

Generic Selection Criteria for Safety and Patient Benefit [IV] – Physicochemical and pharmaceutical properties of brand-name and generic ketoprofen tapes

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Summary

The physicochemical and pharmaceutical properties (pH, peel force, water-vapor permeability, and stretchability) of brand-name and generic ketoprofen products were evaluated and compared. The pHs of Mohrus as a brand-name product and Teikoku as a generic product were low (about 4). Among the other generic products, Patell and Nichi-Iko had a pH of about 4.3 while Frestol, Raynanon, BMD, and Touchron showed a pH of 4.6-5.2, which was in the pH range of normal healthy skin (4.5-6.5). The adhesive force was high (≥ 1.38) for Mohrus as a brand-name product as well as for Teikoku and Patell as generic products, but it was low (≤ 0.57) for the other 5 generic products. The water-vapor permeabilities of Mohrus as a brand-name product and Teikoku and Patell as generic products were low, being less than 1/6 of those for the other 5 generic products. Among the 5 generic products, BMD showed the highest water-vapor permeability (1,330 g/m²), and the other products also showed a value $\geq 1,100$ g/m². The elongatedness of Mohrus was the lowest (15.5 cm), and that of Raynanon was the highest (24.5 cm); the difference was 9 cm. In this study, the physicochemical and pharmaceutical properties of ketoprofen tapes were clarified, which will allow pharmacists to provide products according to the needs of each patient when a brand-name product is changed to a generic one.

Keywords: Ketoprofen tape, generic, abrasion power, water-vapor permeability, pharmaceutical properties

1. Introduction

In Japan, several generic drugs are commercially available to replace brand-name drugs. As health expenditure for the elderly will markedly increase in the future, the widespread use of generic drugs whose prices are low is being promoted (1). In clinical practice, whether or not generic drugs should be selected is evaluated by insurance pharmacists, excluding prescriptions for which there is a check in the column of "impossible to change" and an insurance doctor's signature is present (2). When selecting generic drugs,

information on differences in the efficacy and quality between brand-name and generic products is necessary.

In the field of orthopedics, a non-steroidal anti-inflammatory analgesic agent, Ketoprofen tape, which is effective for low back pain, osteoarthritis, muscle pain, and rheumatoid arthritis, has recently been routinely used in clinical practice (3). This tape is characterized by its adhesive force persisting for many hours, achieved even in articulating regions, such as the knees and elbows. However, when removing this tape, the corneal layer of the skin is exfoliated due to its high peel force (adhesive force), leading to pruritus, pain, or rubefaction. For this reason, a dosage form design to reduce skin irritation is required (3,4). Currently, many generic products of Ketoprofen tape are commercially available from various pharmaceutical manufacturers. The base component other than the active ingredient, support material, and manufacturing process are based on each manufacturer's individual techniques.

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Pharmacists must select products meeting patients' wishes, considering the properties of each product, and explain about them to patients. In particular, it is necessary to select preparations appropriate for patients from many generic drugs. In addition, some products are commercially available not only by prescription but also as over-the-counter (OTC) drugs. Pharmacists' knowledge and evaluation on selecting products are important. However, few studies have reported the properties of various preparations, which may become selection criteria. They are not sufficiently utilized in clinical practice (5,6). In this study, we evaluated the physicochemical properties of brand-name (7) and generic products of Ketoprofen tape, and examined criteria for selecting these products as information useful in clinical practice.

2. Materials and Methods

2.1. Materials

As Ketoprofen tape, a brand-name product, Mohrus[®] Tape L40 mg (Hisamitsu Pharmaceutical Co., Inc., Tokyo, Japan), and generic products, such as Ketoprofen tape 40 mg "Teikoku" (Teikoku Seiyaku Co., Ltd., Kagawa, Japan), Patell[®] tape 40 (Oishi Koseido Co., Ltd., Saga, Japan), Frestol[®] tape 40 mg (Towa Pharmaceutical Co., Inc., Osaka, Japan), Raynanon[®] tape 40 mg (Shiono Chemical Co., Ltd., Tokyo, Japan), Ketoprofen tape 40 mg "BMD" (Biomedix Co., Ltd., Tokyo, Japan), Touchron[®] tape 40 (Kyukyu Pharmaceutical Co., Ltd., Tokyo, Japan), and Ketoprofen tape 40 mg "Nichi-Iko" (Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan), were purchased, and used in this experiment (Table 1). All the other reagents were of analytical grade.

2.2. Measurement of pH

We measured pH values, as described by Ohtani *et al.* (5). Briefly, each preparation was cut into sections measuring 70 × 50 mm, placed in sample bottles containing 20 mL of purified water, and agitated for 24 h. Subsequently, the pH of the solution was measured using a Benchtop pH meter F-74 (HORIBA, Ltd., Kyoto, Japan). For each product, measurement was conducted 3 times, and the

mean was adopted as its pH value.

2.3. Measurement of the peel force

The peel force (adhesive force) was measured according to the adhesive tape/sheet test method established in the Japanese Industrial Standards (JIS) (8) and method described by Miura *et al.* (9). Briefly, a laboratory jack was fixed on an experimental table, and the unilateral side of the jack was rolled with Controlled Caliper Ethylene Vinyl Acetate membrane (EVA, 3M CoTran[™] 9702) as a type of artificial skin. On its surface, a section of each product measuring 30 × 52 mm was longitudinally attached. In addition, a cylindrical weight (4 kg) was rolled over each section to a specific site and back. Each section was allowed to stand for 30 minutes. Subsequently, the peel force was measured by pinching a 2-mm area of the upper margin with a clip and pulling it at a constant rate (1 mm/sec) so that the adhesive surface was vertical to a digital force gauge, ZTS-20N (Imada Co., Ltd., Aichi, Japan), until the tape had been completely exfoliated from the EVA membrane. With respect to each product, measurement was conducted 3 times, and the mean was regarded as the peel force.

2.4. Measurement of the water-vapor permeability

A water-vapor permeability test was performed, as described by Hiyoshi *et al.* (3). Briefly, 10 mL of purified water was placed in a glass container, and its opening was covered with a round section of each product measuring 40 mm in diameter. After the periphery was fixed with a piece of elastic paraffin film (Parafilm: Pechiney Plastic Packaging Company, U.S.A.), the weight was measured. Subsequently, each sample was allowed to stand for 24 h under the following conditions: temperature, 40°C; relative humidity, 50%. Additionally, the weight was measured. The water-vapor permeability was calculated from the rate of change in the weight using the following formula: Water vapor permeability (g/m²·24 h) = (W₀ - W₁) · 10,000/A [W₀: Weight before testing (g), W₁: Weight after testing (g), A: Area of the glass container's opening (cm²)]. With respect to each product, measurement was conducted 3 times, and the mean was regarded as the water-vapor permeability.

Table 1. Various products have been used in this experiment

Product name	Class	Abbreviated name	Company	Serial number
Mohrus [®] Tape L40 mg	brand-name	Mohrus	Hisamitsu Pharmaceutical Co., Ltd.	LC12U
Ketoprofen tape 40 mg "Teikoku"	generic	Teikoku	Teikoku Seiyaku Co., Ltd.	7104
Patell [®] tape 40	generic	Patell	Oishi Koseido Co., Ltd.	621110
Frestol [®] tape 40 mg	generic	Frestol	Towa Pharmaceutical Co., Ltd.	A007
Raynanon [®] tape 40 mg	generic	Raynanon	Shiono Chemical Co., Ltd.	ZS03
Ketoprofen tape 40 mg "BMD"	generic	BMD	Biomedix Co., Ltd.	1W17
Touchron [®] tape 40	generic	Touchron	Kyukyu Pharmaceutical Co., Ltd.	1Y11
Ketoprofen tape 40 mg "Nichi-Iko"	generic	Nichi-Iko	Nichi-Iko Pharmaceutical Co., Ltd.	1S12

2.5. Measurement of the stretchability

The end (10 mm) of a section of each product measuring 20 × 100 mm was fixed on an experimental table with the adhesive surface facing upward. The maximum extension distance (cm) was measured by pulling the diagonal side. For each product, measurement was conducted 6 times, and the mean was regarded as the stretchability.

2.6. Statistical analysis

The values were compared using *Welch's t*-test. A *p*-value of 0.05 or 0.01 was regarded as significant.

3. Results

3.1. Measurement of pH

The results of pH measurement of each product are shown in Figure 1. Some brand-name and generic products showed differences in the pH. In particular, the pH values of the brand-name product, Mohrus, and a generic product, Teikoku, were 4.0 and 3.9, respectively. On the other hand, concerning the other generic products, the pH values of Patell and Nichi-Iko were 4.3 and 4.4, respectively. In addition, they were comparable to those of Frestol (pH 4.8), Raynanon (pH 4.6), BMD (pH 5.2), and Touchron (pH 4.8). Furthermore, significance tests were conducted to compare brand-name products with various generic products. Frestol and BMD showed significant differences in comparison with the brand-name product, Mohrus ($p < 0.01$) (Figure 1).

3.2. Measurement of the peel force

The peel force (adhesive force) of each product was measured. The results are presented in Figure 2. The peel forces of the brand-name product, Mohrus (1.38 N), and generic products, Teikoku (1.82 N) and Patell (1.77 N), were high, but those of the other generic products, Frestol (0.43 N), Raynanon (0.57 N), BMD (0.51 N), Touchron (0.45 N), and Nichi-Iko (0.50 N), were low. In addition, significance was tested between the brand-name and generic products. There were significant differences in the peel force between Mohrus and Frestol/Touchron/Nichi-Iko/BMD/Raynanon ($p < 0.01$)/Teikoku ($p < 0.05$) as shown in Figure 2.

3.3. Measurement of the water-vapor permeability

The water-vapor permeability of each product was measured. The results are shown in Figure 3. We compared the water-vapor permeability of each product. There were marked differences among the products. Briefly, the water-vapor permeabilities of the brand-name product, Mohrus (117 g/m²), and generic products,

Teikoku (95 g/m²) and Patell (85 g/m²), were low, whereas those of the other generic products, Frestol (1,125 g/m²), Raynanon (1,200 g/m²), BMD (1,338 g/m²), Touchron (1,125 g/m²), and Nichi-Iko (1,231 g/m²), were high. In addition, significance was tested between the brand-name and generic products. There were significant differences in the water-vapor permeability between Mohrus and Touchron/Frestol/Raynanon/Nichi-Iko/BMD ($p < 0.01$) as shown in Figure 3.

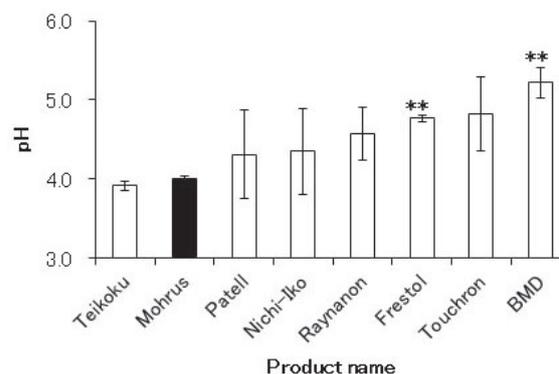


Figure 1. pH comparison of various products ($n = 3$). ■, brand-name product; □, generic product; ** $p < 0.01$ (brand-name vs. various generics; *Welch's t*-test)

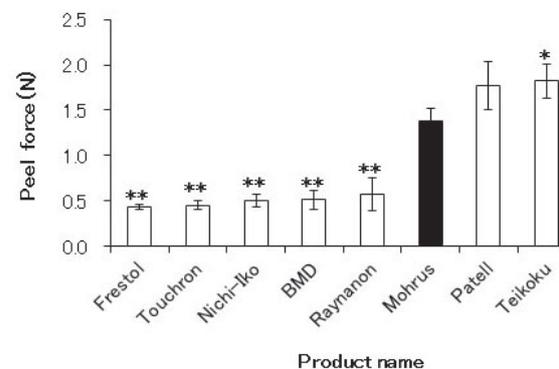


Figure 2. Comparison of the peel force (N) of various products ($n = 3$). ■, brand-name product; □, generic product; * $p < 0.05$, ** $p < 0.01$ (brand-name vs. various generics; *Welch's t*-test)

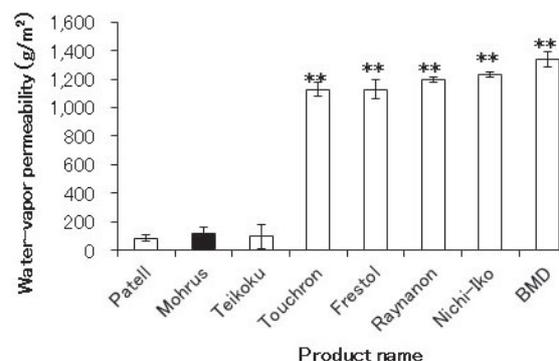


Figure 3. Comparison of the water-vapor permeability (g/m²) of various products ($n = 3$). ■, brand-name product; □, generic product; ** $p < 0.01$ (brand-name vs. various generics; *Welch's t*-test)

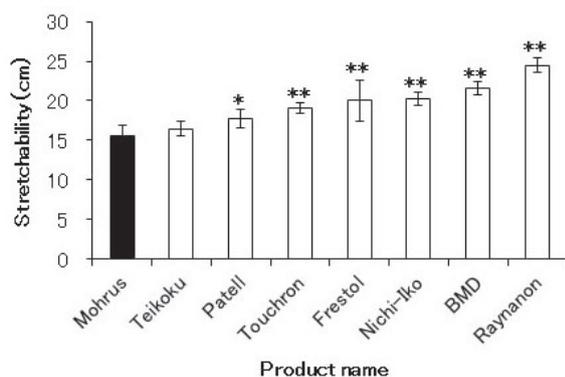


Figure 4. Comparison of the stretchability (cm) of various products ($n = 6$). ■, brand-name product; □, generic product; * $p < 0.05$, ** $p < 0.01$ (brand-name vs. various generics; Welch's *t*-test)

3.4. Measurement of the stretchability

The stretchability of each product was measured. The results are presented in Figure 4. The stretchabilities of the brand-name product, Mohrus (15.5 cm), and a generic product, Teikoku (16.5 cm), were low. Those of the other generic products, Patell (17.7 cm), Touchron (19.1 cm), Frestol (20.0 cm), Nichi-Iko (20.2 cm), BMD (21.6 cm), and Raynanon (24.5 cm), were high. In addition, significance was tested between the brand-name and generic products. There were significant differences in the stretchability between Mohrus and Touchron/Frestol/Nichi-Iko/BMD/Raynanon ($p < 0.01$)/Patell ($p < 0.05$) as shown in Figure 4.

4. Discussion

4.1. Measurement of pH

The pH of healthy skin ranges from 4.5 to 6.5 (slightly acidic). As tape preparations are directly attached to the skin, their pH may markedly influence patients' impressions of their use. The pH of each product is shown in and Figure 1. There were differences in the pH among the products. In particular, the pH values of the brand-name product, Mohrus, and a generic product, Teikoku, were approximately 4.0. Concerning the other generic products, the pH values of Patell and Nichi-Iko were approximately 4.3. In addition, those of Raynanon, Frestol, Touchron, and BMD ranged from 4.6 to 5.2, within a healthy skin pH range of 4.5 to 6.5. These results suggest that Mohrus and Teikoku become skin-stimulating factors, because their pH values were lower than the pH range of healthy skin.

4.2. Measurement of the peel force

The peel force (adhesive force) of tape preparations may directly influence impressions of their use, such as ease of peeling, in accordance with its intensity. Tape preparations with a weak peel force may come off due

to frictions with clothes or in articulating regions, such as the elbows and knees. We measured the peel force (N) of each product. The results are presented in Figure 2. The peel forces of the brand-name product, Mohrus, and 2 generic products, Teikoku and Patell, were high (1.38 N or higher). However, those of the other generic products were low (0.57 N or lower). These results showed that there were differences in the peel force among the products, suggesting that impressions of their use markedly differ. These 3 tape preparations with a high peel force (Mohrus, Teikoku, and Patell) may not come off even in articulating regions, facilitating application for a relatively long period. However, at the time of exfoliation, they may cause detachment damage of the stratum corneum, in which the corneal layer of the skin surface is simultaneously peeled, and physical stimuli derived from dermal stress may lead to support stress, inducing symptoms such as hypersensitivity, erythema, eruption, rubefaction, swelling, feeling of stimulation, and pruritus (7).

4.3. Measurement of the water-vapor permeability

Tape preparation-related stimulations of the skin include physical stimuli on exfoliation, drug allergy, chemical stimuli related to additives/impurities, and maceration stimuli, such as corneal-layer hydration, sweat-gland blocking, and bacterial proliferation associated with occlusion at the site of attachment (10). Of these, maceration stimuli may occur in areas to which products with a low water-vapor permeability are attached. Therefore, we measured the water-vapor permeability of each product. The results are shown in Figure 3. We compared the water-vapor permeability of each product. There were marked differences among the products. Briefly, the water-vapor permeabilities of the brand-name product and 2 generic products (Teikoku and Patell) were low (1/6 or less of those of the other 5 generic products). On the other hand, of the 5 generic products, BMD showed the highest water-vapor permeability (1,338 g/m²). The values of the other products were also 1,100 g/m² or higher. The products used in this experiment were designed to be applied over 24 h (attached once a day). Therefore, the use of products with a high permeability may prevent maceration stimuli (11). However, an increase in the permeability reduces the sealing property, decreasing skin transfer of the drug. Therefore, when selecting products, it may be important to sufficiently understand their properties (4).

4.4. Measurement of the stretchability

Ketoprofen tape preparations are attached to articulating regions, such as the lumbar spine, elbows, and knees, in many cases. Therefore, the stretchability of tape preparations is considered an important factor. In

particular, when tape preparations are attached to the elbows or knees, they may promptly come off due to unfavorable stretchability. The stretchability of each product is shown in Figure 4. There was a 9-cm difference between Mohrus (15.5 cm: minimum) and Raynanon (24.5 cm: maximum). The stretchability may be related to the material composition of each product. Low-stretchability products may restrict dermal expansion and contraction, stimulating the site of attachment with tension.

The results of this study showed that there were differences in physical properties among Ketoprofen tape preparations. This makes it possible for pharmacists to provide products based on patients' wishes (products that are painless on peeling them off, and those that are breathable) when switching a brand-name drug to a generic.

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