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Enhanced solubility and dissolution rate of itraconazole by a solid dispersion technique

Jae-Young Jung [a], Sun Dong Yoo [b,*], Sang-Heon Lee [a], Kye-Hyun Kim [a], Doo-Sun Yoon [a], Kyu-Hyun Lee [a]

[a] *Formulation Research Laboratory, Choongwae Pharma Co., 146–141 Annyung-ri, Taeane-up, Hwasung-kun, Kyunggi-do 445-970, South Korea*

[b] *College of Pharmacy, Sungkyunkwan University, 300 Chonchon-dong, Jangan-ku, Suwon, Kyunggi-do 440-746, South Korea*

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Abstract

The aim of the present study was to improve the solubility and dissolution rate of a poorly water-soluble drug, itraconazole, by a solid dispersion technique. Solid dispersion particles of itraconazole were prepared with various pH-independent and -dependent hydrophilic polymers and were characterized by differential scanning calorimetry, powder X-ray diffraction and scanning electron microscopy. Of the polymers tested, pH-dependent hydrophilic polymers, AEA® and Eudragit® E 100, resulted in highest increases in drug solubility (range, 141.4–146.9-fold increases). The shape of the solid dispersion particles was spherical, with their internal diameter ranging from 1–10 μm. The dissolution rate of itraconazole from the tablets prepared by spray drying (SD-T) was fast, with $>90\%$ released within 5 min. SD-T prepared with AEA® or Eudragit® E 100 at a 1:1 drug to hydrophilic polymer ratio (w/w) showed approximately 70-fold increases in the dissolution rate over a marketed product.

Keywords: AEA®; Dissolution; Eudragit® E 100; Itraconazole; Solid dispersion; Solubility; Spray drying

1. Introduction

Itraconazole is an orally administered antifungal agent with a broad spectrum activity against mycotic infections. It is a weakly basic drug, possessing an extremely low water solubility and pK_a of 3.7 (Heykants et al., 1989). Various techniques have been used to improve the solubility of poorly water-soluble drugs, including the use of surfactants (Schott et al., 1982), inclusion complexation (Veiga et al., 1996) and solid dispersion techniques (Kislalioglu et al., 1991; Hsiu-O and Huei-Lin, 1996; Moyano et al., 1997; Okonogi et al., 1997). Improvement of itraconazole solubility has been reported by conjugating the drug with hydroxypropyl-β-cyclodextrin followed by fluidized-bed coating of pellets (Janssen Pharmaceutica, 1994) and by the melt extrusion process

* Corresponding author. Tel.: +82-331-290-7717; fax: +82-331-292-8800.

E-mail address: sdyoo@yurim.skku.ac.kr (S.D. Yoo)

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(Janssen Pharmaceutica, 1997). These processes, however, require specialized preparation techniques and equipment and involve complex manufacturing steps. To our knowledge, no information is available on the improvement of itraconazole by solid dispersion techniques.

The aim of the present study was to enhance the solubility and dissolution rate of itraconazole by a simple solid dispersion method using various pH-independent and -dependent hydrophilic polymers. The solvent method was used to prepare solid dispersion particles containing itraconazole. The prepared solid dispersion particles were characterized by differential scanning calorimetry, powder X-ray diffraction, scanning electron microscopy and solubility measurement. The dissolution behavior of itraconazole from the tablets containing spray-dried solid dispersions was further examined.

2. Materials and methods

2.1. Materials

Aminoalkyl methacrylate copolymers (Eudragit® E 100) and polyvinylacetal diethylaminoacetate (AEA®) were purchased from Röhm Pharma (Germany) and Sankyo (Japan), respectively. Itraconazole was synthesized at Choongwae Research Laboratory (South Korea) and was used without further purification (purity 99.2%). Polyoxyethylene–polyoxypropylene copolymers (Poloxamer® 188) and polyvinylpyrrolidone (PVP) were purchased from BASF Aktiengesellschaft (Germany). Polyethylene glycol (PEG) 20,000 and hydroxypropylmethylcellulose (HPMC) were purchased from Yakuri Pure Chemical (Japan) and Shin-Etsu Chemical (Japan), respectively.

2.2. Preparation of solid dispersions

Solid dispersions of itraconazole were prepared by a spray drying method. Itraconazole was dissolved in appropriate volumes of methylene chloride together with pH-independent hydrophilic polymers, Poloxamer® 188, PEG 20,000, PVP and HPMC, and pH-dependent hydrophilic polymer, AEA® and Eudragit® E 100. The weight ratio of the drug to the hydrophilic carrier was 1:1.5 (w/w). The coating solutions were filtered through a 10-μm filter. In addition, spray drying solutions for the pH-dependent hydrophilic polymers were prepared at the drug-to-polymer composition ratios (w/w) of 1:0.5, 1:1, 1:1.5 and 1:2 (Asd 0.5, Asd 1.0, Asd 1.5 and Asd 2.0, respectively) for AEA® and 1:0.5, 1:0.75, 1:1, 1:1.5, 1:1.75 and 1:2 (Esd 0.5, Esd 0.75, Esd 1.0, Esd 1.5, Esd 1.75 and Esd 2.0, respectively) for Eudragit® E 100. Solid dispersion particles were prepared by spray drying (B-190 Minispray dryer, Büchi Labortechnik, Switzerland) under the following conditions: pump speed, 5 ml/min; air flow rate, 800 Nl/h; aspirator level, 10–15; inlet air temperature, 45°C; outlet air temperature, 38°C.

2.3. Drug solubility

The solubility of itraconazole was determined in the pH 1.2 simulated gastric juice for the solid dispersions with pH-independent hydrophilic polymers, PEG 20,000, HPMC, PVP and Poloxamer® 188 as well as pH-dependent hydrophilic polymers AEA® and Eudragit® E 100. Briefly, to solid dispersion particles equivalent to 20 mg itraconazole in a test tube was added 15 ml of pH 1.2 simulated gastric juice. The tube was sonicated for 30 min followed by shaking in water bath (25°C) for 24 h. A portion of the solution (10 ml) was taken, centrifuged at $2200 \times g$ for 20 min, filtered (0.45 μm) and centrifuged again at $7000 \times g$ for 10 min twice. An upper portion (1 ml) was then taken and diluted with 9 ml of methanol and the diluted solution was subjected to drug analysis. Drug concentrations were determined by HPLC (Hewlett-Packard 1100, Germany). The mobile phase consisted of 0.2% diisopropylamine in methanol and 0.05% ammonium acetate in distilled water (82:18). The effluent was monitored at a UV absorption wavelength of 254 nm at a flow rate of 1.0 ml/min.

2.4. Differential scanning calorimetry (DSC)

Thermal characteristics of the physical mixtures of itraconazole and AEA® or Eudragit® E 100, and the solid dispersions were determined by a differential scanning calorimeter (DSC 200, Netzsch-Gerätebau, Germany). Samples equivalent to approximately 5 mg itraconazole were placed in aluminum pans and DSC analyses were carried out at a nitrogen flow of 20 ml/min and a heating rate of 10°C/min from 30 to 200°C.

2.5. Powder X-ray diffraction

The powder X-ray diffraction patterns were determined for itraconazole, AEA® or Eudragit® E 100 alone, their physical mixtures and the solid dispersions. X-ray diffractograms were obtained using the X-ray diffractometer (FR 590, Enraf Noinus, The Netherlands), with Ni-filtered Cu-target, voltage 30 kV, current 15 mA and 2θ over a 10–70° range.

2.6. Scanning electron microscopy

The photomicrographs of itraconazole and its spray-dried solid dispersions were obtained by scanning electron microscopy (JSM-35CF, Jeol, Japan). Itraconazole or spray-dried solid dispersions were mounted on a double-faced adhesive tape, sputtered with platinum. The obtained micrographs were examined at a magnification ratio of $\times 2000$.

2.7. Content uniformity

Exactly weighed amounts of spray-dried solid dispersions of itraconazole were dissolved in ethanol and were sonicated for 10 min to destroy any agglomerates. The drug content was determined by HPLC.

2.8. Measurement of residual organic solvent

The residual amount of methylene chloride remaining in spray-dried powders was determined by a gas chromatographic method. The standard solutions were prepared by diluting with *N*,*N*-dimethylformamide at concentrations of 1.25, 2.5 and 5 ppm. A portion (165 mg) of the spray-dried powders was added into a 5-ml volumetric flask which was then filled with *N*,*N*-dimethylformamide. The prepared samples were assayed for the organic solvent by a Hewlett-Packard 5890 Series II gas chromatograph equipped with a flame ionization detector. The analysis was carried out using a DB-5 MS capillary column (30 m $\times$ 0.32 mm, 1 μm, 5% phenylmethyl polysiloxane, J&W Scientific, USA) at a detector temperature of 250°C. The initial oven temperature was maintained at 50°C for 8 min, with a heating rate of 30°C/min and the final oven temperature of 200°C maintained for 5 min.

2.9. Preparation of tablets (SD-T)

Spray-dried solid dispersions of itraconazole were added with 10% lactose solution and granulated by passing through a 35-mesh screen. The granules were dried in an oven at 40°C for 16 h and were mixed with lactose (1:1, w/w) and Explotab® (5%, w/w). This mixture was lubricated using 0.5% (w/w) magnesium stearate and compressed on IR press (Carver Laboratory Press-C, Fred S. Carver, USA). The content of itraconazole was maintained at 100 mg per tablet.

2.10. Drug release study

Dissolution profiles of powdered itraconazole and the tablets containing spray-dried solid dispersions were determined at 37 ± 0.5°C at a stirring rate of 100 rpm using the paddle method (USP XXIII). In addition, the drug release profile from a marketed product, Sporanox® capsules, was examined for comparison purposes. The dissolution medium was the pH 1.2 simulated gastric juice consisting of 7 ml of c-HCl and NaCl (2 g/l). In each dissolution test, a weighed quantity of samples containing 100 mg itraconazole were placed in 900 ml of the dissolution medium. Aliquots (2 ml each) were withdrawn at 5, 10, 30 and 60 min through a filtering rod (10 μm) followed by centrifugation at $7000 \times g$ for 5 min. At each sampling time, an equal volume of the test medium was replaced. Filtered samples were ap-

propriately diluted and assayed for drug concentration by HPLC. Drug concentrations were determined and expressed as the percentage of drug released over time ($n = 6$ each).

3. Results and discussion

3.1. Solubility

Solid dispersions of itraconazole prepared with the pH-independent and -dependent hydrophilic polymers all showed increased drug solubility over the pure material (Table 1). The extent of increase in solubility was greater for the pH-dependent polymers, AEA® and Eudragit® E 100 (range, 141.4–146.9-fold increases) than for the pH-independent polymers, Poloxamer® 188, PEG 20,000, PVP and HPMC (range, 7.6–92.6-fold increases).

3.2. Differential scanning calorimetry (DSC)

DSC curves obtained for pure itraconazole, Eudragit® E 100, AEA®, their physical mixtures and the solid dispersions prepared with Eudragit® E 100 and AEA® are shown in Fig. 1. Pure powdered itraconazole showed a melting endotherm at 165.5°C but this endothermic peak was shifted to 165.0°C for the spray-dried itraconazole. As the amounts of AEA® and Eudragit® E 100 were increased, the size of their endothermic peaks was reduced (Fig. 1). At the spray drying ratio (w/w) of 1:0.5 with Eudragit® E 100, a small but shifted endothermic peak was observed at 162°C. Further, at the ratio of 1:0.75 and above, the endothermic peak of itraconazole was no longer observed (Fig. 1). In case of the solid dispersions with AEA®, the melting endotherm of itraconazole was not observed over the ratio range from 1:1.0–1:2.0 (w/w) (Fig. 1). The physical mixtures of itraconazole and Eudragit® E 100 or AEA®, on the other hand, showed an apparent endothermic peak of itraconazole at 165.5°C at the ratio of 1:1.5. Similar observations have been reported for piroxicam and atenolol (Tantishaiyakul et al., 1996; Moneghini et al. 1998).

The possibility of alterations in the physical state of itraconazole from an amorphous state to a crystalline state during wet granulation was examined by performing DSC. After wet granulation, a small endothermic peak corresponding to the pure itraconazole was found for the Esd granules but not for the Asd granules. It is unknown what caused the difference in the formation of this endothermic peak between the two formulations. Further work is needed to see if dry granulation can alter the integrity of the solid dispersions for Asd and Esd.

Table 1
Solubility of itraconazole in solid dispersions with hydrophilic polymers tested in pH 1.2 simulated gastric juice (drug:polymer ratio, 1:1.5, w/w)[a]

Preparation method	Polymer	Solubility (μg/ml)
Spray drying	Poloxamer® 188	13.7 ± 0.9
	PEG 20,000	166.5 ± 1.5
	PVP	75.2 ± 4.8
	HPMC	162.8 ± 4.7
	AEA®	264.5 ± 0.8
	Eudragit® E 100	254.5 ± 2.1
Itraconazole powder	–	1.8 ± 0.0

[a] Mean ± S.D. for three different batches of solid dispersions.

3.3. Powder X-ray diffraction

Fig. 2 shows the representative X-ray diffraction patterns for the pure powdered itraconazole, AEA® or Eudragit® E 100 alone, physical mixtures and the solid dispersions. X-ray diffraction patterns of the physical mixtures were similar to those obtained for the pure material. The characteristic crystalline peak of itraconazole was also observed for the polymer–itraconazole physical mixtures but the peak size was reduced. However, solid dispersions of itraconazole prepared by spray drying with AEA® and Eudragit® E 100 did not show the peak, indicating a transition of itraconazole from a crystalline to an amorphous state. Taken together with DSC data, these results indicate a formation of amorphous itraconazole in solid dispersions with both AEA® and Eu-

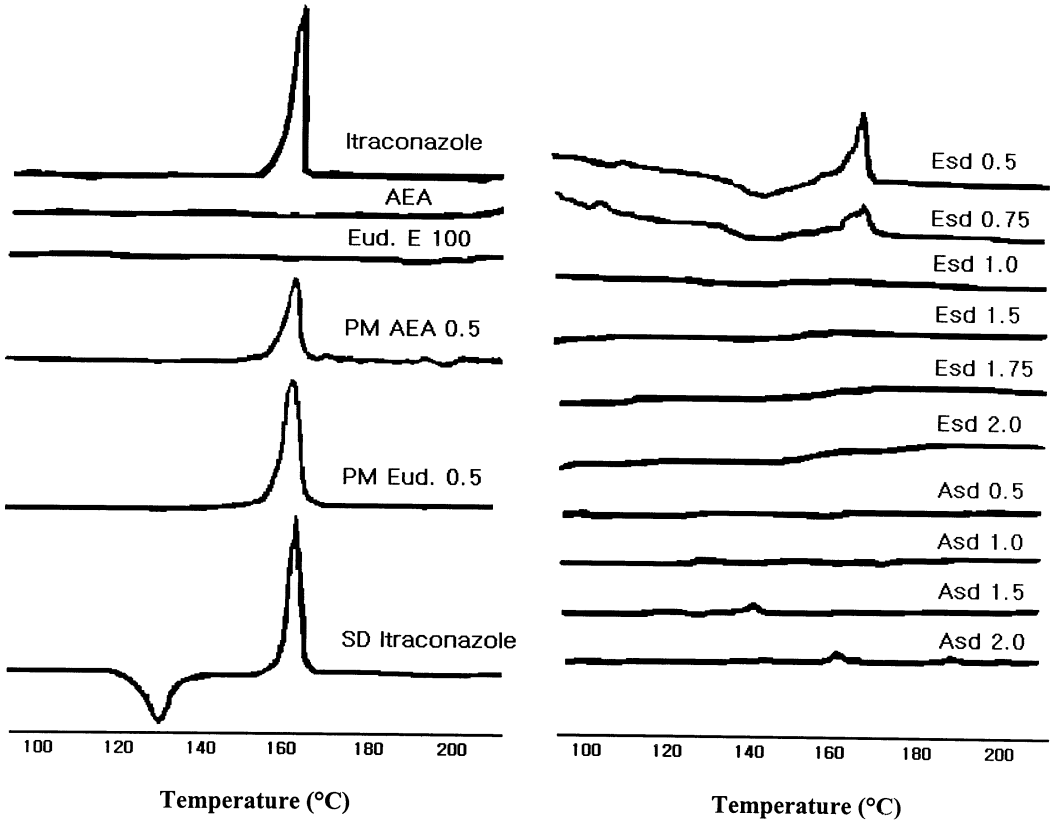

Fig. 1. DSC curves of itraconazole, AEA®, Eudragit® E 100 (Eud E), physical mixtures (PM) and solid dispersions (SD). The numbers indicate the composition rate (wt. ratio) for itraconazole. Esd and Asd represent the solid dispersions of itraconazole prepared with Eudragit® E 100 and AEA®, respectively.

dragit® E 100 at the drug:polymer ratio of 1:1.0 and above. This observation is consistent with the results of the thermal analysis data described above. Similar observations have been reported for furosemide where spray-dried dispersion products contained an amorphous form of furosemide, with significantly improved dissolution characteristics over the pure material (Doherty and York, 1987; Okimoto et al., 1997; Veiga et al., 1998).

3.4. Scanning electron microscopy (SEM)

Scanning electron micrographs of the solid dispersions prepared with AEA® and Eudragit® E 100 are shown in Fig. 3 at a magnification ratio of $\times 2000$. Pure itraconazole was irregular crystalline in shape, whereas the solid dispersions prepared by spray drying were spherical in shape, with small internal diameter (1–10 μm). Therefore, it is possible that the reduced particle size, increased surface area, and the close contact between the hydrophilic carrier and itraconazole may be responsible for the enhanced drug solubility and dissolution rate found for the solid dispersion particles.

3.5. Drug content in polymeric solid dispersions

The content of itraconazole in spray-dried solid dispersions prepared with various amounts of Eudragit® E 100 ranged from 99.4 to 107.7% (Table 2). Therefore, the spray-drying method used in this study appears applicable to the preparation of tablets with high content uniformity.

3.6. Residual organic solvent in solid dispersions

The residual amount of methylene chloride remaining in the solid dispersions prepared by spray drying was 16.7 ± 4.0 ppm (mean of three batches) which was comparable to 17.7 ppm determined for the pure material. Therefore, this residual amount was far below the acceptable limit (< 500 ppm) described in the USP XXIII.

3.7. Dissolution profiles of SD-T

Dissolution profiles of itraconazole from the tablets containing spray-dried solid dispersions (SD-T) are shown in Figs. 4 and 5. The drug dissolution rate was faster for SD-T, with 90% released within 5 min as compared to 5% determined for the marketed product. SD-T prepared with AEA® or Eudragit® E 100 at 1:1 (w/w) ratio resulted in approximately 70-fold increases in the initial drug dissolution rate over the marketed product, although the dissolution rate was reduced at higher (1:1.5–1:2) and lower (1:0.5) composition ratios. Nevertheless, SD-T prepared with AEA® and Eudragit® E 100 showed significantly improved dissolution profiles at all the ratios over the SD-raw material (Figs. 4 and 5).

AEA® and Eudragit® E 100 are hydrophilic polymers possessing characteristic tertiary amine functional groups. These polymers are frequently used in a protective or gastric soluble coating. They are also used as the masking agents and to improve drug stability. Unlike other hydrophilic polymers that release drug upon swelling, AEA® and Eudragit® E 100 are solubilized at pH < 5 in a pH-dependent manner. Recently, several reports have shown that AEA® and Eudragit® E 100 increase the solubility and dissolution rate of poorly water-soluble drugs (Hamaguchi et al., 1995a,b; Susuki et al., 1996). Our present findings indicate that AEA® and Eudragit® E 100 may be effective hydrophilic carriers for drugs that are

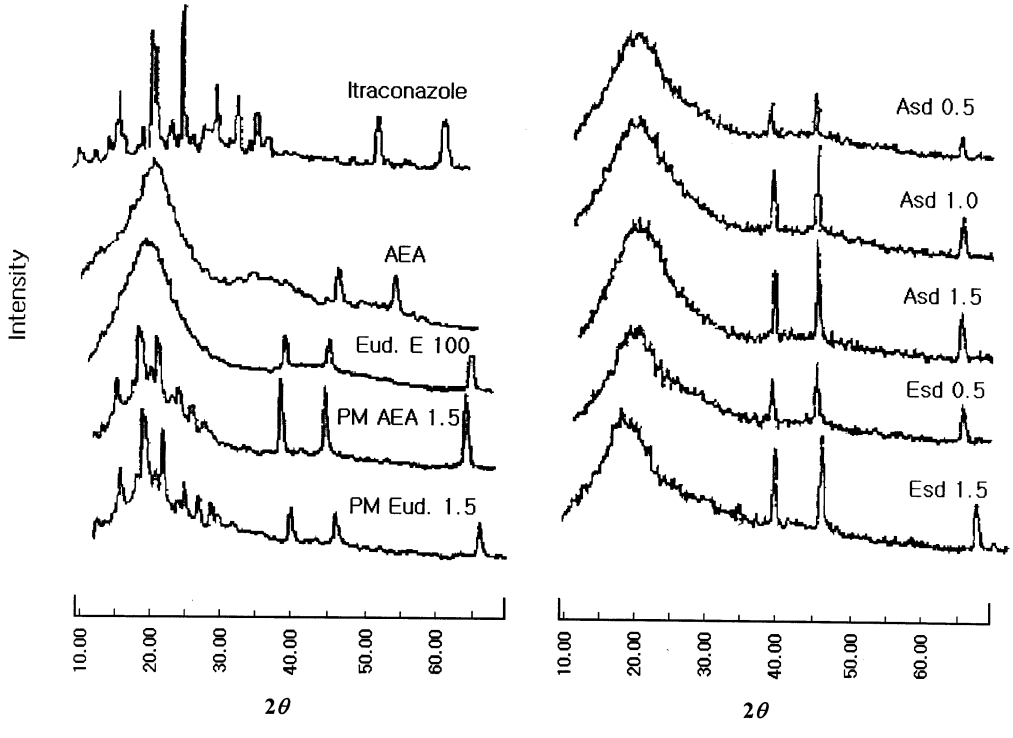

Fig. 2. X-ray diffraction patterns of itraconazole, AEA®, Eudragit® E 100 (Eud E), physical mixtures (PM) and solid dispersions. The numbers indicate the polymer-to-drug composition rate (w/w). Asd and Esd represent solid dispersions of itraconazole prepared with AEA® and Eudragit® E 100, respectively.

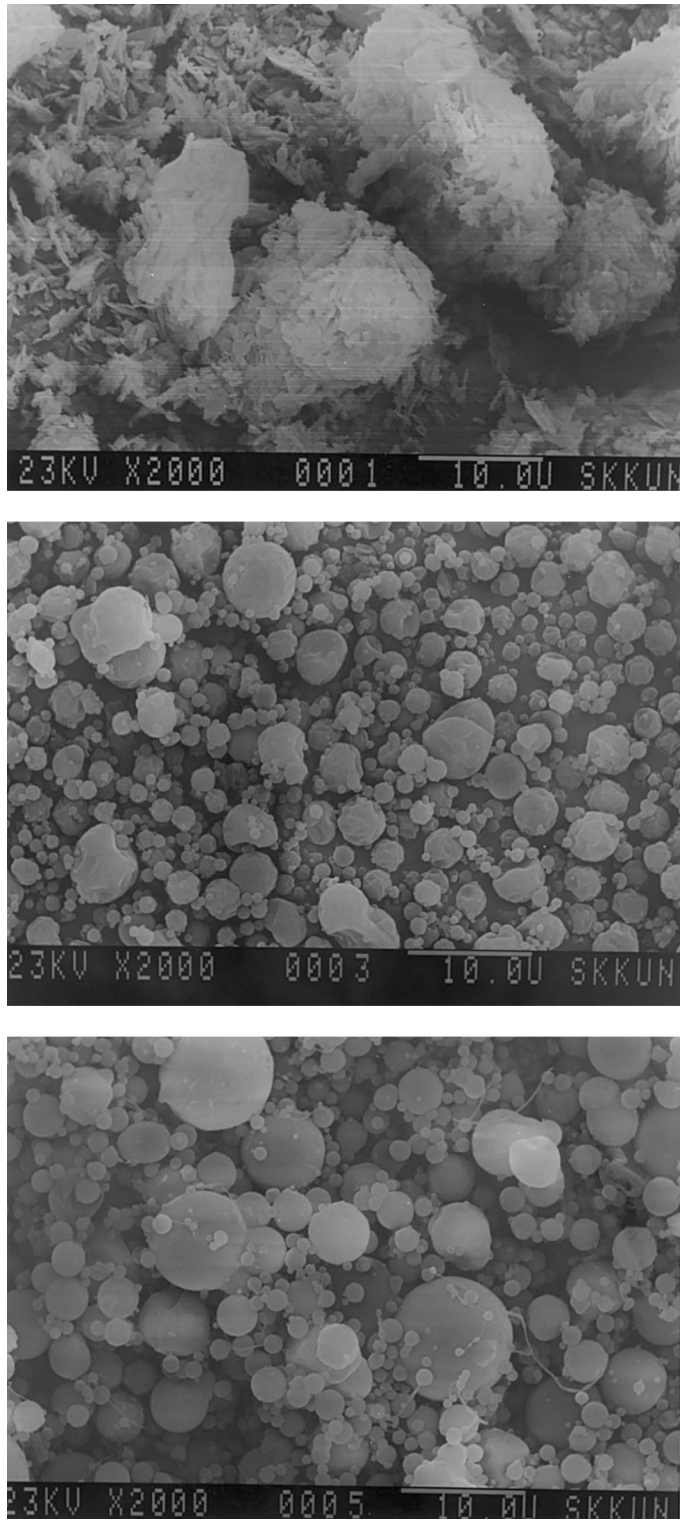

Fig. 3. Scanning electron microphotographs of itraconazole and solid dispersion particle prepared by spray drying: (1) itraconazole, (3) Esd 0.5, (5) Asd 0.5, (7) Esd 1.5 and (9) Asd 1.5. The magnification ratio was set at $\times 2000$.

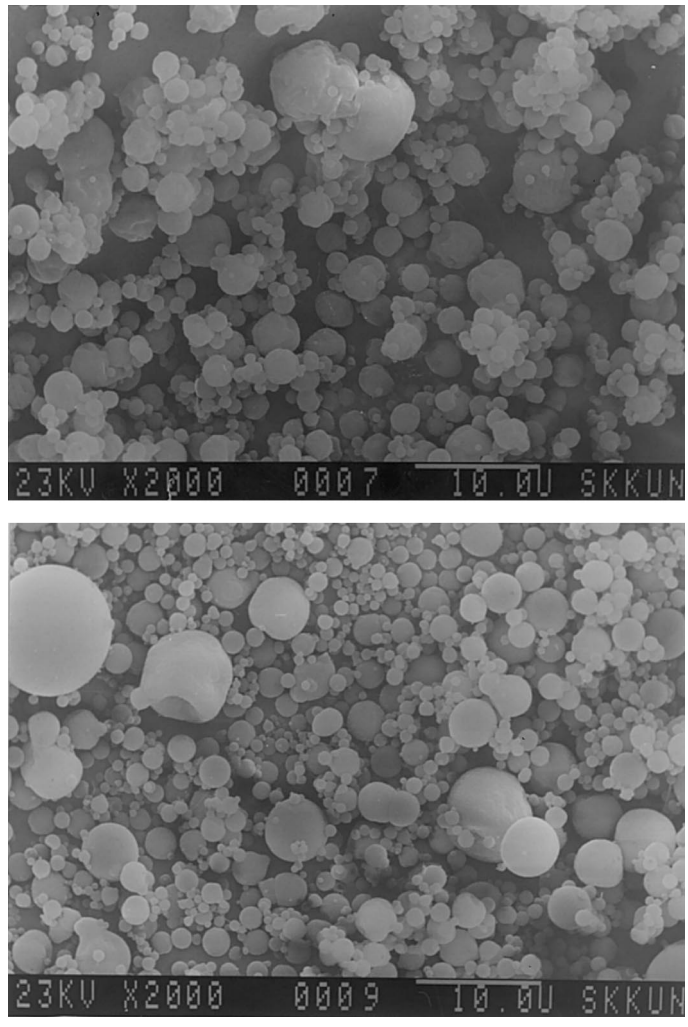

Fig. 3. (*Continued*)

Table 2
Content of itraconazole in Eudragit® E 100 solid dispersions[a]

Mixing ratios of itraconazole to Eudragit® E 100	Solid dispersions equivalent to 20 mg of itraconazole (mg)	Itraconazole content in solid dispersions (%)
Raw material	20	99.4 ± 0.3
1:0.5	30	102.2 ± 0.6
1:0.75	35	107.7 ± 1.1
1:1.0	40	100.2 ± 0.5
1:1.5	50	100.4 ± 0.8
1.1.75	55	100.9 ± 0.5
1:2.0	60	100.0 ± 0.7

[a] Mean ± S.D. for three different batches of solid dispersions.

ionized at low gastric pH only as in the case of itraconazole.

4. Summary and conclusions

Solid dispersions of itraconazole prepared with pH-dependent hydrophilic polymers, AEA® and Eudragit® E 100, resulted in greater increases in drug solubility over those prepared with pH-independent hydrophilic polymers, PEG 20,000, PVP, Poloxamer® 188 and HPMC. Tablets containing the solid dispersion particles prepared by spray drying showed enhanced dissolution profiles of itraconazole over the marketed product. The drug dissolution rate of was highest at the drug-to-polymer composition ratio of 1:1 (w/w). The solid dispersion technique used in our study involves relatively simple preparation steps and may be utilized in preparing granules, tablets, capsules and other oral dosage forms. Further work is warranted to examine if the oral bioavailability of itraconazole is increased for the solid dispersions with enhanced dissolution characteristics.

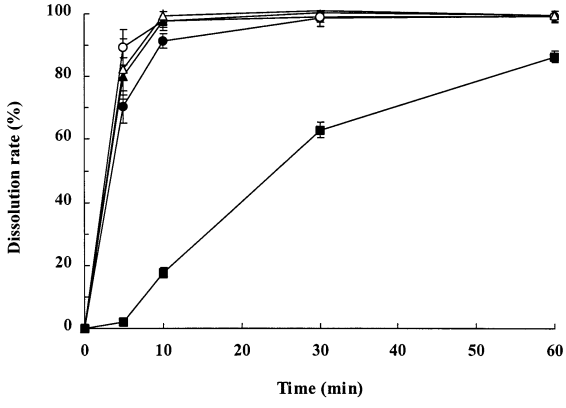

Fig. 4. Dissolution profiles of itraconazole from AEA® spray drying tablets. Key: SD-T 0.5 (●); SD-T 1.0 (○); SD-T 1.5 (▲); SD-T 2.0 (△); marketed product (■).

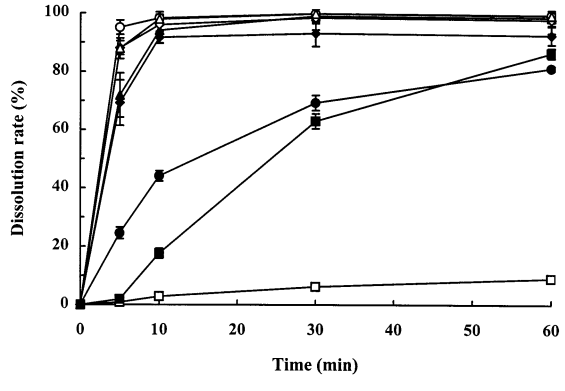

Fig. 5. Dissolution profiles of itraconazole from Eudragit® E 100 spray drying tablets. Key: SD raw material (□); SD-T 0.5 (●); SD-T 0.75 (◆); SD-T 1.0 (○); SD-T 1.5 (▲); SD-T 1.75 (◇); SD-T 2.0 (△); marketed product (■).

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