Application of the Solid Dispersion Method to the Controlled Release of Medicine. III.[1] Control of the Release Rate of Slightly Water Soluble Medicine from Solid Dispersion Granules[2]

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In order to control the release rate of slightly water soluble medicine by using the solid dispersion (SD) method, the SD was prepared with a water soluble polymer and the slightly soluble medicine, and the medicine release from the solid dispersion granules was studied. The SD granules were prepared by the evaporation of ethanol after dissolving into ethanol a slightly water soluble medicine (flurbiprofen (FP)) and soluble polymers (hydroxypropyl cellulose (HPC)). HPC has four grades of molecular weight. The release rate of FP from SD was measured by the rotating basket method (JP XII).

The release rate of FP from the SD granules was markedly larger than that from FP powder, and it was larger with a lower HPC molecular weight. It is speculated that these results were mainly based on the molecular dispersion state of FP and HPC in SD.

Keywords slightly water soluble medicine; flurbiprofen; solid dispersion; granule; water soluble polymer; release rate

Generally, solid dispersion (SD) is defined as a solid in which the drug is dispersed into its inert carrier.[3,4] The SD method is one of the pharmaceutical techniques for controlling medicine release, and is used to improve the dissolution properties and bioavailability of slightly water soluble medicines.[5–9] Hasegawa *et al.* reported that the SD which was prepared with nifedipine increased the dissolution properties and bioavailability of nifedipine.[10–16]

In our previous paper,[1] we applied the SD method using water soluble and slightly water soluble polymers to a highly water soluble medicine, and showed that it was possible to control the medicine release. In the experiment of this paper, SD granules were prepared by using slightly water soluble flurbiprofen (FP) and four grades of hydroxypropyl cellulose (HPC) having different molecular weights, and a precise control of the release rate of FP depending on the difference in molecular weight of HPC was attained.

Experimental

Materials FP, known as a non-steroidal anti-inflammatory and slightly water soluble medicine, was supplied by Nissin Flour Milling Co., Ltd., Saitama. Its pK_a is about 3.8 and the solubility is about 30 mg/l of water at 37 °C. Three particle sizes of FP powder were used, and the sizes of 355—250, 180—150 and 106—75 μm were collected as particle size L, M and S, respectively. Four grades of HPC having different molecular weights were obtained from Nippon Soda Co., Ltd., Tokyo. The name of HPC grade, densities and mean molecular weight (MW) are shown in Table I.

Preparation of SD Granules 0.5 g FP and 9.5 g of each grade of HPC were dissolved in 400 ml ethanol, and then the solvent was evaporated to make the SD. The SD was ground and sieved. The fractions of 1.00 mm—850 μm, 710—590 μm and 500—350 μm were collected as granule sizes L, M, and S, respectively. L size granules were used in the cases where no description is given of the granule size.

TABLE I. Density and Mean Molecular Weight of Used Polymer

Polymer		Density (g/ml)	$\overline{MW}$
HPC	HPC-SL	1.21	73500
	HPC-L	1.21	105000
	HPC-M	1.20	270000
	HPC-H	1.21	357000

Dissolution Study The dissolution behavior of FP from the granule and FP powder was observed with a flow sampling system (dissolution tester; DT-300, triple flow cell; DTF-359, spectrophotometer; UVITEC-340, Freund-JASCO), following the rotating basket method (JP XII), using 0.2 g of the granule sample (corresponding to 40 mg FP) and 900 ml of the dissolution medium at 37±0.5 °C and a rotating basket at 100 rpm. The quantity of FP was determined with the absorbance at 246 nm. Distilled water (pH 5.8), buffer solutions composed of NaCl and KCl of pH 1.2, KH_2PO_4 and Na_2HPO_4 of pH 5.5, KH_2PO_4 and NaOH of pH 6.8, H_3PO_4, KCl and NaOH of pH 9.0 and Na_2HPO_4 and NaOH of pH 11.0 were used for the dissolution medium. The release rate was calculated from the release profiles from the start of the dissolution test up to 5 min by using the linear least square method.

Analysis of Solid State of SD The solid state of the SD was analyzed by the powder X-ray diffraction patterns with a diffractometer (Geigerflex RAD-IB, Rigaku, Ni-filter, CuK_α ray (40 kV, 20 mA)) and the thermal analysis with differential scanning calorimetry (DSC) (SSC/560S, Seiko Instruments & Electronics Ltd.) at the heating rate of 4 °C/min. DSC sample weight corresponded to 0.4 mg FP.

Results and Discussion

Effects of the Granule Size of SD on the Dissolution Behavior of FP Figure 1 shows the release profiles from different sizes of SD granules prepared with different molecular weights of HPC and different sizes of FP powder. The release rate of FP from each SD granule was larger than that from any FP powder. The release rate increased with a smaller granule size in every SD granule prepared with four different molecular weights of HPC. It was thought that the reduction in granule size caused an increase in the effective surface area of the granule for the dissolution of FP.

Effects of Molecular Weight of HPC on the Release Rate of FP from SD Granules The effects of the molecular weight of HPC on the release rate of FP from SD granules are shown in Fig. 2. In all the SD granules, high release rates were observed compared with that from FP powder. The release rate of FP from SD granules increased with a smaller molecular weight of HPC. It was thought that these results were caused by the difference in the solubility of HPC in the dissolution medium and the diffusion rates of FP in the swelled phase HPC.

Effects of pH on the Release Rate Figure 3 shows the

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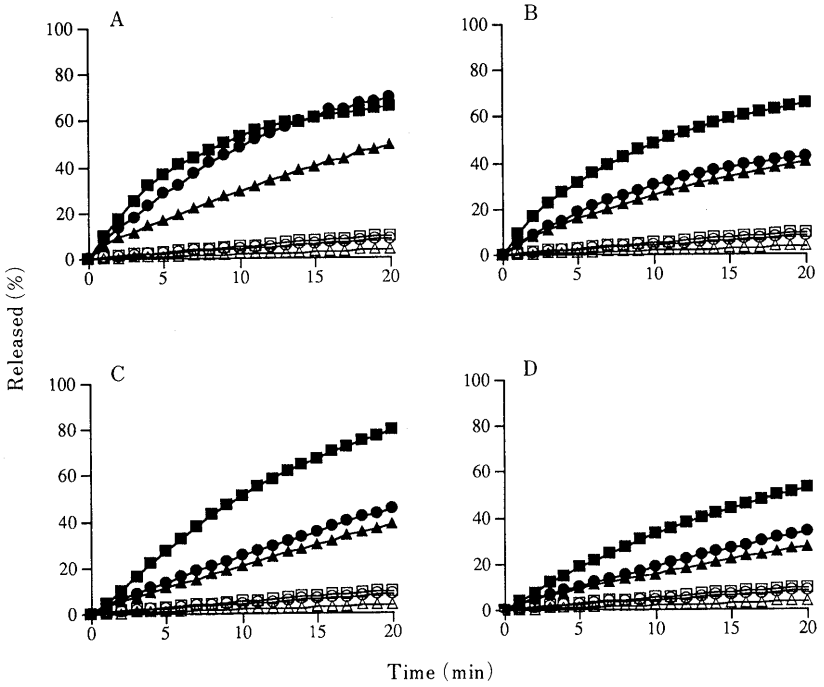

Fig. 1. Effects of the Granule Size of SD and FP Powder on the Dissolution Behavior of FP

Used polymer: HPC-SL (A), HPC-L (B), HPC-M(C), HPC-H(D). Granule size of SD: ■, S; ●, M; ▲, L. Particle size of FP powder: □, S; ○, M; △, L. Each point represents the mean of three experiments.

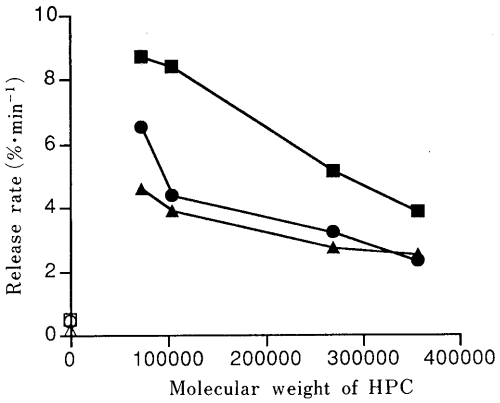

Fig. 2. Effects of Molecular Weight of HPC on the Release Rate of FP from SD Granules

Granule size of SD: ■, S; ●, M; ▲, L. Particle size of FP powder: □, S; ○, M; △, L. Each point represents the mean of three experiments.

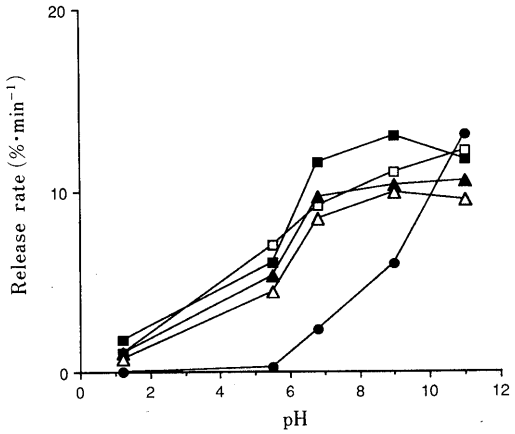

Fig. 3. Effects of pH on the Release Rate of FP from SD Granules and FP Powder

■, HPC-SL; □, HPC-L; ▲, HPC-M; △, HPC-H; ●, FP powder. Each point represents the mean of three experiments.

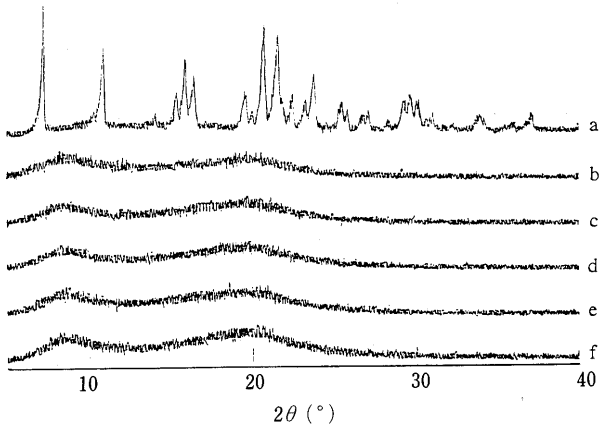

Fig. 4. Powder X-Ray Diffraction Patterns of FP Powder (a), Physical Mixture Prepared with HPC-H (b) and SD Prepared with HPC-SL (c), HPC-L (d), HPC-M (e), HPC-H (f)

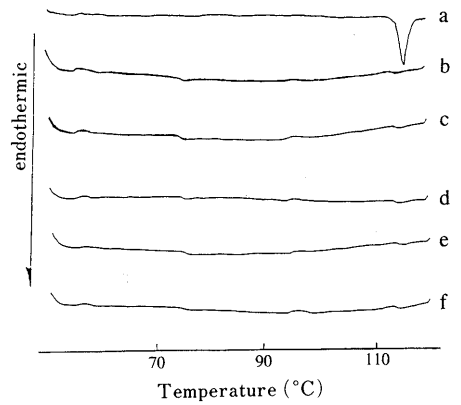

Fig. 5. DSC Curves of FP Powder (a), Physical Mixture Prepared with HPC-H (b) and SD Prepared with HPC-SL (c), HPC-L (d), HPC-M (e), HPC-H (f)

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effect of pH of the dissolution medium on the release rate of FP. In both cases of FP powder and SD granules, the release rates increased with a higher pH of the dissolution medium. The release rate of FP from SD granules were larger than that from FP powder in a wide range of pH. Particularly, in the pH range of 1—7, which is the pH in the digestive tract, a significant improvement was observed in the solubility of FP. These results suggest that the bioavailability of FP may be improved by using the SD method.

Physicochemical State of SD The powder X-ray diffraction patterns and the DSC curves of FP powder, the physical mixture prepared with HPC-H and the four SDs are shown in Figs. 4 and 5, respectively. In all the SDs and the physical mixture, the X-ray diffraction peaks of FP disappeared in Fig. 4 and the melting endothermic peak of FP around 110 °C was not observed in Fig. 5. The other three physical mixtures prepared with different grades of HPC showed the same results as Figs. 4b and 5b (data not shown). These results suggest that FP existed in the amorphous state in the SD, and that a slight amount of FP was contained in the SD. However, as the solubility of FP was markedly improved by preparing FP into the SD (in Figs. 1 and 2), it was thought that FP and HPC were dispersed in the molecular level in the SD, and so FP existed in the amorphous state. For the disappearance of the X-ray diffraction peaks and the melting endothermic peak of FP in the physical mixtures, further study is now under way.

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