Application of the Solid Dispersion Method to the Controlled Release of Medicine. V.[1] Suppression Mechanism of the Medicine Release Rate in the Three-Component Solid Dispersion System[2]

Tetsuya OZEKI,*,[a] Hiroshi YUASA,[a] Yoshio KANAYA,[a] and Katsutoshi OISHI[b]

Tokyo College of Pharmacy,[a] 1432–1 Horinouchi, Hachioji, Tokyo 192–03, Japan and Nihon Pharmaceutical Industry Co., Ltd.,[b] 2–12–12 Honkomagome, Bunkyo-ku, Tokyo 113, Japan. Received June 28, 1993; accepted October 1, 1993

Solid dispersions were prepared with a highly water soluble medicine (oxprenolol hydrochloride (OXP)), water insoluble ethylcellulose (EC) and water soluble hydroxypropyl cellulose (HPC). The release profiles of OXP from the solid dispersion granules at various composition ratios of the components, and the suppression mechanism of the release rate in the OXP–EC–HPC system, were studied.

The release rate of OXP reached a minimum level at the HPC composition ratio of 5—10%. It was difficult to control the release rate with more than 10% HPC. It was found that a marked decrease in the release rate at the HPC composition ratio of 5—10% was caused by the formation and retention of the swelled phase of HPC in the EC matrix. At more than 10% HPC, because OXP molecules enclosed by HPC molecules or incorporated in the swelled HPC phase increased and most of the OXP molecules were released together with HPC by erosion, the release rate of OXP increased drastically in the early stages of the release process. At the OXP composition ratio of 30% or more, the diameter and volume of the pores formed by the OXP release markedly increased, since the aggregates of OXP molecules that showed crystallinity began to be formed in the solid dispersion.

Keywords solid dispersion; composition ratio; controlled release; oxprenolol hydrochloride; ethylcellulose; hydroxypropyl cellulose

The solid dispersion method was originally used to enhance the dissolution rate of slightly water soluble medicines by dispersing them into water soluble carriers.[3] Hasegawa *et al.*[4] and Law *et al.*[5] reported that it was possible to enhance the dissolution rate of nifedipine by using this method. We previously reported enhancing the release rate of flurbiprofen.[6] Conversely, the control of the release of water soluble medicines using wax or water insoluble polymers has been studied.[7] We have studied[1,8] the solid dispersion composed of a highly water soluble medicine (oxprenolol hydrochloride (OXP)) and cellulose polymers, and reported that when 5% of water soluble hydroxypropyl cellulose (HPC) was added into water insoluble ethylcellulose (EC), the release rate of OXP from the solid dispersion granules markedly decreased. It was speculated that this was caused by the formation of the HPC swelled phase in the granules. In this paper, to clarify the above speculation and to discuss it in more detail, the solid dispersion granules at various composition ratios of the components were prepared, and the effects of the composition ratios in the solid dispersion on the OXP release and the suppression mechanism of the release rate in the OXP–EC–HPC system were studied in consideration of the internal structure of the granules.

Experimental

Materials OXP (known as a ß-adrenaline inhibitor, 1 g of which dissolves in less than 2 ml of water at 37 °C) was supplied by Nihon Pharmaceutical Industry Co., Ltd., Tokyo. The density (d) and the molecular weight are 1.20 and 301.8, respectively. EC (N-100, $d=1.21$, the weight-average molecular weight (Mw) is 230000) was purchased from Shin-Etsu Chemical Industry Co., Ltd., Tokyo. HPC (L-grade $d=1.21$, Mw=105000) was obtained from Nippon Soda Co., Ltd., Tokyo. The densities of OXP, EC and HPC were calculated from the volume measured with an Air Comparison Pycnometer (Toshiba-Beckman Co., Ltd., model 930). 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 Thirty six types of solid dispersion granules consisting of 5, 10, 15, 20, 30 or 40% OXP and 0, 5, 10, 20, 30 or 40% HPC and the residual % EC were prepared as follows: The mixed powder (16 g) of the medicine and the polymers at various ratios was dissolved in ethanol (400 ml), and the solvent was then evaporated. The solid dispersions were ground and sieved (850 μm—1 mm). The granules obtained were dried at 60 °C for 4 h *in vacuo*.

Dissolution Study The release behavior of OXP from the granules which contained 80 mg of OXP was observed with a dissolution tester (TR-5S3, Toyama Sangyo Co., Ltd.), following the paddle method (JP XII) at 100 rpm, using 900 ml distilled water as the dissolution medium at 37 ± 0.5 °C. The quantity of OXP was determined spectrophotometrically by the absorbance at 273 nm.

Measurement of Pore Size Distribution in the Granules The pore size distribution in the solid dispersion granules before and after the dissolution test was measured by mercury intrusion porosimetry,[9] employing a mercury porosimeter (Quantachrome Co., Autoscan-33). The contact angle of mercury with the samples and the surface tension of mercury were regarded as 140° and 480 dyn/cm, respectively.[10]

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

Thermal Analysis The 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.

Release Profile of HPC The granules consisting of EC and HPC were prepared in the same manner as that for the solid dispersion granules. The EC–HPC granules were taken at appropriate intervals during the dissolution test, and weighed after thorough drying. The amount of released HPC was calculated from the difference between the weights before and after the dissolution test.

Observation of the Surface of Granules A scanning electron microscope (SEM) (JASCO, model JSM T-200) was used to observe the change in the surface of granules during the release process.

Results and Discussion

Effect of the Composition Ratios in the Solid Dispersion on the OXP Release Figure 1 shows the release profiles

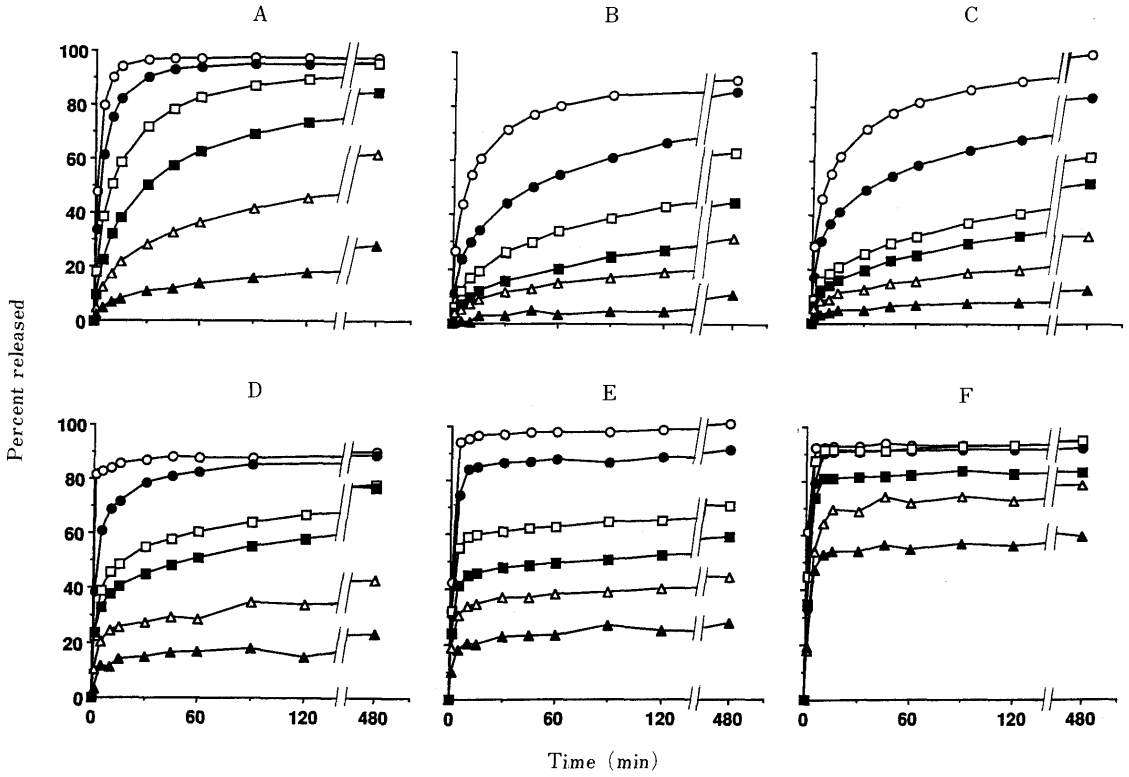

Fig. 1. Effects of Composition Ratios of Components in Solid Dispersion on Release Profiles of OXP

Percent of HPC: (A), 0% (OXP–EC system); (B), 5%; (C), 10%; (D), 20%; (E), 30%; (F), 40%. Percent of OXP: ▲, 5%; △, 10%; ■, 15%; □, 20%; ●, 30%; ○, 40%.

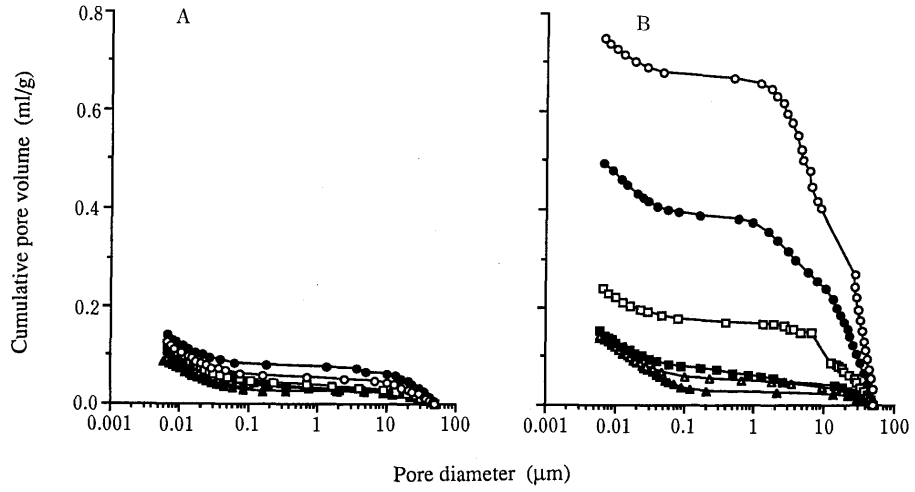

Fig. 2. Pore Size Distribution in Solid Dispersion Granules of the OXP 20%–EC–HPC System before (A) and after (B) Dissolution Test

Percent of HPC: ▲, 0% (OXP–EC system); △, 5%; ■, 10%; □, 20%; ●, 30%; ○, 40%.

of OXP from the solid dispersion granules at various composition ratios of the components. In all cases involving OXP in the composition ratio, the release rate of OXP at the HPC composition ratios of 5% (B) and 10% (C) decreased markedly compared with that of the HPC 0% granules, that is, the OXP–EC system (A). When HPC was more than 10% (D, E, F), the release rate increased drastically in the early stages of the release process, in a so-called initial burst. These results suggest that the release rate of OXP reaches a minimum level at 5—10% HPC, and it is difficult to control the release rate when HPC is more than 10%. Subsequently, the mechanism involved in the release suppression at different HPC composition ratios was investigated from the aspect of the internal structure of the granules.

Effect of the Composition Ratios of HPC on the Release Mechanism Figure 2 shows the pore size distributions before and after the dissolution test in the OXP 20% solid dispersion granules at various HPC composition ratios. Before the dissolution test, a small pore volume and the same shape of the distribution were observed in all the solid dispersions. After the dissolution test, the volume of

pores with pore diameters of less than about 0.1 μm, which were formed by the release of OXP,[11] increased in the OXP–EC system; that is, the no HPC system. In the OXP–EC–HPC system, after the test, an increase in the volume of pores with diameters of more than 0.1 μm was observed. Particularly, when HPC exceeded 10%, the volume of the pores with several to several tens of μm obviously increased as the HPC composition ratio increased. This result suggests that the pores were formed not only by the release of OXP but also by the release of HPC. Therefore, to examine in more detail the size distribution of the pores formed by the release of HPC, the pore size distribution after the dissolution test in the EC–HPC granules and the granules composed of EC alone were measured, and the results are shown in Fig. 3. When HPC is more than 10%, the pore volume evidently increased with increasing composition ratios of HPC, and the shape of the pore size distribution was similar to that in Fig. 2B. These results show that the pore size distribution observed after the dissolution test in the OXP–EC–HPC system was attributed mainly to the HPC release. However, almost no increase in the pore volume was observed in the granules in which the HPC composition ratio was 5—10%, suggesting that there was little release of HPC from the EC matrix in these granules. Therefore, the release profiles of HPC from the EC–HPC system were studied.

The decrease in granular weight of the EC–HPC system during the dissolution test was measured. This decrease was attributed to the released HPC, a water soluble polymer. The percentage of released HPC was calculated from the weight lost during the release process, and the release profiles of HPC from the EC–HPC granules are shown in Fig. 4. In all cases, HPC was released from the EC matrix in the early stages of the dissolution process, and then plateaued. The percentage of released HPC at 5—10% of HPC composition ratio was only about 10. This means an extremely small amount of HPC was released in accordance with the above mentioned speculation. When HPC accounted for more than 10%, the released HPC increased with the increasing HPC composition ratio. These results support the results of the pore size distribution in Fig. 3.

The SEM photographs of the OXP 20% system during the release process are shown in Fig. 5. Before the dissolution test, all the granules had smooth surfaces. In the case of the granules at 10% of HPC (A), little change in the surface was observed, even after 480 min. The formation of the pores had already taken place after 60 min at 20% of HPC, and the granules at 40% of HPC showed a slough-like porous EC matrix.

It is thought that OXP enclosed by HPC molecules or incorporated in the swelled HPC phase in the solid dispersion increased with increasing HPC composition ratios. HPC was released from the EC matrix in the early stages of the dissolution (Fig. 4). In the OXP–EC–HPC system, after the dissolution test, the volume of the pores with diameters of several to several tens of μm evidently increased when HPC was more than 10%, and the shape of the pore size distribution was similar to that formed by the HPC release from an EC matrix, shown in Fig. 3. These results indicate that at more than 10% HPC, because

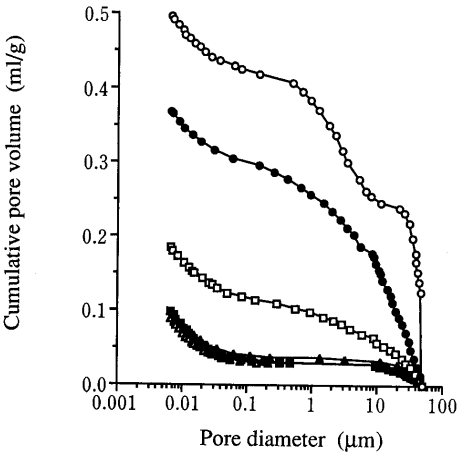

Fig. 3. Pore Size Distributions in Granules of the EC–HPC System and Granules Composed of EC alone after Dissolution Test

EC alone: ▲, Percent of HPC: △, 5%; ■, 10%; □, 20%; ●, 30%; ○, 40%

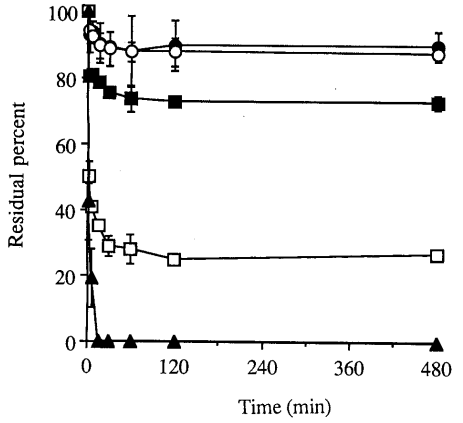

Fig. 4. Release Profile of HPC from Granules of the EC–HPC System

Percent of HPC: ●, 5%; ○, 10%; ■, 20%; □, 30%; ▲, 40%. Each point represents the mean ±S.D. (n=5—7).

OXP molecules enclosed by HPC were released together with HPC by erosion, the release rate increased drastically in the early stages of the release process. In the case of the granules at 5—10% of HPC, there was little release of HPC, and the retained HPC was swelled in the granules by the permeating fluid, so the release of OXP diffusing into the swelled HPC phase occurred, causing a marked decrease in the release rate. These results support the propriety of the conjecture in our previous paper.[1,8]

Correlation of the Release Data with the Release Model Higuchi,[12] and Baker and Lonsdale[13] have proposed a model for the release of medicine from spherical matrices as follows:

$$3/2[1-(1-F)^{2/3}]-F=Kt$$

where F is the ratio of the medicine released at time t, and K is the release rate constant. When the medicine release is controlled by the diffusion of medicine through the matrix or into the dissolution medium that fills the channels, the plots of the left side against time should be linear.[14] The release data for OXP in Fig. 1 were replotted according to the Higuchi and Baker–Lonsdale model and are shown in Fig. 6. In the granules in which HPC is more

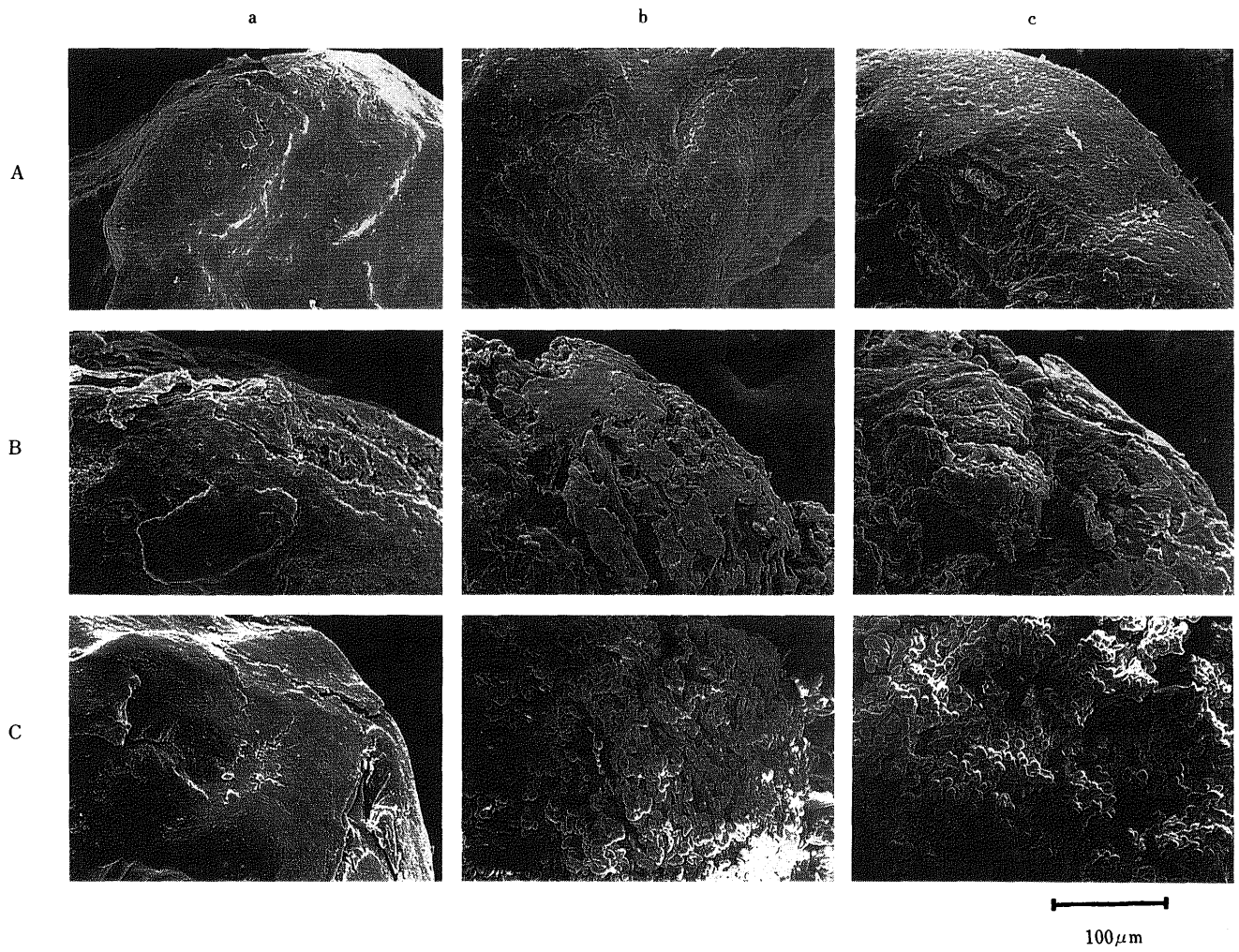

Fig. 5. SEM Photographs of Solid Dispersion Granules of the OXP 20%–EC–HPC System during Release Process
Percent of HPC: 10% (A); 20% (B); 40% (C), dissolution time: before dissolution test (a); 60 min (b); 480 min (c).

than 10% (D, E, F), the values markedly increased in the early stages, suggesting that the OXP release did not obey the diffusion model. It is thought that this was cuased by the release of OXP that occurred together with the HPC release in the early stages of the release process. In the OXP–EC system (A), the relationship was more linear with smaller OXP composition ratios. At HPC composition ratios of 5% and 10% (B, C), a good linear relationship was found for a long period of release time at not more than 20% of OXP, suggesting that the release obeyed the Higuchi and Baker–Lonsdale model. But no good linear relationship was observed at 30% or more of OXP. Therefore, the effects of OXP composition ratios on OXP release were studied from the aspect of the internal structure of the granules.

Effect of the Composition Ratios of OXP on the Release Mechanism Figure 7 shows the pore size distribution before and after the dissolution test in the HPC 10% system with various OXP composition ratios. At 30% or more of OXP, a composition ratio that did not show good linearity in Fig. 6, a marked increase in pore volume was observed after the dissolution test.

To understand the effects of the OXP composition ratios on the internal structure of the granules in more detail, we investigated the two-component OXP–EC system. The existing state of OXP in the solid dispersion should affect the formation of pores in the granules in the release process. Therefore, the state of OXP in the solid dispersion was analyzed by X-ray diffractometry and thermal analysis.

The powder X-ray diffraction patterns and the DSC curves of the powders of OXP and EC, and solid dispersions of the OXP–EC system, are shown in Figs. 8 and 9, respectively. The X-ray diffraction peaks and a melting endothermic peak based on OXP crystals were observed at the OXP composition ratio of 30% or more. These results suggest that OXP exists in an amorphous state at not more than 20% of OXP, but that OXP which shows crystallinity occurs at 30% or more.

The pore size distribution in the granules of the OXP–EC system before and after the dissolution test was measured, and the result is shown in Fig. 10. After the dissolution test, the pores were formed by the release of OXP, causing an increase in pore volume. The granules at a larger OXP composition ratio shows a larger amount of increased pore volume, and a particularly remarkable increase was observed at 30% or more of OXP. Further, it is apparent that the increase in the pore volume was due to a marked

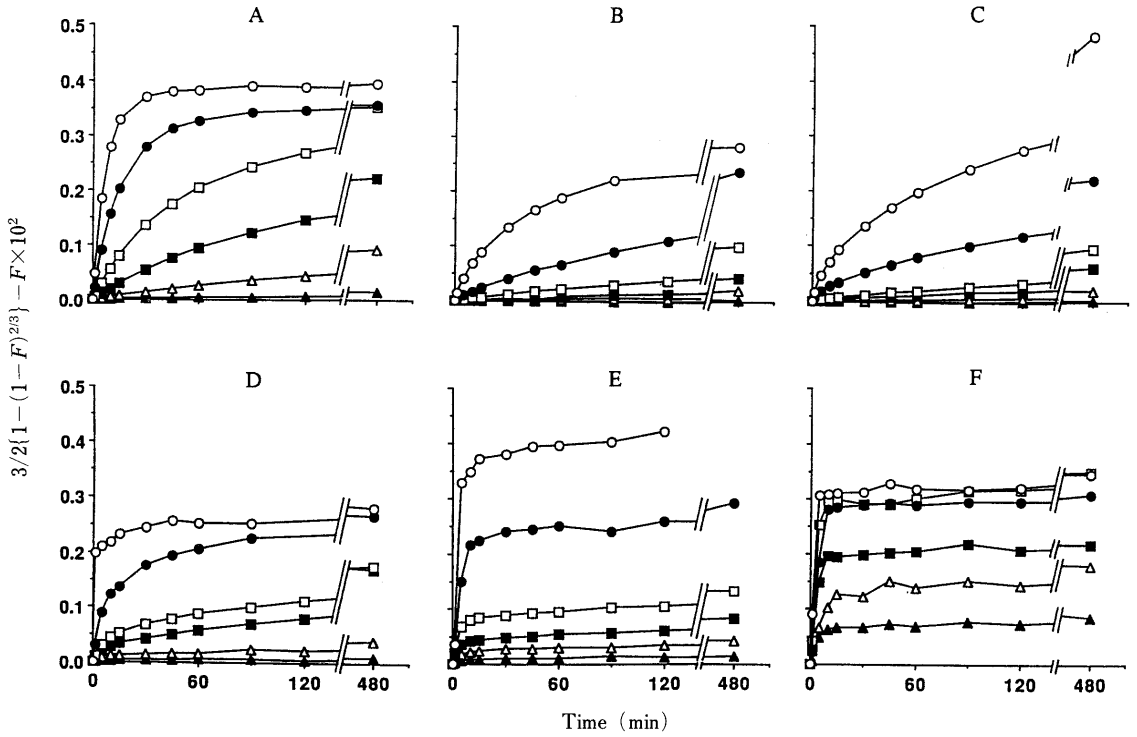

Fig. 6. Plots of Calculated Values of $3/2\,[1-(1-F)^{2/3}]-F$ against Time

Percent of HPC: (A), 0% (OXP–EC system); (B), 5%; (C), 10%; (D), 20%; (E), 30%; (F), 40%. Percent of OXP: ▲, 5%; △, 10%; ■, 15%; □, 20%; ●, 30%; ○, 40%.

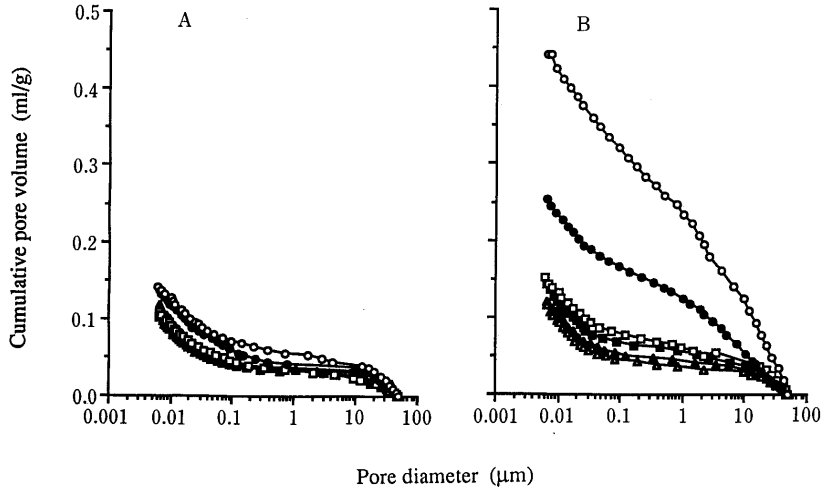

Fig. 7. Pore Size Distribution in Solid Dispersion of the OXP–EC–HPC 10% System before (A) and after (B) Dissolution Test

Percent of OXP: ▲, 5%; △, 10%; ■, 15%; □, 20%; ●, 30%; ○, 40%.

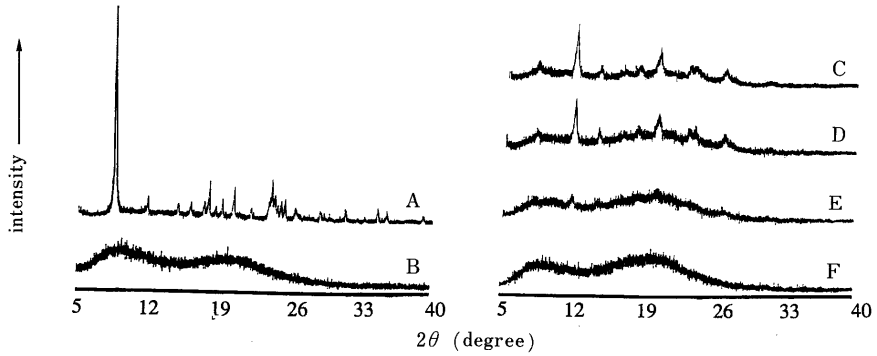

Fig. 8. Powder X-Ray Diffraction Patterns of Powders of OXP and EC, and Solid Dispersion of the OXP–EC System

OXP powder (A); EC powder (B); solid dispersion (percent of OXP: 40% (C); 30% (D); 20% (E); 10% (F)).

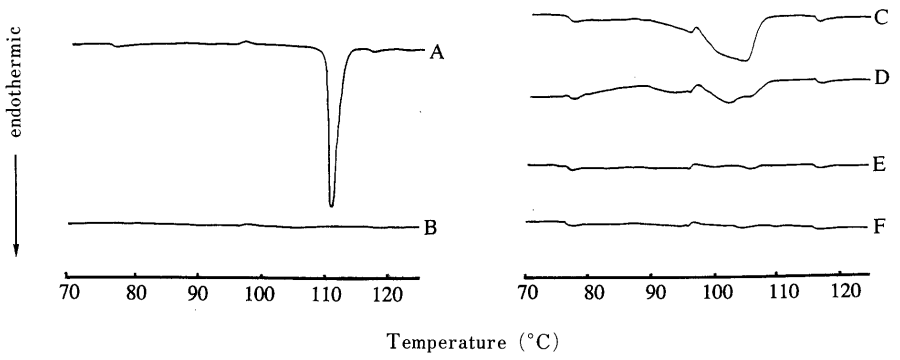

Fig. 9. DSC Curves of Powders of OXP and EC, and Solid Dispersion of the OXP–EC System
OXP powder (A); EC powder (B); solid dispersions (percent of OXP: 40% (C); 30% (D); 20% (E); 10% (F)).

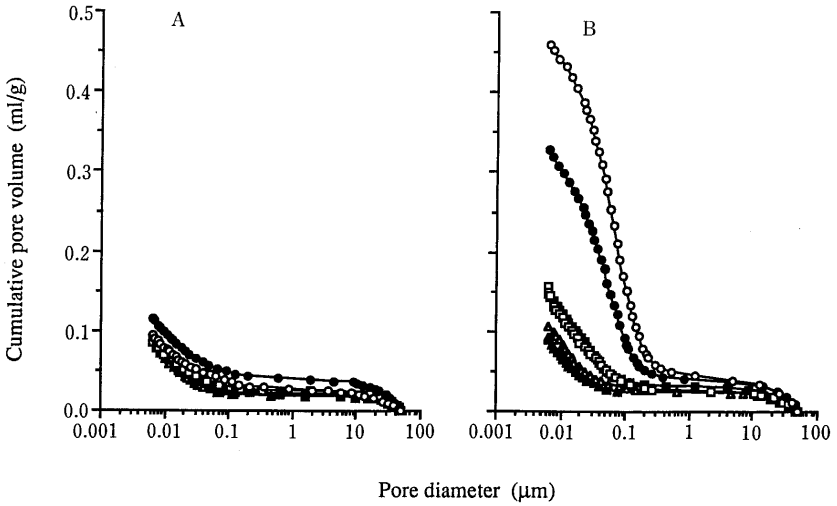

Fig. 10. Pore Size Distribution in Solid Dispersion Granules of the OXP–EC System before (A) and after (B) Dissolution Test
Percent of OXP: ▲, 5%; △, 10%; ■, 15%; □, 20%; ●, 30%; ○, 40%.

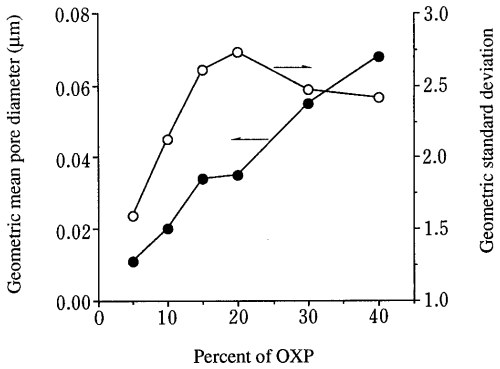

Fig. 11. Effects of OXP Composition Ratio in Solid Dispersion on Geometric Mean Pore Diameter and Geometric Standard Deviation of Pores Formed by Release of OXP

increase in the volume of the pores which had diameters of lessl than about 0.2 μm. For more detailed consideration, the pore size distribution of the pores newly formed by the release of OXP was obtained from the difference in the pore size distribution before and after the dissolution test in Fig. 10, and we attempted to fit the pore size distribution of these pores to log-normal distribution using a log probability paper.[15] The correlation coefficients are shown in Table I. At all OXP composition ratios, the correlation coefficients exhibited high values, suggesting that the pore size distribution of the pores formed by the release of OXP approximated the log-normal distribution. Figure 11 shows the relationship between OXP composition ratios and the geometric mean pore diameter (D_{g50}) and the geometric standard deviation (sd_g) of the pore size distribution which are obtained by fitting it to the log-normal distribution. D_{g50} increased with increasing OXP composition ratios. On the other hand, sd_g increased with increasing OXP composition ratios up to 20% of OXP, but decreased at 30% or more.

Table I. Correlation Coefficients in Fitting the Pore Size Distributions Formed by the Release of OXP from the OXP–EC Granules to the Log-normal Distribution

Percent of OXP	Correlation coefficient
5	0.9290
10	0.9503
15	0.9803
20	0.9935
30	0.9970
40	0.9990

It is thought that because EC has an extremely large molecular volume compared with that of OXP, OXP will have to be packed in the intermolecular space of EC molecules during the preparation of the solid dispersion; that is, during the evaporation of the solvent from the OXP–EC organic solution. When the OXP composition ratio was significantly low, because the dispersibility of OXP in the solid dispersion could be high, the size of the aggregates of OXP molecules was small. Therefore, D_{g50} and sd_g were small. With increasing OXP concentrations, because the probability of the mutual adjoining of the OXP molecules was increased and various sizes of OXP aggregates were formed, the pore size and the range of the distribution of the pores formed after the release of OXP increased. Therefore D_{g50} and sd_g might increase with increasing OXP composition ratios up to 20%. When OXP concentrations further increased, that is, at 30% or more, large aggregates showing crystallinity began to form, as shown in Figs. 3 and 4. When the number of such large aggregates increased, the number of small aggregates would decrease relatively. Therefore, the pore size distribution after OXP release was largely determined by the pores with large diameters, and the range of the distribution became small. Thus D_{g50} increased, while sd_g decreased at 30% or more of OXP. Incidentally, we speculated previously, about the disintegration of tablets, that the critical amount of a disintegrant was determined by the same mechanism.[16]

These results suggest that at an OXP composition ratio of 30% or more, which shows crystallinity, because the diameter and the volume of the pores formed by the release of OXP increased markedly, the medicine release did not obey the diffusion model at the HPC composition ratio of 5—10%. As for the OXP–EC system, it is thought that, as was conjectured in our previous paper,[1,11] because the solubility of OXP is extremely high, OXP could be released successively and rapidly through the channels which were formed at the preparation of the solid dispersion or formed by the release of OXP distributed in the surface part of the granules. Therefore, no good linear relationship was observed in Fig. 6.

Conclusion

The release rate of OXP reached a minimum level at the HPC composition ratio of 5—10%. It was clarified that at this HPC composition ratio, the swelled HPC phase was formed and retained in the EC matrix, and so OXP diffused into the swelled HPC phase, causing a marked decrease in the release rate. At more than 10% of HPC, because OXP molecules enclosed by HPC molecules or incorporated in the swelled HPC phase increased and most of the OXP molecules were released together with HPC by erosion, the release rate of OXP increased drastically in the early stages of the release process, and therefore, it was difficult to control the release rate.

References and Notes

1) Part IV: H. Yuasa, T. Ozeki, Y. Kanaya, K. Oishi, *Chem. Pharm. Bull.*, **41**, 933 (1993).
2) A part of this study was presented at the 113th Annual Meeting of the Pharmaceutical Society of Japan, Osaka, March 1993.
3) W. L. Chiou, S. Riegelman, *J. Pharm. Sci.*, **59**, 937 (1970); I. Sugimoto, A. Kuchiki, H. Nakagawa, K. Tohgo, S. Kondo, I. Iwane, K. Takahashi, *Drug Dev. Ind. Pharm.*, **6**, 137 (1980); S. A. H. Khalil, S. A. El-Fattah, L. M. Mortada, *ibid.*, **10**, 771 (1984).
4) A. Hasegawa, M. Taguchi, R. Suzuki, T. Miyata, H. Nakagawa, I. Sugimoto, *Chem. Pharm. Bull.*, **36**, 4941 (1988).
5) S. L. Law, W. Y. Lin, C. H. Chaing, *Int. J. Pharmaceut.*, **84**, 161 (1992).
6) H. Yuasa, H. Takahashi, T. Ozeki, Y. Kanaya, M. Ueno, *Chem. Pharm. Bull.*, **41**, 397 (1993).
7) Y. Goto, T. Ishizaka, M. Koishi, *Zairyougijutu*, **3**, 48 (1985); S. A. El-Fattah, N. N. Salib, M. El-Massik, *Drug Dev. Ind. Pharm.*, **10**, 649 (1984); Y. Takahashi, H. Ochiai, T. Tsukuda, C. Izumi, K. Ikemoto, K. Tomidokoro, Y. Kitamura, N. Yagi, M. Takada, *Yakuzaigaku*, **52**, 32 (1992); T. Uchida, T. Yasutake, S. Goto, *Chem. Pharm. Bull.*, **40**, 463 (1992).
8) H. Yuasa, T. Ozeki, Y. Kanaya, K. Oishi, T. Oyake, *Chem. Pharm. Bull.*, **39**, 465 (1991).
9) H. Yuasa, J. Yamashita, Y. Kanaya, *Chem. Pharm. Bull.*, **41** 731 (1993).
10) H. L. Ritter, L. C. Drake, *Ind. Eng. Chem., Anal. Ed.*, **17**, 782 (1945).
11) H. Yuasa, T. Ozeki, Y. Kanaya, K. Oishi, *Chem. Pharm. Bull.*, **40**, 1592 (1992).
12) T. Higuchi, *J. Pharm. Sci.*, **52**, 1145 (1963).
13) R. W. Baker, H. K. Lonsdale, "Controlled Release of Biological Active Agents," A. C. Tanquary, R. E. Lacey, Eds., Plenum Press, New York, 1974, pp. 15—71.
14) T. Seki, T. Kawaguchi, H. Endo, K. Ishikawa, K. Juni, M. Nakano, *J. Pharm. Sci.*, **79**, 985 (1990).
15) H. Yuasa, Y. Kanaya, K. Asahina, *Yakuzaigaku*, **45**, 171 (1985).
16) H. Yuasa, Y. Kanaya, *Chem. Pharm. Bull.*, **34**, 5133 (1986).