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Evaluating the Effects of Crystallinity on Drug Release Behaviour in Itraconazole- or Miconazole-Loaded PLGA Microparticles Prepared Using a Co-Grinding Method

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Abstract

This study aimed to prepare and characterize itraconazole (ITCZ)- or miconazole (MCZ)-loaded poly (lactide-*co*-glycolide) (PLGA) microparticles (MP) using a co-grinding method with ball milling, which is a solvent-free and convenient procedure. PLGA MP was prepared by grinding for 60 min, and the fixed theoretical drug loading was set at 9.1% and 16.7% for both drugs. The obtained loading efficiency for both drugs was estimated to be approximately 100%. The average diameters of the drug-loaded PLGA MP were approximately 20 - 35 μm. Powder X-ray diffraction (PXRD) or differential scanning calorimetry (DSC) confirmed amorphization of ITCZ and MCZ in ITCZ- or MCZ-loaded PLGA MP in all formulations. The drug release percentage from 9.1%-loaded ITCZ-PLGA7505 MP at 24 h was almost 50%, which was higher than that of ITCZ powder. The drug release percentage from MCZ-loaded PLGA7505 MP at 4 h was over 80%, which was higher than that of MCZ powder. This enhancement of release rate is caused by the amorphization of ITCZ or MCZ in the PLGA matrix. MCZ-loaded PLGA7510 MP showed a sustained release profile up to 24 h, suggesting that MCZ exists in an amorphous form in the PLGA matrix; however, the release rate declined owing to the large molecular weight of PLGA. Therefore, the release enhancement of antifungal drugs loaded on PLGA MP could be achieved by their amorphization using a co-grinding method with ball milling.

Keywords

Co-Grinding Method, Ball Milling, Poly (Lactide-*co*-Glycolide),

Itraconazole, Miconazole, Amorphization

1. Introduction

Enhancing or controlling the release rate of poorly soluble drugs, such as antifungal drugs, is essential in the design of oral dosage forms or injection formulations because these drugs are extremely lipophilic and have a low solubility. Several approaches have been devised to increase the release rate of poorly soluble drugs in various oral dosage formulations, such as complexation with cyclodextrins [1], solid dispersion [2], gel-based systems [3], eutectic mixtures [4], and the preparation of co-crystals [5]. In contrast, the injection of antifungal drug delivery systems has been performed using poly (lactide-*co*-glycolide) (PLGA) [6] or poly(lactide-*co*-glycolide)-block-poly(ethylene glycol) (PLGA-PEG) nanoparticle conjugates [7] to increase the antifungal drug uptake to the target cell. However, since PLGA is a hydrophobic polymer that is non-water-soluble, an organic solvent might be required in the preparation of a microparticle delivery system using PLGA. In this case, when scaled up to the production level, the construction of a recovery system for organic solvents in the subsequent preparation process is essential for preventing environmental pollution. The preparation of drug-loaded PLGA microparticle using the hot-melt extrusion (HME) method has been used for injectable or depo formulations to achieve sustained drug delivery without the use of organic solvents [8] [9] [10] [11] [12]. Although this preparation method seems to be advantageous since it does not require organic solvents, it requires many preparative processes, and the optimization of process parameters is essential [13]. Moreover, the stability of the drug against heat during the manufacturing process must be considered [14] [15] [16]. In addition, the typical HME method is not suitable for the preparation of granule-sized products under 150 μm as the criteria of particle size suitable for suspension injection, as written in the Japanese pharmacopoeia 18th. A recent study loaded PLGA microspheres (MS) with a water-soluble drug using a solvent-free ball mill method, after which they evaluated the loading efficiency and drug release profile [17]. During the ball milling process, exothermic heat occurs owing to the collision between balls and samples, which allows for the drug to be incorporated into the PLGA matrix through the rubber-like state of PLGA. However, preparation and evaluation of poorly soluble drugs loaded PLGA MS using a ball mill method have not been reported.

Itraconazole (ITCZ) and Miconazole (MCZ) are poorly soluble antifungal drugs with an aqueous solubility of <0.1 μg/mL and <1 μg/mL, respectively [18] [19]. Many strategies have been proposed to increase the release rates and bioavailability of these antifungal drugs [6] [20] [21] [22] [23] [24]. In our previous study [25], for injection delivery, we prepared PLGA MS loaded with ITCZ or MCZ at different evaporation temperatures (25˚C or 40˚C) using an oil-in-water emulsion solvent evaporation method to evaluate the initial burst release of

drugs. The obtained PLGA MS had a diameter of approximately 20 μm and could control the release rate of lipophilic antifungal drugs to some extent via its self-healing effect. Nevertheless, this method required the use of dichloromethane, an organic solvent, which needed to be evaporated. Therefore, using organic solvents in the preparation process seems to be disadvantageous, and this issue should be addressed when developing drug delivery systems using PLGA.

In the present study, we developed a method to prepare ITCZ- or MCZ-loaded PLGA microparticles (MP) within 1.5 h using a co-grinding method by ball milling without the addition of solvents, including organic solvents or water, and subsequently characterized the drug content, loading efficiency, particle size, and morphology of PLGA MP. The theoretical drug content was fixed at 9.1% or 16.7%, and the diameters of the obtained PLGA MP were 20 - 30 μm, which is almost the same size as that of common subcutaneous injections. The amorphization of ITCZ or MCZ in PLGA MP was evaluated through powder X-ray diffraction (PXRD) or differential scanning calorimetry (DSC), and the surface morphology of PLGA MP was examined through scanning electron microscopy (SEM). Moreover, the effect of the crystallinity of ITCZ or MCZ on drug release characteristics in ITCZ- or MCZ-loaded PLGA MP was evaluated through *in vitro* drug-release studies.

2. Material and Methods

2.1. Materials

ITCZ and MCZ were purchased from FUJIFILM Wako Pure Chemical Corporation (Miyazaki, Japan) and Sigma-Aldrich (St. Louis, MO, USA), respectively. PLGA copolymer (75:25; PLGA 7505 and 7510; average molecular weights 5000 and 10,000, respectively; FUJIFILM Wako Pure Chemical Corporation) was used as the MP substrate. Tween 80 (Nacalai Tesque Ltd., Kyoto, Japan) was used as a dispersant in the dissolution test for the prepared PLGA MP. Acetonitrile was purchased from FUJIFILM Wako Pure Chemical Corporation and dimethyl sulfoxide (DMSO) from Nacalai Tesque Ltd. All other reagents were of special reagent grade.

2.2. Preparation of ITCZ- or MCZ-PLGA MP Using Co-Grinding Method

ICTZ or MCZ powder (200 mg or 400 mg) and 2000 mg of PLGA (PLGA7505 or PLGA7510) were placed into a glass sample vessel and mixed for 5 min to prepare the physical mixture in advance. The physical mixture was grinded through ball milling (βmill RM-201, Mitsubishi Chemical Engineering Corp., Japan) with φ20-mm balls for 10 min or 60 min. After co-grinding, the ITCZ or PLGA MP was sieved through a 150-μm sieve. PLGA MP with a theoretical drug content of 9.1% and 16.7% were prepared. The preparative conditions for ITCZ-PLGA MP and MCZ-PLGA MP are summarized in Table 1 (formulation Nos 1 - 6) and Table 2 (formulation Nos 7 - 9), respectively.

Table 1. Characterization of Itraconazole (ITCZ)-loaded poly (lactide-*co*-glycolide) (PLGA) Microparticles (MP) (Experimental drug content, loading efficiency, and particle size).

MP formulation No.	PLGA type	Co-grinding time (min)	TDC (%)	EDC (%)	LE (%)	Particle size (μm)
1	PLGA7505	10	9.1	9.4 ± 0.0	103.2 ± 0.4	32.9 ± 18.5
2	PLGA7510	10	9.1	9.1 ± 0.0	99.7 ± 0.0	30.4 ± 19.1
3	PLGA7505	10	16.7	17.1 ± 0.1	102.2 ± 0.5	32.3 ± 19.6
4	PLGA7510	10	16.7	17.1 ± 0.2	102.3 ± 1.0	29.2 ± 20.4
5	PLGA7505	60	9.1	9.5 ± 0.0	104.2 ± 0.5	20.5 ± 10.1
6	PLGA7505	60	16.7	17.3 ± 0.1	103.8 ± 0.6	25.2 ± 16.6

All data are presented as the mean ± S. D. (n = 3). TDC = Theoretical drug content, EDC = Experimental drug content, LE = Loading efficiency.

Table 2. *In vitro* release kinetic parameters of Itraconazole (ITCZ)-loaded Poly (lactide-*co*-glycolide) (PLGA) Microparticles (MP).

MP formulation No.	First-order	
	R^2	K_1 (h^{-1})
1	0.80	0.03
2	0.80	0.02
3	0.90	0.02
4	0.90	0.01
5	0.69	0.04
6	0.80	0.03
ITCZ	0.96	0.01

R^2 = regression coefficient, K_1 = first-order release rate constant.

2.3. Drug Content and Encapsulation Efficiency of ITCZ- or MCZ-PLGA MP

ITCZ or MCZ-PLGA MP (5 mg) were mixed with 25 mL of dimethyl sulfoxide (DMSO) for the extraction of ITCZ or MCZ, respectively. The solution was homogenized using a sonicator, and the concentration of ITCZ or MCZ was determined using high-performance liquid chromatography (HPLC). The HPLC methods for ITCZ and MCZ was based on the Japanese Pharmacopoeia and a previous report [25]. In brief, 10 μL was injected onto a chromatograph (LC-10AT VP, Shimadzu Corporation, Kyoto, Japan) equipped with a UV detector (SPD-10A VP, Shimadzu Corporation), an integrator (LC solution, Shimadzu Corporation), and reverse-phase column (CAPCELL PAK C18 UG120 S5: 150 mm × 4.6 mm i.d.; Shiseido Co., Ltd., Tokyo, Japan). The column temperature was maintained at 30˚C. The mobile phase composition for ITCZ was acetonitrile:

water (60:40, v/v) and that for MCZ was (A) an aqueous solution of 2.7% (w/v) tetra-*n*-butyl ammonium hydrogen sulfate and (B) acetonitrile, respectively, and the flow rate was 1.0 mL/min. Run time was 10 min for ITCZ and 25 min for MCZ, with a linear gradient elution of: 0 - 4 min (20% B), 4 - 15 min (20% - 50% B), 15 - 16 min (50% - 20% B), and 16 - 25 min (20% B). The ultraviolet detection wavelengths for ITCZ and MCZ were set at 261 and 221 nm, respectively.

The drug content and loading efficiency for prepared MP were defined as follows:

Theoretical drug content (TDC) (%) = drug used for preparation of MP/(drug + polymer used for preparation of MP) × 100

Experimental drug content (EDC) (%) = loaded drug/microparticle (MP) weight

Loading efficiency (LE) (%) = EDC/TDC × 100

2.4. *In Vitro* Drug Release from ITCZ- or MCZ-PLGA MP

In vitro drug-release studies of ITCZ- or MCZ-PLGA MP (1 mg) were performed using the paddle method at 37˚C and 100 rpm using 500 mL phosphate buffer containing 0.2% Tween-80 (pH 7.0). At various time intervals, 1 mL aliquots were withdrawn and replaced with the same volume of fresh medium. The drug concentration was analyzed through HPLC. For the percentage of MCZ released in MCZ-PLGA MP, the drug release amount at 24 h was set as 100%, and the released percentage at every time point was corrected. The first-order rate constant was calculated from the slope of the plots obtained in the *in vitro* drug release study, and the correlation coefficient was determined.

2.5. Particle Size Measurement

The prepared MP were suspended in 0.2% (w/v) Tween-80 solution using a vortex mixer and measured using a Multisizer™ 3 Coulter Counter® (Beckman Coulter, Inc., USA).

2.6. Scanning Electron Microscopy (SEM)

The surface morphology of ITCZ- or MCZ-PLGA MP was examined using SEM images taken with a JEOL JSM-6510 LV Scanning Electron Microscope (JEOL, Tokyo, Japan). Briefly, MP were fixed on a brass stub using double-sided adhesive tape and were made electrically conductive by coating, in a vacuum, with a thin layer of gold. Images of the MP surfaces were taken at an excitation voltage of 10 kV.

2.7. Powder X-Ray Diffraction (PXRD)

The PXRD patterns of ITCZ- or MCZ-PLGA MP and their respective powders were measured using an X'pert Pro diffractometer (PANalytical, Netherlands). The X-ray tube voltage and current were 40 kV and 50 mA, respectively, and the scanning rate was 0.05˚/min over a 2θ range of 3˚ - 40˚.

2.8. Differential Scanning Calorimetry (DSC)

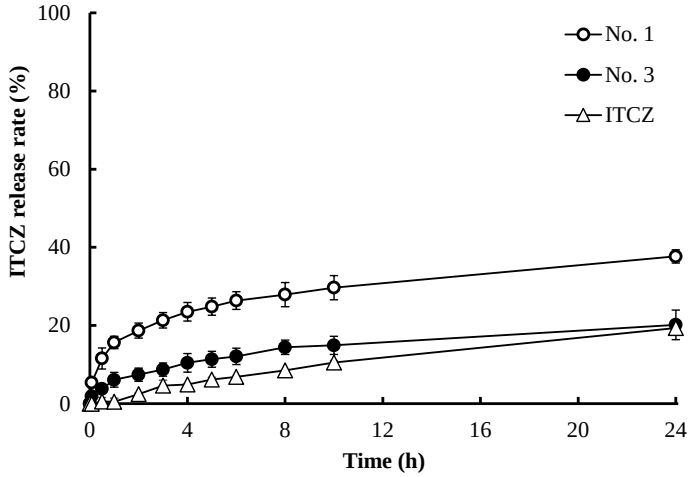
DSC of ITCZ, MCZ powder, PLGA7505, PLGA7510, ITCZ, and MCZ-PLGA MP was performed using a differential scanning calorimeter (DSC6200, Seiko Instruments Inc., Chiba, Japan). The samples were sealed in aluminum hermetic pans, and the temperature range was 20˚C - 100˚C or 200˚C at a rate of 10˚C/min under a purged nitrogen atmosphere.

3. Results and Discussion

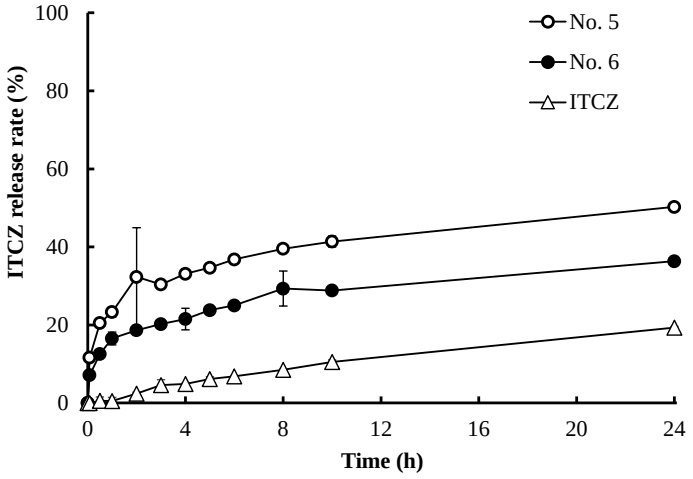
3.1. *In Vitro* Characterization of ITCZ-PLGA MP with Theoretical Drug Content of 9.1% or 16.7%

The preparative conditions and characterization of ITCZ-loaded PLGA MP prepared using a co-grinding method with ball milling for 10 or 60 min are shown in **Table 1** The loading efficiency of six batches of formulations prepared by the co-grinding method was 100% - 104%, which was higher than the 80% - 97% loading efficiency of the formulations prepared using the oil-in-water emulsion solvent evaporation method [25]. In another study using water-soluble drugs [17], the loading efficiency of formulations prepared using a ball milling method was higher than those prepared using a solvent evaporation method. The co-grinding method has a simple preparation process using only the drug and PLGA without the addition of solvents, resulting in almost 100% loading efficacy with little chance of losing the drug in the preparation process. The average diameters of the drug-loaded PLGA MP were in the range of approximately 20 - 30 μm in all batches. The drug release rate from ITCZ-PLGA MP with a theoretical drug content of 9.1% or 16.7% prepared using PLGA7505 through co-grinding for 10 min are shown in **Figure 1(a)**.

The release rates for formulation No. 3 with a theoretical drug content of 16.7% prepared through co-grinding for 10 min were exceedingly small, approximately 20% at 24 h, and similar to that of ITCZ powder. The crystallinity of ITCZ in PLGA MP prepared under this condition was expected to be a mixture of crystalline and amorphous phases, judging from the PXRD results (**Figure 2**). In the following step, to increase the release rate of ITCZ, the co-grinding time was set to 60 min to achieve a completely amorphous state. The release rates for batches (No. 5 and No. 6) prepared using PLGA7505 by co-grinding for 60 min were significantly higher than those of batches prepared by co-grinding for 10 min (**Figure 1(b)**). The crystallinity of ITCZ in PLGA MP prepared by co-grinding for 60 min was expected to be in an amorphous state, based on the PXRD results (**Figure 2**). The DSC curves of each formulation and ITCZ are shown in **Figure 3**. The ITCZ-PLGA MP had thermal behaviour indicating a glass transition at *ca.* 40˚C - 45˚C, attributed to PLGA, and a small endothermic peak at 140˚C - 150˚C, which was considered to be attributable to the presence of ITCZ crystals in some formulations. Therefore, the amorphous state gives rise to an increased release of ITCZ from PLGA MP. The internal wall temperature, measured using a non-contact infrared thermometer, of the ball mill container



(a)



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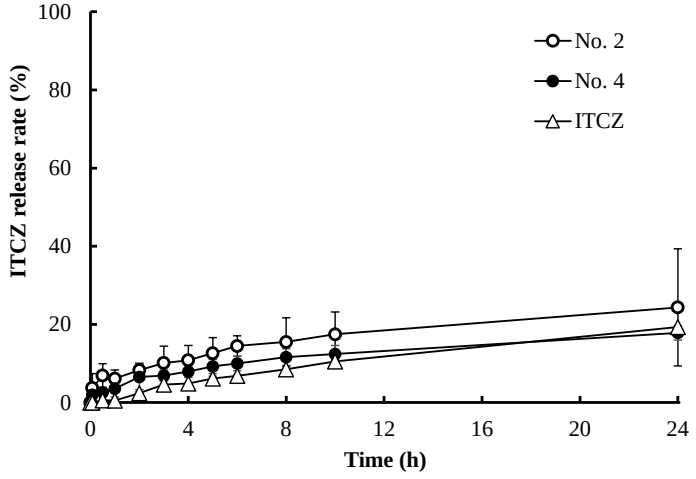


(c)

Figure 1. *In vitro* drug-release profile of Itraconazole (ITCZ) or ITCZ-loaded Poly (lactide-*co*-glycolide) (PLGA) Microparticles (MP) Prepared by Co-grinding for 10 or 60 min. (a)-(c) Formulation results (as listed in **Table 1**) of ITCZ-PLGA MP. Open (○) and closed symbols (●) represent theoretical ITCZ contents of 9.1% and 16.7%, respectively.

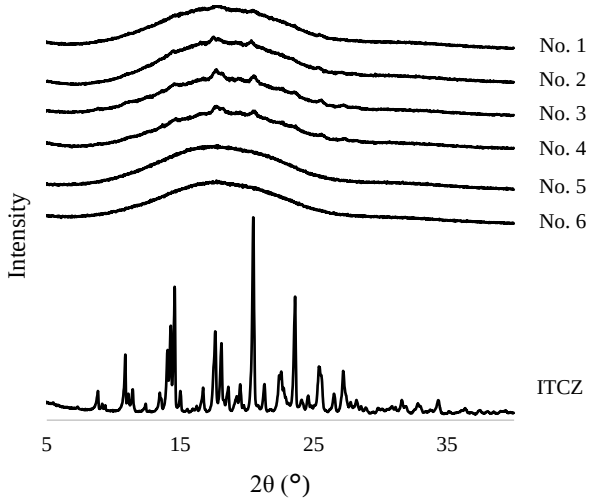


Figure 2. Powder X-ray diffraction (PXRD) patterns of (ITCZ)-loaded poly (lactide-*co*-glycolide) (PLGA) microparticles (MP) and ITCZ.

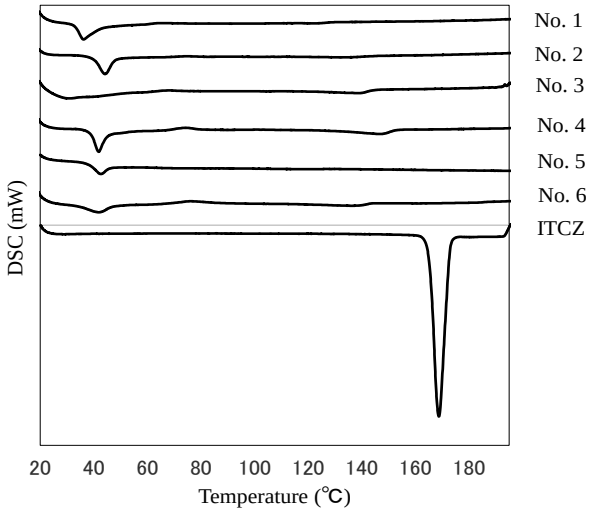
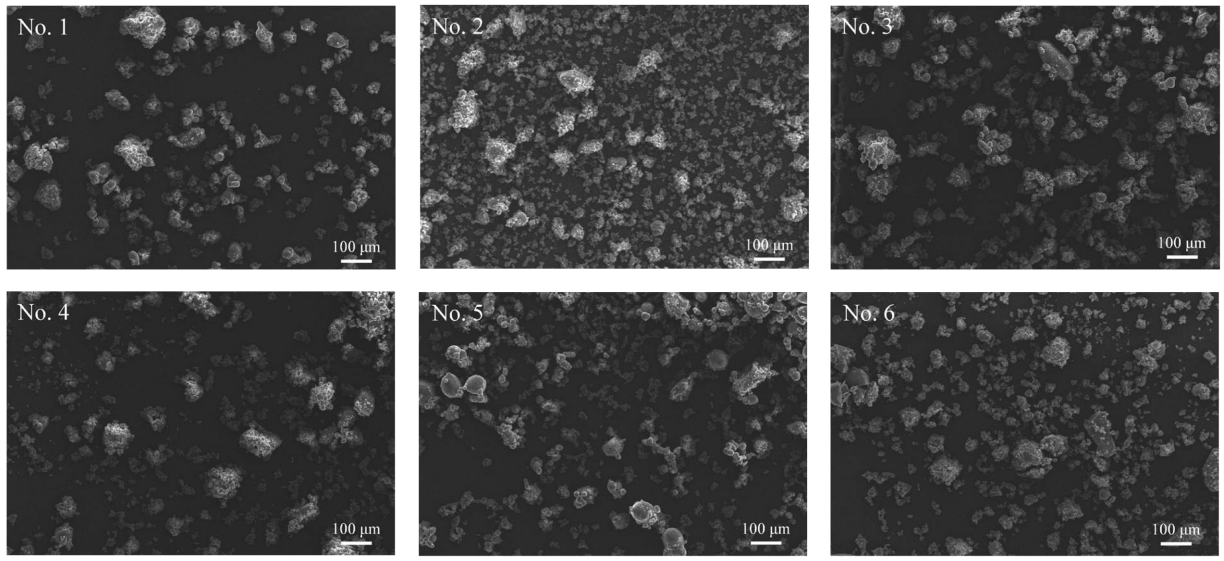


Figure 3. Differential scanning Calorimetry (DSC) curves of (ITCZ)-loaded Poly (lactide-*co*-glycolide) (PLGA) Microparticles (MP) and ITCZ.

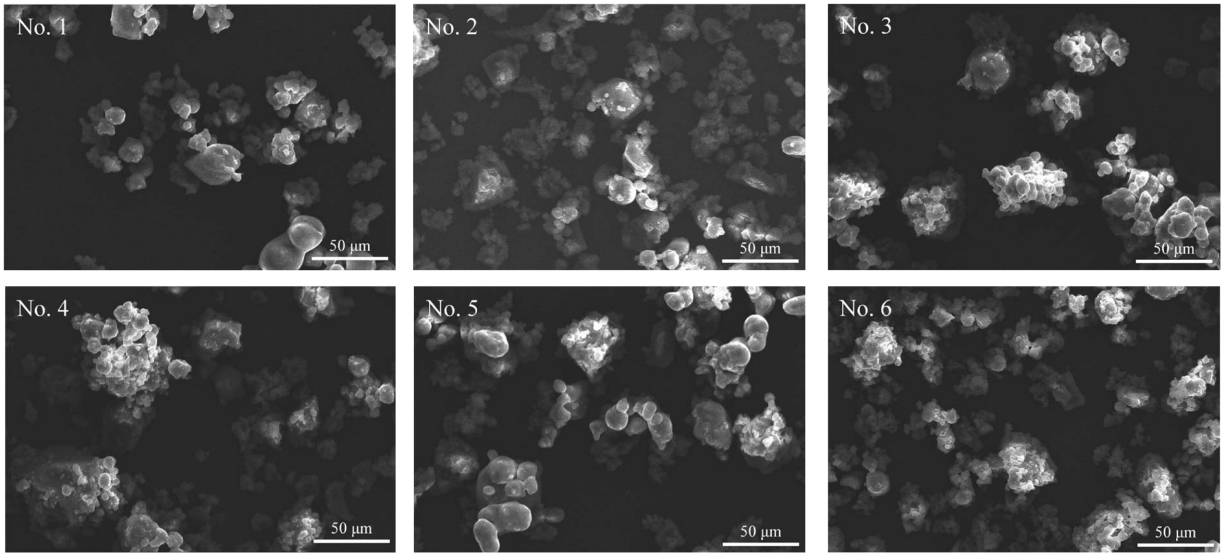
before and after co-grinding was 23˚C and approximately 30˚C, respectively. We considered that PLGA became rubber-like owing to localized heat caused by collisions between balls and samples in the container and that ITCZ was incorporated into the PLGA matrix in an amorphous state. Even in batches processed using different grinding times, the release rate of ITCZ with a theoretical drug content of 16.7% in the PLGA MP was lower than that of ITCZ with a theoretical drug content of 9.1%. This phenomenon might be caused by the saturation of ITCZ solubility in PLGA matrices, and similar release profiles were observed in our previous study [25]. The drug release rates of ITCZ-PLGA MP with a theoretical drug content of 9.1% or 16.7% prepared using PLGA7510 by co-grinding for 10 min are shown in **Figure 1(c)**. The release rates for both batches (No. 2 and No. 4) were exceedingly small, approximately 20% at 24 h, and similar to

that of ITCZ powder. The crystallinity of ITCZ in PLGA7510 MP prepared through co-grinding for 10 min was expected to be a mixture of crystalline and amorphous phases, based on the PXRD results (Figure 2). The kinetic parameters of the formulations were calculated, based on the first-order model, for all formulations and the results are summarized in Table 2. The drug release from PLGA MP appeared to belong to first-order release, based on the correlation coefficient of the regression analysis for the release model.

The SEM results for the batch listed in Table 1 are shown in Figure 4. No major differences were observed regarding the surface morphologies of these batches. Overall, the surface morphology of ITCZ-PLGA MP was rough and the



(a)



(b)

Figure 4. Scanning Electron Microscopy (SEM) Images of Prepared (ITCZ)-loaded Poly (lactide-*co*-glycolide) (PLGA) Microparticles (MP). (a) and (b) SEM images with microscopic magnification of ×100 and ×500, respectively.

particle size distribution was broad. Because the particles obtained using a co-grinding method are formed by collision and grinding, it is difficult to obtain spherical and smooth surfaces and narrow particle size distributions, such as in the oil-in-water emulsion solvent evaporation method [25]. In other studies [17] [26], the particle shapes of samples prepared through ball milling were similar to that of the present study.

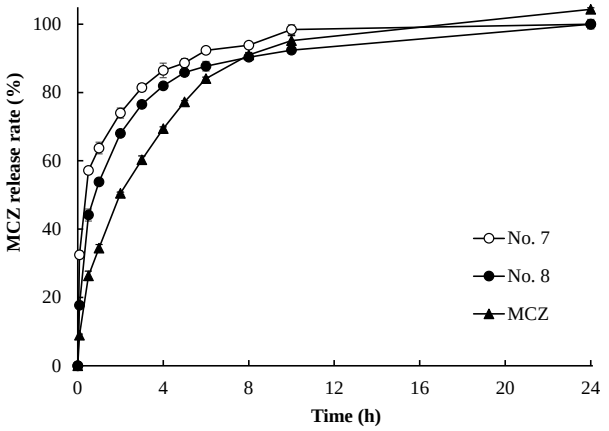
3.2. *In Vitro* Characterization of MCZ-PLGA MP with Theoretical Drug Content of 9.1% or 16.7%

The characterization of MCZ MP prepared using a co-grinding method with ball milling for 60 min is listed in **Table 3**. The loading efficiency was almost 100% in every batch because no solvent was used in the procedure, which resulted in no drug loss in the preparative process. The average diameters of the drug-loaded PLGA MP were in the range of approximately 25 - 35 μm in all batches. The drug release rates of MCZ-PLGA MP with a theoretical drug content of 9.1% or 16.7% are shown in **Figure 5**. The *in vitro* drug release percentage from PLGA7505 MP loaded with 9.1% and 16.7% MCZ almost reached 100% at 4 h, and their release rates were faster than that of MCZ powder (**Figure 5(a)**). This enhancement of release rate is caused by the amorphization of MCZ in the PLGA matrix. The release rate of MCZ-PLGA MP was higher than that of ITCZ-PLGA MP. The aqueous solubility of ITCZ (<0.1 μg/mL) and MCZ (<1 μg/mL) were different, which was similar to the findings of our previous study using the oil-in-water emulsion solvent evaporation method [25]. However, MCZ-loaded PLGA7510 MP (No. 9) loaded with 16.7% MCZ showed a sustained release profile up to 24 h (**Figure 5(b)**), and its release rate was slower than that of MCZ powder. The PXRD results and DSC curves (**Figure 6** and **Figure 7**) suggest that this seems to be due to the molecular weight of PLGA, even though MCZ existed in an almost amorphous state in the PLGA matrix. The kinetic parameters of the formulations were calculated, based on the first-order model, for all formulations and the results are summarized in **Table 4**. The drug release from PLGA MS appeared to belong to first-order release, based on the correlation coefficient of the regression analysis for the release model. The release rate constant of MCZ in PLGA MP was larger than that of ITCZ-PLGA MP.

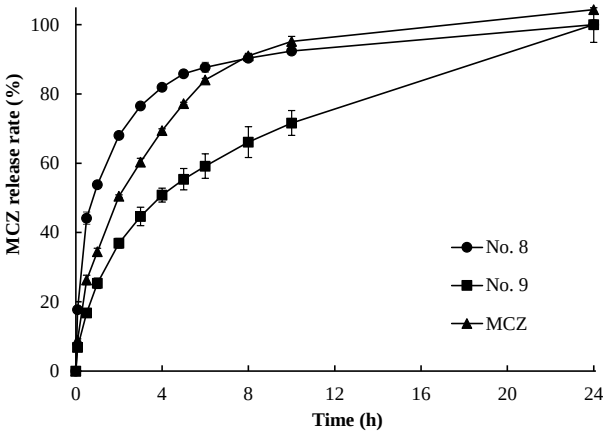
Table 3. Characterization of Miconazole (MCZ)-loaded Poly (lactide-*co*-glycolide) (PLGA) Microparticles (MP) (Experimental drug content, loading efficiency, and particle size).

MP formulation No.	PLGA type	Co-grinding time (min)	TDC (%)	EDC (%)	LE (%)	Particle size (μm)
7	PLGA7505	60	9.1	9.4 ± 0.0	103.6 ± 0.2	24.2 ± 9.5
8	PLGA7505	60	16.7	17.8 ± 0.0	106.5 ± 0.1	27.1 ± 13.9
9	PLGA7510	60	16.7	18.0 ± 0.4	108.1 ± 2.5	33.5 ± 5.8

All data are presented as the mean ± S. D. (n = 3). TDC = Theoretical drug content, EDC = Experimental drug content, LE = Loading efficiency.



(a)



(b)

Figure 5. *In Vitro* drug-release profile of Miconazole (MCZ) or MCZ-loaded Poly (lactide-*co*-glycolide) (PLGA) Microparticles (MP). (a) and (b) Formulation results (as listed in **Table 3**) of MCZ-PLGA MP. Open (○) and closed symbols (●, ▪) represent theoretical MCZ content of 9.1% and 16.7%, respectively.

Table 4. *In vitro* first-order release rates of Miconazole (MCZ)-loaded Poly (lactide-co-glycolide) (PLGA) Microparticles (MP) and MCZ.

MP formulation No.	First-order	
	R^2	K_1 (h^{-1})
7	0.92	0.37
8	0.91	0.25
9	0.96	0.12
MCZ	0.99	0.29

R^2 = regression coefficient, K_1 = first-order release rate constant.

The SEM results for the batch listed in **Table 3** are shown in **Figure 8**. No major differences were observed in the surface morphologies of these batches. The surface morphology of MCZ-PLGA MP was rough and the particle size distribution was broad, similar to that of ITCZ-PLGA MP.

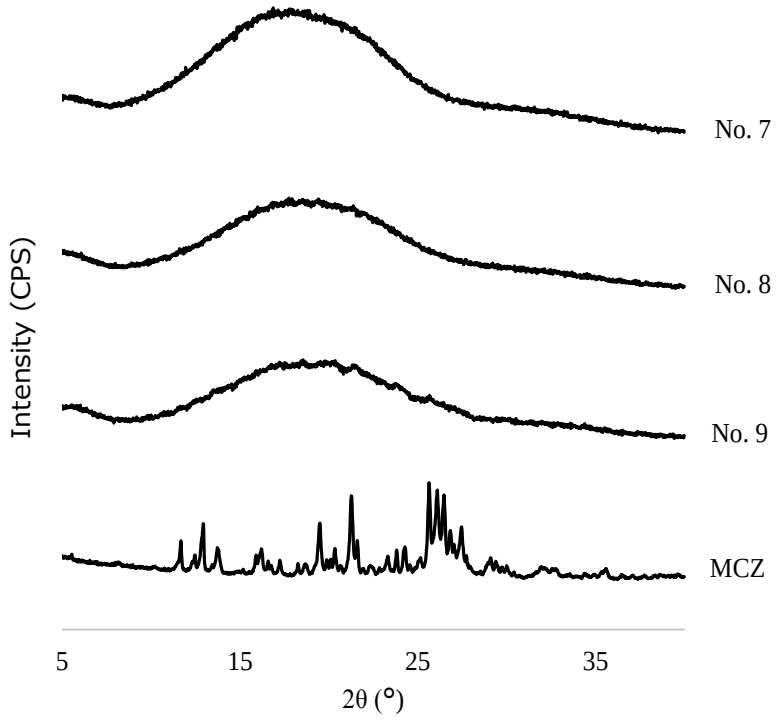


Figure 6. Powder X-ray diffraction (PXRD) Patterns of Miconazole (MCZ)-loaded Poly (lactide-*co*-glycolide) (PLGA) Microparticles (MP) and MCZ.

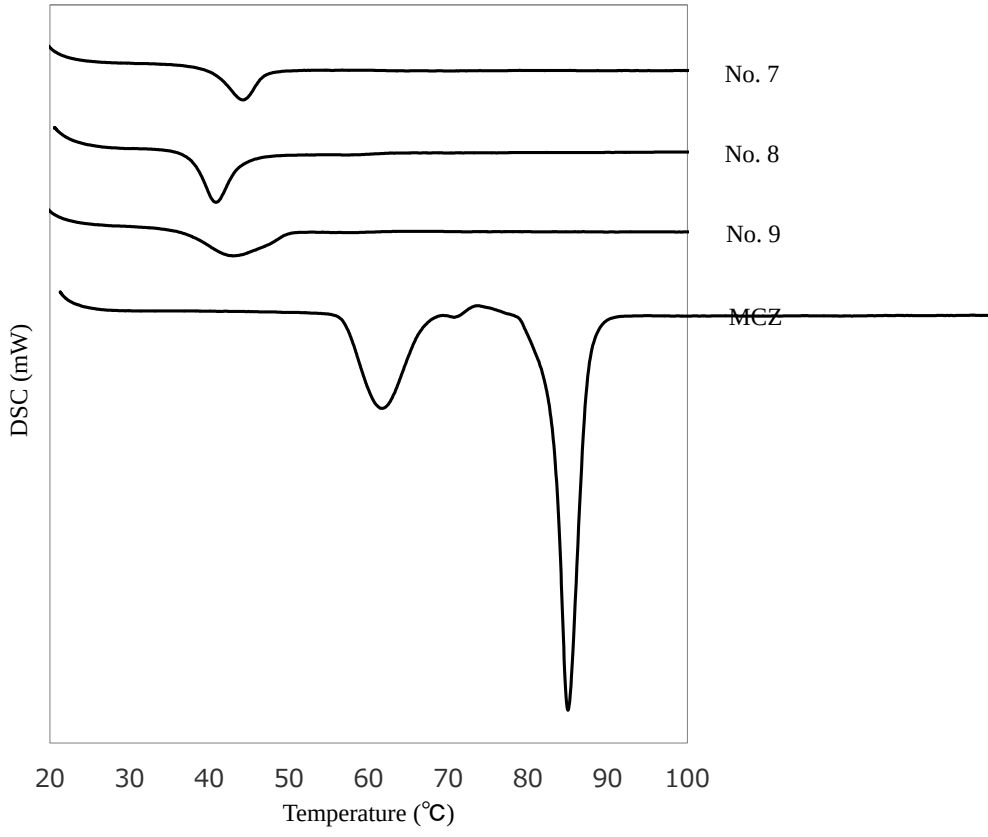


Figure 7. Differential scanning calorimetry (DSC) Curves of Miconazole (MCZ)-loaded Poly (lactide-*co*-glycolide) (PLGA) Microparticles (MP) and MCZ.

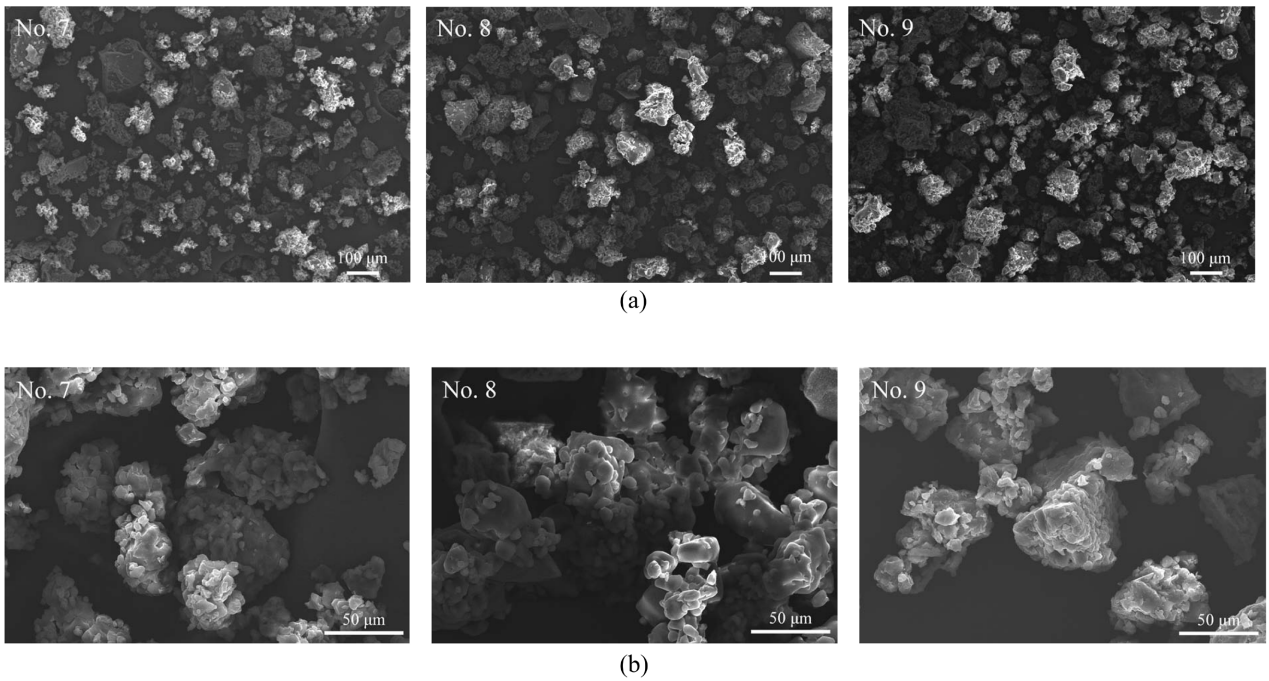


Figure 8. Scanning electron microscopy (SEM) Images of Miconazole (MCZ)-loaded Poly (lactide-*co*-glycolide) (PLGA) Microparticles (MP). (a) and (b) SEM images with microscopic magnification of ×100 and ×500, respectively.

4. Conclusion

In ITCZ- or MCZ-loaded PLGA7505 MP prepared using co-grinding with ball milling for 60 min, the drug release percentage from the drug-loaded PLGA MP was higher than that of the drug powder. This enhancement of release rate is caused by the amorphization of the drug in the PLGA matrix. Although MCZ-PLGA MP using PLGA7510 showed a sustained release profile, this seems to be due to the molecular weight of PLGA, even though MCZ existed in an amorphous state. The release enhancement of antifungal drugs loaded on PLGA MP could be achieved by the amorphization of these drugs using a co-grinding method with ball milling, which is a solvent-free and convenient procedure. In addition, by using PLGA of differing molecular weights, drug release could possibly be controlled. The controlled release of drugs other than MCZ using a co-grinding method should be studied in future.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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