Application of the Solid Dispersion Method to the Controlled Release of Medicine. VI.[1] Release Mechanism of a Slightly Water Soluble Medicine and Interaction between Flurbiprofen and Hydroxypropyl Cellulose in Solid Dispersion[2]

Hiroshi YUASA,[a] Tetsuya OZEKI,*,[a] Hiroyuki TAKAHASHI,[a] Yoshio KANAYA,[a] and Masao UENO[b]

Tokyo College of Pharmacy,[a] 1432–1 Horinouchi, Hachioji, Tokyo 192–03, Nissin Flour Milling Co., Ltd.,[b] Irumagun, Saitama 354, Japan. Received August 31, 1993; accepted October 12, 1993

Solid dispersion (SD) was prepared with a slightly water soluble medicine (flurbiprofen (FP)) and a water soluble polymer (hydroxypropyl cellulose (HPC)) having five grades of different molecular weights. The release mechanism of FP from the SD granules and the interaction between FP and HPC in the SD were studied.

The release rate of FP from the SD granules increased with decreasing HPC molecular weight or increase in the composition ratio of HPC. The powder X-ray diffraction patterns and DSC curves suggest that FP exists in an amorphous state in the SD. The IR spectra show an interaction of hydrogen bonding between FP and HPC. The percent of FP forming a hydrogen bond with HPC in the SD increased with decreasing HPC molecular weight or increase in the composition ratio of HPC. A linear relationship was found between the release rate of FP and the percent of the hydrogen bonded FP in the SD. An increase in the dispersibility of FP and the degree of mixing of FP and HPC will cause an increase in the effective surface area of FP and HPC for dissolution, thus increasing the release of FP and the percent of hydrogen bonded FP.

Keywords solid dispersion; hydrogen bonding; release mechanism; flurbiprofen; hydroxypropyl cellulose

The solid dispersion (SD) method can be used to improve the dissolution properties and bioavailability of slightly water soluble medicines by dispersing them into inert carriers.[3-5] In a previous paper,[6] we prepared SD granules with a slightly water soluble medicine (flurbiprofen (FP)) and hydroxypropyl cellulose (HPC) and reported that the release rate of FP from the SD granules was markedly larger than that from FP powder, and that it was possible to precisely control the medicine release by varying the molecular weight of HPC in the SD. In this paper, in consideration of the interaction between FP and HPC, the release mechanism of FP was studied in terms of varying molecular weights of HPC.

Experimental

Materials FP, known as a non-steroidal anti-inflammatory and slightly water soluble medicine, was supplied by Nissin Flour Milling Co., Ltd., Saitama. Five grades of HPC having different molecular weights were obtained from Nippon Soda Co., Ltd., Tokyo. The names of HPC grades, densities and mean molecular weights are shown in Table I. The molecular weights of the polymers were estimated by gel-permeation chromatography, which was conducted on a Shimadzu LC-6A GPC system (Shimadzu Seisakusho Co.) with a Shim-pack GPC-805 and a GPC-804 column (8.0 mm i.d. × 300 mm, Shimadzu Seisakusho Co.). The solvent was tetrahydrofuran at a flow rate of 1.0 ml/min.

Preparation of Samples The powders of FP and each grade of HPC (total amount: 10 g) were dissolved into 400 ml ethanol, and then the solvent was evaporated to make SD. The SD was ground and sieved at 850 μm—1 mm. The SD granules were dried at 60 °C for 24 h *in vacuo*. Physical mixtures (PM) were prepared by simply mixing the powdered FP and HPC, each of which was preliminarily sieved at 75—106 μm (total amount: 2 g), at the same composition ratios as those of the SD. The HPC granules composed of HPC alone were prepared in the same manner as the SD granules.

Dissolution Study The release profiles of FP from the SD granules and FP powder were observed by using 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 the granule sample corresponding to 15 mg FP and 900 ml distilled water as the dissolution medium at 37±0.5 °C and a rotating

TABLE I. Densities and Average Molecular Weights of Polymers Used

Polymer	Density (g/ml)	$\overline{M}_n$ [a]	$\overline{M}_w$ [b]	$\overline{M}_z$ [c]	$\overline{M}_w/\overline{M}_n$ [d]
Hydroxypropyl cellulose (HPC)					
HPC-SSL	1.23	18000	37000	64500	2.055
HPC-SL	1.21	33500	73500	139000	2.194
HPC-L	1.21	46000	105000	178500	2.282
HPC-M	1.20	99500	270000	419500	2.713
HPC-H	1.21	154000	357000	537500	2.318

a) Number-average molecular weight. *b*) Weight-average molecular weight. *c*) Z-average molecular weight. *d*) Polydispersity coefficient.

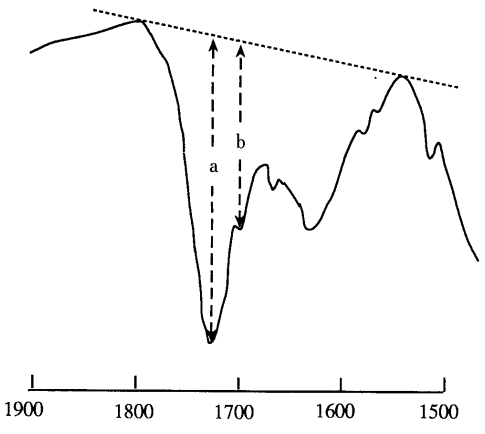

Fig. 1. Typical IR Spectra of the SD and Used Base Line for Estimating Percent of FP Hydrogen Bonding with HPC

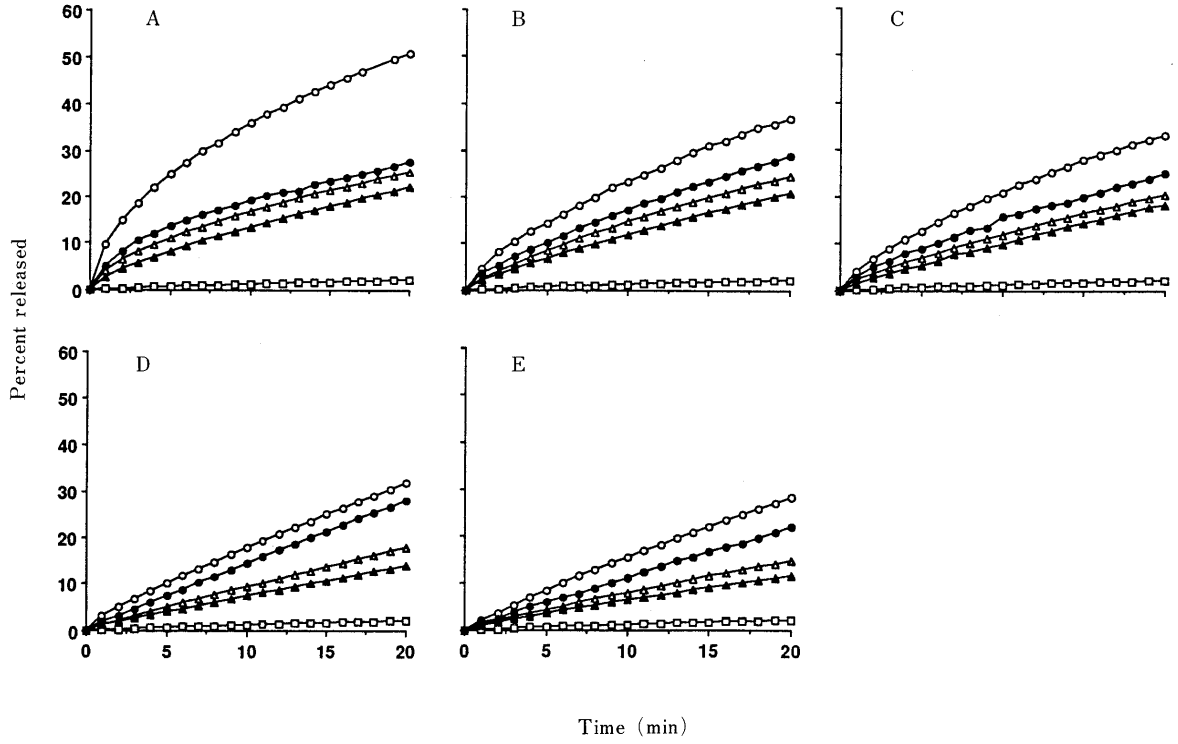

Fig. 2. Effects of Composition Ratio and Molecular Weight of HPC on the Release Profile of FP from the SD Granules

A, HPC-SSL; B, HPC-SL; C, HPC-L; D, HPC-M; E, HPC-H. Percent of HPC (○, 95%; ●, 90%; △, 85%; ▲, 80%); □, FP powder. Each point represents the mean of three experiments.

basket at 100 rpm. The quantity of FP was determined spectrophotometrically at 246 nm. The release rates were calculated from the release profiles from the start of the dissolution test up to 5 min using the linear least squares method.

Measurement of Decrease in Granule Weight A dissolution test was carried out by the rotating basket method (JP XII) with a dissolution tester (DT-300, Freund-JASCO), using 0.5 g of the samples after drying at 70 °C for 3 h *in vacuo*. The samples were taken out at appropriate intervals and weighed after drying thoroughly. The degree of the decrease in granule weight was calculated from the difference in weight before and after the dissolution test.

Powder X-Ray Diffractometry Powder X-ray diffraction patterns were measured with a diffractometer (Geigerflex RAD-IB, Rigaku, Ni-filter; CuK_α ray; 40 kV; 20 mA; $2\theta = 4°$/min).

Thermal Analysis Differential scanning calorimetry (DSC) curves were measured with a DSC instrument (SSC/560S, Seiko Instruments & Electronics Ltd.) at the heating rate of 4 °C/min.

IR Spectroscopy IR spectra were recorded with an infrared spectrophotometer (IR-810, JASCO) by the KBr disk method. The percent of FP hydrogen bonding with HPC was evaluated on the basis of the base line method.[7] The typical IR spectra of the SD and the base line used are shown in Fig. 1. The percent of FP hydrogen bonding with HPC was estimated as follows:

$$FP_h\% = (a/a+b) \times 100$$

where $FP_h\%$ is the percent of FP hydrogen bonding with HPC, a is the peak height at 1730 cm^{-1}, and b is the peak height at 1700 cm^{-1}.

Results and Discussion

Effects of the Molecular Weight and the Composition Ratio of HPC on the Medicine Release Figure 2 shows the release profiles of FP from the SD granules with varied molecular weights and the composition ratios of HPC. The release rates obtained from the slopes in the early stages of the release process were plotted against percent of HPC, and are shown in Fig. 3. In Fig. 2, all the SD

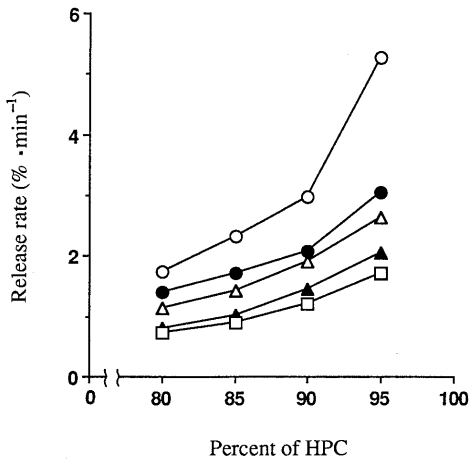

Fig. 3. Effects of Composition Ratio and Molecular Weight of HPC on the Release Rate of FP from the SD Granules

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

granules show a markedly larger release rate than FP powder. In Fig. 3, the release rate increased with increase in the composition ratio and decrease in the molecular weight of HPC. The medicine release from the SD granules is believed to be greatly affected by the state of the medicine in the SD, as reported by Hasegawa *et al.*[8] Therefore, powder X-ray diffractometry and thermal analysis were carried out to investigate the effects of the difference in the molecular weight and the composition ratio of HPC on the state of FP in the SD.

The powder X-ray patterns and the DSC curves of FP powder, HPC powders and the PMs and SDs using

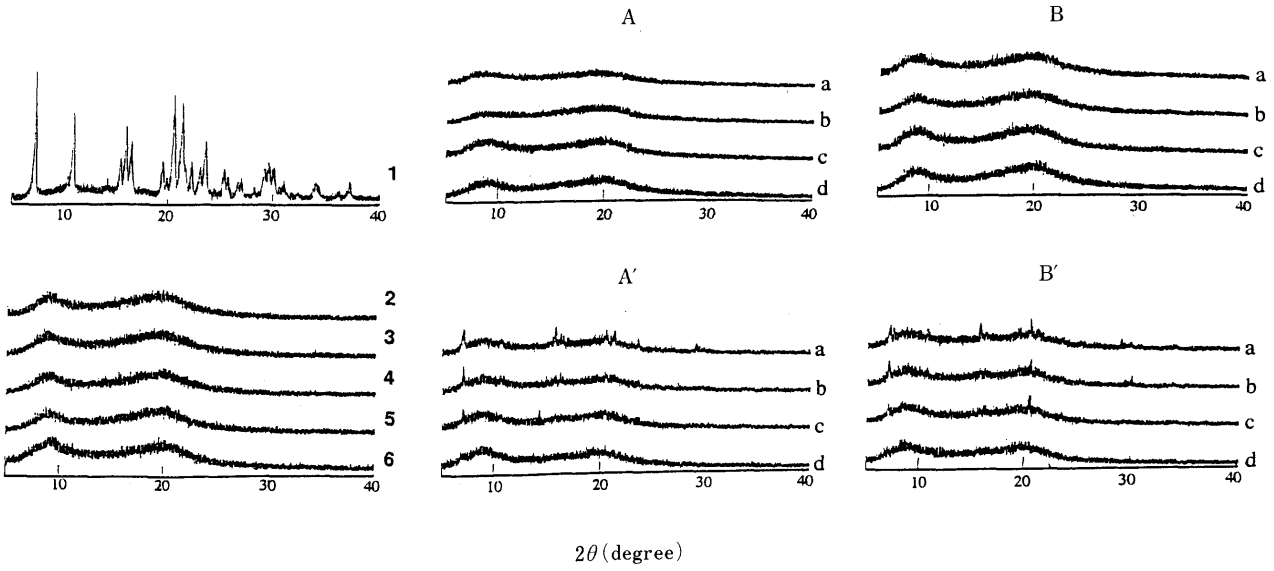

Fig. 4. Powder X-Ray Diffraction Patterns of FP Powder (1), HPC-SSL (2), HPC-SL (3), HPC-L (4), HPC-M (5), HPC-H (6), the SD Prepared with HPC-SSL (A) and HPC-H (B) and the Physical Mixture Prepared with HPC-SSL (A′) and HPC-H (B′)

Percent of HPC in the solid dispersion and the physical mixture; a: 80%, b: 85%, c: 90%, d: 95%.

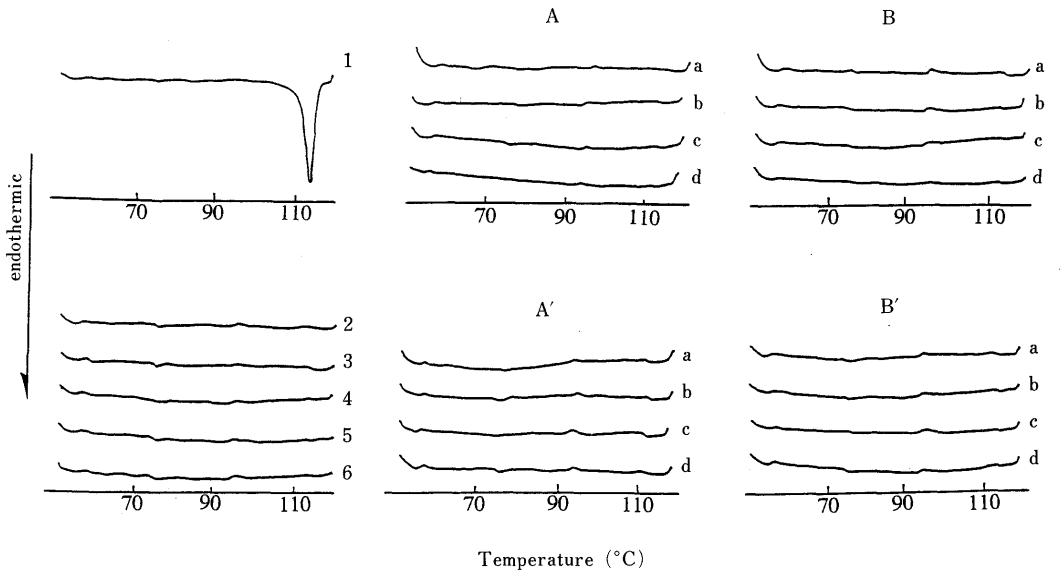

Fig. 5. DSC Curves of FP Powder (1), HPC-SSL (2), HPC-SL (3), HPC-L (4), HPC-M (5), HPC-H (6), the SD Prepared with HPC-SSL (A) and HPC-H (B) and the PM Prepared with HPC-SSL (A′) and HPC-H (B′)

Percent of HPC in the SD and the physical mixture; a: 80%, b: 85%, c, 90%, d: 95%.

HPC-SSL and HPC-H are shown in Figs. 4 and 5, respectively. In Fig. 4, the FP crystalline peaks were not observed in the SD, although the peaks appeared in PM. In Fig. 5, no melting endothermic peak based on FP crystal was observed in either SD or PM. The samples prepared using HPC having other molecular weights showed the same results (data not shown). These results suggest that FP exists in an amorphous state in the SD. The reason for the disappearance of the endothermic peak in the PM was presumably that the crystalline state of FP became the amorphous state because of the enhancement in molecular mobility during the heating process, which is in agreement with the manner reported by Sugimoto *et al.*[9] The markedly larger release rate of FP from the SD granules compared with that of FP powder was believed attributable to the amorphous state of FP in the SD. However, the effects of the molecular weight and the composition ratio of HPC on the FP release, which are shown in Figs. 2 and 3, were not clarified by the powder X-ray diffractometry or the thermal analysis.

We therefore suspected that the difference in the molecular weight and the composition ratio of HPC might affect the dispersibility of FP and the degree of mixing of FP and HPC in the SD, and studied the weight decrease profiles of the SD granules and the HPC granules during the dissolution test. The results are shown in Fig. 6.

In both the HPC granules (composed of HPC alone) and the SD granules, the degree and the rate of weight

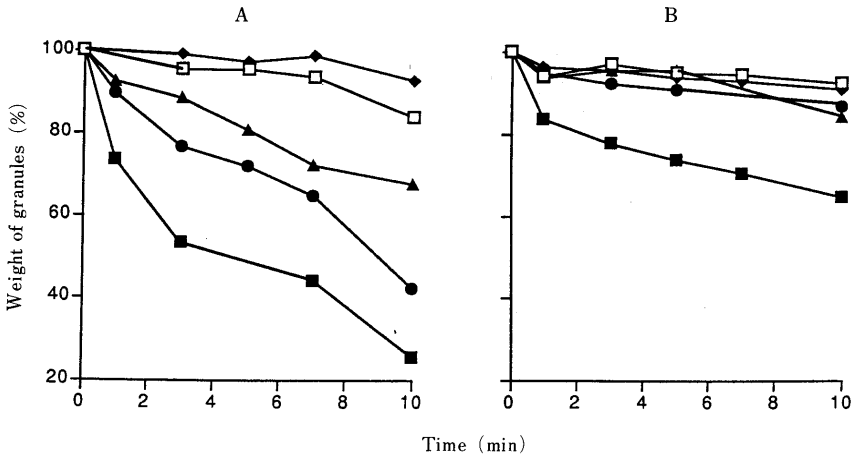

Fig. 6. Decreasing Profiles of Weight of the HPC Granules (A) and the SD Granules (B)

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

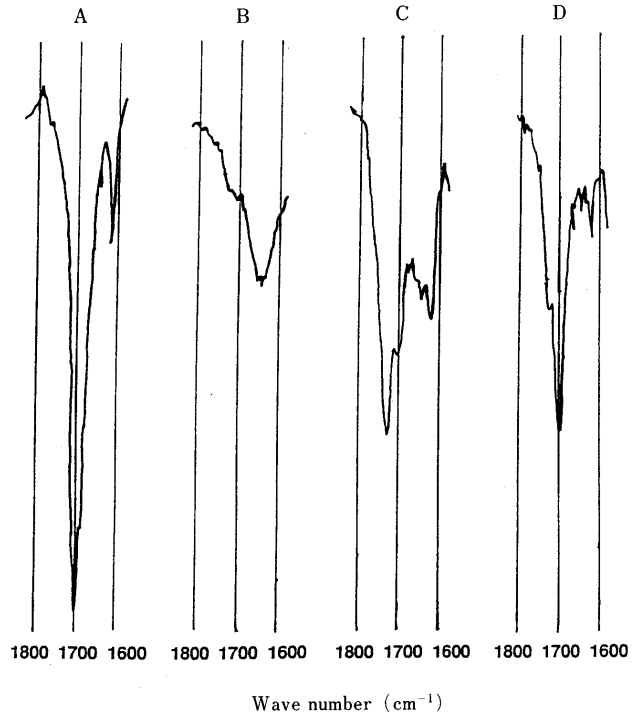

Fig. 7. IR Spectra of FP (A), HPC-L (B), the SD (C) and the PM (D)

The SD and the PM were composed of 80% HPC-L.

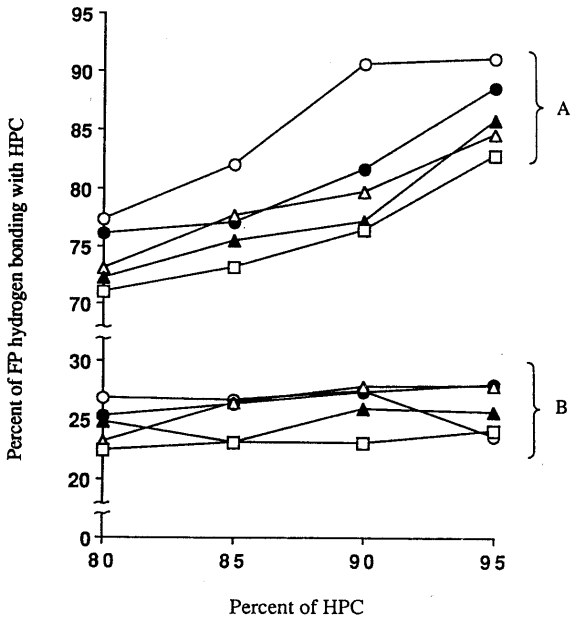

Fig. 8. Effects of Composition Ratio and Molecular Weight of HPC on Percent of FP Hydrogen Bonding with HPC

The SD (A), the PM (B). ○, HPC-SSL; ●, HPC-SL; △, HPC-L; ▲, HPC-M; □, HPC-H. Each point represents the mean of three experiments.

decrease increasd with decrease in the molecular weight of HPC. The reason for this is speculated to be as follows: Because the molecular volume of HPC is smaller when the molecular weight of HPC is decreased, the degree of mixing of FP molecules and HPC molecules increases with decreasing molecular weight of HPC. This would cause an increase in the effective surface area of FP and HPC for dissolution, and, therefore, the rate of dissolution of FP and HPC would increase. The rate of weight decrease of the SD granules was smaller than that of the HPC granules. This may be due to the extremely small molecular weight of FP compared with that of HPC.

When the degree of mixing of FP molecules and HPC molecules increases and the effective surface area of FP and HPC for dissolution increases, the probability of the interaction between FP and HPC is believed to increase. Therefore, these points were studied.

Interaction between FP and HPC and Release Mechanism of FP from SD Granules Figure 7 shows the IR spectra of FP powder, HPC powder, the SD and the PM at 1600—1800 cm^{-1}. FP powder has the carbonyl stretching band at 1700 cm^{-1} because of being in hydrogen bonding dimers.[10] In the SD and the PM, these carbonyl stretching bands were shifted to a higher wave number and appeared at 1730 cm^{-1}. These results can be explained as follows: FP was dissolved in the state of mixture of monomers and dimers,[10] HPC was also dissolved in ethanol during the preparation of the SD, and, when this ethanol solution was evaporated, the SD was formed while FP and HPC were interacting with each other by hydrogen bonding. The new band at 1730 cm^{-1} in the SD and the PM was assigned to hydrogen bonding between the carbonyl group

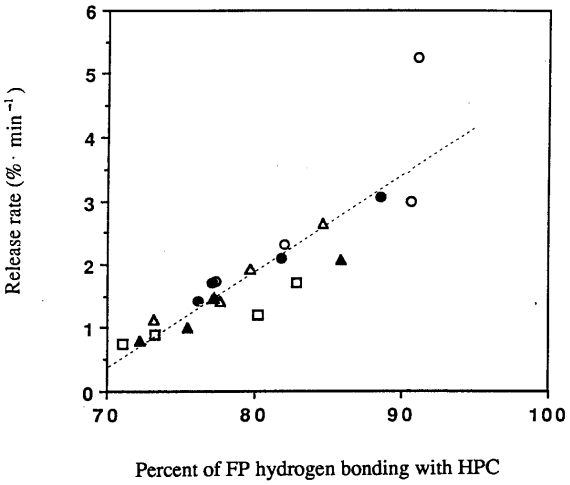

Fig. 9. Relationship between Release Rate of FP from the SD Granules and Percent of FP Hydrogen Bonding with HPC

○, HPC-SSL; ●, HPC-SL; △, HPC-L; ▲, HPC-M; □, HPC-H.

of FP and HPC.[11,12] Thus the interaction occurred between FP and HPC, and it is obvious that the interaction was mainly attributable to the hydrogen bonding between FP and HPC. Incidentally, with regard to the mutual interaction of HPC, it has been confirmed that the absorption spectra of the hydroxyl group forming intra- and intermolecular hydrogen bonding appear around 3200—3600 cm^{-1}.[13]

Accordingly, to clarify the relationship between the interaction of FP-HPC by hydrogen bonding and the degree of mixing of FP and HPC, we evaluated the value of the peak height at 1730 cm^{-1}/that at 1700 cm^{-1} + that at 1730 cm^{-1}, as an indication of the percent of FP hydrogen bonding with HPC. Figure 8 shows the value of the peak height ratio in the SD and the PM with varying molecular weights and composition ratios of HPC. In the SD, the percent of hydrogen bonded FP is much larger than that in the PM. Furthermore, in the SD with the same composition ratio of HPC, the percent was larger with a smaller molecular weight of HPC. In the case of the same molecular weight of HPC, the percent increased with increase in the composition ratio of HPC. These results are thought explainable by the following; The rotation and moving of HPC molecules in the preparation of the SD and the degree of mixing of FP in the SD increase with decreasing molecular weight of HPC. The number of the –OH groups and the dispersibility of FP in the SD increase with increasing composition ratio of HPC. These actions would cause an increase in the probability of a linear orientation of O–H–O required to form the hydrogen bond. Therefore, the percent of FP hydrogen bonding with HPC in the SD increases with decrease in the molecular weight and increase in the composition ratio of HPC.

Table II. Correlation Coefficients of SDs between Release Rate and Percent of FP Hydrogen Bonding with HPC

HPC grade in SD	HPC-SSL	HPC-SL	HPC-L	HPC-M	HPC-H
Correlation coefficient	0.814	0.990	0.977	0.977	0.949

Figure 9 shows the relationship between the release rate of FP from the SD granules and the percent of FP forming the hydrogen bond with HPC; a linear relationship between these two factors was observed. The correlation coefficients with different molecular weights of HPC, calculated by the linear least squares method, are shown in Table II. The correlation coefficients exhibited relatively high values in every grade of the SD granules with different molecular weights of HPC, suggesting that the release rate of FP was nearly proportional to the ratio of the hydrogen bonded FP.

The following is concluded; FP is dispersed into the SD in the molecular level when HPC is added, the dispersibility of FP in the SD is higher with increasing HPC composition ratio, and the degree of reciprocal mixing of FP and HPC in the SD is higher with decreasing HPC molecular weight. An increase in the dispersibility of FP and the degree of mixing of FP and HPC will cause an increase in the effective surface area of FP and HPC for dissolution, thus increasing the release of FP and the percent of hydrogen bonded FP.

References and Notes

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