DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(5), 671-689 (1989)

EFFERVESCENT SOLID DISPERSIONS OF PREDNISONE, GRISEOFULVIN AND PRIMIDONE

Sushama R. Desai, M.S., Loyd V. Allen*, Jr., Ph.D., Robert B. Greenwood+, Ph.D., M. L. Stiles, M.S., and Donald Parker, Ph.D.

* The University of Oklahoma
Health Sciences Center
College of Pharmacy
1110 N. Stonewall Avenue
Oklahoma City, Oklahoma 73190

ABSTRACT

Various prednisone (Pd), griseofulvin (Gr), and primidone (Pr) solid dispersions made by the fusion method utilizing different carriers and drug:carrier ratios were evaluated. Citric acid (CA), succinic acid (SA) and tartaric acid (TA) were employed in various ratios with sodium bicarbonate (SB) as carriers for the respective drugs.

CA:SB was the most effective carrier for releasing Pd and Pr, and SA:SB was found to be the best carrier for Gr. Results showed that there was an increase in in dissolution rate as the proportion of SB increased in the carrier system.

* Correspondence
+ Present address is Campbell University School of Pharmacy, P.O. Box 1090, Buies Creek, NC 27506

DSC thermograms revealed no complex formation between the drugs and the carriers indicating the increased dissolution rates were not due to complexation. The increase in dissolution rate is not attributed to bulk changes in the pH of the dissolution fluid as no significant change in pH was observed.

This study shows that effervescent solid dispersions may be useful for increasing the dissolution rates of poorly water soluble drugs.

INTRODUCTION

Previous studies have demonstrated that solid dispersions can improve the dissolution rate and bioavailability of some poorly water soluble drugs like Pd, Gr, Pr, digoxin, and other drugs. Allen et al conducted a series of studies on dissolution rates of corticosteroids contained in solid dispersions[1]. The increase in dissolution rate was attributed to the presence of the corticosteroid in a very fine state of subdivision.

The literature shows that dispersions with certain carriers may be superior for a specific drug in releasing the drug into solution[2]. CA and SA have proven to be excellent carriers for the preparation of selected solid dispersions. CA, SA, and TA react with SB to give an effervescent mixture and by combining poorly soluble drugs with organic acids, one should obtain an effervescent solid dispersion which may increase the dissolution and absorption rates of selected poorly soluble drugs.

The objectives of this study were to (1) increase the dissolution rate of the poorly soluble drugs Pd, Pr, and Gr using solid dispersions containing organic acids combined with SB, (2) optimize the carrier acid:SB and drug ratio to yield the highest dissolution rate, and

(3) study the compatibility between the drugs and the different carriers.

MATERIALS AND METHODS

Preparation of the Solid Dispersions

The following chemicals were used in the preparation of the solid dispersions: Pd (Sigma Chemicals, Lot No. P-6254), Gr (Sigma Chemicals, Lot No. G-4753), Pr (Ayerst Laboratories Inc., Lot No. B-388144), SB (Mallinckrodt Inc., Lot No. KJCB), CA (Fisher Scientific, Lot No. 741721), SA (Fisher Scientific, Lot No. 732818), and TA (Mallinckrodt Inc., Lot No. KJRD).

The equipment used for the experiment consisted of a Cahn 26 Electrobalance, Mettler H80 analytical balance, Vanderkamp 600 Dissolution Testing Apparatus, Perkin Elmer DSC-2 Differential Scanning Calorimeter (DSC), Perkin Elmer Model 3600 Data Station, Manostat Cassette Pump, Perkin Elmer Lambda 3 Spectrophotometer, Orion Ionanalyzer 901, and Data General M600 Minicomputer.

Solid dispersions with four different drug to carrier ratios (Table 1) for each of the three drugs were prepared for the dissolution studies as previously reported [3].

For obtaining thermograms, the solid dispersions were prepared in the following ratios of drug:acid and drug:SB: 100:0, 90:10, 75:25, 60:40, 45:55, 30:70, 15:85, 10:90, 0:100.

Dissolution Rate Determinations

Dissolution rate determinations were carried out using a semiautomated USP XXI Dissolution Apparatus I. An appropriate amount of dispersion containing 5 mg of Pd, 5 mg of Gr, or 40 mg of Pr, was weighed using an electronic balance, placed in the dissolution basket, and lowered into the dissolution vessel containing 1 liter of deaerated water maintained at 25°C. The baskets

were rotated at 100 rpm and the peristaltic pump started. Samples were continuously propelled through an in-line filter, analyzed at 0, 5, 10, 15, 20, 25, and 30 minutes and the data recorded. The percent drug dissolved from the solid disperison was compared with drug dissolved from an equal amount of the plain, untreated drug. Solid dispersions were prepared in triplicate for each formulation and dissolution data obtained on each batch in triplicate.

Compatibility Study

Compatibility of drug and carrier was studied using differential scanning calorimetry. One mg of the finely powdered dispersions was weighed and encapsulated in flat aluminum pans. Thermograms and heats of fusion (ΔH) were obtained (using the TADS DSC Standard Program) by heating the dispersions and individual ingredients at 40°K per per minute.

pH Study

Solid dispersions containing different drugs and carriers in different ratios were added to the dissolution media and the pH of the media recorded at the end of 30 minutes.

Data Handling

Means and standard deviations were calculated from the dissolution data and mean % drug dissolved was plotted against time. The time for 50% (T50) and 75% (T75) of the drug dissolved were determined from the plots and the various T50 and T75 values were compared and examined by analysis of variance.

The dissolution rate constants were obtained by plotting the successive increments in the cumulative percent dissolved-time data semi-logarithmically against time. The slope of the resulting line was equal to the dissolution rate constant and was obtained using the MINITAB statistical program.

TABLE 1

Quantities of Drug, Carrier Acid, and Sodium Bicarbonate Used to Prepare the Solid Dispersions

Dispersion Designation	Drug	Carrier		Carrier		Carrier	
		Sodium Bicarbonate	Citric Acid	Sodium Bicarbonate	Succinic Bicarbonate	Sodium Bicarbonate	Tartaric Acid
	Prednisone						
I	2%	0%	98%	0%	98%	0%	98%
II		2%	96%	2%	96%	0%	96%
III		4%	94%	4%	94%	4%	94%
IV		8%	90%	8%	90%	8%	90%
	Griseofulvin						
I	2%	0%	98%	0%	98%	0%	98%
II		2%	96%	2%	96%	2%	96%
III		4%	94%	4%	94%	4%	94%
IV		8%	90%	8%	90%	8%	90%
	Primidone						
I	16%	0%	84%	0%	84%	0%	84%
II		2%	82%	2%	82%	2%	82%
III		4%	80%	4%	80%	4%	80%
IV		8%	76%	8%	76%	8%	76%

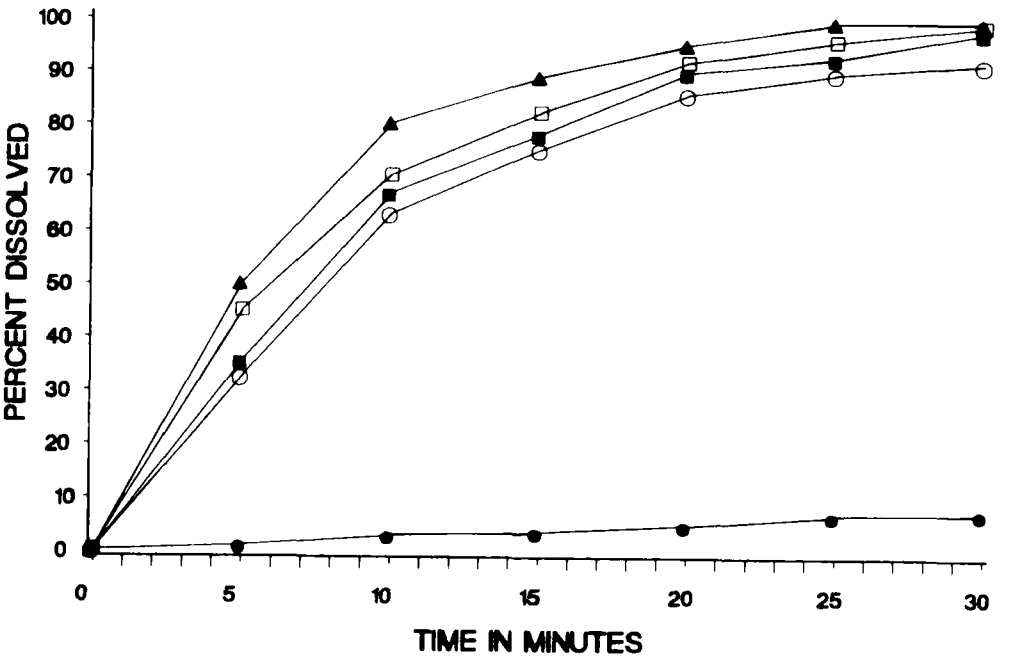

FIGURE 1

Dissolution profiles of prednisone in citric acid: sodium bicarbonate; O = pure prednisone, O = I, ■ = II, □= III, ▲ = IV.

RESULTS AND DISCUSSION

Dispersion System Formation

The dispersions of Pd, Gr, and Pr with CA as carrier were soft, sticky, and hygroscopic on preparation. Upon storage for 48 hours in a dessicator, they became hard and brittle and were easy to pulverize. The dispersions of Pd, Gr, and Pr with SA as carrier were hygroscopic and required storage in a dessicator for 24 hours. The dispersions of Pd, Gr, and Pr with TA as the carrier acid were easy to manipulate and had good flow properties.

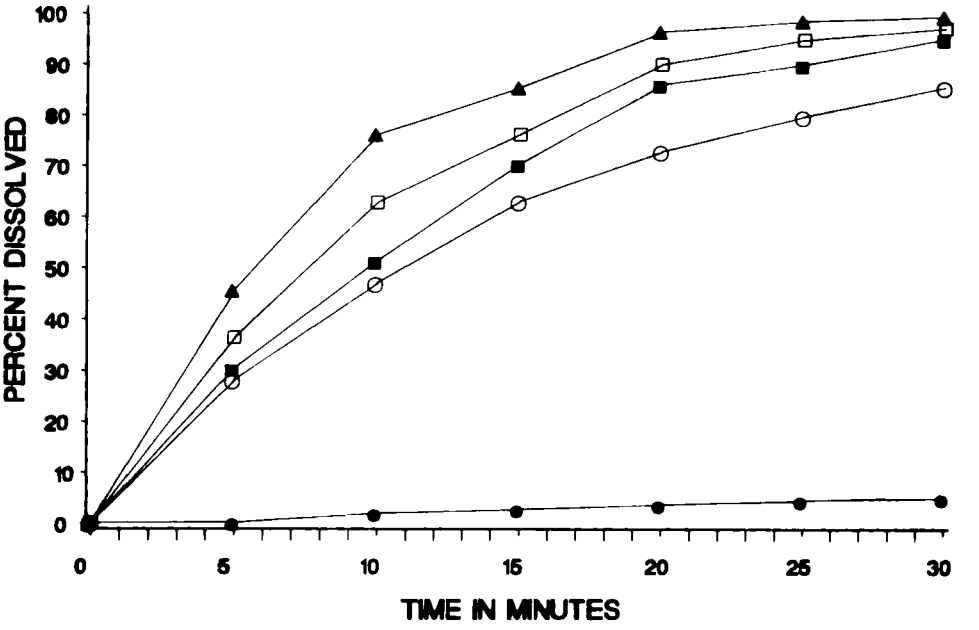

FIGURE 2

Dissolution profiles of griseofulvin in citric acid: sodium bicarbonate; O = pure griseofulvin, O = I, ■ = II, □ = III, ▲ = IV.

Dissolution Rates of Pd, Gr, and Pr in Different Carriers

Examples of dissolution profiles of solid dispersions of the drugs and carriers are shown in Figures 1-3. The T50 and T75 values are shown in Table 2 and the calculated dissolution rate constants shown in Table 3.

DSC Thermograms

DSC thermograms are shown in Figures 4-6. The heats of fusion were obtained and plotted against mole fraction of the different carrier acids and are shown in Figures 7-10.

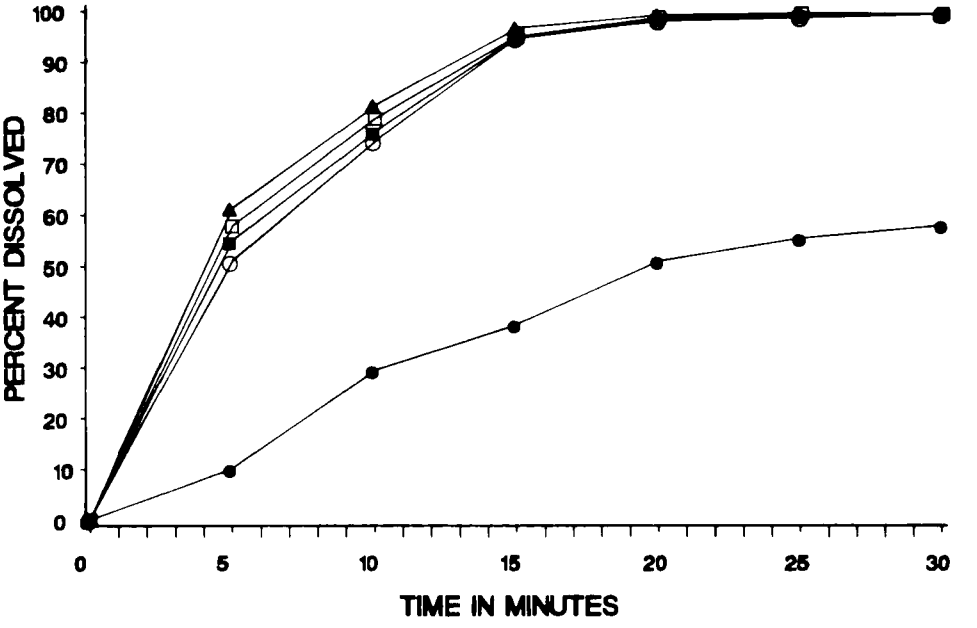

FIGURE 3

Dissolution profiles of primidone in citric acid: sodium bicarbonate; O = pure primidone, O = I, □ = II, ■ = II, = III, ▲ = IV.

pH Study

The pH values of the dissolution medium after adding the various solid dispersions are listed in Table 4.

Prednisone

In the Pd:CA:SB systems prepared by the fusion method, the 2:90:8 ratio of Pd:CA:SB produced the lowest T50 value.

Systems containing larger amounts of SB have enhanced dissolution rates compared to systems containing less SB.

It is evident from the dissolution rate constants of the various solid dispersions that dispersions of

TABLE 2

Time for 50 and 75 Percent Dissolution

	I		II		III		IV	
	Time (Minutes)							
	50%	75%	50%	75%	50%	75%	50%	75%
Prednisone								
Citric Acid	8.0	16.0	7.5	15.0	6.5	13.0	5.0	10.0
Succinic Acid	10.5	24.0	9.0	20.5	8.0	19.0	7.5	16.0
Tartaric Acid	16.5	26.0	14.0	24.0	13.0	22.5	11.5	18.0
Griseofulvin								
Citric Acid	14.0	25.5	10.5	22.5	9.0	21.0	7.5	21.0
Succinic Acid	12.0	22.5	10.0	17.5	8.0	15.5	6.0	10.5
Tartaric Acid	16.5	>30	12.0	29.0	10.5	26.0	8.5	22.5
Primidone								
Citric Acid	5.0	12.0	4.5	11.0	4.2	10.0	9.0	4.0
Succinic Acid	13.0	20.0	8.5	18.5	8.0	16.5	7.5	15.0
Tartaric Acid	19.0	29.0	14.0	20.8	10.0	21.0	8.0	19.0

TABLE 3

Dissolution Rate Constants (Min^{-1})

	Dispersion Designation			
	I	II	III	IV
Prednisone				
Citric Acid	.103	.127	.128	.157
Succinic Acid	.064	.067	.080	.093
Tartaric Acid	.023	.057	.064	.084
Griseofulvin				
Citric Acid	.057	.068	.074	.082
Succinic Acid	.066	.108	.123	.186
Tartaric Acid	.049	.053	.053	.067
Primidone				
Citric Acid	.239	.255	.256	.278
Succinic Acid	.052	.076	.080	.086
Tartaric Acid	.050	.073	.074	.076

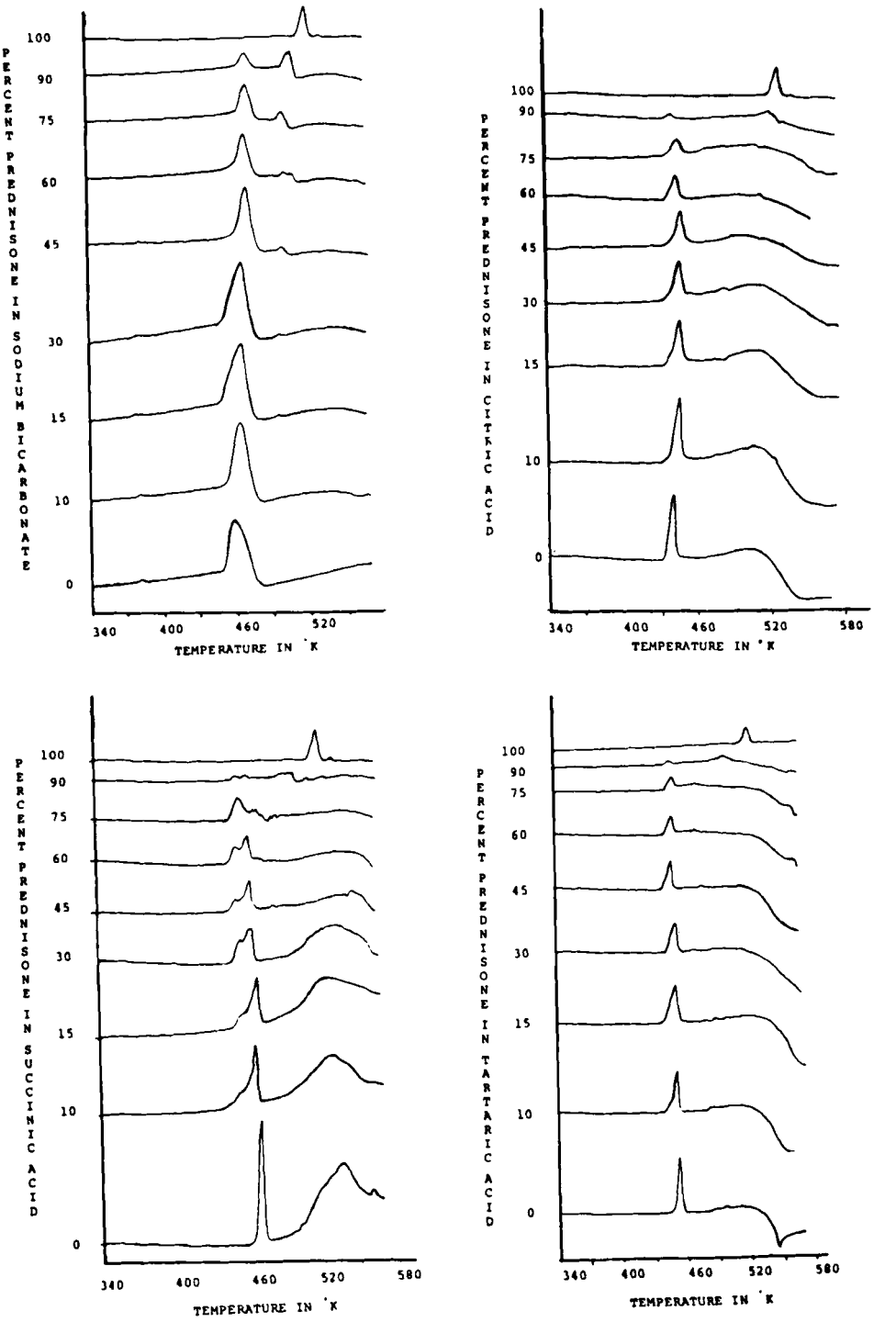

FIGURE 4

Thermograms of prednisone in different carriers

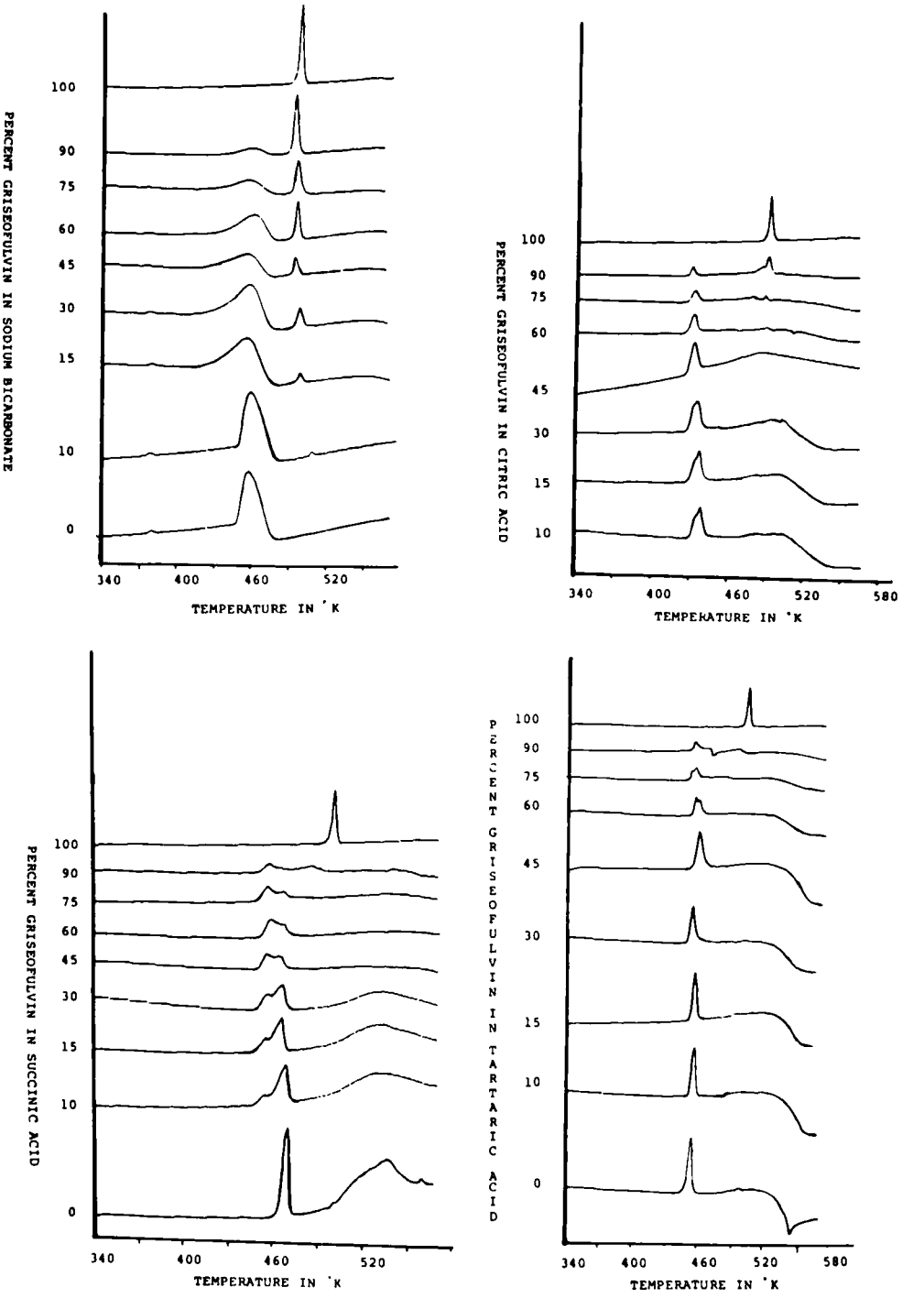

FIGURE 5

Therr ,grams of griseofulvin in different carriers.

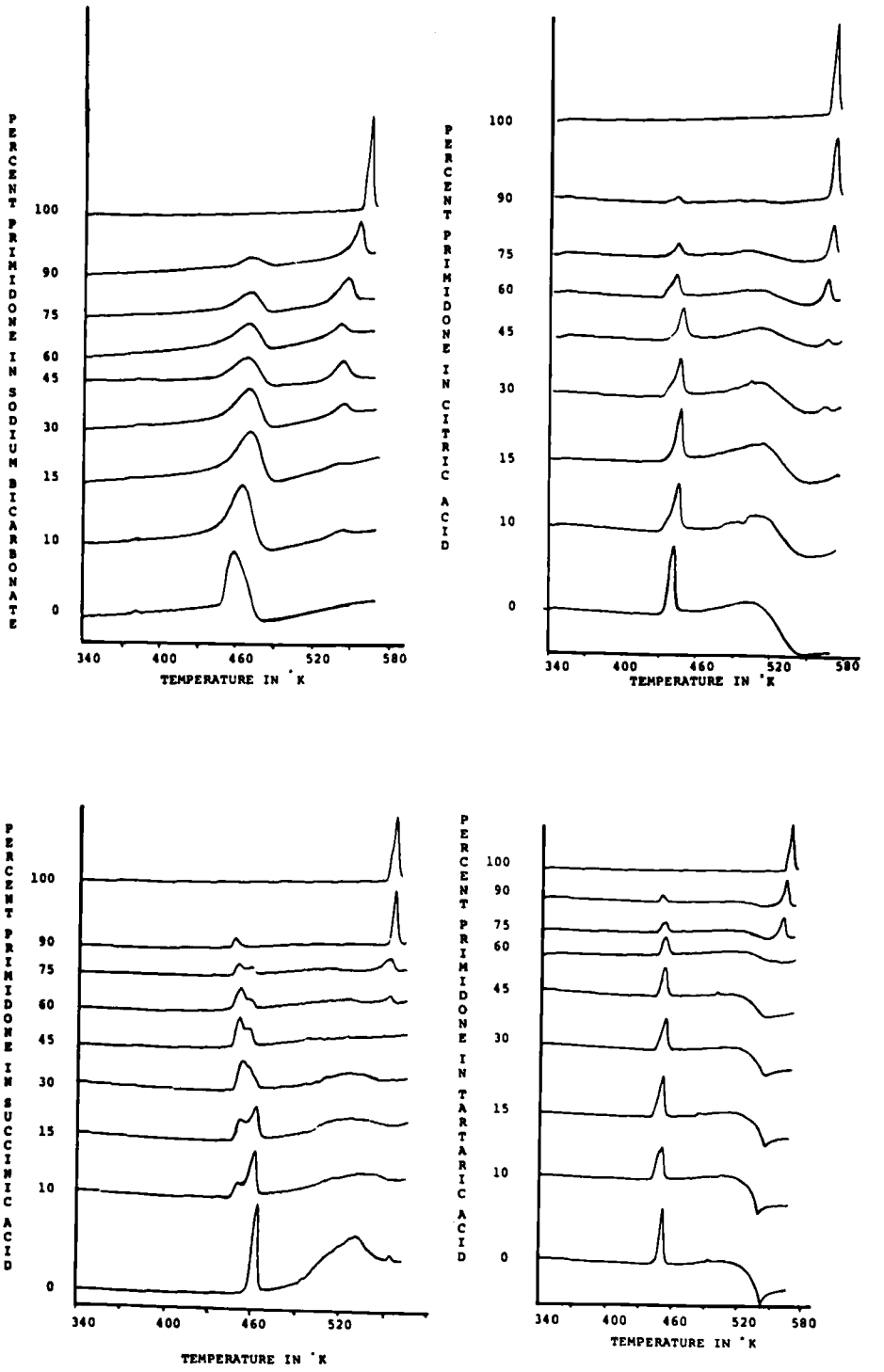

FIGURE 6

Thermograms of primidone in different carriers.

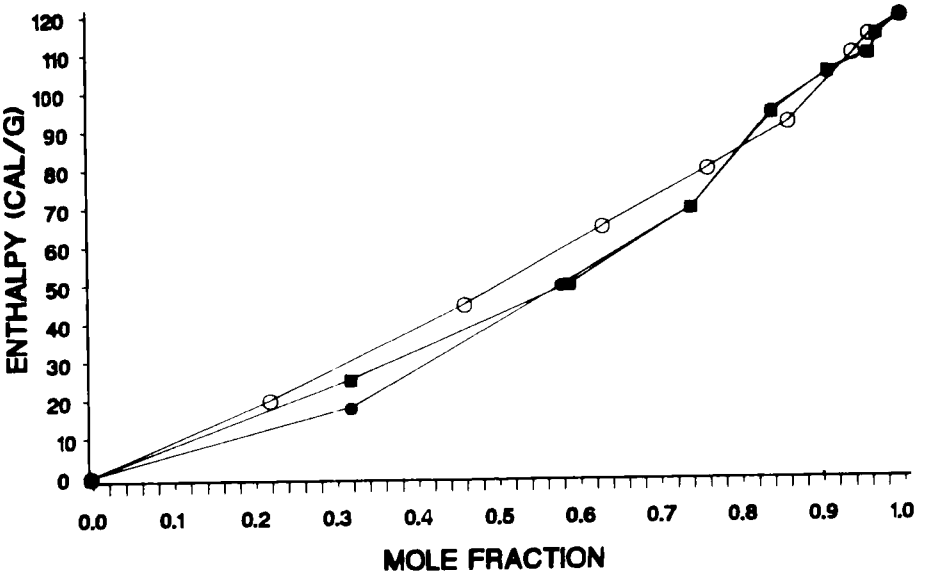

FIGURE 7

Enthalpy changes in drug:citric acid mixtures as a function of citric acid composition; O = prednisone, O = griseofulvin, ■ = primidone.

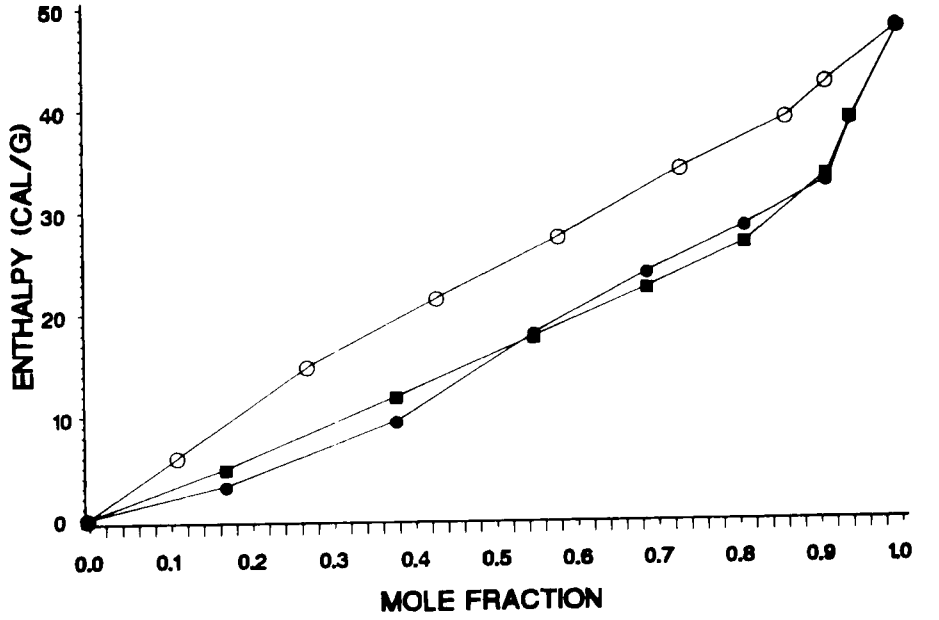

FIGURE 8

Enthalpy changes in drug:succinic acid mixture as a function of succinic acid composition; O = prednisone, O = griseofulvin, ■ = primidone.

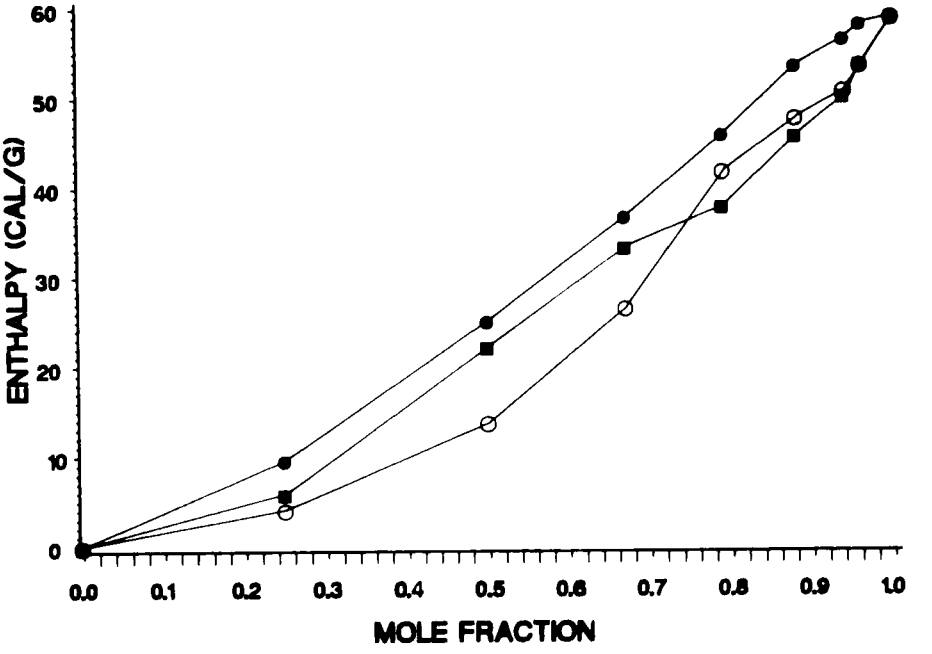

FIGURE 9

Enthalpy changes in drug:tartaric acid mixtures as a function of tartaric acid composition; O = prednisone, O = griseofulvin, ■ = primidone.

Pd:CA:SB have enhanced dissolution rates as compared to the dissolution rates of dispersions of Pd combined with SA and TA. Pd has been reported to form a glass with CA which, along with the presence of SB, appears to increase the rate of release of Pd from the solid dispersion.

Griseofulvin

In the solid dispersions containing Gr:CA:SB in the ratio of 2:90:8, the most rapid T50 value and the highest dissolution rate constant were produced.

It is evident from the dissolution rate constants and the T50 values of various dispersions of Gr in SA

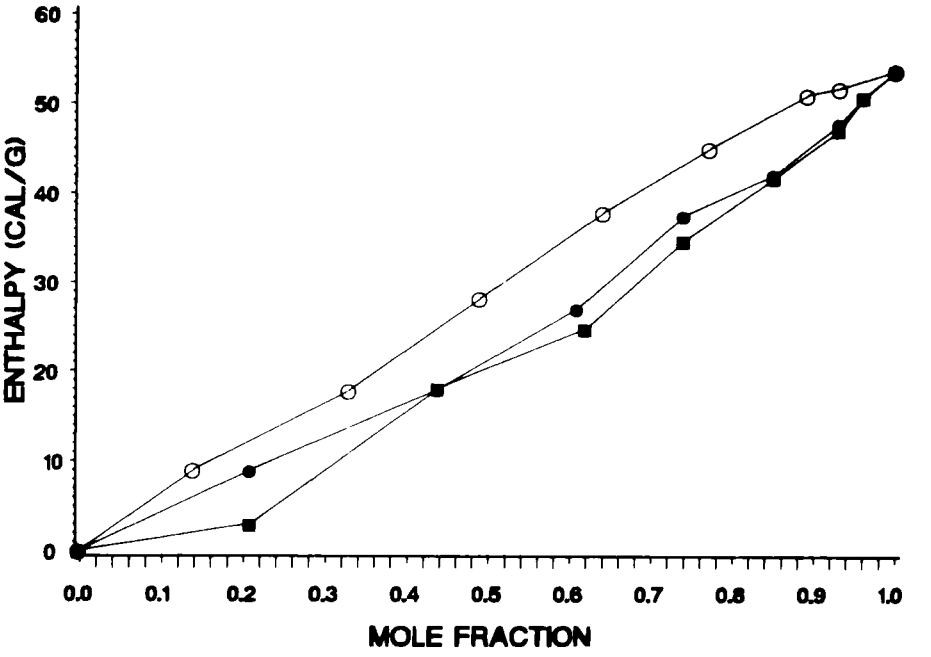

FIGURE 10

Enthalpy changes in drug:sodium bicarbonate mixtures as a function of sodium bicarbonate composition; O = prednisone, O = griseofulvin, ■ = primidone.

or TA and SB that an increase in the amount of SB in the dispersion results in an increase in its dissolution rate.

Gr has been reported to form a eutectic with SA[4], which, along with the presence of effervescence, increases the rate of release of Gr from the solid dispersion, and this is consistent with our results.

Primidone

In the Pr:CA:SB systems the 16:76:8 ratio produced the lowest T50 value. The T50 values decrease (the dissolution rate increases) with an increase in the amount of SB.

TABLE 4
pH of Dissolution Media
After Adding the Dispersions

Mg of Drug	Mg of NaHCO3	Mg of Carrier Acid	Citric Acid	Succinic Acid	Tartaric Acid
			Citric Acid		
Prednisone					
5	5	190	3.370	3.630	3.285
5	0	190	3.247	3.686	3.312
5	10	185	3.402	3.643	3.292
5	0	185	3.319	3.710	3.325
5	20	175	3.472	3.650	3.300
5	0	175	3.310	3.813	3.340
Griseofulvin					
5	5	190	3.365	3.626	3.280
5	0	190	3.245	3.680	3.310
5	10	185	3.400	3.643	3.290
5	0	185	3.315	3.709	3.319
5	20	175	3.470	3.644	3.300
5	0	175	3.305	3.810	3.339
Primidone					
40	5	155	3.396	3.508	3.294
40	0	155	3.344	3.564	3.308
40	10	150	3.448	3.657	3.303
40	0	150	3.398	3.740	3.325
40	20	140	3.561	3.684	3.315
40	0	140	3.376	3.887	3.425

The dissolution rate constants for the various dispersions of Pr:SA:SB are lower than the corresponding dissolution rate constants of dispersions of Pr:CA:SB. Solid dispersions of Pr in TA and SB as carriers show higher T50 and T75 values as compared to the T50 and T75 values for dispersions of Pr:SA:SB and dispersions of Pr:CA:SB. The dissolution rate constants for the dispersions of Pr:TA:SB increase with an increase in the amount of SB in the solid dispersions. Pr has been

reported[5] to form a glass with CA which, along with the effervescence, increases the rate of release of Pr from the solid dispersion.

Thermal Analysis

DSC has previously been used to demonstrate the formation of complexes using physical mixtures[6]. From the thermograms it is evident that there was no interaction between the respective drugs and each of the carriers (Figures 4-6). Hamed and Peck used DSC to investigate the possible interaction of ampicillin trihydrate with anhydrous dextrose[7]. Conclusions regarding the formation of complexes can be based on the changes in enthalpy.

In the case of the mixtures of the carrier acids with Pd, Gr, and Pr, the peak area and enthalpy change increases as the amount of the carrier acid in the mixtures increase (Figures 7-10). A steady increase in change in enthalpy is observed in the mixtures with increases in the carrier acids, indicating that no complex is formed.

In the case of thermograms of physical mixtures of SB with Pd, Gr and Pr, the change in enthalpy increased with an increase in the amount of SB in the physical mixtures indicating no complex formation.

Complex formation between the drugs and carriers played no role in the increased dissolution rates of the dispersions.

Changes in pH Observed in the Solid Dispersions Due to the Presence of Sodium Bicarbonate

There was no significant ($p<.05$) changes in pH (Table 4) observed in the solid dispersions, therefore the increase in dissolution rate with the increase in the amount of SB is not due to a change in bulk pH.

SUMMARY AND CONCLUSION

CA, SA, TA AND SB were employed to evaluate various Pd, Gr and Pr solid dispersions made by the

fusion method utilizing different drug:carrier ratios. CA in combination with sodium bicarbonate was the most effective carrier for releasing Pd and Pr, followed by SA:SB and TA:SB. Pr and Pd have been reported to form glasses with CA which, along with the formation of effervescence, increases the rate of release of Pd and Pr from the solid dispersions[5].

SA in combination with SB was found to be the best carrier for Gr followed by CA:SB and TA:SB. Gr is known to form a eutectic with SA[4], which, along with the effervescence produced by the presence of SB, contributes to the effectiveness of SA:SB in releasing Gr.

DSC thermograms of the physical mixtures of the drugs with the different carriers revealed no complex between the drugs and the carriers.

The increase in the dissolution rate is not attributed to the bulk change in pH due to the addition of SB because no significant change in pH was observed upon the addition of SB.

The drug:carrier ratio study showed that the dissolution rate increases with an increase in the amount of SB in the solid dispersions.

Solid dispersion systems are potential dosage form modifications for poorly water soluble drugs. Findings in this study hold true for Pd, Gr and Pr and may provide information for increasing the dissolution rates of other poorly water soluble drugs.

REFERENCES

1. L.V. Allen, Jr., "Increasing the Dissolution Rate of Some Corticosteroids Utilizing Glass Dispersions and Partial Solid Solutions", Dissertation submitted to the Graduate Division College of Pharmacy, University of Texas, Austin, Texas (1972).

2. J.W. McGinity, D.D. Maness, and G.J. Yakatan, Drug Dev. Comm., 1, 369 (1974/1975).

3. L.V. Allen, Jr., V.A. Yanchick, and D.D. Maness, J. Pharm. Sci., 66, 494 (1977).

4. W.L. Chiou and S. Niazi, J. Pharm. Sci., 62, 498, (1973).

5. M.P. Summers and P.R. Enever, J. Pharm. Sci. 65, 1613 (1976).

6. H. Hamed, D.O. Kildsig, and G.E. Peck, Drug Development and Industrial Pharmacy, 8, 3 (1982).

7. Ibid, p. 5.