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Characterization of Orally Disintegrating Films Containing Fluconazole

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Patients with decreased swallowing function, such as children and the elderly, find it difficu lt to take tablets and capsules, resulting in reduced compliance. An orally disintegrating films (ODFs) are expected to be an excellent oral dosage form for such patients because it rapidly disintegrates in the oral cavity and can be taken without or with a small amount of water. In this study, ODF loaded with fluconazole (FLCZ) a synthetic antifungal agent was prepared using hydroxypropyl cellulose (HPC) or hydroxypropyl methyl cellulose (HPMC) as the film base. The ODFs were prepared using a flat-bottom polypropylene weighing boat as the mold. The formulation characteristics were evaluated with respect to their disintegrating, dissolving, mechanical, and morphological properties. And we compared the changes in their physical properties caused by the loaded with FLCZ. Therefore, we suggested that is effective to use HPC, prepared using a weighing boat, as a base for an FLCZ-loaded film.

Key Words: fluconazole, orally disintegrating film, hydroxypropyl cellulo se, hydroxypropyl methyl cellulose

Introduction

Oral dosage is the most common form of drug administration; however, patients with decreased swallowing function, such as children and the elderly, find it difficult to take tablets and capsules, leading to reduced compliance. Drug-bearing formulations that rapidly disintegrate in the oral cavity and can be taken without water or with a small amount of water help such patients and improve medication compliance[1,2]. Orally disintegrating films (ODFs) are expected to an excellent oral dosage form because they rapidly disintegrate in the oral cavity, and are durable and portable owing to their thin, flexible form[3].

Hydroxypropyl cellulose (HPC) and hydroxypropyl methyl cellulose (HPMC) are water-soluble polymers used as a film base. ODFs with various drugs have been prepared and their formulation properties and usefulness have been evaluated[3-7]. ODFs containing different drugs in the same film base have different formulation properties[3]. In addition, even if the film base is different in the same drug, the formulation properties are different, so it is important to formulation design for preparing a formulation with excellent disintegration characteristics and strength.

Fluconazole (FLCZ) is a synthetic antifungal agent belonging to the group of triazoles[8]. FLCZ is available in various dosages forms in market like

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capsules, powder for oral suspension and others. And there are reports of mucoadhesive buccal films [9,10], vaginal films [11].

In this study, orally disintegrating films were prepared using HPC or HPMC as the film base, and we compared the changes in their physical properties caused by the loaded with FLCZ. The disintegration time, tensile strength, elongation, and bending number of times were measured. The formulation characteristics were evaluated with respect to whether films were loaded with FLCZ. The release of FLCZ from the loaded films was confirmed, and their morphology was observed using a scanning electron microscope.

Materials and Methods

Materials

Hydroxypropyl cellulose (HPC) was obtained for SL grade of NISSO HPC from Nippon Soda (Tokyo, Japan). Hydroxypropyl methylcellulose (HPMC) was procured from Shin-Etsu Chemical (Tokyo, Japan). FLCZ was obtained from LKT. Labs. (St. Paul, MN). Diflucan® capsules 50 mg were acquired from Pfizer (Tokyo, Japan).

Methods

1. Film preparation

FLCZ was dissolved in ethanol. HPC was dissolved in ethanol and then mixed with an FLCZ solution for HPC film preparation. For the HPMC film preparation, HPMC was suspended in ethanol and mixed with FLCZ, then diluted with a half volume of water (containing an appropriate amount of glycerol dissolved). To prepare the film, FLCZ containing the dispersion was transferred to a flat-bottom polypropylene weighing boat (20 × 20 × 15 mm^3). The weighing boats were dried at room temperature for 24 h. The film formulations are shown in Table 1.

Table 1. Film formulations

	Formulation code			
Ingredient (mg/film)	A	B	C	D
FLCZ	-	10	-	10
HPC	50	40	-	-
HPMC	-	-	45	36
Glycerol	-	-	5	4
Total	50	50	50	50

2. Evaluation film thickness

The thickness of each film formulation was measured using a micrometer (Mitutoyo, Tokyo, Japan). The thickness of each film was calculated as the mean of the four corners and the center.

3. FLCZ content measurement

FLCZ was dissolved in water from the film by sonication at room temperature. The FLCZ concentration in the extract was evaluated by HPLC. Reversed-phase chromatography was done using a LaChrom Elite System (Hitachi, Tokyo, Japan). HPLC system consisting of a L-2130 pump, a L-2300 column oven, a D-2500 integrator, a L-2400 UV-VIS detector. The HPLC analysis was performed on a 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); flow rate was 1.1 mL/min; and detection wavelength was 260 nm. A sample of 20 μL was injected on column using Chromaster 5280 autosampler.

4. Evaluation of disintegration time

Disintegration time was measured using the Petri dish method described by Takeuchi et al [12]. The time taken by a film floating on water (50 mL) in a Petri dish (100 mm diameter) to completely disintegrate was recorded. In addition, for objective evaluation, disintegration time was measured using a device developed for the oral disintegrating tablet (Tricorptester®, Okada Seiko, Tokyo, Japan). Measurement method (Tricorptester

method) of the disintegration test using the device was developed by Takeuchi et al [13]. They designed an exclusive fixture for ODFs, made an opening in the center of the fixture. A set of fixtures, with which a sample film is fixed, was placed on the stage. An artificial saliva solution, composed of 1.44 g/L NaCl, 1.47 g/L KCl and 0.3% polysorbate 80, was used as the test medium. The medium was kept at 37°C in an incubator and dropped on a film with a flow pump (dropping speed, 6 mL/min; dropping height, 8 cm). The disintegration time, defined as the time until a film tore and the test medium passed through an opening of the fixture, was automatically recorded using an optical passage sensor.

5. Evaluation of tensile strength

Mechanical properties were measured using a creep meter (RE-3305S, Yamaden, Tokyo, Japan). The films were cut into 5 × 30 mm^2 pieces. The films were fixed with two grips, which pulled at a constant rate and stretched the film until breakage occurred. A stress–strain curve was created using these results. The tensile strength and elongation at break of the films were calculated from the stress–strain curve using the following formulas:

Tensile strength (MPa) = fracture force (N) / cross section area (mm^2)

Elongation at break (%) = increase in length (mm) / original length (mm) × 100

6. Evaluation of film folding endurance

Folding endurance was measured using a bending tester (TCDM111LH, Yuasa, Okayama, Japan). The films were cut into 20 × 30 mm^2 pieces. The films were repeatedly folded at the same place, at a bending angle of 135 ° and testing speed of 90 rpm. The total number of times the films was folded before the films cracked was measured as the folding endurance value.

7. Evaluation of dissolution tests

Drug dissolution tests were performed using a dissolution tester (NTR-6200AC, Toyama Sangyo, Osaka, Japan). The tests were performed in 900 mL of water at 37.0°C, with a paddle stirring speed of 50 r.p.m. Without using a sinker, the film was floated on the medium and tested. At time intervals of 1, 3, 5, 10, 20, and 30 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 determined using HPLC. The analysis conditions of HPLC for FLCZ were as described above.

8. Morphological observations

The surface aspects (top and bottom) of an FLCZ-loaded film were observed using a scanning electron microscope (SEM) (JSM-6010LA; JEOL, Tokyo, Japan) operated at an acceleration voltage of 10 kV.

9. Statistical Analysis

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

Results

The results of the measurements of film thickness are summarized in Fig 1. In the HPC film, thickness decreased with FLCZ loading, whereas in the HPMC film, the thickness increased with FLCZ loading.

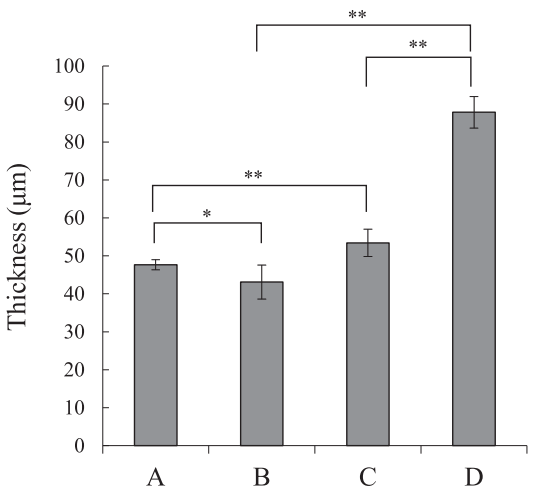

Fig 1. Thickness of film formulation

Film A: HPC film unloaded; Film B: HPC film loaded with FLCZ; Film C: HPMC film unloaded; and Film D: HPMC film loaded with FLCZ. Values are presented as mean ± S.D. (n = 14). * $p<0.005$, ** $p<0.01$.

The results of content measurement are presented in Table 2. The FLCZ content in the formulations was approximately 92%, and there was no statistically significant difference ($P > 0.05$) in FLCZ content between the formulations.

Table 2. FLCZ content in the films

Formulation Code	Mean (%)	S.D. (%)
B	92.33	1.28
D	91.59	5.42

Film B: HPC film loaded with FLCZ, Film D: HPMC film loaded with FLCZ ($n = 3$)

The results of the disintegration test using the Petri dish method are shown in Fig 2 (a) and those obtained using the Tricorptester method are shown in Fig 2 (b). For HPC-based films, loading with FLCZ reduced the disintegration time, whereas for HPMC-based films, loading with FLCZ increased the disintegration time. For films loaded with FLCZ, the disintegration time of those prepared using HPC was shorter than those prepared using HPMC.

The results of the measurements of tensile strength and elongation are shown in Fig 3. In HPC-based films, no significant difference was observed in tensile strength, but elongation increased with the addition of FLCZ. In HPMC-based films, no significant difference was observed in tensile strength or elongation owing to the addition of FLCZ. HPC-based films had weaker tensile strength than HPMC-based films; however, the addition of FLCZ increased the elongation at break of HPC-based films, resulting in greater elongation than that noted in HPMC-based films.

The results of the folding endurance test are shown in Fig 4. In the film using HPC as a base, the number of folds formed before breaking was increased by the addition of FLCZ; however, in HPMC-based, there was no significant difference caused by the addition of FLCZ.

The drug dissolution profiles of FLCZ-containing formulations are presented in Fig 5. At 3 min after the start of the test, film B released 74.0% of the drug load and film D released 42.8%. Films B and D released 80% of the drug within 5 min. There was no statistically significant difference between the film formulations; however, significant differences were found in the dissolution rates of the two film formulations compared with the capsule formulations.

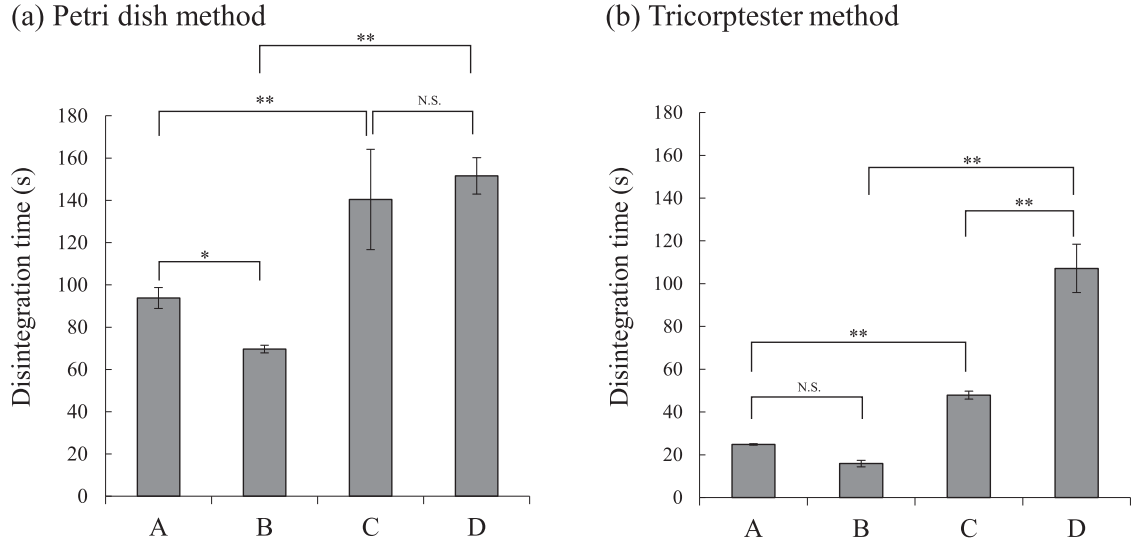

Fig 2. Evaluation of disintegration

Disintegration time was measured using the Petri dish method and Tricorptester method. (a) Petri dish method (n = 5), (b) Tricorptester method (n = 3). Film A: HPC film unloaded; Film B: HPC film loaded with FLCZ; Film C: HPMC film unloaded; and Film D: HPMC film loaded with FLCZ. Values are presented as mean ± S.D. *$P < 0.05$, **$P < 0.01$.

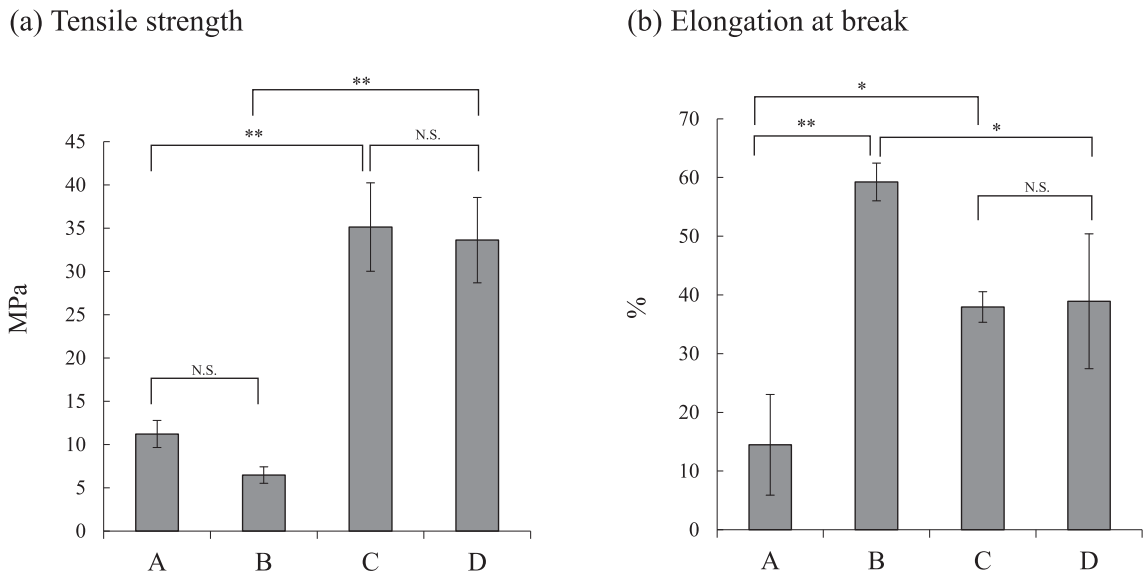

Fig 3. Effect of FLCZ in film on mechanical properties

Tensile strength and elongation at break were measured as mechanical properties using a creep meter. (a) Tensile strength (b) Elongation at break. Film A: HPC film unloaded; Film B: HPC film loaded with FLCZ; Film C: HPMC film unloaded; and Film D: HPMC film loaded with FLCZ. Values are presented as mean ± S.D. (n = 3). **P* < 0.05, ***P* < 0.01.

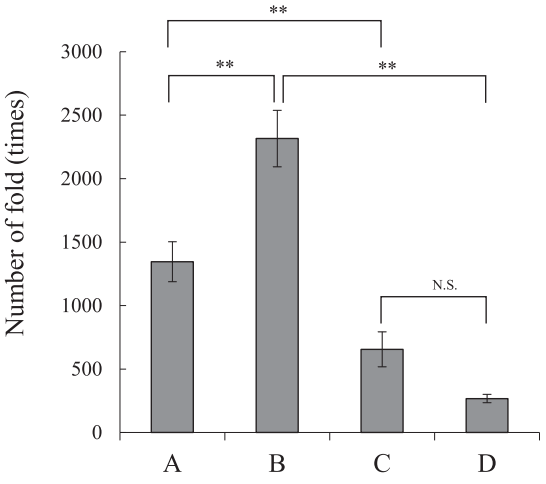

Fig 4. Effect of FLCZ in film on folding endurance

Folding endurance was measured with a bending meter. Film A: HPC film unloaded; Film B: HPC film loaded with FLCZ; Film C: HPMC film unloaded; and Film D: HPMC film loaded with FLCZ. Values are presented as mean ± S.D. (n = 3). **P* < 0.05, ***P* < 0.01.

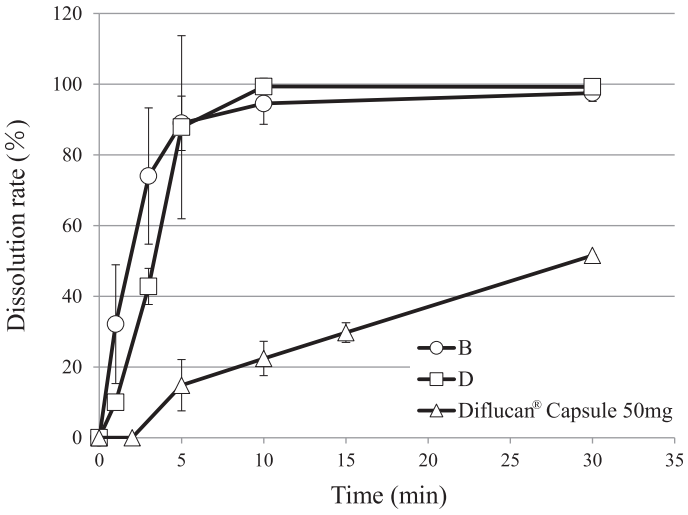

Fig 5. Dissolution profile of film loaded with FLCZ

Film B: HPC film loaded with FLCZ and Film D: HPMC film loaded FLCZ. Control experiment on dissolution rate was performed using Diflucan® capsule (50 mg). Values are presented as mean ± S.D. (n = 3).

An SEM image is shown in Fig 6. This image shows that both films B and D had smooth top surfaces. The bottom of the film was affected by the shape of the mold surface, and it was confirmed that the surface had several irregularities.

Discussion and Conclusions

While developing film preparation method, preparation at an in-hospital pharmacy without an applicator was considered. In the casting method, the preparation solution is uniformly applied on a base film plate using an applicator, dried, and cut to form a film. In this work, using a polypropylene weighing boat as a mold, the film was formed on a weighing boat to shorten the cutting process.

To improve ODFs, they should be designed to rapidly disintegrate. Although the disintegration

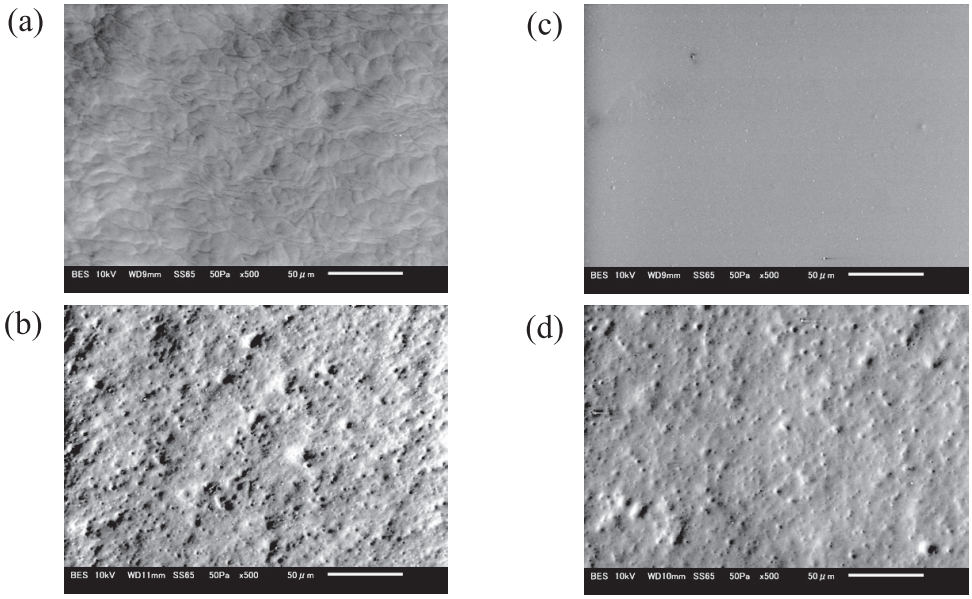

Fig 6. Scanning electron microscope observation of films

(a) Top of film B, (b) Bottom of film B, (c) Top of film D, and (d) Bottom of film D. Film B: HPC film loaded with FLCZ and Film D: HPMC film loaded with FLCZ.

time is correlated with film thickness, with the addition of FLCZ, the thickness of the HPC decreased and disintegration time reduced. The influence of FLCZ loading on film thickness is considered to be owing to the wettability of the weighing boat when spreading the film preparation, and in HPC, the wettability is improved by FLCZ loading.

In addition to rapid disintegration, mechanical strength is also required. Tensile strength is one of the indicators of the mechanical strength of a film[14], and elongation and folding endurance are used to evaluate the properties of film deformation, mechanical strength, and flexibility. It was evaluated using a tensile test and a folding endurance test to determine whether the film can withstand the stress received when it is removed from the mold or during storage. Although the tensile strength of the HPC film decreased with the addition of FLCZ, an increase in elongation and the number of times of refraction resistance were confirmed. It was also confirmed that the HPC film was more flexible and easy to handle than the HPMC film; however, its tensile strength was inferior to that of HPMC.

The dissolution test indicated that the film base did not significantly affect the release of FLCZ. The film formulation was confirmed to exhibit faster dissolution than Diflucan® capsules. Compared with HPMC, HPC was evaluated to be superior in disintegration and dissolution because it exhibited a higher dissolution rate from 3 min after the start of the test.

The results of tests for the disintegrating, mechanical, dissolving, and morphological properties suggested that is effective to use HPC as a base for the FLCZ-loaded film prepared using a weighing boat.

ODF that rapidly disintegrates in the oral cavity and can be taken without water or with a small amount of water helps patients with decreased swallowing function, such as children and the elderly, and improve medication compliance. Moreover, these films have high durability and portability owing to their thin, flexible form. It is expected that these films will be widely used as a dosage form depending on patient's condition and taste preference.

Conflict of interest

The authors declare no conflicts of interest.

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