its use to the medical field.

We used PVA for the fabrication of the MN patch owing to the advantages of water solubility, biocompatibility, and excellent physical properties.9−12 Also, PVA has promising biomedical applications in various fields such as tissue mimicking, vascular cell culturing, and implanting. Especially, transparent PVA hydrogel has been used for minimal-invasive surgery with needle intervention.13 Moreover, the microneedle is an efficient platform to make easy handling and reduce the fear of invasiveness.14 Among these advantages, solubility is a significant factor in biodegradable MN patches that determines the properties of PVA because it is highly dependent on saponification.9,10 Substances with a degree of saponification of 99.0 mol% or more have a strong intermolecular hydrogen bond and a high melting point due to increased conversion to alcohol in acetic acid, and they are difficult to dissolve in water. Therefore, we have tried to improve the solubility by adding a substance with a low degree of saponification.10 The PVA with higher saponification used $M_w$ 85,000−124,000, >99% hydrolyzed, and the lower saponification also used $M_w$ 13,000−23,000, 87−89% hydrolyzed.

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2. MATERIALS AND METHODS

2.1. Materials. As shown in Figure 1, the template (Smicna, Pte. Ltd.) used in the molding process provides a needle length of 500 μm in width and a length of 30 × 30 mm², consisting of silicone material. Two types of PVA are used in the production of MN patches, poly(vinyl alcohol) (PVA) of \(M_w\) 74,800, 97−100 mol % hydrolyzed (Tokyo Chemical Industry Co., Ltd.), and PVA of \(M_w\) 13,000−23,000, 87−89% hydrolyzed (Sigma Aldrich Chemistry Co., Ltd.). For the dye, marine sponge pigment (Microbulbifer echini; MPRBM-20201022008) and methylene blue solution (Sigma Aldrich Chemistry Co., Ltd.) were used.

2.2. PVA-Based MN Patch Fabrication. A patch was prepared by introducing a PVA blend solution into the mold and applying a solution casting method of drying as it is under certain conditions. Low-saponification PVA and high-saponification PVA were used in the ratio of 10:0 (PVA10), 9:1 (PVA9), 7:3 (PVA7), 5:5 (PVA5), 3:7 (PVA3), 1:9 (PVA1), and 0:10 (PVA) to prepare the PVA solutions, and these samples were used for the measurement of mechanical properties. Additionally, PVA6 (6:4) and PVA8 (8:2) were conducted by penetration and degradation tests, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). Ten milliliters of distilled water was mixed (10 wt %) so that the total PVA weight was 1 g. Then, the mixture was thoroughly stirred in a water bath to mix the solution. The solution was poured into a mold and stored in an oven at 40 °C for 24 h to produce a filmlike MN patch as shown in Figure 2. Moreover, active ingredients are added to the PVA-based MN patch to confirm whether active ingredients remain in the patch after mold processing. The active ingredients are contained in 5 wt % of the PVA solution.

2.3. Observation of MN Array Needle Observation Using Scanning Electron Microscope (SEM) and Optical Microscope. The needles of the prepared MN array patch were well formed, and their shapes were observed using a scanning electron microscope (SEM; SU8230, Hitachi, Japan and JSM-7610FPlus, JEOL, Japan) and an optical microscope.

2.4. Measurement of the Physical Properties of the MN Patches. The mechanical properties were measured using a Universal Testing Machine (UTM, AG-X, Shimadzu, Japan) to check whether the prepared MN patch had the strength to penetrate the stratum corneum of the skin. A 500 N load cell was used for the tensile test. The tensile speed was 60 mm/min. The sample size was 20−25 mm in length, 5.0 ± 0.2 mm in width, and 0.3 ± 0.14 mm in thickness. Each tensile experiment was repeated five times for each sample.

The compression strength measurement experiment was conducted at 1 mm/min in a 100 N load cell. The sample was used by cutting the prepared MN patch into an area of one needle. While compressing the microneedle, the bending strength refers to the section where the needle endurance bends. This was set as the value of the part where the force increased constantly and was then rapidly increased.

2.5. Degradability Measurement of PVA-Based Patches. Purple pigment extracted from the marine sponge and 1 wt % of methylene blue solution were added to the sample for visual confirmation of the degradation. Additional experiments were conducted under phosphate buffer saline (PBS) (Hyclone), which appears in the human body. At this time, the sample size was cut to 2 × 2 cm². The sample was immersed in PBS to have an initial hydration process. After that, the mass of the degraded weight of the sample was measured at regular time intervals. The results of the exploded view were graphed with percentages of the initial hydrated mass and the degraded mass.

2.6. Measured Skin Permeability of the MN Array Patches. 2.6.1. Gelatin Sheet Preparation. First, for the permeability experiment, a gelatin sheet with the same elastic modulus as that of an actual human stratum corneum was prepared. For this reason, gelatin was added to distilled water at each ratio (5, 7, 10, 15, 20 wt %). Then, after boiling at 40−60 °C, it was poured into a Petri dish and gelated overnight in the refrigerator. The elastic modulus of the produced sample was measured through a compression experiment with a UTM.

2.6.2. Measurement of MN Permeability. A sample of MN patches was stained with purple pigment extracted from the marine sponge and 1 wt % of methylene blue solution were added to the sample for visual confirmation of the degradation. Additional experiments were conducted under phosphate buffer saline (PBS) (Hyclone), which appears in the human body. At this time, the sample size was cut to 2 × 2 cm². The sample was immersed in PBS to have an initial hydration process. After that, the mass of the degraded weight of the sample was measured at regular time intervals. The results of the exploded view were graphed with percentages of the initial hydrated mass and the degraded mass.
marine sponge and methylene blue for certain samples to see if they could permeate over the gelatin sheets produced. We put 12 × 10 needles horizontally on a gelatin sheet and pushed it with a 1 kg weight for about 2 min. The above sample was removed, and the number of points stained on the sheet was confirmed. At this time, the permeability was calculated by dividing the total number of needles in the sample by the number of needles stained on the sheet. Also, the microneedle was observed by an optical microscope to ensure the microneedle's shape degradation (Figure S4).

2.7. TGA Measurements of PVA-Based MN Patches. The TGA (TA Instrument SDT Q600) was measured using a sample obtained by powdering the prepared film-type patch with a freezer grinder (SPEX 6775 Freezer/Mill). It was performed for each sample for 3−5 mg at a heating rate of 10 min in a nitrogen atmosphere. Pyrolysis occurred for each sample in the programmed temperature range of 25−600 °C, and the continuous weight loss and temperature were recorded and analyzed.

2.8. DSC Measurement of PVA-Based MN Patches. The DSC (2910, TA Instruments) measurement was performed using samples obtained by powdering the prepared film-type patch with a freezer grinder (SPEX 6775 Freezer/Mill). PVA10, PVA9, PVA8, PVA7, and PVA6 samples were heated from 25 to 250 °C at a rate of 10 °C/min. After reaching the target temperature, it was stabilized for 5 min. While lowering from 250 to 25 °C again, the temperature was lowered at the rate of 10 °C/min and stabilized for 5 min after reaching the target temperature. By performing this process twice, the melting temperature ($T_m$) and crystallization temperature ($T_c$) of each sample could be obtained.

2.9. Measurement of the Cytotoxicity of MN Patches. The sample was sterilized with UV at 2.5 × 2.5 cm², DMEM 89%, FBS 10%, and 2.5 mL of antibiotic 1% were added as the sample gel, positive control, and negative control, respectively. After that, the mixture was eluted in a CO₂ 5% incubator at 37 °C for 72 h. After subculturing the mMSCs, 10,000 of them were added to a 96-well plate each, including 100 mL of the culture solution. After eluting for 72 h, the culture medium in the 96-well plate was suctioned and the eluate was added. The eluate was put in a ratio of 1x = 100% eluate; 2x = 50% eluate and 50% culture; 4x 25% eluate and 75% culture; and 8x = 12.5% eluate and 87.5% culture. After 24 h of adding the eluate, the culture solution: MTS solution (EZ-Cytox) = 10:1 ratio. Then, after waiting for sufficient color development for about 1 h, the absorbance was measured.

3. RESULTS AND DISCUSSION

3.1. MN Patch Fabrication. The low- and high-saponification PVA blend MN patches produced through the molding process were confirmed to have excellent overall shape stability. The needles were well formed, as shown in Figure 3, which consists of photographs observed via SEM and an optical microscope. In addition, the shape stability was excellent even when the active ingredient was added. After solution casting of the PVA solution mixed with the active ingredient, Niacinamide was added. Then, Fourier transform infrared spectroscopy (FT-IR) measurement confirmed that the active ingredient remained in the patch (Figure S2).

![Figure 3. SEM observation image of MN: (a) MN viewed from above at 1.00 mm magnification, (b) MN viewed from above at 100 μm magnification, (c) MN viewed from the side at 1.00 mm magnification, and (d) MN viewed from the side at 100 μm magnification.](http://pubs.acs.org/journal/acsodf)
3.2. Measurement of Mechanical Properties and Strength of the MN.

Mechanical properties of MN patch were conducted by a tensile test. Figure 4 indicates the graphs of the fracture stress, fracture strain, and elastic modulus. The fracture stress—fracture strain curve showed that mechanical properties of PVA decreased according to the degree of saponification because the high degree of saponification of PVA was more translated into the alcohol group than in the lower group. Therefore, the high degree of saponification has a lot of hydrogen bonds. This structure leads to higher levels of stress and strain. However, PVA9 and PVA10, with a low degree of saponification, have more acetate groups, which makes the distance between molecular chains remote and intermolecular hydrogen bonds weak. As a result of this, PVA9 and PVA10 have increased strength.

The elastic modulus also decreased depending on the saponification ratio and showed a similar trend with the fracture stress (Figure 4a). The result of the compression test to confirm the strength of the fabricated needle is as shown in Figure 4b, the force decreased rapidly at 1.37 N. The moment when the force declines momentarily indicates that the needle was bent (Figure 4c). This value is considered to indicate that the needle can penetrate the skin when it has a strength of 0.08 N/needle, as shown in previous studies. Therefore, it can be seen to have sufficient physical properties for skin penetration.

3.3. Degradability Measurement of MN.

Experiments were conducted with PVA6, PVA7, PVA8, PVA9, and PVA10 to clarify the ratio of saponification because degradation occurred after PVA7 in the previous research. All of the samples are the results of the initial hydration process. In the case of PVA8, PVA9, and PVA10 films, as shown in Figure 5, complete degradation was confirmed to have occurred with the degradability reaching 100%. However, in the case of PVA6 and PVA7, degradation was not found. In addition, the shape of the microneedle after immersion in PBS has proper degradation (Figure S7). To confirm the detailed degradation ratio, degradability experiments were conducted with PVA8, PVA7.75, PVA7.5, and PVA7.25. In the case of PVA8, complete degradation occurred after 28 min, but that of the remaining PVA7.75, PVA7.5, and PVA7.25 were confirmed to be partially degraded (Figure S8). However, for PVA7.25, degradation was not observed overall, and the characteristic swelling behavior of general hydrogels was observed.

3.4. Measurement of the Permeability of the MN.

Needles with the appropriate physical properties were subjected to permeability experiments to see if they could penetrate the stratum corneum of the actual skin. The elastic...
modulus of human skin is about 0.013 MPa, and the elastic modulus of the gelatin sheet produced at 7 wt % was confirmed to be 0.013 MPa (Figure S3). The penetration experiment on the 7 wt % gelatin sheets confirmed via microscopic observation the presence of 120 blue dots normally stained on the gelatin sheet out of a total of 120 needles. This confirmed that the microneedle had a high permeability of 100% (Figure S4).

In addition, the penetration experiment with porcine skin showed a higher permeability of 100% (Figure S5). Moreover, the subcutaneous tissue permeation experiment of leporine confirmed that the needle did not bend and was dissolved after permeation during microscopic observation. Therefore, it was also confirmed to have permeated the subcutaneous tissue (Figure S6).

3.5. TGA Measurement of PVA-Based MN Patches. TGA experiments were performed to analyze the composition of the MN patches prepared by varying the ratio of the low degree of saponification and the high degree of saponification in the PVA. From Figure 6, an increase in temperature to 100 °C reveals the weight loss due to water evaporation. The sudden loss of the initial weight was likely to be caused by further thermal decomposition of large polymer chains after thermal decomposition into smaller pieces. Due to the difference in the ratio, a slight difference was confirmed in the first major pyrolysis. The major pyrolysis of PVA10 and PVA9 occurred at higher temperatures. The weight loss at up to 350 °C was about 80%, and the samples show pyrolysis with a slow weight reduction of about 15% at 350–500 °C. After that, a constant weight of about 5% was maintained at over 500 °C.

3.6. DSC Measurement of PVA-Based MN Patch. The results of the degradability experiment predicted that the difference between the exploded views of PVA8 and PVA7 was due to structural changes. The reason why there is a change in structure is that PVA has a saponification process that switches from poly(vinyl acetate) to poly(vinyl alcohol), which is affected by degradation because of the transition in the structure. Therefore, the difference in the melting points ($T_m$) of the PVA polymer blend films was confirmed via DSC measurements. In the DSC curve, the melting temperature ($T_m$) was 166.48 °C for PVA10, 167.10 °C for PVA9, 168.61 °C for PVA8, 180.15 °C for PVA7, and 182.64 °C for PVA6, as shown in Figure 7. The $T_m$ was confirmed to be higher when the film had not degraded than when the film had degraded.

3.7. Measurement of the Cytotoxicity of MN. Cytotoxicity experiments were conducted to find out whether it is suitable for the human body, since it is to be used for human skin. The experiment was conducted with a company’s...
product, a basic PVA patch and a PVA patch with Niacinamide added. The cell viability of both of the prepared patches (Figure 8) was confirmed to be 80% or more, and they were not toxic. In addition, it showed appropriate cell viability even when compared with commercially available products. As a result of this, the cell viability of the PVA hydrogel and the Niacinamide hydrogel in PVA-based hydrogel is applicable to humans, observing that cell morphology was well formed in 80−100%.19

4. CONCLUSIONS

The saponification degree is one of the dissolution characteristics of PVA, and it can be used to create an MN patch with controllable degradation time by blending low-saponification PVA with high-saponification PVA. The overall morphological stability was confirmed to be excellent when fabricated using a mixture of molding process PVA. In addition, the needle formation was confirmed via an optical microscope and SEM to have formed well. The MN patch formation according to the ratio was confirmed to be the best with a low degree of saponification and a high degree of saponification of a 9:1 ratio (PVA9), and experiments were conducted based on this ratio. Even when the active ingredient was loaded into the PVA9 patch, the shape stability was maintained, and the needle formation was well formed.

The measurements of the tensile and compression mechanical properties confirmed that fracture stress and strain decrease depending on the degree of saponification because of the structure through the hydrolysis process. Also, in the elastic modulus, showed a decreasing figure, however PVA9, 10 rose the figure. According to these results, PVA9 is the ideal sample, considering the fracture stress and strain and the elastic modulus. The results of measuring the strength of the needle showed that the force rapidly decreased at the portion where the needle was bent, with the value of 1.37 N, showing sufficient physical properties to penetrate the skin.

The degradability experiment was performed with PVA6, PVA7, PVA8, PVA9, and PVA10, but PVA6 and PVA7 did not degrade and swell. Degradation occurred for PVA8, PVA9, and PVA10, and the initial degradation was fastest at PVA10, consisting of low-saponification substances, followed by PVA9 and PVA8. Accordingly, the degradation time could be seen to have adjusted according to the saponification ratio. In the degradability experiment, PVA7.25, PVA7.5, PVA7.75, and PVA8 ratios were further performed. Complete degradation occurred in PVA8, but partial degradation occurred in PVA7.25, PVA7.5, and PVA7.75. Degradation was considered not to occur in areas where high-saponification materials are concentrated due to structural crystal changes according to the polymer blend and that degradation occurred only in areas where a low degree of saponification was concentrated.

A permeability experiment was conducted to confirm the degree of permeation of a needle having suitable physical properties in the gelatin sheet with the same elastic modulus as that of the actual human skin. For convenience to observe the permeation of the needle in the gelatin sheet, the sample was prepared by mixing methylene blue solution to conduct the experiment. The microneedle has high permeability of 100%. The blue dot was observed with a microscope to confirm that the needle penetrated and dissolved. As a result of this, it could be seen that blue dots were completely dyed on the gelatin sheet.

The DSC measurement was performed to determine the change in the molecular structure that is expected to affect the degree of degradability from saponification. As a result, the change in the melting point between PVA8, PVA9, and PVA10 that degrade and PVA7 and PVA6 that do not degrade was confirmed. A higher melting point was confirmed when it was not degraded. Through this, the molecular structure, that is, the crystal structure, was found to have been formed with a higher ratio of high-saponification PVA, indicating a higher melting point.

Cytotoxicity tests were conducted to determine whether it is suitable for use in humans. The results confirmed that the cell viability was 80% or more, which is nontoxic. In addition, sufficient cell viability was confirmed even compared to the existing products.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c01993.

Shape of microneedle compared with the added niacinamide, IR curve for confirmation of active ingredient, elastic modulus of gelatin sheet, gelatin sheet penetration test, porcine skin penetration test, experiment on the permeability using subcutaneous tissue of the leporine, the microneedle after immersion in PBS, and degradability experiment (PDF)

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Author Contributions
Y.H.N. perceived the idea and designed the experiments. N.G.O. and S.Y.H. developed the materials and performed the
characterization. N.G.O., S.Y.H., and Y.H.N. analyzed the data. N.G.O. and Y.H.N. wrote the paper. All authors have reviewed the manuscript and approved the final version of the manuscript.

Notes
The authors declare no competing financial interest.

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