

Generic selection criteria for safety and patient benefit [XI]: Usability scores of brand-name and generic tapes containing sodium diclofenac by questionnaire survey

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SUMMARY The aim of this study was to evaluate patient satisfaction and usability scores of different tape treatments and examine the scores in relation to the mechanical characteristics of the tape formulation. A questionnaire for the assessment of comfort level and satisfaction with two brand-name (Nabopal, Voltaren) and four generic tapes (Yutoku, Teikoku, Rakool, Towa) containing sodium diclofenac was developed and then applied to 12 healthy volunteers. Results showed that Voltaren was difficult to apply to the skin and easier to peel off the skin than Nabopal ($p < 0.01$). Moreover, Rakool was easier to peel than Nabopal ($p < 0.05$). The mechanically measured peeling force was associated with pain during peeling off ($r = -0.65$), and the measured value of bending rigidity was associated with ease of peeling off ($r = -0.97$). The knowledge obtained regarding the influence of pharmaceutical properties on the degree of satisfaction with and usability of different tape formulations may be useful for supporting the selection of generic tapes tailored to individual needs or pharmacist preferences, and thus improve treatment adherence and clinical outcomes.

Keywords Brand-name drug, generic drug, tape, satisfaction research, usability

1. Introduction

In recent years, the active use of generic drugs has been promoted for the purpose of reducing medical costs, and the volume share of generics in Japan is currently 79.0% (1), with the Ministry of Health, Labor and Welfare requesting an even higher share of over 80%. In contrast, according to a survey of 870 insurance pharmacies conducted by the Central Social Insurance Medical Council, the most common reason given for returning to brand-name drugs ($n = 585$) from generics was that generics did not suit the patient's needs (30%), suggesting that generics should be selected based on patient comfort and ease of use in order to further promote their use (2).

The most common reason for switching from generic to brand-name drugs was "ease of peeling during motion", followed by "comfortability of applying" and "difficulty of applying", indicating that the difference in feel from brand-name drugs is a major issue (3). Pharmacists are then required to take into account the characteristics of each product, select the one that best suits the patient's needs, and explain the

product to the patient. However, there have been few reports on the usability characteristics that serve as selection criteria for various formulations (4,5), and they have not been fully utilized in the medical field. Although some studies have predicted usability based on physicochemical measurements (6-9), few have investigated the relationship between actual usability and physicochemical measurements.

In the present study, we evaluated the usability of diclofenac sodium-containing tape formulations of brand-name and generic drugs through the use of a questionnaire survey. In addition, we analyzed the correlation between physicochemical properties of the drug products and evaluation results of their physicochemical properties (10), the latter of which we have previously reported.

2. Materials and Methods

2.1. Materials

Six different diclofenac sodium tape (7 × 10 cm)

products were purchased for evaluation: two brand-name drugs, Naboal[®] tape 15 mg (Hisamitsu Pharmaceutical Co., Inc., Tokyo, Japan) and Voltaren[®] tape 15 mg (Dojin Iyaku-kako Co., Ltd., Tokyo, Japan); and four generic drugs: diclofenac sodium tape 15 mg "Yutoku" (Yutoku Pharmaceutical Ind. Co., Ltd., Saga, Japan), diclofenac sodium tape 15 mg "Teikoku" (Teikoku Seiyaku Co., Ltd., Kagawa, Japan), diclofenac sodium tape 15 mg "Rakool" (Mitomo Yakuhin Co., Ltd., Tokyo, Japan), and diclofenac sodium tape 15 mg "Towa" (Towa Pharmaceutical Co., Ltd., Osaka, Japan). Table 1 shows

the classification, product name, abbreviated name, company name, and lot number of each diclofenac sodium tape used in this study.

2.2. Usability survey

Subjects were 12 individuals (mean age 23 ± 1.5 years, all female) who gave consent to participate in the study. Two brand-name and four generic formulations of the target drugs (Table 2) were assigned A - F and blinded. Subjects applied one tape agent symmetrically to each

Table 1. Product name, abbreviated name, company name, and lot number of the drugs used in this study

Class	Product name	Abbreviated name	Company name	Lot number
BN	Naboal [®] tape 15 mg	Naboal	Hisamitsu Pharmaceutical Co., Inc.	50402
BN	Voltaren [®] tape 15 mg	Voltaren	Dojin Iyaku-kako Co., Ltd.	40420
GE	Diclofenac sodium tape 15 mg "Yutoku"	Yutoku	Yutoku Pharmaceutical Ind. Co., Ltd.	5C150
GE	Diclofenac sodium tape 15 mg "Teikoku"	Teikoku	Teikoku Seiyaku Co., Ltd.	4J150
GE	Diclofenac sodium tape 15 mg "Rakool"	Rakool	Mitomo Yakuhin Co., Ltd.	B191S
GE	Diclofenac sodium tape 15 mg "Towa"	Towa	Towa Pharmaceutical Co., Ltd.	A102

BN: Brand-name drug; GE: Generic drug.

Table 2. Description of questionnaire for the evaluation of the degree of satisfaction with various tapes

Tapes	Tape A	Tape (B • C • D • E • F)		
When applying				
(1) Ease of application to the skin	1. Very difficult to apply 2. Difficult to apply 3. Easy to apply 4. Very easy to apply	1. Very difficult to apply 2. Difficult to apply 3. Easy to apply 4. Very easy to apply	1. More difficult to apply than A 2. Slightly more difficult to apply than A 3. Same as A 4. Slightly easier to apply than A 5. Easier to apply than A	
While applying				
(2) Ease of moving of joint with tape affixed	1. Difficult to move 2. Slightly difficult to move 3. Slightly easier to move 4. Easy to move	1. Difficult to move 2. Slightly difficult to move 3. Slightly easier to move 4. Easy to move	1. More difficult to move than A 2. Slightly more difficult to move than A 3. Same as A 4. Slightly easier to move than A 5. Easier to move than A	
(3) Cooling sensation	1. Too cold, too painful 2. Very cold 3. Cold 4. Not too cold 5. Not cold	1. Too cold, too painful 2. Very cold 3. Cold 4. Not too cold 5. Not cold	1. Colder than A 2. Slightly colder than A 3. Same as A 4. Slightly warmer than A 5. Not colder than A	
(4) Peeling resistance	1. Most of the tape peels off 2. Part of tape peels off 3. No peel off at all	1. Most of the tape peels off 2. Part of tape peels off 3. No peel off at all	1. Easier to peel than A 2. Slightly easier to peel than A 3. Same as A 4. Slightly harder to peel than A 5. Harder to peel than A	
When peeling				
(5) Ease of peeling off	1. Very difficult to peel 2. Difficult to peel 3. Easy to peel 4. Very easy to peel	1. Very difficult to peel 2. Difficult to peel 3. Easy to peel 4. Very easy to peel	1. More difficult to peel than A 2. Slightly more difficult peel to apply than A 3. Same as A 4. Slightly easier to peel than A 5. Easier to peel than A	
(6) Pain during peeling off	1. Very painful 2. Painful 3. Slightly painful 4. Painless	1. Very painful 2. Painful 3. Slightly painful 4. Painless	1. More painful than A 2. Slightly more painful than A 3. Same as A 4. Slightly less painful than A 5. Less painful than A	
(7) Skin stiffness after peeling off	1. Very moist 2. Moist 3. Normal	1. Very moist 2. Moist 3. Normal	1. More moist than A 2. Slightly more moist than A 3. Same as A 4. Slightly less moist than A 5. Less moist than A	
(8) Total score	1. Bad 2. Not good 3. Good 4. Very good	1. Bad 2. Not good 3. Good 4. Very good	1. Worse than A 2. Slightly worse than A 3. Same as A 4. Slightly better than A 5. Better than A	

shoulder or knee (with tape A applied on one side and one of tapes B to F applied on the other side). The application site was always the same on the left and right sides of the body. After the application time of 12 h, the tapes were peeled off one side at a time. "Ease of application to the skin", "ease of moving joints with tape affixed", "cooling sensation", "peeling resistance", "ease of peeling off", "pain during peeling off", "skin stiffness after peeling off", "total score" the results were evaluated using the questionnaire shown in Table 2. In addition, as an overall evaluation, a rating based on a 3 - 5 scale score (hereinafter referred to as "absolute scale") was performed. Usability evaluation was also performed in conjunction with a relative scale compared to the brand-name drug, Naboal tape. This study was conducted under the supervision of a physician and with the approval of the Ethics Review Committee within Meiji Pharmaceutical University (Reception No. 2855).

2.3. Relationship between physicochemical measurements and usability scores

The correlation coefficients between our previously reported evaluation results of the physicochemical properties (10) of the formulations and the questionnaire-based usability scores for each formulation obtained in the present study were calculated using the Statcel 3 statistical software (11).

2.4. Statistical analyses

For each result, the values were compared using *Dunnett's* test. A *p*-value of 0.05 (marked with * in figures) or 0.01 (marked with **) was regarded as significant.

3. Results

3.1. Questionnaire survey results for usability

The results of the "ease of application" evaluation of each formulation based on the questionnaire survey are shown in Figure 1 as the (A) absolute scale and (B) relative scale. The brand-name Voltaren was perceived as "difficult to apply" in absolute and relative evaluation compared to the brand-name Naboal, with a significant difference ($p < 0.01$) in the absolute evaluation results. On the other hand, for the four generic formulations tested (Yutoku, Teikoku, Rakool, and Towa), there were no significant differences from the brand-name Naboal.

The evaluation results of the "peeling resistance" of each formulation are shown in Figure 2. Compared to the brand-name Naboal, the five other formulations tended to be perceived as easy to peeling in both absolute and relative evaluation. In particular, Voltaren had the lowest scores in both absolute and relative evaluation, suggesting that patients find it easier to peel off Voltaren

than other formulations.

First, the evaluation results of the "ease of peeling off" of each product are shown in Figure 3. Compared to the brand-name Naboal, the five other formulations tended to be perceived as "easy to peel" in both absolute and relative evaluation. In particular, Rakool showed high evaluation scores in both absolute and relative evaluation, and there was a significant difference ($p < 0.05$) in absolute assessment results between Naboal and Rakool.

Next, to examine what properties of a formulation contribute to the patient's overall evaluation of the formulation, we examined the overall evaluation score of each formulation (Figure 4). Voltaren tended to have a lower evaluation score than Naboal. On the other hand, no significant differences were observed among the four generic formulations. In addition, Table 3 shows the correlation coefficients between the usability evaluation scores from the questionnaire survey and the overall evaluation for each formulation. A formulation's "ease of application" ($r = 0.81$), "peeling resistance" ($r = 0.67$), and not giving patients a "cooling sensation" ($r = -0.86$) may lead to a high evaluation of the formulation.

3.2. Relationship between physicochemical measurements and usability scores

Table 4 shows the correlation coefficients between the experimental measurements (based on previously reported physicochemical properties of the formulations) (8) and the questionnaire survey results (evaluation scores of usability for each formulation).

First, the "elongatedness" of each formulation was calculated as the ratio of the length of the maximally elongated formulation divided by the length of the original formulation when the short end of each formulation was fixed to the test stand, and the other end was pulled with a 300 g suspended weight. As shown in Table 4, measured "elongatedness" had positive correlation trends with evaluation scores of "ease of application" ($r = 0.55$) and "peeling resistance" ($r = 0.63$), and a negative correlation trend with the evaluation score of "pain during peeling off" ($r = -0.69$) and "cooling sensation" ($r = -0.66$). We also examined scatter plots examining the relationship between the "elongatedness" and the "ease of movement" evaluation scores from the questionnaire survey and found no correlation ($r = 0.16$).

The ball tack adhesive force was measured according to the inclined ball tack test method (12) listed in the Japanese Pharmacopoeia, Eighteenth Edition. That is, a stainless ball was rolled onto a formulation fixed with the adhesive side up on an inclined plate with an angle of 30°, and the weight (g) of the largest ball that stopped on the adhesive side was used as the measurement value. As shown in Table 4, positive correlations were identified between the "adhesive force" measured by the ball tack test and the "cooling sensation" evaluation score ($r =$

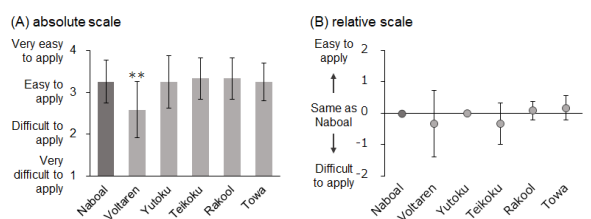


Figure 1. Satisfaction with the ease of application of each product to the skin. Results are shown as mean \pm S.D. ($n = 12$) for the (A) absolute scale (**: $p < 0.01$; *Dunnnett's* test vs. Nabopal) and (B) relative scale to compare with the brand-name drug, Nabopal.

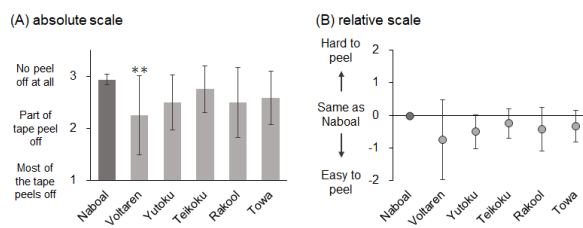


Figure 2. Evaluation results of peeling resistance of each formulation based on questionnaire survey. Results are shown as mean \pm S.D. ($n = 12$) for the (A) absolute scale (**: $p < 0.01$; *Dunnnett's* test vs. Nabopal) and (B) relative scale to compare with the brand-name drug, Nabopal.

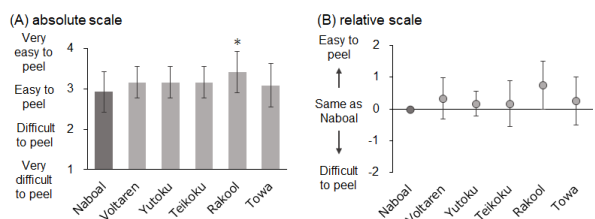


Figure 3. Satisfaction with the ease of peeling off of each product. Results are shown as mean \pm S.D. ($n = 12$) for the (A) absolute scale (**: $p < 0.01$; *Dunnnett's* test vs. Nabopal) and (B) relative scale to compare with the brand-name drug, Nabopal.

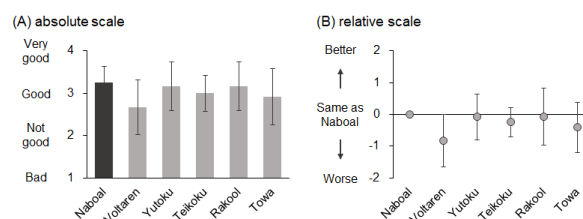


Figure 4. Total evaluation scores of each product. Results are shown as mean \pm S.D. ($n = 12$) for the (A) absolute scale (*: $p < 0.05$, **: $p < 0.01$; *Dunnnett's* test vs. Nabopal) and (B) relative scale to compare with the brand-name drug, Nabopal.

Table 3. Correlation coefficients between usability evaluation scores and total score based on questionnaire surveys for tape preparations

	Ease of application	Peeling resistance	Ease of peeling off	Pain during peeling off	Ease of movement	Cooling sensation	Skin stiffness after peeling off
Total score	<u>0.81</u>	0.67	-0.05	-0.41	-0.14	<u>-0.86</u>	0.27

Numbers in bold font indicate weak correlations, whereas numbers in bold font and with underline indicate strong correlations.

Table 4. Correlation coefficients between usability evaluation scores and physical property measurements based on questionnaire surveys for tape preparations

Physicochemical properties	Patient satisfaction and usability scores in absolute scale (parentheses are relative scale)							
	Ease of application	Peeling resistance	Ease of peeling off	Pain during peeling off	Ease of movement	Cooling sensation	Skin stiffness after peeling off	Total score
Elongatedness	0.55 (-0.11)	0.63 (0.52)	-0.32 (-0.58)	-0.69 (-0.69)	0.16 (0.49)	-0.66 (-0.65)	0.07 (-0.70)	0.66 (-0.18)
Adhesive force	-0.32 (0.59)	-0.22 (-0.11)	-0.29 (0.01)	0.19 (0.25)	-0.14 (-0.44)	0.54 (0.77)	0.42 (0.04)	-0.14 (-0.34)
Peel force (after 0 h)	0.65 (-0.28)	0.51 (0.43)	0.15 (-0.13)	-0.47 (-0.34)	-0.15 (0.50)	-0.74 (-0.74)	-0.37 (-0.36)	0.42 (0.24)
Peel force (after 24 h)	0.39 (-0.35)	0.36 (0.23)	-0.15 (-0.50)	-0.65 (-0.75)	0.21 (0.28)	-0.46 (-0.59)	-0.24 (-0.55)	0.37 (0.13)
Inflexibility (horizontal)	0.02 (-0.38)	0.34 (0.23)	-0.68 (-0.87)	-0.74 (-0.93)	-0.08 (-0.37)	0.12 (0.07)	-0.10 (-0.35)	-0.18 (-0.12)
Inflexibility (vertical)	0.02 (0.13)	0.58 (0.54)	-0.97 (-0.89)	-0.53 (-0.63)	0.06 (-0.05)	0.00 (0.13)	0.68 (-0.44)	0.24 (-0.79)
Water-vapor permeability	0.03 (0.19)	0.53 (0.56)	-0.79 (-0.58)	-0.34 (-0.27)	-0.46 (-0.28)	0.14 (0.40)	0.45 (-0.10)	-0.11 (-0.62)

Numbers in bold font indicate weak correlations, whereas numbers in bold font and with underline indicate strong correlations. The numbers in the table represent absolute scale, and the numbers in parentheses represent relative scale.

0.54) as well as the "skin stiffness after peeling off" evaluation score ($r = 0.42$).

Next, scatter plots representing the relationship between the "peel force" (at 0 or 24 hours) and the "pain during peeling off" evaluation scores from a questionnaire survey were examined. That is, the peel force of each formulation was measured by applying each formulation (cut to 30 mm × 52 mm) to a test plate wrapped with a polymer (ethylene-vinyl acetate; EVA) film, at a specified time (0 h or 24 h after application), using a digital force gauge ZTA-50N (IMADA Co., Ltd., Aichi, Japan) at a speed of 60 mm/min, and peeled off at an angle of 90 degrees. As shown in Table 4, there was a negative correlation between the "peel force" (after 0 h and 24 h) and the "pain during peeling off" score from the questionnaire ($r = -0.47$ and -0.65 , respectively).

The rigidity and softness of each formulation was measured by a partially modified version of the 6.7 Rigid-softness cantilever method (13) from the Japanese Industrial Standards (JIS) "JIS L 1913:2010 General Nonwoven Fabrics Testing Methods". Briefly, the tape material (20 mm × 100 mm) was cut with the adhesive side facing upward and placed in a device with a horizontal portion and a 30° sloping portion aligned with the edge of the horizontal portion. The tape was then moved gradually toward the sloping portion and the distance traveled (mm) until the edge of the tape agent touched the slope was measured. The higher the rigidity measurement, the stiffer and harder the tape agent is to bend. As shown in Table 4, negative correlation trends were observed between stiffness (horizontal and vertical) and the "ease of peeling off" evaluation score ($r = -0.68$ and -0.97 , respectively), as well as between stiffness (horizontal and vertical) and the "pain during peeling off" score ($r = -0.74$ and -0.53 , respectively).

The "water-vapor permeability" of each formulation was measured by covering the opening of a 20 mL triangular flask containing 10 mL purified water with a formulation cut into a 25 mm diameter circle and measuring the weight after 24 h at 25°C and 55% relative humidity to determine the amount of purified water loss. A positive correlation ($r = 0.45$) was found between the measured "water-vapor permeability" and the "skin stiffness after peeling off" evaluation score (Table 4).

4. Discussion

Fujino reported that the most common reason for switching from a generic to a brand-name tape was "ease of peeling during motion", followed by "comfortability of applying" and "difficulty of applying" (3). Therefore, we conducted a questionnaire survey on the usability of each tape formulation and evaluated it against the brand-name Naboal.

Figure 1 shows that the brand-name Voltaren was significantly ($p < 0.01$) "harder to apply" than the brand-name Naboal. This result suggests that patients who

have difficulty applying the brand-name Voltaren may find it easier to apply the brand-name Naboal or one of the generic products, Yutoku, Teikoku, Rakool, or Towa. Switching from Voltaren to Naboal or one of the generic products may improve ease of application and reduce or eliminate the problems associated with using Voltaren.

In Figure 2, there was a significant difference ($p < 0.01$) between Voltaren and Naboal in the absolute evaluation results. This result suggested that patients using Voltaren who have problems with easy peeling may be more likely to switch to the brand-name Naboal or the generic Teikoku to reduce peeling and increase their satisfaction with the tape.

In addition, a questionnaire survey was conducted on other potentially problematic sensations: "ease of peeling", "pain during peeling off", "ease of moving joint with tape affixed", "cooling sensation", and "skin stiffness after peeling off".

The evaluation results of the "ease of peeling" of each product are shown in Figure 3. There was a significant difference ($p < 0.05$) in absolute assessment results between the generic Rakool and the brand-name Naboal. Based on these results, patients who find Naboal "hard to peel off" could be recommended to switch to the generic Rakool.

Next, the "pain during peeling off" evaluation results of each formulation were examined. The results showed that there was no significant difference between the brand-name Naboal and the generics Yutoku, Teikoku, and Towa. On the other hand, Voltaren and Rakool tended to be perceived as less painful to peel off in both absolute and relative evaluations.

The evaluation results of "ease of moving joint with tape affixed" showed no significant difference between Voltaren, Yutoku, Teikoku, and Rakool compared to Naboal. Towa, on the other hand, tended to be difficult to move in both absolute and relative evaluations.

Next, we examined the evaluation results of "cooling sensation" while each preparation was applied. There were no significant differences between Voltaren, Yutoku, Teikoku, and Rakool compared to the brand-name Naboal.

The results of the "skin stiffness" evaluation after each formulation was peeled off show that, compared to Naboal, all five other formulations felt "moist" in absolute evaluation. On the other hand, the relative evaluation showed that patients felt that all five formulations were similar to "moist" when compared to Naboal. And the results of the "stiffness" evaluation showed a large standard deviation, which indicates high variability compared to the other evaluation items. This may be because the "stiffness" condition is affected by various factors such as the temperature and humidity on the day as well as the patient's health. Many patients also commented that it was difficult to assess whether the skin surface was moist or not.

Next, Table 3 shows the correlation coefficients

between the usability evaluation scores from the questionnaire survey and the overall evaluation for each formulation. "Ease of application" ($r = 0.81$), "peeling resistance" ($r = 0.67$), and "cooling sensation" ($r = -0.86$) were considered to have a significant influence on the overall evaluation score. In other words, the easy to apply and the hard to peel the formulation, the higher the overall evaluation tended to be. Moreover, the more difficult it was to peel off a formulation after application, the higher the overall evaluation tended to be. That is, a formulation's ease of application, capacity to provide patients with a cooling sensation, and ability to remain adhered to the skin after application may lead to a high evaluation of the formulation.

Table 4 shows the correlation coefficients between usability evaluation scores and physical property measurements based on questionnaire surveys for tape preparations.

First, regarding the elongation of the formulation, the easier it is to apply to non-flat areas, such as joints, and the more difficult it is to peel off because the formulation expands and contracts with the movement of the joint during application. Thus, upon peeling off a tape formulation, the peeling force stretches the tape formulation, thus reducing the force spent on peeling, which increases the peeling force and resulting in pain. We also examined scatter plots examining the relationship between the measured elongation and the "ease of movement" evaluation scores from the questionnaire survey and found no correlation ($r = 0.16$). This finding suggests that the degree of elongation is not an indicator of the ease of movement of the joints.

Next, scatter plots representing the relationship between the "adhesive force" determined by the ball tack test and the "cooling sensation" evaluation scores or "skin stiffness after peeling off" evaluation scores from a questionnaire survey were examined. That is, adhesive force in the ball tack test was evaluated by stopping the force of the ball rolling over the adherend of the tape agent by its adhesive strength, and is known to be affected by the amount of "wetting" of the adhesive to the surface of the adherend (adhesion of the interface) (10). Therefore, a highly-adhesive formulation increases interface adhesion between the skin and the formulation, resulting in skin wetting. Furthermore, the high adhesiveness of the interface may facilitate in the permeation of ingredients from the formulation to the skin, allowing menthol (the main ingredient that causes a cooling sensation) to penetrate the skin and resulting in a stronger cooling sensation. These findings support that formulations with high peel force values require a large amount of force to peel the tape from the skin, and that the skin is pulled while still adhering to the adhesive during peeling, resulting in a strong sensation of pain. Therefore, peel force measurement may be used as an indicator of "pain during peeling off". Thus, considering that a formulation is pulled in a bent state when peeled

off, the peel-off may increase pain due to the bending rigidity of the formulation.

In addition, the negative correlation trends were observed between "inflexibility" (horizontal and vertical) and the "ease of peeling off" evaluation score, as well as between "inflexibility" (horizontal and vertical) and the "pain during peeling off" score. This suggests that the inflexibility of the support makes it difficult to peel off and causes pain when peeling off.

Furthermore, a high negative correlation trend was observed between "water-vapor permeability" and "ease of peeling off" evaluation scores. This suggested that the lower the water-vapor permeability, the easier it was to peel off. The reason for this was thought to be that moisture accumulated due to steam between the skin and the tape, which made it easier to peel off.

These results of this study may be useful as a basis for health care providers in selecting a suitable formulation and in selecting a generic drug according to the desired use of each individual patient. The findings also suggest that the physicochemical measurements of a formulation may predict the feel of the product. However, while these are useful findings, they are limited by including only a small number of young women. This does not ensure these interventions would have similar results in other ages and genders. Further studies with a larger number of ages, genders, and races would help to further corroborate our findings.

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