Original Article

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Skin permeability of tulobuterol in two transdermal formulations and their followability

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Summary **Various generic transdermal formulations of tulobuterol containing rubber and acrylate base polymers are commercially available in Japan. However, none of the formulations have been compared directly with respect to the skin permeability of tulobuterol and to their follow ability. Tulobuterol Tape Sawai of rubber base and Tulobuterol Tape NP of acrylate base were used to conduct the *in vitro* 24-hour skin permeability test of tulobuterol at receiver solution temperatures of 32°C, 37°C, and 40°C. Furthermore, the followability of these tapes were examined by measuring the depth of the pores that were formed in their adhesive layer. Consequently, the maximum flux of tulobuterol was greater for Tulobuterol Tape NP. Arrhenius plot analysis revealed that Tulobuterol Tape Sawai was more sensitive to skin surface temperature compared with Tulobuterol Tape NP. Skin abrasion had a greater effect on the skin permeability of tulobuterol in Tulobuterol Tape Sawai than in Tulobuterol Tape NP. Followability was greater for Tulobuterol Tape NP than for Tulobuterol Tape Sawai. These results suggest that a transdermal formulation of acrylate base is preferable to that with a rubber base when skin surface temperature varies or when the skin is abraded. In clinical settings, therefore, a formulation of acrylate base is preferable to a formulation of rubber base when skin surface temperature varies or when the skin is abraded. The formulation needs to be applied to the skin of less asperity for the achievement of better transdermal absorption of tulobuterol.**

Keywords: Tulobuterol, transdermal, rubber base, acrylate base, intact skin, abraded skin

1. Introduction

Various transdermal formulations of tulobuterol, including the pioneer transdermal patch, Hokunalin®, are commercially available in Japan (Table 1). Hokunalin® contains a rubber base polymer, in which only a small portion of tulobuterol is dissolved and most of the drug crystals is suspended in the adhesive layer. Thus, the concentration of tulobuterol dissolved in the layer is thus kept constant by a mechanism called the "crystal reservoir system (CRS)" that enables the stable release of tulobuterol from the formulation across the skin (*1,2*). In generic transdermal formulations, on the other hand, tulobuterol is dissolved in two types of base polymers (*i.e.*, rubber and acrylate; Table 1).

Previous studies compared the skin permeability of tulobuterol between the pioneer and generic products (*1-3*). In an *in vitro* hairless mouse skin permeability test, the difference in permeability between the intact and abraded skin was smaller in the pioneer than generic products, suggesting that the drug release across the skin is well controlled by the CRS and that generic drugs were more prone to be influenced by skin abrasion.

The skin permeability of tulobuterol has not been compared directly among generic products of different base polymers. The rubber base polymers contain

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Table 1. Characteristics of the transdermal formulations of tulobuterol commercially available in Japan

Approval year	Manufacturer	Product name	Base polymer
1998	Abbott Japan Co., Ltd.	Hokunalin®	PIB
2006	Sawai Pharmaceutical Co., Ltd.	Tulobuterol Tape Sawai	SIS
	Nichi-Iko Pharmaceutical Co., Ltd.	Tulobuterol Tape Nichi-Iko	
	Yutoku Pharmaceutical Ind. Co., Ltd.	Tulobuten Tape	
	Hisamitsu Pharmaceutical Co., Inc.	Tulobuterol Tape HMT	Acrylate
	Towa Pharmaceutical Co., Ltd.	Sekinarin Tape	
	Takata Pharmaceutical Co., Ltd.	Tulobuterol Tape Takata	
2007	Ohara Pharmaceutical Co., Ltd.	Tulobuterol Tape Ohara	SIS
	Teikoku Seiyaku Co., Ltd.	Tulobuterol Tape Teikoku	
	Medisa Shinyaku Inc.	Tulobuterol Tape MED	
2008	Shiono Chemical Co., Ltd.	Tulobuterol Tape SN	SIS
2009	Nipro Corporation	Tulobuterol Tape NP	Acrylate

PIB, polyisobutylene; SIS, styrene-isoprene-styrene.

nonpolar functional groups, while acrylate base polymers contain polar functional groups (*e.g*., amido). The polar functional groups of acrylate base polymers interact with the polar functional groups (*e.g*., hydroxyl groups) of drugs, resulting in retention of drugs in base polymers (*4,5*). Hence, the skin permeability of tulobuterol that has the hydroxyl group may be affected by the polarity of base polymers.

Morimoto *et al*. conducted the release test of drugs containing the amido, carboxyl, or ester group into the 40% aqueous solution of polyethyleneglycol (PEG) at 37°C; they calculated the distribution coefficients (logD), glass-transition temperature (Tg), and wavelength of the hydroxyl group and reported the amido group, amino group, carboxyl group, and ester group in decreasing order of the interactions of the function groups with base polymers (*4,5*).

Kato *et al*. prepared the transdermal formulations of tulobuterol containing gum, silicon, or acrylate polymers to examine the 24-hour releasability of the drug across rabbit skin (*1*). Consequently, they reported gum base, silicon base, and acrylate base in decreasing order of drug releasability. These findings led us to hypothesize that drug releasability would be controlled by base polymers, and we conducted an *in vitro* hairless mouse skin permeability test to confirm our hypothesis.

Transdermal formulations, also called pressure-sensitive agents (PSAs), acquire adhesion between the skin and their adhesive layer by applying a slight pressure when attached to the skin. Transdermal formulations are endowed with the function of PSAs by selecting base polymers with a low Tg to exert adhesion or by adding a tackifier at skin surface temperature (*6,7*).

Tojo *et al*. reported lower elasticity and greater peeling strength in association with the lower Tg of acrylate base polymers (*3*). Furthermore, Zhao *et al*. added isopropyl myristate to the acrylate adhesive to decreases Tg and degree of elasticity (G') and to increase tack adhesiveness (*8*).

Another important index of base polymers for the transdermal formulations is followability that enables close contact between the formulation and the skin surface (*6*). In the present study, we examined the skin permeability of tulobuterol in and the followability of two tulobuterol tapes.

2. Materials and Methods

2.1. *Materials, animals, and devices*

Tulobuterol Tape Sawai (2 mg; 32 × 32 mm, Sawai Pharmaceutical Co., Ltd., Osaka, Japan) and Tulobuterol Tape NP (2 mg; 32 × 32 mm, Nipro Corporation, Osaka, Japan) were purchased from the market.

Male Hos:HR-1 hairless mice aged 7-8 weeks (17-25 g in body weight) were purchased from Japan SLC Co., Inc. (Shizuoka, Japan). Animals were handled in accordance with the rules established by the Institutional Animal Care and Use Committee at Josai International University.

In an *in vitro* 24-hour hairless mouse skin permeability test of tulobuterol, a vertical diffusion cell (LGA-1084-CL, Laboratory Glass Apparatus, Berkeley, CA) was used to diffuse tulobuterol across the resected hairless mouse skin and an autosampler (FOXY200, Nikkaki Bios Co., Ltd., Tokyo, Japan) to collect the sample solution.

2.2. *In vitro 24-hour hairless mouse skin permeability test of tulobuterol*

The skin was resected from mice after cervical dislocation. The resected skin was inverted to remove subcutaneous fat, followed by standing of the dermis placed downward onto the filter paper that was impregnated with saline.

Tulobuterol Tape Sawai and Tulobuterol Tape NP were punched out into 15 round pieces of 24 mm in diameter, and the protective liner was peeled off and then attached to the resected skin. Test material was set onto the vertical diffusion cell, and the upper and lower rims of the cell were fixed with a metallic pinch clamp. The

interior of the cell was filled with the receiver solution (40% PEG 400 [NOF Corporation, Tokyo, Japan]) to remove air bubbles, followed by passage through the cell at a rate of 10 mL/h. Aliquots of the solution were collected every 2 h up to 24 h. Subsequently, 500 µL of the internal reference solution (760 µg/mL celecoxib, Edmond Pharma, Paderno Dugnano, Italy) were mixed with 400 µL of the sample solution, and an ultra-performance liquid chromatograph (Nihon Waters Co., Ltd., Tokyo, Japan) with a ODS C18 column (2.1 × 50 mm; detection wavelength: 215 nm; column temperature at measurement: 40°C; and injection volume of sample: 5 µL) was used to measure the tulobuterol concentration. Tulobuterol (Shiono Chemical Co., Ltd., Tokyo, Japan) was used as reference standard and celecoxib as internal standard. The flow rate for the mobile phase (0.5% phosphoric acid [Wako Pure Chemical Industries Ltd., Osaka, Japan], 0.01 M sodium dodecyl sulfate [Wako Pure Chemical Industries], and 55% acetonitrile [Wako Pure Chemical Industries]) was 5.0 mL/min (*3*). In consideration of clinical application, the temperature of the receiver solution was varied from the skin surface temperature, 32°C to the temperature at the time of taking a sauna or bath, 40°C (*9*).

The flux was calculated based on the ratio of tulobuterol in the reference standard solution to that in the internal standard, and the *Flux* (µg/cm^2/h) and maximum flux values (J_{max}) were calculated according to the following equation (*10*):

$$Flux = (VdC/dt)/A$$

where, C: drug concentration in the sample, t: measurement time (hr), V: volume (mL) of the receiver in the sample, and A: effective diffusion area (cm^2).

2.3. *Preparation of the abraded skin and measurement of water content in the skin surface*

The resected skin was placed onto an aluminum tray, followed by the stripping of the stratum corneum (SC) 7 times with Scotch Brand BookTape 845 (3M Japan Co., Ltd., Tokyo, Japan) as described previously (*9*). A water content meter (Corneometer® CM 825; Courage + Khazaka Electronic GmbH, Cologne, Germany) was used to measure water content in the skin surface. The probe was cleaned with absorbent cotton impregnated with ethanol before application onto the skin surface. Water content in the skin surface was measured six times to calculate the mean value.

2.4. *Followability test of 2 transdermal formulations*

At a room temperature of 25°C, a sandpaper (Fuji Star #120, Sankyo Rikagaku Co., Ltd., Saitama, Japan) was cut into 2 sheets (3 × 4 cm in size), and each sheet was placed on a table, with the grinding surface upward. Subsequently, the adhesive surface of the sample was applied to the grinding surface of the sandpaper, a sheet of paper towel (Kim Towel®, Nippon Paper Crecia Co., Ltd., Tokyo, Japan) was put onto each sample, and a 1-kg cylinder weight was then placed onto the sample for 1 min. Subsequently, the weight, the paper towel, and the sandpaper were removed, and a laser microscope (LS-5040, Keyence Co., Ltd., Osaka, Japan) was used to measure the depth of the pores that were formed in the adhesive layer of the examined tapes.

2.5. *Statistical analysis*

Welch's *t*-test was conducted to test differences in flux between the intact and abraded skin in the skin permeability test of tulobuterol and differences in pore depth before and after treatment in the followability test by using Microsoft Excel for windows (Microsoft, Tokyo, Japan). A value of $p < 0.05$ was considered statistically significant. All values are expressed as mean ± SE.

3. Results

3.1. *Skin permeability of tulobuterol at 3 temperatures*

Tulobuterol Tape Sawai and Tulobuterol Tape NP have rubber and acrylate base polymers, respectively. Time-course changes in the *Flux* of tulobuterol from both formulations at 32°C, 37°C, and 40°C are shown in Figure 1. At all temperatures, the J_{max} values were higher in Tulobuterol Tape NP than in Tulobuterol Tape Sawai. Both formulations showed an increase in J_{max} in association with temperature elevations (Figure 1). Tulobuterol Tape Sawai exhibited a greater rate of increase than did Tulobuterol Tape NP (Table 2). Namely, the J_{max} of Tulobuterol Tape Sawai increased 1.19- and 1.29-fold at 37°C and 40°C, respectively,

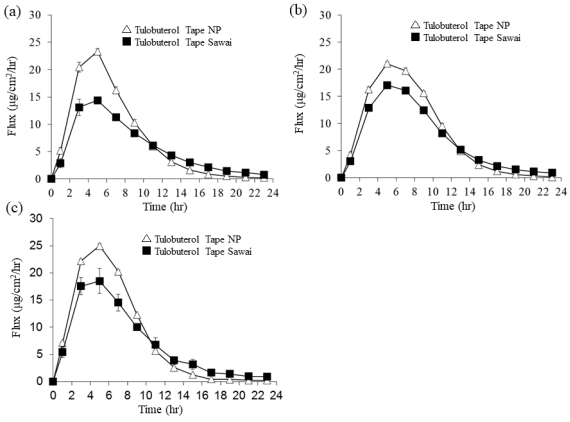

Figure 1. Time-course changes in *J* at various receiver solution temperatures. The *Flux* of tulobuterol released from Tulobuterol Tape Sawai and Tulobuterol Tape NP was determined at 32°C **(a)**, 37°C ***(b)***, and 40°C **(c)**. Values are expressed as mean ± SE ($n = 3$). SE, standard error.

Table 2. J_{max} values of tulobuterol in tulobuterol Tape Sawai and tulobuterol Tape NP in an *in vitro*, 24-hour hairless mouse skin permeability test

Items	J_{max} (μg/cm^2/h), Tulobuterol Tape Sawai (n = 3)	J_{max} (μg/cm^2/h), Tulobuterol Tape NP (n = 3)
Temperature		
32°C	14.37 ± 0.29	23.34 ± 0.52
37°C (*vs*. 32°C)	17.10 ± 0.19 (1.19 fold)	21.07 ± 0.33 (0.90 fold)
40°C (*vs*. 32°C)	18.50 ± 2.28 (1.29 fold)	24.99 ± 0.33 (1.07 fold)
Skin		
Intact skin	10.73 ± 0.99	22.44 ± 0.76
Abraded skin (*vs*. intact skin)	15.66 ± 0.40 (1.46 fold)	28.94 ± 0.11 (1.29 fold)

Values are expressed as mean ± SE. SE, standard error. J_{max}, maximum value of flux.

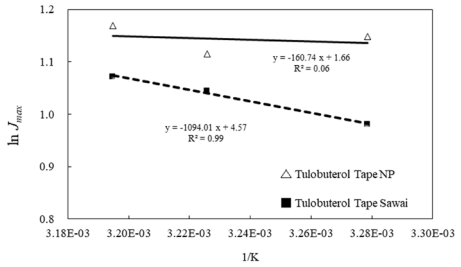

Figure 2. Arrhenius plot analysis on the skin permeability of tulobuterol. The natural logarithms of J_{max} of the skin permeability of tulobuterol in Tulobuterol Tape Sawai and Tulobuterol Tape NP were plotted against the inverse of skin surface temperature to depict linear approximations of skin permeability. ln, skin permeation; J_{max}, maximum flux; K, skin surface temperature.

against at 32°C. On the other hand, the J_{max} of Tulobuterol Tape NP increased 0.09- and 1.07-fold at 37°C and 40°C, respectively, against at 32°C. Arrhenius plot analysis disclosed a steeper slope by linear approximations for Tulobuterol Tape Sawai compared to Tulobuterol Tape NP (Figure 2), suggesting that the former is more prone to be influenced by skin surface temperature.

3.2. *Skin permeability of tulobuterol across the intact and abraded skin*

The J values of tulobuterol in the intact and abraded skin at 32°C were compared between Tulobuterol Tape Sawai and Tulobuterol Tape NP (Figure 3). Namely, the J_{max} of tulobuterol in Tulobuterol Tape Sawai increased 1.46-fold in the abraded skin against the intact skin, while that of Tulobuterol Tape NP increased 1.29-fold (Table 2).

Water content of the skin was measured because of its importance for skin permeability. The water contents of the intact (n = 6) and abraded (n = 6) skin were 26.83 ± 10.72 a.u. and 75.5 ± 8.5 a.u., respectively. A statistically significant difference ($p < 0.05$) was found between these two types of skin, indicating that the water content of the abraded skin had increased as a consequence of SC stripping. In the test using Tulobuterol Tape Sawai, a statistically significant difference ($p < 0.05$) was found in the water contents of

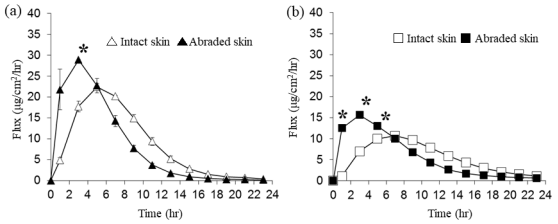

Figure 3. Time-course changes in flux with intact and abraded skin. The flux of tulobuterol from Tulobuterol Tape NP **(a)** and Tulobuterol Tape Sawai **(b)** was determined at 32°C in intact or abraded skin. Values are expressed as mean ± SE (n = 3). *$p < 0.05$ (Welch's t-test). SE, standard error.

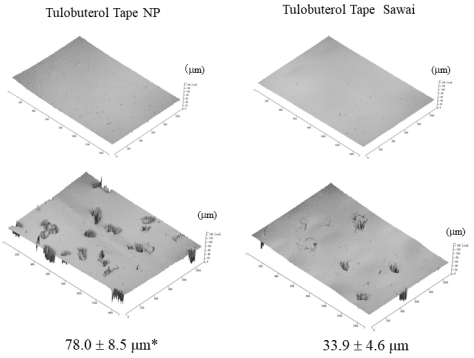

Figure 4. Followability test. Tulobuterol Tape Sawai and Tulobuterol Tape NP were placed on sandpapers. 1 min later, the sandpaper was removed to measure the depth of 6 pores with a laser microscope. Values are expressed as mean ± SE (n = 6). $p < 0.05$ (Welch's t-test). SE, standard error.

the intact and abraded skin (32.3 ± 13.1 a.u. and 77.5 ± 10.1 a.u., respectively). In the test using Tulobuterol Tape NP, a statistically significant difference ($p < 0.05$) was also found in the water contents of the intact and abraded skin (26.5 ± 8.6 a.u. and 75.2 ± 11.9 a.u., respectively).

3.3. *Followability test of 2 transdermal formulations*

A statistically significant difference ($p < 0.05$) was found in the depths of the pores that had been formed in the adhesive layer of Tulobuterol Tape Sawai and Tulobuterol Tape NP (33.9 ± 4.6 μm and 78.0 ± 8.5 μm, respectively). This result suggests that followability is greater for Tulobuterol Tape NP than for Tulobuterol Tape Sawai (Figure 4).

4. Discussion

Tulobuterol containing the hydroxyl group in its molecule interacts with the polar function group of the acrylate base polymer with the amido group, while Tulobuterol Tape Sawai with a rubber base that does not contain the polar function groups exhibits no such interaction. Kato *et al*. conducted a 24-hour rabbit skin releasability test of the transdermal formulations of tulobuterol of gum, silicon, and acrylate bases and reported gum base, silicon base, and acrylate base in decreasing order of drug releasability (*1*). Furthermore, Kokubo et al. prepared the transdermal formulations of dipropylphthalate, ketoprofen, ampicillin, and lidocaine that contained acrylate, gum, and silicon base polymers to examine drug releasability (*11*). Consequently, they reported no effect of gum and silicon base polymers on drug releasability and a decrease in drug releasability in the transdermal formulations of acrylate base due to the interactions of carboxyl group-containing drugs and acrylate base polymers. Therefore, the skin permeability of tulobuterol was predicted to be greater in Tulobuterol Tape Sawai. Surprisingly, however, the skin permeability of tulobuterol was greater for Tulobuterol Tape NP than for Tulobuterol Tape Sawai; the result was probably attributable to the greater followability of Tulobuterol Tape NP compared with Tulobuterol Tape Sawai.

The skin permeability of tulobuterol in both Tulobuterol Tape Sawai and Tulobuterol Tape NP increased in association with elevations in receiver solution temperature. Similar results were obtained in an *in vitro* skin permeability test of nonsteroidal anti-inflammatory drugs in the transdermal formulations of rubber base (*12*). Drug solubility into the skin increased exponentially in association with elevations in receiver solution temperatures, resulting in higher skin permeability at higher temperatures (*12,13*). We speculate that a similar mechanism is responsible for higher skin permeability at higher receiver solution temperatures in the present study. Arrhenius plots analysis suggested that Tulobuterol Tape Sawai is more sensitive to changes in skin surface temperature compared to Tulobuterol Tape NP. The interaction of the polar functional groups of acrylate base polymers with tulobuterol probably reduces the skin permeability of tulobuterol at 37°C and 40°C where the skin permeability of tulobuterol is increased.

The skin is composed of the epidermis containing the stratum corneum (SC) and dermis. The SC is a biobarrier that prevents water evaporation and the penetration of foreign matter from the exterior into the body and also functions as a biomembrane that controls drug diffusion into the skin (*14-17*). Both Tulobuterol Tape Sawai and Tulobuterol Tape NP showed a higher J_{max} in abraded skin than in intact skin. We consider that these findings are attributable to the fact that the thinner SC of the abraded skin lost its function as the drug release-controlling membrane. Furthermore, the increase rate of J_{max} in the abraded skin was higher for Tulobuterol Tape Sawai than for Tulobuterol Tape NP. Again, we speculate that the interaction of the polar functional groups of the acrylate base with tulobuterol inhibits the skin permeability of tulobuterol which is enhanced by skin abrasion.

The followability of Tulobuterol Tape NP was greater compared with Tulobuterol Tape Sawai, suggesting that the former is more flexible than the latter. The skin surface has asperity. The transdermal formulations of drugs that do not follow the asperity produce a less effective area of contact between the adhesive surface and the skin and cause concerns about a decrease in the skin absorbability of the drugs.

Miyazaki *et al*. used the transdermal formulations of acrylate base with different storage elastic moduli to examine the relationships between the followability of the formulations and the severity of SC detachment (*6*). Consequently, they reported the better followability to skin surface asperity with respect to the transdermal formulations of adhesive bases that had lower storage elastic moduli and that these formulations homogeneously detached the SC. Tojo *et al*. reported lower storage elastic moduli and greater peeling strengths in acrylate base polymers with lower Tg values (*7*). Thus, in general, base polymers with a lower Tg value and/or a lower storage elastic modulus exhibit greater followability at skin surface temperature (*6-8*).

Tulobuterol Tape Sawai has styrene-isoprene-styrene (SIS) block copolymers that contain polyisoprene as a soft segment and polystyrene as a hard segment. On the other hand, Tulobuterol Tape NP has acrylate 2-ethylhexyl as a soft segment and diacetone-acrylamide, acetoacetoxyethyl methacrylate, and methyl methacrylate copolymers as a hard segment (*18-20*). SIS block copolymers, which contain polystyrene, have a higher Tg compared with diacetone-acrylamide, acetoacetoxyethyl methacrylate, and methyl methacrylate copolymers; therefore, Tulobuterol Tape Sawai would have a higher Tg compared with Tulobuterol Tape NP, resulting in lower followability.

In conclusion, a formulation of acrylate base is clinically preferable to a formulation of rubber base when skin surface temperature varies or when the skin is abraded. The formulation needs to be applied to the skin of less asperity for the achievement of better transdermal absorption of tulobuterol.

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