Application of the Solid Dispersion Method to the Controlled Release of Medicine. VIII.¹⁾ Medicine Release and Viscosity of the Hydrogel of a Water-Soluble Polymer in a Three-Component Solid Dispersion System²⁾

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Solid dispersions were prepared with a highly water-soluble medicine (oxprenolol hydrochloride (OXP)), water-insoluble ethylcellulose (EC) and four grades of water-soluble hydroxypropylcellulose (HPC) having different molecular weights. The effects of the composition ratio within the range of 5% of HPC and of the viscosity of HPC hydrogels on the release of OXP were studied. The bulk viscosity of HPC hydrogels was evaluated from the relationship between shear rate and shear stress. The microscopic viscosity was evaluated by the spin probe method of the electron spin resonance (ESR) technique.

The release rate of OXP decreased with increasing HPC composition ratio and became almost constant at the HPC composition ratio of 3% and more. This result suggests that the release of OXP will occur through its diffusion into the swollen HPC gel phase formed in a solid dispersion at the HPC composition ratio of 3% and more. The bulk viscosity of HPC hydrogels markedly increased with increasing molecular weight of HPC, but there was little noticeable change in release rate and activation energy for the diffusion of OXP. This result can be explained by the fact that the microscopic viscosity was hardly affected by the molecular weight of HPC, suggesting that the resistance to diffusion of OXP into the swollen HPC gel phase in the solid dispersion was almost the same regardless of the molecular weight of HPC.

Key words solid dispersion; medicine release; bulk viscosity; microscopic viscosity; ethylcellulose; hydroxypropylcellulose

The solid dispersion method is one of several pharmaceutical techniques for controlling medicine release, and is used to improve the dissolution properties and bioavailability of slightly water-soluble medicines.³⁾ We have applied the solid dispersion method to the control of the release of a water-soluble medicine, have studied solid dispersions composed of a highly water-soluble medicine (oxprenolol hydrochloride (OXP)), water-insoluble ethylcellulose (EC) and water-soluble hydroxypropylcellulose (HPC), and found that at the HPC composition ratio of 5–10%, the release rate of OXP from the solid dispersion markedly decreased because OXP diffused into the swollen HPC phase formed and retained in the solid dispersion.^{4–6)} We have also reported that it was feasible to control the release rate of OXP by varying the molecular weight of EC and that the mechanism is likely due to the change in the proportion of OXP release *via* the swollen HPC phase depending on the molecular weight of EC.^{1,7)}

In the present study, to clarify the effects of the composition ratio within the range of 5% of HPC and the viscosity of HPC hydrogels on the release of OXP, the release behavior of OXP from a solid dispersion, the activation energy for the diffusion of OXP, and the bulk viscosity and microscopic viscosity of HPC hydrogels were studied.

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 (d) and molecular weight of OXP are 1.20 and 301.8, respectively. EC (EC100, $d=1.21$, the weight-average molecular weight (M_w) is 230000) was supplied by Shin-Etsu Chemical Industry Co., Ltd., Tokyo. Four grades of HPC having different molecular weights (HPC-SL, HPC-L, HPC-M, HPC-H,

$d=1.21$, 1.21, 1.20, 1.21, $M_w=73500$, 105000, 270000, 357000, respectively) were 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-804 and a GPC-805 column (8.0 mm i.d. $\times$ 300 mm, Shimadzu Seisakusho Co.). The solvent was tetrahydrofuran at a flow rate of 1.0 ml/min.

Preparation of Solid Dispersions Powders (16 g) consisting of 20% OXP and 0, 1, 2, 3, 4 or 5% HPC and the residual % EC were dissolved in ethanol (400 ml) at 50°C. The solid dispersion granules were prepared by the evaporation of ethanol, and then ground and dried at 60°C for 4 h *in vacuo*. The granules obtained were sieved (850 μ m—1 mm). The solid dispersion films were prepared as follows: The ethanol solution was cast on a Teflon plate using a film applicator (Baker Film Applicator, Ueshima Seisakusho Co.). After being dried in a desiccator, the film obtained was further 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 (Toyama Sangyo Co., Ltd., TR-5S3), according to the paddle method (JPXII) at 100 rpm, using 900 ml distilled water as the dissolution medium at 37 $\pm$ 0.5°C.

The dissolution test of the films was carried out by the same method as previously reported.¹⁾ That is: films with a dimension of 2.5 $\times$ 3.2 cm and a thickness of 120 $\pm$ 5 μ m were used for the dissolution test. Four such films were fixed on a handmade holder using paraffin so that the surface area exposed to the dissolution medium would remain constant. Five hundred ml of distilled water was used as the dissolution medium. Other operating conditions were set in the same way as in the case of the granules. The OXP content in the films was calculated from the composition ratio of OXP and the weight of the films.

The quantity of OXP was determined spectrophotometrically by measuring the absorbance at 273 nm.

Measurement of Porosity of 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 with the dimension of 2.5 $\times$ 3.2 cm. The apparent film volume was calculated from the film thickness and the known film area. The porosity of the film was calculated from the apparent film

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volume and the theoretical value of the true film volume calculated by using the true densities of OXP, EC and HPC.

Water Penetration into Solid Dispersion Films The measurement of the penetration time of water into the solid dispersion films was carried out by the same method as previously reported.¹⁾ That is: the solid dispersion film was fixed in a diffusion cell and one side of the cell was filled with distilled water. The change in the electric resistance of the film caused by the water penetration into the film was detected as the change in the voltage and was recorded with a recorder (Hitachi Co., QPD54) as a function of time. We regarded the time required until the voltage became almost constant as the penetration time.

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, $2\theta = 4^\circ/\text{min}$.

Thermal Analysis Differential scanning calorimetry (DSC) curves were measured with a DSC instrument (Seiko Instruments & Electronics, Ltd., SSC/560S) at the heating rate of $4^\circ\text{C}/\text{min}$.

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

Measurement of Bulk Viscosity of HPC Hydrogels The bulk viscosity of HPC hydrogels was evaluated from the relationship between shear rate and shear stress with a corn-plate viscometer (Brookfield Engineering Laboratories, Inc., a digital viscometer model DV-II+) at 37°C .

Measurement of Microscopic Viscosity of HPC Hydrogels The microscopic viscosity of HPC hydrogels was evaluated by the spin probe method of the electron spin resonance (ESR) using 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (4-hydroxy-TEMPO, Aldrich Chem. Co.), which is a stable nitroxide radical, as the probe. The HPC hydrogels were prepared with distilled water containing $1 \times 10^{-4}\text{M}$ 4-hydroxy-TEMPO, and used for the ESR measurement. The ESR spectra of 4-hydroxy-TEMPO were measured with an ESR spectrometer (JEOL JES-RE1X). The operating conditions were as follows: microwave power, 4 mV; field, $336 \pm 4\text{mT}$; sweep time, 8 min; field modulation width, 0.32 mT (100 kHz); time constant, 0.01 s; temperature, 25°C . The estimation method for a microscopic viscosity is described later in detail.

Results and Discussion

Effects of Composition Ratio and Molecular Weight

of HPC on Release Behavior of OXP from Solid Dispersion Granules The release profiles of OXP from the solid dispersion granules at various composition ratios and molecular weights of HPC are shown in Fig. 1. In all cases of the molecular weight of HPC, the release rate of OXP decreased with increasing HPC composition ratio and became almost the same at 3—5% of HPC. We have previously reported that OXP was released by diffusion through the swollen HPC gel phase formed and retained in the solid dispersion at the HPC composition ratio of 5—10%, causing a marked decrease in the release rate of OXP.⁴⁻⁶⁾ These results suggest that the addition of 3% of HPC allows the formation and retention of the swollen HPC gel phase in the solid dispersion, and the release of OXP will thus occur through its diffusion into the swollen HPC gel phase at 3—5% of HPC.

Bulk Viscosity of HPC Hydrogel and Release of OXP Figure 2 shows the release profiles of OXP from the solid dispersion granules at the HPC composition ratio of 5% in Fig. 1. The release profiles were almost the same and the effect of the molecular weight of HPC on the release of OXP was hardly observed. It was thought that at this HPC composition ratio, OXP diffused into the HPC gel phase formed in the solid dispersion as mentioned above. Therefore, the viscosity of the HPC hydrogel was studied. The bulk viscosity of the HPC hydrogels evaluated from the relationship between shear rate and shear stress is shown in Fig. 3. The bulk viscosity clearly varied depending on the molecular weight of HPC and a markedly larger bulk viscosity was observed with a higher molecular weight of HPC. Thus, although the bulk viscosity was different depending on the HPC molecular weight, the change in the release profiles of OXP was hardly observed as shown in Fig. 2. Accordingly, the solid dispersion films at an HPC composition ratio of 5% were

Fig. 1. Release Profiles of OXP from Solid Dispersion Granules with Different Molecular Weights and Composition Ratios of HPC

A, HPC-SL; B, HPC-L; C, HPC-M; D, HPC-H. Percent of HPC: ●, 0% (OXP-EC system); ○, 1%; ■, 2%; □, 3%; ▲, 4%; △, 5%. Each point represents the mean of three experiments.

prepared to study the diffusion properties of OXP in the solid dispersion.

Diffusion Property of OXP in Solid Dispersion Films with Different Molecular Weights of HPC The drug release from monolithic polymer film devices can be expressed as follows, based on Fick's second law⁸⁾:

$$F = 4(Dt/\pi\delta^2)^{1/2} \quad (1)$$

where F is the fractional release (< 0.6), D is the diffusion coefficient, t is the release time and δ is the film thickness. It is known that the diffusion coefficient D in polymers changes depending on the temperature, and the tempera-

ture dependency is given by an Arrhenius equation as follows^{9,10)}:

$$D = D_0 \exp(-E_a/RT) \quad (2)$$

where D_0 is the hypothetical diffusivity at infinite temperature, E_a is the activation energy for diffusion, R is the gas constant and T is the absolute temperature. Figure 4 shows the release profiles of OXP from the solid dispersion films with different molecular weights of HPC at 37, 30 and 20 °C. A linear relationship between the fractional release of OXP and the square root of the release time was observed at every temperature of the dissolution test. Then, the diffusion coefficients at each temperature calculated using Eq. 1 were substituted in Eq. 2, and the logarithms of the diffusion coefficients were plotted as a function of the reciprocal of the absolute temperature, as shown in Fig. 5. The Arrhenius plots show a straight line with almost the same slope at all molecular weights of HPC, and so the activation energies for the diffusion of OXP in the solid dispersion calculated from the slope were almost the same, as shown in Fig. 6. It is reported that the values of the activation energies in polymers commonly range from 7–20 kcal/mol.⁹⁾ The values here were about 7.2–7.8 kcal/mol and thought to be proper value in consideration of the monolithic type devices, the hydration and swelling of HPC and the high water-solubility of OXP.

We previously reported that the internal structure of the solid dispersion changed depending on the molecular weight of EC, causing a change in the OXP release behavior.¹⁾ Therefore, the porosities of the solid dispersion films and the penetration times of water into the films were measured to study the effect of the HPC molecular weight on the internal structure.

Porosity of Solid Dispersion Films and Penetration of Water into Films The porosities of the solid dispersion films are shown in Table 1. All the films showed almost the same values and the effect of the HPC molecular weight was hardly observed. The penetration of water into the films is shown in Fig. 7. A linear relationship between film thickness and the square root of the penetration time was observed at every molecular weight of HPC, suggesting that the penetration process of water followed the same mechanism.^{1,11)} Further, no difference in the penetration time depending on the molecular weight of HPC was

Fig. 2. Release Profiles of OXP from Solid Dispersion Granules at HPC Composition Ratio of 5%

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

Fig. 3. Bulk Viscosity of HPC Hydrogels

⊙, HPC-SL; ○, HPC-L; △, HPC-M; □, HPC-H.

Fig. 4. Release Profiles of OXP from Solid Dispersion Films with Different Molecular Weights of HPC at Various Temperatures

A, HPC-SL; B, HPC-L; C, HPC-M; D, HPC-H. Experimental temperature: ○, 37 °C; □, 30 °C; △, 20 °C. Each point represents the mean $\pm$ S.D. ($n=3$).

Fig. 5. Arrhenius Plots of Diffusion Coefficients of OXP in Solid Dispersion Films with Different Molecular Weights of HPC

●, HPC-SL; ○, HPC-L; △, HPC-M; □, HPC-H. Each point represents the mean $\pm$ S.D. ($n=3$).

Fig. 6. Effect of Molecular Weight of HPC on Activation Energy for Diffusion of OXP in Solid Dispersion

observed. These results suggest that the internal structure of the film was scarcely affected by the HPC molecular weight.

We also studied the crystallinity of OXP and the interaction between OXP and the polymers by X-ray diffractometry, thermal analysis and IR spectroscopy. The results suggest that OXP existed as a hydrochloride and 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 HPC (data not shown).

Microscopic Viscosity of HPC Hydrogel and Release of OXP According to the free-volume theory, the diffusivity of a small molecule in a polymer solution or gel depends on the free volume of the system.^{12,13} Free volume can be conceptually interpreted as the void volume between such constituents as atoms, molecules or segments in a certain system or as the space where the constituents can be redistributed.¹⁴ It is thought that the diffusion of a small molecule in a polymer solution or gel occurs *via* the space generated by the movement of segments of polymer chains (the free volume), and the diffusivity is determined by the probability of the generation of the free volume. The resistance against the movement of segments of polymer chains in such a microscopic environment is termed microscopic viscosity.¹⁵ Namely, microscopic viscosity means resistance to the diffusion of solute molecules on the molecular level and is an im-

Table 1. Porosities of Solid Dispersion Films with Varying Molecular Weights of HPC

HPC grade	$\bar{M}_w^a$	Porosity (%)	S.D. (%) ^b
HPC-SL	73500	25.10	2.34
HPC-L	105000	24.40	1.81
HPC-M	270000	22.29	1.82
HPC-H	357000	22.37	1.14

a) Weight-average molecular weight of HPC. b) Standard deviation ($n=10$).

Fig. 7. Water Penetration Behavior into Solid Dispersion Films with Different Molecular Weights of HPC

●, HPC-SL; ○, HPC-L; △, HPC-M; □, HPC-H.

portant factor in determining the diffusivity of a drug in a polymer gel.¹⁶ Then, the microscopic viscosity of HPC hydrogels was evaluated by the ESR probing technique.

When a nitroxide radical is tumbling isotropically and rapidly in an extremely low viscous medium, the ESR spectra show three narrow, symmetrically spaced peaks of equal height. If the rotational movement of the spin probe is restrained (namely, the microscopic viscosity is increased), the line width of each peak is broadened, particularly at a high magnetic field.¹⁷ The ESR spectra of 4-hydroxy-TEMPO in distilled water and in the HPC hydrogel (40% (w/v)) are shown in Fig. 8. The peak height at a high magnetic field in the HPC hydrogel decreased compared with that in distilled water, suggesting that the microscopic viscosity increases because the height of the peak of the ESR spectra is inversely proportional to the square of the line width.¹⁷

The mobility of a nitroxide radical is estimated in terms of rotational correlation time (τ).¹⁸ τ (in seconds) can be expressed as follows:

$$\tau = 6.5 \times 10^{-10} W_0 \{ (h_0/h_{-1})^{1/2} - 1 \} \quad (3)$$

where W_0 is the line width of the mid-field peak in gauss (G, 10 G = 1 mT), and h_0 and h_{-1} are the peak heights of the mid- and high-field lines, respectively. The viscosity of water (η_{H_2O} , 0.8903 mPa·s)¹⁹ and the rotational correlation time of 4-hydroxy-TEMPO in water (τ_{H_2O}) were taken as standards, and the microscopic viscosity of the HPC hydrogels (η_{gel}) was relatively estimated from Eq. 4.¹⁵

$$\eta_{gel} = (\eta_{H_2O}/\tau_{H_2O})\tau_{gel} \quad (4)$$

where τ_{gel} is the rotational correlation time in the HPC hydrogels. The calculated value of τ_{H_2O} was 0.0604 ns. The

Fig. 8. ESR Spectra of 4-Hydroxy-TEMPO in Distilled Water (A) and 40% (w/v) HPC Hydrogel (B)

Fig. 9. Effect of Molecular Weight of HPC on Microscopic Viscosity of HPC Hydrogels

HPC concentration % (w/v): Δ , 5%; $\blacktriangle$, 10%; $\square$, 20%; $\blacksquare$, 30%; $\circ$, 40%. Each point represents the mean $\pm$ S.D. ($n=3-5$).

microscopic viscosities of the HPC hydrogels with various concentrations of HPC obtained by using Eqs. 3 and 4 are plotted against the weight-average molecular weight of HPC and shown in Fig. 9. The microscopic viscosity increased with increasing HPC concentration. This may be caused by the fact that the rotational movement was restrained due to the matrix structure of the HPC hydrogel becoming denser with increasing HPC concentration. However, in all levels of HPC concentration, a change in microscopic viscosity depending on the molecular weight of HPC was hardly observed, suggesting that the diffusional resistance in the HPC hydrogels hardly varied depending on the molecular weight of HPC.

These results could be explained as follows: HPC has a number of hydroxyl groups in the intramolecule and is extensively hydrated by hydrogen bonding in water. When the chains of the HPC molecule move, their hydration

layers are dragged along, causing a markedly large size of flow unit. The size of the flow unit is larger with a higher molecular weight of HPC and the resistance to flow increases. The size of the flow unit further increases with increasing concentration of HPC by the mutual entanglement of HPC molecules. Therefore, the bulk viscosity increases almost exponentially with increasing HPC concentration, and larger values were observed with a higher molecular weight of HPC, as shown in Fig. 3. On the other hand, microscopic viscosity represents the diffusional resistance in a microscopic environment as mentioned above. It is thought that the movement and diffusion of a solute molecule in a polymer hydrogel matrix will occur *via* the part occupied by water hydrated among the segments of polymer chains. The proportion of water contained in the hydrogel was equal in the case of the same HPC concentration and size of the solute molecules; the radical molecules here, were significantly smaller than those of the polymer chains. Therefore, the resistance to the movement was hardly affected by the molecular weight of HPC and the microscopic viscosity was hardly changed.

These results suggest that in the OXP-EC-HPC system, the resistance to the diffusion of OXP in the HPC gel phase hardly varied because the microscopic viscosity of the HPC hydrogels was hardly affected by the molecular weight of HPC, and therefore, the activation energy for diffusion in the solid dispersion was hardly changed. Further, because the diffusion rate of OXP in the swollen HPC phase was almost the same, the release rate of OXP from the solid dispersion hardly changed, despite changes in the molecular weight of HPC.

Conclusion

In the OXP-EC-HPC solid dispersion system, it is suggested that the release of OXP will occur through its diffusion into the swollen HPC gel phase when 3% HPC

is added. The bulk viscosity of the HPC hydrogels markedly increased with increasing molecular weight of HPC, but the activation energy for the diffusion of OXP in the solid dispersion was hardly changed by the molecular weight of HPC. This might be because the microscopic viscosity which affects the diffusivity of OXP in the hydrogels hardly varied, despite changes in HPC molecular weight. These results suggest that because the diffusion rate of OXP in the swollen HPC phase was almost the same, the change in the release rate of OXP depending on the molecular weight of HPC was hardly observed in the OXP-EC-HPC solid dispersion system.

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