Preparation and dissolution rate of gliquidone-PVP K30 solid dispersions

P. MARTNEZ, M.M. GOÑI, R.G. CANTERA, C. MARTIN, C. DIOS-VIÉITEZ, C. MARTÍNEZ-OHÁRRIZ

Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Navarra, 31080 Pamplona Spain

Keywords: Dissolution rate, solid dispersions, gliquidone, polyvinylpyrrolidone K30.

SUMMARY

Solid dispersions of gliquidone in PVP K30 were prepared by the solvent method. These dispersions were characterized using X-ray diffraction. In comparison with the drug alone, the physical mixtures and even more the solid dispersions showed an increase in the dissolution rate. Moreover these solid dispersions were stable during storage

INTRODUCCION

The solubility and dissolution rate are two essential characteristics of active molecules. Both greatly influence the bioavailability of drugs.

Solid dispersions in which the carriers were water-soluble agents have been investigated with the aim of improving the solubilities and dissolution rates of poorly water soluble drugs (1). On the other hand, many studies have been carried out on the enhancement of the dissolution rate of hypoglucaemiant drugs by means of solid dispersions (2-7). The solid dispersions can be prepared by different methods and dissolution of the drug and the carrier in a common solvent is a very feasible procedure (8).

The purpose of the present work is to investigate the possibility of improving the dissolution rate of gliquidone, a hypoglucaemiant drug which exhibits a very low water solubility, via solid dispersion technique, using PVP K30 as a carrier. The effect of ageing was also investigated.

MATERIALS AND METHODS

Materials

Gliquidone (Europharma), PVP K30 (GAF Corporation) and analytical grade ethanol (Merck) were used as supplied.

Preparation of solid dispersions

Solid dispersions were prepared by the solvent method (9). Gliquidone and PVP K30 were combined at various ratios (90:10; 80:20; 75:25; 70:30 and 50:50) in ethanol, then the solvent was evapored in vacuo at about 50 °C using a rotatory evaporator. The coprecipitate was stored at room temperature.

For purposes of comparison, physical mixtures of drug and carrier were prepared by mechanically mixing the two substances using a mortar and pestle.

X-ray diffraction

X-ray powder diffraction patterns were collected with a Siemens Kristalloflex 810 diffractometer, Cu K_ radiation (λ = 1.5418 Å).

Dissolution studies

The dissolution rates of free and dispersed gliquidone were determined in triplicate according to the disk method described by Wood et al. (10). Drug dissolution tests were carried out in a USP 23 dissolution apparatus 2 (Dissolutest 07170025). For each sample, 900 ml of pH 8 buffer were stirred at 100 ± 1 rpm and maintained at 37 ± 0.5 °C.

A hydraulic press was used to prepare 13 mm compressed disks in similar fashion to those used for

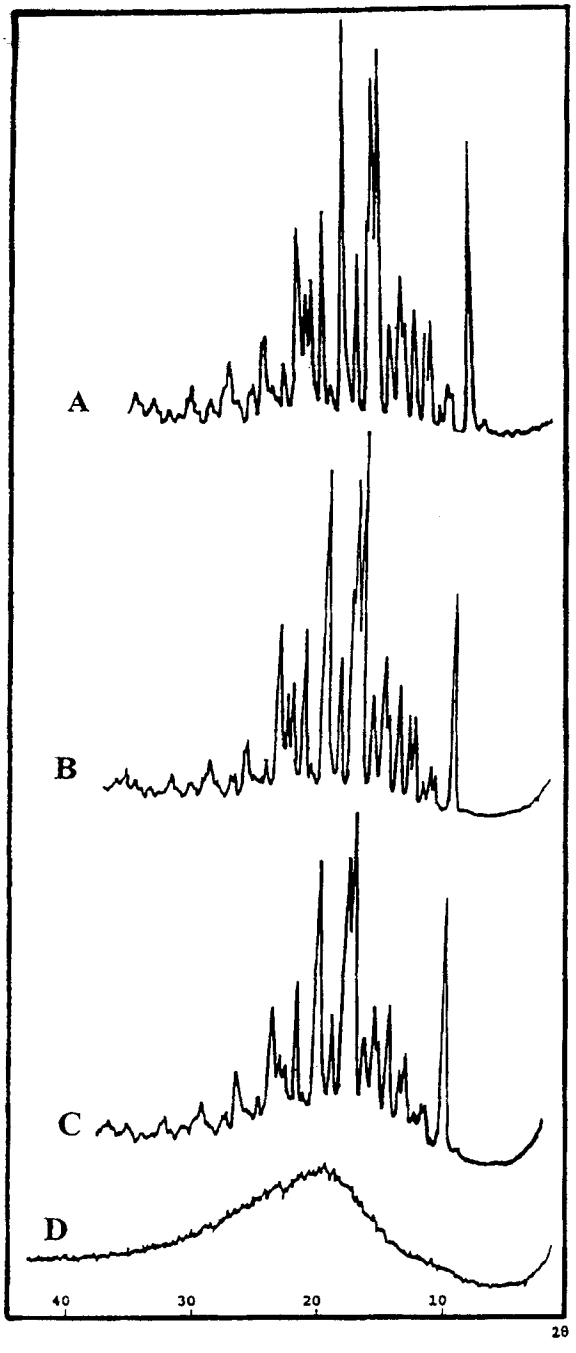

Fig. 1: X-ray diffraction patterns of: (A) pure gliquidone, gliquidone-PVP K 30 solid dispersion of (B) 10% PVP, (C) 20% PVP and (D) 25% PVP.

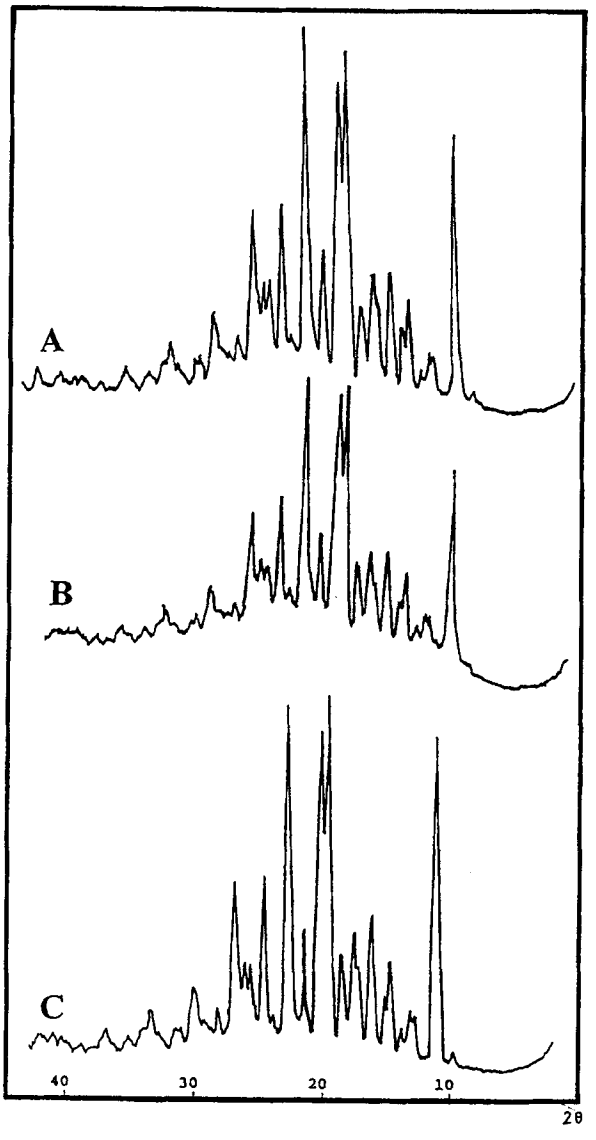

Fig. 2: X-ray diffraction patterns of the gliquidone-PVP K30 physical mixture of (A) 10% PVP, (B) 20% PVP and (C) 25% PVP.

infrared spectroscopy using the conventional procedure. Samples ranging in weight from 20 to 30 mg were used.

At appropiate intervals, 5 ml of solution were withdrawn and filtered through a 0.8 μm filter. The volume in the vessel was replaced with pure pH 8 buffer after each sampling. The concentration of gliquidone dissolved in the medium was determined spectrophotometrically at 220 nm (Perkin-Elmer Lambda 2 spectrophotometer) by reference to a suitable calibration curve. The presence of PVP K30 did not exhibit any interference.

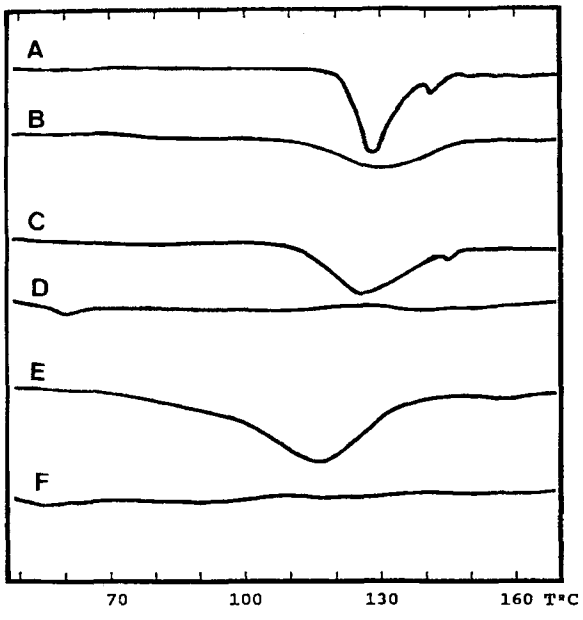

Fig. 3: DSC curves of physical mixtures of (A) 20% PVP, (C) 25% PVP, (E) 50% PVP and solid dispersions of (B) 20% PVP, (D) 25% PVP, (F) 50% PVP.

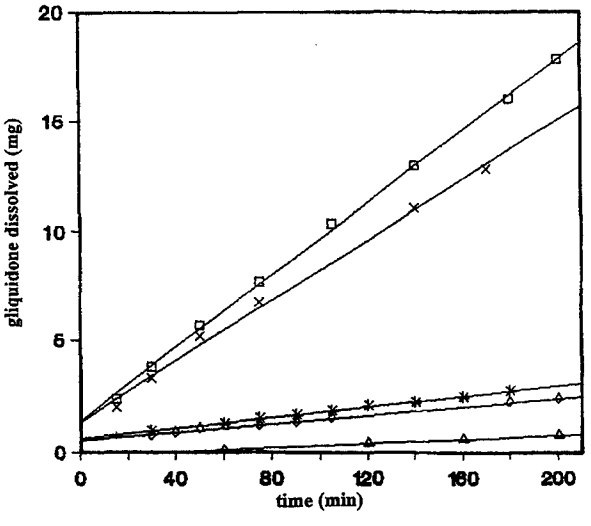

Fig. 4: Dissolution profiles of: (Δ) pure gliquidone, gliquidone-PVP K30 solid dispersion of (◊) 10% PVP, (*) 20% PVP, (x) 25% PVP and (□) 50% PVP

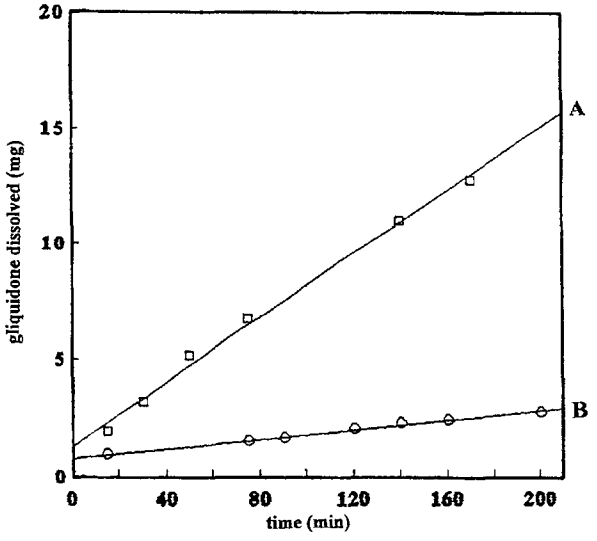

Fig. 5: Dissolution profiles of: (A) the gliquidone-PVP K30 solid dispersion of 25% PVP and (B) the physical mixture of 25% PVP.

Ageing studies

The dispersions containing 25, 30 and 50% of carrier were maintained at room temperature for 9 months. After storage, solid dispersions were observed by X-ray diffraction.

RESULTS AND DISCUSSION

The X-ray diffractograms for the pure gliquidone and the solid dispersions systems of 9:1, 4:1, 3:1 drug to polymer weight ratios are shown in Fig. 1. The peaks atributable to gliquidone crystals disappeared in the system containing 25% of PVP K30. Thus gliquidone is present in solid dispersions in a crystalline, partially crystalline or amorphous state depending on de PVP content.

Sharp diffraction peaks atributable to guiquidone were still apparent in the physical mixtures at the highest PVP K30 content (Fig. 2).

DSC thermograms of solid dispersions are depicted in Fig. 3 The disappearance of the drug peak from the dispersions containing 75% gliquidone indicates that all of the drug has interacted with the polymer and this excludes the presence of a crystalline drug in the dispersion.

Figures 4 to 6 show the amount of gliquidone released from constant surface area disks as a function of time. The dissolution of the drug dispersed in PVP

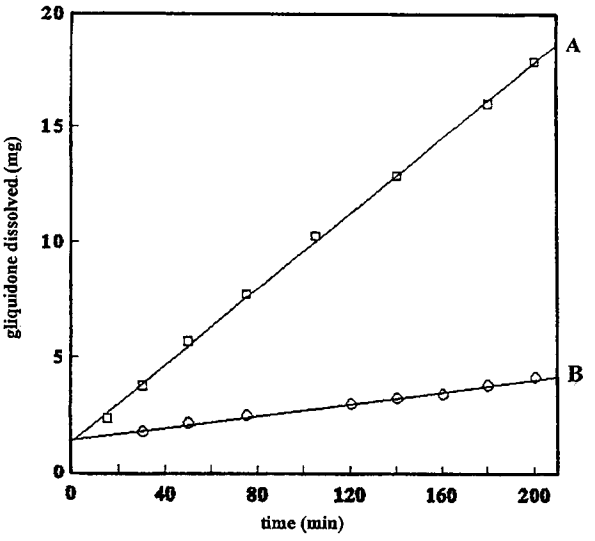

Fig. 6: Dissolution profiles of: (A) the gliquidone-PVP K30 solid dispersion of 50% PVP and (B) the physical misture of 50% PVP.

K 30 was faster than from the physical mixture of the same composition and both were faster than the dissolution of the pure drug.

The increase in the dissolution of the drug when physically mixed with PVP K30 is possibly due to a local solubilization action operating in the microenvironment or the diffusion layer inmediately adjacent to the drug particle in the early stages of the dissolution process as the polymer dissolves in a short time. Thus improving the wettability and hence the dissolution of the drug particle (11).

The higher dissolution of gliquidone from the solid dispersions when compared with that of gliquidone alone or physical mixture could be attributed to codissolution with the water-soluble PVP molecule and to a minor crystallinity of gliquidone dispersed in the system. The rate of drug dissolution from its binary system was greater when its ratio to PVP K30 was smaller. This could be due to the fact that as the proportion of the PVP is increased, the proportion of PVP unreacted with the drug is increased Therefore the PVP K30 coat thickness around the particles is increased. As the PVP is highly water soluble, it dissolves rapidly upon exposure to the aqueous medium thus improving the wettability and hence dissolution of the dispersed drug (12).

The dissolution date of solid dispersions containing 20 and 25% of PVP K30 were consistent with a physical

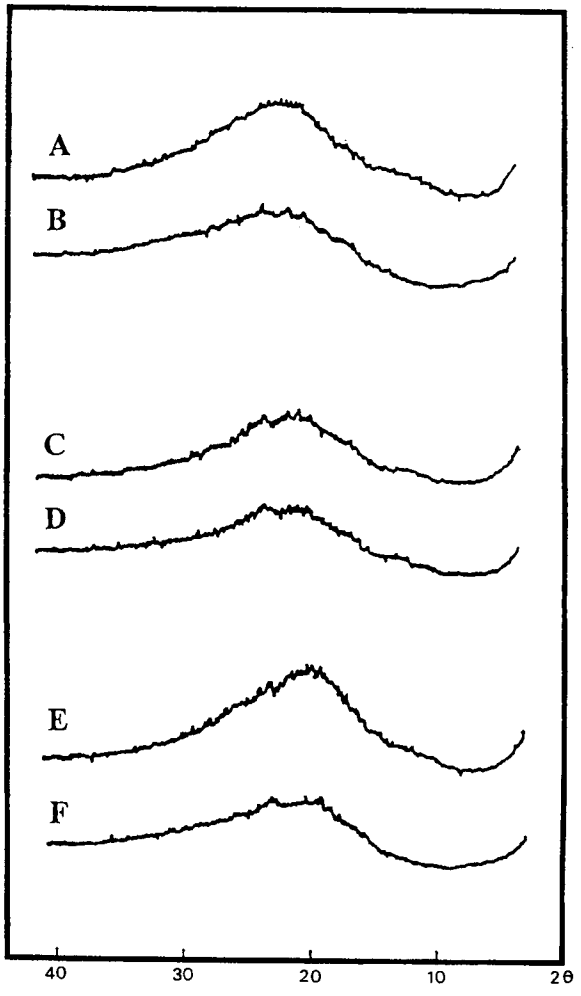

Fig. 7: X-ray diffraction patterns of the gliquidone-PVP K30 solid dispersions of (A) 50% PVP unaged, (B) 50% PVP after 9 months at room temperature, (C) 30% PVP unaged, (D) 30% PVP after 9 months at room temperature, (E) 25% PVP unaged and (F) 25% PVP after 9 months at room temperature.

model which takes account of the roles played by crystalline and amorphous gliquidone.

The plots obtained were linear suggesting the adherence of the dissolution process to the Noyes-Whitney equation. This indicates that dissolution of free and dispersed gliquidone is diffusion controlled. Thus, although dispersing gliquidone in PVP K30 increases its dissolution rate, the kinetics of the dissolution process remain unaltered.

Since solid dispersions are often suceptible to changes during storage, it was of interest to know if

ageing of the samples can affect the physical stability of gliquidone.

After storage of the gliquidone-PVP K30 solid dispersions at room temperature for 9 months, no difference in the X-ray diffraction pattern was found with respect to the fresh solid dispersions (Fig. 7).

The present study showed that marked increases in the dissolution rate of gliquidone can be obtained from its solid dispersion with PVP K30. As a result of the improvement of gliquidone dissolution rate, a better bioavailability can be expected. Moreover these solid dispersions were stable during storage showing the potencial utilization of these dispersed systems.

REFERENCES

1. Fujii M., Terai H., Mori T., Sawada Y. and Matsumoto M. (1992). The properties of solid dispersions of indometacin, ketoprofen and flurbiprofen in phosphatidylcholine. STP Pharm. Sci. 2, 186-192
2. Millares M.J., McGinty J.W. and Martin A. (1982). Combined water-soluble carriers for coprecipitates of tolbutamide. J. Pharm. Sci. 71, 302-304
3. Vila-Jato J.L. and Alonso M.J. (1986). Biopharmaceutical study of glybornuride-polyethylene glycol systems. Drug Dev. Ind. Pharm., 12, 701-711
4. Vila-Jato J.L., Blanco J. and Torres J.J. (1987). Biopharmaceutical aspects of the glibornuride-_-cyclodextrin inclusion compound. STP Pharma, 3,28-32
5. Vila-Jato J.L., Blanco J. and Torres J.J. (1988). Biopharmaceutical aspects of the tolbutamide-_-cyclodextrin inclusion compound. Il Farmaco. Ed. Pr., 43, 37-45
6. Uekama K., Matuso N., Hirayama F., Yamaguchi T., Imamura Y. and Ichibagase H. (1979). Inclusion complex of acetohexamid with _-cyclodextrin and its hipoglycemic activity in rabbit. Chem. Pharm. Bull. 27, 398-402
7. Geneidi A.S., Adel M.S., Shehata E. (1981). Enhanced dissolution of glibenclamide from glibenclamide-poloxamer and glibenclamide-PVP coprecipitates. Can. J. Pharm. Sci. 15, 81-84
8. Zingone G., Moneghini M., Rupena P., Vojnovic D. (1992). Characterization and dissolution study of solid dispersions of theophylline and indomethacin with PVP/VA copolymer. STP Pharma Sciences 2, 186-192
9. Chiou W., Riegelman S. (1971). Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. 60, 1281-1302
10. Wood J.H., Syarto J.E., Letterman H. (1965). Improved holder for intrinsic dissolution rate studies. J. Pharm. Sci. 54, 1068
11. Najib N.M., Suleiman M.S. (1989). Characterization of a diflunisal polyethylene glycol solid dispersion system. Int. J. Pharmac. 51, 225-232
12. Najib M., Suleiman M., Malakh A. (1986). Characteristics of the in vitro release of ibuprofen from polyvinylpyrrolidone solid dispersions. Int. J. Pharm. 22, 229-236