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Dissolution Behavior of Prednisolone from Solid Dispersion Systems with Cyclodextrins and Polyvinylpyrrolidone[1)]

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Solid dispersion systems of prednisolone–cyclodextrins (CD) and prednisolone–polyvinylpyrrolidone (PVP) were prepared by the spray-drying method. The dissolution rates of prednisolone were markedly increased in these solid dispersion systems in the pharmacopeial disintegration medium at pH 6.8. In particular, the solid dispersion systems of prednisolone–CD inhibited and/or retarded the crystallization of prednisolone. The interaction of prednisolone with CD and PVP in water was also investigated. The apparent stability constants of the β- and γ-CD systems were both larger than that of the PVP system.

Keywords——prednisolone; β-cyclodextrin; γ-cyclodextrin; polyvinylpyrrolidone; spray-drying method; solid dispersion system; dissolution rate; apparent stability constant

Prednisolone, one of the synthetic adrenocortical hormones, is widely used to treat various diseases,[2)] but it has been pointed out that the drug exhibits large differences in bioavailability[3,4)] following oral administration because of its poor water-solubility.

Previously, the authors were successful in improving the dissolution characteristics of some poorly water-soluble drugs by coprecipitation by polyvinylpyrrolidone (PVP),[5,6)] and also in obtaining better bioavailability by using a solid dispersion system of dicumarol–β-cyclodextrin (β-CD).[7)]

In the present study, the authors attempted to modify the dissolution characteristics of prednisolone by preparing solid dispersion systems using CD and PVP by the spray-drying method. Inclusion complex formation of prednisolone with CD using the coprecipitation method has been examined by Uekama *et al.*[8)] The spray-drying method has several advantages for preparing solid dispersion systems. For example, by controlling the temperatures at the inlet and outlet, the flow rate or the air pressure for spraying, approximately uniform particle size is obtained. Moreover, spray-drying is convenient even for a drug which is unstable to heat.

Experimental

Materials——Prednisolone, β- and γ-CD were obtained from Nakarai Chemicals, Ltd., Kyoto, and recrystallized from ethanol–water and water, respectively. PVP k-15 was obtained from Daiichi Pure Chemicals Co., Tokyo. All other chemicals were of reagent grade.

Preparation of Solid Dispersion Systems——Solid dispersion systems were prepared by the spray-drying method. Both prednisolone and CD or PVP were dissolved in 50% (v/v) ethanol. The molar or weight ratio of solid dispersion systems was 1 : 2 drug-to-β-CD molar ratio, 2 : 3 drug-to-γ-CD molar ratio, and 1 : 10 or 1 : 14 drug-to-PVP weight ratio. The solution was fed into a Pulvis minispray GA-31, Yamato Kagaku Co., Tokyo. The temperatures at the inlet and outlet of the drying chamber were 110—120°C and 65—70°C, respectively. The other conditions were: flow rate, 5 ml/min; air pressure for spraying, 1.5 kg/cm^2; amount of drying air, 0.45 m^3/min.

Dissolution Studies——Dissolution rates of prednisolone from the preparation in 500 ml of JP X disintegration medium No. 2 (pH 6.8) were measured at 25±0.5°C with stirring at 100 rpm by a paddle method. The amount of the preparation (80 mesh) used was 800 mg prednisolone equivalent. At appropriate intervals, suitable aliquots were pipetted through a cotton filter, diluted with water and assayed for prednisolone at 246 nm using a Hitachi 100—20 spectrophotometer.

Solubility Studies——Solubility measurements were carried out according to the method of Higuchi and Connors.[9] Prednisolone (50 mg) was added to 10 ml aliquots of aqueous solutions containing various concentrations of CD or PVP and each mixture was shaken at 25±0.1°C. After equilibrium had been reached (14 d), the drug concentration of the samples was assayed by the above method.

X-Ray Diffraction Patterns——X-ray diffraction patterns were obtained with a Rigaku Denki Geigerflex model 2013 diffractometer.

DSC Study——This was done at a scanning rate of 10°C/min on a Shimadzu DSC-30M instrument.

Results and Discussion

The Properties of Solid Dispersion Systems of Prednisolone with the Three Additives

Figure 1 shows the DSC curves of various samples. The endothermic peak due to melting at around 250°C, which was observed for prednisolone alone and for the physical mixtures of prednisolone with β- and γ-CD, disappeared in the solid dispersion systems using CD and PVP. This peak was not observed in the physical mixture of prednisolone with PVP. The reason for this was considered to be that prednisolone was highly diluted with PVP, which was used in a large amount.

Figure 2a shows the X-ray diffraction patterns of prednisolone–CD systems. The diffraction patterns of the physical mixtures still showed peaks attributable to both

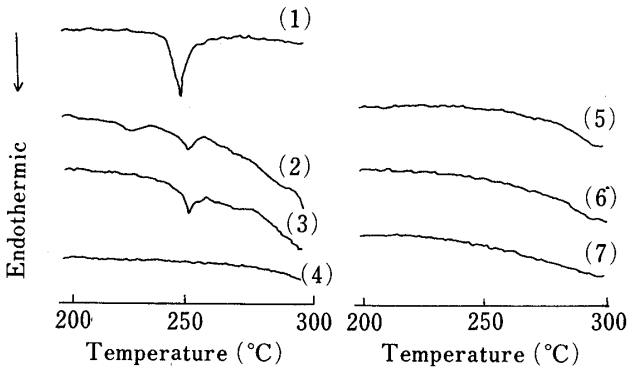

Fig. 1. DSC Curves of Prednisolone–CD and PVP Systems at a Scanning Speed of 10 °C/min

(1), prednisolone alone; (2), prednisolone : β-CD = 1 : 2 physical mixture; (3), prednisolone : γ-CD = 2 : 3 physical mixture; (4), prednisolone : PVP = 1 : 10 physical mixture; (5), prednisolone : β-CD = 1 : 2 solid dispersion; (6), prednisolone : γ-CD = 2 : 3 solid dispersion; (7), prednisolone : PVP = 1 : 10 solid dispersion.

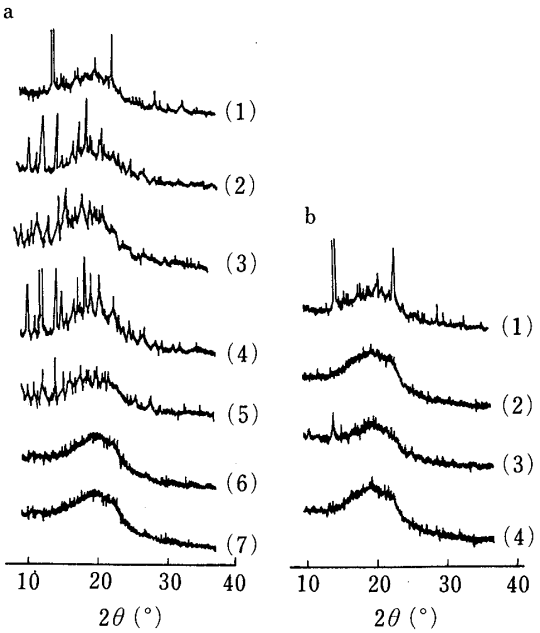

Fig. 2a. Comparison of X-Ray Diffraction Spectra of Prednisolone–CD Systems

(1), prednisolone alone; (2), β-CD alone; (3), γ-CD alone; (4), prednisolone : β-CD = 1 : 2 physical mixture; (5), prednisolone : γ-CD = 2 : 3 physical mixture; (6), prednisolone : β-CD = 1 : 2 solid dispersion; (7), prednisolone : γ-CD = 2 : 3 solid dispersion.

Fig. 2b. Comparison of X-Ray Diffraction Spectra of Prednisolone–PVP Systems

(1), prednisolone alone; (2), PVP alone; (3), prednisolone : PVP = 1 : 10 physical mixture; (4), prednisolone : PVP = 1 : 10 solid dispersion.

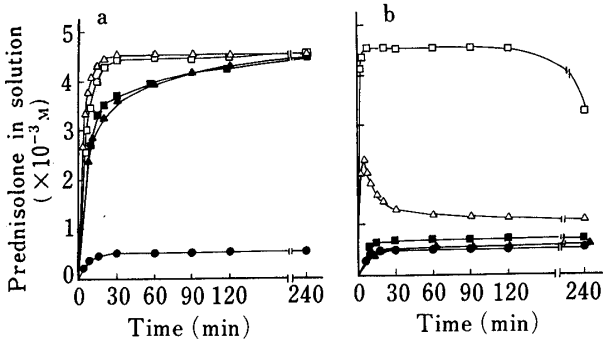

Fig. 3a. Dissolution Profiles of Prednisolone–CD Systems

●, prednisolone alone; ▲, prednisolone : β-CD = 1 : 2 physical mixture; ■, prednisolone : γ-CD = 2 : 3 physical mixture; △, prednisolone : β-CD = 1 : 2 solid dispersion; □, prednisolone : γ-CD = 2 : 3 solid dispersion.

Fig. 3b. Dissolution Profiles of Prednisolone–PVP Systems

●, prednisolone alone; ▲, prednisolone : PVP = 1 : 10 physical mixture; ■, prednisolone : PVP = 1 : 14 physical mixture; △, prednisolone : PVP = 1 : 10 solid dispersion; □, prednisolone : PVP = 1 : 14 solid dispersion.

Each point represents the means of three determinations.

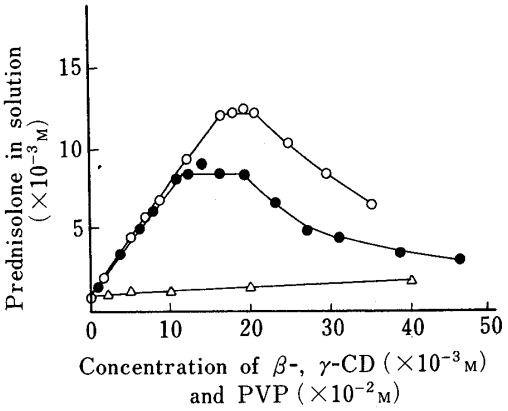

Fig. 4. Phase Solubility Diagrams of Prednisolone–CD and PVP in Water at 25 °C

○, β-CD; ●, γ-CD; △, PVP.

Each point represents the mean of three determinations.

prednisolone and CD crystals. However, diffraction peaks were not observed in the solid dispersion systems. Prednisolone might be present in an amorphous state in CD.

Figure 2b shows the X-ray diffraction patterns of prednisolone–PVP systems. In the physical mixture of 1 : 10 drug-to-PVP weight ratio, a weak diffraction peak attributable to prednisolone crystals was observed at around 14°, but at 1 : 14 drug-to-PVP ratio, it was no longer observed. This is compatible with the results of DSC.

Dissolution Studies

Figure 3a shows the dissolution behavior of prednisolone–CD systems. Prednisolone alone was dissolved to the extent of only about 1/8 of the added amounts at 240 min. In contrast, the solid dispersion systems with β- and γ-CD were both completely dissolved within 30 min and the crystallization of prednisolone was clearly inhibited and/or retarded. The physical mixtures were also dissolved at 240 min, although the initial dissolution rate was slow compared to those of the two solid dispersion systems. The faster dissolution rates of the drug from the physical mixtures compared to prednisolone alone might be attributed to easy complex formation in the test solution.

Figure 3b shows the dissolution behavior of prednisolone–PVP systems. The dissolution rates of the physical mixtures were rather similar to that of prednisolone alone. In the solid dispersion system of 1 : 14 drug-to-PVP weight ratio, the drug solubility was superior to that of the 1 : 10 system. However, the 1 : 14 solid dispersion system gradually crystallized after 120 min, though it was completely dissolved within 10 min.

Solubility Studies

The phase solubility diagrams for prednisolone with the three additives are shown in Fig. 4. The types of phase solubility diagrams and apparent stability constants (K') of β- and γ-CD were in good accordance with the report of Uekama *et al.*[8] (β- and γ-CD systems showed B_s-type behavior and the values of K' were 3600 and 3240 M^{-1}, respectively). On the other hand,

the PVP system showed A_L-type behavior and the value of K' was $3\,M^{-1}$. The low solubility in the PVP system is consistent with the crystallization of the drug in Fig. 3b.

From these results it is concluded that in solid dispersion systems of prednisolone–CD there is a strong interaction between the drug and CD. Generally, solid dispersion systems of poorly water-soluble drugs with CD are expected to provide better bioavailability[10] because they exhibit greater dissolution rates of the drugs, and dissolved drugs are kept in a supersaturated state in the presence of CD for a long period.

References and Notes

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