Drug Development and Industrial Pharmacy, 22(11), 1161-1165 (1996)

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Dissolution Properties of Glibenclamide in Combinations with Polyvinylpyrrolidone

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ABSTRACT

Investigations were done on the enhanced aqueous solubility of glibenclamide. Eight kinds of glibenclamide coprecipitates, using two kinds of polyvinylpyrrolidone (PVP) having different molecular weights, were prepared in a solid powdered form by the conventional evaporation method. The formation of coprecipitates was confirmed by powder x-ray diffractometry, differential scanning calorimetry and Fourier-transform infrared spectroscopy. The aqueous solubility of glibenclamide was improved by increasing the concentrations of PVP. The coprecipitates prepared in this study were found to have higher dissolution rates compared to intact glibenclamide and physical mixtures of glibenclamide and PVP.

INTRODUCTION

Various methods to improve the solubility of poorly water soluble drugs have been investigated since Sekiguchi and Obi (1) first proposed the utilization of solid dispersions. The aqueous solubility and absorption improvements of glibenclamide have been investigated by the use of surfactants (2–4), micronization of the drug (5–7), and by the preparation of solid dispersions (8). It has also been reported that the dissolution rate and aqueous solubility of glibenclamide was increased by coprecipitation with PVP (9).

In this study, we investigated the preparation of glibenclamide–PVP coprecipitates with different weight ratios and assessed their effects on the aqueous solubility of glibenclamide.

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EXPERIMENTAL PROCEDURES

Materials

Polyvinylpyrrolidones (PVP) of MW 24,000 (K25) and MW 40,000 (K30) of commercial grade were used without further purification. All the other chemicals used were of analytical grade.

Preparation of Coprecipitates

Mixtures of glibenclamide and PVP (K25 or K30) at four different weight ratios (glibenclamide:PVP = 1:1, 1:5, 1:10, 1:20) were dissolved in absolute ethanol at room temperature, giving a clear solution. After removal of the solvent by evaporation at 30°C under reduced pressure, the residue was powdered with a mortar. The particles of coprecipitate used for this experiment were those remaining after passing the powder through a 100-mesh sieve (less than 150 μm).

Intact glibenclamide was also dissolved in absolute ethanol and treated in a similar manner as above.

Preparation of Physical Mixtures

Glibenclamide and PVP were weighed accurately in four different weight ratios, the same as the coprecipitates, and mixed thoroughly. The blended powders were passed through a 100-mesh sieve.

Solubility Studies

An excess amount of the sample was added to 10 ml of pH 7.4 buffer solution and stirred at 37°C. After equilibration for at least 24 hr, the saturated solutions were filtered through a 0.45-μm membrane filter, diluted with methanol, and analyzed by high performance liquid chromatography (HPLC).

The HPLC conditions were as follows: column, Nucleosil C18 (5 μm, 4.6 mm i.d. × 150 mm) (Nagel Co.); mobile phase, acetonitrile–0.023 M ammonium sulfate aqueous solution (55:45); flow rate, 1.2 ml/min; and a detection wavelength of 299 nm.

Dissolution Studies

The paddle method described in the Pharmacopoeia of Japan (edition XII—JPXII), was used in pH 7.4 buffer solution. A certain amount of each sample, corresponding to 5 mg of glibenclamide, was placed in a beaker containing 900 ml of the medium equilibrated to 37°C. The paddle was rotated at 100 rpm, and 5-ml samples of the solution were withdrawn at appropriate times. The concentrations of glibenclamide were determined by HPLC, as in the solubility studies. The volume of the dissolution medium was kept constant throughout the dissolution run by adding the same volume of fresh medium to the breaker after each sample was taken.

Powder X-ray Diffraction Study

Powder x-ray diffractometry was carried out using a MXP3 diffractometer (Mac Science Co.). The operating conditions were as follows: target, Cu; filter, Ni; voltage, 30 kV; current, 10 mA; receiving slit, 0.15 mm; scanning speed, 5°/min.

Differential Scanning Calorimetry (DSC)

This was done using a 8085E2 differential scanning calorimeter (Rigaku Denki Co.). The heating rate was 10°C/min.

Fourier-Transform Infrared (FT-IR) Spectroscopy

The FT-IR spectra of the glibenclamide and coprecipitates were obtained by the potassium bromide disk method using an FT-IR spectrophotometer (JIR-5500, JEOL Co.).

RESULTS AND DISCUSSION

Table 1 shows the effects of PVP on the solubility of glibenclamide. The solubility of glibenclamide was increased by further addition of PVP, and there was no difference between PVP (K25) and PVP (K30). In contrast to PVP–hydroflumethiazide (10), lowering of the solubility of glibenclamide in these glibenclamide–PVP systems was not observed at the PVP concentrations studied. These results suggest that glibenclamide and PVP may form a soluble complex in solution.

Figures 1 and 2 show the dissolution profiles of glibenclamide, glibenclamide–PVP coprecipitates, and their physical mixtures. Intact glibenclamide exhibited the slowest dissolution behavior, and its concentration in solution after 2 hr was approximately 10% of its equilibrium solubility (13.5 mg/900 ml). The evaporation-treated glibenclamide was slightly more soluble in comparison with intact glibenclamide, because the crystallinity of glibenclamide was decreased by evaporation

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Table 1

Solubilities (mg/ml) of Glibenclamide–PVP Coprecipitates at Various Weight Ratios

	Weight Ratio (Glibenclamide:PVP)				
PVP	1:1	1:5	1:10	1:15	1:20
PVP (K25)	0.024	0.033	0.041	0.051	0.078
PVP (K30)	0.021	0.032	0.039	0.058	0.073

Note. The saturated solubility of intact glibenclamide was 0.015 mg/ml. The solubilities of the coprecipitates at 1:15 were measured and only compared with the 1:10 and 1:20 coprecipitates. Each solubility value is the mean of 3 determinations.

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treatment. We also found that the effect of evaporation alone, on solubility, was not so large. On the other hand, all glibenclamide–PVP coprecipitates exhibited considerably faster dissolution behavior than that of intact glibenclamide. Beyond a 1:5 PVP weight ratio the degree of enhanced solubility was almost same. There were no large differences between glibenclamide–PVP (K25) coprecipitates and glibenclamide–PVP (K30) coprecipitates . The dissolution profiles of the 1:1 glibenclamide–PVP coprecipitates (both K25 and K30) showed that these coprecipitates dissolved slowly compared to those of other large weight ratio glibenclamide–PVP coprecipitates. This result may arise through the inability of glibenclamide to disperse into the PVP matrix. The dissolution profiles of glibenclamide–PVP physical mixtures showed nearly the same dissolution behavior at all weight ratios, and their concentrations in solution after 2 hr was approximately 70% of the equi-

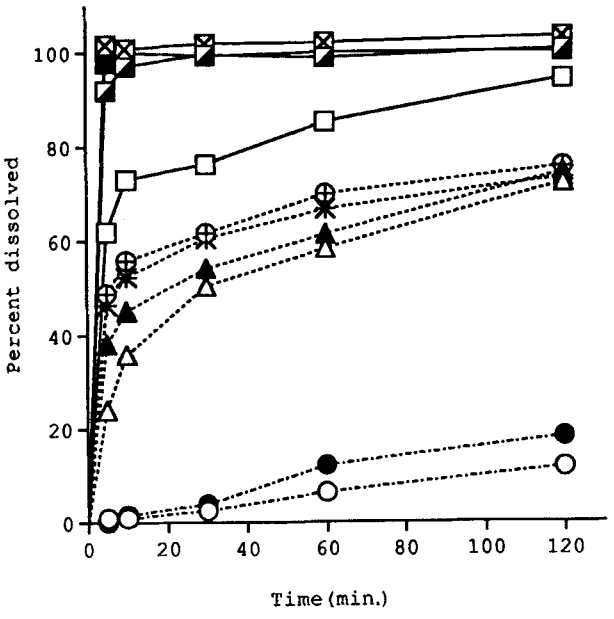

Figure 1. Dissolution patterns of glibenclamide, glibenclamide–PVP (K25) coprecipitates, and physical mixtures of glibenclamide and PVP (K25). Each value represents the mean of 3 determinations. Key: ○, intact glibenclamide; ●, evaporated glibenclamide from ethanol; glibenclamide–PVP (K25) coprecipitates: □, at 1:1; □, at 1:5; □, at 1:10; ■, at 1:20; glibenclamide–PVP (K25) physical mixtures: Δ, at 1:1; ▲, at 1:5; ⊕, at 1:10; *, at 1:20.

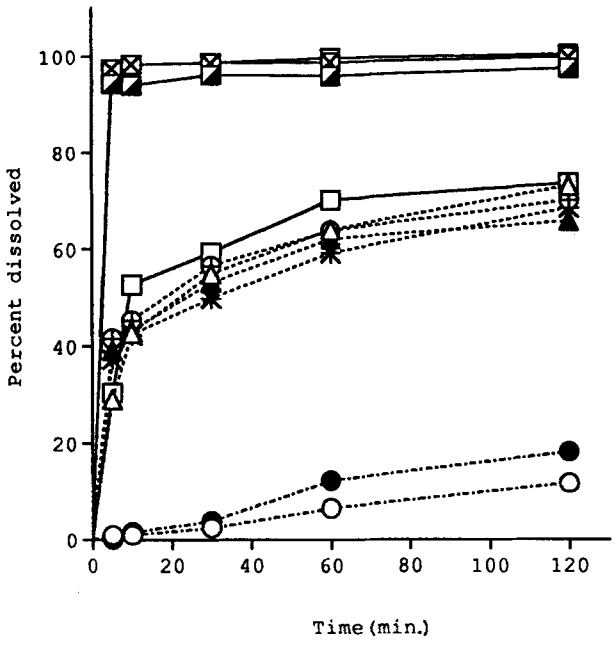

Figure 2. Dissolution patterns of glibenclamide, glibenclamide–PVP (K30) coprecipitates, and physical mixtures of glibenclamide and PVP (K30). Each value represents the mean of 3 determinations. Key ○, intact glibenclamide; ●, glibenclamide evaporated from ethanol; glibenclamide–PVP (K30) coprecipitates: □, at 1:1; □, at 1:5; □, at 1:10; ■, at 1:20; glibenclamide–PVP (K30) physical mixtures: Δ, at 1:1; ▲, at 1:5; ⊕, at 1:10; *, at 1:20.

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librium solubility. The studies with physical mixtures indicated that the presence of PVP, in amount equivalent to those present in the coprecipitates, was partly responsible for the enhanced dissolution of glibenclamide. In addition, it was suggested that the enhanced dissolution of glibenclamide was also responsible for the amorphous state of glibenclamide via the formation of glibenclamide–PVP coprecipitates.

Figure 3 illustrates the powder x-ray diffraction patterns of glibenclamide, glibenclamide–PVP (K25) coprecipitates and the physical mixtures. The diffraction pattern of glibenclamide showed that glibenclamide has high crystallinity because of the presence of numerous distinct peaks. Several peaks, attributed to glibenclamide crystals, could be detected in the x-ray patterns of glibenclamide–PVP physical mixtures at weight ratios 1:1, 1:5, and 1:10. However, all glibenclamide–PVP coprecipitates, except the 1:1 coprecipitate, did not show the characteristic peaks of glibenclamide. The peaks of the diffraction patterns of the 1:1 coprecipitate were small than those of its 1:1 physical mixtures and were almost the same as those of the 1:5 physical mixture. These results suggested that the glibenclamide crystals were well dispersed into the PVP matrix in coprecipitates with higher weight ratio. This finding is compatible with the enhanced dissolution of glibenclammide–PVP coprecipitates mentioned above. The glibenclamide–PVP (K30) system showed results similar to those of the glibenclamide–PVP (K25) system.

Figure 4 shows the DSC curves of glibenclamide–PVP (K25) coprecipitates at 1:1 and 1:5 weight ratios in comparison with those of their physical mixtures at the same weight ratios, and that of intact glibenclamide. An endothermic peak at 173°C was observed for intact glibenclamide. Physical mixtures of glibenclamide–PVP showed a slightly broader peak at around 160°C. This endothermic peak at 160°C also appeared in the glibenclamide–PVP coprecipitates. The intensity of the peaks of the 1:1 weight ratio coprecipitate were smaller than those of the physical mixture at same weight ratio. This result suggested that glibenclamide crystal dispersed into the PVP matrix and became partially amorphic. This does not conflict with the x-ray diffraction study. In order to clarify the interaction mechanisms between glibenclamide and PVP, FT-IR spectra of glibenclamide–PVP coprecipitates at 1:1 weight ratios were measured and compared with those of its physical mixture and an intact glibenclamide. FT-IR spectra of the physical mixtures were found to be simple superimpositions of the mixtures components, while those of the coprecipitates were slightly different. However, the differences in their spectra are too small to determine the interactions between glibenclamide and PVP in detail (data not shown).

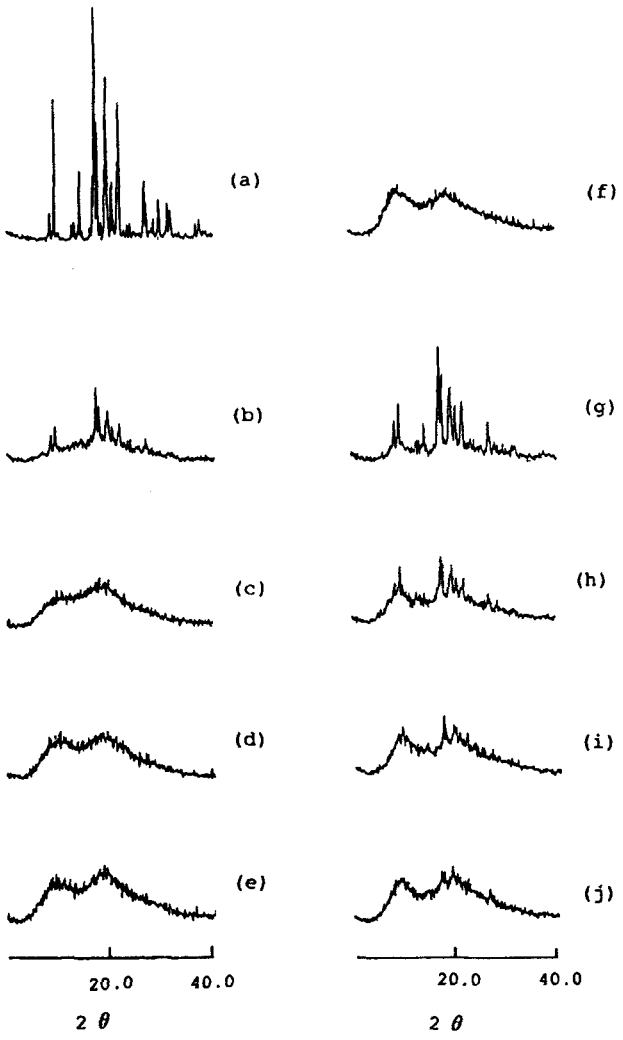

Figure 3. Powder x-ray diffraction patterns of glibenclamide, glibenclamide–PVP coprecipitates, and physical mixtures of glibenclamide and PVP. Key (a) intact glibenclamide; (b) glibenclamide–PVP (K25) coprecipitate at 1:1; (c) 1:5 coprecipitate; (d) 1:10 coprecipitate; (e) 1:20 coprecipitate; (f) intact PVP(K25); (g) glibenclamide–PVP (K25) physical mixture at 1:1; (h) 1:5 physical mixture; (i) 1:10 physical mixture; (j) 1:20 physical mixture.

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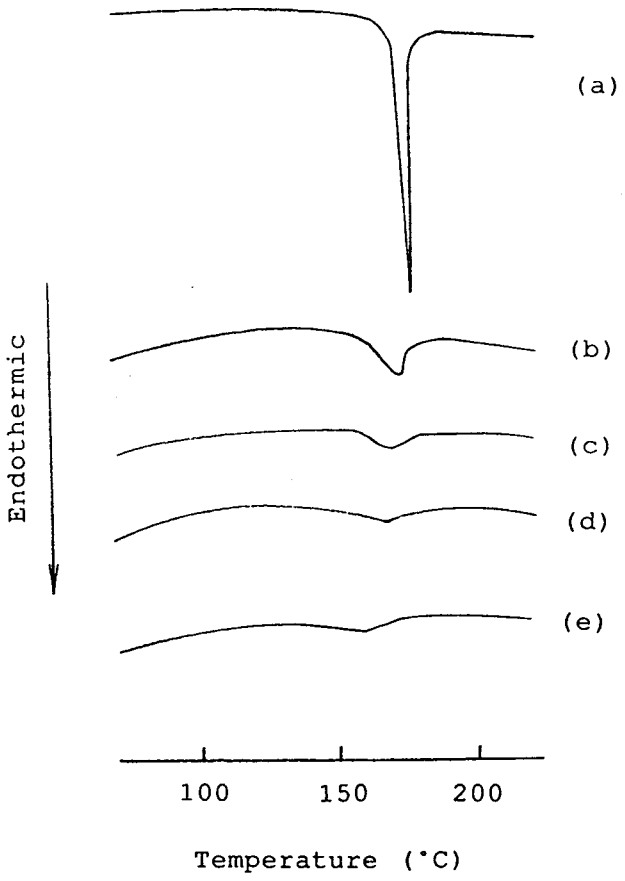

Figure 4. DSC curves of glibenclamide PVP (K25), glibenclamide–PVP coprecipitates, and physical mixtures of glibenclamide and PVP (K25). Key (a) intact glibenclamide; (b) glibenclamide–PVP (K25) physical mixture at 1:1; (c) glibenclamide–PVP (K25) coprecipitate at 1:1; (d) glibenclamide–PVP (K25) physical mixture at 1:5; (e) glibenclamide–PVP (K25) coprecipitate at 1:5.

In conclusion, glibenclamide–PVP (K25, K30) coprecipitates with a weight ratio of more than 1:5 showed a significantly increased dissolution rate of glibenclamide.

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