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Dissolution Enhancement of Fenticonazole Nitrate from Hydrophilic Polymer Solid Dispersions

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친수성 고분자와의 고체분산체로부터 질산펜티코나졸의 용출 증가

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Solid dispersion of fenticonazole nitrate (FN) with poloxamer 407, polyethylene glycol 6000, povidone (K-90) were prepared by the solvent method. To characterize the state of the drug in solid dispersions, the x-ray diffractometry and differential scanning calorimetry were carried out. The identification of these systems suggested that FN in the poloxamer 407 system remained in crystalline state, and the drug in the PVP system was amorphous. A marked increase in the dissolution rate of FN was attained by dispersing the drug in the hydrophilic polymers used, and the dispersion with poloxamer 407 was superior to the other two carriers in releasing the drug into solution.

Keywords—solid dispersion, fenticonazole nitrate, poloxamer 407, polyethylene glycol 6000, povidone, dissolution, differential scanning calorimetry, x-ray diffractometry

The preparation of solid dispersions with water-soluble polymers by fusion and solvent techniques has successfully increased dissolution properties[1,2] and the bioavailability of poorly water-soluble drugs.[3-18] Physical properties of water-soluble polymers such as large molecular size and high viscosity, and the supercooling process can provide the colloidal dispersion of drugs in a metastable or fast-release form.[1,2,7,8] Among the hydrophilic polymers, polyethylene glycols[19-32] polyvinylpyrrolidones,[33-44] and poloxamers[3,4,25] have been selected as inert carriers for solid dispersions. Solid dispersions (or solutions) may function to increase dissolution rate by reducing the crystal lattice energy, and concomitantly decreasing the size of the drug theoretically to the colloidal and even molecular level.[45] Thus, there is a subsequent increase in the rate of solution which is inversely proportional to particle size.

Fenticonazole nitrate (FN) is white crystalline powder and practically insoluble in water. It is used as an antifungal agent[46]. Therefore, its topical bioavailability is expected to depend on the dissolution rate. In this work, solid dispersions of FN with hydrophilic polymers were prepared and their dissolution behaviours were investigated. Also an attempt was made to characterize their physical properties by differential scanning calorimetry (DSC) and

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powder x-ray diffractometry.

EXPERIMENTAL

Materials

Fenticonazole nitrate (FN) was supplied from Recordati Co., Italy. Poloxamer 407 (Pluronic F-127®, BASF-Wyandotte Corp.) was obtained from BASF Korea. Polyethylene glycol 6000 (PEG 6000) and povidone (PVP K-90) were obtained from commercial sources. Drug and polymers were used as received. All other chemicals were either USP or official analytical grade.

Preparation of Solid Dispersions

Mixtures of various ratios of the drug to polymer (1:1, 1:3 and 1:5 w/w) were dissolved into absolute ethanol. Evaporation was carried out *in vacuo* at room temperature. The resulting mass was left under vacuum overnight followed by grinding and sieved. 250-400 μm fractions were obtained.

Each batch of the prepared dispersions was determined for constant uniformity before use. This was done by dissolving an appropriate amount of the solid dispersion equivalent to 50 mg of FN in 100 m*l* of methanol. 10 m*l* of this solution was appropriately diluted to make 100 m*l* with methanol and the amount of drug was determined spectrophotometrically at 250 nm using a suitable calibration curve. This was repeated 3 times for every batch. The three determinations resulted in 98.1-103.4% for solid dispersion of poloxamer 407, 99.6-101.1% for PEG 6000, and 100.9-101.8% for PVP.

Equilibrium Solubility Determinations

Equilibrium solubilities of the drug in hydrophilic polymer solution of different concentrations were determined by a method similar to that of Najib *et al.*[47].

X-ray Diffraction Studies

X-ray diffraction patterns were obtained on powder samples using monochromated Cu-Kα radiation.

Differential Scanning Calorimetry (DSC)

Samples (2-4 mg) were examined using Dupont Instrument (Model 9900) at a scanning speed of 10°/min.

Table I—*Effects of Hydrophilic Polymers on Aqueous Solubility of Fenticonazole Nitrate at 25°C.*

Polymers	Content used (%, w/v)	Solubility (mg/100 m*l*)
None	0	8.8
PEG 6000	1	11.6
	5	17.3
PVP (K-90)	1	13.8
	5	22.9
Poloxamer 407	1	154.5
	5	422.1

Dissolution Studies

The dissolution tests were carried out using the USP paddle dissolution apparatus. As the dissolution medium, 900 m*l* of 0.1N hydrochloric acid was maintained at 37±0.1°C and an appropriate amount of the solid dispersion equivalent to 50 mg of FN were added. The rotation speed of the paddle was maintained at 100 rpm, samples were withdrawn at appropriate time intervals and analyzed for drug contents. Fresh aliquots of dissolution medium were added each time to maintain a constant volume. Each experiment was done in triplicate.

RESULTS AND DISCUSSION

Solubility Studies

Equilibrium solubility studies were carried out to determine the solubilizing effect of hydrophilic polymers on FN. As shown in Table I, poloxamer 407 was found to interact significantly with FN in aqueous solution. The equilibrium solubility of FN in water at 25 ± 1 °C was 8.8 mg/100 m*l*. In the 5% (w/v) polymer solution, the solubility of FN was increased 2-, 2.5- ad 50-fold for PEG 6000, PVP and poloxamer 407, respectively. The remarkable solubilizing effect of poloxamer 407 might be due to the possiblity of micellar complexation.[3,4]

X-Ray Diffraction Studies

Fig. 1 shows the powder x-ray diffraction patterns of 1:5 (w/w) FN-polymer solid dispersions.

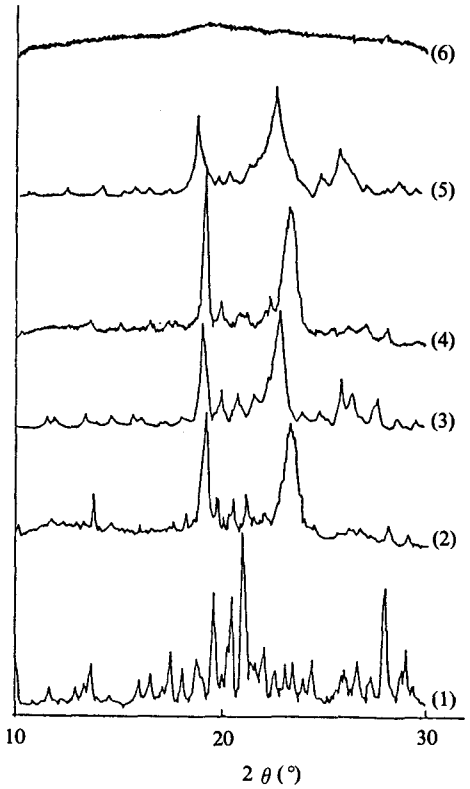

Figure 1—Powder X-ray diffraction patterns of 1:5 (w/w) fenticonazole nitrate-polymer solid dispersions.
Key: (1), fenticonazole nitrate; (2), physical mixture with poloxamer 407; (3), physical mixture with PEG 6000; (4), solid dispersion with poloxamer 407; (5), solid dispersion with PEG 6000; (6), solid dispersion with PVP

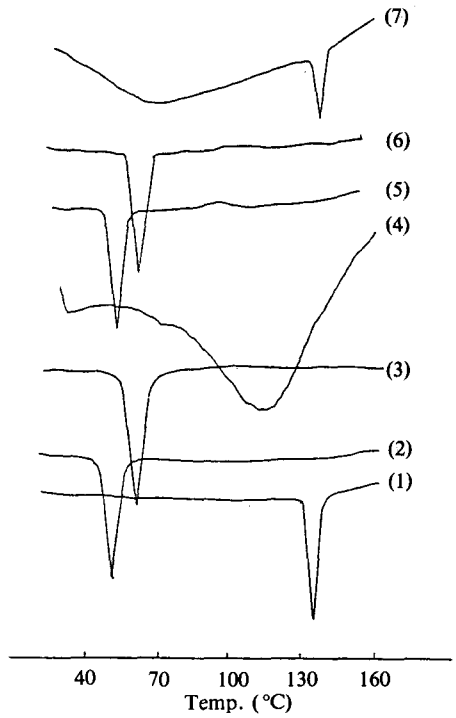

Figure 2—The DSC curves of 1:5 fenticonazole nitrate-polymer physical mixtures.
Key: (1), fenticonazole nitrate alone; (2), poloxamer 407; (3), PEG 6000; (4), PVP(K-90); (5), with poloxamer 407; (6), with PEG 6000; (6) with PVP

For the solid dispersion with poloxamer 407 and PEG 6000, the major FN diffraction peaks at 13.6, 19.6, 20.5 and 21.0° could be identified as weak intensity. The intensities of major drug peaks were substantially reduced in the solid dispersion compared to the physical mixture, which may indicate a significant loss of the crystallinity of intact drug during the process. This result is similar to the findings with dicumarol-PEG 4000 solid dispersion[27]. In the case of the dispersion with PVP, several sharp diffraction peaks attributed to FN crystals disappeared after processing. Similar results were reported for the solid dispersions of other drug-PVP systems[5,15,40,42]. Therefore, x-ray diffraction patterns demonstrated that FN was crystalline in the poloxamer 407 system and PEG 6000 system, and amorphous in PVP system.

DSC Studies

The DSC curves of 1:5 (w/w) FN-polymer physical mixtures are depicted in Fig. 2. The DSC curves of FN, poloxamer 407 and PEG 6000 exhibited one endothermic peak corresponding to the melting points of FN (135 °C), poloxamer 407 (52 °C), and PEG 6000 (60 °C). However, PVP showed a very broad endothermic peak which might be attributed to the loss of moisture and fusion (or melting). The DSC curves of the physical mixtures with poloxamer 407 and PEG 6000 showed only one endothermic peak corresponding to the melting of each polymer. In these cases, the disappearance of the endothermic peak corresponding to the melting of FN is thought to be due to its dissolution in the melted polymer[4,32]. For the physical mixture with PVP, the DSC curve showed the distinct endothermic peak corresponding to the melting of FN.

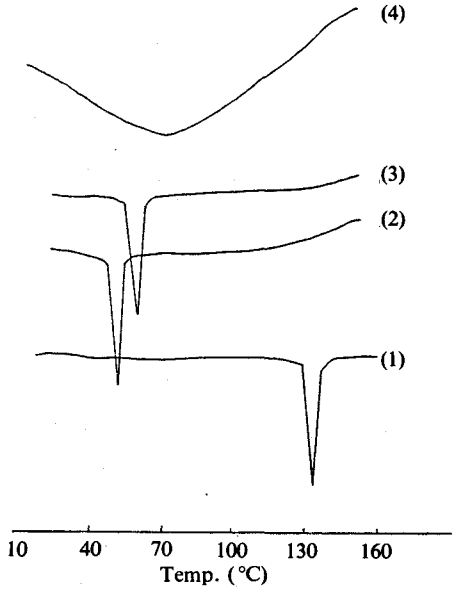

Figure 3—The DSC curves of 1:5 (w/w) fenticonazole nitrate-polymer solid dispersions.
Key: (1), fenticonazole nitrate (solvent treated); (2), poloxamer 407; (3), PEG 6000; (4), PVP

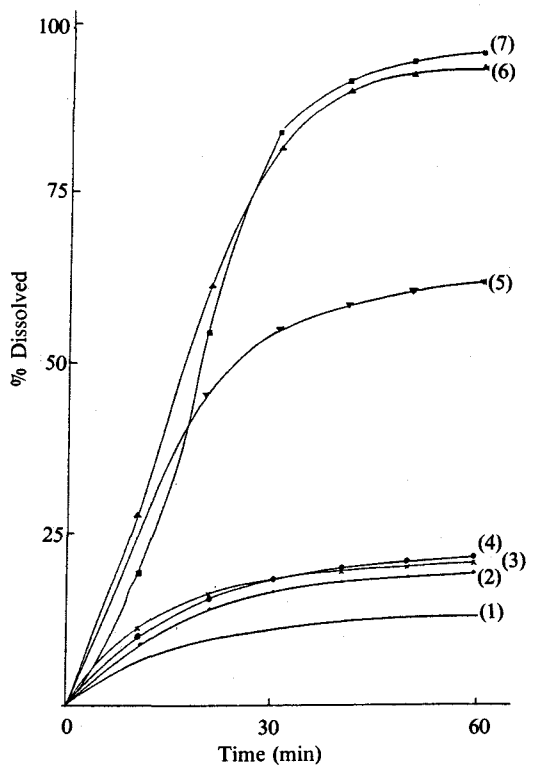

Figure 4—Dissolution profiles of fenticonazole nitrate-poloxamer 407 solid dispersions in 0.1N HCl.
Key: (1), fenticonazole nitrate; (2), 1:1 physical mixture; (3), 1:3 physical mixture; (4), 1:5 physical mixture; (5), 1:1 solid dispersion; (6), 1:3 solid dispersion; (7), 1:5 solid dispersion

Fig. 3 shows the DSC curves of the 1:5 (w/w) solid dispersions and FN treated with solvent. From Figs. 2 and 3, pure and treated FN gave endotherms at 135 °C. It is evident that the presence of ethanol during the preparation of the solid dispersion did not result in a different polymorphic form. The endothermic peak corresponding to the melting of FN disappeared in the 1:5 (w/w) solid dispersions. In cases of poloxamer 407 and PEG 6000, solid dispersions showed exactly the same thermal behaviour as the physical mixture because of drug's dissolving in the melted polymer. From the result of x-ray diffraction studies, however, there is a reason why FN exists in the amorphous state in solid dispersion with PVP.

Dissolution Studies

The dissolution characteristics of FN-poloxamer 407 systems are illustrated in Fig. 4. FN-poloxamer 407 solid dispersions exhibited a faster dissolution rate than the corresponding physical mixtures, as well as intact drug. The dissolution rate of the drug was greatly enhanced by increasing the poloxamer content in the solid dispersion to 1:5 drug-poloxamer ratio. Highly water-soluble poloxamer 407 (10g/100 m*l* at 25 °C) dissolves rapidly in the dissolution medium. In addition, poloxamer 407, a nonionic surfactant, reduces surface tension and facilitates wetting of the drug as manifested by the improvement of the dissolution behaviour of physical mixtures. Although it has been shown that surfactants[3,4,25] can increase the solubility of poorly soluble compounds, the amount of poloxamer present in the dissolution media was probably too small (0.6×10^{-4} w/v%, 1.1×10^{-4} w/v%, and 2.8×10^{-4} w/v% for 1:1, 1:3, and 1:5, respectively) to affect the solubility of the drug in the bulk solution (900 m*l* of 0.1N HCl). However the surfactant present inside and/or outside of drug crystals might enhance the solubility of the drug in the diffusion layer during the dissolution process[4]. The dissolu-

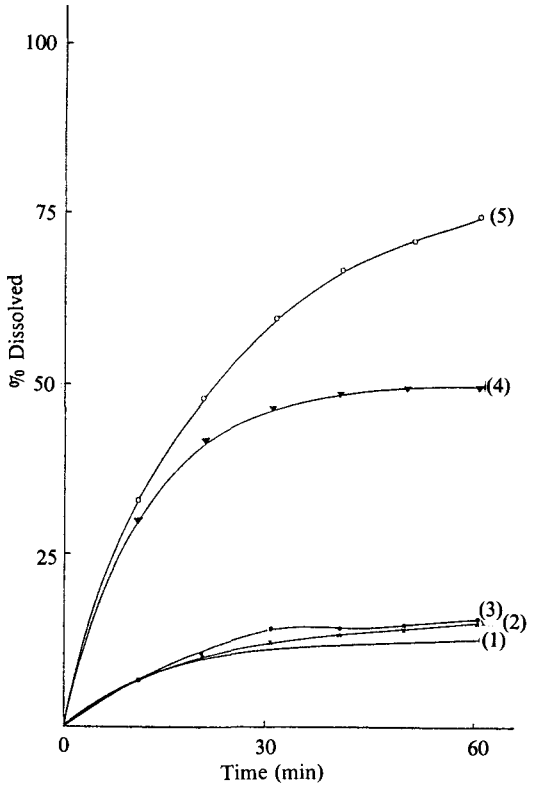

Figure 5—Dissolution profiles of 1:5 (w/w) fenticonazole nitrate-povidone solid dispersion and 1:5 (w/w) solid dispersion with PEG 6000 in 0.1N HCl.
Key: (1), fenticonazole nitrate; (2), physical mixture with PEG 6000; (3), physical mixture with PVP; (4), solid dispersion with PEG 6000; (5), solid dispersion with PVP

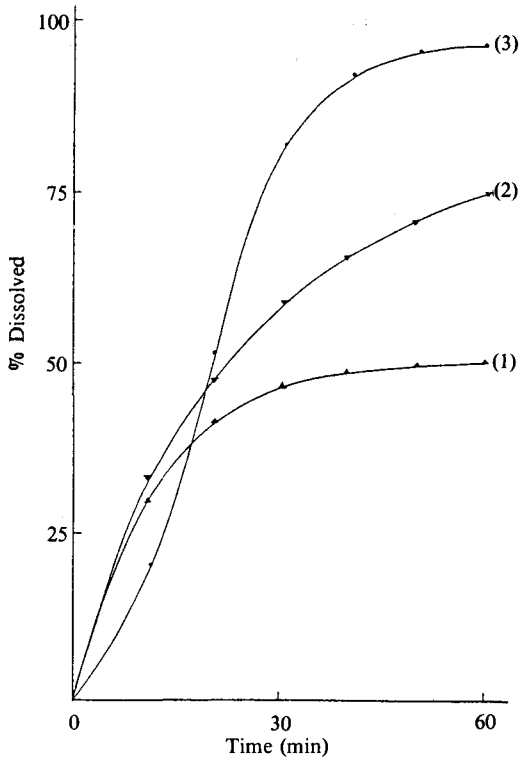

Figure 6—Comparision of dissolution profiles for 1:5 (w/w) fenticonazole nitrate-hydrophilic polymer solid dispersions.
Key: (1), PEG 6000; (2), PVP; (3), poloxamer 407

tion profiles for FN-PEG 6000 and FN-PVP solid dispersions are shown in Fig. 5. In these systems, the dissolution of the drug was faster than that from the physical mixtures having the same composition. The increased dissolution in the case of the dispersed drug could be attributed to one or more of several factors such as the local solibilization effect, particle size reduction and alteration of the surface properties of the particles. It is anticipated that this rapid dissolution may be due to the particle size reduction of FN in the carriers. From Fig. 6, it was found that the dissolution of FN from the solid dispersions studied was the fastest in FN-poloxamer 407 system. It is expected that this result may be attributed to the surfactant effect of poloxamer 407 and the reduction in particle size of the drug in the dispersing process. In conclusion, hydrophilic polymers studied can be successfully applied to enhance the dissolution of FN.

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