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Anomalous Dissolution Behavior of the Diazepam – γ-Cyclodextrin Complex in Polymer Solutions

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Abstract. The dissolution process of the diazepam – γ-cyclodextrin complex in aqueous polymer solutions has been studied. Hydroxypropyl cellulose and polyvinylpyrrolidone stabilize the supersaturated state of the complex, maintaining the higher drug level for a longer period. Polyethyleneglycol and dextran accelerated the dissociation of the complex, and caused a rapid decrease in drug concentration. These anomalous dissolution behaviors are discussed on the basis of viscosity changes of the polymer solutions along with the competitive interaction of polymers for the inclusion complex.

Key words: Diazepam – γ-cyclodextrin complex, dissociation of inclusion complexes, water soluble polymers as additives, supersaturated behavior.

1. Introduction

Because it has the largest cavity size and the highest water solubility among the three cyclodextrins (α-, β-, and γ-cyclodextrins), γ-cyclodextrin is known to be useful for the improvement of dissolution and absorption characteristics of poorly soluble drugs, particularly for bulky molecules such as digitalis glycosides [1], steriod hormones [2], and prostaglandins [3]. We have previously reported that diazepam, one of the most prescribed minor tranquilizers, forms a soluble complex with γ-cyclodextrin [4]. The fast-dissolving form of this complex, however, readily dissociated in water, and resulted in a rapid decrease in the drug concentration showing supersaturation. This kind of dissolution behavior may provide a variation of drug absorption when the complex is administered orally. Recently, a variety of polymers has been utilized to modify the dissolution rate of many pharmaceuticals [5,6]. In the present study, therefore, an attempt was made to improve the dissolution characteristic of the diazepam – γ-cyclodextrin complex using water-soluble polymers, and the factors affecting the dissolution and membrane permeation rates are discussed.

2. Experimental

In this preliminary investigation, the following polymers were used as a 10 g dm^{-3} aqueous solution: hydroxypropyl cellulose-SL (HPC; Nippon Soda Co. Ltd., Osaka), polyvinylpyrrolidone K-30 (PVP; Katayama Chemical Co. Ltd., Nagoya), polyethyleneglycol 4000 (PEG; Katayama Chemical Co. Ltd., Nagoya), and Dextran 4 (DX; Serva Feinbiochemica,

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Heiderberg). The viscosities of these polymer solutions were measured by using a rotational viscometer (Low-Shear 30, Contraves Industrial Products Ltd.) at shear rate of 2.37 s^{-1}. The preparation of the diazepam – γ-cyclodextrin complex and the measurements of dissolution and membrane permeation behaviors were the same as those described previously [4].

3. Results and Discussion

Figure 1 shows the dissolution profiles of diazepam and its γ-cyclodextrin complex in water in the absence and in the presence of water-soluble polymers. Although the complex exhibited a faster dissolution rate than diazepam alone, the drug concentration decreased rather rapidly because of the precipitation of diazepam crystallites. The decrease in drug concentration has been ascribed to the dissociation of the complex following the dissolution, since the apparent stability constant of the diazepam – γ-cyclodextrin complex in water is quite small (120 $dm^3\ mol^{-1}$), as reported previously [4]. By the addition of HPC or PVP to the dissolution medium, no appreciable change was observed for the dissolution rate of the drug alone, but the supersaturated state of the complex was significantly stabilized, maintaining the higher drug levels for a long period.

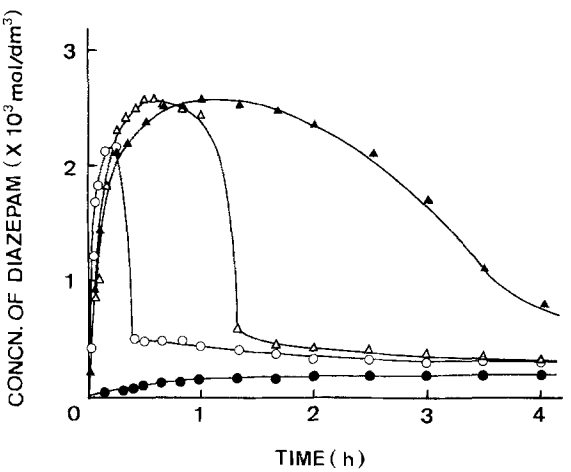

Fig. 1. Effects of HPC and PVP on the dissolution of diazepam and its γ-cyclodextrin complex in water at 25 °C. ●: diazepam alone in water, ○: complex in water, ▲: complex in 10 g dm^{-3} HPC solution, △: complex in 10 g dm^{-3} PVP solution.

The dissolution process of diazepam from the complex was also observed by means of optical microscopy. In the absence of polymers, the fine diazepam crystals were found at 30 min after the start of dissolution and subsequently the crystal growth was observed in the solution. In the presence of HPC, no crystals of diazepam appeared even after 2 h, probably because of the increase in viscosity of the solution (Table I). PVP also inhibited the crystallization of the drug, but the effect was less than that of HPC. These facts indicate that a viscosity-enhancing polymer is preferred for the retardation of crystal growth and/or the inhibition of complex dissociation.

In sharp contrast, when the complex was dissolved in the PEG or DX solution, the drug levels decreased because of the precipitation of fine diazepam crystallites immediately after

Table I. Relative viscosities of 10 g dm^{-3} aqueous polymer solutions at 25 °C

Polymer	Relative viscosity
Hydroxypropyl cellulose SL	2.69
Polyvinylpyrrolidone K-30	1.50
Polyethyleneglycol 4000	1.06
Dextran 4	1.06

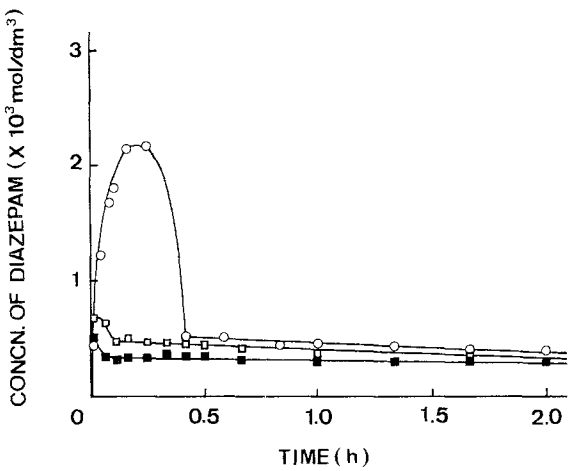

Fig. 2. Effects of PEG and DX on the dissolution of the diazepam – γ-cyclodextrin complex in water at 25 °C. ○: complex in water, □: complex in 10 g dm^{-3} PEG solution, ■: complex in 10 g dm^{-3} DX solution.

the start of dissolution (Figure 2). These anomalous dissolution behaviors may be explained on the basis of the competition between γ-cyclodextrin and the polymer, since the viscosities of the PEG and DX solutions were not significantly different from that of the PVP solution. It is, therefore, likely that PEG and DX may facilitate the dissociation of the γ-cyclodextrin complex to form the more stable polymer complexes with diazepam.

It is interesting to note that the change in dissolution behavior of the γ-cyclodextrin complex in the presence of polymers was clearly reflected in the membrane permeation profiles. Figure 3 shows a typical example of the effects of HPC and DX on the permeation behavior of diazepam through a cellophane membrane following the dissociation of the γ-cyclodextrin complex in a donor cell. In the case of HPC, the increase in drug concentration in the donor cell provided a great increase in the net amount of drug that permeated into the receptor cell. On the other hand, DX retarded the permeation rate because of the decrease in drug concentration in the donor cell.

Although further studies of these anomalous dissolution behaviors of inclusion complexes in polymer solutions, should be investigated, the results described here provide a rational basis for the formulation and a means for improving efficacy of the cyclodextrin complex by using a viscosity-enhancing polymer such as HPC.

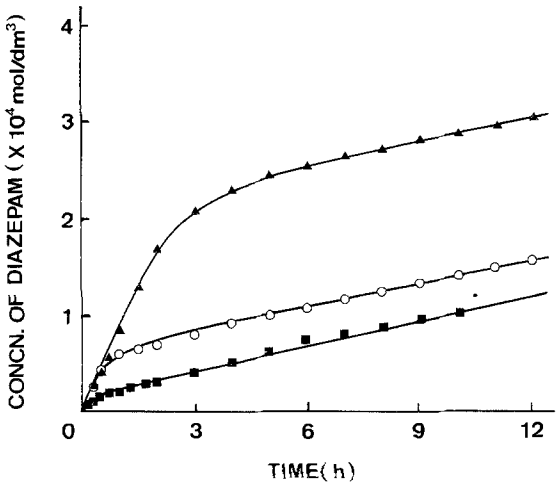

Fig. 3. Effects of HPC and DX on the permeation of diazepam through a cellophane membrane following the dissolution from the γ-cyclodextrin complex in a donor cell at 25 °C. ○: complex in water, ▲: complex in 10 g dm^{-3} HPC solution, ■: complex in 10 g dm^{-3} DX solution.

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