Water Mobility in Aqueous Solutions of Macromolecular Pharmaceutical Excipients Measured by Oxygen-17 Nuclear Magnetic Resonance

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The dynamics of water molecules associated with water-soluble polymers were studied by ^{17}O-NMR. The observed spin-lattice relaxation time, $T_{1(\mathrm{obs})}$, of water in aqueous solutions of polyethylene glycol (PEG), poly(vinylpyrrolidone) (PVP) and gelatin at polymer concentrations below 0.12 g/g of water could be described by an isotropic two-state model with a fast exchange. The tendency for the polymers to reduce the $T_{1(\mathrm{obs})}$ of water was on the order of PEG < gelatin < PVP. At higher concentrations, deviations from the model were observed for PVP and gelatin. The $T_{1(\mathrm{obs})}$ of water in the PEG solution was not affected by the molecular weight of the polymer. This suggests that the microviscosity around the polymer molecules is governed by the interaction between the polymer unit and water molecules, and is not affected by the molecular weight of polymers in contrast to the "macroviscosity". The polymer–water interaction that reduced the $T_{1(\mathrm{obs})}$ of water was found to decrease with increasing temperature for all the polymers studied. The $T_{1(\mathrm{obs})}$ of water in the gelatin solution exhibited the largest temperature dependence, suggesting that changes might occur in the molecular structure of gelatin at higher temperatures.

Key words spin-lattice relaxation time; water mobility; polyethyleneglycol; poly(vinylpyrrolidone); gelatin

Water-soluble polymers are commonly used ingredients in various dosage forms. Interaction between these water-soluble polymers and water often affects the chemical and physical stability of the dosage forms. The hydrolysis rates of drugs in hydrogels such as gelatin[1]) and poloxamine gel[2]) depended on the gel microviscosity, which was determined not only by the water content of the gels but also by the quality and quantity of polymer–water interaction. The physical stability of amorphous drugs in water-soluble polymers was reduced by water adsorption, and crystallization was enhanced depending on the quality and quantity of polymer–water interaction.[3,4]) This enhanced crystallization is thought to be due to the plasticizing effect of water.[4,5])

The effects of polymer–water interaction on the stability of dosage forms appear to be related to their effect on the dynamic behavior of molecules in the dosage forms. Water mobility is one of the parameters used to describe the dynamic state of molecules in dosage forms, and can be represented by the spin-lattice relaxation time (T_1) of water.[1,4,6,7])

In the present study, the T_1 of water in aqueous solutions of polyethylene glycol (PEG), poly(vinylpyrrolidone) (PVP) and gelatin, which are commonly used ingredients in various dosage forms, was determined by oxygen-17 nuclear magnetic resonance (^{17}O-NMR). The quality and quantity of the interaction between the water-soluble polymers and water are discussed on the basis of the water mobility as measured by T_1.

Experimental

Materials Sucrose, glucose, PEG (400, 20000) and PVP K30 were purchased from Wako Pure Chemical Industry Co. (Osaka). Gelatin powder (G-0252P) was obtained from Nitta Gelatin Co. (Osaka). These polymers were used without further purification. Water used in the study was purified by deionization and distillation.

^{17}O-NMR Measurement ^{17}O-NMR spectra of PEG, PVP and gelatin solutions were recorded at 54.2 MHz using a Varian VXR-400S NMR spectrometer. The inversion recovery method was used to obtain the T_1 of $H_2{}^{17}O$. A 90° ^{17}O pulse width of 50 μs and a recycling time of 250 ms were used. The temperature of samples was controlled at 15, 20, 30 or 40 °C. Temperature was calibrated based on the difference in chemical shift between the methyl proton and the hydroxy proton of methanol.

Figure 1 shows a typical spectrum obtained for polymer solutions. The signal can be assigned to $H_2{}^{17}O$, and peaks due to polymers were not detected.

Results and Discussion

The Effect of Polymer Concentration on the Observed T_1 of Water Figure 2 shows the T_1 of water determined for the aqueous solutions of sugars and polymers at 30 °C. The reciprocal of the ratio of the observed T_1 to the T_1 of pure water, T_1°, is plotted against polymer concentration in units of g/g of water. The $T_1^\circ/T_{1(\mathrm{obs})}$ of PEGs of both 400 and 20000 exhibited an almost linear increase with increasing polymer concentration. No significant difference was observed between the two different molecular weights of PEG (400, 20000). At lower concentrations, the increase in the $T_1^\circ/T_{1(\mathrm{obs})}$ of the PEG solution was larger than that of sugars, indicating that PEG tends to reduce the $T_{1(\mathrm{obs})}$ of water more than sugars do. The reduction of the $T_{1(\mathrm{obs})}$ of water caused by PVP and gelatin was more pronounced than by PEG. The increase in $T_1^\circ/T_{1(\mathrm{obs})}$ was not linear but concave because of a larger increase in $T_1^\circ/T_{1(\mathrm{obs})}$ at higher concentrations.

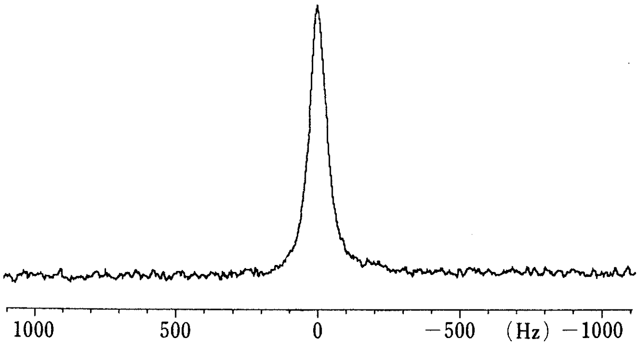

Fig. 1. ^{17}O-NMR Spectrum of a PVP Solution (0.12 g/g Water) 30 °C

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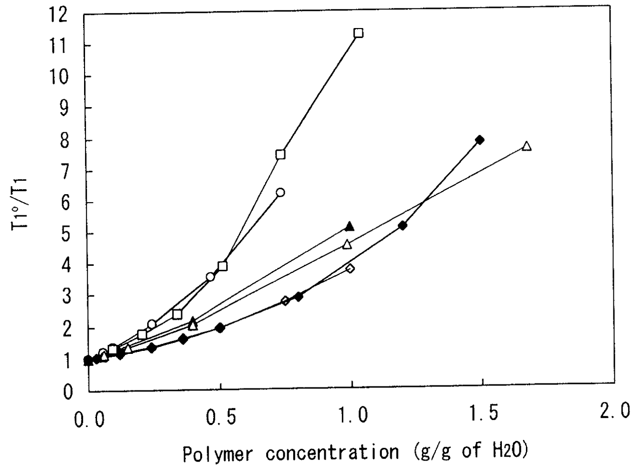

Fig. 2. Reciprocal of Ratio of Spin-Lattice Relaxation Time ($T_{1(\mathrm{obs})}$) of Water in Water-Soluble Polymer Solutions to That of Pure Water (T_1°) as a Function of Solute Concentration

30 °C. ○: PVP K30; □: gelatin; △: PEG 400; ▲: PEG 20000; ◇: glucose; ◆: sucrose.

When two populations of water exist in an aqueous polymer solution, for example, highly mobile water and less mobile water having spin-lattice relaxation time of $T_{1(1)}$ and $T_{1(2)}$, respectively, and when the exchange between the two populations is fast, the apparent relaxation time of water in the solution, $T_{1(\mathrm{obs})}$, can be described by Eq. 1 as:

$$\frac{1}{T_{1(\mathrm{obs})}}=\frac{1-f}{T_{1(1)}}+\frac{f}{T_{1(2)}} \qquad (1)$$

where f is the fractional population of less mobile water in the solution. If $T_{1(1)}$ is represented by the relaxation time of pure water, T_1°, Eq. 1 can be rewritten as follows:

$$\frac{T_1^\circ}{T_{1(\mathrm{obs})}}=1+\left(\frac{T_1^\circ}{T_{1(2)}}-1\right)f \qquad (2)$$

A linear relationship between $T_1^\circ/T_{1(\mathrm{obs})}$ and f has been reported for the diluted aqueous solutions of various compounds such as sugars[8,9] and maltodextrins.[10] The linear behavior has been explained by an isotropic two-state model with a fast exchange.

Figure 3 shows the plots of Eq. 2 for PEG, PVP and gelatin solutions of low concentrations at 30 °C. These polymers also exhibited a linear relationship at low concentrations, while deviations from the linear behavior were observed at higher concentrations, as shown in Fig. 2. The linear behavior indicates that apparent T_1, which represents the average mobility of the water molecules present in these polymer solutions, can be described by Eq.1 using the relaxation times of highly mobile water and less mobile water, $T_{1(1)}$ and $T_{1(2)}$. The slope of the line for PVP was larger than that for gelatin. PEG showed the smallest slope. This indicates that the tendency to reduce the average water mobility is on the order of PEG < gelatin < PVP.

As shown in Fig.2, the deviation from linear behavior in the plots for PVP and gelatin became more marked as polymer concentration increased. Similar deviation at higher concentrations has also been reported for maltodextrin.[11] It has been suggested that the deviation begins at a concentration where maltodextrin aggregation begins to affect the apparent T_1 of water by forming trapped water regions. This consideration may be applicable to the deviation observed for the PVP and gelatin solutions in the present study. However, another assumption that $T_{1(1)}$ and $T_{1(2)}$ as well as f in Eq. 1 vary with polymer concentration can also explain the deviation from the linear behavior. Further studies are required to interpret the dependence of the apparent T_1 on the polymer concentration.

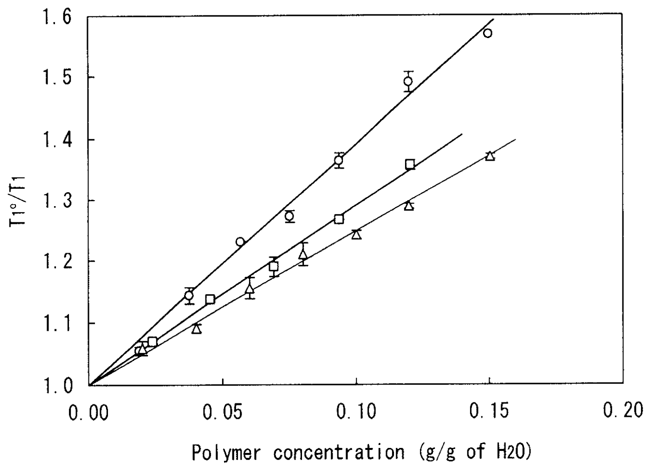

Fig. 3. Reciprocal of Ratio of $T_{1(\mathrm{obs})}$ of Water in Diluted Solutions of PVP K30 (○), Gelatin (□) and PEG 400 (△) to That of Pure Water (T_1°) as a Function of Solute Concentration (Mean ± S.D.)

30 °C.

It is well known that the viscosity of polymer solutions increases as the molecular weight of polymers increases. PEGs of 400 and 20000 exhibited similar plots based on Eq. 2, as shown in Fig. 2, indicating that the $T_{1(\mathrm{obs})}$ of water is not affected by the molecular weight of the polymer. This suggests that polymer–water interaction depends on the chemical properties of the polymer unit and affects the microviscosity around the polymer molecules which is different from the "macroviscosity" governed by the molecular weight of the polymers.

The Effect of Temperature on the Observed T_1 of Water The effect of temperature on the T_1 of water in PEG, PVP and gelatin solutions was studied at a polymer concentration of 0.12 g/g of water where a linear relationship between $T_1^\circ/T_{1(\mathrm{obs})}$ and polymer concentration was observed. Figure 4 shows the Arrhenius-like plots of the observed T_1. PEG exhibited linear Arrhenius-type plots with a steeper slope than pure water, and the $T_{1(\mathrm{obs})}$ was smaller than that of pure water at all the temperatures studied. This suggests that the association of water with PEG reduces the average mobility of water molecules as indicated by the decreased $T_{1(\mathrm{obs})}$. This association may decrease as temperature increases, resulting in the steeper slope of Arrhenius-type plots compared to that for pure water.

PVP showed a smaller $T_{1(\mathrm{obs})}$ than PEG at all the temperatures studied, although the slope of the Arrhenius-type plots was similar. A decrease in the $T_{1(\mathrm{obs})}$ of water represents an increase in the intensity of polymer–water interaction or an increase in the number of water molecules associated with polymer molecules. The smaller T_1

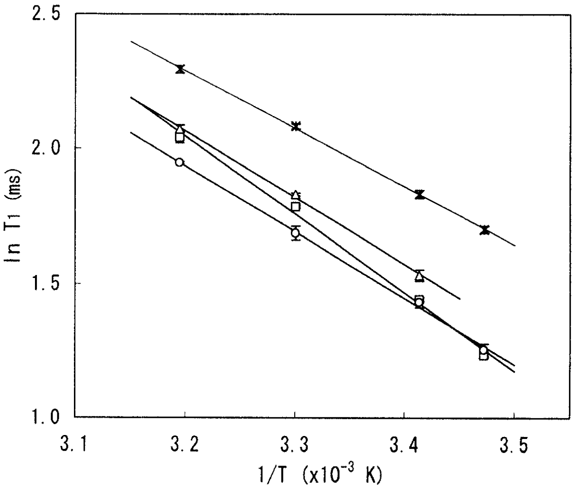

Fig. 4. Effect of Temperature on $T_{1(\mathrm{obs})}$ of Water in Pure Water (×) and Solutions of PVP K30 (○), Gelatin (□) and PEG 400 (△) (Mean ± S.D.)

Polymer concentration is 0.12 g/g of water.

observed for the PVP solutions indicates that PVP interacts with water to a greater extent, qualitatively and/or quantitatively, than does PEG. On the other hand, the similar Arrhenius-type plots observed for both polymers indicates that the effect of temperature on the polymer–water interaction is similar for PEG and PVP.

In contrast, gelatin exhibited Arrhenius-type plots with a steeper slope than PEG and PVP, indicating that the increase in average water mobility accompanied by increased temperature is larger for gelatin than PEG and PVP. This suggests that the structure of gelatin molecules might change at a higher temperature in a manner such that water association is reduced.

Conclusion

The $T_{1(\mathrm{obs})}$ of water in aqueous solutions of PEG, PVP and gelatin at concentrations below 0.12 g/g of water could be described by an isotropic two-state model with a fast exchange. The tendency for the polymers to reduce the $T_{1(\mathrm{obs})}$ of water was on the order of PEG < gelatin < PVP. At higher concentrations, deviations from the model were observed for PVP and gelatin. Although the mechanism of these deviations is still unclear, it may result from changes in the spin-lattice relaxation times of highly mobile water and less mobile water, $T_{1(1)}$ and $T_{1(2)}$, as a function of polymer concentration.

The $T_{1(\mathrm{obs})}$ of water in the PEG solution was not affected by the molecular weight of PEG. This suggests that microviscosity around the polymer molecules is governed by the interaction between the polymer unit and water molecules, and is not affected by the molecular weight of polymers, as is the macroviscosity.

Polymer–water interaction, which reduces the $T_{1(\mathrm{obs})}$ of water, was found to decrease with increasing temperature for all the polymers studied. The $T_{1(\mathrm{obs})}$ of water in the gelatin solution exhibited the largest temperature dependence, suggesting that changes might occur in the molecular structure of gelatin at higher temperatures.

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