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Application of the solid dispersion method to the controlled release of medicine. IX. Difference in the release of flurbiprofen from solid dispersions with poly(ethylene oxide) and hydroxypropylcellulose and the interaction between medicine and polymers

Tetsuya Ozeki, Hiroshi Yuasa *, Yoshio Kanaya

Laboratory of Medical and Pharmaceutical Technology, School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

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Abstract

Solid dispersions were prepared with a slightly water-soluble flurbiprofen (FP) and water-soluble hydroxypropylcellulose (HPC) or poly(ethylene oxide) (PEO). The release of FP from the FP-HPC and the FP-PEO solid dispersion systems was studied. The state of FP and the interaction between FP and the polymers in the solid dispersions were analyzed by powder X-ray diffractometry, thermal analysis and IR spectrometry. The release rate of FP from the FP-PEO system was significantly larger than that from FP powder and the FP-HPC system that we have previously studied. The dissolution property of the polymer base greatly affected the release of FP from the solid dispersions. In the FP-PEO system, the release rate increased with the increasing percent of PEO. In FT-IR spectra, FP has the carbonyl stretching band at 1703 cm^{-1} because it is in dimer. The new band was observed at 1736 cm^{-1} which was attributed to hydrogen bonding between FP and PEO in the FP-PEO system. The peak height ratio (the peak height at 1736 cm^{-1}/the sum of that at 1703 cm^{-1} and that at 1736 cm^{-1}) was evaluated as the indication of interaction between FP and PEO on the basis of a base-line method. A linear relationship between the peak height ratio and the release rate of FP was observed. These results were probably due to an increase in the ratio of hydrogen bonding of FP with the increasing percent of PEO in the solid dispersion. © 1997 Elsevier Science B.V.

Keywords: Solid dispersion; Poly(ethylene oxide); Hydroxypropylcellulose; Hydrogen bonding; Release rate; Flurbiprofen

* Corresponding author.

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1. Introduction

The solid dispersion method is one of several pharmaceutical techniques for controlling medicine release, and has been used to improve the dissolution properties and bioavailability of slightly water-soluble medicines (Chiou and Riegelman, 1970; Sekikawa et al., 1979; Fujii et al., 1990; Law et al., 1992; Suzuki et al., 1996; Yamamura and Rogers, 1996). We have reported that it is feasible to control the release rate of an extremely high water-soluble medicine (oxprenolol hydrochloride) by combining water-insoluble ethylcellulose and water-soluble hydroxypropylcellulose (HPC), both having different molecular weights, and clarified the medicine release mechanism from the solid dispersions (Yuasa et al., 1991, 1992, 1993b; Ozeki et al., 1994, 1995a,b). We have also studied the solid dispersions composed of a slightly water-soluble medicine (flurbiprofen (FP)) and HPC, and reported the effects of the composition ratio and the molecular weight of HPC on the release behavior of FP (Yuasa et al., 1993a, 1994).

Poly(ethylene oxide) (PEO) is a kind of water-soluble linear resin. PEO has been used in agricultural engineering, food, dental and pharmaceutical fields because of its aqueous solubility, high gelation and low toxicity (Nakamura, 1973; Graham and McNeill, 1984; Yang et al., 1996). PEO has recently been used for a directly compressed tablet matrix (Apicella et al., 1993; Kim, 1994).

In the present study, we prepared FP-PEO and FP-HPC solid dispersion granules and comparatively studied the FP release from the FP-PEO system and that from the FP-HPC system, which we have previously studied, in consideration of the interaction between FP and polymers.

2. Material and methods

2.1. Materials

FP, known as a non-steroidal anti-inflammatory and slightly water-soluble medicine (the solubility is about 30 mg/ml of water at 37°C) was purchased from Namiki Shoji, Tokyo. The density and molecular weight of FP are 1.25 g/cm^3 and 244.27, respectively. The chemical structure of FP is shown in Fig. 1. HPC (HPC-M, the viscosity-average molecular weight (Mn) is about 130 000, the density is 1.21 g/cm^3) was supplied by Nippon Soda, Tokyo. PEO (ALKOX R-150, Mn is about 135 000, the density is 1.24 g/cm^3, Meisei Chemical Works, Kyoto) was supplied by Higuchi, Tokyo. The densities of FP, PEO and HPC were calculated from the volume measured with an Air Comparison Pycnometer (Toshiba-Beckman, Model 930).

2.2. Preparation of samples

Powders of FP and PEO or HPC (total amount 10 g) were dissolved in ethanol (200 ml) at 50°C. The solid dispersion granules were prepared by the evaporation of ethanol, and then ground and dried at 40°C for 24 h under reduced pressure. The granules obtained were sieved (0.85–1.00 mm). The physical mixtures were prepared by simply mixing the powdered FP and PEO or HPC. Each of them was preliminarily sieved at 75–106 μm.

2.3. Release studies

The release profiles of FP from FP powder (sieved at 75–106 μm) and the solid dispersion granules containing 10 mg of FP were observed with a dissolution tester (Toyama Sangyo, TR-5S3), according to the rotating basket method (JP XII) at 100 rpm, using 900 ml distilled water as the dissolution medium at 37 ± 0.5°C. The quantity of FP was determined spectrophotometrically by measuring the absorbance at 246 nm.

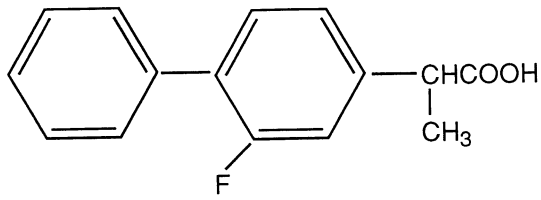

Fig. 1. Chemical structure of FP.

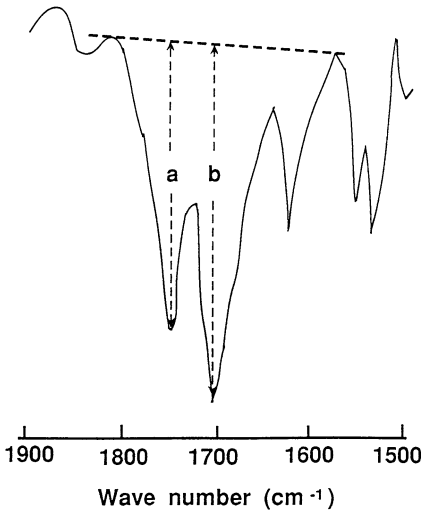

Fig. 2. Typical IR spectra of solid dispersion.

2.4. Powder X-ray diffractometry

Powder X-ray diffraction patterns were measured with a diffractometer (Rigaku, Geigerflex RAD-IB). The operating conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV; current, 20 mA and scanning speed, $2\theta = 4°$/min.

2.5. Thermal analysis

Differential scanning calorimetry (DSC) curves were measured with a DSC instrument (Seiko Instruments and Electronics, SSC/560S). The heating rate was 4°C/min and nitrogen gas flowed at a rate of 70 ml/min.

2.6. IR spectroscopy

IR spectra were recorded with an infrared spectrophotometer (Perkin-Elmer, 1710 FT-IR). IR spectra of powder samples and 2.0×10^{-2} M FP in CCl_4 solution were measured by the KBr disk method and through NaCl plates with a path length of 6 mm, respectively. Interaction between FP and polymers was evaluated on the basis of the base-line method (Ikekawa and Hayakawa, 1991; Yuasa et al., 1994). Typical IR spectra of the solid dispersion are shown in Fig. 2, where a is the peak height at 1726 cm^{-1} (in the case of the FP-HPC system) or at 1736 cm^{-1} (in the case of the FP-PEO system) and b is the peak height at 1703 cm^{-1} due to hydrogen bonding dimer of FP. The peak height ratio $\{a/(a+b)\}$ was used as the indication of interaction between FP and polymers.

2.7. Dissolution behavior of polymer

The solid dispersion granules were taken at appropriate intervals during the dissolution test, and weighed after thorough drying. The percent of decrease in the overall granule weight ($\%_{g.w.all}$) was calculated from the difference in weight before and after the dissolution test. The percent of decrease in the granule weight due to the FP release ($\%_{g.w.FP}$) was calculated as: (the percent of FP released) × (the percent of FP in the solid dispersion/100). The percent of decrease in the granule weight due to the polymer dissolution ($\%_{g.w.polymer}$) was calculated as: $\%_{g.w.all} - \%_{g.w.FP}$. The percent of polymer dissolved ($\%_{dis.polymer}$) was calculated as: ($\%_{g.w.polymer}$) × (100/the percent of polymer in the solid dispersion).

The PEO and HPC granules composed of polymer alone were prepared in the same manner as the solid dispersions. The percent dissolved of PEO and HPC from the PEO and HPC granules was calculated from the difference in weight before and after the dissolution test.

3. Results and discussion

3.1. Release profiles of FP from FP-HPC and FP-PEO solid dispersion granules

The release profiles of FP from FP powder and the solid dispersion granules of the FP-HPC and FP-PEO systems are shown in Fig. 3. The percent of FP in both solid dispersions was 20%. The solid dispersions show a larger release rate than FP powder. A markedly larger release rate was observed in the FP-PEO system compared with the FP-HPC system. In order to investigate the effect of polymer on the FP release, the powder X-ray diffractometry, DSC, FT-IR and the dissolution behavior of polymer bases were studied.

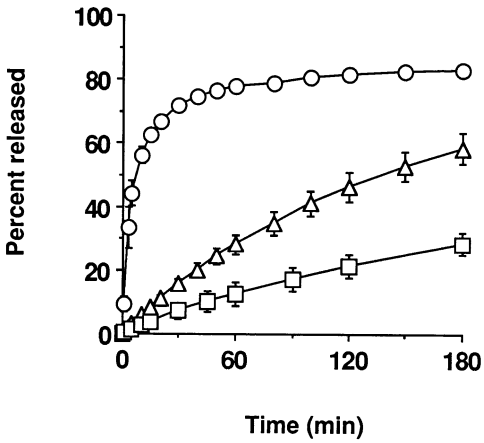

Fig. 3. Release profiles of FP from FP powder and solid dispersion granules of FP-PEO and FP-HPC systems. (□) FP powder, (○) FP-PEO system, (△) FP-HPC system. Each point represents the mean ± S.D. ($n = 3$).

The powder X-ray diffraction patterns and the DSC curves of FP, HPC, PEO, the physical mixtures and the solid dispersions are shown in Figs. 4 and 5, respectively. In Fig. 4, the FP crystalline peaks were observed in all the physical mixtures, but were hardly observed in the solid dispersions. The intensity of the PEO crystalline peaks in the solid dispersions decreased compared with that in the physical mixtures. In Fig. 5, the melting endothermic peaks based on FP and PEO crystal were observed around 116 and 67°C, respectively. The endothermic peak based on FP crystal was not observed in the physical mixtures or solid dispersions. The change in the PEO endothermic peak was not observed in the physical mixtures, whereas the peak broadened in the solid dispersions. These results suggest that FP existed in an amorphous state in the solid dispersions and the crystallinity of PEO in the FP-PEO solid dispersion was lower than that in the physical mixture and in PEO powder. Incidentally, the reason for the disappearance of the endothermic peak of FP in the physical mixtures is presumably as follows:

It was reported that, in the FP-HPC system, the interaction by hydrogen bonding between the hydroxyl group on the surface of HPC and the carboxyl group on the surface of FP already occurred in the physical mixture state (Yuasa et al., 1994). The interaction between FP and HPC further progressed because of the enhancement in molecular mobility during the heating process. In the FP-PEO system, precedent melting of PEO prompted the mobility of PEO molecules and its probability of interaction with FP was increased.

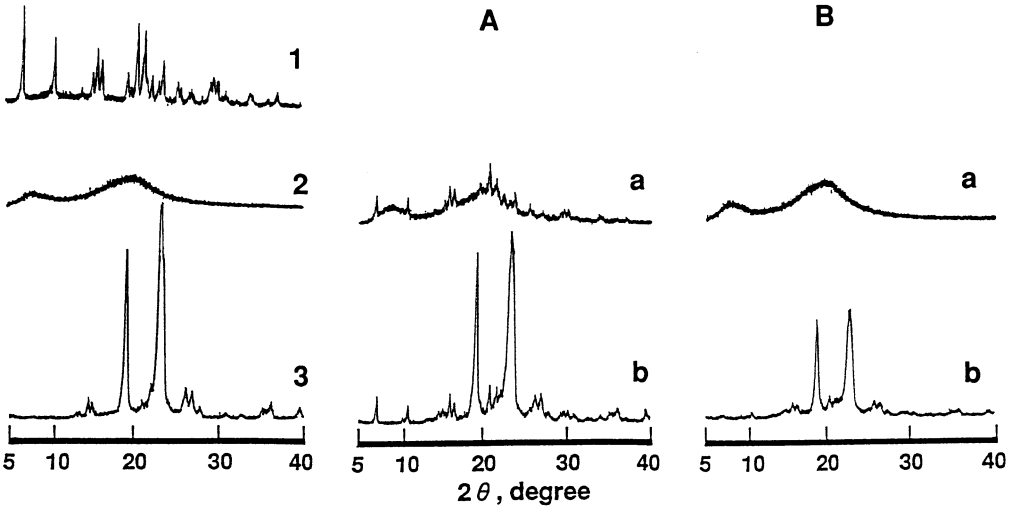

Fig. 4. Powder X-ray diffraction patterns of FP (1), HPC (2), PEO (3) and physical mixtures (A) and solid dispersions (B) containing 20% FP ((a) FP-HPC system, (b) FP-PEO system).

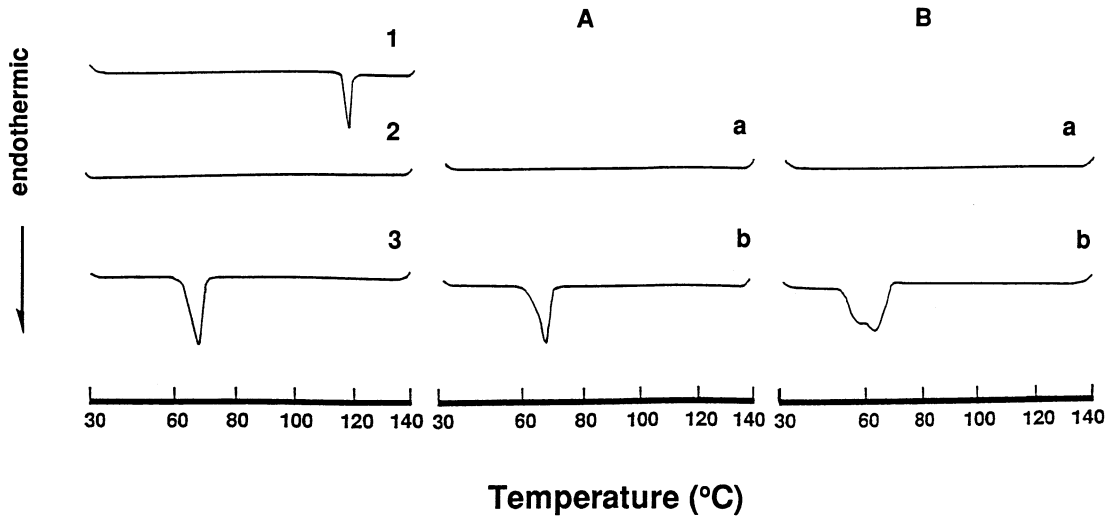

Fig. 5. DSC curves of FP (1), HPC (2), PEO (3) and physical mixtures (A) and solid dispersions (B) containing 20% FP ((a) FP-HPC system, (b) FP-PEO system).

The interaction further progressed during the heating process. Thus, the FP crystal peak in the physical mixtures disappeared.

Fig. 6 shows the IR spectra of powders of FP, HPC, PEO and the FP-HPC and FP-PEO solid dispersions and FP in CCl_4 solution at 1600–1800 cm^{-1}. FP in CCl_4 solution has the carbonyl stretching bands at 1760 cm^{-1} and 1710 cm^{-1} due to monomer and hydrogen bonding dimer, respectively (Nakanishi, 1962; Bellamy, 1971; Nakai et al., 1980). FP powder, which is in the solid state, has the carbonyl stretching band due to hydrogen bonding dimer at 1703 cm^{-1}. The new bands were observed at 1726 cm^{-1} and 1736 cm^{-1} in the case of the FP-HPC and the FP-PEO systems, respectively. Reportedly, the peak at 1726 cm^{-1} is due to the carbonyl group of FP forming the hydrogen bonding with the hydroxyl group of HPC (Yuasa et al., 1994). Since PEO consists of repeat units of $-CH_2-CH_2-O-$, the parts mainly responsible for the interaction with FP are the ether groups. Therefore, the peak at 1736 cm^{-1} in the FP-PEO system would be due to the carbonyl band of FP shifted by hydrogen bonding between the ether group of PEO and the hydroxyl group of the carboxyl group of FP. The peak height ratio of the FP-HPC system was higher than that of the FP-PEO system (about 0.72 and 0.41 in the case of the FP-HPC system and the FP-PEO system, respectively) although the percent of FP in them was equal. These results suggest that the ratio of FP hydrogen bonding with the polymer in the FP-HPC system was higher than that in the FP-PEO system.

We prepare the HPC and PEO granules composed of polymer alone in the same manner as the solid dispersion granules. The dissolution behaviors of the polymer bases from the HPC and PEO granules and the FP-HPC and FP-PEO solid dispersion granules are shown in Fig. 7. In the granules composed of polymer alone, the dissolution rate of PEO was significantly larger than that of HPC. In the solid dispersion granules, a larger dissolution rate was also observed with PEO than with HPC. These results indicate that the dissolution rate of the polymer base from the solid dispersion strongly depended on the dissolution property of the polymer itself.

A larger release rate of FP was observed in the FP-PEO system than in the FP-HPC system, although the ratio of high energy FP due to the interaction with the polymer was higher in the

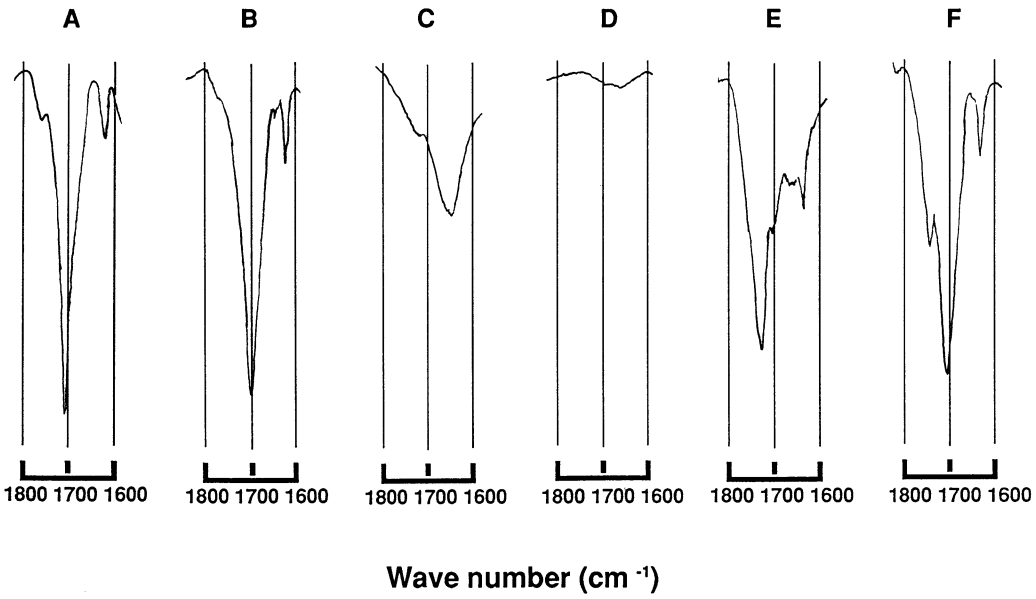

Fig. 6. IR spectra of FP in CCl_4 solution (A) and powder of FP (B), HPC (C), PEO (D) and FP-HPC (E) and FP-PEO (F) solid dispersions containing 20% FP. The concentration of FP in CCl_4 solution is 2.0×10^{-2} M.

FP-HPC system. Thus, the medicine release from the solid dispersion with different polymer bases could be greatly affected by the dissolution property of the polymer base as well as the interaction of the medicine with polymer.

The FP-PEO system showed a markedly larger release rate than the FP-HPC system that we have previously studied, suggesting that PEO has a great potential as a solid dispersion base to enhance the dissolution property of FP. Therefore, the release profiles of FP from the FP-PEO system with various percents of FP were studied.

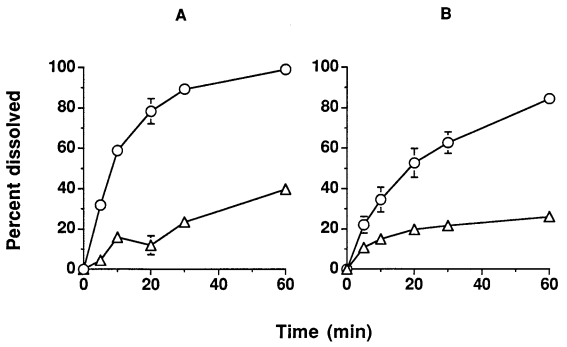

Fig. 7. Dissolution profiles of polymers from granules composed of polymer alone (A) and solid dispersion granules containing 20% FP (B). (○) PEO system, (△) HPC system. Each point represents the mean ± S.D. ($n = 3$).

3.2. FP release from FP-PEO solid dispersion granules with various percents of FP

Fig. 8 shows the release profiles of FP from the FP-PEO solid dispersion granules with various percents of FP. We studied the composition ratios within the range of 30% of FP because the FP crystal peak was found in excess of 30% of FP in the powder X-ray diffraction patterns (data not shown). In Fig. 8, the release rate of FP increased with the increasing percent of PEO.

Fig. 9 shows the IR spectra of FP, PEO and the FP-PEO solid dispersion with various percents of FP at 1600–1800 cm^{-1}. The height of the peak at 1736 cm^{-1} due to the carbonyl group of FP hydrogen bonding with PEO decreased with the increasing percent of FP. Fig. 10 shows the relationship between the release rate of FP obtained by the initial slope of the release profile up to 5

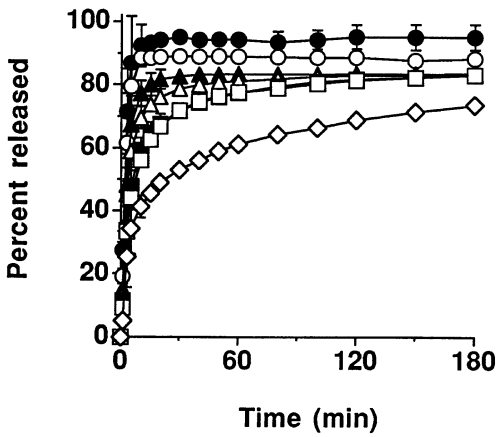

Fig. 8. Release profiles of FP from solid dispersion granules of FP-PEO system. Percent of FP ((●) 2.5%, (○) 5.0%, (▲) 10.0%, (△) 12.5%, (■) 15.0%, (□) 20.0%, (◇) 30.0%).

min of the dissolution test and the peak height ratio as the indication of the degree of interaction between FP and PEO on the basis of the base-line method. A linear relationship between these two factors was observed. These results are thought by following:

The number of –O– groups of PEO which can sterically form hydrogen bonding with FP relatively increases with the increasing percent of PEO. This action might increase the probability of a linear orientation of O–H–O required to form the hydrogen bonding. Therefore, the ratio of FP hydrogen bonding with PEO increases with the increasing percent of PEO, adding to the ratio of high energy FP in the solid dispersion. Thus, the release rate of FP is increased.

4. Conclusion

In the solid dispersion granules using HPC and PEO, the release rate of FP from the FP-PEO system was markedly larger than that from the FP-HPC system. The release of FP from the solid dispersions was greatly affected by the dissolution property of the polymer base. In the FP-PEO system, a linear relationship between the release rate of FP and the peak height ratio used as the indication of the interaction between FP and PEO was observed. This result is probably due to an

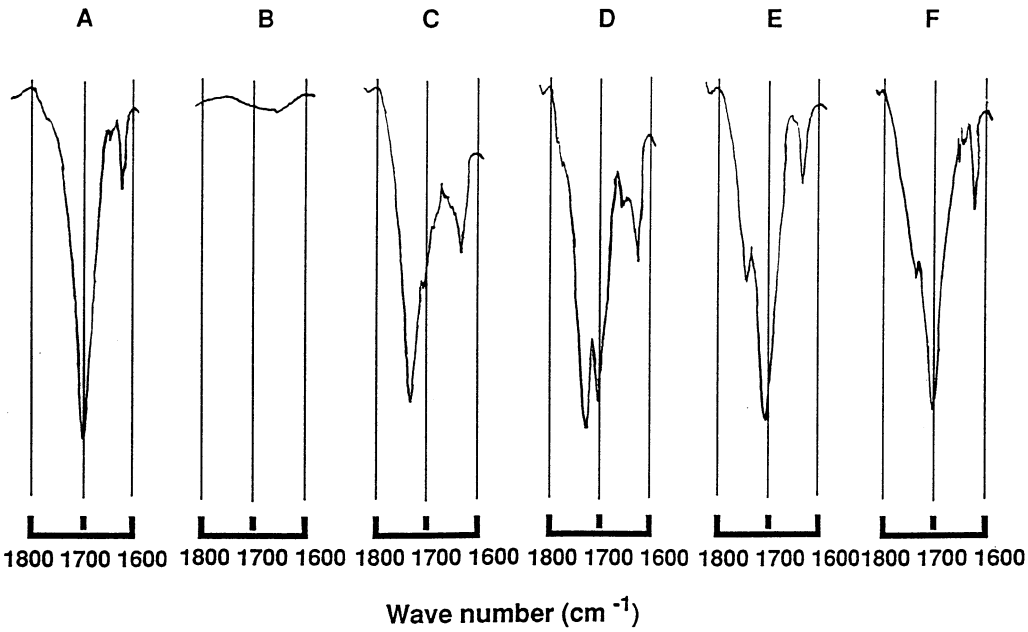

Fig. 9. IR spectra of FP (A), PEO (B) and FP-PEO solid dispersion systems (percent of FP; (C) 5%, (D) 10%, (E) 20%, (F) 30%).

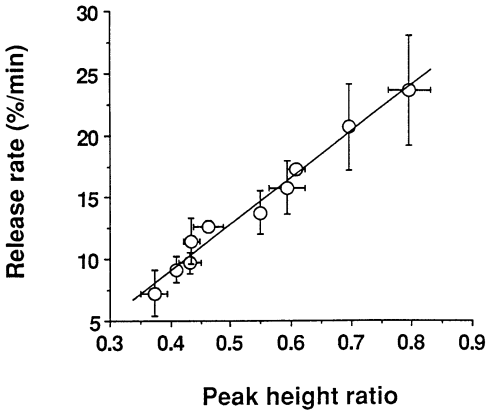

Fig. 10. Relationship between peak height ratio $\{a/(a+b)\}$ and release rate of FP. a is the peak height at 1736 cm^{-1} and b is the peak height at 1703 cm^{-1} in IR spectra. Each point represents the mean $\pm$ S.D. ($n=3$).

increase in the ratio of hydrogen bonding of FP with PEO with the increasing percent of PEO, causing an increase in the ratio of high energy FP in the solid dispersion.

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