

Note

Control of medicine release from solid dispersion through poly(ethylene oxide)-carboxyvinylpolymer interaction¹

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Abstract

Poly(ethylene oxide) (PEO)-carboxyvinylpolymer (CP) solid dispersions containing phenacetin (PHE) were prepared using water/ethanol mixture as a solvent. The solvent composition and the release behavior of PHE from the solid dispersions were studied. It was found that the mixture of water/ethanol (1/1, v/v) was useful for the solvent to prepare solid dispersions. The release rate of PHE from the PHE-PEO system was larger than that from PHE powder. In the PHE-CP system, almost the same release rate was observed as PHE powder. The release rate from the PHE-PEO-CP system obviously varied depending on the PEO/CP ratio and reached the minimum level at the PEO/CP ratio of 1/1 (w/w). FT-IR spectra suggested the interaction of hydrogen bonding between PEO and CP. These results indicate that it is feasible to control the medicine release from the solid dispersions by using PEO and CP. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Solid dispersion; Poly(ethylene oxide); Carboxyvinylpolymer; Controlled release; Complex; Phenacetin

1. Introduction

The solid dispersion method is one of several pharmaceutical techniques for controlling medicine release and has been used to improve the dissolution properties and bioavailability of slightly water-soluble medicines (Chiou and Riegelman, 1970; Yamamura and Rogers, 1996). We have reported that it is feasible to control the

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release rate of an extremely high water-soluble medicine (oxprenolol hydrochloride) by combining water-insoluble ethylcellulose and water-soluble hydroxypropylcellulose (HPC) (Yuasa et al., 1991; Ozeki et al., 1994, 1995a,b). We have also reported that poly(ethylene oxide) (PEO) has a great potential as a solid dispersion base to enhance the dissolution properties of a slightly water-soluble medicine, and found a linear relationship between the release rate of the medicine and the degree of the interaction between PEO and the medicine (Ozeki et al., 1997).

PEO is a class of water-soluble linear resin. It has been used in agricultural engineering, food, dental and pharmaceutical fields because of its aqueous solubility, high gelation and low toxicity, and has recently been used for a directly compressed tablet matrix (Graham and McNeill, 1984; Apicella et al., 1993; Yang et al., 1996). It is known that PEO forms complexes with alkaline metal salts, alkaline earth metal salts and urea (Bailey et al., 1961; Bogdanov et al., 1994). We have noticed the interaction between PEO and poly(carboxylic acid). Carboxyvinypolymer (CP) is a kind of poly(carboxylic acid) and has been studied as a bioadhesive and controlled release matrix by using it together with HPC (Machida et al., 1980; Ishida et al., 1981; Satoh et al., 1989; Mortazavi and Smart, 1994), hydroxypropylmethylcellulose (Garcia-Gonzales et al., 1992; Perez-Marcos et al., 1996) and polyvinylpyrrolidone (Takayama and Nagai, 1987).

In the present study, we attempted to prepare the solid dispersion using PEO and CP and control the medicine release from the solid dispersion through the interaction between PEO and CP.

2. Experimental

2.1. Materials

PHE (an antipyretic, the density and molecular weight are 1.21 g/cm³ and 179.22, respectively. The solubility is 1.31 mg/ml at 37 °C. Tsukishima, Tokyo) was used as the model medicine. PEO (ALKOX[®] R-150, the viscosity average molecu-

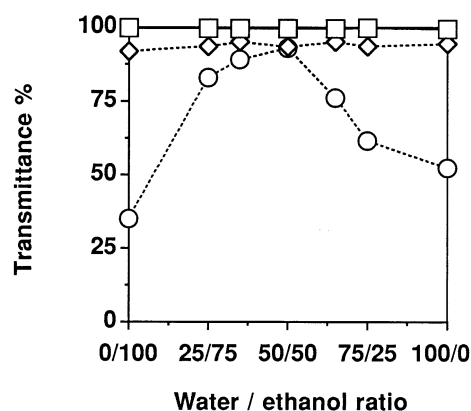


Fig. 1. Effect of water/ethanol ratio on transmittance of polymer solution. □, PEO; ◇, CP; ○, PEO/CP, 50/50. Each point represents the mean \pm S.D. ($n = 3$).

lar weight is about 135000, the density is 1.24 g/cm³, Meisei, Kyoto) was supplied by Higuchi (Tokyo). CP(CARBOPOL[®] 934P, the nominal average molecular weight is about 3000000, the density is 1.41 g/cm³, B.F Goodrich, Brecksville, OH) was supplied by Chugai Boyeki (Tokyo). The densities of PHE, PEO and CP were calculated from the volume measured with an air comparison pycnometer (Toshiba-Beckman, Model 930).

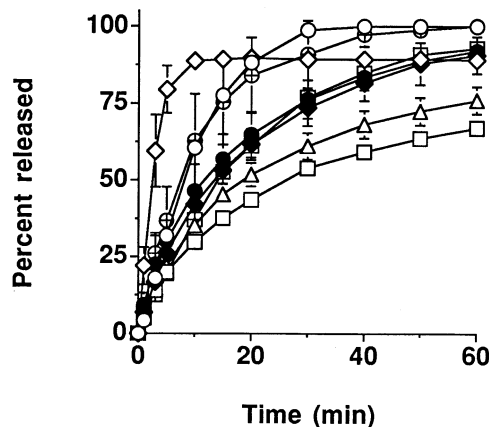


Fig. 2. Release profiles of PHE from solid dispersion granules with various composition ratios of PEO and CP. ○, PHE powder; solid dispersions (PEO/CP: ◇, 100/0; ●, 75/25; ◆, 62.5/37.5; □, 50/50; △, 37.5/62.5; ■, 25/75; ⊕, 0/100). Each point represents the mean \pm S.D. ($n = 3$).

2.2. Preparation of solid dispersions

A water/ethanol mixture was used as the solvent. Transmittance was determined with a spectrophotometer (Ubest-30, JASCO) to study the solvent composition ratio. Powders of PHE, PEO and CP (total amount 5 g) were dissolved in the water/ethanol mixture (400 ml), and the solvents were then evaporated. The solid dispersion was ground and dried at 50°C for 24 h under reduced pressure. The granules obtained were sieved (0.85–1.00 mm).

2.3. Release studies

The release profiles of PHE from PHE powder (sieved at 75–150 μm) and from the solid dispersion granules containing 6 mg of PHE were studied with a dissolution tester (Toyama Sangyo, TR-5S3), according to the paddle method (JP XIII) at 100 rpm, using 900 ml of distilled water as the dissolution medium at $37 \pm 0.5^\circ\text{C}$. The quantity of PHE was determined spectrophotometrically by measuring the absorbance at 243 nm.

2.4. IR spectroscopy

IR spectra were recorded with an infrared spectrophotometer (Perkin-Elmer, 1710 FT-IR). IR spectra of the solid dispersions containing PHE were measured by the KBr disk method. The polymer films were prepared by casting the polymer solution on a Teflon petri dish and directly used for the IR measurement.

3. Results and discussion

3.1. Determination of water/ethanol ratio in solvent for preparation of solid dispersion

When PEO aqueous solution and poly(carboxylic acid) aqueous solution are mixed together, immediate precipitation results (Smith et al., 1959). In the solution for preparation of the solid dispersions, it is strongly desirable that the medicine and polymers are dissolved and mixed

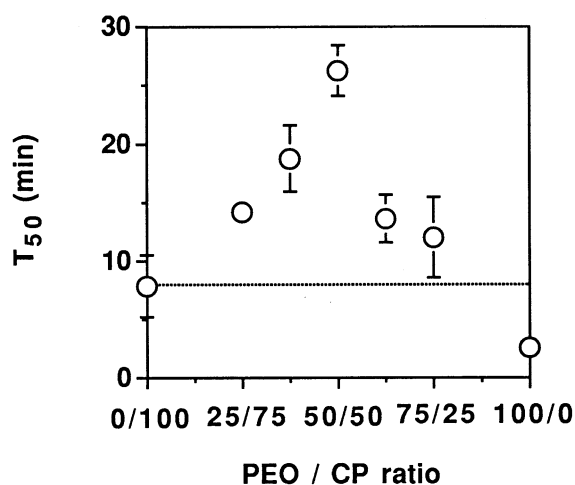


Fig. 3. Plots of T_{50} as a function of PEO/CP ratio. The dotted line shows T_{50} of PHE powder. Each point represents the mean \pm S.D. ($n = 3$).

homogeneously in the solvent. We used water/ethanol as the solvent and studied the composition ratios. Fig. 1 shows the transmittance of the polymer solutions of PEO, CP and the mixture of PEO/CP (1/1, w/w) at 600 nm as a function of the water/ethanol (v/v) ratio. The PEO-CP mixture was prepared by mixing their respective solutions. The concentration of the polymer solutions was 0.02% (w/v). In the PEO or CP solution, a very high transmittance was observed in all the cases of the water/ethanol ratio. In the PEO-CP mixture, the transmittance varied depending on the solvent composition and markedly low values were observed in the pure water or ethanol. This indicates that the precipitation was formed. Transmittance showed the maximum value at the water/ethanol ratio of 1/1, which was almost the same level as that of the CP solution. It is known that the solubility of solute in the solvent mixture occasionally increases compared with that in each pure solvent (Paruta et al., 1965; Gould et al., 1984). This might be due to an increase in the electron acceptor or donor ability of the solvent molecules in the mixture, causing the promotion of the solvation of the solutes (Gutmann, 1983; Suzuki et al., 1996). Water in the liquid state still retains its ice-like, low density structure, joined together by hydrogen bonds. When ethanol is added to

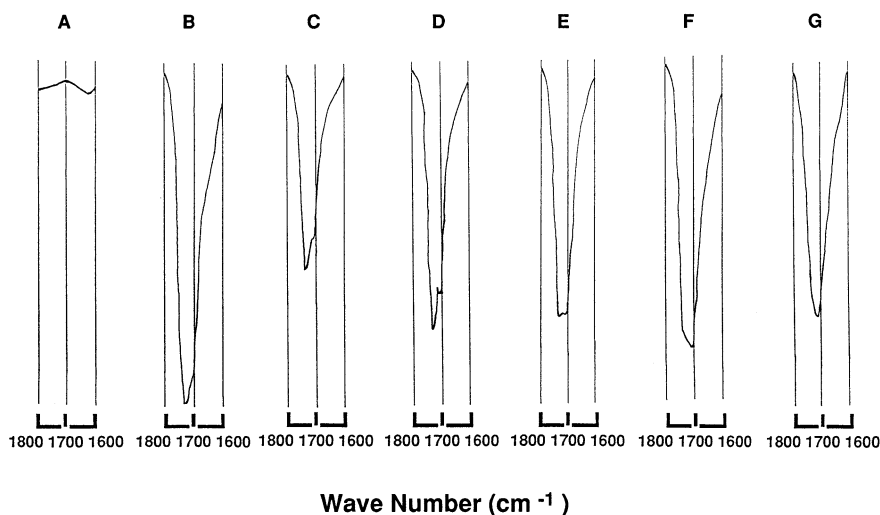


Fig. 4. IR spectra of PEO, CP and PEO-CP system with various composition ratios of PEO and CP. PEO/CP: A, 100/0 (PEO); B, 75/25; C, 62.5/37.5; D, 50/50; E, 37.5/62.5; F, 25/75; and G, 0/100 (CP).

water, the cluster structure of water gets to be broken (Martin et al., 1983). The breaking of the clusters increases the number of free water molecules that can contribute to hydration. These actions might increase the solvate or hydrate ability of ethanol or water molecules, causing the suppression of precipitation. Although the reason for the highest suppression of precipitation at the water/ethanol ratio of 1/1 is not clear, it is thought that the clusters of ethanol molecules begin to be formed and the effect of hydrophobicity of the C_2H_4 group of ethanol appears with the increasing ethanol ratio (Taneya et al., 1997). Based on these results, we used the mixture of water/ethanol ratio of 1/1 as the solvent for preparation of the solid dispersions.

3.2. Effect of composition ratio of PEO and CP on release profiles of PHE from solid dispersion granules

The release profiles of PHE from PHE powder and the solid dispersion granules with various PEO/CP ratios and the plots of the time required to release half of the amount of PHE (T_{50}) are shown in Figs. 2 and 3, respectively. The percentage of PHE in the solid dispersions was 20%. The release rate of PHE from the PHE-PEO system

was larger than that from PHE powder. In the PHE-CP system, almost the same release rate was observed as PHE powder. The release rate from the PHE-PEO-CP system obviously varied depending on the PEO/CP ratio. These results indicate that it is feasible to control the PHE release from the solid dispersion by varying the PEO/CP ratio. T_{50} was the longest at the PEO/CP ratio of 1/1, showing the lowest release rate.

We studied the interaction between PHE and the polymers by IR spectroscopy. The change in the IR spectra due to PHE was not observed at any PEO/CP ratio. Therefore, we studied the interaction between PEO and CP.

Fig. 4 shows the IR spectra of the PEO-CP system with various PEO/CP ratio at 1600–1800 cm^{-1} . CP has the carbonyl stretching band at 1710 cm^{-1} . A new band was observed at 1734 cm^{-1} in the PEO-CP system. The height of peak at 1734 cm^{-1} increased with the increasing PEO ratio. Since PEO consists of repeat units of $-CH_2-CH_2-O-$, the parts mainly responsible for the interaction with CP are the ether groups. Therefore, the peak at 1734 cm^{-1} in the PEO-CP system may be due to the carbonyl band of CP shifted by hydrogen bonding between the ether group of PEO and the hydroxyl group of the carboxyl group of CP. These results indicate that

the interpolymer complexation between PEO and CP by hydrogen bonding occurred in the solid dispersion, as suggested by Osada and Saito (1976). The interpolymer complexation might greatly affect the release behavior of PHE. The details are being studied for the present.

In conclusion, it is feasible to control the PHE release from the solid dispersion by varying the PEO/CP ratio. The release rate shows the minimum at the PEO/CP ratio of 1/1. It has been indicated that the interpolymer complexation between PEO and CP by hydrogen bonding occurs in the solid dispersion. For the mechanism of PHE release, further study is now under way.

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