Drug Development and Industrial Pharmacy, 23(12), 1167-1176 (1997)

RESEARCH PAPER

Carbamazepine and Polyethylene Glycol Solid Dispersions: Preparation, In Vitro Dissolution, and Characterization

D. H. Doshi[1] W. R. Ravis,[2] and G. V. Betageri[2,*]

[1]College of Pharmacy, Midwestern University, Downers Grove, Illinois 60515
[2]Department of Pharmacal Sciences, School of Pharmacy, Auburn University, Auburn, Alabama 36849-5503

ABSTRACT

The objective of this study was to prepare solid dispersions of carbamazepine (CBZ) using polyethylene glycol (PEG) 4000 and PEG 6000, measure the dissolution, and characterize using x-ray diffraction, DSC, and IR spectroscopy. Solid dispersions were prepared by either the melt or solvent methods. A comparison of dissolution profiles of the solid dispersions indicated dramatic increases in the rate and extent of CBZ dissolution from solid dispersions. The dissolution of physical mixtures provided evidence of the solubilizing effects of PEGs. Untreated CBZ exhibited 10.09 ± 2.92% dissolution in 10 min (D_{10}); whereas, a melt of PEG 6000 and CBZ at a ratio of 6:1 provided 36.49 ± 1.97% and a melt of PEG 4000 and CBZ at a ratio of 6:1 gave a D_{10} of 23.59 ± 1.45%. The rate and extent of dissolution of CBZ were significantly higher when blends of the PEGs were employed to prepare solid dispersion. The melt method provided significantly higher rate and extent of dissolution of CBZ than the solvent method. Also, the rate and extent of dissolution of CBZ were significantly greater when the solid dispersion was cooled at room temperature as opposed to with ice (faster). X-ray diffractometry revealed almost a complete loss of crystallinity of CBZ in solid dispersions. IR spectrometry indicated an increase in amorphocity of the PEGs after melting. IR spectra suggested that no complexation occurred between the PEGs and CBZ. Alterations in the crystallinity of the system were also supported by the DSC thermograms. Decreasing heats of fusion implied decrease in crystallinity, which would be expected to provide greater dissolution rates. Peak melt-

*To whom correspondence should be addressed.

ing temperatures obtained from the thermograms ruled out the possibility of the formation of a eutectic mixture. However, the formation of solid solution could also be a possible mechanism for the increase in dissolution.

INTRODUCTION

Carbamazepine (CBZ) is the drug of first choice for the relief of pain associated with trigeminal neuralgia. CBZ is white to off-white powder and practically insoluble in water. The gastrointestinal absorption of CBZ in humans is slow, unpredictable, and erratic (1). This neutral drug is highly lipophilic, and its absorption would be expected to be rapid if higher amounts of CBZ are dissolved in the gastrointestinal tract, suggesting that the rate-limiting step is dissolution in the overall absorption process (2,3). This would also provide consistent and predictable absorption. One way to achieve better absorption is to prepare solid dispersions of CBZ to increase the rate and extent of dissolution.

Solid dispersions were introduced in the early 1960s (4), and since then a variety of insoluble drugs have been formulated as solid dispersions (5–9). The term solid dispersion refers to the dispersion of one or more active ingredients in an inert matrix at solid state (10). The matrix is composed of higher molecular weight water-soluble polymer(s). Solid polyethylene glycols (PEGs) have been the polymers of choice because they are inert, nontoxic, and easily available. The type and amount of PEG and the method of preparation dictate the dissolution of a drug from solid dispersion (11–13). Solid-state changes taking place within the physical structure of the carrier and the drug are considered responsible for enhanced dissolution. Loss of crystallinity, formation of solid solution, eutectic mixture, or soluble complexes either alone or in combination increases the dissolution. Formulation variables such as the drug:polymer ratio, properties of the polymer, and technological variables such as cooling rates, melting temperatures, and type of solvent determine some of these solid-state structures.

Attempts to understand the mechanisms responsible for faster dissolution of drugs from such systems have been reported (13,14–16). Solid state physical changes within the polymer and the drug were indicated in almost all the cases. These changes include formation of a eutectic mixture, solid solution, soluble complexes, increased amorphocity, and monotectic systems. Normally, more than one of these changes determine the rate and extent of dissolution. X-ray diffractometry (17,18), differential scanning calorimetry (DSC) (11), and infrared spectroscopy (IR) (19) are routinely employed to study these systems. X-ray diffraction detects the changes in the crystallinity of the system; DSC registers thermal behavior of the system in terms of melting temperature and heat of fusion. IR spectra reveal complexation between the drug and the polymer and crystallographic changes.

The objective of this study was to prepare solid dispersions of CBZ using PEGs and optimize the abovementioned formulation variables to enhance the dissolution of CBZ. The present study characterized the CBZ-PEG 6000/4000 solid dispersion systems solidified at different cooling rates. X-ray diffraction, DSC, and IR were used to investigate the solid state physical structure of the CBZ–PEG solid dispersion system

MATERIALS AND METHODS

Materials

The following materials were used as received: carbamazepine, PEG 4000, PEG 6000 (Sigma Chemical Co., St. Louis, MO), potassium dibasic phosphate, sodium hydroxide, chloroform, acetonitrile (Fisher Scientific, Fairlawn NJ), and absolute alcohol (Florida Distillers Co., Lake Alfred, FL).

Methods

Composition of Solid Dispersions

The solid dispersions were composed of either 4 or 6 parts of PEG 4000 and/or PEG 6000 for every part of CBZ.

Preparation of Solid Dispersions

Melt Method

The required amounts of PEG were melted in an aluminum dish on a hot plate. CBZ was added to this molten mass; heating and stirring was continued until a

homogenous liquid was obtained. The liquid was cooled either (*a*) at room temperature (slower cooling), (*b*) on an ice bath (faster cooling), or (*c*) by blowing ambient air.

Solvent Method

The PEG was dissolved in absolute alcohol and CBZ was dissolved in chloroform. The solutions were mixed followed by evaporation of the solvent in a water bath.

The dispersions prepared by either of the above methods were stored in a desiccator for hardening. The dispersions were passed through U.S. standard sieve #60.

Physical mixtures were prepared by mechanically mixing the appropriate amounts of PEG and CBZ. Prior to being mixed, the components were passed through a U.S. standard sieve #60.

Stability of CBZ During Preparation of Solid Dispersions

Assessment of degradation of CBZ during preparation of solid dispersions was conducted by a stability indicating high-performance liquid chromatographic (HPLC) assay method. Chromatograms of CBZ in solid dispersions showed identical retention time and area under the curve, indicating no degradation of CBZ during preparation of solid dispersions.

Nonequilibrium Solubility Studies

Dissolution studies were conducted in a 1000-ml, three-necked, round-bottom flask containing 700 ml of simulated intestinal fluid, USP (without enzymes) maintained at 37 ± 0.5°C and stirred at 75 rpm by means of a sleeve stirrer at a depth of 2 cm from the bottom of the flask. Powders containing 100 mg of CBZ were introduced into the flask; seventeen 3-ml samples (with medium replaced each time) were withdrawn over a period of 6 hr. The samples were filtered through 0.45 μm filters and diluted with an equal amount of absolute alcohol to prevent possible precipitation of CBZ. The samples were assayed for CBZ concentrations by UV spectrophotometry at 285 nm. All the products were studied at least in duplicate.

X-Ray Diffraction

Solid dispersion, CBZ physical mixture, and a mixture of pure PEGs were subjected to x-ray diffraction in a Siemens Nicolet I2 diffractometer using CuKα radiation. Diffractographs were compared for the presence or absence of peaks and peak intensities.

Infrared Spectroscopy

The spectra of pure CBZ, pure PEGs, solid dispersions, and the corresponding physical mixtures were recorded with a Perkin-Elmer Series 1600 FT-IR spectroscope. The samples were prepared as potassium bromide discs. The spectra were compared for migration or loss of typical CBZ and PEG bands.

Differential Scanning Calorimetry

A DuPont DSC Cell Base was used with samples ranging in weight from 5.4 to 6.7 mg and a heating rate of 10°C per min from 0 to 250°C. Peak transition temperature and the heat of melting were determined by means of a Thermal Analyst 2000 (TA Instruments). Indium was used as a reference. The peak transition temperatures and heat of fusion of the pure components, solid dispersions, and corresponding physical mixtures were compared.

Statistical Comparisons

The dissolution profiles were compared using two parameters: D_{10}, the percent of CBZ dissolved at 10 min, and D_{360}, the percent of CBZ dissolved at 360 min. The comparisons were made among the methods and carriers by ANOVA and least squares difference at $p < 0.05$.

RESULTS AND DISCUSSION

Nonequilibrium Solubility Studies

Fig. 1 compares dissolution profiles of PEG 4000:CBZ (6:1) dispersions and PEG 6000:CBZ (6:1) dispersions. Preparations containing 6 parts of PEG 4000 and 6 parts of PEG 6000 displayed D_{10} of 23.59 ± 1.45%, and 36.49 ± 1.97%, respectively. This indicates that PEG 6000 is a better carrier than PEG 4000. Preparations containing 4 parts of PEG 6000 or PEG 4000 support this observation. Preparations composed of 4 parts of PEG 6000 exhibit a 45% higher D_{10} than the preparations containing 4 parts of PEG 4000. PEG 6000 products gave higher D_{360} than corresponding PEG 4000 products.

A comparison of dispersions containing different amounts of the same PEG shows that the higher the

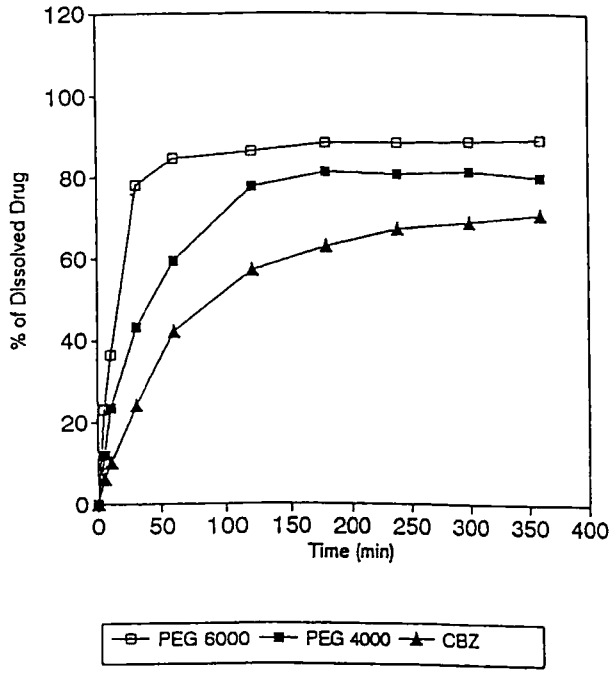

Figure 1. Dissolution profiles of pure carbamzepine (CBZ) and from CBZ:PEG 4000 and CBZ:PEG 6000 prepared by melt method (ice-cooled) at 37°C in phosphate buffer (pH 7.4).

amount of PEGs, the higher the D_{10} values (Fig. 2). Dispersions containing the higher amount of PEG 6000 exhibit 17% higher D_{10}. However, no significant differences in D_{360} are seen and also the amount of PEG 4000 had no effect on the dissolution profiles.

Dissolution profiles of dispersions containing a mixture of PEG 4000 and PEG 6000 are given in Fig. 3. A 1:1 mixture of PEG 4000 and PEG 6000 was tested with different concentrations of CBZ. Preparation containing 6 parts of this mixture shows a D_{10} of 43.63 ± 3.5% as opposed 36.49 ± 1.97% and 23.59 ± 1.45% for PEG 6000 and PEG 4000 dispersions, respectively. This preparation also displays complete release of CBZ compared to 88% release for PEG 6000. Multi-PEG preparations also supported the earlier observation that the higher the amount of PEGs, the faster is the dissolution.

The results presented here demonstrate that the use of PEG 4000 and PEG 6000 as solid dispersion carriers increase the rate and extent of dissolution of CBZ. However, the magnitude of enhancement depends upon the molecular weight of the PEGs, concentration of CBZ in the dispersion, method of preparation, and rate of cooling in the melt method.

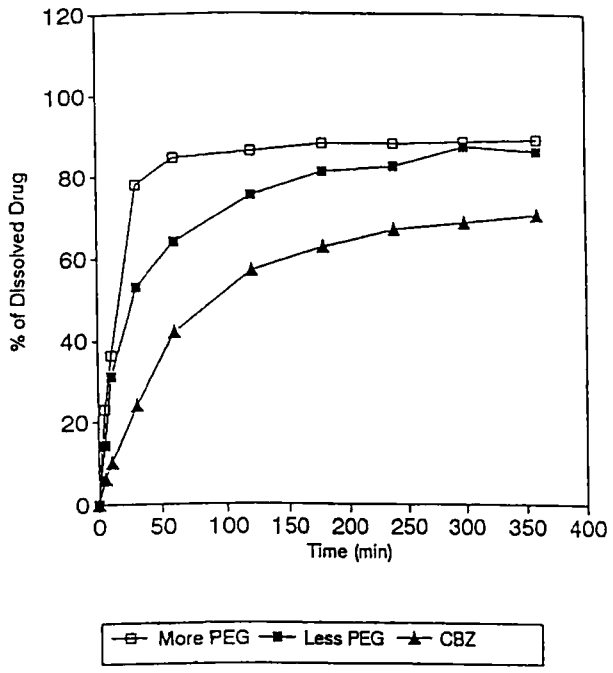

Figure 2. Dissolution profiles of pure carbamazepine (CBZ) and from CBZ:PEG 6000 (1:4 and 1:6) solid dispersions prepared by melt method (ice-cooled) at 37°C in phosphate buffer (pH 7.4).

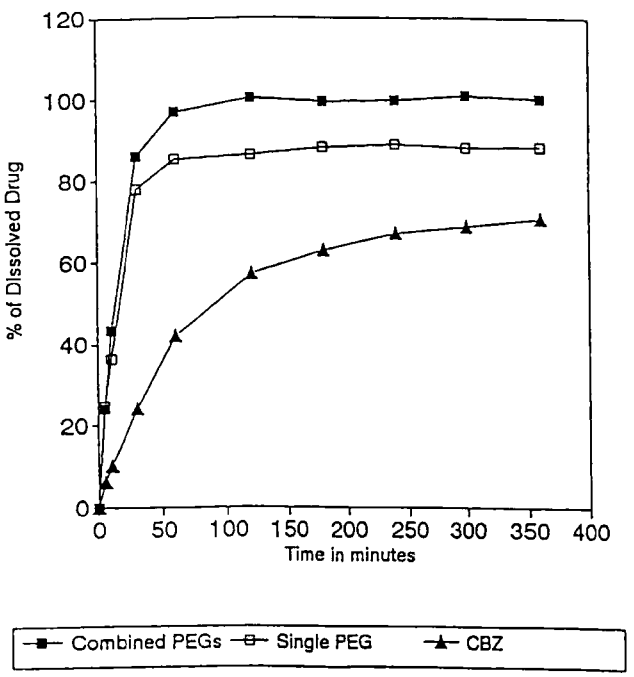

Figure 3. Dissolution profiles of pure carbamazepine (CBZ) and from CBZ:PEG 6000 and CBZ:PEG mixture (PEG 4000 and PEG 6000, 1:1) solid dispersions prepared by melt method (ice-cooled) at 37°C in phosphate buffer (pH 7.4).

Physical Mixtures

Tables 1 and 2 compare dissolution profiles of PEG solid dispersion and corresponding physical mixture. All physical mixtures show higher dissolution than pure untreated CBZ. However, solid dispersions display faster and often higher dissolution than the corresponding physical mixtures. The physical mixtures demonstrated the solubilizing effect of PEGs. PEG 6000 enhanced the rate and extent of dissolution better than PEG 4000.

Effect of Method of Preparation on Dissolution

Fig. 4 compares dissolution profiles of dispersions of identical compositions prepared using different methods. The solid dispersions prepared by the melt method using single and multi-PEG dispersions show faster and higher dissolution than those prepared by the solvent method. The dispersions prepared by the melt method containing a blend of PEGs show a 30% higher D_{10} and complete dissolution when compared to the solid dispersion prepared by solvent method.

Effect of Cooling Rate on Dissolution

Fig. 5 compares dissolution of dispersions subjected to different cooling rates. The melt solidified at room temperature exhibits strikingly higher D_{10} (86.25 ± 2.22%): a twofold increase over the melt cooled using ice. Differences in cooling rates do not have any effect on the extent of dissolution. However, the rates of dissolution are significantly different.

PEGs improved the rate and extent of dissolution of CBZ irrespective of the composition and method of preparation. In general, the greater the amount of PEG, the larger the improvement. Solid dispersions containing combined PEGs had faster and higher dissolution

Table 1

Effects of Formulation Variables on Dissolution of Pure Carbamazepine, Physical Mixture (PM), and Solid Dispersions (SD) Prepared by Melt Method and Ice-Cooled at 10 min (D_{10}) and 360 min (D_{360})

Carrier	Drug:Carrier Ratio	Type of Preparation	D_{10} CBZ Dissolved (%) Mean ± SD	D_{360} CBZ Dissolved Mean ± SD
PEG 4000	1:4	PM	16.45 ± 2.05	73.40 ± 1.91
	1:4	SD	21.39 ± 2.12	75.56 ± 1.64
	1:6	PM	20.38 ± 1.31	77.46 ± 2.40
	1:6	SD	23.59 ± 1.45	80.47 ± 0.54
PEG 6000	1:4	PM	22.34 ± 3.43	73.70 ± 0.10
	1:4	SD	31.20 ± 1.89	86.12 ± 2.33
	1:6	PM	28.13 ± 4.81	85.46 ± 2.12
	1:6	SD	36.49 ± 1.97	88.34 ± 0.36
CBZ		Pure drug	10.09 ± 2.92	69.55 ± 1.82

Table 2

Effects of CBZ:Polyethylene Glycol Mixture (PEG 4000 and PEG 6000) Ratio on Dissolution of Physical Mixture (PM) and Solid Dispersions (SD) Prepared by Melt Method and Ice-Cooled

CBZ:PEG Ratio	Type of Preparation	D_{10} CBZ Dissolved (%) Mean ± SD	D_{360} CBZ Dissolved (%) Mean ± SD
1:4	PM	19.20 ± 1.49	88.13 ± 1.48
1:4	SD	26.37 ± 3.99	91.10 ± 0.81
1:6	PM	34.15 ± 2.09	95.00 ± 4.08
1:6	SD	43.61 ± 3.50	100.33 ± 0.80
CBZ	Pure drug	10.09 ± 2.92	69.55 ± 1.82

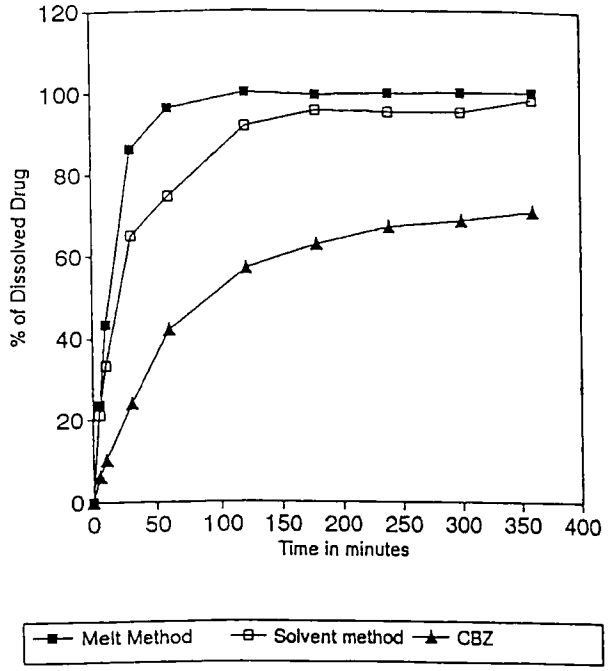

Figure 4. Dissolution profiles of pure carbamazepine (CBZ) and from CBZ:PEG 6000 solid dispersions prepared by melt and solvent method at 37°C in phosphate buffer (pH 7.4).

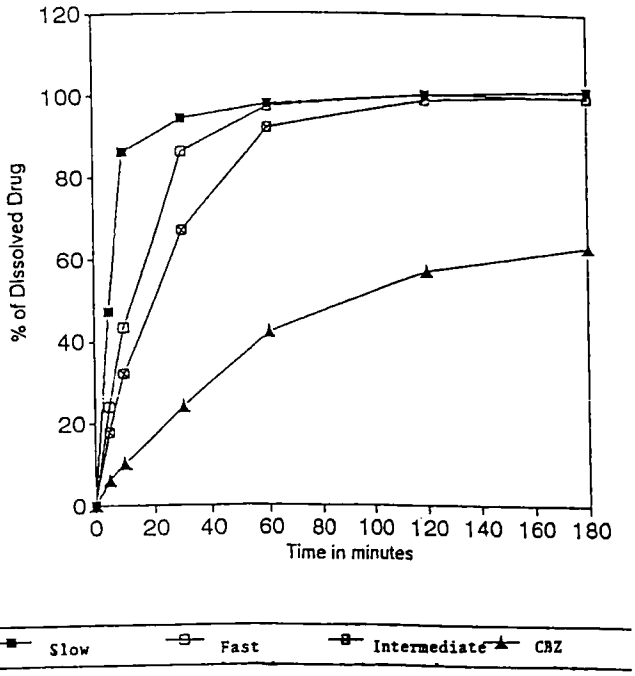

Figure 5. Dissolution profiles of pure carbamazepine (CBZ) and from CBZ:PEG 6000 solid dispersions prepared by melt method and subjected to different cooling rates at 37°C in phosphate buffer (pH 7.4).

than single PEG preparations. Complete dissolution of CBZ could be obtained from a blend of the PEGs. The melt method appeared superior to the solvent method. The rates of cooling affected the dissolution rates. The slow-cooled melt provided faster dissolution than the fast-cooled melt. Mechanisms other than solubilization play an important role in improving dissolution from the solid dispersions.

The increased dissolution of CBZ from the physical mixtures demonstrates solubilizing effects of the PEGs. However, solid dispersions display significantly higher and faster dissolution than corresponding physical mixtures. Such behavior indicates that mechanisms other than solubilization play a major role in improving dissolution of CBZ. Alterations in the solid-state structures of the polymer and drug during fabrication of the system are responsible for increased dissolution. These structural changes include: (*a*) Formation of solid solution; (*b*) formation of a eutectic mixture, in which the components of a homogenous liquid crystallize as distinct phases upon solidification. In this case, the drug is present as fine particles; (*c*) formation of a soluble complex between the drug and the carrier; and (*d*) formation of amorphous drug and carrier particles or loss of crystallinity of drug and polymer.

Thermal history of the components dictates the crystallinity of the system. Fusion of PEGs decreases their degree of crystallinity. Also, the high viscosity provided by the PEGs retards aggregation and agglomeration of drug particles. For most solid dispersions more than one of the above factors is probably responsible for dissolution enhancement. Physical analyses of the structure of solid dispersions would help to determine these mechanisms.

X-Ray Diffraction

The x-ray diffraction pattern of CBZ (Fig. 6a) revealed high crystallinity of the drug with major diffraction peaks at a 2Q angle of 13°, 15.8°, and 23.7°. Figs. 6b and 6c are the diffraction patterns of untreated PEG 6000 and PEG 4000, respectively, with two major peaks at 2Q angle of approximately 19.1° and 23.3° for both PEGs which are highly crystalline. The crystallinity of untreated PEG 6000 and PEG 4000 has been estimated to be 92% and 91%, respectively (20).

The diffraction patterns of the solid dispersions are shown in Figs. 6d, 6e, and 6f, which represent slow, intermediate, and fast cooling rates, respectively. All of

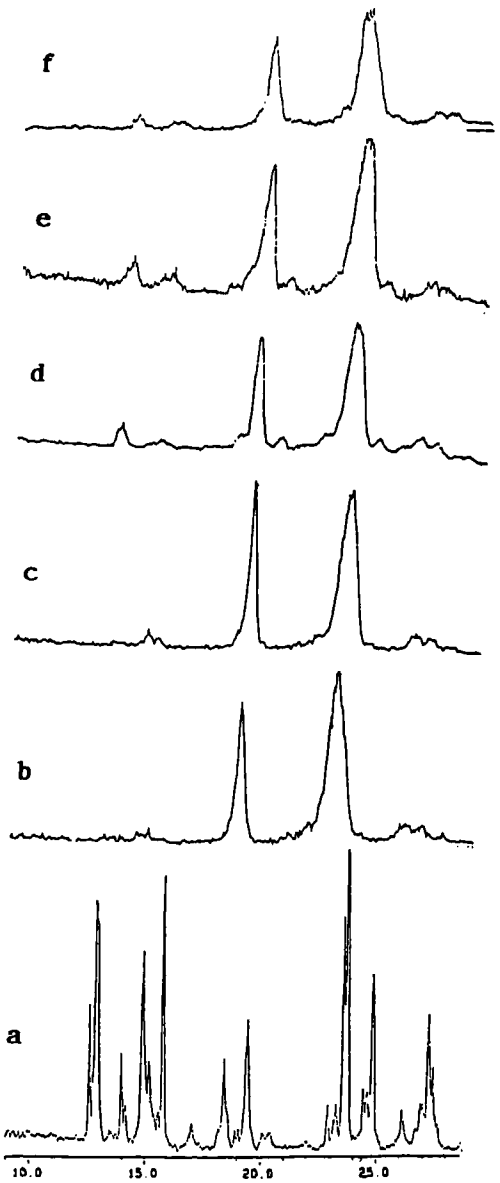

Figure 6. X-ray powder diffractograms of a) pure carbamazepine; b) pure PEG 6000; c) pure PEG 4000; d) solid dispersion (CBZ:PEG 6000; slow cooled); e) solid dispersion (CBZ:PEG 6000; intermediate cooled); f) Solid dispersion (CBZ:PEG 6000; fast cooled).

these patterns are nearly identical to that of PEG 6000 and PEG 4000. The two major peaks in 6d, 6e, and 6f in the region of 19.2° and 23.2° represent the PEGs. The CBZ peak at 15.8° is completely missing in the slow-cooled and fast-cooled dispersions; whereas, the intermediate-cooled dispersion shows a small and broad hump instead of a sharp peak. The CBZ peak at 13° disappears in the fast-cooled dispersion and the slow-cooled and intermediate-cooled dispersion exhibit a small and broad hump instead of a sharp peak. The wide PEG peak at 23.2° makes it very difficult to detect the CBZ at 23.7°. This CBZ peak may be absent or it may have been superimposed by the PEG peak. It can be concluded that during preparation of solid dispersion, the crystallinity of CBZ was at least partially lost. However, the degree to which the crystallinity was lost depended on the rate of cooling. The loss of crystallinity as noted by the intensity of the peaks was the greatest for the fast-cooled (ice-cooled) dispersion, followed by the slow-cooled dispersion. However, the rank-order established on the basis of dissolution rates was different.

Infrared Spectroscopy

The IR spectra of CBZ, blend of PEGs, and physical mixture are shown in Figs. 7a, 7b, and 7c, respectively. The IR spectra of the PEGs is well established (21). The bands occurring in the region of 1110 cm^{-1} and 1450 cm^{-1} as singlets and at 960 cm^{-1} as a doublet are typical of PEG 6000 and PEG 4000. The IR spectrum of the physical mixture shows all of the CBZ and PEG bands; 1450 cm^{-1} as singlets and at 960 cm^{-1} as a doublet are typical of PEG 6000 and PEG 4000. The IR spectrum of the physical mixture shows all of the CBZ and PEG bands.

The IR spectra of slow, intermediate, and fast cooled solid dispersions are represented in Figs. 7d, 7e, and 7f, respectively. Fusion introduces minor, but detectable, changes in either the width or position of some of the bands in the spectra of PEGs. The band at 1966 cm^{-1} for untreated PEGs shifted to 1961 cm^{-1} upon fusion and the band at 1651 cm^{-1} disappeared. Ford and coworkers showed that the amorphocity of PEGs increased following fusion and recrystallization (19). The spectra of CBZ and all solid dispersions showed minor differences. The CBZ band at 1679 cm^{-1}, 1594 cm^{-1}, and 1385 cm^{-1} for untreated CBZ shifted to 1691 cm^{-1}, 1603 cm^{-1}, and 1397 cm^{-1}, respectively, in the solid dispersions. The intensity of most of the PEG bands in slow-cooled dispersions (Fig. 7d) was lower than those in the fast-cooled dispersions (Fig. 7f). This suggests that the degree of crystallinity of PEGs may be higher in fast-cooled dispersions. The presence of all CBZ peaks would indicate no complexation between CBZ and PEGs.

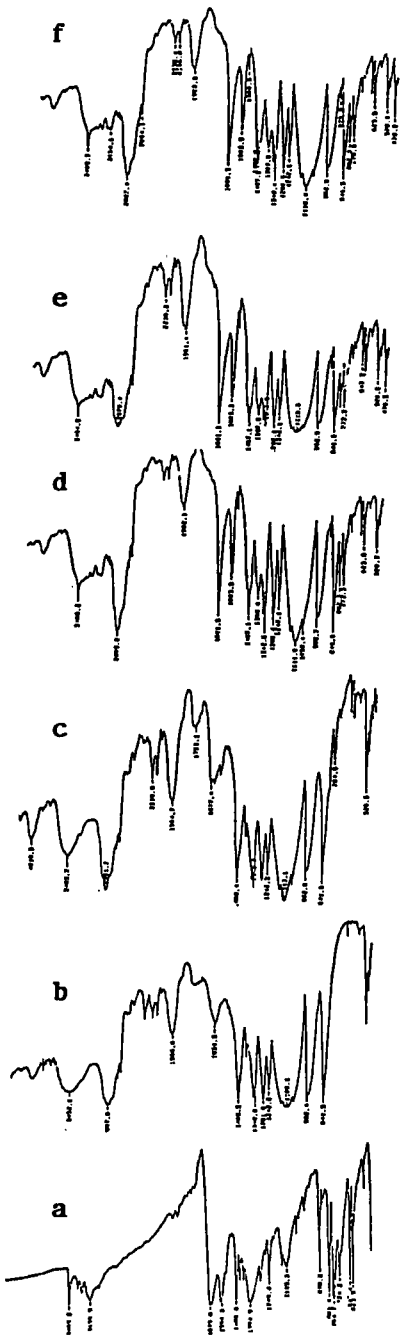

Figure 7. Infrared spectra of a) pure carbamazepine; b) pure PEG 6000; c) pure PEG 4000; d) solid dispersion (CBZ:PEG 6000; slow cooled); e) solid dispersion (CBZ:PEG 6000; intermediate cooled); f) solid dispersion (CBZ:PEG 6000; fast cooled).

Differential Scanning Calorimetry

DSC thermograms of pure untreated CBZ and untreated PEGs are shown in Figs. 8a and 8b, respectively. The major CBZ endotherm at 191°C represents the CBZ melting point. The endothermic depression at 162°C may represent the loss of water of hydration from CBZ. The endothermic doublet in Fig. 3b illustrates the melting of the two PEGs (63.23°C is the melting point of PEG 6000 and 59.55°C is the melting point of PEG 4000).

Fig. 8c is a thermogram of the physical mixture. The endothermic doublet in the region of 60°C corresponds to the melting of PEG 6000 and PEG 4000. A very small endothermic depression in the region of 190°C corresponds to the melting of CBZ. The amount of CBZ in the physical mixture was only 14% w/w. Also, a part of CBZ probably dissolves in the molten PEGs. Both of these contributed to a small endothermic peak for CBZ in the physical mixture.

Figs. 8d, 8e, 8f represent thermograms for slow, intermediate, and fast cooled solid dispersions. All thermograms show only one endothermic peak at temperatures of 61.4, 61.6, and 60.5°C for slow-, intermediate-, and fast-cooled dispersions, respectively. The lowest melting point component in the dispersions is PEG 4000 at 59.55°C. Since no preparation melted at a temperature lower than 59.55°C, the possibility of formation of a eutectic mixture can be ruled out.

The DSC data for the CBZ dispersions support the crystallinity changes noted through the x-ray and infrared characterizations. The heat of fusion of untreated PEGs was 190.8 J/g. This accounts for approximately 90% crystallinity based on the theoretical heats of fusion of the 100% crystalline polymer of 214 J/g. Among the three rates of cooling, the heat of fusion increased from slow cooled (126 J/g) to fast cooled (150.4 J/g) to intermediate cooled (177.6 J/g). The heat of fusion of the dispersions was below that of the pure polymers. The extent of decrease for each dispersion differed despite their identical composition. Thus, the differences in the heats of fusion are due to different cooling rates and may explain the differences in the dissolution. The lower the heat of fusion the more amorphous the product. Based on this, the three solid dispersions, when arranged in the decreasing order of amorphocity, gives the following rank order: slow, fast, and intermediate cooled. This ranking was parallel to the ranking obtained from the dissolution rates.

In summary, x-ray diffraction revealed almost complete loss of crystallinity of CBZ. IR spectra provided evidence for increased amorphocity of PEG 6000 and

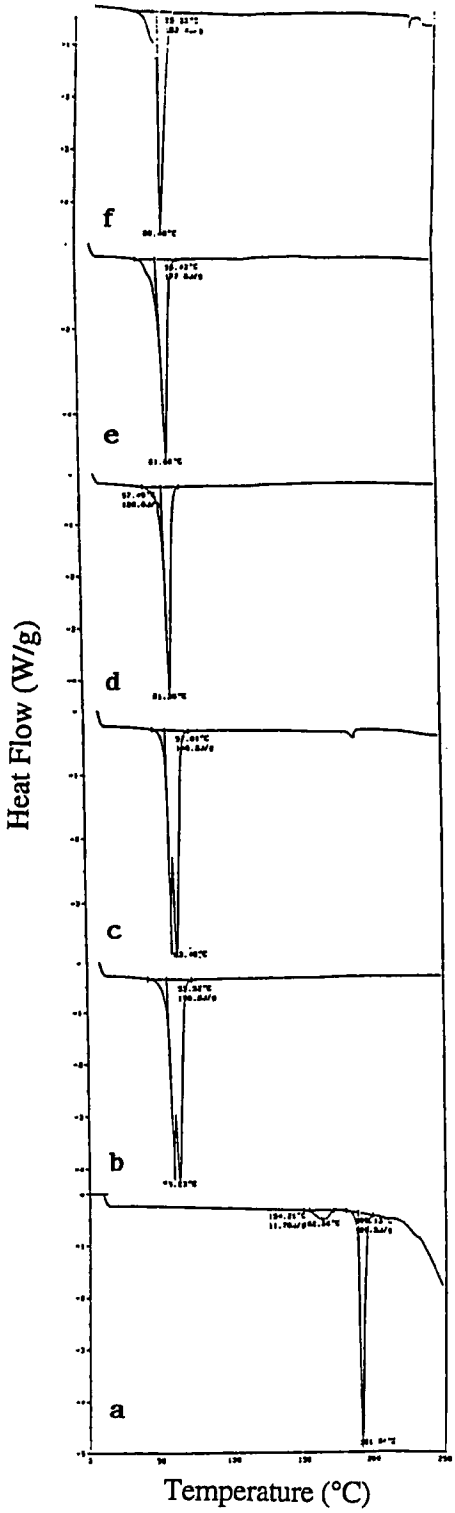

Figure 8. DSC thermograms of a) pure carbamazepine; b) pure PEG 6000; c) pure PEG 4000; d) solid dispersion (CBZ:PEG 6000; slow cooled); e) solid dispersion (CBZ:PEG 6000; intermediate cooled); f) Solid dispersion (CBZ:PEG 6000; fast cooled).

PEG 4000 following fusion and recrystallizations and a lack of complexation between the PEGs and CBZ. DSC thermograms supported the proposed crystalline changes. Heats of fusion revealed that crystallinity was a function of cooling rates. Thermograms confirmed the ranking of the preparations based on dissolution rates. DSC data also ruled out the formation of eutectic mixture. Alteration in crystallinity of PEGs and CBZ dictates that the dissolution profiles and formation of solid solution is also possible.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Ben Hajek and Mrs. Peggy Mitchell, Agricultural Experiment Station, Auburn University for assistance in x-ray diffraction and differential scanning calorimetry studies, and Mr. Shridhar Andurkar, Dept. of Pharmacal Sciences, Auburn University, for his technical assistance in infrared spectroscopy.

REFERENCES

1. P. L. Moreselli, Carbamazepine: absorption, distribution, and excretion, in *Antiepileptic Drugs* (R. H. Levy, F. E. Dreifuss, R. H. Matson, B. S. Meldrun, and J. K. Penry, eds.), Raven Press, New York, 1989 pp. 473–490.
2. D. Bloomer., L. L. Dupus, D. MacGregor, and S. J. Soldin, Clin. Pharm., 6, 646 (1987).
3. P. J. Neuvoenn, Int. J. Clin Pharmacol. Ther. Toxicol., 53, 691 (1991).
4. K. Sekiguchi and N. Obi, Chem. Pharm. Bull. 9, 861 (1961).
5. B. R. Hajratwala, Aust. U. of Pharm. Sci., NS3, 101 (1974).
6. W. R. Ravis and C. Chen, J. Pharm. Sci., 70, 1353 (1981).
7. A. M. Rabasco, J. M. Gines, M. Fernanadez-Arevalo, and M. A. Holgado, Int. J. Pharm. 67, 201 (1991).
8. M. T. Sheu, C. M. Yeh, and T. D Sokoloski, Int. J. Pharm. 103, 137 (1994).
9. G V. Betageri and K. R. Makarla, Int. J. Pharm. 126, 155 (1995).
10. W. L. Chiou and S. Riegelman, J. Pharm. Sci., 60, 281 (1971).
11. J. L. Ford, Drug Dev. Ind. Pharm., 13, 1741 (1987).
12. Y. Chiba, N. Kohri, K. Iseki, and K. Miyazaki, Chem. Pharm. Bull., 3439, 2158 (1991).
13. E. Sjokvist and C. Nystorm, Int. J. Pharm. 54, 51 (1988).
14. O. I. Corrigan, Drug Dev. Ind. Pharm., 11, 697 (1985).
15. O. I. Corrigan, Drug Dev. Ind. Pharm., 12, 1777 (1986).

16. D. Q. M. Craig, Drug Dev. Ind. Pharm., 16, 2501 (1990).
17. W. L. Chiou and S. Riegelman, J. Pharm. Sci., 66, 989 (1977).
18. J. Kreuter, Solid dispersion and solid solution, in *Topics in Pharmaceutical Sciences* (P. Speiser, ed.), Elsevier Science Publishers, B.V., 1983, pp. 350–370.
19. J. L. Ford, A. F. Stewart, and J. L. Dubois, Int. J. Pharm., 28, 11 (1986).
20. R. H. Beaumont, B. Clegg, G. Gee, J. B. M. Herbert D. J. Marks, R. C. Roberts, and D. Sims, Polymer, 7, 401 (1966).
21. H. Matsuura and T. Miyazawa, J. Polym. Sci., 27, 1735 (1969).