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## Physical Properties of Solid Dispersions of Poorly Water-Soluble Drugs with Enteric Coating Agents<sup>1)</sup>

AKIHIKO HASEGAWA,\* RIE KAWAMURA, HIROSHI NAKAGAWA,  
and ISAO SUGIMOTO

*Pharmaceuticals Research Center, Kanebo, Ltd., 1-5-90,  
Tomobuchi-cho, Miyakojima-ku, Osaka 534, Japan*

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Enteric coating agents, such as hydroxypropylmethylcellulose phthalate, methacrylic acid-methacrylic acid methyl ester copolymer, cellulose acetate phthalate, carboxymethylcellulose, were investigated as possible carriers for poorly water-soluble drugs in solid dispersions. In most cases, the drugs were present in amorphous form in the solid dispersions of 1:3 weight ratio of drug to polymer, though griseofulvin and phenytoin were not. Dissolution behavior was investigated using nifedipine, griseofulvin or spironolactone as a drug. The amorphous solid dispersions showed supersaturation phenomena in JP X 2nd fluid (pH 6.8), but the dissolution rate was suppressed in JP X 1st fluid (pH 1.2). It was confirmed that the physicochemical state of solid dispersions plays a predominant role in the dissolution of the drug from the solid dispersions.

**Keywords**—solid dispersions; coprecipitate; poorly water-soluble drug; enteric coating agent; nifedipine; griseofulvin; spironolactone

Chiou and Riegelman defined a "solid dispersion" as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting (fusion), solvent, or melting-solvent method.<sup>2)</sup> Sekikawa *et al.* defined a coprecipitate as an amorphous dispersion system of drug and carrier obtained by a solvent method.<sup>3)</sup> The solid dispersion technique was originally used to enhance the dissolution rate of poorly soluble drugs.<sup>4)</sup> We attempted to apply a solid dispersion technique using different types of enteric coating agents as inert carriers to control the release rate of water-insoluble and short-acting drugs, and reported the physicochemical properties,<sup>5a)</sup> bioavailability,<sup>5b)</sup> and application to sustained-release preparations<sup>5c)</sup> of solid dispersions or coprecipitates obtained from nifedipine and enteric coating agent (hydroxypropylmethylcellulose phthalate or methacrylic acid-methacrylic acid methyl ester copolymer) by a solvent method. Nifedipine in these solid dispersions was amorphous and was practically insoluble in JP X 1st fluid (JP disintegration medium, pH 1.2). However, it dissolved rapidly in JP X 2nd fluid (JP disintegration medium, pH 6.8) and showed supersaturation phenomena.<sup>5a)</sup> These solid dispersions were chemically and physically stable,<sup>5b)</sup> and provided delayed absorption of nifedipine with good bioavailability when given by oral administration.<sup>5b,c)</sup> This kind of new drug delivery system may provide a useful approach to obtain good bioavailability and delayed absorption behavior of poorly water-soluble drugs. In this work, solid dispersions were prepared with various combinations of poorly water-soluble drugs and enteric coating agents, and X-ray diffraction and dissolution studies were performed.

### Experimental

**Materials**—Nifedipine, mp 171—172 °C was prepared in our plant. Hydroxypropylmethylcellulose phthalate (HP-50, HP-55, JP X grade, Shin-Etsu Chemical Ind. Co., Ltd.), methacrylic acid-methacrylic acid methyl ester

copolymer (Eudragit L, Eudragit S, Röhm Pharma GmbH, W. Germany), carboxymethylethylcellulose (CMEC, Freund Ind. Co., Ltd.), cellulose acetate phthalate (CAP, JP X grade, Wako Pure Chemical Ind., Ltd.) were used as received. Griseofulvin, spironolactone, phenytoin, furosemide, indomethacin and ibuprofen were of JP X grade. Trimethoprim (Alps Pharmaceutical Ind. Co., Ltd.) and metronidazole (Fujikawa & Co., Ltd.) were used as received. Other chemicals were of reagent grade.

**Preparation of Solid Dispersions**—A drug (3 g) and a polymer (3–27 g) were dissolved in 30–270 ml of mixed solvent (ethanol: dichloromethane = 1 : 1) and then the solvent was evaporated off under reduced pressure at about 60 °C. The residual solid was pulverized and the 32–80 mesh fraction was used in the dissolution study.

**X-Ray Diffraction Study**—The X-ray diffraction patterns were determined with an X-ray diffractometer (Geigerflex 2027, Rigaku Denki, Ltd.;  $\text{CuK}_{\alpha}$ ; 30–40 kV; 10–20 mA).

**Dissolution Study**—A simple beaker-stirrer dissolution method as reported in the previous paper<sup>6)</sup> was employed. In all cases, the sample containing the equivalent of 50 mg of drug was dispersed in 500 ml of the dissolution medium at 37 °C. The test solution was filtered (Millipore, 0.22  $\mu\text{m}$  pore size) and assayed by spectrophotometry, or monitored with a recording spectrophotometer using a flow cell apparatus. Nifedipine, griseofulvin and spironolactone were assayed at 325, 330 and 242 nm, respectively. All dissolution experiments were carried out in duplicate and the results were highly reproducible. Thus, only mean values are reported.

**Storage Conditions**—In order to study the physical stability of solid dispersions, the samples were kept in a desiccator maintained at 40 °C/80% relative humidity (R.H.) for 2 months.

## Results and Discussion

### Crystallinity of Several Poorly Water-Soluble Drugs in Solid Dispersions

Several solid dispersions of poorly water-soluble drugs and enteric coating agents were prepared in order to investigate the crystallinity of the drugs in these systems. The term crystallinity refers to the ratio of crystalline regions of a drug to amorphous regions.<sup>7)</sup> Crystallinity has been recognized as an important factor affecting physical and chemical properties,<sup>8)</sup> dissolution behavior,<sup>9)</sup> and bioavailability.<sup>10)</sup> X-Ray diffraction analysis is the traditional method for qualitative identification of the crystalline phase, but this method is not well suited for quantitative crystallinity measurement.<sup>11)</sup> Thus, the degrees of crystallinity of solid dispersions were not investigated quantitatively in this paper. Table I shows the X-ray diffraction data for various solid dispersions containing 1 : 3 weight ratio of drug to polymer.

In this table, (+) indicates that diffraction peaks attributable to drug crystals were observed by X-ray analysis, and (–) indicates that no diffraction peaks were observed by X-ray analysis. Most of the drugs in the solid dispersions were found to be in amorphous form, though some of the drugs, such as griseofulvin and phenytoin, were present in crystalline form in the case of 1 : 3 weight ratio of drug to polymer. Griseofulvin and phenytoin were present in

TABLE I. Crystallinity of Drugs in Solid Dispersions (Drug : Polymer = 1 : 3)  
Determined by the X-Ray Diffraction Method

Drug	Polymer					
	HP-50	HP-55	Eudragit L	Eudragit S	CAP	CMEC
Nifedipine	–	–	–	–	–	–
Spironolactone	–	–	–	–	–	–
Indomethacin	–	–	–	–	–	–
Trimethoprim	–	–	–	–	–	–
Metronidazole	–	–	–	–	–	–
Ibuprofen	N.M. <sup>a)</sup>	N.M. <sup>a)</sup>	–	–	–	–
Furosemide	–	–	+	–	–	–
Griseofulvin	+	+	+	+	+	+
Phenytoin	+	+	+	+	+	+

+ : Diffraction peak. – : No diffraction peak. a) Not measured.

amorphous form in the solid dispersions (drug : polymer = 1 : 6) using HP-50 or HP-55 as a carrier. However, these drugs were present in crystalline form in the solid dispersions (drug : polymer = 1 : 6) using Eudragit L, Eudragit S, CAP or CMEC as a carrier. In the case of ibuprofen, the X-ray diffraction pattern of HP-50 or HP-55 solid dispersion was not determined, since these samples could not be pulverized. Sekikawa *et al.*<sup>3)</sup> investigated the inhibitory effect of polyvinylpyrrolidone (PVP) on the crystallization of several drugs in organic solvents, and showed that the mechanism responsible for the lack of crystallinity of the drug in the PVP solid dispersions might be the inhibition of crystallization of the drug by PVP when the solvent was evaporated off to prepare the solid dispersions. It is thought that many factors affect the final physical properties of solid dispersions, such as the interaction between polymer and drug,<sup>2,3)</sup> the solubility of the drug in the solvent used,<sup>1,2)</sup> the viscosity properties of the solution,<sup>2)</sup> control of temperature and time of evaporation,<sup>2)</sup> and others. In this paper, the factors affecting the drug crystallinity were not investigated. Further investigation is in progress to elucidate the mechanism of the lack of crystallinity.

### Dissolution Study of Solid Dispersions

i) **Nifedipine-CMEC or CAP**—Figure 1 shows the dissolution properties of CMEC and CAP solid dispersions (nifedipine : polymer = 1 : 3) in JP X 1st and 2nd fluids.

The dissolution rate of nifedipine was suppressed in JP X 1st fluid. It was markedly increased in the initial stage of dissolution and showed high supersaturated concentrations in JP X 2nd fluid. In the case of both CMEC and CAP, nifedipine was present in amorphous form in the solid dispersions (Table I). These results are similar to the cases of HP-50, HP-55

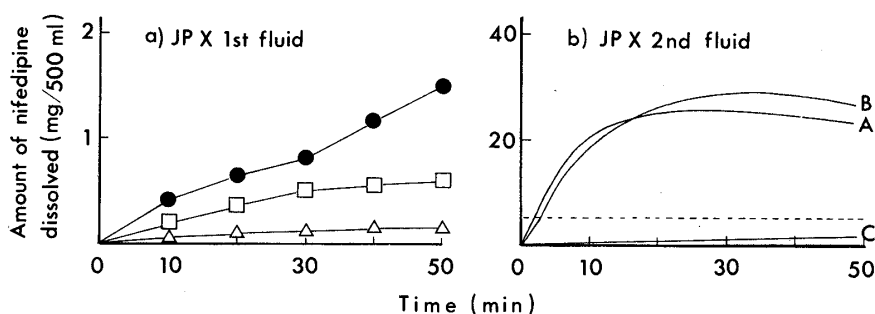


Fig. 1. Dissolution Behavior of Nifedipine from Solid Dispersions (Drug : Polymer = 1 : 3) in JP X 1st (pH 1.2) and 2nd (pH 6.8) Fluids

(□, A), CMEC; (△, B), CAP; (●, C), nifedipine crystals.  
The dotted line shows the solubility of nifedipine.

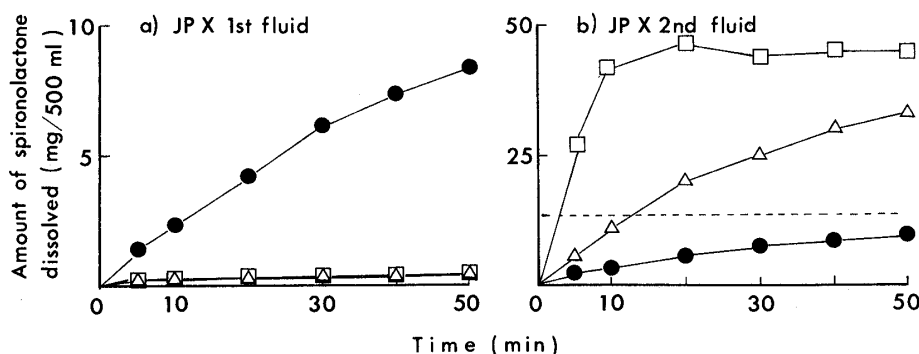


Fig. 2. Dissolution Behavior of Spironolactone from Solid Dispersions (Drug : Polymer = 1 : 3) in JP X 1st and 2nd Fluids

□, CMEC; △, Eudragit L; ●, spironolactone crystals.  
The dotted line shows the solubility of spironolactone.

and Eudragit L.<sup>5a)</sup> That is, nifedipine was present in amorphous form in a solid dispersion of 1 : 3 weight ratio of nifedipine to HP-50, HP-55, Eudragit L or Eudragit S, and these solid dispersions suppressed the dissolution rate of nifedipine in JP X 1st fluid and showed supersaturation following rapid dissolution in JP X 2nd fluid, except for the case of Eudragit S (Eudragit S dissolves above pH 7).

**ii) Spironolactone—CMEC or Eudragit L**—Spironolactone was present in amorphous form in the solid dispersions (Table I). Thus, the dissolution properties of spironolactone in JP X 1st and 2nd fluid from a solid dispersion using CMEC or Eudragit L were studied. However, HP-55 or CAP was not studied, since the phthalate groups of these polymers disturbed the drug analysis by the ultraviolet (UV) method. Figure 2 shows the dissolution properties of spironolactone from the solid dispersions in JP X 1st and 2nd fluids.

These solid dispersions remarkably suppressed the dissolution rate of spironolactone in JP X 1st fluid, and showed supersaturation phenomena in JP X 2nd fluid.

**iii) Griseofulvin—HP-55, CMEC, CAP or Eudragit L**—In the case of griseofulvin or phenytoin, a larger amount of carrier was required to obtain amorphous solid dispersions compared with the other cases (Table I). Griseofulvin was selected as a model drug and the physical properties of the solid dispersions were investigated. The dissolution properties of griseofulvin from the solid dispersions (drug : polymer = 1 : 3) in JP X 2nd fluid are shown in Fig. 3.

None of the solid dispersions gave high supersaturated concentrations of drug. The X-ray diffraction patterns showed many sharp peaks attributable to griseofulvin crystals in all the solid dispersions (Table I). It was suggested that the inferior dissolution behavior compared with the cases of nifedipine and spironolactone resulted from the presence of the

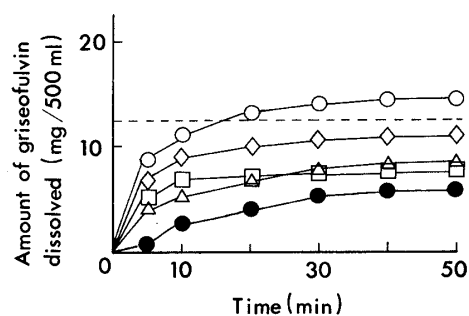


Fig. 3. Dissolution Behavior of Griseofulvin from Solid Dispersions (Drug: Polymer = 1 : 3) in JP X 2nd Fluid

◇, HP-55; △, Eudragit L; ○, CAP; □, CMEC; ●, griseofulvin crystals.  
The dotted line shows the solubility of griseofulvin.

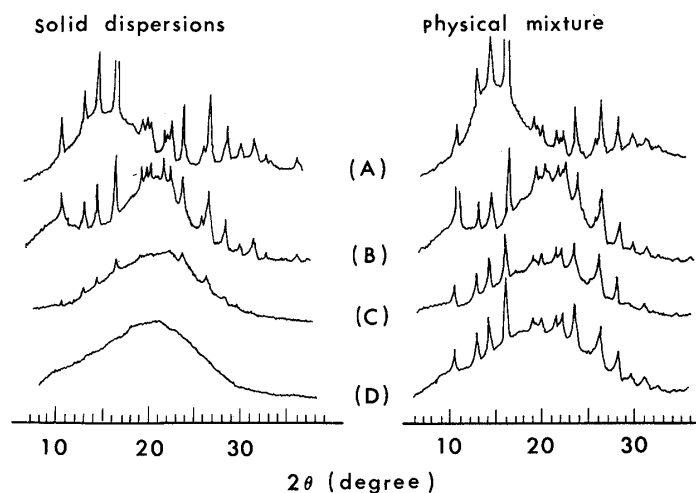


Fig. 4. X-Ray Diffraction Spectra of Griseofulvin-Polymer (1 : 6) Solid Dispersions

(A), Eudragit L; (B), CMEC; (C), CAP; (D), HP-55.

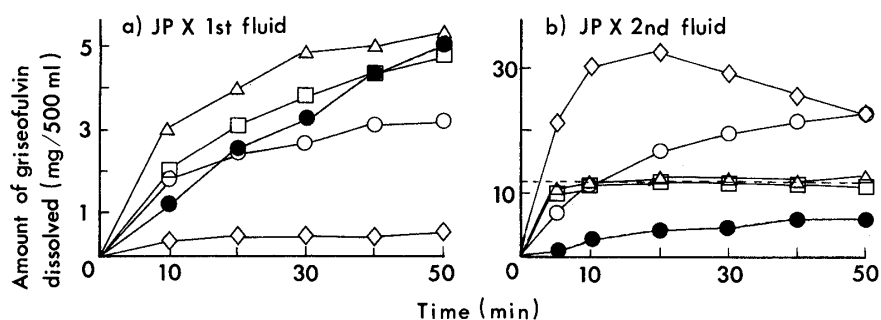


Fig. 5. Dissolution Behavior of Griseofulvin from Solid Dispersions (Drug: Polymer = 1 : 6) in JP X 1st and 2nd Fluids

◇, HP-55; △, Eudragit L; ○, CAP; □, CMEC; ●, griseofulvin crystals.  
The dotted line shows the solubility of griseofulvin.

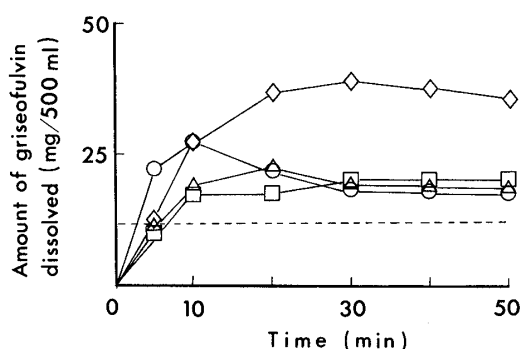


Fig. 6. Dissolution Behavior of Griseofulvin from Solid Dispersions (Drug: Polymer = 1 : 9) in JP X 2nd Fluid

○, HP-55; △, Eudragit L; ◇, CAP; □, CMEC.

crystalline form of griseofulvin. Figure 4 shows the X-ray diffraction patterns of the solid dispersions (griseofulvin : polymer = 1 : 6) and the corresponding physical mixtures.

The solid dispersion using HP-55 or CAP as a carrier showed marked differences in the X-ray diffraction pattern from the physical mixtures. No sharp peaks were observed in the solid dispersion using HP-55. The solid dispersion using CAP may contain a small part of griseofulvin in the crystalline form. Many sharp peaks attributable to griseofulvin crystals were observed in the other enteric coating agent matrices, as well as in the corresponding physical mixtures. Figure 5 shows the dissolution properties of griseofulvin from the solid dispersions (drug : polymer = 1 : 6) in JP X 1st and 2nd fluids.

The solid dispersion using HP-55 showed a particularly suppressed dissolution rate in JPX 1st fluid compared with that of the drug alone (Fig. 5-a). This remarkable suppression might be due to the homogeneous distribution of drug in the polymer matrix, which is insoluble at pH 1.2. That is, recrystallization of the drug was observed clearly during the evaporation process to obtain the solid dispersions in the cases of CMEC and Eudragit L, but it was not observed in the case of HP-55. In the case of CAP, the solution became turbid during the evaporation. Therefore, the possible recrystallization of the drug could not be observed clearly. HP-55 and CAP solid dispersions showed supersaturation in JP X 2nd fluid (Fig. 5-b).

Figure 6 shows the dissolution properties of griseofulvin from the solid dispersions (drug : polymer = 1 : 9) in JPX 2nd fluid. All of the solid dispersions showed supersaturation phenomena. In the cases of HP-55, CAP and Eudragit L, the solid dispersions showed no sharp peaks in the X-ray diffraction pattern. The solid dispersion using CMEC showed small peaks attributable to griseofulvin, whereas the corresponding physical mixture showed many sharp peaks. Thus, a small part of the griseofulvin might be present in the crystalline form in CMEC solid dispersion. It was confirmed that the physicochemical state of griseofulvin in the

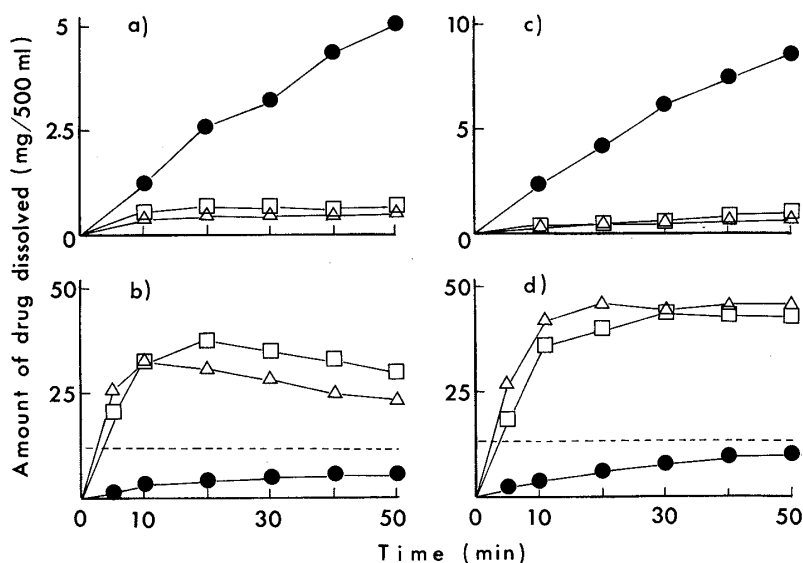


Fig. 7. Effect of Storage (40°C/80% R.H., 2 Months) on the Dissolution Behavior of Solid Dispersions

a) griseofulvin-HP-55 (1:6), JP X 1st fluid; b) griseofulvin-HP-55 (1:6), JP X 2nd fluid; c) spironolactone-CMEC (1:3), JP X 1st fluid; d) spironolactone-CMEC (1:3), JP X 2nd fluid.  $\triangle$ , initial;  $\square$ , 40°C/80% R.H., 2 months;  $\bullet$ , drug crystals. The dotted line shows the drug solubility.

polymer matrix plays a predominant role in the dissolution behavior from these solid dispersions, and only systems in which the crystallinity of griseofulvin was decreased showed the supersaturation phenomenon.

### Physical Stability of Solid Dispersions

Storage of a solid dispersion of nifedipine and PVP under humid conditions resulted in a decrease of nifedipine dissolution, and it was confirmed that this was due to the crystallization of nifedipine, which was initially dispersed in the PVP matrix in a nearly amorphous form.<sup>13)</sup> The stability of griseofulvin-HP-55 (1:6) and spironolactone-CMEC (1:3) solid dispersions was also studied. These samples were stored at 40°C/80% R.H. for 2 months, and the dissolution and X-ray diffraction properties of the solid dispersions were studied. Figure 7 shows the effect of storage on the dissolution behavior of the solid dispersions in JP X 1st and 2nd fluids.

The dissolution behavior of the solid dispersions did not change during storage, and the X-ray diffraction pattern did not show any sharp peaks attributable to the crystalline form of the drugs. Thus, the physical state of the solid dispersions did not change under rather hot and humid conditions.

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