Application of the Solid Dispersion Method to Controlled Release of Medicine. II.[1] Sustained Release Tablet Using Solid Dispersion Granule and the Medicine Release Mechanism[2]

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In our previous paper, the utility of the solid dispersion for the control of medicine release was studied and the solid dispersion was prepared by the evaporation of ethanol after dissolving a water soluble medicine (oxprenolol hydrochloride), soluble hydroxypropyl cellulose and insoluble ethylcellulose into ethanol. In this paper, the tableting of the above mentioned solid dispersion granule and the mechanism of medicine release from this solid dispersion granule were studied. Microcrystalline cellulose was used as the excipient in this tableting. The disintegration time, crushing strength and porosity were measured for the obtained tablets. The pore size distribution in the solid dispersion granules was measured before and after the dissolution test with a mercury porosimeter to clarify the mechanism of medicine release from the granules. The state of medicine in the granules was analyzed by infrared spectrometry, thermal analysis and X-ray diffractometry.

As a result, it was clarified that oxprenolol hydrochloride in ethylcellulose was released from the granules by diffusing and dissolving into the medium in the channels formed by the dissolving of hydroxypropyl cellulose and oxprenolol hydrochloride, as inferred in the previous paper. Furthermore, the compression pressure and pH scarcely affected the dissolution behavior of oxprenolol hydrochloride from the granules. It was thought that the homogeneity of the content of oxprenolol hydrochloride in the granules was very high, and the dissolution rate from the granules could be controlled by the particle size of the granules and the composition ratio of ethylcellulose and hydroxypropyl cellulose in the granules. These results suggest the solid dispersion granule and the tablet prepared with this granule are useful for the sustained release granule and tablet.

Keywords solid dispersion; evaporation; polymer; granule; tablet; compression; sustained release; matrix

For the development of preparations of sustained or controlled medicine release, addition of or coating with wax or water insoluble cellulose has generally been adopted.[3-7] Recently, Hasegawa *et al.*[8-15] and Fujii *et al.*[16-20] used the solid dispersion method for this purpose. In our previous paper, the utility of the solid dispersion for the control of medicine release was studied and the solid dispersion was prepared with the evaporation of ethanol after dissolving a water soluble medicine (oxprenolol hydrochloride (OXP)), soluble hydroxypropyl cellulose (HPC) and insoluble ethylcellulose (EC) into ethanol. In this paper, the tableting of the above mentioned solid dispersion granule and the mechanism of medicine release from this solid dispersion granule were studied.

Experimental

Materials OXP, known as a receptor inhibitor and water soluble medicine, was supplied by Nihon Pharmaceutical Industry Co., Ltd., Tokyo. EC 45cp was purchased from Wako Pure Chemical Industries, Ltd., Osaka. HPC L grade was obtained from Nippon Soda Co., Ltd., Tokyo. Microcrystalline cellulose (MCC) used as the excipient was Avicel® PH 101 which was obtained from Asahi Kasei Kogyo Co., Tokyo.

Preparation of Granules EC, HPC and OXP were dissolved into ethanol under heating at 50 °C, and ethanol in the solution was evaporated to make the solid dispersion. The solid dispersion was ground and sieved. The fractions of 18—20, 24—28, and 32—42 mesh were collected as the granule size L, M and S, respectively.

Preparation of Tablets For each granule size, the powder mixture composed of 320 mg granule and 80 mg of MCC was compressed at varying pressures of 250—1500 kg/cm^2 into tablets by the direct compression method, using a tableting machine (Nichiei Seiko Co., Tokyo, type UPF-6) with a single flat punch of 1 cm^2 cross section and equipped with a strain gauge.

Observation of Dissolution Behavior of OXP from Granule and Tablet The dissolution behavior of OXP from the granule and the tablet was observed with a dissolution tester (Freund-JASCO, DT-300), following the paddle method (JP XII), using 900 ml pure water as the dissolution medium and 400 mg of the granule or the tablet sample. The quantity of OXP was determined spectrophotometrically with the absorbance at 273 nm.

Measurement of Crushing Strength of Tablets The crushing strength of 10 tablets of each kind was measured with a hardness tester (Kiya Seisakusho Co., Tokyo).

Measurement of Density of Granules and MCC The densities of granules and MCC were measured with an Air Comparison Pycnometer (Toshiba-Beckman Co., Ltd., Model 930). Measurement was repeated 5 times for each kind of granule or MCC.

Measurement of Porosity of Tablets The porosity of 10 tablets of each kind was determined by measuring the weight, diameter and thickness of the tablets, using each of the densities of granules or MCC.

Measurement of Disintegration Time The disintegration time was determined by the JP XII method. Pure water was used as the disintegration medium.

Measurement of Pore Size Distribution of Granules before and after Dissolution Test The pore size distribution was measured for the L size granules before and after the dissolution test by the mercury porosimetry method described in the previous paper.[21] The measuring apparatus was a porosimeter (Aminco, motor driven, 15000 psi). The contact angle of mercury on the tablets was regarded as 130°.[22]

Analysis of Solid State of Solid Dispersion The solid state of the solid dispersion was analyzed by thermal analysis with a differential scanning calorimetry (DSC) (SSC/560S, Seiko Instruments & Electronics Ltd.), the powder X-ray diffraction with a diffractometer (Geigerflex RAD-IB, Rigaku) and the infrared (IR) spectra with a spectrophotometer (IR-810, JASCO).

Results and Discussion

Effects of Tableting on Release Profile Figure 1 shows the release profiles of OXP from solid dispersion granules and solid dispersion tablets consisting of different granule sizes. These tablets were tableted at 1000 kg/cm^2 of compression pressure. The released amount was large with both the granule and the tablet in proportion to the reduction in the granule size. The degree of increase in the released amount was larger when the larger solid dispersion granules were tableted. These results suggest that the larger solid dispersion granule was subject to fracture, resulting in a larger specific surface area at the compression.

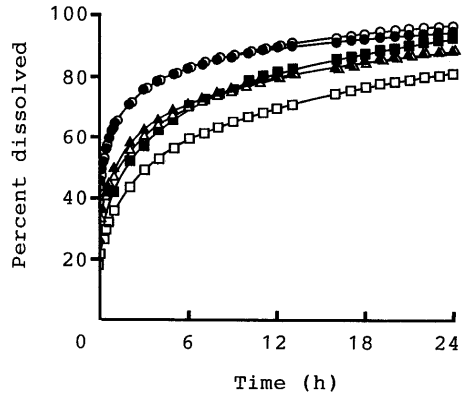

Fig. 1. Release Profiles of OXP from Solid Dispersion Granules and Solid Dispersion Tablets Consisting of Different Granule Sizes

□, L size granule; ■, L size tablet; △, M size granule; ▲, M size tablet; ○, S size granule; ●, S size tablet.

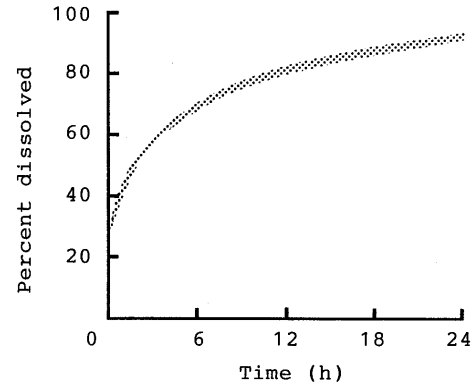

Fig. 2. Release Profiles of OXP from Tablets Composed of L Size Granules and Compressed at 250—1500 kg/cm²

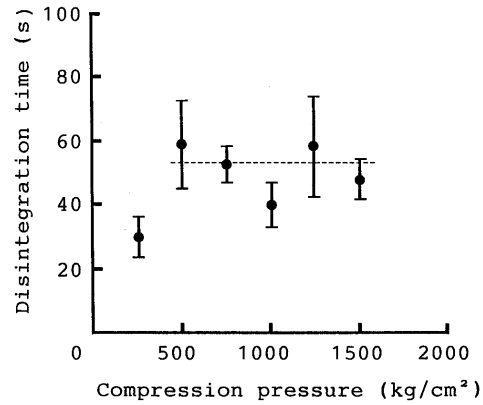

Fig. 3. Effect of Compression Pressure at Tableting on Disintegration Time of Tablet

Each point represents the mean ± S.D. for 6 tablets.

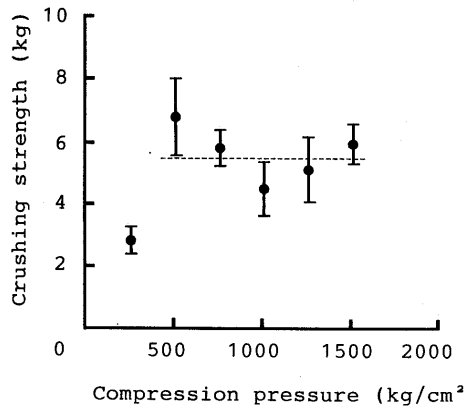

Fig. 4. Effect of Compression Pressure at Tableting on Crushing Strength of Tablet

Each point represents the mean ± S.D. for 10 tablets.

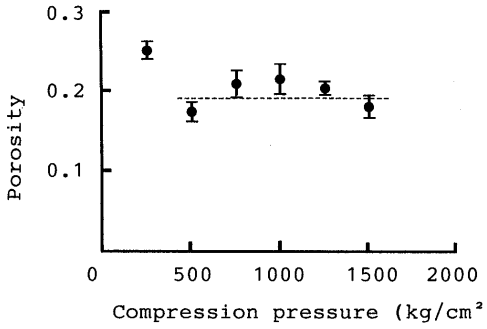

Fig. 5. Effect of Compression Pressure at Tableting on Porosity of Tablet

Each point represents the mean ± S.D. for 10 tablets.

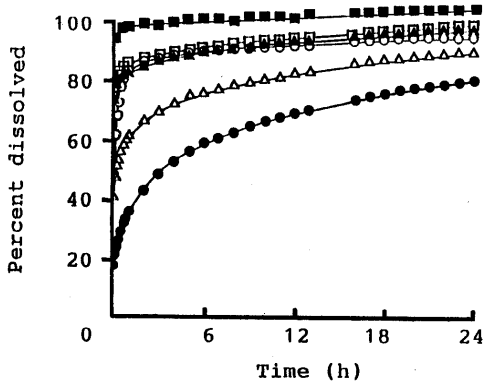

Fig. 6. Effect of Composition Ratio of OXP, EC and HPC in Solid Dispersion Granule on Dissolution Behavior of OXP

Percent of EC and HPC: ■, 30% and 45%; □, 40% and 35%; ▲, 50% and 25%; △, 60% and 15%; ●, 70% and 5%; ○, 75% of EC.

As the S size granule showed the same release profile as the tablet composed of the S size granule, it was thought that the S size granule was not fractured below about 1000 kg/cm² of compression pressure.

Effects of the Compression Pressure on Medicine Release Figure 2 shows the release profiles from the tablets composed of L size granules and compressed at 250—1500 kg/cm³. The profiles at varied pressures are all the same, and it was obvious that the L size granules fractured at the tableting in Fig. 1. These results suggest that the fracture of the L size granules will be finished at less than 250 kg/cm² of compression pressure.

Effects of Compression Pressure on Disintegration Time, Crushing Strength and Porosity of Tablets The effects of compression pressure at the tableting with the L size granules on the disintegration time, the crushing strength and the porosity of the tablets are shown in Figs. 3, 4 and 5, respectively. The disintegration time, the crushing strength and the porosity hardly changed at above 500 kg/cm² of compression pressure. These results suggest that the internal structure, that is, the number of contact

points and the contact area between the particles in the tablets hardly change at above 500 kg/cm^2 of compression pressure.

Release Mechanism from Solid Dispersion Granule Figure 6 shows the dissolution profile of OXP from L size granules of the solid dispersion composed of 25% OXP and 75% mixture at varied ratios of EC and HPC. In the solid dispersion granules including HPC, the initial dissolution rate and the percent dissolved were larger with a larger content of HPC as shown in the previous paper.[1] Figures 7 and 8 show the pore size distributions in the solid dispersion granules before and after the dissolution test for 24 h, respectively. Before the dissolution test a small amount of pore volume and the same shape of the pore size distribution are observed in every kind of solid dispersion granules, while after the dissolution test, the pore volume at the pore diameter of several to about 50 μm increased with a higher ratio of HPC in the granule. In the granule composed of 25% OXP and 75% EC without HPC, the pore volume at the pore diameter of less than 0.1 μm increased. These results support the conjecture in our previous paper that the dissolution of HPC forms

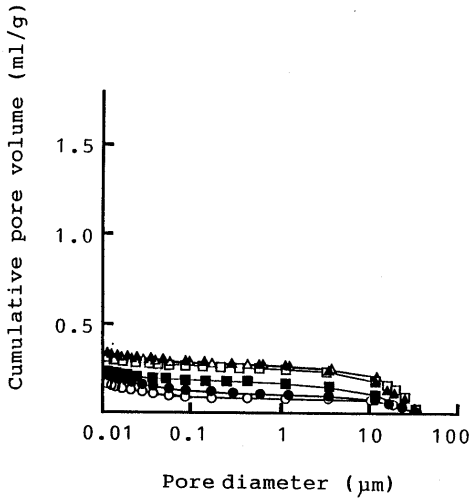

Fig. 7. Pore Size Distributions in Solid Dispersion Granules before Dissolution Test for 24 h

Percent of EC and HPC: ■, 30% and 45%; □, 40% and 35%; ▲, 50% and 25%; △, 60% and 15%; ●, 70% and 5%; ○, 75% of EC.

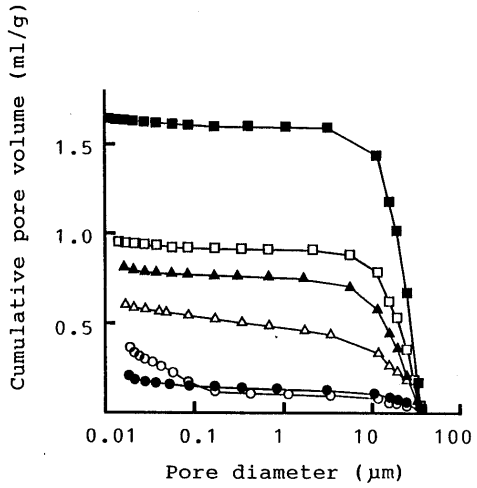

Fig. 8. Pore Size Distributions in Solid Dispersion Granules after Dissolution Test for 24 h

Percent of EC and HPC: ■, 30% and 45%; □, 40% and 35%; ▲, 50% and 25%; △, 60% and 15%; ●, 70% and 5%; ○, 75% of EC.

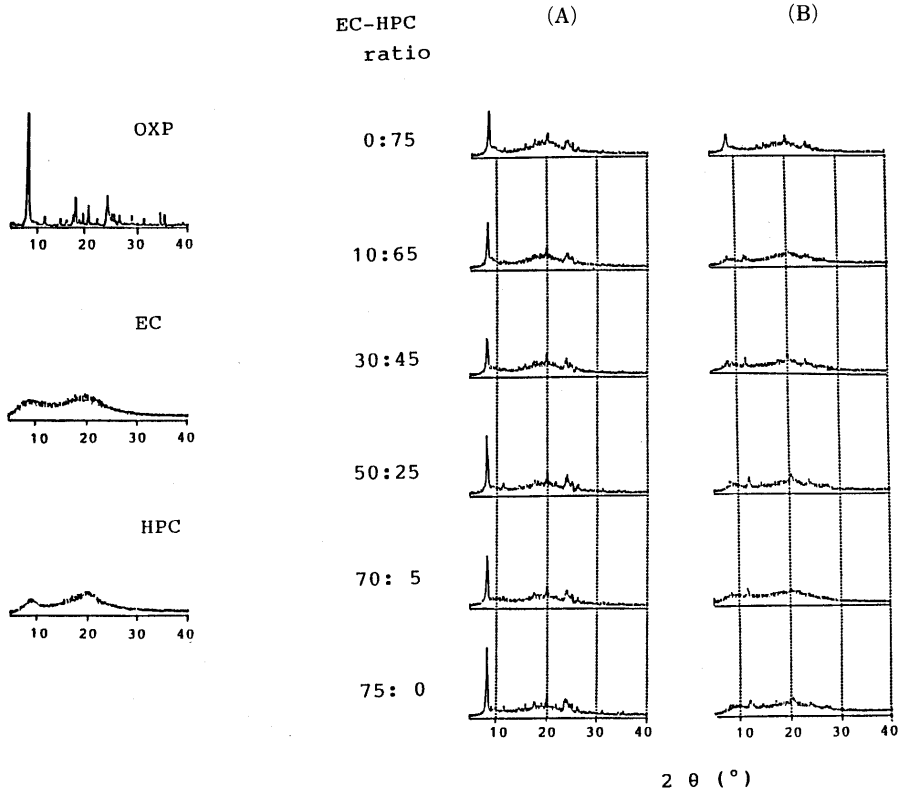

Fig. 9. Powder X-Ray Diffraction Patterns of Powders of OXP, EC, HPC, Physical Mixtures (A) and Solid Dispersions (B) Composed of 25% OXP and 75% Mixture with Varied Ratios of EC and HPC

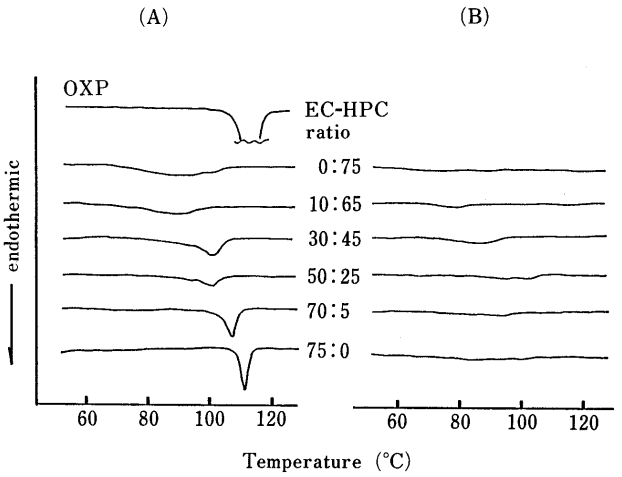

Fig. 10. DSC Curves of OXP Powder, Physical Mixtures (A) and Solid Dispersions (B) Composed of 25% OXP and 75% Mixture with Varied Ratios of EC and HPC

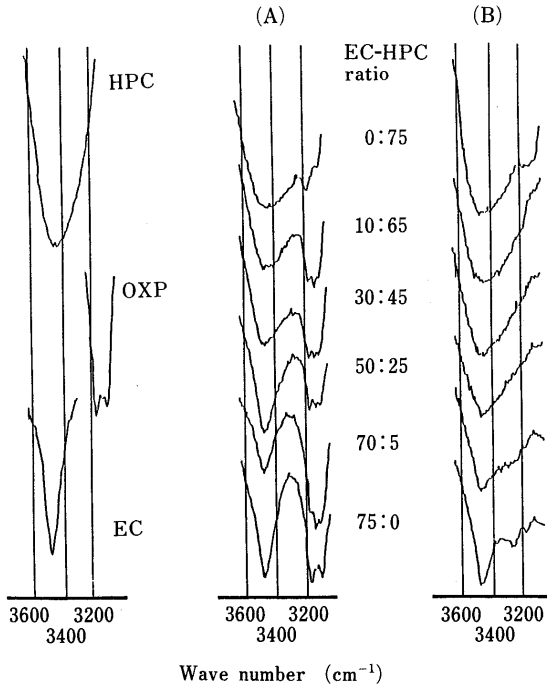

Fig. 11. IR Spectra of Powders of OXP, EC, HPC, Physical Mixtures (A) and Solid Dispersions (B) Composed of 25% OXP and 75% Mixture with Varied Ratios of EC and HPC

the channel in the granule. It was thought that with the granule including HPC, as HPC which has a larger molecular volume than OXP dissolves, causing the dissolution of OXP in the HPC molecules, the channel having a larger diameter of several to about 50 μm was formed and the amount of released OXP increased, and in the granule composed of OXP and EC without HPC, OXP on the surface of the granule dissolved easily, as OXP, which has high solubility, formed smaller channels (about 0.1 μm diameter) than those formed by the dissolution of HPC, and OXP in the EC molecules dissolved through these channels. Thus in the granule without HPC, a relatively large amount of OXP was released from the granule.

State of Solid Dispersion The powder X-ray diffraction patterns, the DSC curves and the IR spectra of the powders of OXP, EC, HPC, the physical mixtures and the solid dispersions composed of 25% OXP and 75% mixture with varied ratios of EC and HPC are shown in Figs. 9, 10, 11, respectively. In Fig. 9, in most cases of the solid dispersion, the X-ray diffraction peaks of OXP markedly decreased. In Fig. 10, although the melting point of OXP was around 106 °C, the melting endothermic peaks of OXP were scarcely observed in every kind of solid dispersion. In the physical mixtures, these peaks grew broader with an increase in the HPC ratio. In Fig. 11, the absorption spectra of the –OH forming inter- and intramolecular hydrogen bonding of HPC, OXP and EC were observed around 3430, 3150 and 3480 cm^{-1} respectively. Although these spectra hardly changed in the physical mixtures, the spectrum at 3150 cm^{-1} of –OH hydrogen bonding (mainly intermolecular, as OXP is a hydrochloride and scarcely has intramolecular hydrogen bonding,) shifted towards higher frequency for about 70 cm^{-1}, and the intensity of the spectrum decreased in the solid dispersions added with EC. These results suggest that EC suppressed the intermolecular hydrogen bonds of OXP in the solid dispersion.

It was thought that all the components of the solid dispersion existed in low crystallinity, as the components were presummed to be dispersed and mixed in the solid dispersion on the molecule level from the results of the X-ray diffraction patterns, DSC curves and IR spectra. The broadening of the endothermic peak assigned to OXP melting in the physical mixtures (shown in Fig. 10) is still not clearly explained.

Conclusion

It was clarified that as inferred in our previous paper, the OXP in EC was released from the granule by diffusing and dissolving into the medium through the channels formed by the dissolution of HPC and OXP. Furthermore, the compression pressure and pH scarcely affected the dissolution behavior of OXP from the granule. It was thought that the content homogeneity of OXP in the granule was very high, as all the components in the solid dispersion were dispersed and mixed on the molecule level. The dissolution rate from the granule was controlled by the particle size of the granule and the composition ratio of EC and HPC in the granule. These results suggest that the solid dispersion granule and the tablet prepared from this granule are useful for the sustained and controlled release of medicine.

References and Notes

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