Clinical Disintegration Time of Orally Disintegrating Tablets Clinically Available in Japan in Healthy Volunteers

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Orally disintegrating tablets (ODTs) have the superior physical property of excellent disintegration that allows them to be taken with little or no water, and are well proven to be easily administered by rapidly dissolving or disintegrating in the mouth. (2) Orally disintegrating tablets have appropriate disintegration properties. However, there is no specific description of the disintegration time or method for measuring disintegration time. On the other hand, guidance regarding ODTs has been issued by the United States Food and Drug Administration (FDA) in 2008. The guidance provides a definition of ODTs, stating that ODTs should rapidly disintegrate in saliva without the need for chewing or liquids. It also states that the disintegration time should be within approximately 30 s, which is presented only as a recommended time to express the rapid disintegration of ODTs in the oral cavity. These guidelines recommend the United States Pharmacopeia (USP) disintegration test as the method for measuring disintegration time, while allowing any alternative method that provides equivalent results. Disintegration time is an important quality attribute of ODTs, and the evaluation of disintegration time is positioned as a key step in formulation development, manufacturing, and clinical practice. Therefore, an appropriate method is required to evaluate the disintegration time of ODTs. However, when ODT disintegration time is to be evaluated in humans, ethical issues arise because tablets containing active pharmaceutical ingredients are administered to humans. On the other hand, the compendial disintegration test does not seem to accurately reproduce the disintegration behavior of ODTs in the oral cavity as the test is carried out in a large volume of test solution (i.e., 900 mL). Therefore, the actual disintegration time of ODTs in the oral cavity does not often correlate with the in vitro disintegration time measured by disintegration tests of USP or JP.

In this study, we aimed to evaluate the clinical disintegration time of 17 ODTs that are currently available for clinical use in Japan. We first validated the methods for measuring the disintegration time in oral cavity (the clinical disintegra-

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tion time) to develop the methods. In addition, we attempted to evaluate the correlation between the clinical disintegration time and the in vitro disintegration time of ODTs which was measured using Tricorptester, a newly developed disintegration testing apparatus.

MATERIALS AND METHODS

Test Drugs The drugs used in this study are listed in Table 1, including 26 ODT products that are currently available for clinical use. All other chemicals were of reagent grade.

Measurement of in Vitro Disintegration Time in Clinically Available ODTs In vitro disintegration time of 26 ODT products (Nos. 1–26) was measured by Tricorptester (Okada Seiko Co., Ltd., Tokyo, Japan). Tricorptester is a test device composed of 2 meshes; a lower mesh, on which an ODT is placed, and an upper mesh, which is attached to holders and is in contact with the ODT, on which artificial saliva is dripped from above. The disintegration time is measured as the time elapsed until the tablet completely disintegrates and the 2 meshes touch each other. The test solution (NaCl, 1.44 g/L; KCl, 1.47 g/L; and Tween 80, 0.3%) was warmed to 37°C and dripped from a height of 80 mm at a flow rate of 6.0 mL/min. This measurement was performed on 10 tablets of each type of ODT and the mean disintegration time was calculated.

Validation of the Method for the Measurement of Clinical Disintegration Time To evaluate the intra-assay precision, we randomly divided 18 healthy volunteers (age range, 21–28 years) into 3 groups and performed a randomized crossover trial to determine the clinical disintegration time for placebo ODT-A and ODT-B. The placebo ODTs were prepared by direct compression method using a single-station tabletting machine (HANDTAB-100; Ichihashi-seiki Co., Ltd., Kyoto, Japan). All compressed conventional and ODTs weighed 250 mg and had a diameter of 9.0 mm. ODT-A contained Ludiflash (BASF, Ludwigshafen, Germany), and ODT-B contained Ludiflash and cocoa powder (NF-15, Morinaga Shoji Co., Ltd., Yokohama, Japan).

All volunteers who provided written informed consent participated in the study. Before the test, the oral cavity of participants was rinsed with a cup of water (120 mL). Each ODT was placed on their tongues, and it disintegrated in their oral cavities. They were allowed to move the tablet gently against the upper palate of the mouth with their tongue without biting. The clinical disintegration time of each ODT was measured by an investigator with a stopwatch. The remnants of each ODT were removed and rinsed from the mouth with water after each test. Participants took a 15-min interval between tests of ODT-A and ODT-B. All protocols of the clinical trials were approved by the Ethics Committee of the University of Shizuoka.

Measurement of Clinical Disintegration Time in Clinically Available ODTs The clinical disintegration time was measured for 17 ODT products (Nos. 1–17). Healthy volunteers (n, 9–10; age range, 21–28 years) participated in this randomized crossover trial. Each tablet was placed on their...
tongues and disintegrated in their oral cavities. The clinical disintegration time of each ODT was measured.

**Relationships of in Vitro Disintegration Time to Tablet Characteristics** The relationships of the measured in vitro disintegration time to tablet hardness, diameter, weight, and thickness were evaluated. The hardness of ODT was determined by a load cell-type hardness tester, PC-30 (Okada Seiko Co., Ltd., Tokyo, Japan) using 10 tablets for each product. Tablet diameter, weight, and thickness were obtained from the package insert or interview form for each product. The wetting time of each ODT product was measured as described previously with minor modification.8,9 In brief, a piece of paper tissue folded twice was placed in a culture dish containing 6mL of the test solution (NaCl, 1.44 g/L; KCl, 1.47 g/L; and Tween 80, 0.3%) at 37°C. A tablet was put on the paper, and the time for complete wetting was measured using 3 tablets for each product.

**Statistical Analysis** Statistical analysis was performed using Graphpad Prism v.5.02 (Graphpad Software, San Diego, U.S.A.). Tukey’s test was performed to examine the significance at \( p < 0.05 \).

**RESULTS**

**Validation of the Method for the Measurement of Clinical Disintegration Time** To validate the method for measuring the clinical disintegration time of ODTs, the subjects were randomly assigned to 3 groups, and the clinical disintegration time was measured. The clinical disintegration time of ODT-A in the 3 groups was 13.8\( \pm \)3.8 s, 16.6\( \pm \)3.4 s, and 16.6\( \pm \)2.5 s, and that for ODT-B was 30.8\( \pm \)3.6 s, 31.5\( \pm \)2.6 s, and 28.4\( \pm \)5.6 s (Fig. 1). No significant difference was observed in the clinical disintegration time of ODT-A and ODT-B among the 3 groups.

**Clinical and in Vitro Disintegration Time in Clinically Available ODTs** The mean in vitro disintegration times of the 26 clinically used ODT products, measured using Tri-corptester, ranged from 4.40 to 30.4 s (Table 1). The clinical
disintegration time of 17 ODT products, measured as the time required for oral disintegration in a clinical trial, was between 17.6 and 33.8 s (Fig. 2). A significant positive correlation was observed between \textit{in vitro} and clinical disintegration times of 17 ODT products ($r=0.79$; $p<0.001$, Fig. 3).

\textbf{Relationships of \textit{in Vitro} Disintegration Time of ODTs with Hardness, Diameter, Weight, Thickness and Wetting Time} The hardness of ODTs used in this study ranged between 26.8 N (Takepron OD Tablets 15) and 110.1 N (Magmitt Tab. 250 mg). The tablet diameter was between 6.0 and 11.5 mm, weight was between 80 and 570 mg, and thickness was between 2.4 and 4.9 mm. When the relationships of the measured \textit{in vitro} disintegration time with tablet hardness, diameter, weight, and thickness were evaluated for each ODT product, there was no significant correlation between the \textit{in vitro} disintegration time and any of the parameters (Fig. 4). On the other hand, wetting time of ODTs correlated significantly with \textit{in vitro} disintegrating time ($r=0.718$; $p<0.001$, Fig. 4e).

\textbf{DISCUSSION}

In this study, the clinical disintegration time of 17 clinically available ODTs in Japan was measured, and the correlation between the clinical disintegration time and the \textit{in vitro} disintegration time of ODTs was evaluated.

To date, no studies have described validation of the method for measuring the clinical disintegration time of ODTs although a few studies have reported the disintegration time in the oral cavity.\textsuperscript{7,10,11} Thus, we first validated the method for measuring the clinical disintegration time of ODTs in healthy volunteers who were randomly assigned to 3 groups. No significant difference was observed in the clinical disintegration time of placebo ODT-A and ODT-B, which had different disintegration times. This result indicates the reproducibility of our method for measuring the clinical disintegration time. In addition, standard deviation (S.D.) calculated from results of our study \textit{(ca. 3 to 5 s)} indicated that 7 to 17 subjects are required to detect a 5-s difference in the disintegration time of 2 ODTs, with 5% alpha error and 80% power at a two-sided 5% significance level.

The clinical disintegration time of 17 ODT products was between 17.6 s and 33.8 s. The 16th edition of the Japanese Pharmacopoeia describes the optimum characteristics of ODTs, but there is no specific description about the disintegration time of ODTs.
tion time. FDA guidelines indicate that the disintegration time of ODTs should be approximately within 30 s. 1) Our result indicated that ODT products, which are clinically used in Japan, have good disintegration (within approximately 30 s) and that the disintegration time varies according to the product. Similarly, the in vitro disintegration times of the 26 clinically used ODT products ranged between 4.4 and 30.4 s. Currently, there are couples of apparatus for measuring disintegration time of ODTs. In this study, we have selected Tricorptes, which is a newly developed disintegration testing apparatus, because it has not been reported the relationship of the in vitro disintegration time measured of ODTs by this apparatus with the clinical disintegration time which were evaluated from a validated clinical trial. The result of this study showed that a significant positive correlation was found between in vitro and clinical disintegration times, which showed that the in vitro disintegration time of ODTs measured using Tricorptester is a good reflection of the disintegration time in the oral cavity.

We added other 9 ODT products (Nos. 18–26) to 17 ODTs in order to perform the further evaluation of relationships between the in vitro disintegration time and tablets characteristics, after the evaluation of the in vitro disintegration time by using Tricorptester. Interestingly, a significant correlation was observed between the in vitro disintegration times of the tested ODTs and the wetting times of the corresponding tablet. In contrast, there were no relationship between in vitro disintegration time and tablet hardness, diameter, weight, and thickness. While swelling, particle deformation, capillary action, and interparticle repulsion are proposed as mechanisms for tablet disintegration, most cases have been explained by swelling and capillary action. In other words, wetting by liquid is the first requisite for tablet disintegration, even though swelling, wetting, liquid surface tension, viscosity, and capillary action may all be involved. Liquid penetrates through pores deep into the tablet, and the disintegrant exerts its disintegrating function by absorbing the water that reached into the tablet. Therefore, it is likely that the easier water penetrates the tablet, the faster the tablet disintegrates. The same applies to ODT disintegration time. Improved disintegration of ODTs has been achieved by increasing the porosity to let the liquid penetrate the tablet easily, and by using disintegrants that have excellent water absorption and wetting capacities. 2) Thus, the oral disintegration behavior may vary by product; some ODTs are designed to disintegrate while leaving the core intact and others are formulated to quickly disintegrate and spread in the mouth. In this study, a significant positive correlation was observed between the measured and clinical disintegration times, demonstrating that ODT disintegration time measured by Tricorptester is a good reflection of the oral disintegration time, regardless of manufacturer, formulation technology, and size of tablet.

In conclusion, this study shows that all the tested products, which are clinically available in Japan, showed good disintegration and that the disintegration time varied according to the product. In addition, the in vitro disintegration time of ODTs measured using Tricorptester is a good reflection of the disintegration time in the oral cavity.

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