Original Article

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Generic selection criteria for safety and patient benefit [XII]: Comparing the physicochemical and pharmaceutical properties of brand-name and generic tulobuterol tape

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SUMMARY Physicochemical properties (drug release, peel strength, adhesion, and stiffness) of Hokunalin® Tape (Hokunalin) and 13 generic transdermal bronchodilator patches containing tulobuterol were characterized and evaluated for comparison. Drug-release studies evaluating sustained release behavior demonstrated better performance by the drug Hokunalin, than the generics MED, YP, Sawai, and Teikoku. Hokunalin yield a 16.2% release 1 hour after initiation, 30.1% at 3 hours, 50.0% at 8 hours. In comparison, the generics MED, YP, Sawai, and Teikoku showed an intermediate release behavior to that of Hokunalin, with more than 80% release after 8 hours. A 90-degree peel adhesion test for tape peel strength demonstrated that the generic MED (4.99 N), YP (3.26 N), Sawai (4.17 N), and Teikoku (4.37 N) tapes yielded significantly higher values compared to Hokunalin (2.66 N). Probe tack tests, evaluating adhesive strength, yielded significantly higher values for the generics HMT (4.89 N) and Towa (4.25 N) compared to Hokunalin (3.66 N). Furthermore, for the stiffness-softness test, a significantly higher value was obtained for each generic yielded compared to Hokunalin (3.7-degree). These factors are important components of product qualities that affect treatment efficacy, including "ease of application" and other usability factors.

Keywords Transdermal therapeutic drug, brand-name drug, generic drug, tulobuterol tape

1. Introduction

Tulobuterol Tape is a β_2 stimulant used to relieve dyspnea-like symptoms due to airway obstructive disorders, such as bronchial asthma. It is designed as an extended-release formulation with an expected sustained effect. As only once-daily application is required, it has a high level of compliance and is used by many patients, especially the elderly, with many generic versions available. However, prescription substitution from generic drugs to brand-name drugs can lead to poorer compliance and health outcomes due to differences in feel or insufficient efficacy (*1*). Common performance variations reported between brand-name and generic drugs include differences in peeling and adhesive strength (*2-5*) due to tape formulation additives. For tulobuterol tape formulations, the effect of these formulation variants are not yet systematically evaluated among brand-name and generic drugs. Furthermore, Hokunalin® Tape has a sustained drug release mechanism, formulated using the Crystal Reservoir System (*6,7*). As the generic drugs cannot employ this patented formulation design, variations in drug release properties are a strong possibility, potentially impacting on therapeutic outcomes. Furthermore, in patients with increased skin permeability due to factors including atopic dermatitis, long-term steroid administration, and aging, drug release rates may be affected, altering transfer across the tape-skin-blood interface (*8-11*). Due to these variations in drug-transfer properties resulting from different patient skin conditions, side effects may occur, such as tremors and palpitations, associated with rapidly rising blood drug levels immediately after administration, and then, due to early drug depletion, a shortened tape drug-delivery lifetime may insufficiently suppress asthma attacks.

Therefore, this study compares the brand-name and available generic drugs in terms of both physicochemical properties and drug-release properties, providing information to best identify treatments options for patient-focused care.

2. Materials and Methods

2.1. Materials

This study evaluated the brand name Hokunalin® Tape 2 mg (Mylan EPD G.K., Tokyo, Japan), a tulobuterol-containing tape formulation (2 mg of tulobuterol in one (3.2 cm × 3.2 cm) sheet), and 13 generic 2 mg tulobuterol tapes, including "EMEC" (Nipro Pharma Corp., Osaka, Japan), "HMT" (Hisamitsu Pharmaceutical Co., Ltd., Tokyo, Japan), "MED" (Medisa Shinyaku Inc., Tokyo, Japan), "NP" (Nipro Corp., Osaka, Japan), "QQ" (Kyukyu Pharmaceutical Co., Ltd., Tokyo, Japan), "YP" (Yutoku Pharmaceutical Industries, Ltd., Saga, Japan), "Ohara" (Ohara Pharmaceutical Industries, Ltd., Shiga, Japan), "Sawai" (Sawai Pharmaceutical Co., Ltd., Osaka, Japan), "Takata" (Takata Pharmaceutical Co., Ltd., Saitama, Japan), "Teikoku" (Teikoku Seiyaku Co., Ltd., Kagawa, Japan), "Towa" (Towa Pharmaceutical Co., Ltd., Osaka, Japan), "Nichi-Iko" (Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan), and "Pfizer" (Pfizer Japan Inc., Tokyo, Japan). The 14 tape products used in this study are listed in Table 1.

2.2. Measurement of drug release

The paddle over disk method of release testing for preparations applied to the skin, listed in the 18th edition of the Japanese Pharmacopoeia, was used (*12*). The formulation was placed with double-sided tape on a D2414 disc (Toyama Sangyo Co., Ltd., Osaka, Japan) made of stainless steel (SUS316) mesh with a 125 μm aperture, with the adhesive side up, 32 mm × 32 mm, and eluted in a dissolution tester (Varian VK 7010, Tokyo, Japan) filled with 500 mL of water at a temperature of 32°C. The eluent temperature was 32°C. The formulation was then taped to the disc using a double-sided adhesive tape; Agilent Technologies International Japan Ltd. Solutions were collected at 1, 3, 8, and 24 hours after the start of elution and quantified by HPLC using a YMC-Pack ODS-A analytical column (125 mm × 4.0 mm I.D., YMC Corp., Kyoto, Japan), a PU-4180 pump (Japan Spectroscopic Company, Tokyo, Japan) and absorbance measured at 215 nm using a UV-4075 UV-visible detector (Japan Spectroscopic Company). The mobile phase used was acetonitrile and 20 mM potassium dihydrogen phosphate in a 1:3 ratio. The mobile phase flow rate was 1.0 mL/min, column temperature set 30°C using a column oven CO-4061 (Japan Spectroscopic Company), and sample solutions of 10 μL were injected. ChromNAV (LC-Met II/ADC, Japan Spectroscopic Company) was used for data processing.

2.3. Measurement of peeling force

The 90-degree peel adhesion test was performed according to the 90-degree peel adhesion test method listed in the 18th edition of the Japanese Pharmacopoeia (*13*). That is, a formulation was cut to 28 mm × 32 mm was applied to a stainless-test plate P90-200N (Imada Co., Ltd., Aichi, Japan), and a 2 kg roller passed back and forth at a speed of 5 mm/sec. The 4 mm long side was clipped and peeled off at a speed of 2 mm/sec angle 90-degree using a digital force gauge MX-2-500N (Imada Co., Ltd.) fixed on a vertical motorized test stand M-2-500N (Imada Co., Ltd.). After the start of the measurement, the measured values of 50% of the length pulled off the test plate were averaged to obtain the value (N/cm) for the 90-degree peel adhesion test.

2.4. Measurement of adhesive strength

Probe tack testing was performed according to the Probe tack test method listed in the 18th edition of the Japanese Pharmacopoeia (*14*). That is, a digital force gauge ZTS-20N (Imada Co., Ltd.) was used with the formulation cut to 15 mm × 15 mm and attached to a weight ring MED-IS-20N (Imada Co., Ltd.) and fixed to a vertical motorized test stand MX-2-500N (Imada Co., Ltd.). The maximum force required to move the weight ring at a speed of 5 mm/sec and to pull off the probe and sample after bonding them at 1 N/cm^2 for 1 second was

Table 1. Tape products used in this study

Product name	Abbreviated name	Class	Company name	Lot number
Hokunalin® tape 2 mg	Hokunalin	brand-name	Mylan EPD G.K.	86718YQ1, 9711YQ1
Tulobuterol tape 2 "EMEC"	EMEC	generic	Nipro Pharma Corp.	AS02C
Tulobuterol tape 2 mg "HMT"	HMT	generic	Hisamitsu Pharmaceutical Co., Inc.	U503T, U710T
Tulobuterol tape 2 mg "MED"	MED	generic	Medisa Shinyaku Inc.	17901
Tulobuterol tape 2 mg "NP"	NP	generic	Nipro Corp.	17R321
Tulobuterol tape 2 mg "QQ"	QQ	generic	Kyukyu Pharmaceutical Co., Ltd.	7T11T
Tulobuterol tape 2 mg "YP"	YP	generic	Yutoku Pharmaceutical Ind. Co., Ltd.	8C010
Tulobuterol tape 2 "Ohara"	Ohara	generic	Ohara Pharmaceutical Industries, Ltd.	7Y14
Tulobuterol tape 2 mg "Sawai"	Sawai	generic	Sawai Pharmaceutical Co., Ltd.	18206
Tulobuterol tape 2 mg "Takata"	Takata	generic	Takata Pharmaceutical Co., Ltd.	TZ01
Tulobuterol tape 2 mg "Teikoku"	Teikoku	generic	Teikoku Seiyaku Co., Ltd.	18302
Tulobuterol Tape 2 mg "Towa"	Towa	generic	Towa Pharmaceutical Co., Ltd.	A0048
Tulobuterol tape 2 mg "Nichi-Iko"	Nichi-Iko	generic	Nichi-Iko Pharmaceutical Co., Ltd.	7T13N
Tulobuterol tape 2 mg "Pfizer"	Pfizer	generic	Pfizer Japan Inc.	180217

measured.

2.5. Measurement of stiffness

The angle of flexure was measured visually at 2.5-degree intervals when one half of a 32 mm × 32 mm formulation was affixed to a test stand and a 100 mg weight was attached to the other end (*15*).

2.6. Statistical analysis

Statistical significance was evaluated using *Dunnett's* multiple comparison test method, with a risk rate of 5% or less considered significant (*16*). In graphs, products significantly different from the original drug (Hokunalin® tape) at a risk rate of 1% or less are marked with asterisks (**).

3. Results

3.1. Measurement of drug release

Drug release results are shown in Figure 1 and Table 2. Hokunalin yield a 16.2% release 1 hour after initiation, 30.1% at 3 hours, 50.0% at 8 hours, 65.1% at 12 hours, and 93.5% at 24 hours. In comparison, the generics EMEC, NP, QQ, Ohara, Takata, and Nichi-Iko released over 90% after 1 hour, while HMT, Towa, and Pfizer reached almost 90% release after 3 hours. MED, YP, Sawai, and Teikoku showed an intermediate release behavior to that of Hokunalin, with more than 80% release after 8 hours.

3.2. Measurement of peeling force

The peel force measurements immediately after crimping are shown in Figure 2 and Table 2. Significantly higher values were obtained for generics MED (4.89 N), YP (3.26 N), Sawai (4.17 N) and Teikoku (4.37 N) compared to Hokunalin (2.66 N). However, the other generics (EMEC, HMT, NP, QQ, Ohara, Takata, Towa, Nichi-Iko, and Pfizer) showed significantly lower values.

Figure 3 and Table 2 shows the peel-off force measurements immediately after application (applying), peeling off, and then reapplying. The comparison of affixation, removal, and reapplication showed a

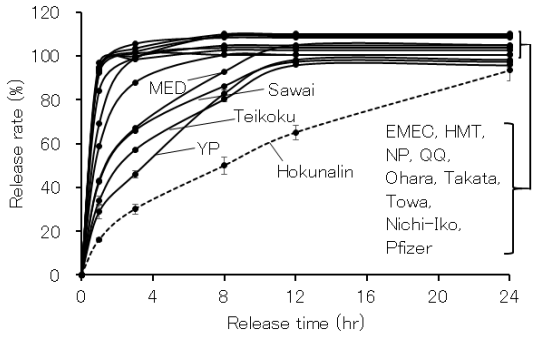

Figure 1. Comparison of drug release curves (*n* = 6). Dotted line: brand-name drug, solid line: generic drugs.

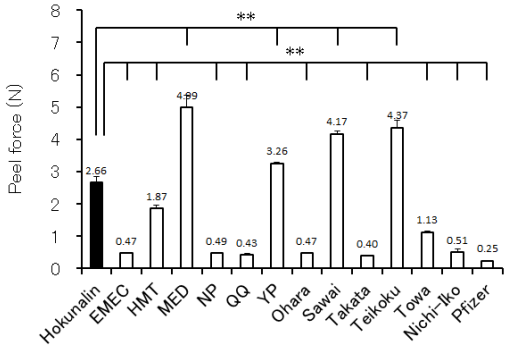

Figure 2. Comparison of peel force by the 90-degree test. (*n* = 6, *vs.* Hokunaline, $**p < 0.01$, *Dunnett's*-test), Black bar: brand-name drug, white bar: generic drugs.

Table 2. Summary of test measurements

Products	Release rate (%) (after 3 h/ 8 h/ 12 h)	Peel force (N)	Peel - re-peel force (N)	Adhesive force (N)	Bending resistance (degree)
Hokunalin	**30.1 / 50.0 / 65.1**	2.66	-0.35	3.66	**3.67**
EMEC	105.7 / - / -	0.47	0.05	1.93	44.17
HMT	87.9 / - / -	1.87	-0.10	**4.89**	59.58
MED	66.9 / 92.8 / -	**4.99**	**-0.79**	3.74	34.58
NP	103.5 / - / -	0.49	0.04	2.11	58.33
QQ	99.9 / - / -	0.43	0.00	1.98	25.42
YP	45.9 / 82.7 / 98.2	3.26	**0.78**	3.79	9.58
Ohara	101.3 / - / -	0.47	0.01	0.83	22.50
Sawai	65.9 / 86.1 / 97.2	**4.17**	**-0.55**	3.41	32.92
Takata	101.7 / - / -	0.40	0.07	1.95	56.25
Teikoku	57.1 / 80.3 / 95.9	**4.37**	**-0.58**	3.31	38.33
Towa	98.9 / - / -	1.13	0.05	**4.25**	**5.83**
Nichi-Iko	98.5 / - / -	0.51	0.01	1.87	22.92
Pfizer	99.1 / - /	0.25	0.02	1.59	26.25

-: Indicates a release rate (%) of 100% or more. Peel- re-peel force: Amount of change in peel and re-peel force.

significant increase in force required for YP, whereas significantly lower forces for Hokunalin and the generics MED, Sawai, and Teikoku. The remaining generics yielded smaller changes in the required peel-off force.

3.3. Measurement of adhesive strength

Adhesion measurements for the probe tack test are shown in Figure 4 and Table 2. The generic drugs HMT (4.89 N) and Towa (4.25 N) yielded significantly higher adhesive strength than Hokunalin (3.66 N). On the other hand, EMEC (1.93 N), NP (2.11 N), QQ (1.98 N), Ohara (0.83 N), Takata (1.95 N), Nichi-Iko (1.87 N), and Pfizer (1.59 N) all yielded significantly lower adhesive values.

3.4. Measurement of stiffness

Rigidity measurements are shown in Figure 5 and Table 2. All generics, except Towa (5.8-degree), yielded significantly higher values compared to Hokunalin (3.7-degree). Particularly, HMT (59.6-degree), NP (58.3-degree), and Takata (56.3-degree) gave rigid softness values greater than 50-degree, indicating they are very soft products.

4. Discussion

In drug release assays, Hokunalin exhibited a slower, more sustained release compared to other tape formulations (Figure 1 and Table 2). The active ingredient release rate for Hokunalin was 30% at 3 hours and 50% at 8 hours, while the generics YP and Teikoku gave release rates of 46% and 57%, respectively, at 3 hours, with both over 80% at 8 hours. The release rate for YP was about 1.5 times greater than that of Hokunalin after 3 hours, and about 2 times greater than that of Teikoku, demonstrating that Hokunalin has better sustained-release characteristics. One reason for this may be the use of the patented "Crystal Reservoir System" (*6*) mechanism, which gradually releases the drug from the tape to the skin, yielding an effective release over 24 hours. Lacking this technique, developing products with similar sustained-release characteristics may be difficult.

Tulobuterol pastes can reduce side effect risks and provide improved efficacy for symptoms like asthma attacks at the latter period of individual treatment times before reapplication, due to better sustained-release properties. On the other hand, patients' skin permeability may also affect drug formulation release rates (*8-11*). Therefore, caution is required in selecting generic drugs for patients with weak skin barrier functions, such as children and patients with skin diseases that compromise skin-barrier integrity.

Next, comparing tape peel strengths showed that the generics MED (4.99 N), YP (3.26 N), Sawai (4.17 N), and Teikoku (4.37 N) were significantly higher than that of Hokunalin (2.66 N) (Figure 2 and Table 2). The peel-off force for MED, Sawai and Teikoku was more than 4 N, indicating that a strong force is required to peel off the tape. A high peeling force implies the tape is difficult to peel off and is expected to be more invasive to the skin, causing pain during the peeling process and an associated exfoliation of dead skin cells. Peeling difficulty and skin

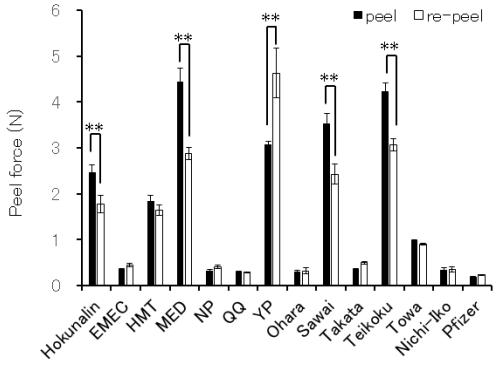

Figure 3. Comparison of re-peel force by the 90-degree test. (*n* = 6, ***p* < 0.01, Paired *t*-test), Black bar: peel force, white bar: re-peel force.

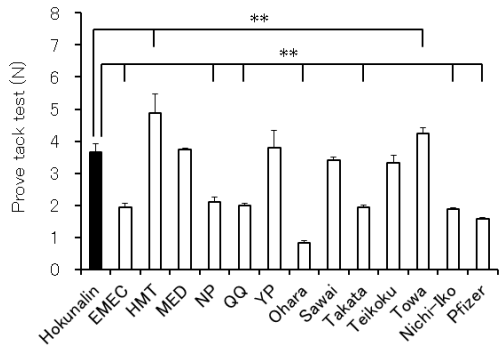

Figure 4. Comparison of adhesive force by the probe tack test. (*n* = 6, *vs.* Hokunaline, ***p* < 0.01, *Dunnett's*-test), Black bar: brand-name drug, white bar: generic drugs.

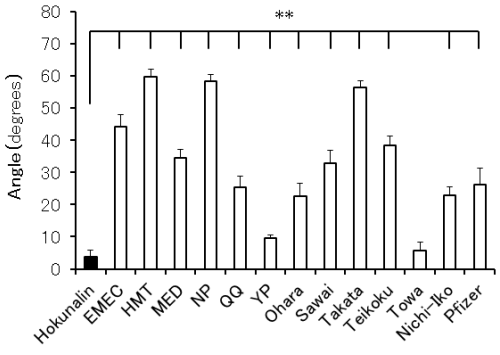

Figure 5. Comparison of bending resistance. (*n* = 6, *vs.* Hokunaline, ***p* < 0.01, *Dunnett's*-test), Black bar: brand-name drug, white bar: generic drugs.

irritation are considered likely problems that patients may experience when using these products. These results assist in appropriate formulation selection according to patients' skin condition.

On the other hand, generics EMEC (0.47 N), HMT (1.87 N), NP (0.49 N), QQ (0.43 N), Ohara (0.47 N), Takata (0.40 N), Towa (1.13 N), Nichi-Iko (0.51 N), and Pfizer (0.25 N) yielded significantly lower peel strength values. Products with a peel strength of less than 1 N indicate easy removal, which may be a positive depending on the patient's skin condition. As these products are applied daily for the prevention of bronchial asthma to either the chest, back, or upper arm, *etc.*, a weaker peel-off force may reduce skin irritation. However, keratin damage during tape removal is not the only source of skin irritation. It can also be caused by "steaming" due to prolonged application, "blistering" by strongly pulling the skin upon application, and "chemical irritation" caused by additives. These irritating factors require minimization to improve patient comfort.

Though it may be considered relatively rare to peel off and reapply the tape, there are cases where tape is wrinkled during application and is reapplied after being peeled off from the skin. Thus, reapplication (reattachment) tests were conducted for each tape formulation (Figure 3 and Table 2). For Hokunalin, and the generics MED, Sawai, and Teikoku, peeling and immediate reapplication on tape adhesive strength led to significantly lower peel-off forces. In this test, the peel force was measured by tape application to a stainless-steel plate, peeled off once, reapplied, and peeled off once more. Usually, tape application to skin involves keratin and other skin substances adhering to the tape adhesive side after removal, strongly decreasing adhesive strength upon reapplication. This test is complicated to perform, so the simplification of application to a stainless plate was used rather than skin, and simply compared the magnitude of change in peeling strength upon reapplication. The four tapes with high peel force values, Hokunalin, MED, Sawai, and Teikoku, all underwent significant decreases in peel strength upon reapplication (Figure 3 and Table 2). On the other hand, YP yielded a significantly higher peel strength after reapplication compared to the first application. This is attributed to part of the tape adhesive surface detaching and contaminating the stainless test plate after the first peeling. This then exposes a new adhesive surface tape adhesive side, which then adheres more strongly to the stainless-steel surface with the deposited adhesive.

Next, the probe tack test measured tape adhesiveness, with the results shown in Figure 4 and Table 2. The probe tack test indicated that the generic drugs HMT (4.89 N) and Towa (4.25 N) were significantly higher than Hokunalin (3.65 N). On the other hand, EMEC (1.93 N), NP (2.11 N), QQ (1.98 N), Ohara (0.83 N), Takata (1.95 N), Nichi-Iko (1.87 N), and Pfizer (1.59 N) all showed significantly lower values. Particularly, Ohara yielded the lowest adhesive stickiness, at less than 1 N. As adhesiveness is generally an ease-of-application indicator, the high adhesive strength of HMT and Towa suggested they are easy-to-apply products.

Next, the tape stiffness measurement results are shown in Figure 5 and Table 2. This shows that all generics, except Towa, were significantly stiffer than Hokunalin. Products with low rigidity and high softness values can flexibly conform to skin movements, which is desirable. However, low rigidity and high softness may also increase difficulties in applying the tape, as the adhesive surface may fold and adhere to itself. Therefore, the appropriate formulation varies depending on user circumstances, physical capability, and skin condition. Thus, the results of these analyses provide a basis to select the appropriate formulation for patient-focused care.

A summary of measured values for each test is shown in Table 2. The highest performing formulations, in terms of active ingredient sustained release, are Hokunalin and the generic products YP and Teikoku. MED, Sawai, and Teikoku yielded high peel-off force values, indicating the possibility of skin damage. No correlation was observed between peeling force and adhesive strength. Furthermore, given the softness of products other than Hokunalin and Towa, they may be difficult to apply, especially when applied by the elderly and people with poor manual dexterity.

Given the varying characteristics among the tapes, pharmacists must select the best product for the patient, accounting for the patient's background (*e.g.*, to include effects of increased skin permeability, *etc.*), patient's dexterity, and the patient's comfort in using the product.

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