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Application of the Solid Dispersion Method to the Controlled Release of Medicine. IV.[1] Precise Control of the Release Rate of a Water Soluble Medicine by Using the Solid Dispersion Method Applying the Difference in the Molecular Weight of a Polymer[2]

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Solid dispersions were prepared by the evaporation of ethanol after dissolving into ethanol a water soluble medicine (oxprenolol hydrochloride (OXP)), four grades of water insoluble ethylcellulose (EC) and four grades of water soluble hydroxypropyl cellulose (HPC), both having different molecular weights. The precise control of the release rate of a water soluble medicine by applying the difference in the molecular weight of polymers was attempted. The pore size distribution in solid dispersion granules was measured before and after the dissolution test by mercury intrusion porosimetry to clarify the mechanism of medicine release from the granules when the molecular weights of polymers were different. The state of medicine in the solid dispersions was analyzed by thermal analysis and X-ray diffractometry.

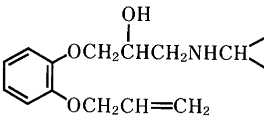
Although the difference was slight, the release rate of OXP from the granules of the OXP–HPC system decreased as the molecular weight of HPC increased. The release behavior of OXP in the OXP–EC system was scarcely affected by the molecular weight of EC. However, in the OXP–EC–HPC system, the release rate markedly decreased with a larger molecular weight of EC. It was thought from the results of the pore size distribution that there were two types of release routes for OXP; dissolving directly into the dissolution medium, and diffusing in the swelled HPC phase, caused by the addition of HPC. The decrease in the release rate of OXP in the OXP–EC–HPC system was caused by the increase in the ratio of OXP dissolving *via* the latter route, occurring with a larger molecular weight of EC. These results suggest that it is feasible to precisely control the release of a water soluble medicine by varying the molecular weight of the polymers in the solid dispersion.

Keywords solid dispersion; oxprenolol hydrochloride; ethylcellulose; hydroxypropyl cellulose; release rate; molecular weight

The solid dispersion method was originally used to enhance the dissolution rate of slightly water soluble medicines by dispersing the medicines into water soluble carriers such as polyethylene glycol or polyvinylpyrrolidone.[3-5] Water insoluble polymers have also been used for solid dispersion carriers. Hasegawa *et al.*[6] studied the sustained release preparation of nifedipine, a slightly water soluble medicine, by using various water insoluble polymers as solid dispersion carriers, and reported that the difference in the swelling property of the polymers caused a variety in the dissolution behavior of nifedipine. We have reported on controlling the release rate of a highly water soluble medicine by the solid dispersion method using water insoluble, non-swellable ethylcellulose (EC) and water soluble hydroxypropyl cellulose (HPC), and the preparation of the sustained release tablets from these granules.[7,8] The purpose of this work is to attain more precise control of the release rate of a highly water soluble medicine by varying the molecular weights of EC and HPC in the solid dispersion.

Experimental

Materials Oxprenolol hydrochloride (OXP) (known as a β-adrenaline receptor 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 chemical structure and the molecular weight of OXP are shown in Fig. 1. Four grades of EC having different molecular weights (EC7, EC10, EC22, EC100) were purchased from Shinetsu Chemical Industry Co., Ltd., Tokyo. Four grades of HPC having different molecular weights (HPC-SL, HPC-L, HPC-M, HPC-H) were obtained from Nippon Soda Co., Ltd., Tokyo. The densities and mean molecular weights of these materials are shown in Table I. The densities of OXP, EC and HPC were 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 Shimazu LC-6A GPC system (Shimazu Seisakusho Co.) with a Shim-pack GPC-805 and a GPC-804 column (8.0 mm i.d. × 300 mm, Shimazu Seisakusho Co.). The solvent was tetrahydrofuran at a flow rate of 1.0 ml/min.



MW 301.8

Fig. 1. Structure and Molecular Weight of Oxprenolol Hydrochloride (OXP)

Preparation of Samples Solid dispersion granules which have four kinds of OXP–EC systems, four kinds of OXP–HPC systems and sixteen kinds of OXP–EC–HPC systems were prepared by the method shown in Fig. 2. The composition ratios of these granules are shown in Table II. Physical mixtures were prepared by simply mixing the powdered OXP and polymers at the same composition ratios as those of the solid dispersions.

Dissolution Study The dissolution behavior of OXP from the granules

TABLE I. Densities and Average Molecular Weights of Used Polymers

Polymer		Density (g/ml)	$\bar{M}_n$[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-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.

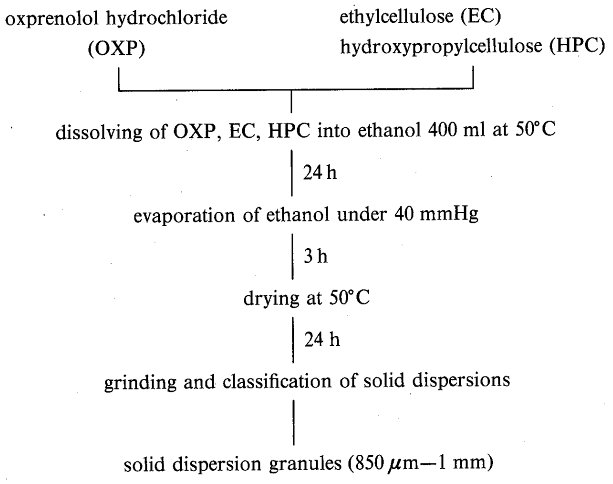


Fig. 2. Preparation Method of Solid Dispersion Granules

TABLE II. Composition Ratios of Solid Dispersion Granule Systems

Solid dispersion granule system	Composition ratio		
	OXP	EC	HPC
OXP–EC system	25	75	—
OXP–HPC system	25	—	75
OXP–EC–HPC system	25	70	5

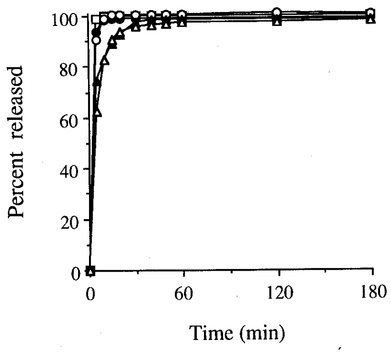


Fig. 3. Effects of Molecular Weight of HPC on Release Behavior of OXP in the OXP–HPC System

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

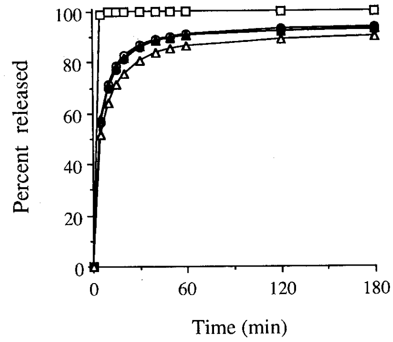


Fig. 4. Effects of Molecular Weight of EC on Release Behavior of OXP in the OXP–EC System

●, EC7; ○, EC10; ▲, EC22; △, EC100; □, physical mixtures. Each point represents the mean of three experiments.

was observed with a dissolution tester (Freund-JASCO, DT-300), following the paddle method (JP XII), using 320 mg of the granule sample (corresponding to 80 mg of OXP) and 900 ml pure water as the dissolution medium at 37 ± 0.5 °C, and 100 rpm. The quantity of OXP was determined spectrophotometrically by the absorbance at 273 nm.

Analysis of Solid State of Solid Dispersion The powder X-ray diffraction patterns were measured with a diffractometer (Geigerflex RAD-IB, Rigaku, Ni-filter, CuK_α ray (40 kV, 20 mA)). 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.

Measurement of Pore Size Distribution of Granules before and after Dissolution Test The pore size distribution in the solid dispersion granules before and after the dissolution test was measured by mercury intrusion porosimetry, employing a mercury porosimeter (AMINCO, motor-driven 15000 psi). The contact angle of mercury on the samples was regarded as 130°.[9]

Results and Discussion

Effects of the Molecular Weight of Polymers on the Medicine Release from Solid Dispersion Granules Figure 3 shows the release behavior of OXP from the OXP–HPC system. The percentage of released OXP in all cases of the OXP–HPC granules reached 100% in a short time (up to about 30 min after the dissolution test was started), and it was observed that the release rate of OXP was slightly smaller with a larger molecular weight of HPC. Figure 4 shows the release behavior of OXP in the OXP–EC system. In this case, the release behavior of OXP from the solid dispersion granules was scarcely affected by the molecular weight of EC, and plateaued in a relatively short time after the dissolution test was started. In both the OXP–HPC system and the OXP–EC system, OXP dissolved rapidly from the physical mixtures, and the percentage of dissolved OXP reached 100% in about 5 min after the dissolution test was started.

Figure 5 shows the release profile of OXP from the physical mixtures and the solid dispersions of the OXP–EC–HPC system, which was made by adding water soluble HPC (5%) to the OXP–EC system. In all the solid dispersions, the release rate decreased remarkably compared with that from the physical mixtures, and although the effect of the molecular weight of HPC on the release behavior of OXP was hardly observed, the release rate decreased with a larger molecular weight of EC.

Plots of the time necessary to release half of the amount (T_{50}) from the solid dispersion granules in Figs. 4 and 5 against the weight-average molecular weight of EC, are shown in Fig. 6. In all the cases of the OXP–EC–HPC system, T_{50} was significantly larger as compared with that in the OXP–EC system, and increased with a larger molecular weight of EC. Donbrow *et al.*[10] reported that the permeability of EC film for caffeine and salicylic acid was enhanced by adding polyethylene glycol. Najib *et al.*[11] studied the dissolution behavior from a sulphadiazin-solid dispersion using EC as a carrier, and reported that the dissolution rate of sulphadiazine was increased by blending water soluble substances into EC. They described that this increase in the dissolution rate was caused by the increased porosity of the EC wall coating the medicine particles. However, in the OXP-solid dispersion system that we prepared, the release rate of OXP was decreased by adding HPC, a water soluble polymer. Furthermore, the variety in the release behavior of OXP depending on the difference of the molecular weight of EC was hardly observed in the OXP–EC system, while in the OXP–EC–HPC system, the release rate decreased with a larger molecular weight of EC.

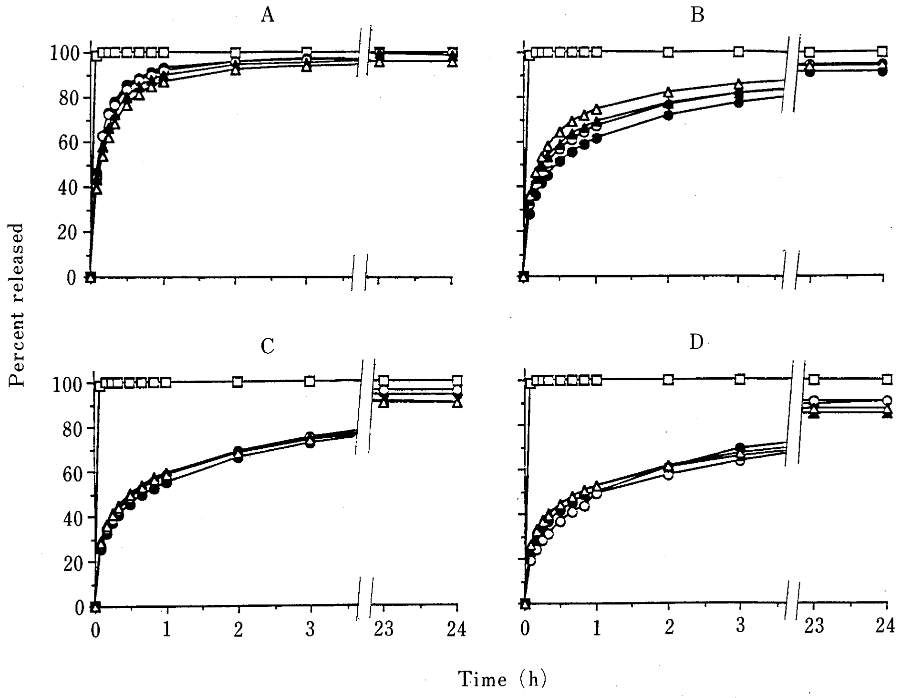


Fig. 5. Effects of Molecular Weights of EC and HPC on Release Behavior of OXP in the OXP–EC–HPC System, EC7 (A), EC10 (B), EC22 (C), EC100 (D)

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

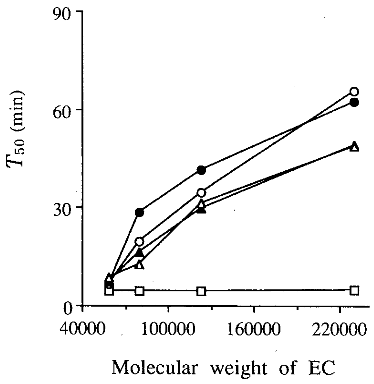


Fig. 6. Plots of T_{50} against the Molecular Weight of EC

OXP–EC system (□), OXP–EC–HPC system (●, HPC-SL; ○, HPC-L; ▲, HPC-M; △, HPC-H).

These results suggest that it is possible to control the OXP release by varying the molecular weight of EC.

Incidentally, as for the powder X-ray diffraction patterns and the DSC curves, neither X-ray diffraction peaks nor the melting endothermic peaks of OXP crystals were observed in all the solid dispersions used in this study. These results show that OXP existed in a low crystallinity in the solid dispersions regardless of the molecular weights of the polymers (data not shown).

Release Mechanism from Solid Dispersion Granules The pore size distribution in the OXP–HPC granules after the dissolution test could not be measured because all of the granules in this system dissolved in about 30 min after the dissolution test was started, regardless of the molecular weight of HPC, but this fact suggests that the release mechanism of OXP from the OXP–HPC granules was of an erosion type, which is the same mechanism reported by Sekikawa *et al.*[12)]

Figure 7 shows the pore size distribution in the solid dispersion granules of the OXP–EC system and the OXP–EC–HPC system before and after the dissolution test. In the OXP–EC system, after the dissolution test, the pore volume at the pore diameter of less than 0.1 μm increased as compared with the volume before the test. Since EC is insoluble in the dissolution medium, it was thought that these pores were formed by dissolved OXP. Further, the pore volume at that approximate diameter increased with a smaller molecular weight of EC. It is thought that the number of EC molecules per unit weight of the solid dispersion granule increases with a smaller molecular weight of EC because Nakagaki describes that a linear polymer generally exists in an almost globular shape as it becomes folded and tangled confusedly in a solution,[13)] suggesting that EC and HPC used in this study probably also exist in a similar state. Also, the density of EC is almost the same even though the molecular weights are different, as shown in Table I. Therefore, the number of intermolecular channels formed among EC molecules increases with a smaller molecular weight of EC. So, it was speculated that the number of channels in the granules formed by the dissolution of OXP increases with a smaller molecular weight of EC.

Although such differences were observed in the pore volume after the dissolution test, the release behavior of OXP from the OXP–EC system was scarcely affected by the molecular weight of EC, as shown in Fig. 4. The reason may be that since the diameter of the channels formed by the release of OXP distributed in the surface part of the granules and the diameter of the pores formed at the preparation of the sold dispersions are much larger than the molecular size of OXP, OXP in the intermolecule of

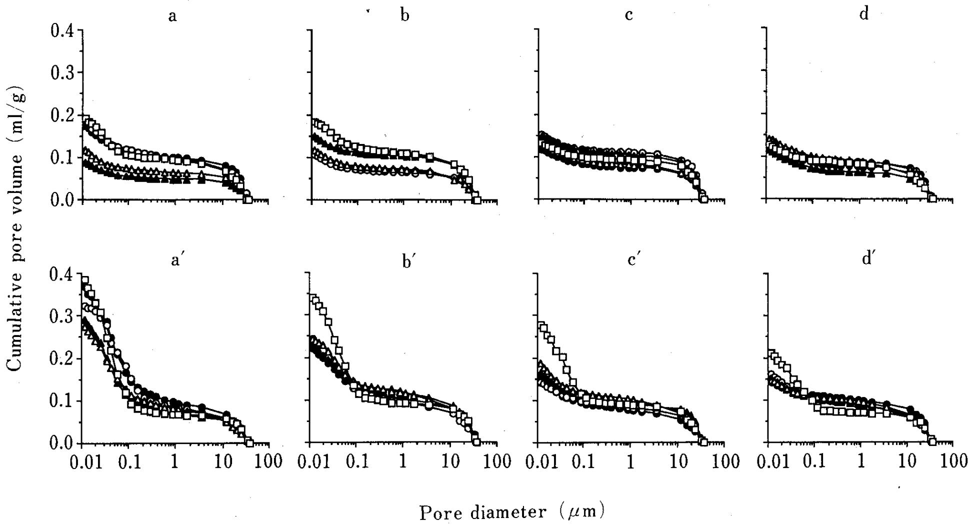


Fig. 7. Pore Size Distribution in Solid Dispersion Granules of the OXP–EC–HPC System before (a, b, c, d) and after (a′, b′, c′, d′) Dissolution Test

EC7 (a, a′) EC10 (b, b′) EC22 (c, c′) EC100 (d, d′) OXP–EC system (□), OXP–EC–HPC system (●, HPC-SL; ○, HPC-L; ▲, HPC-M; △, HPC-H).

EC dissolved successively through these channels and pores.

In all cases of the granules of the OXP–EC–HPC system, after the dissolution test, the volume of the pores at the pore diameter of less than 0.1 μm, which were thought to be formed by the direct dissolution of OXP into the dissolution medium, decreased as compared with that for the OXP–EC system, and the increase in pore volume at the pore diameter of less than 0.1 μm was smaller with a larger molecular weight of EC. These results suggest that in the OXP–EC–HPC granules including water soluble HPC, the HPC was swelled in the granules by the permeating fluid, and the release of OXP diffusing into the swelled HPC phase occurred, so the ratio of OXP which dissolved directly into the dissolution medium decreased. It was thought that this caused a decrease in the pore volume at pore diameters of less than 0.1 μm compared with the OXP–EC system. The swelled HPC phase would operate as a barrier for the dissolution of OXP, thus decreasing the release rate of OXP as compared with that for the OXP–EC system. Furthermore, it was thought that because the ratio of OXP dissolved through the swelled HPC phase increased with a larger molecular weight of EC, the release rate of OXP decreased with a larger molecular weight of EC in the OXP–EC–HPC system.

Conclusion

In this paper, in a two-component system such as the OXP–EC system and the OXP–HPC system, the release behavior of OXP was scarcely affected by a difference in the molecular weight of EC or HPC. But it is clear that in the OXP–EC–HPC system, the release rate of OXP decreased with a larger molecular weight of EC. These results suggest that it is feasible to precisely control the release of a water soluble medicine by varying the molecular weight of the polymers in the solid dispersions. It was thought that the decrease in the release rate was caused by an increase in the ratio of OXP diffusing into the swelled HPC phase, occurring with a larger molecular weight of EC.

References and Notes

1) Part III: H. Yuasa, H. Takahashi, T. Ozeki, Y. Kanaya and M. Ueno, *Chem. Pharm. Bull.*, **41**, 397 (1993).
2) A part of this study was presented at the 111th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March 1991.
3) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **59**, 937 (1970).
4) S. A. H. Khalil, S. A. El-Fattah and L. M. Mortada, *Drug Dev. Ind. Pharm.*, **10**, 771 (1984).
5) I. Sugimoto, A. Kuchiki, H. Nakagawa, K. Tohgo, S. Kondo, I. Iwane and K. Takahashi, *Drug. Dev. Ind. Pharm.*, **6**, 137 (1980).
6) A. Hasegawa, M. Taguchi, R. Kawamura, H. Nakagawa and I. Sugimoto, *Yakuzaigaku*, **48**, 139 (1988).
7) H. Yuasa, T. Ozeki, Y. Kanaya, K. Oishi and T. Oyake, *Chem. Pharm. Bull.*, **39**, 465 (1991).
8) H. Yuasa, T. Ozeki, Y. Kanaya and K. Oishi, *Chem. Pharm. Bull.*, **40**, 1592 (1992).
9) N. M. Winslow and J. J. Shapirio, *ASTM Bull.*, **239**, 39 (1959).
10) M. Donbrow and M. Friedman, *J. Pharm. Pharmacol.*, **27**, 633 (1975).
11) N. Najib and M. S. Suleiman, *Drug. Dev. Ind. Pharm.*, **11**, 2169 (1985).
12) H. Sekikawa, M. Nakano and T. Arita, *Chem. Pharm. Bull.*, **27**, 1223 (1979).
13) M. Nakagaki, "Gendai Butsurikagaku Koza, the 9th series: Surface State and Colloidal State," Tokyo Kagaku Dojin Co., Ltd., Tokyo, 1979, p. 22.