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Preparation of Solid Dispersion Systems of Disopyramide with Polyvinylpyrrolidone and γ-Cyclodextrin[1)]

YASUSHI TAKAHASHI,[a] TOSHIO TSUKUDA,[a] CHIHIRO IZUMI,[a] KATSUHIRO IKEMOTO,[a] KUNIO KOKUBUN,[a] NAOMI YAGI[b] and MASAHIKO TAKADA*,[b]

Department of Pharmacy, Sapporo City General Hospital,[a] Kita-1-jo, Nishi-9-chome, Chuo-ku, Sapporo 060, Japan and Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University,[b] 1757 Kanazawa, Ishikari-Tohbetsu, Hokkaido 061-02, Japan

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An attempt was made to improve the dissolution rate of disopyramide, which is a slightly soluble drug, by the preparation of solid dispersion systems with polyvinylpyrrolidone and γ-cyclodextrin. The resulting solid dispersion systems were examined by the phase solubility method, differential scanning calorimetry and X-ray diffractometry. The dissolution rates of the drug from these solid dispersion systems were greater than that of intact disopyramide.

Keywords——disopyramide; antiarrhythmic drug; solid dispersion system; polyvinylpyrrolidone; γ-cyclodextrin; spray-drying method; phase solubility method; dissolution rate

Disopyramide, 4-diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide, is an antiarrhythmic drug with electrophysiologic, pharmacokinetic and pharmacodynamic properties similar to those of quinidine and procainamide.[2-5)] It is well known that monitoring of disopyramide serum levels in patients is essential because of its narrow therapeutic range.[6)] However, there are very few reports on the bioavailability of disopyramide although the therapeutic use of the drug has been increasing. Disopyramide ($pK_a = 8.36$) is slightly water-soluble. Moreover, due to its extremely bitter taste, the dosage form of disopyramide has been restricted to capsules. Thus, this investigation was carried out to modify the dissolution properties and the taste of disopyramide by preparing solid dispersion systems with polyvinylpyrrolidone (PVP) and γ-cyclodextrin (γ-CD) by the spray-drying method.

Experimental

Materials——Disopyramide was kindly supplied by Searle Pharmaceutical Co., Osaka. γ-CD was purchased from Nakarai Chemicals Ltd., Kyoto, and recrystallized from water. PVP K-15 was purchased from Daiichi Pure Chemicals Co., Tokyo. All other chemicals were of analytical reagent grade.

Preparation of Solid Dispersion Systems——Solid dispersion systems were prepared by the spray-drying method. Disopyramide and PVP or γ-CD were dissolved in 50% (v/v) ethanol. The ratios prepared were 1:4 drug-to-PVP (weight ratio) and 1:1 drug-to-γ-CD (molar ratio). The conditions of the spray-drying were described previously.[7)]

Dissolution Studies——The dissolution rates of disopyramide from the preparations in 100 ml of the 2nd fluid of JP XI were measured at 30±0.5 °C. A stainless steel paddle (25 mm upper length, 14 mm bottom length and about 156 mm² in area) was immersed in the beaker (100 ml capacity and 57 mm in diameter) to a depth of 15 mm from the bottom, and was rotated at 100 rpm. The amount of the preparation used was 100 mg disopyramide equivalent. At appropriate intervals, suitable aliquots were taken with a syringe, then filtered through a membrane filter (0.45 μm). The same volume of fresh medium was added to the beaker. The concentration of disopyramide was determined at 260 nm using a Hitachi 200-20 spectrophotometer.

Solubility Studies——Solubility measurements were carried out to determine the molar ratio which forms a solid dispersion system of disopyramide and γ-CD according to the method of Higuchi and Connors.[8)] Disopyramide

(70 mg) was added to 10 ml of aqueous solutions containing various concentrations of γ-CD and the mixture was shaken at 25±0.1 °C. After equilibration (14 d), the 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.

Differential Scanning Calorimetry (DSC) Study——This was done by using a Shimadzu DSC-40M apparatus with a scanning rate of 10 °C/min.

Results and Discussion

Phase Solubility Diagram

Figure 1 shows the equilibrium phase solubility diagram obtained for the disopyramide/γ-CD system in water. The diagram shows a typical BS-type pattern, and the molar ratio of the solid dispersion system was 1 : 1 drug-to-γ-CD. The apparent stability constant, K', was estimated from the initial linear portion to be $K' = 9.6 \times 10\,\mathrm{M}^{-1}$.

The Properties of Solid Dispersion Systems of Disopyramide with PVP and γ-CD

Figure 2 shows the DSC curves of disopyramide/PVP. The endothermic peak owing to melting at around 90 °C, which was observed for intact disopyramide and physical mixture of disopyramide with PVP, disappeared in the solid dispersion system. Similar DSC curves of the disopyramide/γ-CD system were observed.

Figure 3 shows the X-ray diffraction patterns of disopyramide/PVP. Although X-ray diffraction peaks attributable to disopyramide crystals were apparent in the physical mixture, these crystalline peaks disappeared in the solid dispersion system. Similar diffraction patterns were observed in the case of the disopyramide/γ-CD system. These results corresponded to the changes in the DSC curves, and indicated that disopyramide might be present in an amorphous state in PVP or γ-CD.

Dissolution Studies

Figures 4a and 4b show the dissolution behavior of intact disopyramide, physical mixtures and solid dispersion systems. The dissolution rate of solid dispersion systems was larger than that of intact disopyramide. In particular, the dissolution rates were improved markedly in the solid dispersion systems with PVP or γ-CD and the physical mixture with γ-CD in the initial stage.

The above results suggest that solid dispersion systems with PVP and γ-CD may enhance

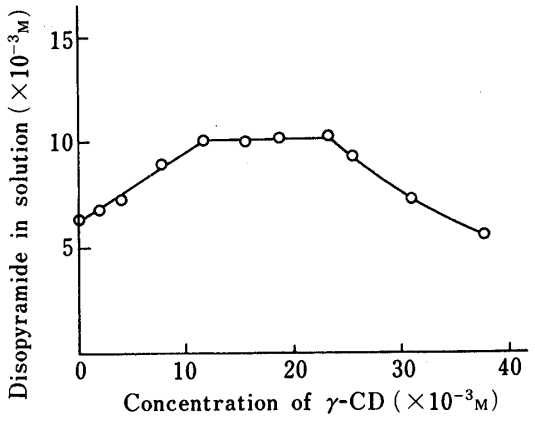

Fig. 1. Phase Solubility Diagram of Disopyramide/γ-CD in Water at 25 °C

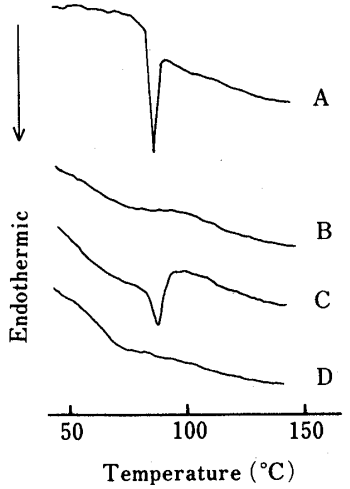

Fig. 2. DSC Curves of Disopyramide/PVP Systems at a Scanning Speed of 10 °C/min

A, intact disopyramide; B, intact PVP; C, disopyramide : PVP = 1 : 4 physical mixture; D, disopyramide : PVP = 1 : 4 solid dispersion.

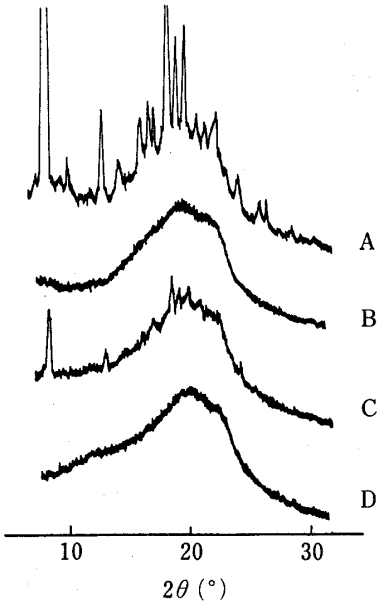

Fig. 3. Comparison of X-Ray Diffraction Spectra of Disopyramide/PVP Systems

A, intact disopyramide; B, intact PVP; C, disopyramide : PVP = 1 : 4 physical mixture; D, disopyramide : PVP = 1 : 4 solid dispersion.

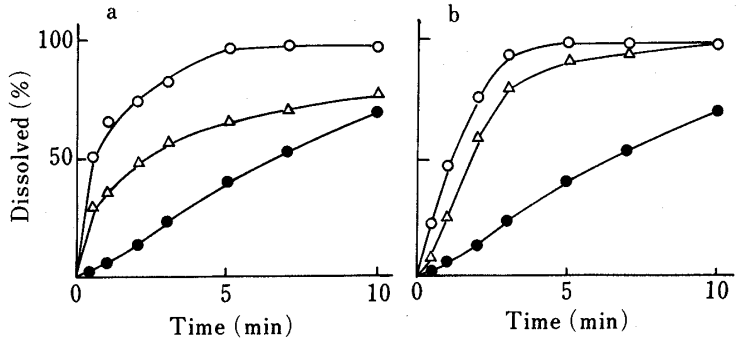

Fig. 4. a, Dissolution Profiles of Disopyramide/PVP Systems

●, intact disopyramide; △, disopyramide : PVP = 1 : 4 physical mixture; ○, disopyramide : PVP = 1 : 4 solid dispersion. Each point represents the mean of three determinations.

b, Dissolution Profiles of Disopyramide/γ-CD Systems

●, intact disopyramide; △, disopyramide : γ-CD = 1 : 1 physical mixture; ○, disopyramide : γ-CD = 1 : 1 solid dispersion. Each point represents the mean of three determinations.

the bioavailability of disopyramide. Furthermore, the bitter taste of disopyramide was reduced by the solid dispersion system with γ-CD, though it was not reduced by the solid dispersion system with PVP. It may be possible to develop new dosage forms (tablet, powder or granules) of disopyramide by making use of the solid dispersion system with γ-CD.

References and Notes

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