医薬品相互作用研究
一　般　論　文
45(1)　9-17（2021）

Characterization of Orally Disintegrating Tablets Containing Fluconazole Prepared at a Hospital Pharmacy

Mari MATSUMOTO[a,b], Katsuma ARAI[c], Sachie HAYAKAWA[b], Katsuhiko SAWAKAMI[d], Kentaro SAWAKAMI[d], Shigenari SHIDA[c], Yukio NOHARA[c], Kenji SUMIYA[a,c], Kazuko MURATA[a,c], Yoshiko TAKEUCHI[e], Hirofumi TAKEUCHI[e], Ryo MURATA[a,c*]

[a] Graduate School of Science and Engineering, Iryo Sosei University
[b] Department of Pharmacy, Iwaki Yumoto Hospital
[c] Faculty of Pharmacy, Iryo Sosei University
[d] Sawakami Pharmacy
[e] Laboratory of Advanced Pharmaceutical Process Engineering, Gifu Pharmaceutical University

（Received May 20, 2020; Revised September 18, 2020; Accepted October 4, 2020）

Abstract

Orally disintegrating tablets（ODTs）, which dissolve rapidly in the oral cavity, can be taken with or without a small amount of water, making them a useful dosage form that helps patients who have difficulty in swallowing and improves compliance. As a preliminarily experiment for hospital preparation of ODTs, in this study, we prepared fluconazole（FLCZ; $C_{13}H_{12}F_2N_6O$）ODTs and evaluated usefulness of the formulation. The ODTs were prepared using lactose and mannitol as excipients. Hardness was the highest for ODTs prepared using lactose and mannitol in a 2:1 ratio. Water-wetting time was delayed for these ODTs. The water absorption ratio was the highest for ODTs prepared using mannitol alone and approximately 25% for those prepared using other formulations. The addition of FLCZ to the excipients with lactose and mannitol, mixed in a 2:1 ratio, decreased the hardness and extended disintegration time. Water-wetting time was longer than for lactose ODTs but remained within the allowable range. In addition, the content and dissolution ratio were determined. The masking efficiency of taste was evaluated using an electronic gustatory system. Additionally, ODT cross-section was observed under a scanning electron microscope, and the FLCZ distribution was observed from the mapping image of elemental fluorine in FLCZ identified using energy-dispersive X-ray spectrometry. The results of this study suggest that ODTs that disintegrate rapidly can be prepared at a hospital pharmacy without the need for manufacturing equipment for tableting.

Keywords : fluconazole, orally disintegrating tablets, scanning electron microscope, hospital preparation

Introduction

Oral administration is the most common route of drug administration. However, tablets and capsules are not always easy to take, especially for patients with decreased swallowing function due to aging or disease and for pediatric patients with undeveloped swallowing function. Orally disintegrating tablets（ODTs）and orally disintegrating films（ODFs）can be taken with or without a small amount of water because they dissolve or disintegrate rapidly in the oral cavity. Therefore, they are a useful dosage form that helps patients who have difficulty in swallowing and improves compliance[1,2].

ODTs need to disintegrate quickly and have good strength. Tablets with both quick disintegration ability and good strength have been developed by preparing tablets with high porosity, adjusting the amount of the disintegrant or binder added, and devising a formulation design[3–7]. Generally, these ODTs are manufactured using manufacturing equipment. In contrast, a simple method of preparing ODTs at a hospital pharmacy without

〒970-8551　福島県いわき市中央台飯野5-5-1
[a, c] 5-5-1 Iino, Chuo-dai, Iwaki, Fukushima 970-8551, Japan
[b] 6 Daiyama, Jobanyumotomachi, Iwaki, Fukushima 972-8321, Japan
[d] 3-6-5 Shimokubo, Misawa, Aomori 033-0023, Japan
[e] 5-6-1 Mitahora -higashi, Gifu-city, Gifu 502-8585, Japan
*Ryo Murata
E-mail: r-murata@isu.ac.jp, Tel: 0246-29-5432 FAX: 0246-29-5432

manufacturing equipment was reported[8,9]. They used lactose as an excipient for ODTs and dried it in a refrigerator to prepare porous tablets.

Mannitol, which is a sugar alcohol, is widely used as an excipient because it is chemically inert to drug substances and other excipients and has low hygroscopicity[10]. It is also used as an excipient for ODTs because of its excellent solubility, sweetness, and good palatability.

As a preliminarily experiment for hospital preparation of ODTs, in this study, we attempted to prepare ODTs with rapid disintegration and suitable strength based on a formulation study using mannitol and lactose. Fluconazole（FLCZ; $C_{13}H_{12}F_2N_6O$）was used as the drug substance. FLCZ is a synthetic antifungal agent from the triazole group[11]. The resultant tablets were characterized by hardness, disintegration, and water absorption tests. Moreover, the tablets' content and dissolution ratio were assessed, and taste evaluation was performed using an electronic gustatory system. For further characterization of the tablets, an ODT cross-section was observed under a scanning electron microscope（SEM）and using energy-dispersive X-ray spectroscopy（EDS）, the distribution of FLCZ in ODTs was confirmed by mapping image of elemental fluorine in the structure formulation of FLCZ.

Materials and Methods

Materials

FLCZ was obtained from LKT. Labs.（St. Paul, MN）, powdered lactose and Diflucan® capsule 50 mg from Pfizer（Tokyo, Japan）, and d-mannitol from B Food Science（Aichi, Japan）.

Table 1. ODT formulations

	Formulation code				
Ingredient（%）	A	B	C	D	E
Lactose	100	75	67	50	-
Mannitol	-	25	33	50	100

ODT, orally disintegrating tablet.

Methods

1. Preparation

ODTs were prepared using lactose and mannitol as excipients, as described previously by Sumiya et al[8]. Table 1 shows the mixing ratio of lactose and mannitol. To prepare FLCZ ODTs, first, FLCZ and the excipients were mixed, and then the mixed powder and purified water were suspended in a mass ratio of 2:1. The suspension was filled in a syringe and was dispensed into molds（300 mg/mold）, dried in a refrigerator for 96 h, and finally taken out of the molds. FLCZ ODTs were prepared, such that one tablet contained 25 mg of FLCZ.

2. Hardness test

A hardness test was performed using a TH-203MP tablet hardness tester（Toyama Sangyo, Osaka, Japan）.

3. Evaluation of disintegration time

A disintegration test was performed using an NT-40H disintegration tester（Toyama Sangyo）with water at 37° C as the immersion fluid.

4. Water absorption

Water absorption was evaluated by measuring wetting time and water absorption ratios with reference to a previously reported method[12,13]. A filter paper（5A, diameter: 9 cm）was placed on a

Petri dish（diameter: 10 cm）and wetted with 2 mL of water tinted with red food color. An ODT was placed at the center of the filter paper, and the time required for complete wetting was measured by visual observation of color change of the ODT. Water absorption ratio, R, was determined according to the following equation:

$R = 100\ (W_a - W_b) / W_b$

where W_b and W_a are the weight before and after water absorption, respectively.

5. FLCZ content measurement

FLCZ ODTs were dissolved in water at room temperature. The FLCZ concentration in the solution was evaluated by high-performance liquid chromatography（HPLC）. Reversed-phase chromatography was performed using the LaChrom Elite System（Hitachi, Tokyo, Japan）. The HPLC system comprised an L-2130 pump, an L-2300 column oven, a D-2500 integrator, and a L-2400 UV-VIS detector. HPLC analysis was performed on TSK GEL ODS-120H（4.6 × 150 mm, Tosoh, Tokyo, Japan）at 40 ° C. The mobile phase was acetonitrile and water（1:4, v/v）with a flow rate of 1.1 mL/min, and detection wavelength of 260 nm. A sample of 20 μL was injected into a column using the Chromaster 5280 autosampler.

6. Evaluation of the dissolution test

A drug dissolution test was performed using an NTR-6200AC dissolution tester（Toyama Sangyo）. The test was performed in 900 mL of water at 37° C, with a paddle stirring speed of 50 rpm. At time intervals of 0.5, 1.5, 3, 5, 10, 20, 40, and 60 min, 5 mL samples were withdrawn. The samples were filtered through a 0.45 μm membrane filter（GL Science, Tokyo, Japan）, and the amount of FLCZ released was measured using HPLC. HPLC analysis conditions for FLCZ were as described before.

7. Taste evaluation

The taste was evaluated using an electronic gustatory system（ASTREE V5, Alpha M.O.S. Japan, Tokyo, Japan）. A sample tablet was completely dissolved in 30 mL of purified water, and 25 mL of the prepared sample solution was used for the measurement. Principal component analysis（PCA）was performed using AlphaSoft V2020, Data points from the samples were compared using calculated Euclidean distances on the PCA map.

8. Morphological observations

ODT cross-sections were observed under JSM-6010LA SEM（JEOL, Tokyo, Japan）at an acceleration voltage of 10 kV. Elemental analysis was performed to confirm the distribution of elemental fluorine in FLCZ using EDS, and FLCZ distribution was observed by mapping the elemental fluorine in FLCZ. The EDS spectra of the contained elements were confirmed, and a tablet without FLCZ and an FLCZ ODT were compared.

9. Statistical analysis

Data were expressed as mean ± standard deviation, and statistical differences were analyzed using one-way analysis of variance, followed by the Tukey–Kramer post hoc test for multiple comparisons. All statistical analyses were performed using Statcel 3 software（OMS Publishing Inc., Saitama, Japan）. $^{*}P < 0.05$ and $^{**}P < 0.01$.

Results

The different tablet properties were changed by changing the type of filler in the formulation. The results of measurements of the hardness test are shown in Fig. 1. Hardness of tablets was lowest for ODTs prepared using only mannitol as an excipient [mannitol ODTs（Man ODTs）]. While the ODT prepared with lactose showed higher hardness than Man ODTs, hardness significantly increased by formulating a suitable mannitol-to-lactose ratio. The highest hardness was observed for ODTs prepared using both lactose and mannitol in a 2:1 ratio among the several formulations with lactose and mannitol. The addition of FLCZ（active substance）, to the tablet formulation decreased hardness of the resultant tablet.

The results of the disintegration test are shown in Fig. 2. The disintegration time decreased as the concentration of mannitol increased. The tablet with lactose and mannitol in a 1:1 ratio as well as a mannitol tablet showed significantly shorter disintegration time than lactose tablet. The addition of FLCZ resulted in an increase in disintegration time.

The water-wetting time was delayed for the tablets prepared with lactose and mannitol in a 2:1 ratio compared with those prepared with the

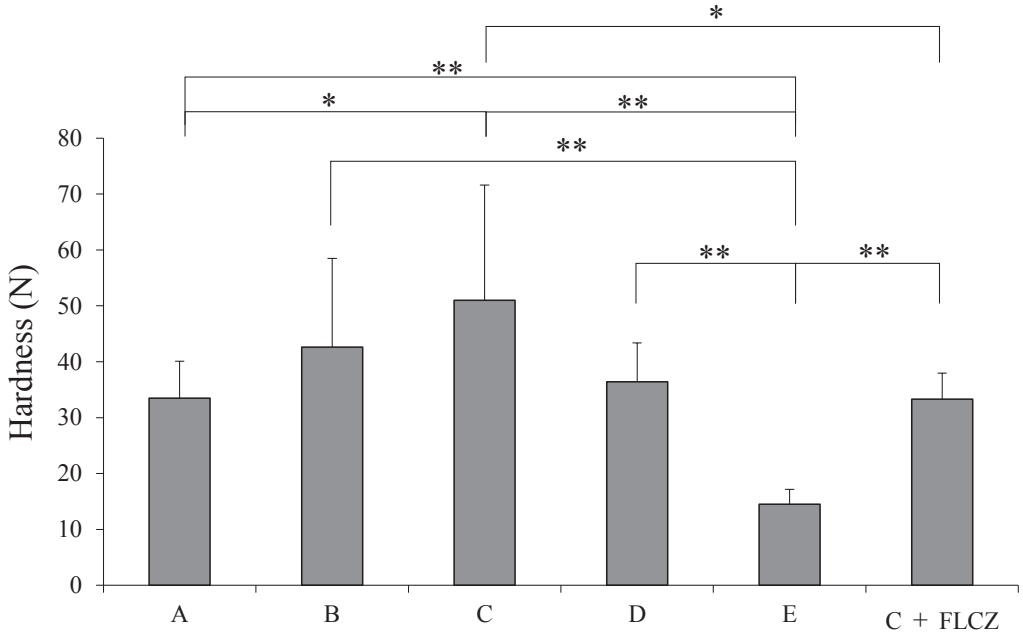

Fig. 1. Hardness evaluation of ODT

（A）Lactose;（B–D）lactose and mannitol mixture in ratios of 3:1, 2:1, 1:1;（E）mannitol and（C + FLCZ）lactose-to-mannitol ratio of 2:1 with 25 mg of FLCZ. Data are presented as mean ± standard deviation（$n = 10$）. *$P < 0.05$; **$P < 0.01$. ODT, orally disintegrating tablet; FLCZ, fluconazole.

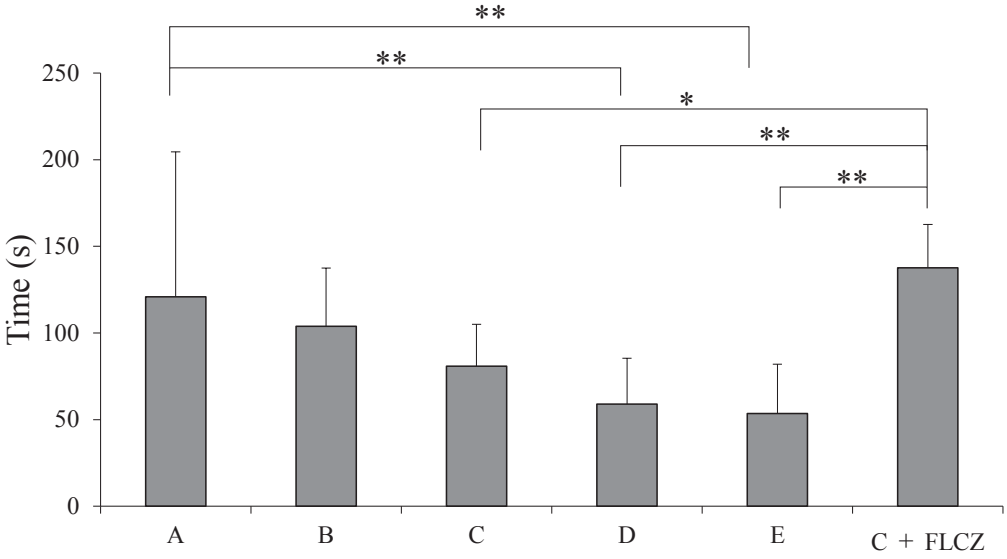

Fig. 2. Disintegration evaluation of ODT

（A）Lactose;（B–D）lactose and mannitol mixture in the ratios of 3:1, 2:1, and 1:1;（E）mannitol and（C + FLCZ）lactose-to-mannitol ratio of 2:1 with 25 mg of FLCZ. Data are presented as mean ± standard deviation（$n = 10$）. *$P < 0.05$; **$P < 0.01$. ODT, orally disintegrating tablet; FLCZ, fluconazole.

other formulations. Similarly, these tablets showed greater hardness（Fig. 3）. Water absorption ratio was the highest for Man ODT and approximately 25% for ODTs prepared with other formulations. The addition of FLCZ to the excipient with lactose and mannitol in a ratio of 2:1 resulted in a longer water absorption time than for lactose ODTs, but the time remained within the allowable range.

The FLCZ content of the tablets was measured for five tablets. The drug content of each formulation

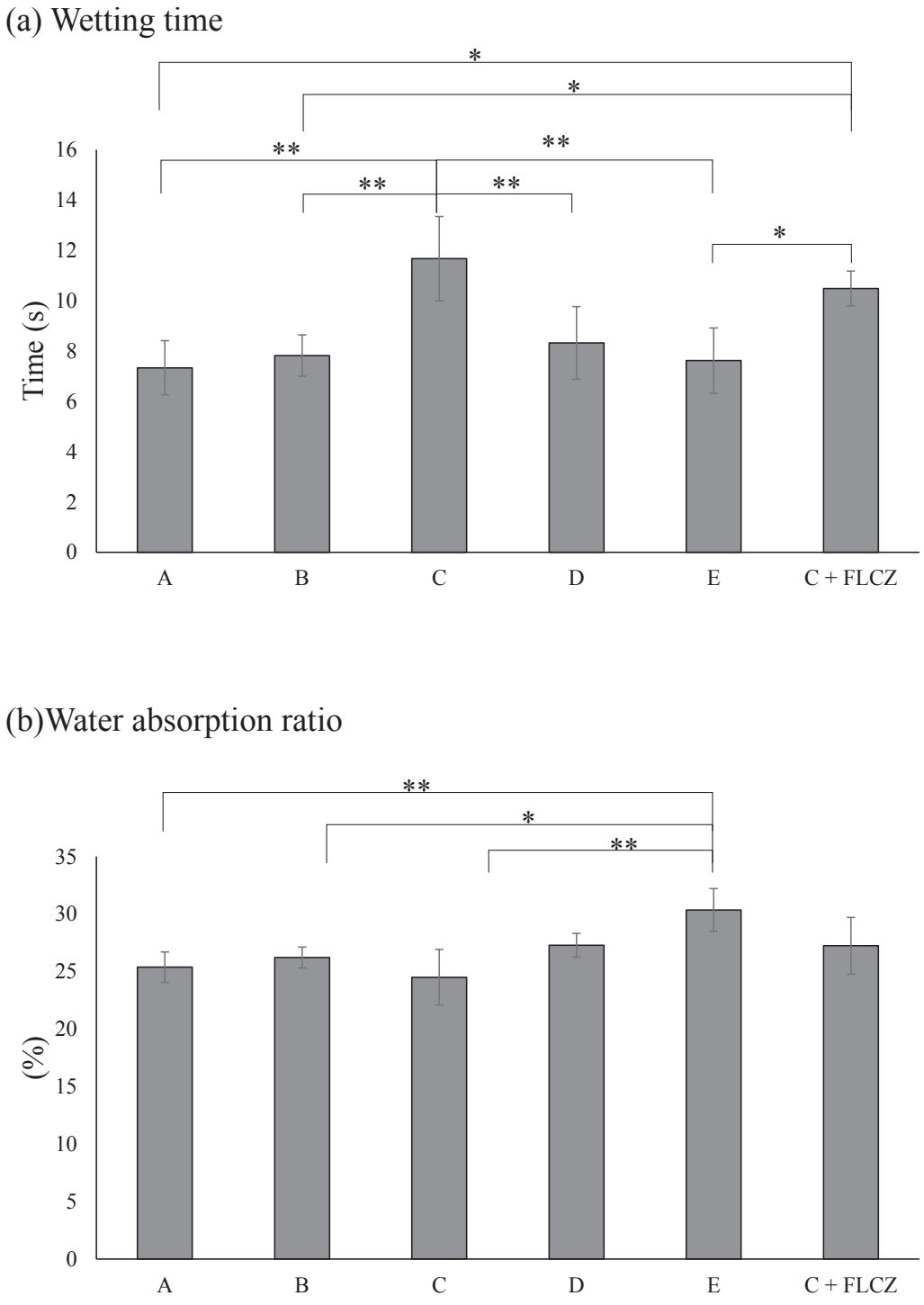

Fig. 3. Wetting time and water absorption ratio of ODT

(a) Wetting time and (b) Water absorption ratio. (A) Lactose; (B–D) lactose and mannitol mixture in the ratios of 3:1, 2:1, and 1:1; (E) mannitol and (C + FLCZ) lactose-to-mannitol ratio of 2:1 with 25 mg of FLCZ. Data are presented as mean ± standard deviation ($n = 5$). *$P < 0.05$; **$P < 0.01$. ODT, orally disintegrating tablet; FLCZ, fluconazole.

was ~99.5% ± 2.2% of the expected value. This result confirmed that the suspended drug crystals well dispersed during tablet preparation.

The drug dissolution profiles of FLCZ-containing formulations are shown in Fig. 4. In FLCZ ODTs, >80% of FLCZ eluted within 10 min after the start of the test. Compared with the commercial product Diflucan® capsules, the FLCZ ODTs eluted FLCZ (active substance) in a shorter time. The dissolution amount of FLCZ at 60 min was the

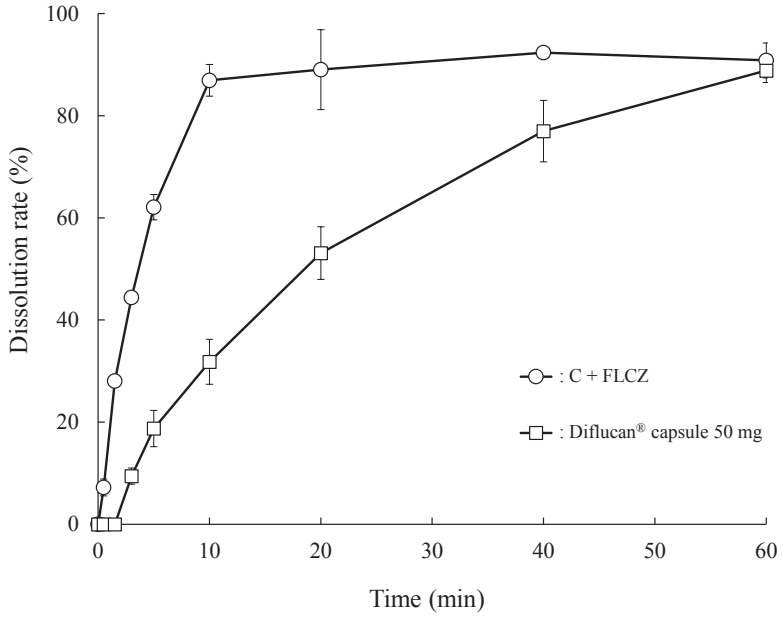

Fig. 4. Dissolution profile of FLCZ formulations

Control experiment on dissolution rate performed using Diflucan® capsules（50 mg）. Data are presented as mean ± standard deviation（$n = 3$）. FLCZ, fluconazole.

same between the two dosage forms.

Euclidean distances were calculated between active sample solutions containing FLCZ and corresponding placebo solution. Controls were used to describe the Euclidean distance between FLCZ and water. The masking effects on taste were calculated by comparing each Euclidean distance with that of the control. The masking efficiency of lactose was 74.3% and lactose and mannitol in a 2:1 ratio was 68.8%（Fig. 5）. However, a statistical comparison of the results showed no noticeable differences.

The SEM image of fracture surface of the tablets is shown in Fig. 6. The FLCZ ODT spectrum

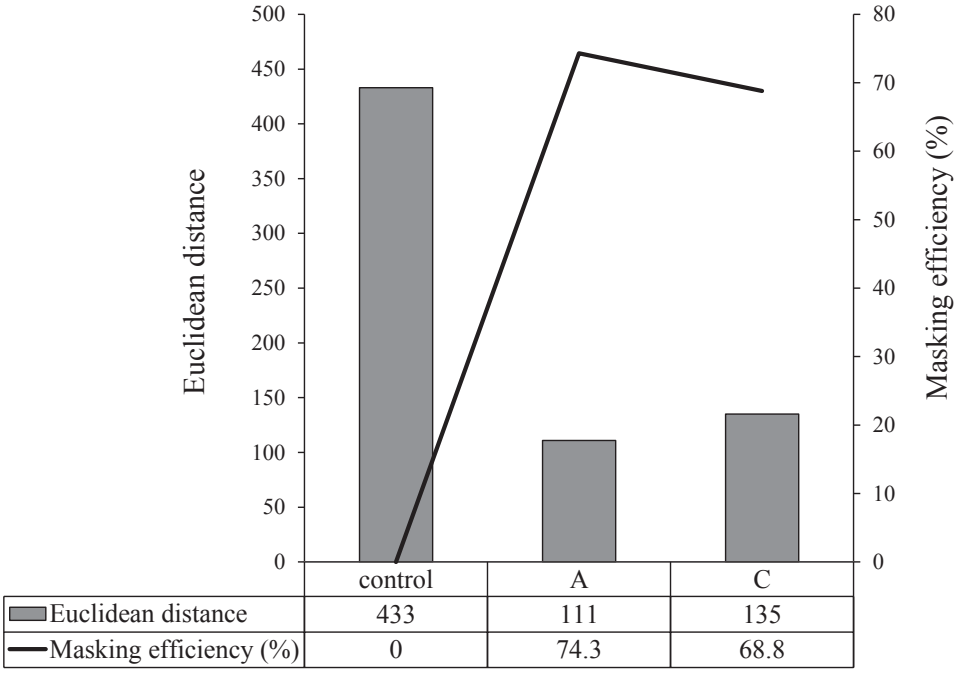

Fig. 5. Masking efficiency of excipient

Euclidean distance was calculated between the active sample solution containing FLCZ and the corresponding placebo sample solution.（Control）FLCZ;（A）Lactose;（C）lactose–to-mannitol ratio of 2:1. ODT, orally disintegrating tablet; FLCZ, fluconazole.

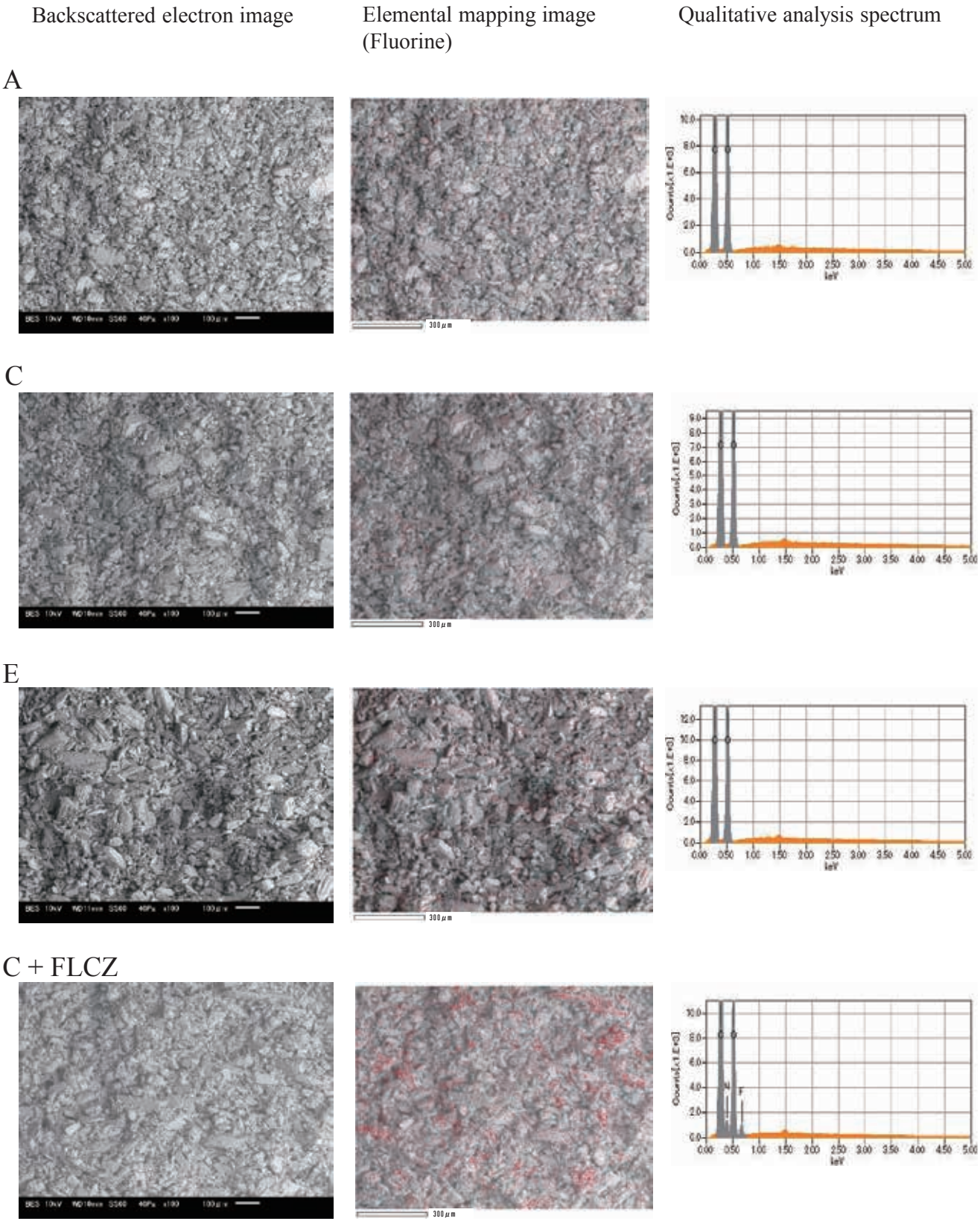

Fig. 6. SEM observation of ODT fracture surface

（A）Lactose;（C）lactose-to-mannitol ratio of 2:1;（E）mannitol; and lactose-to-mannitol ratio of 2:1 with 25 mg FLCZ（C + FLCZ）. SEM, scanning electron microscope; ODT, orally disintegrating tablet; FLCZ, fluconazole.

confirmed the presence of fluorine in the molecular structure of FLCZ, whereas the fluorine spectrum was not detected for the tablet without FLCZ. In addition, the mapping image of fluorine confirmed that FLCZ was uniformly distributed. The morphological observation of the ODT cross-section and comparison of lactose ODTs（Lac ODTs）and Man ODTs showed that Man ODTs have larger particles compared with Lac ODTs. In fact, many Man ODTs were missing when removed from the molds.

Discussion

FLCZ is clinically used in capsules and dry syrups in an oral dosage form. A previous study prepared ODFs containing FLCZ and evaluated their formulation properties[14]. ODF is a flexible thin-film formulation. When ODF disintegrates, the stickiness of the film base may be felt after ingestion. In this study, we prepared ODTs containing FLCZ to broaden the options of its oral dosage form. To improve the essential properties of ODTs prepared with the simple molding method at a hospital pharmacy, we tested the effect of type of excipient used for tablets on their properties.

Man ODTs showed a better disintegration property but lower hardness than Lac ODTs. However, hardness increased by formulating mannitol with lactose as a filler, and ODTs prepared using lactose and mannitol in a 2:1 ratio showed the highest hardness among the tablets prepared in this study.

ODTs prepared with mannitol are probably unable to withstand the pressure applied during removal from molds because mannitol particles are large and their particle–particle bonding is weak. Therefore, when mannitol and lactose are mixed, lactose enters the gaps between the mannitol particles, increasing hardness. It also showed that increasing hardness may affect the water wetting time.

When FLCZ was added with lactose and mannitol in a 2:1 ratio, hardness tended to decrease and disintegration time tended to increased. However, these properties are tolerable in actual clinical use. The prepared ODT displays excellent water absorption and can be expected to disintegrate rapidly. The time taken by Lac ODT until natural disintegration without physical irritation in the oral cavity is approximately 100 sec. This timeframe is appropriate for a useful preparation[8].

In addition, the elution of FLCZ from ODTs was faster than that from capsules, possibly because of the good solubility of mannitol. Moreover, FLCZ is uniformly distributed, and its release from the tablet surface leads to an increase in the dissolution rate.

Euclidean distances between active samples and the corresponding placebo sample were calculated using the electronic gustatory system to evaluate the masking efficiency of the excipients. The Euclidean distance represents taste similarity between the sample pairs[15,16]. The distance between FLCZ and water was expressed as the taste intensity of the drug. The masking efficiency by the fillers was evaluated by comparing the Euclidean distances between the formulations. This efficiency is attributed to the sweetness of the excipients. The excipient of the ODT prepared is expected to show a masking effect on the taste of FLCZ. However, Euclidean distance may not correlate with the actual bitterness score, and further study is warranted to examine human gustatory sensation.

Conclusions

As a preliminarily experiment for hospital preparation of ODTs, we attempted to prepare ODTs capable of rapid disintegration. The results of this study suggested that ODTs with quick disintegration ability can be prepared at a hospital pharmacy without the need for any manufacturing equipment such as a tableting machine.

Conflict of interest

The authors declare no conflicts of interest.

References

1）H. Seager: Drug-delivery products and the Zydis fast-dissolving dosage form, J. Pharm. Pharmcol., 50, 375-382, 1998.
2）N. Koh, S. Sakamoto, F. Chino: Improvement in medication compliance and glycemic control with voglibose oral disintegrating tablet, Tohoku J. Exp.

Med., 216, 249-257, 2008.
3）Y. Bi, Y. Yonezawa, H. Sunada: Rapidly disintegrating tablets prepared by the wet compression method: mechanism and optimization, J. Pharm. Sci., 88, 1004-1010, 1999.
4）M. Sugimoto, K. Matsubara, Y. Koida, M. Kobayashi: The preparation of rapidly disintegrating tablets in the mouth, Pharm. Dev. Technol., 487-493, 2001.
5）K. Mimura, K. Kanada, S. Uchida, M. Yamada, N. Namiki, Formulation study for orally disintegrating tablet using partly pregelatinized starch binder, Chem. Pharm. Bull., 59, 959-964, 2011.
6）S. Sano, Y. Iwao, S. Noguchi, S. Kimura, S. Itai: Design and evaluation of microwave-treated orally disintegrating tablets containing polymeric disintegrant and mannitol, Int. J. Pharm., 448, 132-141, 2013.
7）E. Katsuno, Y. Takeuchi, K. Tahara, H. Takeuchi: Preparation of co-ground mixture of erythritol and micronized crospovidone using a ball mill for orally disintegrating tablets, J. Soc. Powder Technol. Japan., 51, 16-24, 2014.
8）K. Sumiya, Y. Baba, S. Inomata, Y. Toyooka, Y. Kohda: Preparation and clinical evaluation of orally-disintegrating clonidine hydrochloride tablets for preanesthetic medication, Yakugaku Zasshi., 120, 652-656, 2000.
9）M. Homma, K. Sumiya, Y. Kambayashi, S. Inomata, Y. Kohda: Assessment of clonidine orally disintegrating tablet for pre-anesthetic medication in pediatric surgery, Biol. Pharm. Bull., 29, 321-323,2006.
10）HL. Ohrem, E. Schornick, A. Kalivoda, R. Ognibene: Why is mannitol becoming more and more popular as a pharmaceutical excipient in solid dosage forms? Pharm. Dev. Technol., 19. 257-262. 2014.
11）A.K. Dash, W.F. Elmquist: Fluconazole, Analytical Profiles of Drug Substances and Excipients, Brittain, Harry ed., Vol. 27, Academic Press, San Diego CA, pp 67-113, 2001.
12）Y. Bi, H. Sunada, Y. Yonezawa, K. Danjo, A. Otsuka, K. Iida: Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity, Chem. Pharm. Bull., 44, 2121-2127, 1996.
13）S. Chono, M. Matsui, K. Nakamura: Comparison of physical qualities of branded and generic lansoprazole orally disintegrating tablets, Pharmaceutical and Medical Device Regulatory Science, 47, 760-764, 2016.
14）M. Matsumoto, K. Arai, A. Fujita, M. Tsuji, S. Hayakawa, K. Sawakami, K. Sawakami, S. Shida, Y. Nohara, K. Sumiya, K. Murata, Y. Takeuchi, H. Takeuchi, R. Murata: Characterization of orally disintegrating films containing fluconazole, J. Drug Interact. Res., 43, 53-59, 2019.
15）T. Haraguchi, M. Yoshida, T. Uchida: Evaluation of ebastine-loaded orally disintegrating tablets using new apparatus of detecting disintegration time and e-tongue system, J. Drug Del. Sci. Tech., 24, 684-688, 2014.
16）M. Ito, K. Ikehama, K. Yoshida, T. Haraguchi, M. Yoshida, K. Wada, T. Uchida: Bitterness prediction of H1-antihistamines and prediction of masking effects of artificial sweeteners using an electronic tongue, Int. J. Pharm., 441, 121-127, 2013.