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Evaluation of the ease of taking mini-tablets compared with other tablet formulations in healthy volunteers

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ABSTRACT

"Mini-tablets" (MTs) are tablets of diameter ≤ 3 mm and have been widely studied and developed. However, reports comparing MTs with other tablet formulations are few. We wished to evaluate the ease of taking a MT quantitatively in comparison with an orally disintegrating mini-tablet (ODMT), conventional tablet (CT) and conventional orally disintegrating tablet (ODT). Four types of tablets were prepared. We prepared tablets of two diameters (3 mm for MTs and ODMTs vs. 8 mm for CTs and ODTs) and two formulations (MTs and CTs vs. ODMTs and ODTs). Our randomized crossover trial in 18 healthy volunteers (8 men and 10 women; mean age, 22.5 years) indicated that the visual analog scale (VAS) score for the ease and amount of water required for intake of MTs was significantly lower than those of CTs. An ODMT required the least amount of water and smallest VAS score for the ease of taking a tablet. Our results showed that the advantage of MTs with regard to the ease of taking and decreased amount of water required was exerted for a unit of dosing comprising <5 tablets. These data suggested the usefulness of MTs and the importance of the number of MTs for comfortable consumption by patients.

1. Introduction

Tablets are the most widely used drug formulation among various types of formulation (e.g., tablets, capsules, granules). They are easy to handle and convenient to carry and store. However, problems may arise in pediatric or elderly patients whose swallowing functions are inferior to those of adult patients.

Orally disintegrating tablets (ODTs) are a user-friendly formulation (Hirani et al., 2009). ODTs could be beneficial for patients who have difficulty swallowing conventional tablets (CTs). Furthermore, ingestion of ODTs with little water or without water may be beneficial for patients with disorders for which water intake must be restricted (e.g., overactive bladder). Several commercial types of ODTs have become popular in the last decade. However, taste-masking is required for ODTs if the drug substance has an unpleasant taste (Mizumoto et al., 2008). In this case, any other formulation without taste masking is needed.

Mini-tablets (MTs) have a diameter ≤3 mm. They have been studied widely and developed (Lennartz and Mielck, 1998). MTs are considered to be easier to swallow than CTs, whose diameter is >3 mm. This decrease in tablet diameter could improve patient adherence to medication and decrease the risk of aspiration. Many studies on different types of MTs, such as orally disintegrating mini-tablets (ODMTs), sustained-release MTs, "floating" MTs, and bioadhesive MTs, have been carried out (Stoltenberg and Breitkreutz, 2011; Mohamed et al., 2013; Goole et al., 2008; Schmitz et al., 2005).

Several clinical trials of MTs in preschool-aged children have been reported (Thomson et al., 2009; Spomer et al., 2012; Klingmann et al., 2013; van Riet-Nales et al., 2013). These reports suggest that MTs are the most acceptable and preferred oral formulation compared with powder or syrup formulations. Kluk et al. (2015) reported recently that ≤10 MTs mixed with jelly were acceptable to children aged 2–3 years. However, reports of clinical trials comparing MTs and other tablet formulations (e.g., CTs, ODTs) are lacking. In many cases, MTs are administered as a unit of several tablets, but quantitative data for evaluation of the ease of intake of such units are lacking.

We aimed to evaluate the ease of taking MTs quantitatively in comparison with other tablet formulations, as well as the intake of different numbers of MTs. First, one tablet of each formulation was evaluated. We compared 1 MT with 1 ODMT, 1 CT and 1 ODT by measuring the volume of water required for ingestion and the ease of intake using a visual analog scale (VAS), methods that have been employed by our research team previously (Uchida et al., 2013; Sugiura et al., 2012). Next, we evaluated the volume of water required for the intake and ease of taking tablets when units of 1, 2, 5 and 10 MTs were administered.

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2. Materials and methods

2.1. Materials

D-Mannitol (Mannit Q™) was kindly provided by the Mitsubishi Shoji Foodtech Co., Ltd. (Tokyo, Japan). All other samples were obtained commercially. α-Lactose monohydrate (Dilactose®S) was from the Freund Corporation (Tokyo, Japan). Microcrystalline cellulose (CEOLUS™ UF-702) was from the Asahi Kasei Chemicals Corporation (Tokyo, Japan). Low-substituted hydroxypropyl cellulose (L-HPC LH-21) was from the Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Crospovidone (Kollidone® CL) wasfrom the BASF (Rhineland-Palatinate, Germany). Magnesium stearate (Parteck® LUB MST (magnesium stearate vegetable grade)) was from the Merck KGaA (Darmstadt, Germany).

2.2. Preparation of tablets

Compositions of each formulation are shown in Table 1. Shapes of a CT and MTs are depicted in Fig. 1. All excipients were mixed together and compacted. MTs and ODMTs were prepared on a Single-punch Tablet Machine (HANDTAB; Ichihashiseiki, Kyoto, Japan) with a 3-mm, six-tip mini-tableting tool. Six MTs were compacted together, and the force was 6 kN. One MT weighed 20 mg, and average compaction was 1 kN. CTs and ODTs were prepared on the same tablet machine with an 8-mm tableting tool with compaction forces of 8 kN and weight of 200 mg per tablet.

Hardness of tablets was measured using a Tablet Hardness Tester (PC-30; Okada Seiko Co. Ltd., Tokyo, Japan). Hardness, weight and thickness were measured on 10 tablets of each type and the mean value was calculated.

2.3. Clinical trial

All volunteers provided written informed consent to participate in this study. The study was conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the Ethics Committee of the University of Shizuoka (protocol number 25–41; Shizuoka, Japan).

2.3.1. Measurement of the clinical disintegration time of tablets

The clinical disintegration time was measured for four types of tablet (MT, ODMT, CT, ODT) as described previously (Yoshita et al., 2013). Ten healthy volunteers (3 men and 7 women; age (mean ± SD), 22.0 ± 1.2 years) participated in this randomized crossover study. Before the test, the oral cavity of the participants was rinsed with a cup of water (120 mL). Each tablet was placed on the tongue and disintegrated in the oral cavity. The clinical disintegration time of each tablet was measured by an investigator using a stopwatch. Remnants of each tablet were removed and rinsed from the mouth with water after each test.

Table 1
Composition of a mini-tablet, orally disintegrating mini-tablet, conventional tablet and orally disintegrating tablet.

Ingredients (mg)	MT (3 mm)	ODMT (3 mm)	CT (8 mm)	ODT (8 mm)
Dilactose® S	13.8	–	138	–
L-HPC LH-21	2	–	20	–
Kollidone® CL	–	2	–	20
Mannit Q™	–	13.8	–	138
CEOLUS™ UF-702	4	4	40	40
Parteck® LUB MST	0.2	0.2	2	2
Total	20	20	200	200

MT, mini-tablet; ODMT, orally disintegrating mini-tablet; CT, conventional tablet; ODT, orally disintegrating mini-tablet.

2.3.2. Measurement of the amount of water required for the ingestion and ease of taking tablets

Eighteen healthy volunteers (8 men and 10 women; age, 22.5 ± 1.0 years) participated in this randomized crossover trial. Measurement of the amount of water required for ingestion of CTs and ODTs was conducted as described previously (Uchida et al., 2013). Subjects were asked to consume 1 MT and 1 CT with drinking water. In the case of 1 ODMT and 1 ODT, they were asked to drink water after these tablets had disintegrated in the oral cavity. Subjects freely filled the cup with water from a 500-mL bottle and then drank the minimum volume of water required to consume each tablet smoothly. The amount of water was measured using the weight of the cup and bottle. After drinking water, they were asked to evaluate the ease of taking a tablet using a VAS with the most difficult sensation for taking a tablet marked at 100 mm (Fig. 2).

In the second trial, all volunteers randomly took 1 CT or one unit containing 1, 2, 5 or 10 MTs (Fig. 1) with water. Ten MTs and 1 CT are the same weight. One unit of MTs or 1 CT was placed into the mouth simultaneously. After drinking water, the amount of water required and VAS score for the ease of intake of each unit of tablets were measured by the same methods as the first trial.

2.4. Statistical analyses

Data for tablet characteristics are the mean ± standard deviation (S.D.), whereas data from the clinical study (VAS and amount of water) are the median value. Statistical analyses were undertaken using a Graphpad Prism v5.02 (Graphpad Software, San Diego, CA, USA). Each pair of samples was analyzed separately and compared using the non-parametric Wilcoxon signed rank test with the Bonferroni correction to detect differences among the amount of water required for ingestion of tablets and the ease of taking tablets. $p < 0.017$ was considered significant for the first trial, and $p < 0.0125$ for the second trial.

3. Results

3.1. Characteristics of each tablet

Weight, thickness, hardness and clinical disintegration time of each tablet are shown in Table 2. One ODMT disintegrated in <10 s. One MT and one ODT disintegrated in ≈20 s. One CT disintegrated in ≈1 min.

3.2. VAS score for ease and amount of the water required for the ingestion of each tablet in the first trial

The VAS score for the ease and amount of water required for ingestion of a single tablet is shown in Fig. 3. VAS score for 1 CT was the

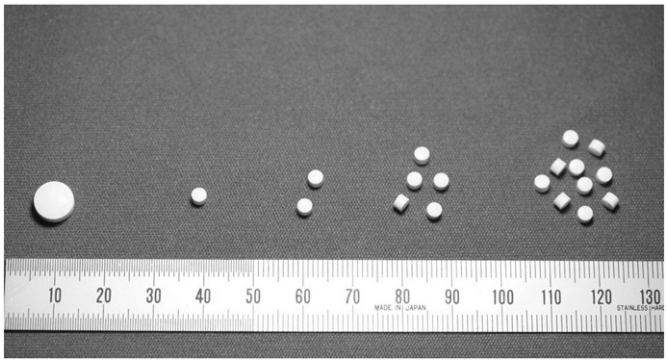

Fig. 1. Conventional tablet and mini-tablet used in this study. The diameters of a conventional tablet (CT) and mini-tablet (MT) were 8.0 and 3.0 mm, respectively. The total weight of tablets between 1 CT and 10 MTs was equal. Volunteers took 1 CT or 1, 2, 5, and 10 MTs in the second trial. Scale is in mm.