Development of Drug-in-Adhesive Patch with a Honeycomb Film as a Backing Layer

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Excess stripping of stratum corneum (SC) layers by patch-peeling from the skin surface is one cause of skin irritation. High SC hydration by patch occlusion may also cause skin irritation, although the occlusive technique is preferable to increase the skin permeation of topically applied drugs. In the present study, film having a honeycomb structure was selected as the backing layer of a drug-in-adhesive (DIA) patch to reduce peeling of the SC without losing adhesion force to the skin surface, as well as decreasing the skin permeation of a model drug, tulobuterol. The usefulness of the DIA patch with honeycomb film was evaluated by transepidermal water loss (TEWL) changes, amount of SC removed by patch-peeling, distribution pattern of removed SC on the adhesive layer, and water permeation through the patch. Furthermore, skin permeation and release profiles of tulobuterol from the DIA patch were investigated. Significantly \( p<0.05 \) less TEWL change was observed after removal of the patch with a honeycomb film compared with the conventional pressure-sensitive adhesive patch, and no difference in tulobuterol permeation through skin from the patches was confirmed regardless of the type of backing layer. In addition, a lower amount of SC was removed by the peeling of the patch with a honeycomb film. The results suggest that DIA patches with a honeycomb film as a backing layer may be used to achieve less SC removal without reducing the skin permeation of drugs.

Key words drug-in-adhesive patch; honeycomb film; backing layer; transepidermal water loss (TEWL) change; skin permeation

As many countries have already become super-aged societies, improvement in quality of life is an important issue in extending healthy life expectancy. Transdermal drug delivery systems (TDDSs) have advantages in terms of ease of use, administration without water, and a comparatively simple dosage regimen such as once a day. Furthermore, elderly patients, especially Alzheimer and/or dementia patients, need help in managing and taking medications. Therefore, TDDSs may be useful for increasing drug adherence and compliance as well as reducing stress for caregivers and elderly patients.

Drug-in-adhesive (DIA) patches with a pressure sensitive adhesive (PSA) polymer have been used in many TDDSs for decades because of the easy inclusion of many drugs in the PSA polymers, suitable adhesive function to skin and controllable drug delivery rate through skin from the PSA polymers. Furthermore, lighter, thinner and more flexible patches can be designed using the DIA. These characteristics are beneficial for skin surface movement as well as patient acceptability. However, physical and physiological skin irritation (acute or delayed acute irritant dermatitis) may be caused by TDDSs due to lack of skin flexibility. Removal of the DIA tapes may also be a reason for skin irritation due to excess stripping of the stratum corneum (SC). In addition, chemical or allergic irritation may be caused by active pharmaceutical ingredients and additives. Furthermore, bacterial infection can be produced by sweating. Impermeable membrane, non-woven fabric, polyethylene and polyester films are options used as a backing layer, and these materials may prevent inadvertent drug loss or exposure. However, high occlusion against moisture vapor and air by the backing layer may cause detachment of the DIA patch from the applied site and possible irritation in the skin, especially with long-term application. In addition, elderly patients generally have low and reduced skin barrier function, probably due to the decreased number of lamellar bodies in the stratum granulosum-SC interface, reduction of lipid synthesis, and the proliferation of keratinocytes. Thus, decreased barrier function due to the peeling of the applied patch is not ideal for TDDS treatment.

Hexagonally packed pore distribution in a flat film, i.e., a honeycomb structure, has superior properties, such as large space area, good structural stability, high mechanical strength, and low density. In the present study, film with a honeycomb structure was used as a backing layer in the DIA patches to improve water vapor permeability. Furthermore, the amount of SC peeled and the change in transepidermal water loss (TEWL) by the peeling of the DIA patches were determined. Additionally, in vitro drug release and in vivo skin permeation profiles were compared with those of DIA patches without a honeycomb structure to confirm the usefulness of DIA patches with a honeycomb structure in the backing film.

Experimental

Materials Tulobuterol was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Acrylic adhesive Duro-tak® 87-5216 (Henkel Japan Ltd., Tokyo, Japan), polyethylene terephthalate (PET) film and silicone-coated PET film (Filmbyn®, thickness 75 μm and width 200 mm, Fujimori Kogyo Co., Ltd., Tokyo, Japan) were kindly provided by Teikoku Seiyaku Co., Ltd. (Higashi-Kagawa, Kagawa, Japan). Sudan II was purchased from Tokyo Chemical Industry Co., © 2018 The Pharmaceutical Society of Japan
UV curable acrylic adhesive film consisting of acrylic acid ester copolymer and urethane acrylate was kindly provided by Lintec Corporation (Tokyo, Japan). All other reagents and solvents were of reagent grade or HPLC grade and used without further purification. Marketed tulobuterol TDDSs (Hisamitsu Pharmaceutical Co., Inc., Tokyo, Japan) were used for comparison.

Preparation of Honeycomb Film
Honeycomb film was kindly provided by Ricoh Company Ltd. (Tokyo, Japan). The preparation procedure is briefly summarized as follows: UV-curable urethane acrylate which composed of a urethane acrylate oligomer having a (meth)acryloyl group at the molecular terminals was laid on a stainless-steel template with regularly arranged dents, moderately pressed by a roller and put into a container. Then, air was decompressed with a vacuum pump to generate a pressure difference between the dent space and airspace in the container. This process provided air expansion in the dent space, whereby the film material plastically deformed and inflated into a hemispherical shape. The cell space was grown upward, and the adjacent cell space was also expanded simultaneously. The cell space was not expanded in the lateral direction by reaching the equilibrium in the force balance for the lateral spaces. UV ray was irradiated to cure the film material. The cured film was removed from the template to obtain film with a plurality of honeycomb structure (one side closed type of honeycomb film). Furthermore, film with a honeycomb structure with both open ends (both open ends type of honeycomb film) was also prepared by cutting the ceiling part in an orthogonal direction to the partition wall with a razor.

Preparation of Adhesive Layers and Patches
Tulobuterol and Duro-tak® 87-5216 were weighed and dissolved in ethyl acetate and agitated thoroughly with a stirrer to obtain homogeneous solution. An adhesive layer was prepared by spreading the solution onto the silicone-coated PET film using a baker type film applicator (Yasuda Seiki Seiskakusho Ltd., Tokyo, Japan) with 1.0 mil thickness. The adhesive layer was dried at room temperature (20±2°C, 20±5 relative humidity (RH)%) for 30 min and oven-dried at 32°C (32±2°C, 20±5 RH%) for 30 min. Then, it was laminated with the honeycomb film or PET film with a print roller (Taniguchi Shoyudo Co., Ltd., Kyoto, Japan).

DIA patches without honeycomb film, one side closed type of honeycomb film and both open ends type of honeycomb film (D-PSA, HC-PSA, and HO-PSA, respectively) were prepared. Average thickness of the adhesive layer was calculated by the measurement of their four corners with a thickness gauge (Teclock Corporation, Okaya, Nagano, Japan). Furthermore, to confirm adhesion force of the PSA layer to skin, Duro-tak® 87-5216 containing an adequate amount of Sudan II was prepared. Sudan blue was also mixed with Duro-tak® 87-5216 to evaluate the residue of PSA layer on the applied skin site after peeling of the patch from hairless mice (see in detail in Animals). The preparation procedure of the patches containing Sudan II and Sudan blue was the same as the DIA patches described above. Figure 1 shows a diagram of the prepared patches.

Animals
Male hairless rats (WBN/lfa-Ht), weighing about 180 g and 8-weeks old were obtained from Ishikawa Laboratory Animals (Saitama, Japan). Male hairless mice (Hos:HR-1) of about 30 g and 7 weeks-old were obtained from Hoshino Laboratory Animals, Inc. (Bando, Ibaraki, Japan). The rats and mice were housed in a room at 25±2°C and the light turned on and off every 12 h. The rats and mice had ad libitum access to water and food (obtained from Oriental Yeast Co., Ltd., Tokyo, Japan). All animal experiments and feeding methods were approved by the Institutional Animal Care and Use Committee of Josai University (Sakado, Saitama, Japan).

Microscopic Observation
The adhesive layers on the HC-PSA and HO-PSA were visually observed with an optical microscope VHX-5000 (Keyence Corporation, Osaka, Japan) to confirm even attachment of the PSA layer on the honeycomb film. The sample was set on the observation stage with the PSA layer up and observed by tilting the lens to an angle of 30 degrees.

Tack Test Using a Rolling Ball
The adhesive tack was measured by the rolling ball-tack test using a SUS304 inclined ball tack test device (Nonaka Rikaki Co., Ltd., Tokyo, Japan). The length of the runway was set to 100±50±150 mm. The sample DIA patch was fixed on the middle of the runway.
(50mm) with the adhesive side up as shown in Fig. 2. The patch size had a width of 22.5mm and a length of 50mm. Numbers 2–11 of the steel balls, which were washed in acetone before the test, were released from the top of the inclined plate at the angle of 15 degrees. The number of the largest ball that stopped on the adhesive patch was set as the value for this tack test, and the ball size that stopped was used for the result. The measurements were performed in triplicate at 24±2°C and a relative humidity of 50±5%.

**Observation of Adhesive Layer Peeling Process by a High-Speed Camera** The prepared patch was applied to a silicone membrane (0.1 mm thickness) and placed on the stage with the backing-layer on top. Then, a tension gauge was connected to the far side edge of the patch on a stage. The peeling process of the PSA layer from the silicone membrane was observed by moving the stage at 5 mm/s with a high-speed camera (shooting speed: 1000 fps, shutter speed: 1/1000s), as shown in Fig. 3.

**In Vitro Release Profile of Tulobuterol** Tulobuterol release from freshly prepared DIA patch was measured with
side-by-side diffusion cells with a receptor volume of 3.0 mL and a diffusion area of 0.95 cm². Physiological saline (0.9% NaCl) was used for the receptor and kept at 32°C. Patches were attached to silicone membrane and mounted between the donor and receptor compartments of the diffusion cells. Aliquots (0.5 mL) were withdrawn at 0.5 h and every one-hour until 8 h to determine drug content. After each sampling, the same amount of fresh 0.9% NaCl was added to maintain the volume in the receiver.

**In Vitro Skin Permeation of Tulobuterol** Hairless rat were anesthetized with intraperitoneal injection of three types of anesthesia (medetomidine hydrochloride; 0.15 mg/kg, midazolam; 2 mg/kg and butorphanol tartrate; 2.5 mg/kg) and killed by cervical dislocation. Then, full thickness skin (i.e., epidermis with SC plus dermis) was excised from the body. The skin was mounted on Franz type diffusion cells and DIA patch was applied on the skin surface to completely cover the exposed skin area. The receptor compartment contained 6.0 mL of 0.9% NaCl. The receptor sample (0.5 mL) was withdrawn from the cell before sample applied and at 0.5, 1, 2, 3, 4, 6 and 8 h to determine the tulobuterol concentration, and the same amount of fresh NaCl solution was added to keep the volume constant. Sink conditions of tulobuterol were maintained throughout the experiment.

**Moisture Permeation Test** A 20 mL-glass bottle filled in 10 mL of purified water was tightly covered with the DIA patch to measure the moisture permeation. The glass bottle was placed in an incubator at a temperature of 32°C and humidity of 20±2%. The change in water weight in the glass bottle was measured at 1, 2, 4, 8 and 24 h with a microbalance (XP-26, Mettler-Toledo K.K., Tokyo, Japan). The amount of moisture permeated through the patch was calculated by dividing the weight change by the opening area of the glass bottle (mg/cm²).

**Change in TEWL after Peeling the Patch** Hairless mice were anesthetized with intraperitoneal injection of three types of anesthesia as mentioned above and the DIA patch was applied on the abdominal skin over 8 h. The change in the TEWL on the application site was measured with a Vapo Scan AS-VT 100RS (Asahi Techno Lab. Ltd., Yokohama, Japan) at a temperature of 20±2°C and relative humidity 50±5%. In addition, the residue of adhesion layer remaining on the SC surface after removal of DIA patch containing Sudan Blue was observed with a digital camera 8 h after its application. The TEWL changes and residue detection of the PSA layer on the SC were separately determined.

**Observation of Distribution Pattern of Peeled SC on the PSA Layer** After DIA-patch was applied on the lateral region of the abdomen in anesthetized hairless mice over 8 h, the weight change of peeled SC on the applied patch was measured by a microbalance (XP-26). Furthermore, the PSA layer of patch was stained by 0.5% eosin solution to observe the distribution pattern of removed keratinocyte cells by microscopy (VHX-5000, Keyence Corporation).

**Tulobuterol Extraction from DIA Patches** The prepared DIA patch was soaked into 20 mL of hexane for 8 h to completely extract tulobuterol. Percentages of the cumulative amount of tulobuterol released and permeated through hairless rat skin were calculated by dividing the value by the drug amount in the patch, respectively. The tulobuterol amount was measured in triplicate with the same lot of prepared patches.

**Tulobuterol Assay** Concentrations of tulobuterol in the samples were determined using an HPLC system (Prominance; Shimadzu, Kyoto, Japan) equipped with a UV detector (SPD-M20A; Shimadzu, Kyoto, Japan). The drug samples were centrifuged at 21500×g and 4°C for 5 min, 20 µL of the supernatant was added to the same volume of acetonitrile, and the solution was injected into the HPLC system. Chromatographic separation was performed using an Inertsil-ODS-3 (5 µm, 150×4.6 mm² i.d.; GL Science, Kyoto, Japan) at 40°C. The mobile phase was 0.004% phosphoric acid containing 1.5% sodium 1-octanesulfonate—acetonitrile (35:65, v/v), the flow rate was adjusted to 1.0 mL/min, and detection was performed at UV 215 nm. 4-Hydroxybenzoic acid methyl ester was used as an internal standard.

**Statistical Analysis** Data are expressed as the mean±standard error (S.E.) or standard deviation (S.D.). The differences among the obtained data were analyzed using the unpaired t-test. The differences were considered significant when p<0.05.

**Results**

**Scanning Electron Microscopy (SEM) Observation** Figure 4 shows SEM of the vertical and horizontal sections of HC- and HO-films. A very similar size of honeycomb structure was confirmed within the same film and between the different types of films. The cell pitch size and average height of the structure were approximately 200 and 350 µm, respectively, independent of the honeycomb film type.

**Observation of the PSA Layer** Figure 5 shows light micrography of the PSA layer on HO- and HC-films. Sudan II was used as a dye to easily observe the adhesive state of the layer on the film. The PSA layers were uniformly covered and were adhered to the honeycomb structures without broken parts. All prepared formulations were visibly confirmed before each experiment to avoid using a defective membrane.

**Adhesive Test** Inclined ball tack test was conducted to measure how quickly the PSA layer achieved optimum adhesion. In our preliminary experiment, the ball tack experiment was performed with the inclined plate angle at 30-degree. However, all sizes of steel balls rolled over the PSA layer of a commercial product mounted on the inclined track. Therefore, an inclined plate angle at 15-degree was used to evaluate the tack properties of the patches. The largest ball numbers that stopped on the PSA layer were, No. 6 (diameter: 4.8 mm), No. 11 (diameter: 8.7 mm), No. 9 (diameter 7.1 mm) and No. 7 (diameter 5.6 mm) for the commercial product, D-PSA, HC-PSA, and HO-PSA, respectively.

**Permeation Experiment of Water Vapor** Permeability profiles of water vapor were determined through DIA patches, especially for their backing layers. The amounts of water vapor permeated through the patches ranged from 0.8 to 35.9 mg/cm² over 8 h. HO-PSA (35.9±2.30 mg/cm²) showed the highest value among the patches, followed by HC-PSA (3.20±0.70 mg/cm²), D-PSA (1.10±0.40 mg/cm²) and the commercial product (0.80±0.40 mg/cm²). Although the amount of water vapor permeated obtained from HO-PSA was lower than that obtained without the patch (77.2±3.40 mg/cm²), the HO-PSA showed significantly higher values (p<0.05) than HC-PSA, D-PSA and a commercial product.

**Weight of Removed SC by Detachment of the Applied Patch** Figure 6a shows the weight of SC layers removed
after peeling of applied patches from the application site of skin. D-PSA showed the highest value, whereas commercial product showed the lowest value. The weight of removed SC by the HO-PSA patches and the commercial product were significantly ($p<0.05$, $p<0.001$, respectively) lower than D-PSA.

Since the weight of SC after peeling the applied patch may have been underestimated, a further experiment was done with the D-, HC- and HO-DIA patch containing Sudan blue. The DIA patch was removed 8h after application. The residue of the PSA layer containing Sudan blue was not visibly confirmed (data not shown) independent of the backing layer structure.

**Change in TEWL after Removal of the Patch** Figure 6b shows the change in TEWL after the peeling of the DIA patch from skin. D-PSA showed the highest TEWL, followed by the commercial product, HC-PSA and HO-PSA. A significant difference ($p<0.001$) was observed between D-PSA and HC-PSA or HO-PSA. On the other hand, no significant differences were observed among TEWL values for commercial product, HC- and HO-PSA patches.

**Distribution Pattern of SC on the Patch after Peeling**

Figure 7 shows the distribution pattern of SC on the PSA layer after peeling the applied patch. Stained keratinocyte cells were observed in all the patches. The stained keratinocyte cells were uniformly observed in the observed area in D-PSA, and the dark red spots (shown in arrows) in D-PSA indicates multiple peeling of keratinocyte cells by the removal process. In contrast, the commercial product, HC- and HO-PSA exhibited a lower number of stained cells, and lower frequency of multiple peeled keratinocyte cells than with D-PSA.

**In Vitro Drug Release Test** The effect of the honeycomb structure was determined on the in vitro release profile of tulobuterol from the DIA patches and the commercial product. Figure 8 shows release profiles of tulobuterol from patches having different types of backing layer. Almost similar drug
release profiles were observed among the prepared DIA patches (D-, HC- and HO-PSAs). Furthermore, no significant drug release profile was confirmed between the commercial products and prepared patches. The drug profile from the commercial product was the same as in the interview form of the product.

**In Vitro Skin Permeation Experiment** An *in vitro* skin permeation experiment was conducted with prepared DIA patches and the commercial product. Figure 9 shows the permeation profile of tulobuterol after application of the patches on the hairless rat skin. The drug permeation from D-PSA was almost same to other prepared patches with or without a honeycomb film in the backing layer.

**Discussion**

Skin irritation caused by long-term application or peeling of an applied patch must be reduced to effectively use transdermal products. Ethylene vinyl acetate films, nonwoven fabrics and polyethylene terephthalate have been used as backing layer in DIA patches. Furthermore, Shi *et al.* reported polyacrylate PSA/cross-linked polyvinyl alcohol composite nanofibrous film that could provide a high breathability and monodirectional water-penetration. However, no reports on the effect of a honeycomb structure as a backing layer in DIA patch on the amount of SC peeled and changes in TEWL values have been published.

During the peeling process of topically applied patches, the...
stress is transmitted through the adhesive matrix to the backing layer. The thickness, composition, shape, and rigidity, which affect flexibility and elongation of the DIA patch, are determination parameters for the peeling force of the applied patch. In the present study, adhesive properties, as well as drug release and skin permeation profiles from the patch, were investigated with the DIA patch with a honeycomb film as a backing layer by comparing the DIA patch with a non-honeycomb PET film and a commercially available product.

The DIA patch requires low tack when accurately applied on skin. The tack values of HC- and HO-PSAs were lower than D-PSA despite the same PSA layer. D-PSA, HC- and HO-PSAs were connected with the PSA layer only at the lattice structure having honeycomb film. The PSA layer on the void space in the honeycomb film could freely move-upside and -downside, and may affect the bond-making and bond-breaking process.

Significantly lower changes in the TEWL values after the detachment of HC- and HO-PSAs were observed compared with D-PSA. When the changes in the TEWL values after peeling of HC- and HO-PSAs were divided by the value of D-PSA, the calculated ratios were 0.39 and 0.30, respectively. Furthermore, the same calculation was done to determine the amount of SC removed by peeling of the applied patch. The calculated ratios of HO- and HC-PSAs were 0.74 and 0.64, respectively. A good relationship was observed between frequency of tape-stripping (the total amount of removed SC) and TEWL value changes. The calculated ratios indicate the same value from TEWL changes and the amount of SC removed. However, the calculated ratios obtained by TEWL values were smaller than those obtained by the amount of SC removed.

The distribution pattern of removed SC by peeling of applied patch was investigated with a light microscope to confirm the reason for the fewer changes in TEWL value by the removal of HC- and HO-PSAs compared with D-PSA. The removed SC was uniformly distributed on the PSA layer in D-PSA, whereas non-keratinocyte distributed areas were found in the HC- and HO-PSAs. Multi-layered keratinocytes were also harvested in the PSA layer in the DIA patches. A comparatively higher distribution frequency of multi-layered keratinocyte was observed in the D-PSA compared with other DIA patches. This difference may be a reason for the extent of TEWL change being higher than in the amount of SC removed by peeling of the applied patch. Almost 100% of drug released was confirmed in 2 to 3h experimental period from prepared patches, suggesting that drug permeation through the stratum corneum is a rate-limiting step in this case. Although the cumulative amount of drug release from HC-PSA was less than those from HO-PAS and D-PSA at 30 min, this would provide little difference on the skin permeation of drug. The contactless PSA layer covering the void spaces in the honeycomb film on the skin surface was thought to be the reason for the non-keratinocyte distributed area on the PSA layer in the HC- and HO-PSAs. The contactless PSA layer on the skin is directly related to a decrease in the skin permeation of tulobuterol from the patch.

Almost similar drug release profiles among the prepared patches were confirmed, and no decrease in the drug permeation from HC- and HO-PSAs was observed compared with D-PSA, suggesting that HC-, HO-, and D-PSAs had a similar skin contact area. To clarify the reason for the lower number of SC removed by peeling of HC- and HO-PSAs, the removal behavior of the PSA layer was observed with a high-speed camera. Figure 10 shows a photographic image of the removal of the PSA layer in the patch from a silicone membrane.

The removal behavior of the PSA layer in the D-PSA was well synchronized with its removal process from the silicone membrane. On the other hand, the time delay was confirmed by the elongation of the PSA layer in HC-PSA, and this is due to the layer covering the void space in the honeycomb film. The PSA layer entirely adhered to the backing layer of D-PSA, and could provide an even peel force to the stratum corneum during the removal process. In contrast, the PSA
layer in HC- and HO-PSAs only tightly adhered at the lattice structure in the honeycomb film. Since increasing peeling angle\textsuperscript{23} and decreasing peeling speed\textsuperscript{20} may provide decreasing peeling force of the adhesive patch, the elongation of the PSA layer in the HC-and HO-PSAs may have changed the peeling angle and speed compared with D-PSA. Therefore, the elongation of the layer may be a reason for the decreased number of SC removed by patch peeling. Furthermore, a thicker patch, not the thickness of the adhesive layer, provides a lower peel force because of the counteraction of the energy dissipated in the backing layer deformation.\textsuperscript{22} HC- and HO-PSAs had a thicker backing layer compared with PET film (10 µm) used in D-PSA. Thus, the hardness of the backing layer may also be a key factor affecting peeling force.\textsuperscript{9}

However, changes in water content in SC with the occlusive effect of the applied patch was not investigated in the present study. Excess hydration by the occlusive effect reduces the adhesion force of the applied patch and barrier function of SC.\textsuperscript{13} Furthermore, SC hydration also affects the recovery function in the SC barrier after such damage.\textsuperscript{25} The present results suggest that a less occlusive effect could be achieved by using HC- and HO-PSAs due to their higher water permeation through the honeycomb structure.

In the present study, the effect of membrane properties on the adhesive properties such as hardness and thickness of the honeycomb film were not investigated. Further investigation related to the mechanical properties of honeycomb films is required to estimate the usefulness such a honeycomb structure as a backing layer in DIA patches. Since drug adsorption into the backing layer was also related to skin permeation from the patch,\textsuperscript{10} it is necessary to evaluate the materials that could form the honeycomb structure. Although further investigation is necessary to reveal the detailed mechanism for decreasing tack value, selection of a honeycomb structure as a backing layer could be one way to reduce the tack value and cause less damage to SC barrier function due to peeling of applied patches.

**Conclusion**

A DIA patch with a honeycomb structure as a backing layer showed high-water permeability and fewer TEWL changes after peeling from the applied skin site without decreasing the drug permeation profiles. The honeycomb structured backing layer could reduce the tack value. Although further clinical studies should be done to confirm the usefulness of the honeycomb structure as a backing layer, the present approach may be important in the development of a new DIA patch that causes little skin damage due to peeling.

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