Evaluation of the Disintegration Properties of Commercial Famotidine 20 mg Orally Disintegrating Tablets Using a Simple New Test and Human Sensory Test

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The purpose of this study was to demonstrate the usefulness and broad-applicability of a simple disintegration test method for orally disintegrating tablets (ODT). Eight types of commercial famotidine 20 mg orally disintegrating tablets with different physical properties (formulation, manufacturing method, tablet weight, shape, diameter, thickness, *etc.*), were used. Disintegration times of these tablets were evaluated employing human sensory test, conventional disintegration test, and the new proposed disintegration test. The human sensory test was performed in 5 healthy volunteers. In the conventional disintegration test, the disintegration apparatus described in the Japanese Pharmacopeia (JP 1st) was used. Our proposed new test which is characterized by a rotating shaft with a low weight (10, 15 g) and rotation speed (10, 25, 50 rpm) was evaluated using tablets with and without storage under severe conditions (60 °C/75%RH for 1 week). The disintegration times of famotidine 20 mg orally disintegrating tablets in human sensory test varied from 9 to 32 s. In contrast, disintegration times in the conventional test were prolonged to over 300 s. Disintegration times in the new proposed test were close to those in human sensory test. Especially, when the new test was conducted with 15 or 10 g weight and 25 rpm, the slope (human sensory test *vs.* new proposed test) was almost 1. We were able to demonstrate that the new proposed test was useful to estimate the actual human disintegration time.

Key words orally disintegrating tablet; rapid disintegrating tablet; disintegration time; new test; famotidine 20 mg tablet

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life (QOL), most of these efforts have been focused on ease of medication. Among the dosage forms developed to facilitate ease of medication, the orally disintegrating tablet is one of the most widely employed as commercial products.[1] Many patients, especially the elder (also children), find it difficult to swallow tablets and hard gelatin capsules; consequently, they do not take medications as prescribed. It is estimated that 50% of the population has this problem which results in a high prevalence of non-compliance and ineffective therapy.[2—4] Thus, innovative dosage forms, which could overcome these problems, are needed. It is generally considered that the orally disintegrating tablet (ODT) could be helpful for these patients.

The ODT has remarkable disintegration properties; without water, it is rapidly disintegrated in the mouth in just a few seconds. The conventional disintegration test (ex JP 1st) is often used for its evaluation, however it is doubtful whether the conventional test, which requires 900 ml of purified water at 37 °C, is suitable to evaluate the disintegration properties of ODTs. Therefore, a suitable disintegration test is strongly necessitated.

Recently, several tests to determine the disintegration time of the ODT have been proposed. These tests employ a modified dissolution test,[5] CCD camera,[6] or others. However, the proposed tests so far lack universality and convenience. El-Arini *et al.*[7] and Abdelbary *et al.*[8] have reported performing an *in vitro* disintegration test of commercially available ODTs using a Texture Analyzer instrument. The differences in the disintegration mechanisms of these ODTs, which derived from the formulation and/or manufacturing process, were reflected in the shape of their disintegration profiles.

Previously, we had proposed a disintegration test that could overcome these problems.[9] This disintegration test method was characterized by a small amount of water uptake, low compression of the ODT, and speed rotation. We had already demonstrated good correlation between the disintegration times of the new proposed test and those of human sensory test using various placebo ODTs of the same size and shape. However, there was some doubt as to whether this good correlation could be coincidental because the reported results were obtained under limited conditions.

In this study, we employed eight types of commercially available ODTs to evaluate our proposed new test. All samples contained 20 mg of famotidine but had greatly different formulations, manufacturing methods, shapes, weights, *etc.* The aim of this study was to demonstrate the broad-applicability and usefulness of this new proposed test method. The new proposed disintegration apparatus was modified with respect to that previously reported.

Experimental

Materials The various famotidine 20 mg tablets used in this study are shown in Table 1. Tablets were purchased from each manufacturer listed. Mean weight of the tablets ranged from 88 to 230 mg, the diameter ranged from 6.0 to 8.5 mm, and the thickness ranged from 3.1 to 4.0 mm. The tablets also varied in shape; some were flat, and others were bi-convex shaped with or without scoring. The disintegration properties were evaluated using samples with or without storage at 60 °C/75%RH (1 week). Further, in this study, the sample name was concealed (random inscription from A to H).

Measurement of Disintegration Time in the Human Sensory Test Disintegration time in human sensory test was measured independently from that in the previous report.[9] Five healthy volunteers tested the disintegration time of the various famotidine 20 mg ODTs. Prior to the test, all volunteers got a detailed briefing on purpose of this test and gave informed consent. And then they were asked to rinse their mouth with a cup of water (200 ml). The ODT was placed on the tongue and immediately a stopwatch was

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Table 1. List of Product Name and Supplier of Famotidine 20 mg Tablets Used in This Study

Product name	Supplier	Diameter× thickness (mm)
BLOSTER® M	Elmet Eisai Co., Ltd.	8.5×3.4
Famotidine D KOBA	Nichi-iko Pharmaceutical Co., Ltd.	6.0×3.3
GASPERAZINE® D	Choseido Pharmaceutical Co., Ltd.	6.0×3.3
GASPORT® D	Taiyo Yakuhin Pharmaceutical Co., Ltd.	8.5×4.0
GASTER® D	Yamanouchi Pharmaceutical Co., Ltd.	8.5×3.6
GASTRIK® D	Sawai Pharmaceutical Co., Ltd.	6.0×3.3
PROGOGUE® D	Yoshindo Inc.	6.0×3.3
STOMARCON® D	Taisho Pharm. Ind., Ltd.	8.0×3.1

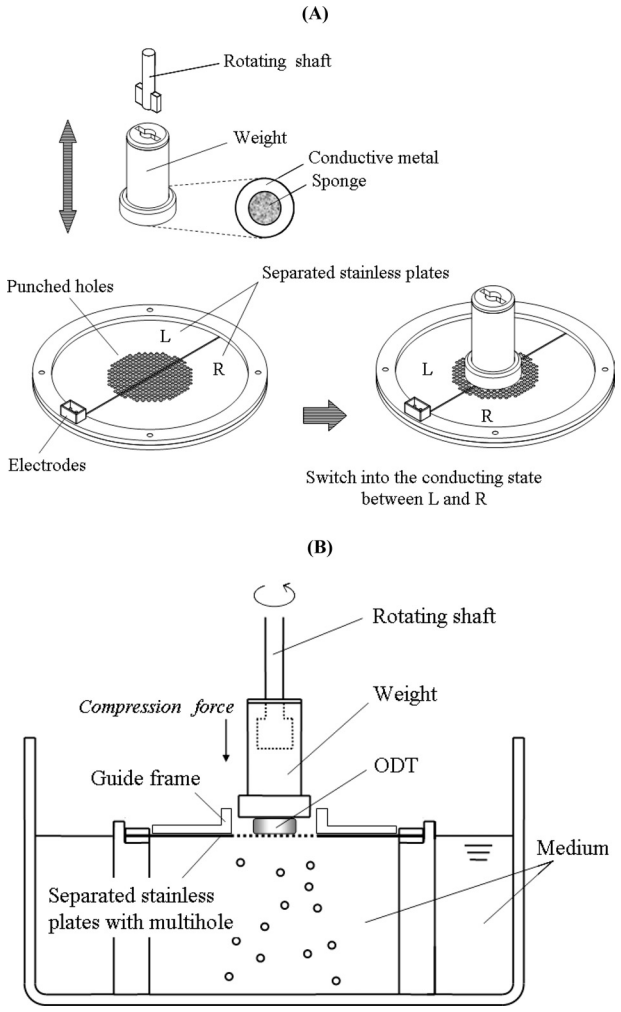

Fig. 1. Apparatus of Proposed New Disintegration Test for ODT

started. They were allowed to move the ODT against the upper palate of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting on it or tumbling it from side to side. Immediately after the last noticeable granule or fragment had disintegrated, the stopwatch was stopped and the time was recorded. The swallowing of saliva was prohibited during the test, and also saliva was rinsed from the mouth after each measurement. The data of the disintegration time were treated by *t*-test.

Conventional Disintegration Test Disintegration time in the conventional disintegration method was measured as directed in the Japanese Pharmacopeia but without a disk. The dissolution medium was 900 ml-purified water at 37 °C. The rotation speed of the shaft was 50 rpm. The disintegration time was also measured with a stopwatch.

New Disintegration Test Figure 1A shows an illustration of core structure of the new proposed apparatus. A weight, which consisted of conductive material, was mounted on the bottom of a rotating shaft. The weight was free to move vertically. A sponge was attached on the undersurface of the weight to increase friction with an ODT sample. The weight therefore transmitted torque of the rotating shaft to the ODT and ground down it on a punched stainless plate. The diameter of punched hole was 1.0 mm, holes pitch was 1.5 mm, and the plate thickness was 0.05 mm. The stainless plate was divided in half. Electrodes applied to each side of plate (L and R). When the weight made contact with the plates, electric resistance between L and R changed significantly. Figure 1B is the front elevational view when the disintegration time of ODT was measured. The ODT was placed on separated stainless plates with multihole and at the center of a guide frame. Purified water was used as medium. The medium temperature was set at 37 °C. The water level was adjusted to the undersurface of the punched stainless plates. When the weight was put on the ODT, the punched plates bended beneath the burden of the weight. Then undersurface of the ODT was slightly immersed in the medium. The rotating weight crushed the ODT, and the ODT was disintegrated into the medium. The compression force was easily adjusted using the weight. The weight was set at 10 and 15 g. In addition, the rotation speed was set at 10, 25, and 50 rpm. When the weight made contact with the separated plates, the electric sensor conveyed a signal that indicated the end of the disintegration of the ODT.

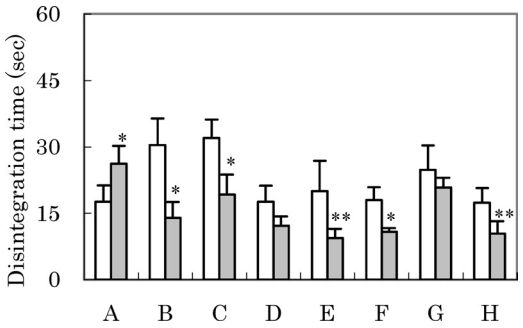

Fig. 2. Disintegration Time of Various Famotidine 20 mg ODTs in Human Sensory Test

Open column: initial sample, gray column: stored sample (60 °C 75%RH, 1 week), values are the means±S.D., (n=5), $*p<0.01$, $**p<0.05$ *vs.* initial.

Results

Disintegration Time in Human Sensory Test As shown in Fig. 2, the disintegration time in the human sensory test was varied. The asterisks here represent the results of significance test. In general, disintegration times ranged from 10 to 30 s. The effect of storage on disintegration time was observed. After storage, the disintegration time of only one sample (sample A) was delayed, but those of five samples (sample B, C, E, F and H) were accelerated. Samples D and G showed no significant change.

Disintegration Time Using Conventional Disintegration Test Disintegration time using the conventional disintegration test was greatly affected by storage (Fig. 3). Especially, disintegration times of samples A and C were prolonged for up to 300 s. Figure 4 shows the disintegration time obtained using the conventional disintegration test plotted against it in human sensory method. The data points were subjected to linear regression analysis. The regression formula and correlation coefficient (R) were written in the figure. These results indicated that it was difficult to predict the disintegration time in human from the results of the conventional test.

Disintegration Time Using Newly Proposed Test Figure 5 shows the disintegration times obtained using the new proposed test. Disintegration time was affected by both the rotation weight and the rotation speed. Higher rotation weight and rotation speed leaded to shorter disintegration

times. Especially, the rotation speed affected significantly the results. The experimental values are in good agreement with the human sensory test. However, the disintegration time of only one sample (stored sample C) was prolonged, even though it was accelerated in the human sensory test.

The correlation of the disintegration time between the human sensory test and the new proposed test is shown in Fig. 6. The regression formula and *R* were also written in the figure. The slope was decreased along with the increase of the rotation weight and the rotation speed. The slope was close to 1 at 10 g/25 rpm or 15 g/25 rpm. These results show that the new proposed test correlate stronger to the human sensory test than the conventional test.

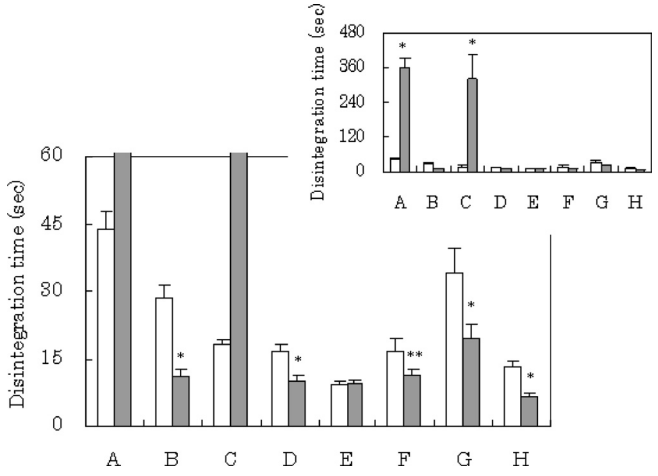

Fig. 3. Disintegration Time of Various Famotidine 20 mg ODTs in the Conventional Disintegration Test

Open column: initial sample, gray column: storage sample (60 °C 75%RH, 1 week), values are the means±S.D., (n=6), $*p<0.01$, $**p<0.05$ *vs.* initial.

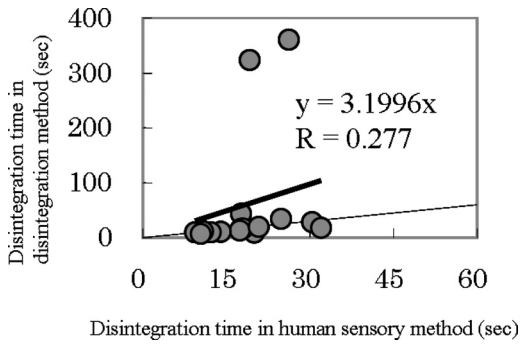

Fig. 4. Relationship between the Disintegration Time in Human Sensory Test and Conventional Disintegration Test

Discussion

Owing to the increasing market share of ODTs, the European Pharmacopoeia (European Pharmacopoeia 4.1, 2002) has adopted the term orodispersible tablet to describe a tablet that disintegrates in less than 3 min using the conventional disintegration test. However, as shown in this study, there is no relationship between the disintegration time of ODTs in the conventional disintegration test and those in human sensory test. The disintegration times using human sensory test were very rapid, however the disintegration times using conventional test were over 300 s (5 min) for some samples. From that perspective, it is anticipated that the need for a suitable and simple *in-vitro* test will escalate. The purpose of the present study was to demonstrate the usefulness and applicability of our proposed new test for ODTs.

In this study, the tablets were subjected to the stress condition of 60 °C/75%RH for 1 week. This condition might be too rigorous but we have already reported that such condition was preferable to evaluate possible changes in the short term.[9] In the human sensory test, the disintegration times of

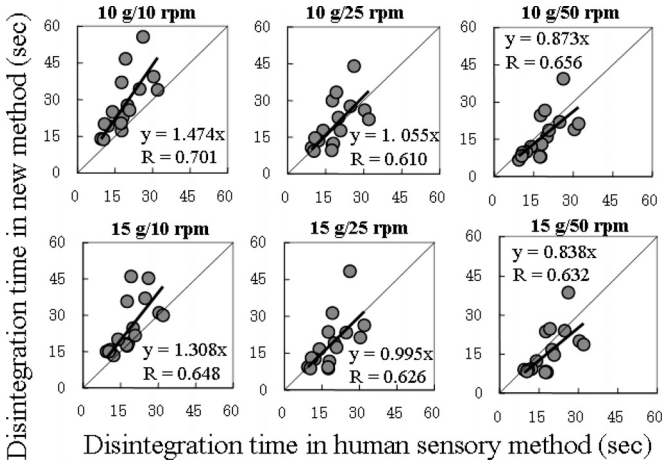

Fig. 6. Relationship between the Disintegration Time in the Human Sensory Test and New Disintegration Test

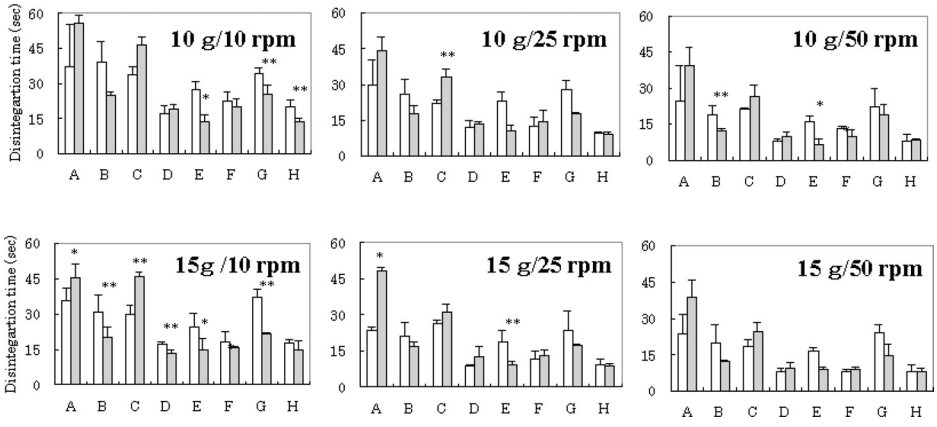

Fig. 5. Disintegration Time of Various Famotidine 20 mg ODTs in New Disintegration Test

Open column: initial sample, gray column: storage sample (60 °C 75%RH, 1 week), values are the means±S.D., (n=3), $*p<0.01$, $**p<0.05$ *vs.* initial.

numerous samples were within 30 s. On the other hand, the disintegration times in the conventional disintegration test were much longer. Especially, the disintegration times of stored samples A and C were over 300 s. These phenomenon might be due to the migration of the some of the components in the tablets. In our previous reports, we assumed that migration had occurred during storage under stress conditions, and that this had accounted for the inconsistencies in the disintegration time between the conventional disintegration test and the human sensory test.[9] We thought that such migration was too weak to extend the disintegration time in human, but enough to extend that in the conventional disintegration test.

In our previous report, good correlation in the disintegration time between the conventional test and human sensory test was observed, but the slope was far from 1. However, in this study, there was no correlation between the conventional test and the human sensory test. This difference might be due to the variety of famotidine formulations. In the previous study, the types of sample were limited, so the correlation of the disintegration time between the conventional test and the human sensory test might have been coincidental. Ultimately, it is not possible to extrapolate the disintegration time in the human sensory test from the results of the conventional disintegration test. Our proposed new test may overcome this difficulty. As shown in Fig. 6, the slope was close to 1 when the conditions of weight and rotation speed were 10 g/25 rpm or 15 g/25 rpm. In addition, good correlation was obtained between the disintegration time determined *in vitro* and *in vivo* for all samples even stored samples. These results demonstrate that the mechanical stress induced by the rotary shaft (rotation and weight) is one of the most important and critical factors for disintegration of the ODT. On the other hand, the disintegration time of stored sample C in the new test was inconsistent with that in the human sensory test. This was probably due to clogging of the punched hole. Sample C was large in volume of the tablet. If ODT with large volume go too far in disintegration at a very early stage, many disintegrated fragments can not pass immediately through the holes of stainless plate. We will improve this problem by balancing the size of hole with the volume of ODT.

In this study, we employed several types of commercial famotidine 20 mg ODTs with different formulation, weight, diameter and shape. Our test method, even for such samples, provided results with excellent correlation to those in the human sensory test.

Conclusions

We were able to demonstrate the usefulness and applicability of the new disintegration test to estimate human disintegration time of ODTs. This method presents clear advantages with respect to the current test and thus, might provide a novel approach for the determination of the disintegration time of ODTs.

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