Original Article

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Generic selection criteria for safety and patient benefit [X]: Water-vapor permeability and peel force properties of brand-name and generic ketoprofen tapes

Mitsuru Nozawa[1], Miho Goto[1], Yuko Wada[2], Fumiyoshi Ishii[2], Ken-ichi Shimokawa[3,*]

[1] Triad Japan Co. Ltd., Kanagawa, Japan;
[2] Department of Self-medication and Health Care Sciences, Meiji Pharmaceutical University, Tokyo, Japan;
[3] Department of Pharmaceutical Sciences, Meiji Pharmaceutical University, Tokyo, Japan.

SUMMARY Tape products containing ketoprofen have transdermal analgesic and anti-inflammatory effects. We compared the physicochemical properties (water-vapor permeability, peel force, peel force-time curve) between one brand-name product and eight generic products. Regarding the measurement of water-vapor permeability, the formulations using methacrylic acid n-butyl acrylate copolymer (MBA) adhesives showed higher water-vapor permeability than those using styrene isopropyl styrene block copolymer (SIS) adhesives. In the case of the formulation using SIS adhesive, the central part of the formulation had higher water-vapor permeability than both ends. In the 90-degree peel test using the methods of adhesion testing, significant differences were observed between the products, especially as the various application times (5 min, 30 min, 9 h and 24 h) increased. This may be because the longer the time of attachment to the adherend, the more the adhesive force with the adherend increased due to the "anchoring effect" of the adhesive. The measurement of the peel force-time curve showed different curves among the products, especially in the peel force curve of Teikoku after 24 h, which showed two characteristic peak curves. Furthermore, when the peel forces at 25°C and 40°C were compared, Mohrus and Toko showed significantly higher values at 40°C compared to 25°C. This study showed that there are many generic drugs with formulation characteristics different from those of brand-name drugs, and that there is a large difference among the products in terms of adhesion and detachment.

Keywords Water-vapor permeability, peel adhesion, tape containing ketoprofen, brand-name drug, generic drug

1. Introduction

In recent years, transdermal analgesic and anti-inflammatory tape formulations of nonsteroidal anti-inflammatory drugs (NSAIDs), which are indicated for the treatment of lumbago, osteoarthritis, tendinitis and rheumatoid arthritis, have been widely used in clinical practice in the field of orthopedics in Japan (*1*). In particular, the tape formulation is very thin and soft, and its strong adhesiveness allows it to be used on movable parts of joints, such as elbows, knees, hips and shoulders, which is why it is often used by the elderly. Since many generic drugs are now available on the market, the Japanese government is actively promoting the use of generic drugs in order to reduce medical costs (*2*). However, the switch from brand-name to generic drugs has been slow. This is because patients placed highest importance on the "efficacy" (analgesic and anti-inflammatory effects) of the formulation, and they were highly satisfied with the current tape formulation and tended to continue using the same product (*3*). In addition, even if pharmacists recommend patients to change from brand-name to generic drugs for the purpose of reducing medical costs, such change has not actually progressed much. The reason is that the patient's burden is extremely small due to the application of medical insurance (the patient's burden is 10 to 30% of the total amount), so the low drug price, which is an advantage of generic drugs, is actually not advantageous. In addition, even after switching from brand-name to generic drugs, some patients reportedly return to brand-name drugs due to reasons related to efficacy, such as "low analgesic and anti-inflammatory efficacy", as well as the feeling of use, such as "ease of peeling off during movement", "uncomfortable application" and "difficulty in application" (*3*).

Ketoprofen-containing tape has always been the top-selling prescription drug in Japan since the brand-

Table 1. Tape products used in this experiment

Product name	Abbreviated name	Class	Company name	Lot number
Mohrus® Tape 20mg	Mohrus	BN	Hisamitsu Pharm. Co., Inc.	Y428
Ketoprofen tape 20mg "Teikoku"	Teikoku	GE	Teikoku Pharm. Co., Inc.	A183S
Ketoprofen tape 20mg "Toko"	Toko	GE	Toko Pharm. Co., Ltd.	SC06T
Ketoprofen tape 20mg "BMD"	BMD	GE	Biomedics Co., Ltd.	5H17
Ketoprofen tape 20mg "SN"	SN	GE	Shiono Chemical Co., Ltd.	EZ02
Ketoprofen tape 20mg "Kyorin"	Kyorin	GE	Kyorin Rimedio Co., Ltd.	04AL
*Touchron® Tape 20	Touchron	GE	Kyukyu Pharm. Co., Ltd.	6TAL
**Frestol® Tape 20mg	Frestol	GE	Towa Pharm. Co., Ltd.	A056
Ketoprofen tape 20mg "Nichi-Iko"	Nichi-Iko	GE	Nichi-Iko Pharm. Co., Ltd.	5A17

BN: brand-name drug, GE: generic drug. Currently, *Touchron® Tape 20 has its name changed to Ketoprofen tape 20mg "Sanwa", **Frestol® Tape 20mg has its name changed to Ketoprofen tape 20mg "Towa".

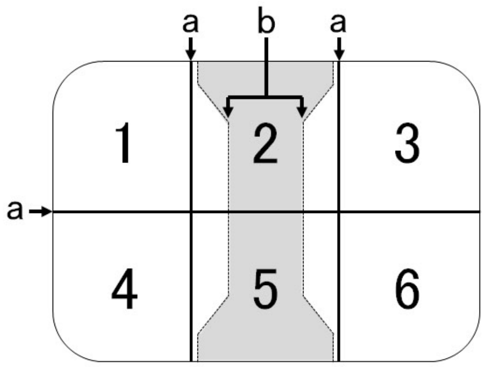

Figure 1. Tape cut area (1-6) and liner film cut position of Ketoprofen Tape "Teikoku". Solid line **(a)** was cut to obtain six fractions, and the dotted line **(b)** shows the cut position in the liner film. The gray area indicates the center flap of the liner film.

name drug, Mohrus® tape, was launched in December 1995 (*4*). It is a drug that is used frequently, especially by the elderly. We previously reported the formulation characteristics (peel force, water-vapor permeability, stretchability, rigidity and softness, *etc.*) of Mohrus® tape (*5,6*). In the current study, we report new findings on the peel power due to the difference in water-vapor permeability and temperature, which is directly related to the feeling of use in the formulation characteristics of Mohrus® tape.

2. Materials and Methods

2.1. Materials

Mohrus® Tape 20 mg (Hisamitsu Pharmaceutical Co., Inc.: Tokyo, Japan), Ketoprofen tape 20 mg "Teikoku" (Teikoku Pharmaceutical Co., Inc.: Kagawa, Japan), Ketoprofen tape 20 mg "Toko" (Toko Pharmaceutical Co., Ltd.: Tokyo, Japan), Ketoprofen tape 20 mg "BMD" (Biomedics Co., Ltd.: Tokyo, Japan), Ketoprofen tape "SN" (Shiono Chemical Co., Ltd.: Tokyo, Japan), Ketoprofen tape 20 mg "Kyorin" (Kyorin Rimedio Co., Ltd.: Tokyo, Japan), Touchron® tape 20 (Kyukyu Pharmaceutical Co., Ltd.: Toyama, Japan), Frestol® tape 20 mg (Towa Pharmaceutical Co., Ltd.: Osaka, Japan) and Ketoprofen tape 20 mg "Nichi-Iko" (Nichi-Iko Pharmaceutical Co., Ltd.: Toyama, Japan) was purchased. Table 1 shows the product name, manufacturer and serial number of each formulation used in this study. All other reagents used were special grade products.

2.2. Measurement of the water-vapor permeability

Water-vapor permeability was measured with reference to the method of Sawai *et al.* (*7*). After cutting the tape into 6 equal parts (Figure 1), the opening of the sample tube containing purified water was covered in advance, and the weight (W_1) was measured. Then, the tube was allowed to stand in a constant temperature and humidity tester KCL-2000W type (Tokyo Rikakikai Co., Ltd., Tokyo, Japan) with a temperature of 40 ± 2°C and humidity of 50 ± 5% relative humidity (RH). After 24 h, the weight (W_1) of the sample tube was measured, and the water-vapor permeability W (g/m^2/24 h) was calculated and evaluated by the following formula. The average of various tapes was calculated after 6 times.

$$W\ (g/m^2/24\ h) = (W_0 - W_1)/A$$

W_0: Weight before test (g), W_1: Weight after test (g), A: Opening area of sample tube (m^2)

2.3. Measurement of the peel force

According to the 90-degree peel test (*8*) of the Japanese pharmacopoeia 17th edition, various tapes (45 mm × 77 mm) cut into a test plate (stainless steel) were attached using a crimping roller (2 kg) (Japanese Industrial Standards: JIS, Z0237, 2009). After crimping, the mixture was allowed to stand for 5 min, 30 min, 9 h, and 24 h under temperature of 25 ± 2°C or 40 ± 2°C and humidity 50 ± 5% RH. After that, the short side of the sample was peeled off completely with a digital force gauge ZTS-20N (Imada Corp. Ltd., Aichi, Japan) at a constant speed at 90 degrees to the adhesive surface. The peeling speed was moved at 5.0 mm (300 mm/min) per second, and the pressure over time was measured 6 times with a recorder. The peel force of 50% length peeled from the test plate was averaged. In addition, the adhesive force-time curve from the start of peeling to complete peeling was measured using the graph drawing software Force Recorder Standerd Ver. 1.03 (Imada Co., Ltd., Aichi, Japan). Furthermore, the peel force of each product at 25°C or 40°C 30 minutes after application was measured.

2.4. Statistical analysis

For each experimental result, significant differences were analyzed using the paired *t*-test and the *Bonferroni/Dunn*-test of multiple comparison test (*9*). When $p \leq 0.05$ and $p \leq 0.01$, there was a difference at a significance level of 0.05 and 0.01, respectively.

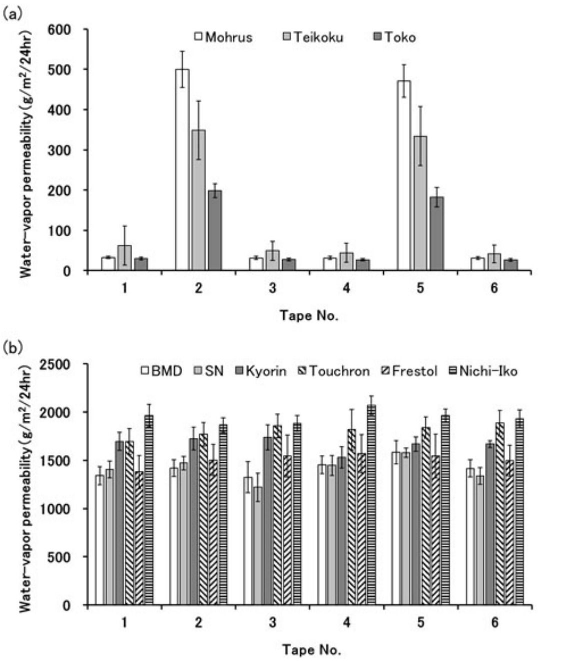

Figure 2. Water-vapor permeability of various tapes (*n* = 6). **(a)** Tapes containing SIS adhesives, **(b)** Tapes containing MBA adhesives.

3. Results

3.1. Measurement of the water-vapor permeability

Figure 2 shows the results of water-vapor permeability measurement for each product. In Figure 2, these nine preparations used in this study were divided into two groups, that is, Mohrus, Teikoku and Toko (Figure 2a) showed predominantly lower water-vapor permeability than six generic drugs group (BMD, SN, Kyorin, Touchron, Frestol and Nichi-Iko) (Figure 2b). In addition, preparations using styrene isopropyl styrene block copolymer (SIS) adhesives (Mohrus, Teikoku and Toko) show water-vapor permeability of 82 to 183 g/m^2/24 hr, whereas, preparations using methacrylic acid n-butyl acrylate copolymer (MBA) adhesives (BMD, SN, Kyorin, Touchron, Frestol and Nichi-Iko), showed water-vapor permeability of 1,410 to 1,810 g/m^2/24 h, which is about 10-fold higher (Table 2). Furthermore, Mohrus, Teikoku, and Toko had significantly higher water-vapor permeability in the central part (Tape No. 2 and 5) of the preparation than in the other parts (Tape No. 1, 3, 4 and 6). (Figure 2a).

3.2. Measurement of the peel force

3.2.1. 90-degree peel force test

Figure 3 shows the results of 90-degree peel adhesive

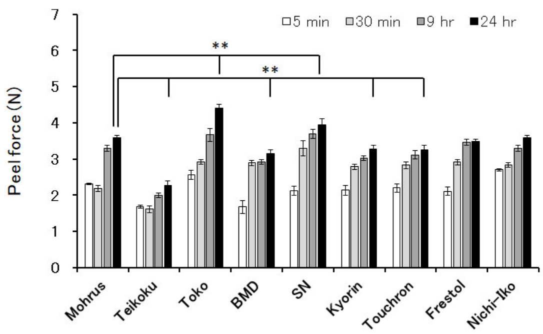

Figure 3. Comparison of 5 min, 30 min, 9 h and 24 h peeling force in various tapes. (n = 6, $^{**}p < 0.01$, Bonferroni/Dunn-test).

Table 2. Measurement of water-vapor permeability (*n* = 6)

Product name	Class	Water-vapor permeability (g/m^2/24h)	Types of Adhesives
Mohrus	BN	183.0 ± 234.6	SIS
Teikoku	GE	146.6 ± 151.1	SIS
Toko	GE	82.1 ± 84.3	SIS
BMD	GE	1423.6 ± 92.9	MBA
SN	GE	1410.3 ± 122.0	MBA
Kyorin	GE	1671.6 ± 74.4	MBA
Touchron	GE	1810.3 ± 69.3	MBA
Frestol	GE	1506.8 ± 67.6	MBA
Nichi-Iko	GE	1945.5 ± 72.7	MBA

BN: brand-name drug, GE: generic drug, ± SD: standard deviation, SIS: Styrene isopropyl styrene block copolymer, MBA: Methacrylic acid n-butyl acrylate copolymer.

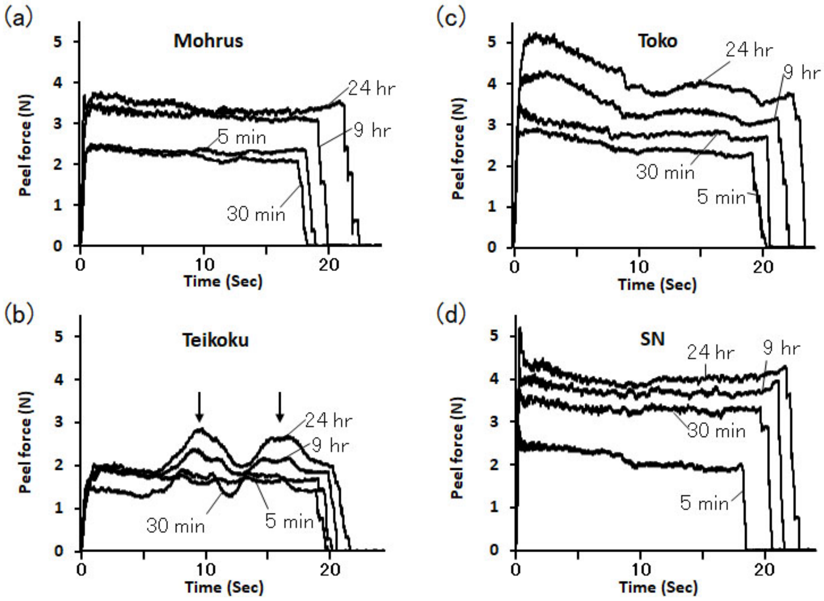

Figure 4. Comparison of 5 min, 30 min, 9 h, and 24 h peel force-time curve in various tapes (*n* = 6). (a) Mohrus, **(b)** Teikoku, **(c)** Toko, **(d)** SN.

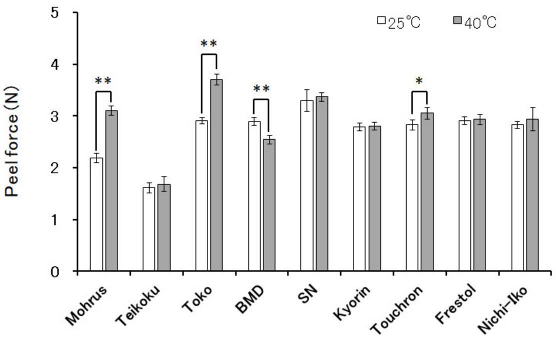

Figure 5. Comparison of peel force due to difference in temperature (n = 6). $^{*}p < 0.05$, $^{**}p < 0.01$ (25°C *vs.* 40°C, Paired *t*-test)

force measurement for each product. In Figure 3, the peel force when each product was separated after 5 min, 30 min, 9 h and 24 h from the start of application was measured, and the peel force tended to increase as the application time increased. In addition, when the peel force of each product after 24 h was compared, the generic drugs Toko (4.4 N) and SN (4.0 N) showed significantly higher values than the brand-name drug Mohrus (3.6 N). On the other hand, Teikoku (2.3 N), BMD (3.2 N), Kyorin (3.3 N) and Touchron (3.3 N) showed significantly lower values.

3.2.2. Comparison of the peel force-time curve

Figure 4 shows the measurement results of the peel force-time curve. When comparing the peel force-time curves of Mohrus (Figure 4a), Teikoku (Figure 4b) and Toko (Figure 4c) using SIS adhesives, Mohrus (Figure 4a) and Toko (Figure 4c) showed similar curves, although there were differences in the peel force. However, Teikoku showed a peculiar curve with two peaks at 9 and 24 h. On the other hand, the MBA adhesives (BMD, Kyorin, Touchron, Frestol and Nichi-Iko) showed similar curves to SN (Figure 4d), although there was a difference in peel force.

3.2.3. Comparison of the peel force due to difference in temperature

Figure 5 shows the measurement results of the peel force due to the difference in temperature. In Figure 5, when the peel force was measured 30 min after the start of application under the conditions of 25 or 40°C, Mohrus showed significantly higher values at 40°C (3.1 N) than at 25°C (2.2 N) (difference of 0.9 N). Similarly, the generic drug Toko showed significantly higher values at 40°C (3.7 N) than at 25°C (2.9 N) (difference of 0.8 N). On the other hand, BMD, showed significantly lower values at 40°C (2.5 N) than at 25°C (2.9 N) (difference of 0.4 N).

4. Discussion

The tape has a strong adhesive force, is difficult to peel off, has good followability to the skin even on moving parts (such as elbows and knees) and can be applied for a relatively long time (*10*).

Since an excellent therapeutic effect can be obtained by adhering to the skin and absorbing the drug through the skin, the component of the adhesive used in the plaster is an important factor affecting the transdermal absorption of the drug. However, it is known that strong adhesive strength and low water-vapor permeability cause physical irritation such as exfoliation of keratin and stuffiness.

The types of adhesives used in tapes are mainly classified into three types (rubber, acrylic, and silicon), and many products use the synthetic rubber type (SIS adhesives) or acrylic type (MBA adhesives). Mohrus, Teikoku and Toho are SIS adhesives listed in the package insert of each formulation, whereas BMD, SN, Kyorin, Touchron, Frestol and Nichi-Iko are MBA adhesives. According to the results of water-vapor permeability measurement, the SIS adhesives was about 10-fold less breathable than the MBA adhesives and tended to get stuffy when applied as a tape (Table 2). In addition, for Mohrus, Teikoku and Toho, which use SIS adhesives, the standard deviation value of water-vapor permeability measurement fluctuated greatly, suggesting that the water-vapor permeability may differ depending on the part of the tape. Therefore, when the tape agent was cut into 6 parts (No. 1 to 6) (Figure 1), and the water-vapor permeability of each piece was measured, Mohrus, Teikoku and Toho showed significantly higher water-vapor permeability in part No. 2 and 5 than No. 1, 3, 4 and 6 (Figure 2a). On the other hand, no such tendency was observed for BMD, SN, Kyorin, Touchron, Frestol and Nichi-Iko (Figure 2b). Such differences may be attributed to the manufacturing process of the tape preparation. The manufacturing process of tapes mainly involves: (I) Mixing (adhesive + drug), (II) Coating/Drying/Support and liner lamination, (III) Cutting/Back cutting, and (IV) Cutting to tape size/Packaging/Manufacturing with four steps of quality inspection. In (III), after the liner is attached to the tape agent, "back cutting" is performed to make a cut for the center flap in the liner to make it easier to attach when using the tape agent (Figure 1b). At the time of this back cutting, not only the liner but also the plaster was lightly cut; thus, it was considered that No. 2 and 5 showed significantly higher water-vapor permeability (Figure 2a). On the other hand, it is possible that BMD, SN, Kyorin, Touchron, Frestol and Nichi-Iko also have light cuts in the plaster, but since the MBA adhesive itself has high water-vapor permeability, a remarkable effect was not observed. From the above results, by confirming the type of adhesive in the package insert, since the SIS adhesives is a product that is easier to get stuffy than the MBA adhesives, such information would be informative to patients.

Next, when the 90-degree peel force was measured by the methods of adhesion testing, differences were observed among the products, and the peel force tended to increase with the extension of the application time (5 min, 30 min, 9 h and 24 h) (Figure 3). This is because when the adhesion time is short (5 min and 30 min), air bubbles are not released between the skin and the plaster containing the adhesive, and the adhesion area is expected to be small. On the other hand, as air bubbles gradually escape with the passage of time (9 and 24 h), a mechanical bonding that increases the contact area, the so-called "anchor effect (also called fastener effect)", occurs (*11,12*). As a result, the peel force was considered to have increased.

When the peel force-time curve was measured, different curves were shown for each product (Figure 4). For the brand-name drug Mohrus using SIS adhesives, the 5 min and 30 min curves were almost the same, and the 9- and 24-h curves were considered to show high values due to the anchoring effect (Figure 4a). The generic drug Teikoku using SIS adhesives showed a lower peel force when compared with Mohrus, and also showed two peaks on the 9 h and 24 h curves (Figure 4b). These peaks were consistent with the position of the cut for the center flap (Figure 1b), suggesting that the anchoring effect was enhanced at the gap. In the case of Toko, the peel force gradually increased with time, 5 min, 30 min, 9 h and 24 h, and the value at 24 h was the highest among other preparations (Figure 4c). The SN using MBA adhesives showed almost the same curve as Toko, and the similar peel force-time curve was shown on other pharmaceuticals (BMD, SN, Kyorin, Touchron, Frestol and Nichi-Iko) (Figure 4d).

In addition, the peel force after 30 min from the application start under the condition of 25°C or 40°C was measured, and Mohrus (brand-name drug) and Toko (generic drug) showed significantly higher values at 40°C. On the other hand, BMD of generic drugs was significantly higher at 25°C. As additives other than SIS or MBA adhesives, hydrogenated rosin glycerin ester (adhesion promoter, adhesive, *etc.*) and polyisobutylene (adhesive) are contained in Mohrus, terpene resin (tackifying resin) in Toko and polybutene (adhesive) in BMD (Table 3). Mohrus and Toko were each added with different adhesives, but both were more difficult to peel off at 40°C. It was also shown that BMD was difficult

Table 3. Main additives described in the package insert of each product

Abbreviated name/Adhesive agent	Mohrus /SIS	Teikoku /SIS	Toko /SIS	BMD /MBA	SN /MBA	Kyorin /MBA	Touchron /MBA	Frestol /MBA	Nichi-Iko /MBA
Adhesive resin									
Hydrogenated rosin glycerol ester (HRG)	●								
Alicyclic saturated hydrocarbon resin		●							
Terpene resin			●						
Polyisobutylene	●								
Polybutene		●		●	●	●	●	●	●

SIS: Styrene isopropyl styrene block copolymer, MBA: Methacrylic acid n-butyl acrylate copolymer.

to peel off at 25°C, but other using MBA adhesives products also contained polybutene, suggesting a difference in the amount of polybutene added.

In this study, the difference in partial water-vapor permeability of each pharmaceutical as well as peel force by the difference in pasting time and temperature condition were clarified. Grasping these detailed pharmaceutical characteristics may be helpful for pharmacists in selecting the appropriate pharmaceutical for the patient.

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**Address correspondence to:*
Ken-ichi Shimokawa, Department of Pharmaceutical Sciences, Meiji Pharmaceutical University, 2-522-1, Noshio, Kiyose, Tokyo 204-8588, Japan.
E-mail: kshimoka@my-pharm.ac.jp

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