

《 Original Article 》

## Examination regarding the force required to push Rx-OTC-switch tablets out of PTP

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For packaged tablets, “press through packages” (PTP) are commonly used. Although PTP have numerous merits, patients with finger hypofunction sometimes have difficulty in pushing out tablets or capsules. In this study, we examined the force required to push loxoprofen sodium tablets/capsules, as an over-the-counter (OTC) drug, out of PTP to provide useful information for selecting products appropriate for individual patients.

We measured the force required to push 4 OTC drugs out of PTP (push-out force), weight, diameter, and thickness. Subjective assessment was conducted using 7 grades after pushing the respective tablets or capsules out of PTP cut in the form of 2 tablets.

The maximum score on the subjective assessment was 4.7 points. The minimum push-out force was 68.1 N. The maximum weight was 301.1 mg. The maximum thickness was 4.1 mm. The diameter of all drugs was 9.1 mm.

Product E was evaluated as the easiest to push out based on the push-out force, weight, diameter, and thickness. However, no significant difference was noted among the drugs in the subjective assessment. For self-medication with OTC drugs, a product should be suitably selected for each patient. For this purpose, data, such as those obtained in the present study, are essential.

**Key words;** push-out force, Rx-OTC-switch drugs, press through packages, self-medication

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### 1. Introduction

Currently, the increase in national health expenditures related to the rapidly aging society is of great concern in Japan. As management

strategies, the government has promoted the utilization of generic products and self-medication. For self-medication, over-the-counter (OTC) drugs are used in many cases; therefore, it is necessary for pharmacists to provide sufficient information.

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In particular, for the sale of drugs requiring guidance or category-1 drugs, information provision by pharmacists is obligatory. However, currently, information on OTC drugs for health care professionals is insufficient, and their package inserts, which can also be inspected by patients, are primarily used. For this reason, several reports on the dissolution behavior or collapsibility, which influences pharmacokinetics, have been published as information necessary for promoting the proper use of OTC drugs<sup>1,2)</sup>.

Press through packages (PTP), which are the commonly used packages for drug tablets or capsules, are advantageous for quality maintenance and portability, and the drug can be easily removed by pressing. On the other hand, one previous study reported that it was sometimes difficult for patients with finger hypofunction to push tablets or capsules out of PTP<sup>3)</sup>. The term “frail” has been proposed due to the rapid aging of society; therefore, the provision of product information based on these circumstances may be useful for selecting products in accordance with individual patients.

The force required to push the drug out of PTP (push-out force) can be measured using a force gauge, which is a device to evaluate the strength or durability of an object. According to a previous study, the strength differs among products<sup>4)</sup>. Furthermore, several studies reported that the push-out force, drug weight, diameter, and thickness were

correlated with the subjective difficulty of pushing out the drug<sup>5,6)</sup>.

In this study, we measured the push-out force, weight, diameter, and thickness of loxoprofen sodium tablets, which are commercially available as a category-1 drug, and examined the results of subjective assessment of the difficulty to push out tablets to provide useful information for selecting products. Loxoprofen sodium is an antipyretic analgesic that has been used as a prescription drug for over 30 years, and it was approved as an OTC drug in 2011. Loxoprofen sodium was selected as the target drug of the survey, because it is the most commonly used antipyretic analgesic in Japan<sup>7)</sup>.

## 2. Methods

### 1. Drugs to be investigated

Of the OTC drugs containing loxoprofen sodium alone, distributed as of September 2018, four products available for purchase through some distribution channels were selected as target drugs (Table 1).

### 2. Measurement of the push-out force

The push-out force was measured using an FGP-5 digital force gauge (Nidec-Shimpo Corporation, Kyoto). It was expressed in Newtons (N). The digital force gauge was attached to an FGS-50E special electric vertical force-gauge stand (Nidec-

Table 1 List of Products

abbreviation	Product	Lot. No.	Manufacturer
L	LOXONIN® S	2830	Daiichi Sankyo Healthcare Co., Ltd.
E	Excedrin LOX	62551	Lion Corporation.
K	Loxoprofen tablet "kunihiro"	ZFL440	Kokando Pharmaceutical Co., Ltd.
Y	Yunipain L	4E6	Kobayashi Pharmaceutical Industries, Ltd.

Shimpo Corporation, Kyoto), and an instrument for fixing PTP was installed at the stand base (Fig. 1).

PTP were set on the instrument, and the digital force gauge was lowered at a velocity of 50 mm/min. The maximum force added until the aluminum sheet of the PTP was broken was taken as the push-out force. Ten measurements/product were conducted, and the mean was calculated. It was previously reported that there is a negative correlation between the force required to push tablets out of PTP measured using a digital force gauge at a velocity of 50 mm/min and the subjectively assessed difficulty in pushing out tablets<sup>5)</sup>. Therefore, in this study, the push-out force was also measured at a velocity of 50 mm/min.

### 3. Measurement of weight, diameter, and thickness

The weight of each product was measured using a GH-300 direct-reading balance (A&D Company, Ltd., Tokyo). Six measurements/product were conducted, and the mean was calculated. The diameter and thickness of each product were measured using a digital Vernier caliper (A&D Company, Ltd., Tokyo). Six measurements/product were conducted, and the mean was calculated.

### 4. Subjective assessment of the difficulty to push out tablets/capsules

The subjects were adult volunteers aged  $\geq 20$  years. We excluded those who were unable to push tablets/capsules out of PTP due to disease-related finger hypofunction. As background factors, an interview regarding age, sex, and handedness was conducted. Subsequently, to evaluate finger function, the grip strength and pinching strength (finger-tip pinching, finger-pulp pinching, and finger-side pinching) were measured 3 times, and the mean was calculated.

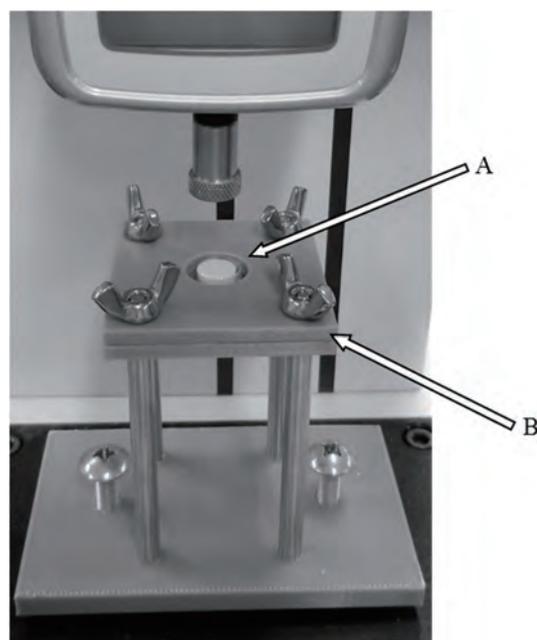


Figure 1 Instrument used to measure the push-out force

A: Tablet in PTP,

B: A tablet was enclosed/fixed.

The subjective assessment of difficulty to push out tablets was performed using the following procedures: the subjects pushed each tablet out of PTP cut into 2-tablet units, and then evaluated the difficulty using 7 grades: “very easy”, “easy”, “slightly easy”, “not either”, “slightly difficult”, “difficult”, and “very difficult”. Scoring was carried out regarding the response “very easy” as 7.

### 5. Statistical analysis

Finger function was analyzed using the Student's t-test. The results of the subjective assessment were analyzed using the Steel-Dwass method and Mann-Whitney U test. The correlation between finger function and the subjective assessment was examined using Spearman's rank correlation coefficient test. The correlations between the push-out force, weight, diameter, or thickness and the subjective assessment were analyzed using

Pearson's correlation coefficient test. For analysis, Statcel 3 software (The Publisher OMS Ltd., Tokyo) was used. A p-value of 0.05 was considered significant.

#### 6. Ethical considerations

Prior to this study, its content was sufficiently explained to the subjects using an explanatory document, and written informed consent was received from those who consented to participate in this study. The protocol of this study was approved by the President of Hyogo University of Health Sciences (Approval No.: 17020).

### 3. Results

#### 1. Subject background

The mean age of the subjects was  $66.8 \pm 17.4$  years. They consisted of 39 (68.4%) aged <75 years and 18 (31.6%) aged  $\geq 75$  years. There were 19 males (33.3%) and 38 females (66.7%). Fifty-three subjects (93.0%) were right-handed and 4 (7.0%) were left-handed. Regarding current drugs, 38 (66.7%) selected "present" and 19 (33.3%) selected "absent".

#### 2. Finger function

The mean grip strength was  $28.4 \pm 10.5$  kg. The mean finger-tip pinching strength was  $9.7 \pm 3.8$  kg. The mean finger-pulp pinching strength was  $10.9 \pm 3.7$  kg. The mean finger-side pinching strength was  $13.7 \pm 4.8$  kg. The values of all grip and pinching strength items for males were higher than those for females, demonstrating significant sex differences. Furthermore, only the mean finger-tip pinching strength was higher among subjects aged  $\geq 75$  years (Table 2).

#### 3. Push-out force, weight, diameter, and thickness

The maximum push-out force was 74.5 N (Product Y). The minimum push-out force was 68.1 N (Product E). The weight of Product E was the highest (301.1 mg), and that of Product K was the lowest (250.9 mg). The diameter of all products was 9.1 mm. The thickness of Product Y was the highest (4.1 mm), and those of Products L and K were the lowest (3.3 mm) (Fig. 2).

#### 4. Subjective assessment

The subjective assessment score for Product E was the highest (4.7 points), and that for Product L was the lowest (4.2 points). Regarding sex, the subjective assessment scores for all products were lower by females. Regarding age, the scores for all products were higher by those aged  $\geq 75$  years. Furthermore, there was a significant difference in the score for Product K between the two age groups ( $P = 0.0012$ ) (Fig. 3).

#### 5. Correlations between the push-out force/weight/diameter/thickness and subjective assessment

The relationship with the subjective assessment was examined, revealing a negative correlation with the push-out force ( $r = -0.404$ ,  $P = 0.595$ ). A positive correlation was noted with the weight ( $r = 0.658$ ,  $P = 0.341$ ). There was no correlation with the diameter ( $r = -0.107$ ,  $P = 0.893$ ). A strong positive correlation was noted with the thickness ( $r = 0.836$ ,  $P = 0.164$ ).

### 4. Discussion

There are several commercially available OTC drugs containing the same component, as

represented by oral preparations containing loxoprofen sodium. In this study, we measured the weight, diameter, and thickness of loxoprofen sodium preparations, in addition to the force required to push tablets out of PTP, and examined their correlations with the subjectively assessed difficulty to push them out in order to provide useful information for selecting products appropriate for individual patients.

Regarding the difficulty to push tablets or capsules out of PTP, previous studies noted a correlation between the push-out force measured using a force gauge and sensory assessment<sup>6)</sup>, and

that it became easier to push out tablets or capsules with an increase in the tablet weight, diameter, or thickness<sup>5)</sup>. Furthermore, another study reported that the push-out force decreased with an increase in the tablet thickness<sup>4)</sup>. This study demonstrated correlations between the push-out force/weight/thickness and subjective assessment, suggesting the usefulness of the results as data on the difficulty to push tablets or capsules out of PTP. Age- or sex-related differences in finger function were previously reported<sup>8)</sup>

In this study, there were also significant differences in the grip strength and pinching

Table 2 Finger Function

item			mean	±	S.D.		
grip strength (kg)		total	(n = 57)	28.4	±	10.5	
		male	(n = 19)	39.2	±	9.1	**
		female	(n = 38)	23.0	±	6.1	
		less than 75 years of age	(n = 39)	29.7	±	10.6	
		over 75 years of age	(n = 18)	25.7	±	10.1	
pinch strength (kg)	tip pinch	total	(n = 57)	9.7	±	3.8	
		male	(n = 19)	12.8	±	3.8	**
		female	(n = 38)	8.2	±	2.8	
		less than 75 years of age	(n = 39)	9.4	±	3.8	
		over 75 years of age	(n = 18)	10.4	±	4.0	
	pulp pinch	total	(n = 57)	10.9	±	3.7	
		male	(n = 19)	14.1	±	3.5	**
		female	(n = 38)	9.3	±	2.7	
		less than 75 years of age	(n = 39)	10.9	±	3.7	
		over 75 years of age	(n = 18)	10.7	±	3.8	
side pinch	total	(n = 57)	13.7	±	4.8		
	male	(n = 19)	18.1	±	4.1	**	
	female	(n = 38)	11.4	±	3.5		
	less than 75 years of age	(n = 39)	14.2	±	4.9		
	over 75 years of age	(n = 18)	12.5	±	4.7		

\*\*  $P < 0.001$ , Student's *t*-test

strength between males and females (Table 2).

On the other hand, when comparing the results between the two age groups, there were no significant differences in any parameter of finger function. An age-based comparison of the subjective assessment revealed a significantly higher score for Product K in subjects aged  $\geq 75$  years. Although no significant difference was noted for other products, the scores tended to be higher in subjects aged  $\geq 75$  years. This can be explained by the higher mean value of pinching strength, critical for pushing tablets out, in subjects aged  $\geq 75$  years than those aged  $< 75$  years.

The push-out force, diameter, and thickness of Product K were the same as those of Product L. In addition, the weights were comparable between the products, with a difference of only 10.5 mg. However, a significant difference was observed only for Product K, suggesting the involvement of the hardness of the PTP sheet. Details remain unknown, because the hardness of the PTP sheet was not measured in the study.

Tablets measuring  $\geq 10$  mm in diameter are visually recognized as large<sup>9)</sup>. Therefore, this may contribute to the impression of difficulty. However, all of the tablets were likely easily ingested because of their small diameter (9.1 mm) (Fig. 2C). Hiraoka et al.<sup>5)</sup> reported that requirements for tablets that can be easily pushed out of PTP included a heavy weight, a diameter of  $\geq 8$  mm, and a thickness of  $\geq 4$  mm. Product E met almost all of these conditions, with the highest score in the subjective evaluation (Fig. 2). In addition, the lowest push-out force for Product E among the four products supports the subjective assessment. However, there were no

significant differences in the subjective assessment score among the products (Fig. 3). Takeshita et al.<sup>6)</sup> reported that an approximately 10-N difference in push-out force can be felt by humans. The largest difference in the push-out force was 6.4 N, precluding subjective recognition (Fig. 2A).

The present study demonstrated that Product E is most easily pushed out in consideration of the push-out force from PTP, and the weight, diameter, and thickness of the tablet. However, there was no significant difference in the subjective assessment, suggesting that the difference in push-out force is hardly noticed. In the present study, neither hardness nor feeling of PTP were evaluated. These factors may have influenced the subjective assessment. In addition, the push-out force necessary for PTP may affect drug compliance.

To support self-medication with OTC drugs, it is important to select products meeting patients' needs. To achieve this, information, such as the results of this study, may be necessary, in addition to information from package inserts, which both pharmacists and patients can inspect.

### Conflicts of Interest

The authors have no conflict of interest to report.

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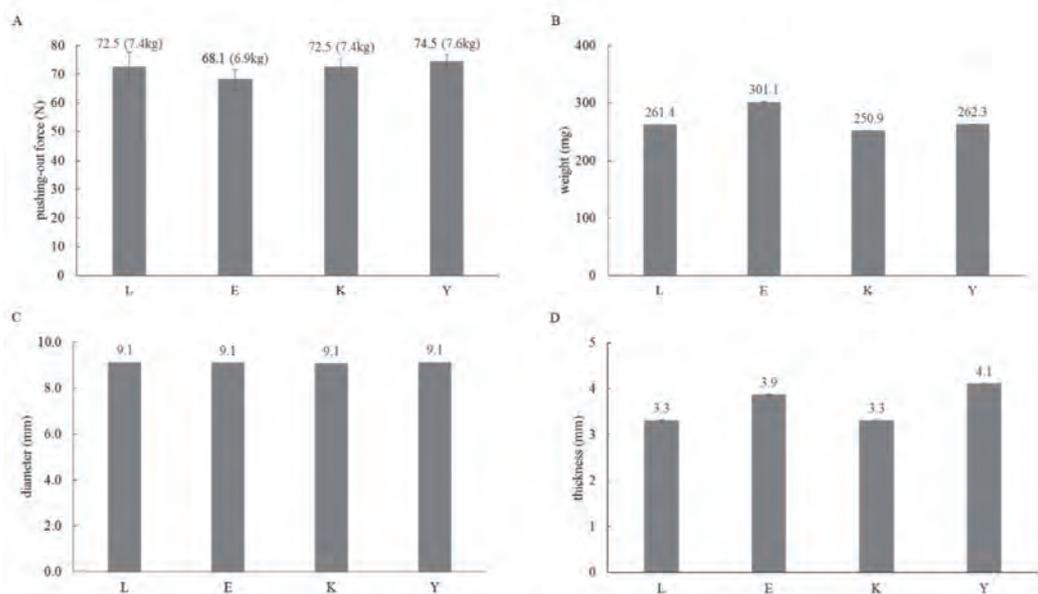


Figure 2 Measurement of the push-out force, weight, diameter, and thickness

A: push-out force (n = 10), B: weight (n = 6), C: diameter (n = 6),  
D: thickness (n = 6). The data are expressed as the mean ± standard deviation.

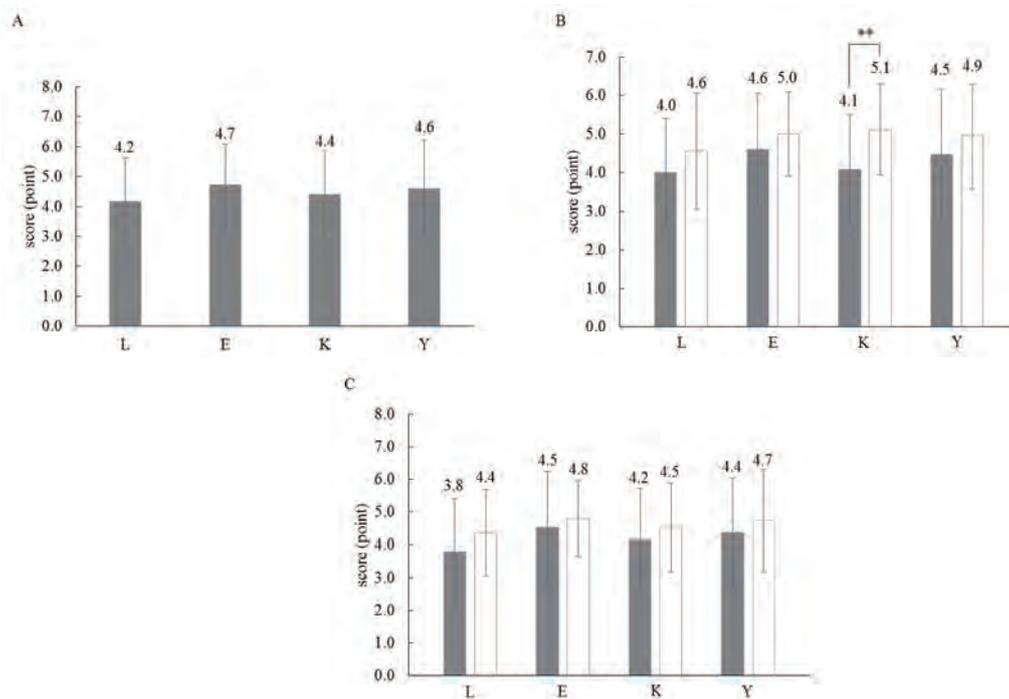


Figure 3 Subjective assessment

A: Overall, B: Comparison with respect to age, C: Comparison with respect to sex.  
A: ■Overall (n = 59), B: ■Subjects aged <75 years (n = 39), □Subjects aged ≥75 years (n = 18),  
C: ■Males (n = 38), □Females (n = 19).  
The data are expressed as the mean ± standard deviation. \*\* $P < 0.01$ . Mann-Whitney  $U$  test

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