

Dissolution Behavior of Probucol from Solid Dispersion Systems of Probucol–Polyvinylpyrrolidone¹⁾

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Solid dispersion systems of probucol–polyvinylpyrrolidone (PVP) K 25, K 30 and K 90 were prepared in various weight ratios by co-evaporation of the drug and PVP ethanolic solution. The observation of solid dispersion systems by powder X-ray diffraction spectra and differential scanning calorimeter indicated that probucol in the systems did not exhibit its crystalline property. The solubility of probucol in water at 25 °C was 5 ng/ml at most, and its dissolution was markedly increased in the solid dispersion systems in the JP XII disintegration media No. 1 (pH 1.2) and No. 2 (pH 6.8) at 37 °C. Probucol concentrations after the dissolution of the solid dispersion systems showed hyper-saturation. The solid dispersion system of 1:9 (probucol:PVP K 30 in weight ratio) showed the best dissolution of probucol among the systems prepared in the study.

Key words probucol; solid dispersion system; polyvinylpyrrolidone; dissolution; solubility; HPLC assay

Probucol, 4,4'-[(1-methylethylidene)bis(thio)]bis[2,6-bis(1,1-dimethylethyl)]phenol is a potent hypocholesterolemic agents and is used worldwide. Probucol lowers both low-density-lipoprotein (LDL) and high-density-lipoprotein (HDL) cholesterol levels.^{2–5)} Though it has been used in the therapy, pharmacokinetics or pharmacodynamics of the drug are still unknown. Probucol is practically insoluble in water. Despite its lipid solubility, absorption from the gastrointestinal tract is less than 10% of an oral dose.^{6,7)} The major pathway of elimination is *via* bile and feces. Blood levels varied greatly following the oral administration of probucol in human.⁸⁾ In this study, we investigated the solubility of probucol and prepared solid dispersion systems of probucol and polyvinylpyrrolidone (PVP) to improve its dissolution.

Materials and Methods

Materials Probucol powder was prepared by extraction and recrystallization using an ethanol–water system from probucol fine granules (Lorelco fine granules, lot No. OB89Z6), obtained from Otsuka Pharmaceutical Co., Osaka, Japan. The mean diameter of probucol powder, as measured by optical microscopy (Olympus BH microscope) was $119.7 \pm 53.6 \mu\text{m}$ (Green diameter, mean \pm S.D., $n = 100$). PVP K 25, K 30 and K 90 (average molecular weight of 25000, 40000 and 1200000, respectively) were obtained from Nacalai Tesque Inc., Kyoto, Japan. Reagent grade pyrene was obtained from Wako Pure Chemical Ind. Ltd., Osaka, Japan, and used as an internal standard for probucol assay. Acetonitrile was HPLC grade from Kanto Chemical Co. Inc., Tokyo, Japan. All other chemicals were of reagent grade.

Preparation of Solid Dispersion Systems of Probucol–PVP The solid dispersion systems of probucol–PVP were prepared as follows: After dissolving probucol and PVP in a suitable weight ratio in ethanol, the solvent was removed *in vacuo* using a rotary evaporator at about 35 °C. Then, the residue was dried *in vacuo* at room temperature for 24 h. The preparation was ground in a mortar, passed through a sieve (JP XII No. 100) and stored in a light-resistant tight container at room temperature. A physical mixture was prepared by blending probucol and PVP in a mortar with a spatula.

Powder X-Ray Diffraction Patterns Powder X-ray diffraction patterns were obtained with a Geigerflex, model 2013 diffractometer, Rigaku Denki Co., Kyoto, Japan. The conditions of measurement were as follows: Ni filter, Cu- K_α ray, 30 kV, 20 mA, scanning rate 1°/min, count range 2000 cps.

Thermal Analysis A differential scanning calorimeter, DSC DT-40, Shimadzu Co., Kyoto, Japan, was used under N₂ gas flow at a scanning rate of 10 °C/min.

Solubility Studies Solubility of probucol in the water–ethanol system

was studied at 25 ± 0.1 °C in a water-jacketed beaker (50 mm in diameter) controlled by water from the thermobath (Type F2, Haake, Berlin, Germany). A Teflon magnetic stirring bar (13 mm long) was employed for agitation of the suspension. After the saturation, a portion was removed from the suspension with a pipette, passed through the membrane filter (cellulose acetate, pore size 0.45 μm for ethanol and mixtures of ethanol and water, cellulose nitrate, pore size 0.45 μm for water, Tokyo Roshi Kaisha, Ltd., Tokyo, Japan).

Dissolution Studies Dissolution of probucol from the preparations in 500 ml of JP XII disintegration medium No. 1 (pH 1.2) and No. 2 (pH 6.8) was measured at 37.0 ± 0.5 °C in dissolution test apparatus of JP XII (Toyama Sangyo Co., Ltd., Osaka, Japan). The paddle was rotated at 150 rpm. The amount of the test samples was 100 mg as probucol equivalent. Each preparation was transferred directly into the dissolution medium. A suitable aliquot was removed at an appropriate time with a syringe, then filtered quickly through a membrane filter (cellulose nitrate, pore size 0.45 μm), diluted appropriately and analyzed for drug by HPLC method.

Analytical Procedure for Probucol The analytical procedure for probucol was followed by the HPLC method. The HPLC conditions were as follows: Column: Shim-pack CLC-ODS (150 \times 6 mm, particle size 5 μm , Shimadzu, Co., Ltd., Kyoto, Japan) maintained at 40 ± 0.1 °C in a column oven (CTO-6A, Shimadzu). Detector: SPD-10A (Shimadzu) monitored at 254 nm. Mobile phase: water–acetonitrile (15:85, v/v %). Flow rate: 1.0 ml/min. Sample solutions were injected into HPLC automatically with a run time of 25 min. The retention times of the peaks of probucol and internal standard were at 21.3 and 4.0 min, respectively. The detection limit of probucol was 10 ng/ml.

Protection from Photodegradation During the study, all processes were protected carefully from photodegradation of probucol in a darkened room.

Results and Discussion

The Solubility of Probucol in Water–Ethanol System The solubility of probucol in water was studied by placing it in the water–ethanol system at 25 °C. The solubility increased exponentially with the concentration of ethanol above 60%. However, the concentrations of probucol were below the limit of detection when ethanol content was less than 10%. Figure 1 shows the values of a logarithm of solubility of probucol in the water–ethanol system at 25 °C. A good straight line was observed ($y = 0.076x - 2.616$, $r^2 = 0.985$). Judging from this line, the solubility of probucol in water was between 2 and 5 ng/ml at 25 °C. This was much lower than other water-insoluble drugs (e.g., phenytoin; 28.0 $\mu\text{g/ml}$,⁹⁾ digitoxin; 6.2 $\mu\text{g/ml}$,¹⁰⁾ nifedipine; 8.25 $\mu\text{g/ml}$,⁹⁾ in water at 25 °C). The extremely poor

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water-solubility might be the reason for the low absorption of probucol in human.^{6,7)}

Powder X-Ray Diffraction Patterns of Solid Dispersion Systems The powder X-ray diffraction patterns of probucol, solid dispersion systems of probucol and PVP and the physical mixture are shown in Fig. 2. PVP is an amorphous powder having no crystalline structure. In solid dispersion systems, sharp diffraction peaks attributed to probucol crystals disappeared. Such a halo was also observed in solid dispersion systems when the weight ratio of PVP K 25, K 30 or K 90 to the drug was above 5, 6 or 1, respectively. Below these values, the peaks

due to crystals of probucol were observed in the X-ray diffraction spectra. Sharp peaks were seen in the physical mixtures.

Thermal Analysis DSC curves showed an endothermic peak accompanied by the melting of probucol crystals at 128 °C (Fig. 3). The peak disappeared in the solid dispersion system of probucol and PVP K 30 at 1:9 weight ratio. Preparations exhibiting the halo in X-ray diffraction spectra also showed no endothermic peak on the DSC chart, although the peak was observed in the spectra of physical mixtures.

From the X-ray diffraction study and DSC study, crystalline probucol was not observed in the solid dispersion systems of probucol and PVP K 30 at 1:6, 1:7, 1:8 and 1:9 weight ratios. Crystalline probucol remained in the 1:5 system. For the dissolution study solid dispersion systems having no crystalline structure were used.

Dissolution Studies Figure 4 shows the dissolution characteristics of solid dispersion systems of probucol and PVP K 25 in JP XII disintegration medium No. 1 (pH 1.2) and No. 2 (pH 6.8) at 37 °C. Probucol concentrations dissolved as powder or as the physical mixture (probucol : PVP K 25 = 1 : 9) were under the detection limit (10 ng/ml), they are not shown in the figure. For the same reason we were not able to obtain the stability constants¹¹⁾ for the interaction of probucol with three kinds of PVP. The solid dispersion systems exhibited faster dissolution of probucol than the powder or physical mixture. The concentrations of probucol following the dissolution of solid dispersion systems showed supersaturation. Concentrations from the solid dispersion systems were higher when the ratio of PVP was larger.

Figure 5 shows the dissolution characteristic of pro-

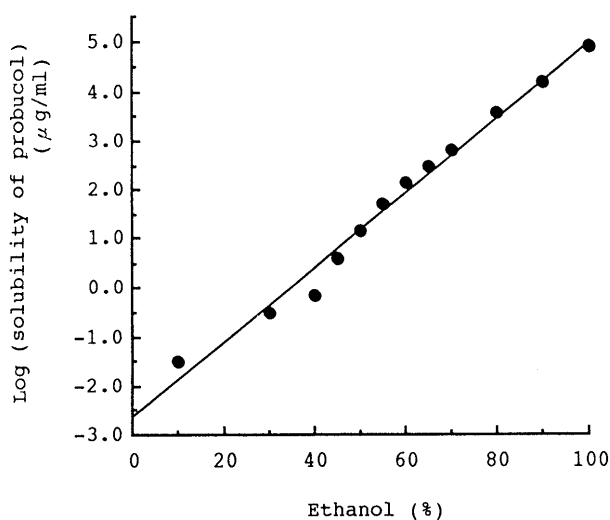


Fig. 1. Log Scale of Apparent Solubility of Probucol in Water-Ethanol at 25 °C

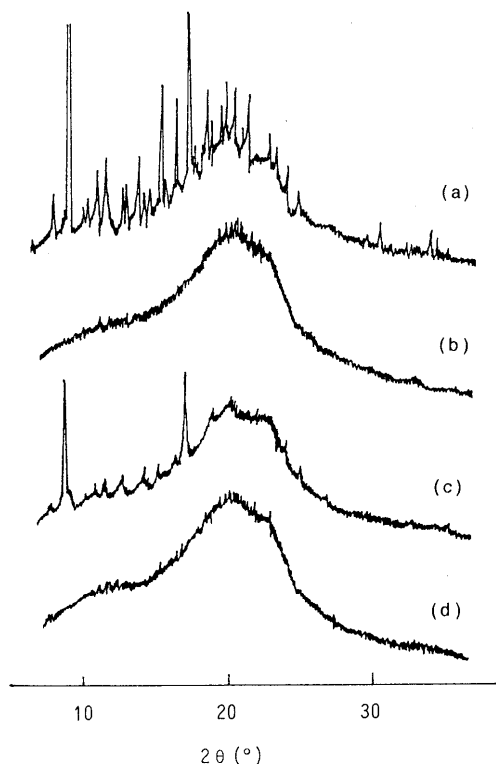


Fig. 2. Powder X-Ray Diffraction Pattern of Probucol-PVP K 30 Systems

(a) Probucol powder; (b) PVP alone; (c) probucol : PVP = 1 : 9 physical mixture; (d) probucol : PVP = 1 : 9 solid dispersion system.

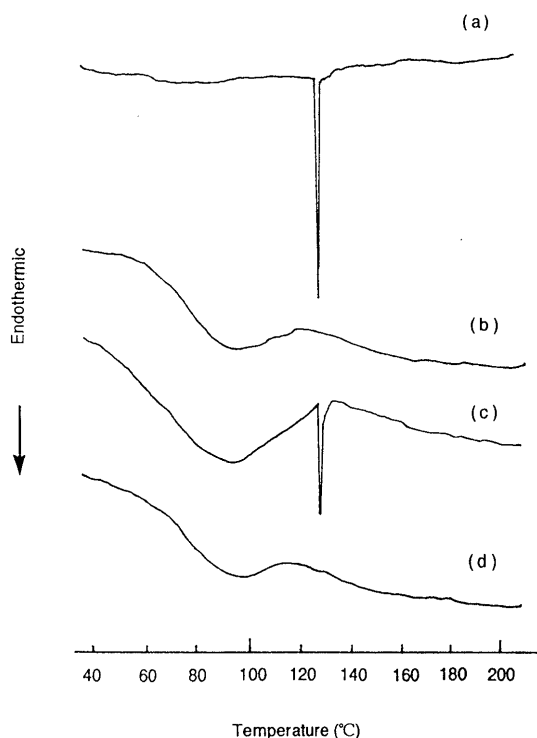


Fig. 3. DSC Curves of Probucol/PVP K 30 Systems

(a) Probucol powder; (b) PVP alone; (c) probucol : PVP = 1 : 9 physical mixture; (d) probucol : PVP = 1 : 9 solid dispersion system.

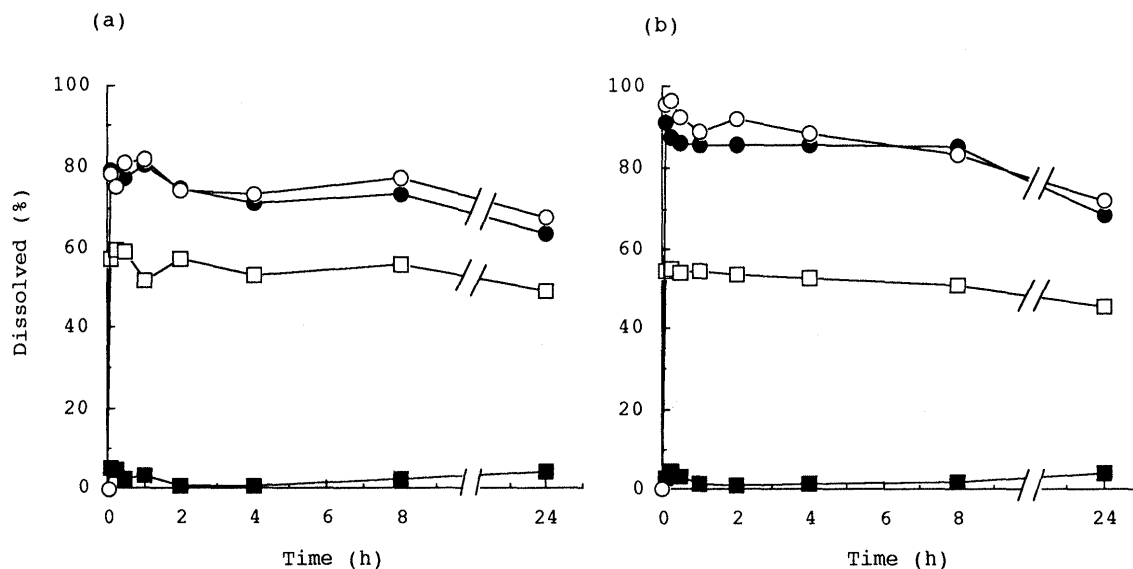


Fig. 4. Dissolution Profiles of Solid Dispersion Systems of Probucol and PVP K 25 in JP XII Disintegration Medium No. 1 (a) and No. 2 (b)
 ■, probucol:PVP=1:6; □, probucol:PVP=1:7; ●, probucol:PVP=1:8; ○, probucol:PVP=1:9. Each point represents the mean of three determinations. All standard deviations were within 5%.

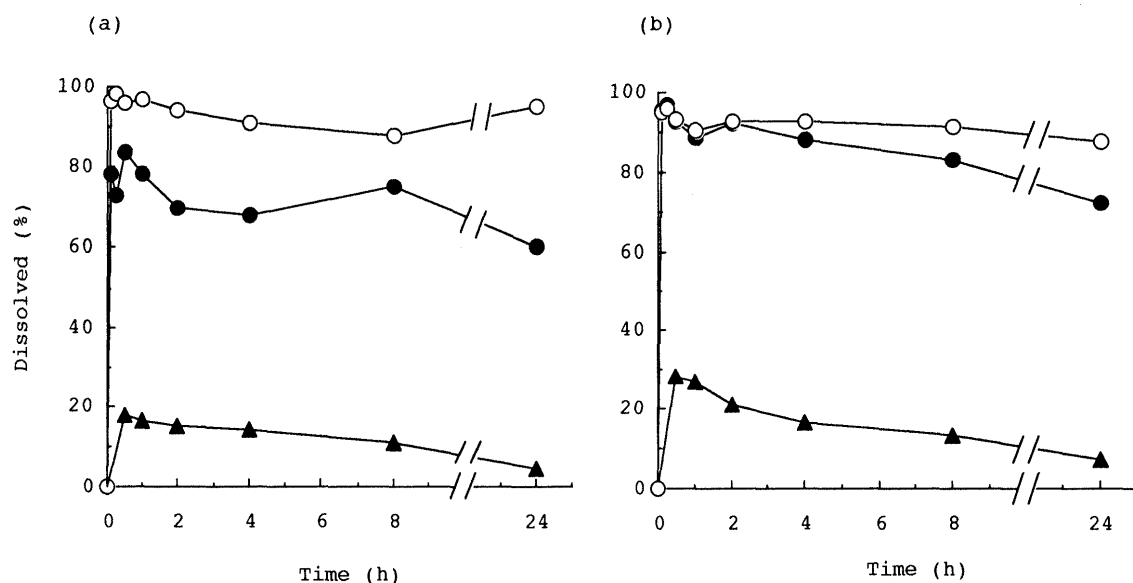


Fig. 5. Dissolution Profiles of Solid Dispersion Systems of Probucol and PVP (1:9) in JP XII Disintegration Medium No. 1 (a) and No. 2 (b)
 ○, PVP K 30; ●, PVP K 25; ▲, PVP K 90. Each point represents the mean of three determinations. All standard deviations were within 5%.

bucol solid dispersion systems using PVP K 25, K 30 and K 90 (probucol:PVP=1:9). Probucol concentrations by dissolving of the physical mixtures with PVP K 30 or 90 were also under the detection limit. Dissolution of the solid dispersion systems with PVP K 30 showed highest concentration of probucol in both JP XII disintegration media No. 1 and No. 2. In this case, the administered amount (100 mg as probucol) almost completely dissolved in both media. When the coprecipitates (solid dispersion systems) of sulfoxazole-PVP¹²⁾ or phenytoin-PVP¹³⁾ were dissolved in water, the coprecipitates with PVP of smaller molecular weight showed faster dissolution of the drugs (PVP K 15>K 30>K 90). Sekikawa *et al.* reported on the dissolution mechanisms of drugs from coprecipitates.¹⁴⁾ When the coprecipitates were dissolved in water, drugs dispersed in the PVP dissolved *via* microcoacervates. PVP having lower molecular weight disappeared

more rapidly. When the concentration exceeded the solubility of a drug, PVP inhibited the drug recrystallization.¹⁵⁾ Intensity of inhibitory effect depended on the concentration of PVP in aqueous solution and was PVP K 30>K 90>K 15. The monomer unit of PVP, *N*-vinyl-2-pyrrolidone did not exhibit the inhibitory effect. Sekikawa *et al.*¹⁵⁾ speculated that the inhibitory effect of PVP on the recrystallization of the drugs might apply up to a certain molecular weight, and decrease as that weight increased. In this study, after dissolution of both probucol and PVP in test medium, PVP K 30 in the medium largely prevented the recrystallization of probucol. With the high dissolution characteristics of probucol, the increased absorption from the gastrointestinal tract might be expected following the administration of solid dispersion systems *in vivo*.

References and Notes

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