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Note

Influence of Stretchiness and Application Times of Tapes on Peel Forces and the Correlation between Peel Forces on Test Plate and *in vivo* Human Skin

Tatsuya Kanemaru, Masaki Uchida, Tsutomu Yamaki, and Hideshi Natsume*

Faculty of Pharmacy and Pharmaceutical Sciences, Josai University

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Summary: The purpose of this study was to evaluate the influence of stretchiness and application times of tapes on the peel forces. Moreover, the correlation between the peel forces on SS (stainless steel) plate and *in vivo* human skin was also evaluated. Non-stretch tape (NST) was prepared from six commercial tape products, which were stretch tapes (STs), to evaluate the influence of stretchiness on the peel force. The influence of stretchiness and application times of the tapes were evaluated by a stretchiness measurement and a peeling test using the test plate. It was found that the stretchiness of ST relaxed the peel forces and changed the peeling angles. In contrast, the relaxation of peeling stresses and the change in peeling angles could be suppressed by using the NST. The peel forces of the NST remarkably increased with increasing application times, and almost plateaued from 180 min after sticking. In order to evaluate the correlation between the peel forces of the tapes on SS plate and *in vivo* human skin, the peel force of the NST on *in vivo* human skin was measured 1 min and 180 min after sticking. No correlation was obtained 1 min after sticking ($p>0.05$). In contrast, good correlation was obtained 180 min after sticking ($p=0.002$). The *in vitro* peeling test method in this study using NST and application times of 180 min is useful for evaluating the peel forces of tapes on *in vivo* human skin.

Keywords: tape, peeling test, peel force, application time, stretchiness

Introduction

Transdermal therapeutic systems (TTSs) including patches, tapes and plaster have a number of advantages, such as avoiding the first pass effect by hepatic enzymes, ease of removal if adverse effects appear, and maintaining drug concentrations in systemic circulation. Improving drug permeation through the skin and enhancing the comfort of applied tapes have become important subjects in the development of tapes[1]. Drug permeability through the skin is dependent on the contact area between the skin and the adhesive layer of TTSs, and the contact area is dependent on the adhesiveness[2]. Moreover, comfortable TTSs need appropriate levels of adhesion, such as tight adhesion to the skin during application and the ability to easily peel off the tape when removing it. Moisture permeability, stretchability, thickness and viscoelasticity are very important characteristics in determining the comfort of applied TTSs, as well as their adhesiveness. Treatment failure (peel off and skin irritation during treatment) due to insufficient levels of these characteristics in TTSs has often been reported[3].

The adhesiveness of tapes is expressed in different ways, including the peel force, tackiness and holding power, which are measured by different methods[3]. In particular, a peeling test has often been used to theoretically analyze the peel force of TTSs on human skin *in vivo*. Peeling tests using a test plate provide peel forces with high reproducibility and accuracy, but the results do not reflect the physiological factors in human skin (such as softness, sebum and sweat)[4–6]. Therefore, peeling tests

* 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan Tel: +81-49-271-7052, Fax: +81-49-271-7052, E-mail: natsume@josai.ac.jp

have been performed by using human skin *in vivo*, in order to evaluate the peel forces of adhesive medical products such as TTSs, wound dressings, the surgical tapes. Since a standard peeling test method using human skin has not been established, they have been validated by comparing the peel forces obtained by using a test plate and human skin[7–10].

The characteristics of the backing and adhesive layer of adhesive products influence the peel forces[11]. It has been reported that stress relaxation and the change in peeling angle by stretching of adhesive tape influenced the peel force in a peeling test[12, 13]. Moreover, the application time of the adhesives also influenced the peel force, due to their viscoelastic properties[14, 15]. Hence, the characteristics of the backing and adhesive layer might influence a comparison between the peel forces on the test plate and human skin.

In the present study, a peeling test on a test plate was performed using commercial tape products. A stainless steel (SS) plate was used as a test plate, as in standard peeling test methods[16–18]. Stretch tape (ST) and non-stretch tape (NST) were prepared from commercial tape products. The peel forces obtained by using the ST and NST were compared to evaluate the influence of the stretchiness of the tapes on the peel force. The influence of the application time on the peel forces was also evaluated by a peeling test of the NST on the SS plate. Moreover, a peeling test of the NST on *in vivo* human skin was performed to evaluate the correlation between peel forces on the SS plate and *in vivo* human skin.

Materials and Methods

1. Materials

Serastar® tape 70 (Astellas Pharma Inc., Tokyo), Yakuban® tape 40 mg (Taisho Pharmaceutical Co., Ltd., Tokyo), Mohrus® tape L 40 mg (Hisamitsu Pharmaceutical Co., Inc., Saga), Sumilu® tape 70 mg (Mikasa Seiyaku Co., Ltd, Tokyo), Zepolas® tape 40 mg (Mikasa Seiyaku Co., Ltd, Tokyo), and Ketoprofen tape 40 mg [TEIKOKU] (Teikoku Seiyaku Co., Ltd., Kagawa) were used as test tapes in this study and numbered I–VI to anonymize them. These test tapes were composed of adhesive and stretchy fabric backings. A stainless steel (SS) plate with a width of 35 mm, a length of 80 mm and a thickness of 1.2 mm was used as a test plate. A roller with a weight of 850 g[19] (Tester Sangyo Co., Ltd., Tokyo) was used to make the tapes stick to the test plate or the *in vivo* human skin. A tensile tester (SV-52NA-2HHT, Imada Seisakusho Co., Ltd., Aichi) conforming to a standard peel test procedure was used to measure the stretchiness and the peel force of the tapes[17, 18].

2. Subjects

This study was performed in accordance with the Declaration of Helsinki. Five volunteers (age: 22±2 year old) without any dermatological diseases or conditions participated in this study, which was approved by the ethical committee of Josai University (approval number: 2017-05A). Informed written consent was obtained from all subjects. In order to minimize variations in the peel forces of the tapes, the subjects were advised not to apply creams, lotions or topical medicines on the inner forearms from the day before the peeling tests were to be conducted. The peel forces were expressed as the means of two measurements for each subject.

3. Preparation of test tapes

Stretch tapes (ST) were prepared by cutting the tapes into a rectangle with a width of 12 mm[16, 19] and a length of 100 mm. In order to suppress the stretchiness of the tapes, non-stretch tapes (NST) were prepared by sticking OPP Packing Tape No.3301EZ (tensile strength: 120 N/25 mm, thickness: 0.055 mm, Nitto Denko, Osaka) to the backing layer of the ST. OPP Packing Tape No.3301EZ was selected in consideration of the tensile strength and the thickness because they influenced the peel force of tape[11].

4. Stretchiness measurement in tapes

One end of each test tape was fixed on a stage of the tensile tester, and then a chuck connected to the load cell secured the other end of the tape, with a distance of 50 mm between the stage and the chuck. The chuck was moved up at 5.0 mm/s until reached 30% tensile strain. In order to evaluate the stretchiness of the tapes, the Young's modulus was calculated from the tensile stress-strain curve described by the following equation:

$$E=\sigma/\varepsilon \qquad (1)$$

where ε is the 30% tensile strain (mm), σ is the corresponding tensile strength (N), and E is Young's modulus (N/mm).

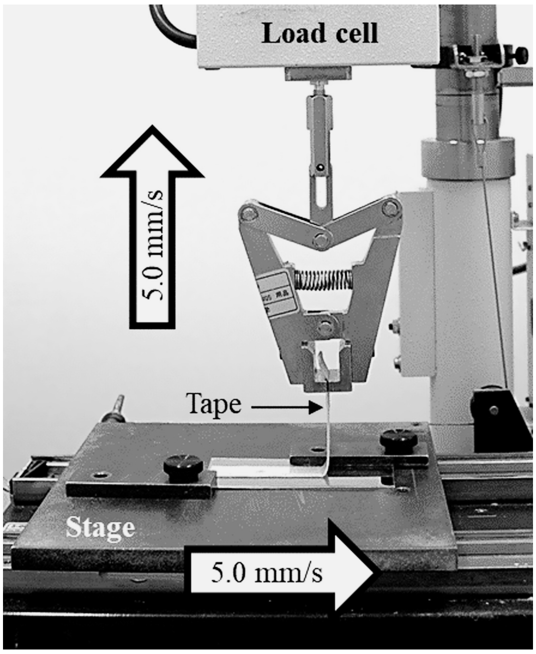

Fig. 1 An aspect of peel force measurement using the SS plate

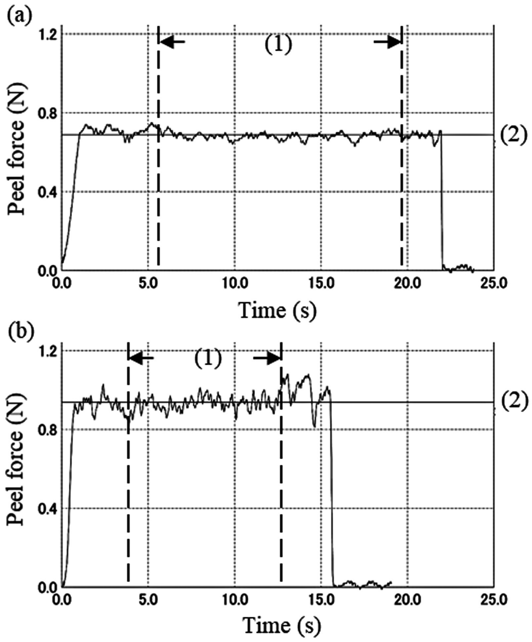

Fig. 2 Typical peel force vs. time curve of ST (a) and NST (b) of tape III (1): measurement area, (2): approximation line of the curve

The peel force ratio (NST/ST) of the NST to the ST was calculated to evaluate the influence of the stretchiness of the tapes on the peel force.

5. Peel force measurement using a test plate

All peel tests were performed under a controlled environment (room temperature: 24.9±0.2°C, relative humidity (R.H.): 59.4±1.9%). The SS plate was wiped with methanol and pre-heated at 32°C before sticking the tapes. The tapes were made to stick on the SS plate by moving the 850 g roller back and forth, one time, over the tapes at about 5.0 mm/s. Immediately, the plates were put on a water chamber to keep at a surface temperature of 32±0.5°C for mimicking human skin conditions. Fig. 1 shows an aspect of peel force measurement using the SS plate. The plates were fixed on the sample stage of the tensile tester 1, 60, 180, 360 or 540 min after sticking the tapes. The chucking allowance (2 cm) was secured with the chuck of the tensile tester. Then, the tensile tester was run at the tension rate of 5.0 mm/s. The first 25% and the end 12.5% of the measurement length were ignored for the calculation of peel force (N/cm)[18]. The peel force was calculated from a linear approximation of the peel force vs. time curve corresponding over 50% of measurement length using ISP-IV software ver. 8.0.1.0 (Imada Seisakusho Co., Ltd., Aichi) (Fig. 2).

6. Peel force measurement using human skin

After subjects entered the controlled environment test room the same as that described in Section 2.5, they were allowed to rest for 30 min before sticking the tapes on their skin to allow them to habituate to the environment in the room. The inner forearms of the subjects were wiped gently with a cotton swab immersed in distilled water. The tapes were stuck on the inner forearms of subjects along the short axis of the arms by moving the 850 g roller back and forth one time at 5.0 mm/s. Three pieces of tape per arm were stuck at intervals of 2 cm in an area 3 cm from the elbow. Then, a surgical tape (Surgical tape No. 12, Iwatsuki Co., Ltd, Tokyo) was stuck between these tapes to suppress skin deformation due to the peel force. The arms of the subjects were placed on the stage of the tensile tester 1 or 180 min after sticking the tapes. The peel force was measured and calculated by the same method as in Section 2.5.

7. Statistical analyses

Comparison of the peel forces between the ST and NST was performed with Student's *t*-test. The influence of the application times on the peel forces for the test plate was analyzed by Dunnett's test. The correlation between peel forces on the test plate and *in vivo* human skin was analyzed by Pearson's test. $P<0.05$ was regarded as significant. All statistical analyses were

Table 1　Peel forces (N/cm) of ST and NST 180 min after sticking on SS plate, Young's modulus (N/mm) of ST and peel force ratio (NST/ST)

Tape	ST		NST	Peel force ratio (NST/ST)
	Peel force (N/cm)	Young's modulus (N/mm)	Peel force (N/cm)	
I	0.168±0.005	0.080±0.007	0.178±0.015	1.06
II	0.741±0.074	0.079±0.005	1.18*±0.04	1.59
III	0.595±0.044	0.057±0.006	0.828*±0.091	1.39
IV	0.737±0.019	0.079±0.009	1.04*±0.05	1.41
V	0.642±0.062	0.080±0.003	0.874*±0.060	1.36
VI	0.538±0.019	0.095±0.008	0.616*±0.055	1.15

Each value is the mean±S.D. (n=4) *p<0.05 compared with peel force of ST (Student *t*-test)

carried out using R software (version 3.5.1 for windows; https://www.R-project.org).

Results and Discussion

1. Influence of tape stretchiness on peel force

Table 1 shows the peel forces (N/cm) of the ST and NST 180 min after sticking on the SS plate, the Young's modulus (N/mm) of the ST, and the peel force ratio of the NST to the ST (NST/ST). The Young's modulus indicates the tensile strength required for stretching of the tapes. When the value is small, the tape has high stretchiness. The tensile strain of ST corresponding to the peel force was less than 30% compared to when no tensile stress is applied to the tape. The peeling time of NST was shorter than that of ST, because NST was hardly stretched in the peeling process (Fig. 2). The peel force of the NST was significantly higher than that of the ST, except for Tape I. The difference of peel forces among these tapes was larger than that of the ST. These results were due to suppressed relaxation of peeling stress in the ST. On the other hand, the peel force of Tape I, which exhibited the lowest peel force among all tapes, was hardly influenced by suppressed relaxation of the peeling stress. Therefore, it was considered that the changing of the thickness due to the OPP tape stuck onto ST hardly influenced the peel force of NST. The peeling angle was slightly changed by stretching the tapes in the peeling test using the ST, even when using the tensile tester, which was kept at a peeling angle of 90°. In contrast, the peeling angle was kept at 90° stably in the peeling test using the NST (data not shown). The rank order of the peel forces of the NST and ST hardly changed. Moreover, the rank order of the peel force ratio was almost consistent with that of the peel forces of the NST rather than that of the Young's modulus. Thus, it was considered that the stretchiness of the tapes influenced the peel forces. The peeling test using the NST provided peel forces without stress relaxation, and the peeling angle was kept at 90°. Therefore, NST was used in the peeling test study described below.

2. Influence of application times on peel force

Fig. 3 shows the influence of application times on the peel forces (N/cm) of the NST on the SS plate. The peel forces of the NST increased in an application time-dependent manner on the SS plate. The peel forces of the NST increased until 180 min after sticking on the SS plate, whereas the peel forces hardly changed from 180 min after sticking. It has been reported the molecular rearrangements of adhesive occur at the interface and the speed depends on temperature. They increase the bond strength after sticking[20]. Thus, it seemed that they required over 180 min. It should be remarked that there was hardly any difference in the peel forces among the tapes 1 min after sticking, except for Tape I. Larger differences in the peel forces among the tapes 180 min after sticking were observed compared with 1 min after sticking. An application time of 1 min is established in standard peeling test methods, such as JIS (Japanese Industrial Standards) Z 0237: 2009 and ASTM (American Society for Testing and Materials) D3330[15, 16], but stable peel forces were not obtained. Accordingly, it seems that an application time of 180 min is more suitable than 1 min in tape peeling tests.

3. Correlation between peel forces on test plate and *in vivo* human skin

Fig. 4 shows the relationships between the peel forces (N/cm) of the NST on the SS plate and *in vivo* human skin 1 min

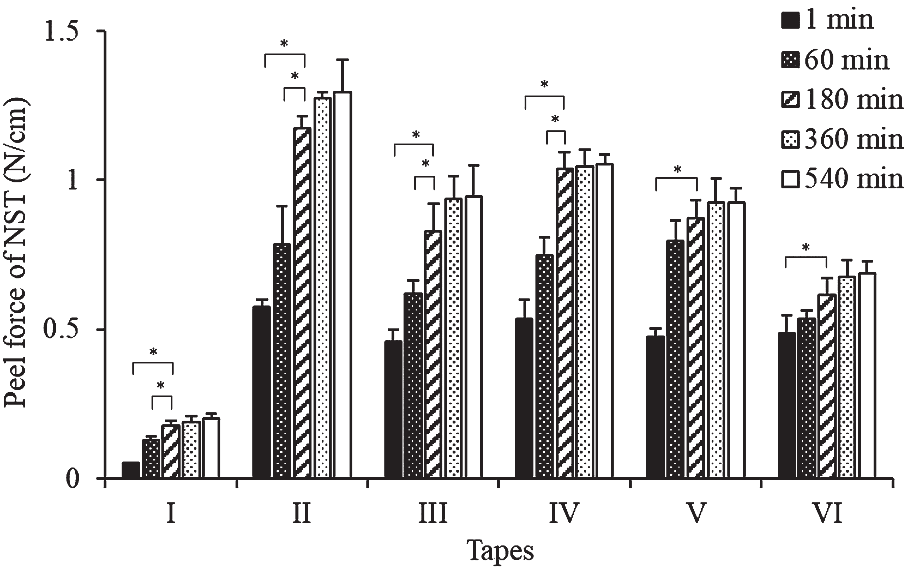

Fig. 3 Influence of application times on peel force (N/cm) of NST on SS plate

The peel forces of NST on test plate are shown as the mean±S.D. (n=4)
*$p<0.05$ compared with peel force 180 min after sticking (Dunnett's test)

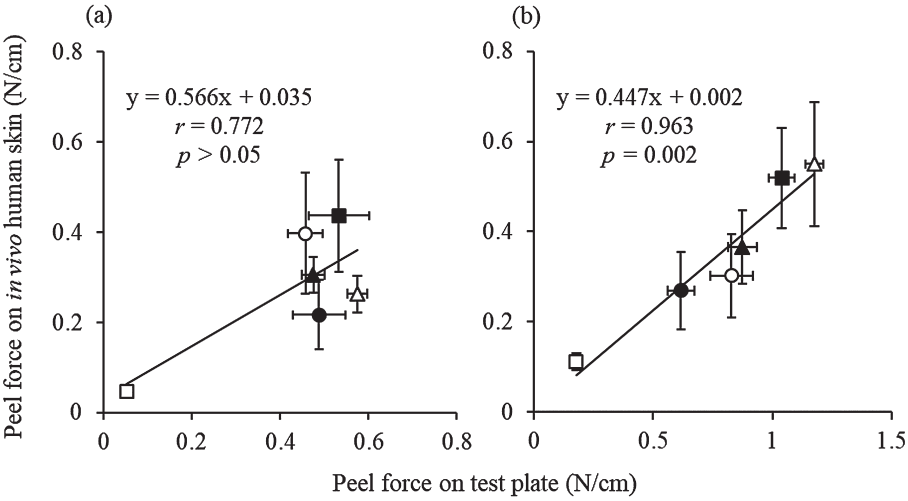

Fig. 4 Relationships between peel forces (N/cm) of NST on SS plate and *in vivo* human skin 1 min (a) and 180 min (b) after sticking

Tape I (open squares), Tape II (open triangles), Tape III (open circles), Tape IV (closed squares), Tape V (closed triangles) and Tape VI (closed circles)
The peel forces of NST on test plate or *in vivo* human skin are shown as the mean±S.D. (n=4–5)

(a) and 180 min (b) after sticking. No correlation between the peel forces of the NST on the test plate and *in vivo* human skin was obtained 1 min after sticking (y=0.566x+0.035, r=0.772, p>0.05). Thus, this application time is insufficient to evaluate the peel forces of tapes on *in vivo* human skin. In contrast, a significant correlation was obtained 180 min after sticking (y=0.447x+0.002, r=0.963, p=0.002). It was considered that this good correlation was obtained due to the large differences of peel forces among the tapes on the test plate with an application time of 180 min. The difference between the peel forces on the test plate and *in vivo* human skin at 180 min after sticking was larger than that at 1 min. The contact area between the adhesive and *in vivo* human skin increases in the application time-dependent manner due to the deformation of the adhesive[15]. It was considered that the difference of peel forces 180 min after sticking was more reflected the difference in the surface characteristics (such as surface tension and roughness) between them than that at 1 min after sticking.

Conclusion

In the present study, the influences of the stretchiness and the application time of tapes on the peel forces were investigated. Good correlation between the peel forces on a test plate and *in vivo* human skin was obtained by using the NST and an application time of 180 min. In particular, the influence of the application times on the correlation has not been investigated yet[7–10]. The *in vitro* peeling test method used in the present study is useful for evaluating the peel force of medical adhesive products on *in vivo* human skin. Further study is needed to evaluate the influence of the type of adhesive (such as rubber, acrylic, silicone and urethane) and the characteristics of test plate on the peel force and the correlation.

Conflicts of Interest

The authors declare no conflicts of interest.

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