Application of the Solid Dispersion Method to the Controlled Release of Medicine. VII.[1] Release Mechanism of a Highly Water-Soluble Medicine from Solid Dispersion with Different Molecular Weights of Polymer[2]

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Solid dispersion films were prepared with a highly water-soluble medicine (oxprenolol hydrochloride (OXP)), four grades of water-insoluble ethylcellulose (EC) having different molecular weights and water-soluble hydroxypropyl cellulose (HPC). The internal structure of the solid dispersion films and the penetration of the dissolution medium into the films were studied to clarify the mechanism of OXP release from the OXP–EC and OXP–EC–HPC solid dispersion systems having various molecular weights of EC.

In the OXP–EC system, the release rate of OXP slightly decreased with increasing molecular weight of EC and the mechanism of OXP release was hardly affected by the molecular weight of EC. In the OXP–EC–HPC system, the release rate of OXP markedly decreased with increasing molecular weight of EC. When EC with the lowest molecular weight of the four grades was used, the same mechanism of OXP release was observed as in the OXP–EC system, but it was clear that OXP was released from the films with the two higher-molecular-weight grades of EC through a diffusion-controlled release mechanism. This result can be explained in terms of diffusion of OXP through the quasi-equilibrium swollen gel region formed by rapid hydration of HPC with water penetrating into the solid dispersion film.

Key words solid dispersion; release mechanism; molecular weight; oxprenolol hydrochloride; ethylcellulose; hydroxypropyl cellulose

The solid dispersion method was originally used to improve the dissolution properties and bioavailability of slightly water-soluble medicines by dispersing them into water-soluble carriers.[3] We have prepared solid dispersion granules with slightly-water soluble flurbiprofen and hydroxypropyl cellulose (HPC) and reported that the release rate of flurbiprofen was markedly larger than that from flurbiprofen powder, and that the degree of the interaction between flurbiprofen and the polymer greatly affected the drug release rate.[1,4] On the other hand, for the control of the release of water-soluble medicines, addition of or coating with wax or water insoluble polymers has been adopted.[5] We have studied solid dispersion granules composed of a highly water-soluble medicine (oxprenolol hydrochloride (OXP)), water-insoluble ethylcellulose (EC) and water-soluble HPC, and found that the formation and retention of the swollen phase of HPC in the granules caused a marked decrease in the release rate of OXP from the solid dispersion granules.[6,7] We have also reported that the release rate of OXP changed depending on the molecular weight of EC, and speculated that this might be caused by changes in the ratio of OXP release *via* the swollen HPC phase depending on the molecular weight of EC.[8] However, the release mechanism has not yet been established in detail. Therefore, in the present study, we prepared the solid dispersion films of the OXP–EC and OXP–EC–HPC systems with different molecular weights of EC. The OXP release from a certain surface area of the films, the internal structure of the solid dispersion films and the penetration of the dissolution medium were studied to clarify the mechanism of OXP release.

Experimental

Materials OXP (known as a β-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 and the molecular weight of OXP are 1.20 and 301.8, respectively. Four grades of EC having different molecular weights (EC7, EC10, EC22, EC100) were purchased from Shin-Etsu Chemical Industry Co., Ltd., Tokyo. HPC (HPC-L) was obtained from Nippon Soda Co., Ltd., Tokyo. The densities and mean molecular weights of the polymers are listed in Table 1. 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 Solid Dispersion Films The composition ratios of the components of the OXP–EC system and the OXP–EC–HPC system were OXP : EC : HPC = 20 : 80 : 0 and 20 : 70 : 10, respectively. The powders of OXP and the polymers (total amount: 16 g) were dissolved in ethanol (200 ml) at 50 °C. The ethanol solution was cast on a Teflon plate using a film applicator (Baker Film Applicator, Ueshima Seisakusho Co.). After drying in a desiccator, the film obtained was further dried at 60°C for 4 h *in vacuo*.

Measurement of the Porosity of the Solid Dispersion Films The film thickness was measured by using a micrometer (Dial Thickness Gage, Mitsutoyo Co.) and evaluated from the average thickness of the four corners and the center of the film cut with dimensions of 2.5 × 3.2 cm. The apparent film volume was calculated from the film thickness and known film area. The porosity of the film was calculated from the apparent film volume and the theoretical value of the true film volume was calculated by using the true densities of OXP, EC and HPC listed in Table 1.

Dissolution Study Films with the dimensions of 2.5 × 3.2 cm and the thickness of $120 \pm 5\,\mu m$ were used for the dissolution test. Four such films were fixed on a handmade holder using wax (Maves Inlay Wax, Maves Co.) so that the surface area exposed to the dissolution medium would remain constant, as shown in Fig. 1. The release behavior of OXP from the solid dispersion films was observed with a dissolution tester

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(TR-5S3, Toyama Sangyo Co., Ltd.), according to the paddle method (JP XII) at 100 rpm, using 500 ml of distilled water as the dissolution medium at 37±0.5 °C. The quantity of OXP was determined spectrophotometrically by measuring the absorbance at 273 nm. The OXP content in the film was calculated from the composition ratio of OXP and the weight of the film.

Powder X-Ray Diffractometry 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, $2\theta=4°/\text{min}$.

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.

Table 1. Densities and Average Molecular Weights of Polymers Used

Polymer		Density (g/cm^3)	$\bar{M}_n$ a)	$\bar{M}_w$ b)	$\bar{M}_z$ c)	$\bar{M}_w/\bar{M}_n$ d)
EC	EC7	1.24	26500	58000	109000	2.189
	EC10	1.21	30000	80000	158000	2.667
	EC22	1.23	43400	123000	250000	2.834
	EC100	1.21	72600	230000	500000	3.168
HPC	HPC-L	1.21	46000	105000	178500	2.282

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

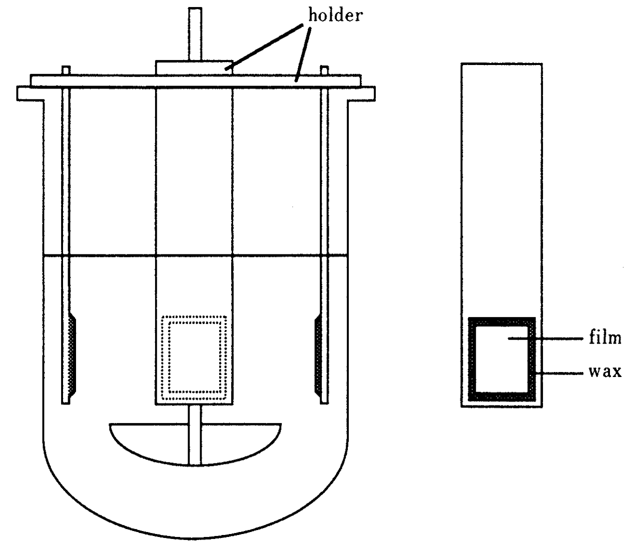

Fig. 1. Schematic Diagram of Dissolution Test Apparatus

IR Spectroscopy IR spectra were recorded with an IR spectrophotometer (IR-810, JASCO) by the KBr disk method.

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

Scanning Electron Microscopy (SEM) A scanning electron microscope (S-2250N or S-2400, Hitachi Co.) was used to observe the morphology of the solid dispersion films after the dissolution test.

Penetration Study A water penetration study of the solid dispersion films was carried out by applying the method of Ishino *et al.*[11] Figures 2 and 3 show a schematic diagram of the apparatus for measurement of the penetration time, a typical chart and an electric circuit diagram. E and E_{R1} in Fig. 3, which are the electromotive force and the potential difference of the resistor F in Fig. 2, respectively, can be expressed as follows, based on Ohm's law;

$$E=i(R_1+R_2) \tag{1}$$

$$E_{R1}=iR_1 \tag{2}$$

From Eqs. 1 and 2, E_{R1} can be rewritten as

$$E_{R1}=(R_1/R_1+R_2)E \tag{3}$$

where R_1 is the electric resistance of the resistor F in Fig. 2, R_2 is the total value of te electric resistances of the water phase, carbon tape and solid dispersion film and i is the electric current.

The solid dispersion film was fixed in a diffusion cell. The surface of the film on one side of the cell was connected to the electrode with electroconductive double-adhesive carbon tape. As soon as the other side of the cell was filled with distilled water, the measurement was started. When the water penetrated into the film and HPC in the film was hydrated, R_2 decreased because the electric resistance of the film decreased, although the resistances of the water phase and carbon type did not change. So E_{R1} gradually increased, as indicated by Eq. 3. Hydration of HPC in the film progressed and reached equilibrium, and we regarded the penetration time I as the time required until E_{R1} became almost constant (because R_2 became constant). The change in E_{R1} caused by the change in the resistance of the film was recorded at room temperature with a recorder (Hitachi, Co. QPD54) as a function of time.

Results and Discussion

Release Profile of OXP from Solid Dispersion Film The release profiles of OXP from the solid dispersion films of the OXP–EC system and the OXP–EC–HPC system with

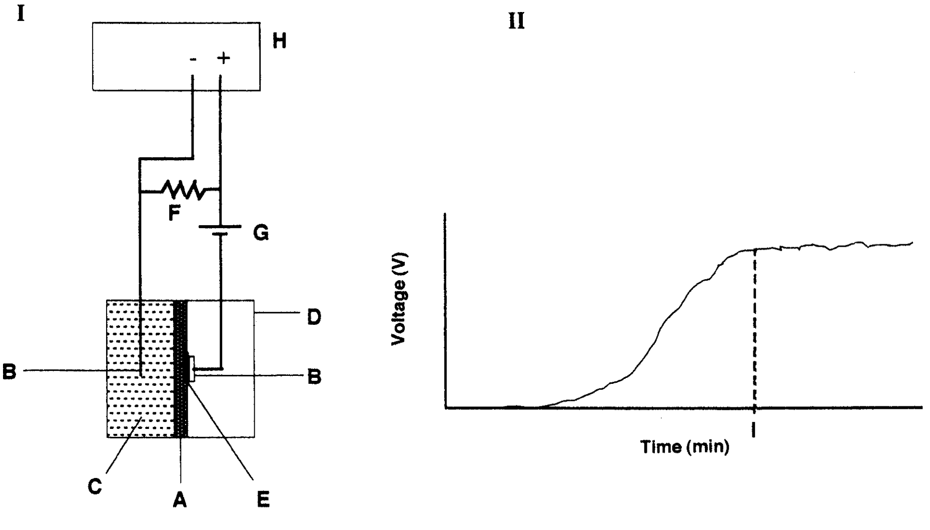

Fig. 2. Schematic Diagram of Apparatus for Measurement of Penetration Time (I) and Typical Chart (II)

A, solid dispersion film; B, electrode; C, distilled water; D, diffusion cell; E, double-adhesive carbon tape; F, resistor (1 kΩ); G, battery (1, 5 V); H, voltmeter; I, penetration time.

different molecular weights of EC are shown in Fig. 4. In the OXP–EC system (A), all films showed large release rates, and the release rate slightly decreased with increasing molecular weight of EC. In the OXP–EC–HPC system (B), the change in the release profiles depending on the molecular weight of EC was more clearly observed and the release rate decreased remarkably with increasing molecular weight of EC. To investigate the effects of the molecular weight of EC and the addition of HPC on the release mechanism, we attempted to analyze the OXP release data according to the semi-empirical equation for drug release from polymer devices proposed by Peppas.[12)]

$$F=Kt^n \qquad (4)$$

where F is the fractional release (<0.6) up to time t, K is a kinetic constant incorporating the structural and geometric characteristics of the release system, and n is the diffusional exponent which is indicative of the release mechanism. The exponent n has the following meaning[13,14)]: when $n=0.5$, the release of medicine corresponds to diffusion-controlled release obeying the Fickian diffusional model; when $n=1$, the swelling or relaxation rate of the matrix polymer is the rate-determining step and zero-order release is observed; and when $0.5<n<1$, the release is non-Fickian, and both Fickian diffusion and relaxation of the polymer contribute to the drug release.

The release data for OXP in Fig. 4 were analyzed according to Eq. 4 and the parameters obtained are summarized in Table 2. In the OXP–EC system, the K value tended to decrease slightly with higher molecular weight of EC. The n value was almost the same at all molecular weights of EC, suggesting that the mechanism of OXP release from the OXP–EC system was hardly affected by the EC molecular weight. In the OXP–EC–HPC system, the K value was significantly smaller than that of the OXP–EC system, except for EC7, and obviously decreased with increasing molecular weight of EC. The n value of EC7, which corresponds to the lowest EC molecular weight, was almost the same as that of the OXP–EC system. It increased with increasing molecular weight of EC and reached 0.5 in the case of EC22 or EC100, suggesting that the release of OXP from these films followed the diffusion theory.

We previously reported that the crystallinity of a drug and the degree of the interaction between the drug and polymer (depending on the molecular weight of the polymer) in a solid dispersion greatly affected the release rate of the drug.[1,7)] Therefore, these points were analyzed by X-ray diffractometry, thermal analysis and IR spectroscopy. The results suggested that OXP existed in an amorphous state and interacted with EC and HPC by hydrogen bonding in the solid dispersion. However, the results were independent of the molecular weight of EC and the addition of HPC (data not shown). Consequently, the release mechanism was further studied from the viewpoint of the internal structure of solid dispersions.

Internal Structure of Solid Dispersion Film Figure 5 shows the porosity of the solid dispersion films of the OXP–EC system and the OXP–EC–HPC system. All the films have pores and a larger porosity was observed with a lower molecular weight of EC. This result can be

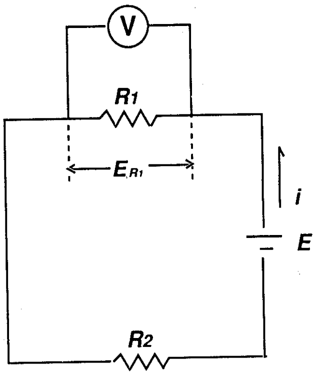

Fig. 3. Electric Circuit Diagram of Apparatus for Measurement of Penetration Time

Table 2. Kinetic Constants, Diffusional Exponents and Correlation Coefficients for OXP Release from Solid Dispersion Films

EC grade	OXP–EC system			OXP–EC–HPC system		
	$K\times10^2$	n	r	$K\times10^2$	n	r
EC7	28.23	0.414	0.994	18.23	0.407	0.995
EC10	27.56	0.415	0.998	4.46	0.455	0.989
EC22	21.46	0.405	0.998	2.80	0.502	1.000
EC100	21.11	0.400	0.999	1.36	0.500	0.999

K: kinetic constant (min^{-n}). n: diffusional exponent. r: correlation cefficient.

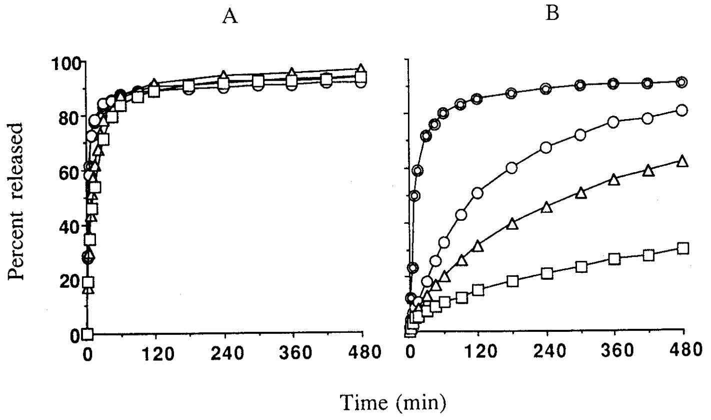

Fig. 4. Release Profile of OXP from Solid Dispersion Films of the OXP–EC System (A) and the OXP–EC–HPC System (B)

◎, EC7; ○, EC10; △, EC22; □, EC100. Each point represents the mean of three experiments.

explained as follows; EC and HPC, both linear polymers, may form an almost globular shape as they become folded and tangled confusedly[15] in the solid dispersion,[8] and the size of EC molecules is smaller when the molecular weigth of EC is lower. The effect of interactions, such as van der Waals' force or hydrogen bonding, on the EC molecules is stronger with decreasing size of EC molecules.[16] Therefore, the porosity is larger with a lower molecular weight of EC. The change in the porosity suggests a change in the internal structure of the films. So, to study the internal structure in more detail, the pore size distribution of the films before and after the dissolution test was measured by mercury intrusion porosimetry.

Figure 6 shows the pore size distribution of the OXP–EC system and the OXP–EC–HPC system before and after the dissolution test. In both systems before the dissolution test, the pore volume at a diameter of less than about 0.04 μm appeared to be smaller for a higher molecular weight of EC. It is thought that the difference in porosity might be caused by the difference in the pore volume at that approximate diameter. In the OXP–EC

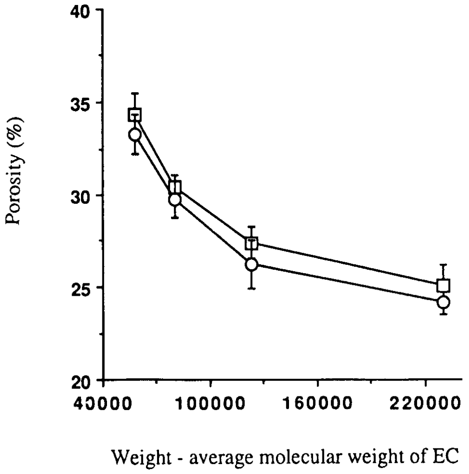

Fig. 5. Effect of Molecular Weight of EC on the Porosity of Solid Dispersion Film

□, OXP–EC system; ○, OXP–EC–HPC system. Each point represents the mean ± S.D. ($n=10$).

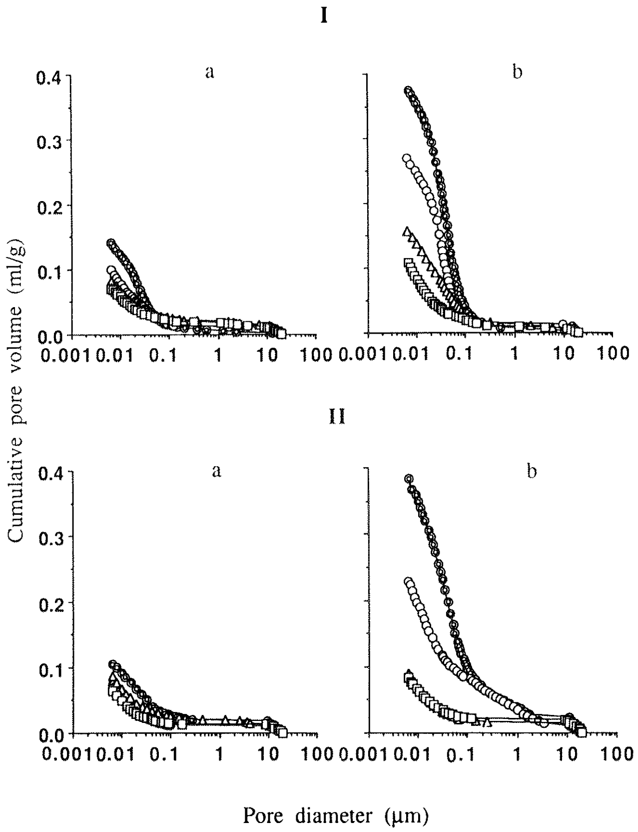

Fig. 6. Pore Size Distribution in Solid Dispersion Films of the OXP–EC System (I) and the OXP–EC–HPC System (II) before (a) and after (b) Dissolution Test

◎, EC7; ○, EC10; △, EC22; □, EC100.

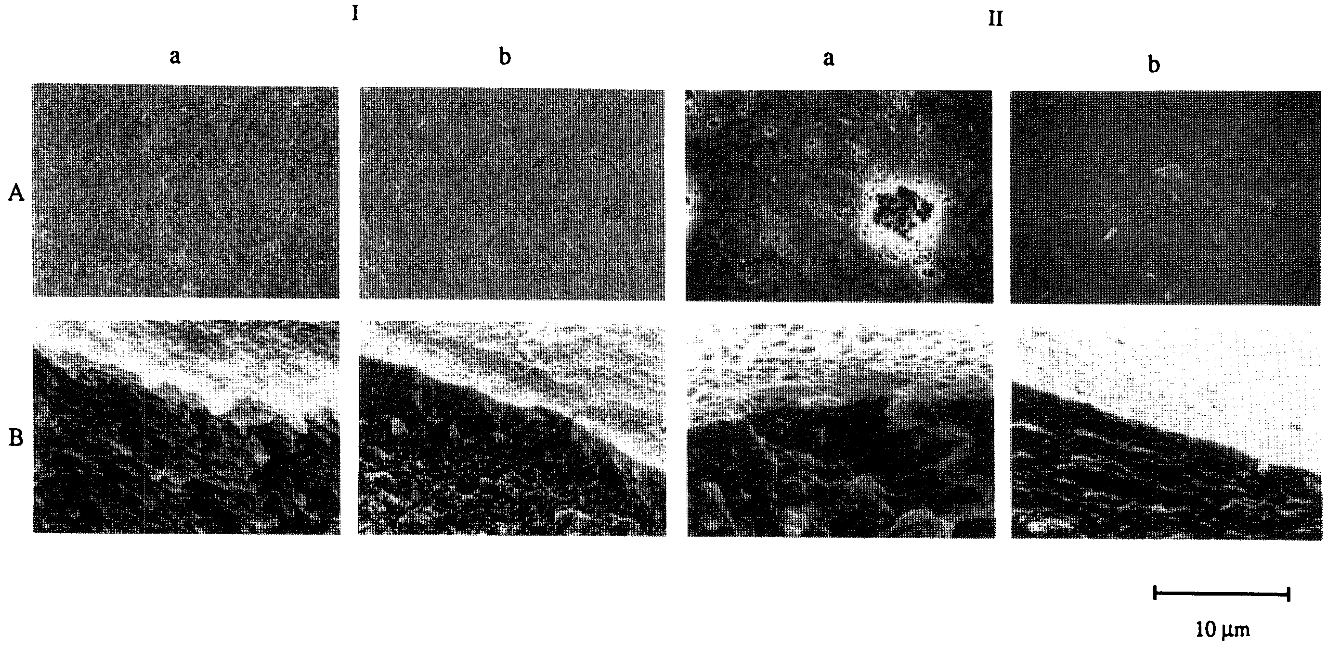

Fig. 7. SEM Photographs of Surface (A) and Cross Section (B) of Solid Dispersion Films of the OXP–EC System (I) and the OXP–EC–HPC System (II) after Dissolution Test

a, EC7; b, EC22.

system after the dissolution test (Ib), the pore volume at a diameter of less than about 0.1 μm (such pores were formed by the release of OXP) increased.[17] The increase in the pore volume was greater at a lower molecular weight of EC. In the OXP–EC–HPC system after the dissolution test (IIb), in the cases of lower molecular weight of EC (EC7, EC10), an increase in the pore volume at a diameter of about 0.1 to several μm was observed. This reflects the release of HPC. The two kinds of higher-molecular-weight EC (EC22, EC100) showed an extremely slight increase in the pore volume at a diameter of less than 0.1 μm compared with that of the OXP–EC system.

Figure 7 shows SEM photographs of the surface and cross section of the OXP–EC and OXP–EC–HPC films using EC7 and EC22 after the dissolution test. In the photographs of the surface (A) of the OXP–EC system (I), pores at a diameter of less than about 0.1 μm formed by the release of OXP were observed in both EC7 and EC22, and more pores were observed in EC7 than EC22. In addition, EC7 showed a rough surface compared with EC22. With the OXP–EC–HPC system (II), EC7 showed large pores formed by the release of HPC and fine pores formed by the release of OXP. Conversely, neigher large pores due to the release of HPC nor fine pores due to the release of OXP were observed in EC22. In the photograph of the cross section (B) of the OXP–EC system (I), it was found that the channels formed by the release of OXP were continuous to the inside of the films. The film using a high-molecular-weight polymer (EC22) showed a denser internal structure than that using EC7, as with the surface. With the OXP–EC–HPC system (II), in EC7, pores due to the release of HPC were also observed inside the film. In the case of EC22, however, no channels formed by the release of OXP or HPC were observed and an extremely dense structure was found.

Based on the internal structure and the SEM photographs of the films, the release mechanism of OXP could be explained as follows. In the case of the OXP–EC system, the water begins to penetrate into the films from the pores formed in the surface part of the films at the time of preparation. Then OXP dissolves in the water and is released. OXP is further released through the pores which have been formed by the release of OXP in the surface part of the films. The pores formed among the molecules of EC, that is, the channels, decrease with increasing molecular weight of EC, as shown by the pore size distribution (Fig. 6I). Therefore, the number of OXP molecules which can contact the water at the initial stages of the release process decreases with increasing molecular weight of EC. Thus, a slight decrease in the release rate with increasing EC molecular weight was observed. The reason for the very slight difference in the release rate is presumably the extremely high solubility and dissolution rate of OXP in water. The diffusional exponent n which is indicative of the release mode was about 0.4, independent of the molcular weight of EC in the OXP–EC system (Table 2). This indicates that the OXP release was not diffusion-controlled release. This might be because EC is insoluble and non-swellable in water.

In the case of the OXP–EC–HPC system, the n value of the film using EC7, with the lowest EC molecular weight, was almost the same as in the OXP–EC system. This might be explained by the fact that, since the channels increase with lower molecular weight of EC in the same manner as in the OXP–EC system, as shown by the pore size distribution, most of the OXP molecules could dissolve in the water in the channels and be released directly through the channels without diffusing through the swollen HPC phase. Since these channels decrease with increasing molecular weight of EC, the proportion of OXP molecules which diffuse into the swollen HPC gel phase increases and the release of OXP becomes dependent on the swelling and relaxation of HPC. Therefore, the n value in Eq. 4 increases with increasing molecular weight of EC, becoming 0.5 in the cases of EC22 and EC100 with higher molecular weights, and corresponding to the Fickian diffusional release of OXP.

The penetration behavior of the dissolution fluid and the hydration and swelling behavior of the polymer, mainly of HPC here, are important factors which affect the release mechanism.[14] So, the penetration of water into the solid dispersion film was studied.

Penetration Properties of Water into the Solid Dispersion Film The amount of water penetrated into the film is proportional to the penetration distance, so the water penetration properties can be estimated from the rela-

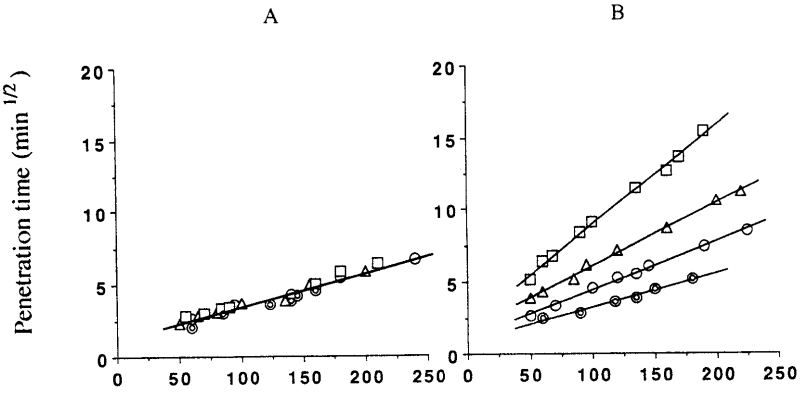

Fig. 8. Water Penetration Behavior into Solid Dispersion Films of the OXP–EC System (A) and the OXP–EC–HPC System (B)
⊚, EC7; ○, EC10; △, EC22; □, EC100.

tionship between the penetration distance and the time required for the penetration. The penetration distance corresponds to the film thickness under our experimental conditions. Vrentas and Duda described the absorption behavior of a solvent into a polymer as follows. If structural change of the polymer does not occur during the absorption process or the relaxation of the polymer is extremely fast, the influence of the relaxation of the polymer on the absorption behavior of the solvent is negligible and the absorption of the solvent is controlled by the diffusion of the solvent molecules into the polymer. Then the amount of absrobed solvent increases with the square root of time, that is, Fickian diffusion is observed. On the other hand, if relaxation of the polymer chains occurs gradually with the penetration of the solvent, the relaxation of the polymer affects the diffusion process of the solvent and non-Fickian diffusion is observed.[18] The penetration of water into the OXP–EC and OXP–EC–HPC solid dispersion films is shown in Fig. 8. With the OXP–EC system (A), a linear relationship between the film thickness and the square root of the penetration time was observed at every molecular weight of EC. This result suggests that the penetration process of water was of Fickian diffusion type. This may be because EC is water-insoluble and does not undergo swelling or relaxation during the penetration process of water. Further, no difference in the penetration time depending on the molecular weight of EC was found. In the OXP–EC–HPC system (B), the penetration process was also of diffusion-controlled type at every molecular weight of EC, but the penetration of water required a longer time with higher-molecular-weight EC. EC7, with the lowest molecular weight, exhibited the same penetration behavior as that of the OXP–EC system, and the penetration time at the film thickness of 120 μm which was used in the dissolution test was extremely short (about 16 min). These results support the validity of the release mechanism assumed from the internal structure. The prolongation of the penetration time with increase in the molecular weight of EC may be caused by the fact that, since the channels among the molecules of EC decreased with increasing molecular weight of EC, the influence of the swelling of HPC on the penetration of water was larger with increasing molecular weight of EC. Even in the cases of EC22 and EC100, which showed a diffusion-controlled release mechanism, the penetration times of the films at the thickness of 120 μm used in the dissolution test were about 48 and 106 min, respectively. It has thus been clarified that the penetration of water and the hydration of the films occurred at early stages of the release process in both cases. These results suggest that the diffusion-controlled release mechanism of the EC22 and EC100 films in the OXP–EC–HPC system was as follows: HPC was hydrated in the films by water penetrating into the matrix and swelled rapidly, and OXP diffused into the quasi-equilibrium swollen gel region of HPC. A different release rate was observed between EC22 and EC100 as shown in Fig. 4, even though the water penetration occurred at early stages of the release process in both cases. This might be because the distribution state, the thickness and so on of the swollen HPC phase in the solid dispersions were different depending on the molecular weight of EC, changing the diffusion rate of OXP in the solid dispersions.

Conclusion

In the OXP-EC system, the *n* value in Peppas's equation, which is indicative of the release mechanism, was about 0.4 and was hardly affected by the molecular weight of EC. In the OXP–EC–HPC system, the *n* value increased with increasing molecular weight of EC and reached 0.5. It is suggested from the study of the internal structure and the water penetration properties of the solid dispersion that at a higher molecular weight of EC, OXP diffuses into the quasi-equilibrium swollen gel region formed by the rapid hydration on HPC by water penetrating into the matrix, and the release mechanism is a diffusion-controlled process. The results presented in this paper support our speculation concerning OXP release from solid dispersions based on our previous studies using the granules; that is, the proportion of OXP diffusing into the swollen HPC phase increases with increasing molecular weight of EC, causing a decrease in the release rate.

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