Drug Development and Industrial Pharmacy, 22(7), 731-734 (1996)

COMMUNICATIONS

Characterization of Glyburide–Polyethylene Glycol Solid Dispersions

G. V. Betageri* and K. R. Makarla†

Department of Pharmacal Sciences, School of Pharmacy, Auburn University, Auburn, Alabama 36849-5503

ABSTRACT

Glyburide (GLY) is an oral hypoglycemic agent that is poorly water soluble. Solid dispersions of polyethylene glycol (PEG) 4000, PEG 6000, and mixtures of PEG 4000 and 6000 were prepared by the melt-and-solvent method. Phase analysis was performed by x-ray powder diffraction and differential scanning calorimetry (DSC) to study the nature of interaction in the solid state. The x-ray diffraction pattern indicated that the dispersion had an amorphous nature as compared to the crystalline drug. The melting endothermal point of GLY was eliminated in the dispersions of DSC thermograms. The results showed that there was no chemical interaction between the drug and the polymer. Also, formation of solid solution is apparent from the DSC thermograms.

INTRODUCTION

In our previous study it was shown that the dispersion of plain as well as lyophilized solid dispersions of glyburide (GLY) with PEG resulted in an increase in the in vitro dissolution of GLY. This increase in dissolution was attributed to the solubilizing effect of PEG and also to an increase in the surface area of the drug upon lyophilization (1). The properties of the polymers used as carriers in solid dispersions are important in terms of dissolution and stability of the formulations (2,3). The structure of the polymers and the interaction between the drug and polymer are important characteristics and of particular interest. It is important to understand the interaction between drug and the polymer at the molecular level in order to predict the physicochemical properties of the solid dispersions.

The objective of this study was to characterize the interaction between glyburide (GLY), a poorly water soluble drug, and polyethylene glycol (PEG) 4000, PEG 6000, and mixture of PEG 4000 and 6000. We investigated the possible interaction between GLY and PEG using x-ray diffraction and differential scanning calorimetry (DSC).

*To whom correspondence should be directed.
†Present address: S.S.S./Pfeiffer Company, PO Box 4447, Atlanta, GA 30302.

MATERIALS AND METHODS

Materials

Glyburide was a gift from Upjohn Laboratories (Kalamazoo, MI); PEG 4000 and PEG 6000 were obtained from City Chemical Corp. (New York, NY). Chloroform (high-performance liquid chromatography—HPLC grade), dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride (anhydrous), cyclohexanol (reagent grade), and methanol (HPLC grade) were purchased from Fisher Scientific Company (Fairlawn, NJ). Absolute ethanol was obtained from Florida Distillers (FL).

Methods

Composition of Solid Dispersions

Single-component solid dispersions contained either 10 parts by weight of PEG 4000 or 8 parts by weight of PEG 6000 and 1 part of glyburide. Multicomponent solid dispersions contained 6 parts by weight of a PEG 4000 and PEG 6000 (1:1, by weight) mixture and 1 part of glyburide.

Preparation of Solid Dispersions

The Fusion (Melt) Method: Accurately weighed amounts of carrier(s) were placed in an aluminum pan on a hot plate and melted, with constant stirring, at a temperature of about 120°C. An accurately weighed amount of glyburide was incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture was heated until a clear, homogeneous melt was obtained. The pan was then removed from the hot plate and allowed to cool at room temperature.

The Solvent Method: Accurately weighed amounts of glyburide and carrier(s) were dissolved in minimum quantities of chloroform in a round-bottom flask. The solvent was removed using a rotary evaporator. The resultant solid dispersion was transferred to an aluminum pan and allowed to dry at room temperature.

X-Ray Diffraction Measurements

The x-ray powder diffraction studies were performed using an automatic powder diffractometer (Siemens Nicolet 12) equipped with a curved graphite monochromator and an automatic slit width adjuster using CuK_α radiation. Diffraction patterns were obtained by scanning at 0.05° intervals. Powdered samples of glyburide, PEG 4000, PEG 6000, and mixture of PEG 4000 and PEG 6000 were examined for comparison.

Differential Scanning Calorimetry Studies

Pure GLY, PEG 4000, PEG 6000, PEG mixture (PEG 4000:PEG 6000 1:1), and solid dispersions were examined using a differential scanning calorimeter (Dupont TA 2000). A heating rate of 10°C/min was employed from 0° to 250°C in an atmosphere of nitrogen with the sample kept in aluminum pans. Indium was used as the calibration standard. A DSC thermal scan curve was obtained, and the peak transition temperature and the enthalpy involved were recorded.

RESULTS AND DISCUSSION

X-ray Powder Diffraction

Figure 1 shows the x-ray diffractograms of pure GLY, PEG 4000, and solid dispersion. The peaks represent the reflections from the crystalline phase. The dif-

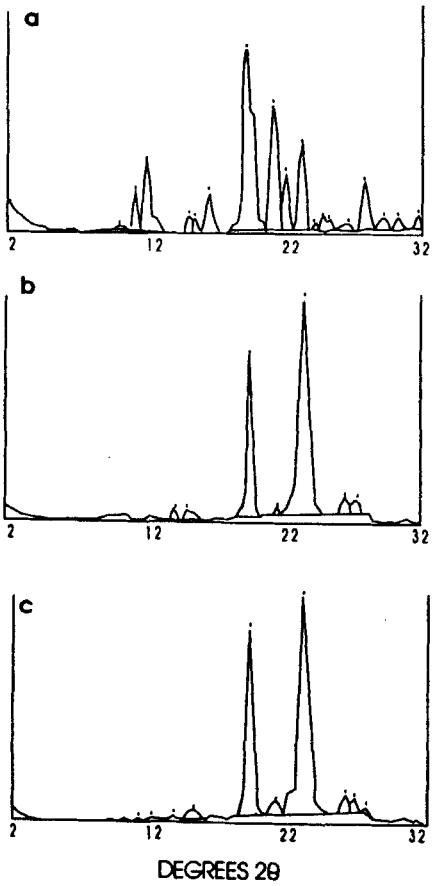

Figure 1. X-ray powder diffractograms of (a) pure glyburide; (b) pure PEG 4000; (c) solid dispersion of glyburide with PEG 4000.

fraction spectra of pure GLY showed that the drug is highly crystalline in nature, as indicated by numerous distinctive peaks in the x-ray diffractogram. PEG 4000 also exhibited crystallinity, as indicated by the two peaks of high intensity and some other peaks of lower intensity. Such an observation is expected from PEGs of this molecular weight. The x-ray diffraction spectra of solid dispersion showed the presence of peaks corresponding to PEG 4000. The lack of peaks characteristic of GLY indicated that GLY had not crystallized out in these solid dispersions, thus suggesting that an interstitial solid may have formed. This type of observation is very common when such carrier is mixed with small amounts of a low molecular weight drug. These results strongly suggest that GLY in the dispersions becomes less crystalline. Similar results were observed with PEG 6000 and solid dispersion prepared using 1 part drug and 8 parts of PEG.

Figure 2 contains diffractographs of GLY, PEG mixture (PEG 4000:PEG 6000 1:1), and solid dispersion prepared using 1 part drug and 6 parts of PEG mixture. The results are similar to solid dispersion prepared using PEG 4000. Similar results were reported for the nature of the solid dispersion of other drug–PEG systems (4–7). The lack of displacement of PEG peaks leads to the conclusion of formation of an interstitial solid solution during preparation of solid dispersion (8).

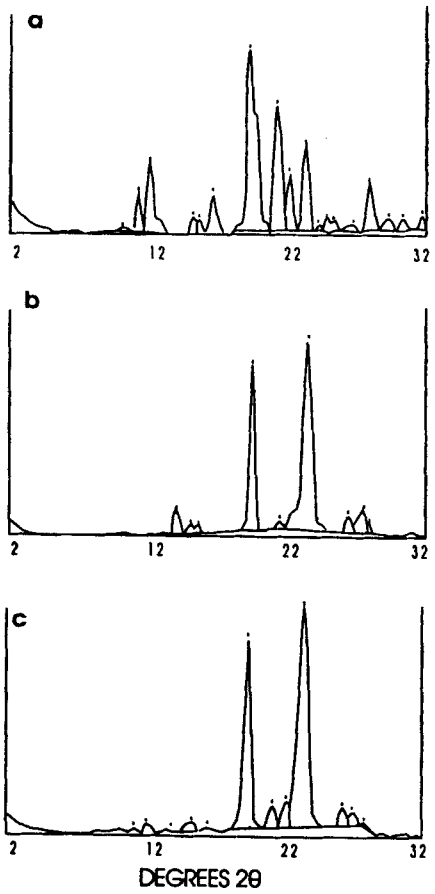

Figure 2. X-ray powder diffractograms of (a) pure glyburide; (b) pure PEG mixture (PEG 4000:PEG 6000 1:1); (c) solid dispersion of glyburide with PEG mixture.

Thermal Analysis

The thermograms of pure GLY, PEG 4000, and solid dispersion are shown in Fig. 3. The DSC curves of the pure products show a single fusion endotherm, with a melting point of 176.03°C for GLY and 59.78°C for PEG 4000. The peak at 61.4°C in the case of solid dispersion prepared by the melt method using 1 part of drug and 10 parts of polymer indicates the formation of solid solution.

Similar results were observed with solid dispersion prepared using 1 part of drug and 8 parts of PEG. Again the melting endothermal point of dispersion is close to that of PEG 6000, giving rise to the probability that a solid solution is formed during the process of solid dispersion preparation. However, in physical mixtures of similar drug-to-PEG composition, the peaks of drug as well as PEG existed, indicating no formation of solid solution.

Figure 4 shows the thermograms of dispersion prepared by the solvent method using 1 part of drug and 6 parts of PEG mixture (PEG 4000:PEG 6000 1:1) compared to GLY and PEG mixture. The doublet in the endothermal peak of the PEG mixture is due to the melting of the two PEGs at slightly different temperatures. However, the doublet was not observed with the solid dispersion prepared using PEG mixture. Thermogram for the solid dispersion showed the fusion endotherm of the polymer, with no change in the melting point. No chemical interaction between the drug and the polymer was evident. Formation of solid solution is apparent from the thermogram for this dispersion. Similar results were reported for solid dispersions prepared with piroxicam and fenofibrate using PEG (6,9).

In conclusion, solid-state solutions were obtained for solid dispersions containing 10 parts of PEG 4000, 8 parts of PEG 6000, and 6 parts of PEG mixture. The results obtained with x-ray diffraction and DSC did not indicate any chemical interaction between GLY and PEGs. Both the melt and the solvent methods resulted in the formation of solid solution. Solid-state binary

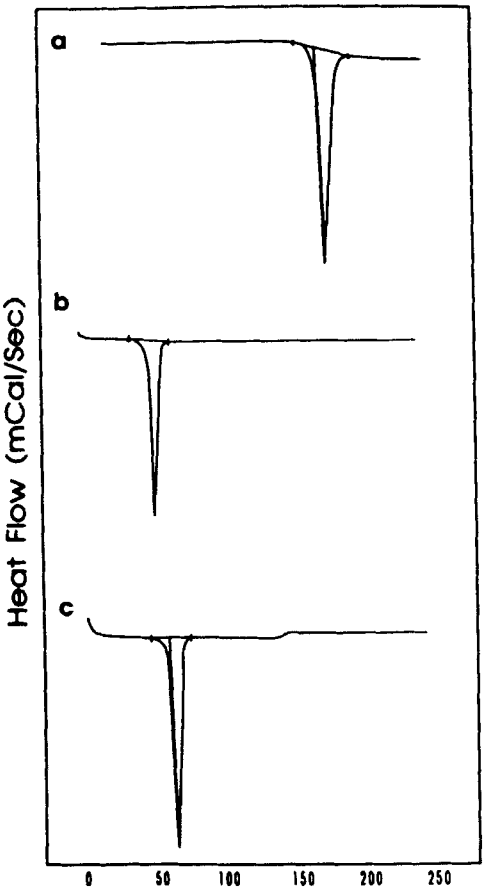

Figure 3. Differential scanning thermograms of (a) pure glyburide; (b) pure PEG 4000; (c) solid dispersion of glyburide with PEG 4000.

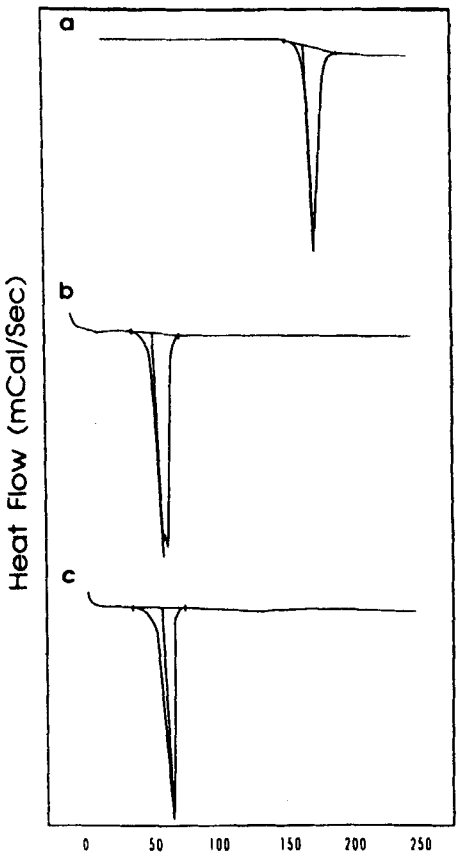

Figure 4. Differential scanning thermograms of (a) pure glyburide; (b) pure PEG mixture (PEG 4000:PEG 6000 1:1); (c) solid dispersion of glyburide with PEG mixture.

systems were obtained with solid dispersions containing at least 6 parts of PEGs and 1 part GLY.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Ben Hajek and Mrs. Peggy Mitchell, Agricultural Experiment Station, Auburn University, for their assistance in conducting x-ray diffraction and differential scanning calorimetry studies.

REFERENCES

1. G. V. Betageri and K. R. Makarla, Int. J. Pharm., 126, 155 (1995).
2. S. M. Chatham. STP Pharma. 3, 575 (1987).
3. W. L. Chiou and S. Riegelman, J. Pharm. Sci., 60, 1281 (1971).
4. W. R. Ravis and C. Chen, J. Pharm. Sci., 70, 1353 (1981).
5. N. M. Najib and M. S. Suleiman, Int. J. Pharm., 51, 225 (1989).
6. M. Fernandez, I. C. Rodriguez, M. V. Margarit, and A. Cerezo, Int. J. Pharm., 84, 197 (1992).
7. T. Save and P. Venkitachalam, Drug Dev. Ind. Pharm., 18, 1663 (1992).
8. R. Duclos, J. Grenet, J. M. Saiter, P. Besancon, and A. M. Orecchioni, Drug Dev. Ind. Pharm., 16, 255 (1990).
9. M. T. Sheu, C. M. Yeh, and T. D. Sokoloski, Int. J. Pharm., 103, 137 (1994).