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Oral Absorption Improvement of Poorly Soluble Drug Using Solid Dispersion Technique

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A new triazol antifungal agent, (+)-2-(2,4-difluorophenyl)-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-3-[6-(1*H*-1,2,4-triazol-1-yl)pyridazin-3-ylthio]butan-2-ol (MFB-1041), shows poor oral absorption and is practically insoluble in water (1.2 μg/ml). Solid dispersion systems with an enteric polymer such as hydroxypropylmethylcellulose phthalate (HP-55®) and carboxymethylethylcellulose (CMEC®), and a nonenteric polymer, hydroxypropylmethylcellulose (Metolose®) were evaluated to improve drug absorption and solubility. The oral bioavailabilities of these solid dispersions in beagle dogs were over 6 times higher than that of a suspension system with increasing drug solubility in an alkaline medium. X-Ray powder diffraction measurement of the solid dispersion showed a complete drug phase change from a crystal to an amorphous state. Further, from the results of a stability test, the preparations were stable in a desiccated condition and the absorption profiles also showed no change. From the results, it was suggested that the oral administrative preparation of MFB-1041 having a superior absorption profile and a high stability could be obtained by a drug phase change from a crystal to an amorphous state, especially in the spray-drying method using enteric polymers.

Key words solid dispersion; oral absorption; stability; antifungal drug; enteric polymer

(+)-2-(2,4-Difluorophenyl)-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-3-[6-(1*H*-1,2,4-triazol-1-yl)pyridazin-3-ylthio]butan-2-ol (MFB-1041) is an orally active triazol antifungal agent which may have therapeutic benefits in aspergillus treatment. The compound has low solubility and potentially poor oral absorption characteristics. It is well known that the bioavailability of slightly water-soluble drugs is limited by the dissolution process in the gastrointestinal tract. This is also the case for MFB-1041, which is practically insoluble in water (1.2 μg/ml). To improve the absorption of MFB-1041, various approaches were investigated. In general, several approaches for solubilization are available and include such techniques as surfactant and cosolvent addition,[1] complexation,[2,3] solid state manipulation[4] and prodrug modification. The pharmaceutical application of a solid dispersion system was first demonstrated by Sekiguchi *et al.*[5] They proposed the formulation of a eutectic mixture of a very slightly water-soluble drug with a freely water-soluble and physiologically inert carrier as a novel method for reducing particle sizes. Sugimoto *et al.*[6,7] and Law *et al.*[8] reported that it was possible to enhance the dissolution rate of nifedipine by using this method. However, there are few reports which systematically discuss the characterization of a drug phase change, drug solubility and *in vivo* improved absorption before and after severe storage. In this study, to enhance oral absorption, the solid dispersion technique (spray-drying method) was applied. Further, the physico-chemical characterizations of the obtained solid dispersions and *in vivo* drug absorption experiments before and after storage using beagle dogs were all performed.

Materials and Methods

Materials MFB-1041 was originally synthesized in our laboratory. Hydroxypropylcellulose (HPC-L®) was commercially obtained from Nippon Soda Co., Ltd., Japan. Hydroxypropylmethylcellulose 2910, HPMC (Metolose® 60SH-50) and carboxymethylethylcellulose, CMEC® were obtained from Freund Industry Co., Ltd., Japan. Hydroxypropylmethylcellulose phthalate 200731, HPMCP (HP-55®), was obtained from Shin-Etsu Chemical Industry Co., Ltd., Japan. All the polymers were used as supplied and other reagents were of reagent grade and used without further purifications.

Preparation of Solid Dispersion System A drug-to-polymer ratio (1 : 1—1 : 5) was selected for the preparation of a solid dispersion from the preliminary study. MFB-1041 was dissolved in a mixed solvent consisting of dichloromethane and ethanol (1 : 1). Each polymer was added to the solution and dissolved perfectly. Solid dispersions were prepared by the spray-drying method using a flow-coater (FL-10, Freund, Japan) apparatus. Drug solution was sprayed in a fluidized bed air at the inlet temperature of 90 °C, and the solid dispersion powder was obtained in a yield of 60%.

X-Ray Analysis Powder X-ray diffractometry was carried out with a Geiger Flex RAD-IA (Rigaku Denki Co., Ltd., Japan) under the conditions of CuK_α, 40 kV, 25 mA.

***In Vitro* Dissolution Experiment** A dissolution experiment was carried out by the JP XII paddle method (100 rpm, 37 °C). JP XII disintegration test medium No. 1 and No. 2 (500 ml) were used as the dissolution media, and an appropriate amount of samples, corresponding to 50 mg of drug, were applied. Drug release was measured periodically with a UV spectrophotometer (278 nm) connected with a flow cell system.

***In Vivo* Absorption Experiments** Male Toyo beagle dogs (10—12 kg) were used. Each preparation was administered *per os* with 20 ml of water under a fasted condition at a dose of 10 mg/kg of body weight. Blood sampling was carried out periodically from the brachial veins with a heparinized disposable syringe.

Drug Measurements Drug plasma concentrations were determined by high performance liquid chromatography (HPLC) (655 system, Hitachi, Tokyo, Japan) using a UV detector (278 nm). The system was used in a reversed phase with a Cosmosil® ODS column (4.6 mm i.d. × 150 mm, Nacalai Tesque, Tokyo, Japan). A mixture of water and acetonitrile (1 : 1) was used as the mobile phase at a flow rate of 1.0 ml/min at room temperature. A 0.5 ml sample of acetonitrile containing an internal-standard compound (MFA-1028, a derivative of MFB-1041) was added to each plasma sample (0.5 ml) for deproteinization. The supernatant was filtered through a 0.45 μm pore-size filter (Nihon Millipore Kogyo, Yonezawa, Japan) and was successively injected onto the column.

Analysis of Plasma Data The maximum plasma concentration (C_{max}) and time to reach the C_{max} concentration (T_{max}) were obtained directly from the plasma concentration-time curve. The area under the curve (AUC) of plasma concentration *vs.* time was calculated by the trapezoidal

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rule for the observed values to 8 h. Relative bioavailabilities were calculated from the comparison of the *AUC* for each solid dispersion with that for the drug suspension.

Stability Test Each drug solid dispersion powder was stored at 60 °C for 2 months in a closed glass bottle. At 2 and 4 weeks and at 2 months, the X-ray powder diffractometric and *in vivo* drug absorption experiments were carried out.

Results and Discussion

Characterization of the Solid Dispersion Powder Various polymers were investigated to evaluate the feasibility of improving the drug absorption. For example, the solid dispersions with hydroxypropylcellulose yielded an agglutinated hard mass after spray-drying. In contrast, solid dispersions with Metolose® and enteric polymers such as CMEC® and HP-55® yielded fluffy powder with a particle size of 500—850 μm. Consequently, these three polymers were selected as candidate materials for further experiments. In all cases, as solid dispersions composed of drug : polymer (1 : 1) exhibited partial drug crystallinity, further evaluations were carried out for ones containing polymer at a ratio of over a 3-fold amount. In addition, each solid dispersion powder was sieved to obtain 500—600 μm sized particles and was employed for further experiments.

The qualitative X-ray diffraction patterns of the CMEC® solid dispersion and a physical mixture (drug : CMEC® = 1 : 5) are shown in Fig. 1. Many peaks attributed to crystals of MFB-1041 were observed in the physical mixture, however no diffraction peaks were observed in solid dispersions. These results imply the absence of apparent crystallinity of MFB-1041 in the solid dispersions. Similar results were also observed in the solid dispersions prepared with Metolose® or HP-55®.

***In Vitro* Drug Dissolution** The dissolution profiles of the HP-55®, CMEC® and Metolose® solid dispersions in media at pH 1.2 and 6.8 are shown in Fig. 2. The dissolution of micronized MFB-1041, which exhibited crystallinity in the X-ray diffraction analysis, was also examined as a control. Micronized MFB-1041 showed low dissolved concentrations because of the limited saturated solubilities of MFB-1041, 1.2 and 3.6 μg/ml at pH 6.8 and 1.2, respectively. On the other hand, the drug dissolution from each solid dispersion showed the attainment of supersaturated concentrations at pH 6.8. In the case of the enteric material of HP-55® (1 : 5), the maximum concentration at pH 6.8, which occurred at 5 min, was 12.5 times higher than that of the micronized MFB-1041 powder, which occurred in 240 min. However, the amount of drug dissolved subsequently decreased, indicating the occurrence of recrystallization. For a 1 : 3 solid dispersion of HP-55® a similar result was also observed, but the dissolution rate and peak concentration were both low to some degree. On the other hand, CMEC® did not show a peak concentration and its decline followed by recrystallization. Metolose® solid dispersion, which has a non-pH-dependent dissolution profile, showed the same profile as CMEC® at each pH of 1.2 and 6.8. In addition, as the drug dissolution was governed by the pH profile of native drug, the dissolved drug concentration at pH 1.2 was higher than that occurring at pH 6.8. In contrast, in the pH 1.2 medium, each enteric solid dispersion showed

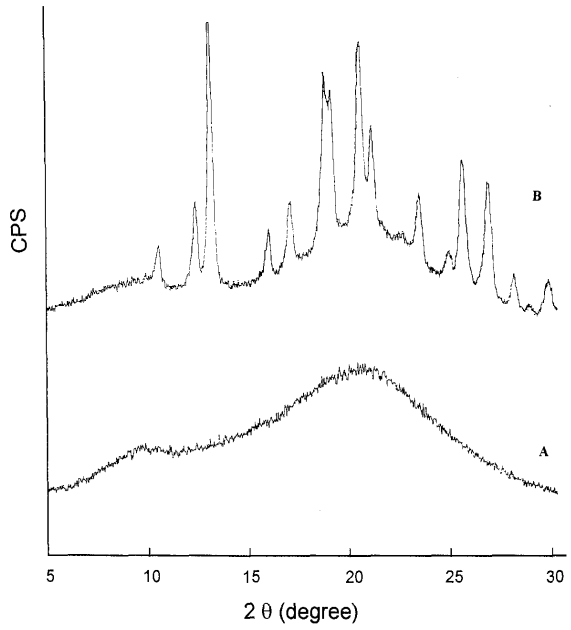

Fig. 1. X-Ray Powder Diffraction Patterns of CMEC® Solid Dispersion (A) and Physical Mixture (B)

Solid dispersion was prepared in the ratio of MFB-1041 : CMEC® = 1 : 5.

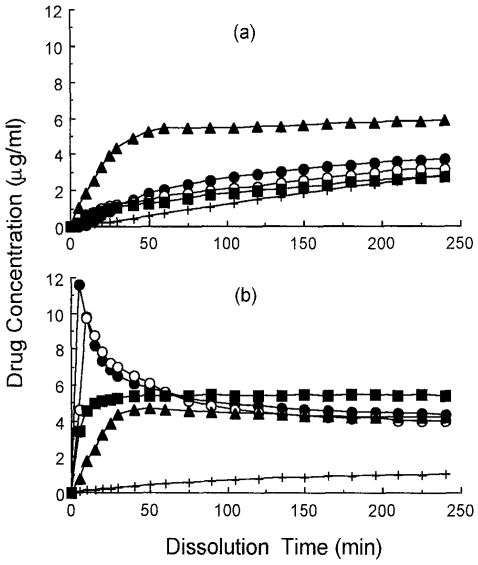

Fig. 2. Comparison of Drug Dissolution Profiles of Solid Dispersions with That of Micronized Drug

(a) pH 1.2; (b) pH 6.8 . +, micronized drug; ●, solid dispersion of HP-55® (MFB-1041 : HP-55® = 1 : 5); ○, solid dispersion of HP-55® (MFB-1041 : HP-55® = 1 : 3); ■, solid dispersion of CMEC® (MFB-1041 : CMEC® = 1 : 5); ▲, solid dispersion of Metolose® (MFB-1041 : Metolose® = 1 : 5).

less drug dissolution than that observed in pH 6.8 medium, but it was larger than that of micronized powder. In an acidic medium, as enteric materials did not dissolve, drug molecules internalized in the polymers could not be released. Drug molecules which existed in the surface or in the neighborhood of the surface of the solid dispersion powder, which possessed an amorphous form, might be extremely dissolved in an exterior medium, compared with micronized powder molecules.

Oral Absorption Studies Micronized MFB-1041 (0.5% MC suspension, 10 mg/10 ml/kg) and the solid dispersions were administered orally to beagle dogs to evaluate

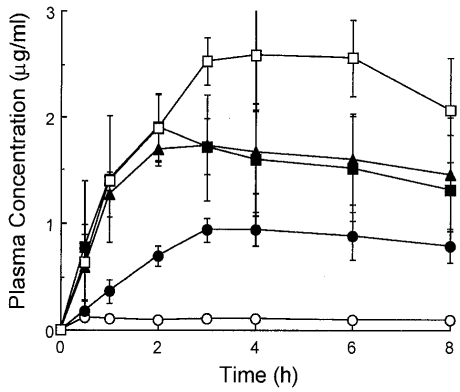

Fig. 3. Plasma Concentration Profiles of MFB-1041 after Oral Administration of Solid Dispersions to Beagle Dogs

○, micronized drug (MC suspension); ●, Metolose® solid dispersion (MFB : Metolose® = 1 : 5); ▲, CMEC® solid dispersion (MFB : CMEC® = 1 : 5); ■, HP-55® solid dispersion (MFB : HP-55® = 1 : 3); □, HP-55® solid dispersion (MFB : HP-55® = 1 : 5). MFB-1041 was administered orally at a dose of 10 mg/kg under a fasted condition. Each point represents the mean ± S.D. of 3 dogs.

Table 1. Pharmacokinetic Parameters of MFB-1041 after Oral Administration to Beagle Dogs

Dosage forms	C_{max} (μg/ml)	T_{max} (h)	AUC (μg/ml h)
Crystal (MC suspension)	—	0.5	1.0
Metolose solid dispersion (1 : 5)	0.95	4	6.0
CMEC solid dispersion (1 : 5)	1.73	3	11.8
HP-55 solid dispersion (1 : 3)	1.90	2	11.8
HP-55 solid dispersion (1 : 5)	2.59	4	16.9

improved absorption. The plasma concentration curves of MFB-1041 after oral administration are shown in Fig. 3. The calculated pharmacokinetic parameters are shown in Table 1. The *AUC* of micronized MFB-1041 (suspension) was small (1.0 μg/ml h) and no obvious T_{max} was observed. On the other hand, each solid dispersion showed high plasma concentration, C_{max}, 0.95, 1.73, 1.90 and 2.59 μg/ml for Metolose®, CMEC®, HP-55® (MFB : HP-55® = 1 : 3) and HP-55® (MFB : HP-55® = 1 : 5), respectively. Further, high *AUC* values were also obtained: 6.0, 11.8, 11.8 and 16.9 μg/ml h, respectively. The oral absorption was better enhanced using enteric materials such as CMEC® and HP-55®, and increased in accordance with the polymer content increase in the case of HP-55® solid dispersion. From the results of *in vitro* dissolution experiments, this phenomenon was supported by the fact that the drug dissolution rate and supersaturated peak concentration of 1 : 5 HP-55® solid dispersion were both higher than those of the 1 : 3 HP-55® solid dispersion. It has frequently been observed that an increase in the amount of drug incorporated results in a reduced dissolution rate. This is normally ascribed to the formation of a coarser particular dispersion of the drug.[9,10] Further, the *AUC* and C_{max} of HP-55® solid dispersion (1 : 5) were both larger than those of CMEC® solid dispersion of the same composition, however, there was no significant difference in T_{max} values.

The differences in oral bioavailability may be due to differences in the drug dissolution profile. As shown in Fig. 2, in the pH 6.8 medium, drug dissolution was rapid

Table 2. Drug Content in the Evaluated Preparations after Stability Tests

Preparation	Initial	Drug content (%)[a]		
		60 °C–2 w.	60 °C–4 w.	60 °C–2 m.
MFB : CMEC (1 : 5)	100	101.06	100.57	—
MFB : HP-55 (1 : 3)	100	102.56	103.21	101.49
MFB : HP-55 (1 : 5)	100	100.64	101.01	100.95

a) Against initial value. w., week; m., month.

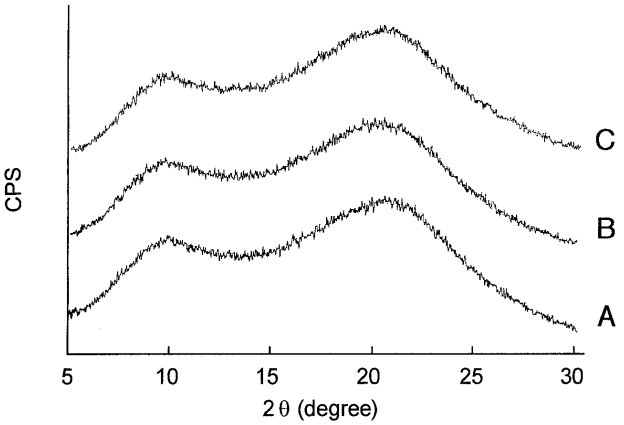

Fig. 4. Changes in X-Ray Powder Diffraction Patterns of CMEC® Solid Dispersion (MFB : CMEC® = 1 : 5) during Storage

A, initial; B, 60 °C–2 w; C, 60 °C–4 w.

from the HP-55® solid dispersion compared with that from the CMEC® one. In addition, neither peak concentration nor recrystallization were observed in the CMEC® solid dispersion. It was suggested that as supersaturated MFB-1041 molecules were rapidly absorbed in the small intestine, recrystallization, which was observed in the *in vitro* dissolution tests of HP-55® solid dispersion, hardly occurred. From these results, it could be confirmed that a higher *in vitro* dissolved MFB-1041 peak concentration resulted in superior *in vivo* absorption.

Our previous work (unpublished) revealed that the absorption site of MFB-1041 was limited to the small intestine, and little absorption was observed in the stomach. So, the *in vivo* dissolution process can be described as follows: a nonenteric solid dispersion (Metolose®) begins to dissolve in the stomach after oral administration. Subsequently, a part of this dissolved MFB-1041 crystallizes before being absorbed in the small intestine. On the other hand, the HP-55® or CMEC® solid dispersion rarely dissolves in the stomach; it begins to dissolve only after reaching the small intestine. Therefore, it is probable that the amount of dissolved MFB-1041 in the enteric solid dispersions at the absorption site is larger than that in the nonenteric one. Because drug in the CMEC® solid dispersion dissolves slowly and the maximum dissolved concentration is low in a higher pH medium compared with those of HP-55® (Fig. 2), the drug dissolution from the CEMC® solid dispersion in the upper small intestine might have been delayed, and that resulted in lower absorption. Needless to say, a higher drug concentration at the absorption site means higher absorption.

Stability Experiments It is well known that the crystal-

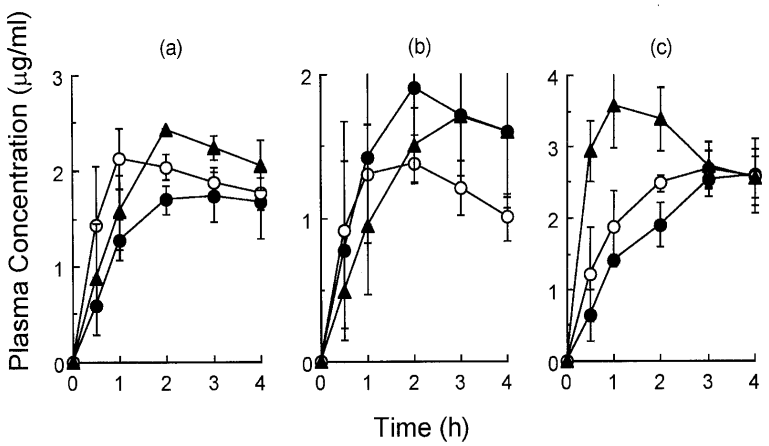

Fig. 5. Storage Effect on MFB-1041 Absorption from Each Solid Dispersion in Beagle Dogs

(a) MFB-1041 : CMEC® = 1 : 5; (b) MFB-1041 : HP-55® = 1 : 3; (c) MFB-1041 : HP-55® = 1 : 5. ●, initial; ○, 60 °C–4 w; ▲, 60 °C–2 m. MFB-1041 was administered orally at a dose of 10 mg/kg under a fasted condition. Each point represents the mean ± S.D. of 3 dogs.

lization of a drug within a polymer matrix can occur during storage of the solid dispersion formulation, resulting in delayed dissolution. To estimate the stability of the HP-55® and CMEC® solid dispersions, the solid dispersion powders were stored in closed glass bottles at 60 °C for 2 months under a darkened condition. Drug contents after the stability test are shown in Table 2. Even after 2 months of storage, none of the solid dispersions exhibited any significant change in appearance or drug content, and the drug dissolution profiles also were not changed (data was not shown). Drug X-ray diffraction patterns of stored samples of CMEC® solid dispersion are shown in Fig. 4. No crystallization of the drug within the solid dispersion was observed. For other HP-55® solid dispersions, the same results were also obtained. Further, *in vivo* drug absorption experiments were carried out. As shown in Fig. 5, there were no remarkable decreases in bioavailability (*AUC*) among intact and stored samples for all solid dispersions. From the results of our previous stability test (arrhenius plots, unpublished data), the condition of 60 °C for 2 months corresponds to 3 years at room temperature. These results demonstrated that a long shelf-life is expected for these formulations. There have been previous reports in which enteric solid dispersions were employed to sustain the release of a water-insoluble drug or to protect these drugs against degradation in the stomach.[11-13] However, our study indicates that enteric solid dispersions can be applied to improve the oral absorption of a water-insoluble drug that showed insufficient absorption, even by conventional solid dispersion techniques.

In conclusion, solid dispersions with bioinert enteric polymers such as HP-55® and CMEC® have been successfully applied to a poorly soluble antifungal agent, with a water solubility of 1.2 μg/ml at 37 °C, resulting in an increase in dissolution and oral absorption. Further, from the stability experiments, it was demonstrated that a long shelf-life is expected for these formulations.

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