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THE INFLUENCE OF VARIOUS DISPERSION METHODS ON THE RATE OF DISSOLUTION OF SULFABENZAMIDE

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ABSTRACT

The solvent and melt methods were employed to prepare solid dispersions with various water soluble carriers and a slightly soluble drug, sulfabenzamide. The carriers investigated included citric acid, succinic acid, dextrose, polyethylene glycol 6000, mannitol and urea. Dispersions with dextrose were superior to other carriers in releasing the drug into solution. Melts with both dextrose and urea produced faster rates of dissolution of sulfabenzamide than the coprecipitates from the solvent method. With mannitol and polyethylene glycol 6000, the coprecipitates produced a faster rate of dissolution of the drug than the melt dispersions.

INTRODUCTION

Formulation of a drug as a solid dispersion effectively causes a reduction in particle size. Enhancement of the rate of dissolution by this method, and thus a possible absorption rate increase for a poorly soluble drug, has generated considerable interest recently (1-11). The definitions, methods of preparation and pharmaceutical applications of these dispersions were thoroughly reviewed by Chiou and Riegelman (9). Many water soluble carriers have been employed in these systems and new agents continue to be tested.

To optimize the bioavailability and absorption rates of poorly or slowly soluble drugs, both the carrier and method of preparation of the solid dispersion should be carefully selected. The present communication examines six water soluble carriers; citric acid, succinic acid, dextrose, polyethylene glycol (PEG) 6000, mannitol and urea, and compares the dissolution characteristics of solid dispersions prepared by the solvent and melt methods, employing the slightly soluble sulfonamide, sulfabenzamide, as the model compound.

EXPERIMENTAL

Materials - The following materials were used: citric acid monohydrate[1], succinic acid[2], dextrose[3], PEG 6000[4], mannitol[5], urea[6], sulfabenzamide[7].

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[1]Fisher Scientific Company, Fair Lawn, New Jersey

[2]Eastman Organic Chemicals, Rochester, New York

[3]Matheson Coleman and Bell, Norwood, Ohio

[4]Baker Chemical Company, Phillipsburg, New Jersey

[5]Atlas Chemical Division, Wilmington, Delaware

Preparation of Samples - Dispersions with each carrier and sulfabenzamide were made via the solvent and melt methods. Coprecipitates from the solvent method were prepared by dissolving the carrier and sulfabenzamide in sufficient methanol-acetone (1:1) to fully solubilize the materials. The solvent was allowed to evaporate by stirring under ambient conditions. The last traces of solvent were removed by heating the sample to constant weight at 45°. Since thermal decomposition occurred with sulfabenzamide in the presence of both citric and succinic acids, the coprecipitates were dried at 35°.

The melts were prepared by heating a physical mixture of sulfabenzamide and the carrier substance in an aluminum pan over a hot oil bath. The melt was stirred until the drug dissolved in the carrier and uniformity of drug in the melt was attained. The melts were solidified by inserting the aluminum pan into a dry ice - acetone bath. The dispersions from both methods were pulverized in a mortar and passed through an 80 mesh screen. Sulfabenzamide controls were prepared by the melt and solvent methods using drug alone, in the absence of the carrier substance.

Dissolution Studies - The dissolution studies were performed on solid dispersions containing 25 mg sulfabenzamide and varying amounts of carrier. The solid dispersions were placed in a 2000 ml. three-necked, round bottom flask containing 1500 ml. of distilled water maintained at 25°C. A polyethylene blade

[6]Allied Chemical, Morristown, New Jersey

[7]Nutritional Biochemicals Corporation, Cleveland, Ohio

[8]Beckman DB spectrophotometer

was lowered to a depth of 5 cm. in the dissolution media and the stirring speed was maintained at 100 rpm. The dissolution medium was circulated through a spectrophotometer[8] at a rate of 100 ml. $min.^{-1}$ providing continuous monitoring of drug concentration as a function of time at 259 nm. The reported data is the average of at least duplicate runs and results were reproducible.

RESULTS AND DISCUSSION

Solid Dispersion of Dextrose and Mannitol - Dextrose and mannitol are among many compounds (12) capable of forming glass solutions upon solidification from the liquid state. Recently Allen et al., (13) examined solid dispersions of various corticosteroids and several sugars, prepared via the melt method and found a substantial increase in the dissolution rates of these sparingly soluble compounds. Coprecipitates and melts of sulfabenzamide with both dextrose and mannitol were prepared and dissolution characteristics examined. As can be seen in Fig. 1, the melt preparation with dextrose resulted in complete solution almost immediately. Coprecipitates with various quantities of dextrose were also very efficient at increasing the drug dissolution rate. The dissolution rate of drug from the mannitol coprecipitate was faster than the melt dispersion (Fig. 2). Sulfabenzamide did not dissolve completely in the mannitol; the cooled melt consisted of two immiscible phases instead of a clear glass solution as was found with dextrose. The poor solubility of the drug in the mannitol carrier may explain the slower dissolution rate of sulfabenzamide from the melt samples. Although coprecipitates of dextrose, and to a

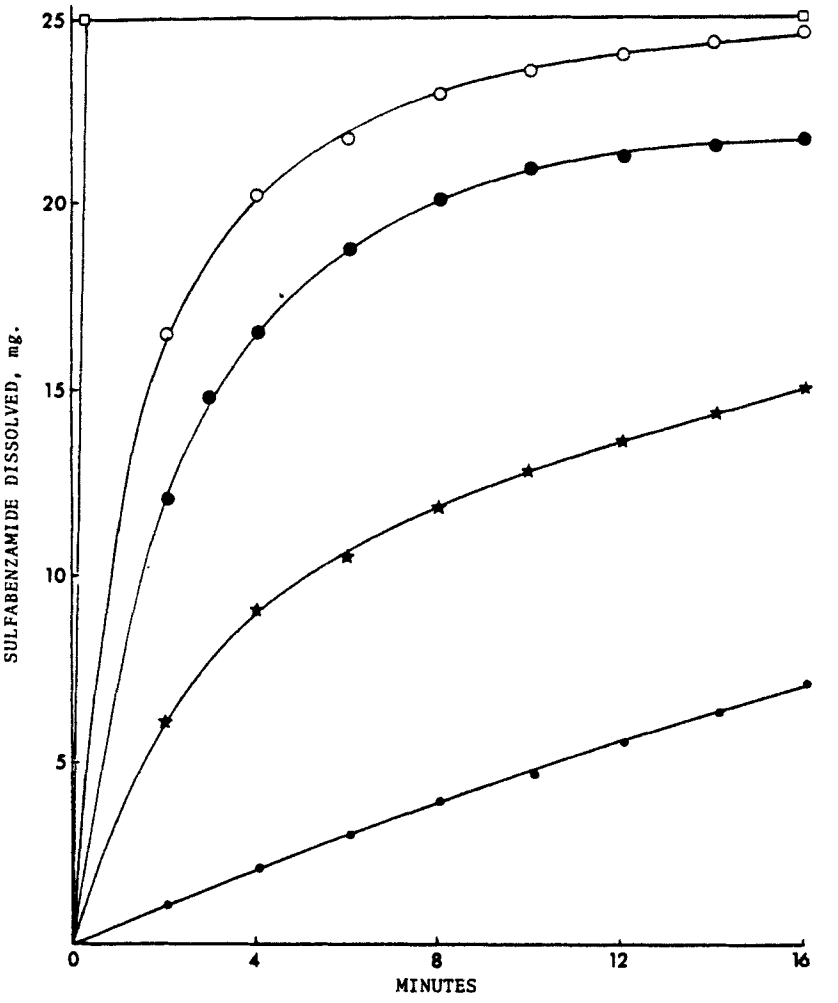

FIGURE 1.

Dissolution profiles of sulfabenzamide and sulfabenzamide - dextrose solid dispersions at 25°. • pure sulfabenzamide. ★1:0.5 co-ppt. ● 1:1 co-ppt. ○1:3 co-ppt. □1:3 melt.

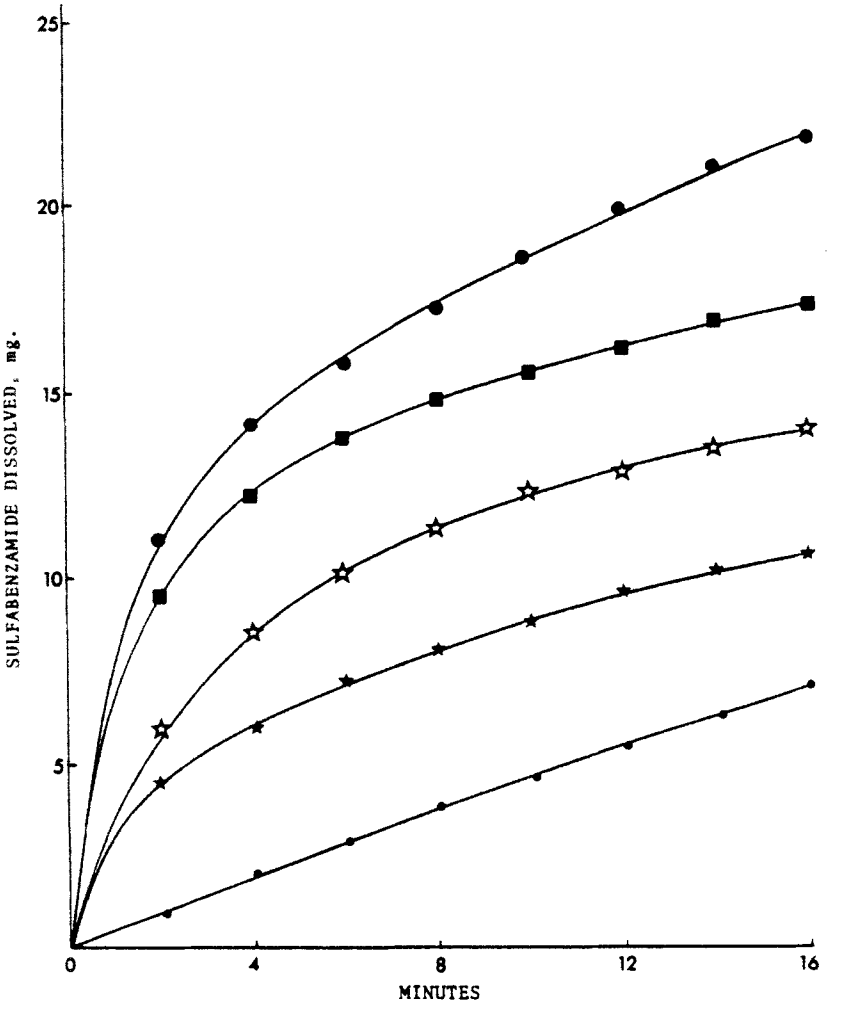

FIGURE 2.

Dissolution profiles of sulfabenzamide and sulfabenzamide - mannitol solid dispersions at 25°. • pure sulfabenzamide. ★1:1 melt. ☆1:1 co-ppt. ■1:3 melt. ●1:3 co-ppt.

lesser extent mannitol, increased the rate of dissolution of sulfabenzamide with only small quantities of carrier, both materials possessed poor solubility in most commonly used organic solvents. Thus, large volumes of equilibrating solvent were necessary in the preparation of coprecipitates.

The melt dispersions of the sugars also present some disadvantages from a formulation stand point. Charring of mannitol and dextrose can occur at high temperatures and the sugar melts required considerable time to resolidify. As reported previously for citric acid melts (7), the sugar melts were found to harden when allowed to stand for a few days at 40°C. Preliminary microscopic studies with dextrose have indicated that the rate of cooling influences the crystal structure of the drug in the melt sample. Investigations are currently being pursued to determine the influence of cooling rate on the dissolution characteristics of the drug from melts prepared with dextrose and other carriers.

Solid Dispersions of Urea - The influence of urea on the dissolution rate of poorly soluble medicinal agents has been reported extensively (3,4,6,14). As shown in Fig. 3, melts and coprecipitates of urea markedly increase the rate of dissolution of sulfabenzamide. In dispersion with urea, solubility difficulties with sulfabenzamide and urea were not encountered. A comparison of dispersions prepared by the solvent and melt methods showed that for samples containing 25% drug, the release of sulfabenzamide from the melt was faster. All the drug from the melt passed into solution in less than 4 minutes. Both melts and coprecipitates of urea -

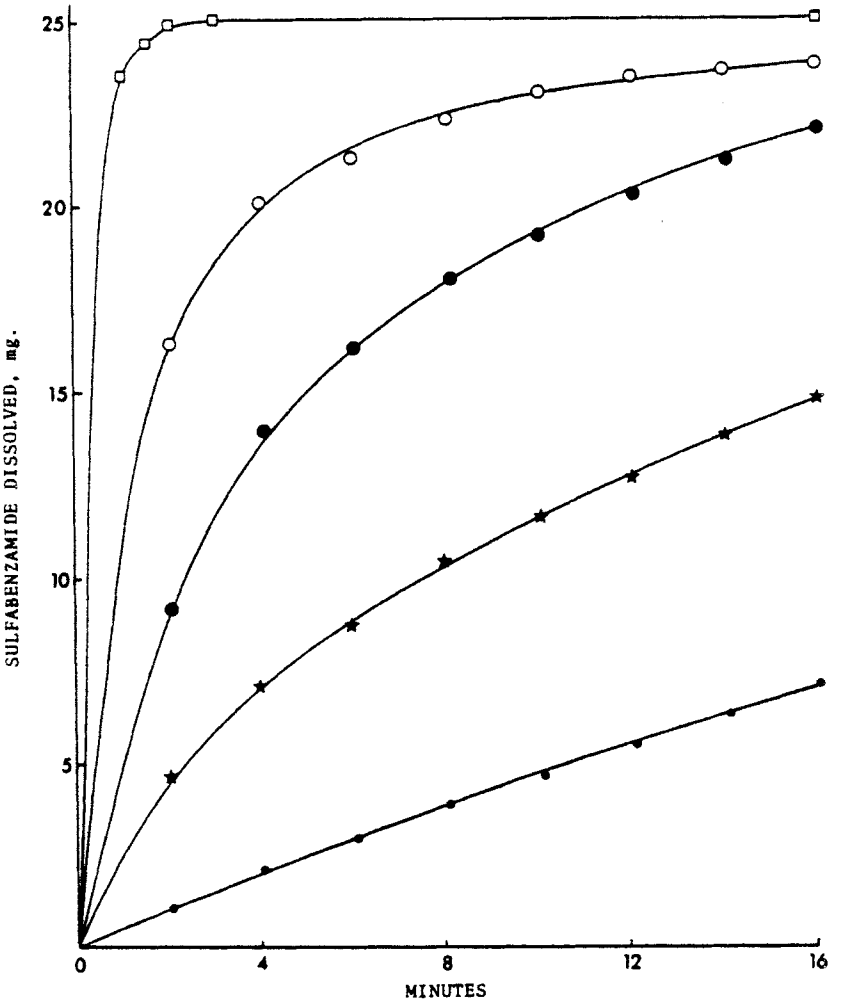

FIGURE 3.

Dissolution profiles of sulfabenzamide and sulfabenzamide - urea solid dispersions at 25°. • pure sulfabenzamide. ★1:0.5 co-ppt. ●1:1 co-ppt. ○1:3 co-ppt. □1:3 melt.

sulfabenzamide could be prepared, crushed and sieved with relative ease. If the melted samples were allowed to air cool, the solidification process was slower than when the samples were flash cooled.

Solid Dispersions of PEG 6000 - Solid dispersions of PEG 6000 have been prepared with both liquid (15) and solid drugs (7, 9-11) and have been shown to increase the dissolution rate of poorly soluble pharmaceuticals. A comparison of the release rates of sulfabenzamide from coprecipitate and melt dispersions of PEG 6000 is shown in Fig. 4. At the three concentration levels studied, the dissolution rate of the drug from the coprecipitates was slightly faster than the melts. Chiou and Riegelman (7) found that for the griseofulvin - PEG 6000 system, drug release was fastest from dispersions prepared by the melt method. The griseofulvin dispersion prepared via the solvent method did not have the drug totally dissolved in the equilibrating medium in the Chiou and Riegelman study, and this could account for the discrepancies between the results for griseofulvin and sulfalbenzamide. The choice of equilibrating solvent with respect to the solubility of the drug and carrier appears to have a marked influence on the final physical properties of the coprecipitate. For the sulfabenzamide - PEG 6000 dispersions, both drug and carrier were dissolved in the equilibrating medium prior to evaporation of solvent. Since the drug readily dissolved in the melted glycol, one might anticipate that drug should approach a molecular level of dispersion. Such a dispersion would be more difficult to achieve with the

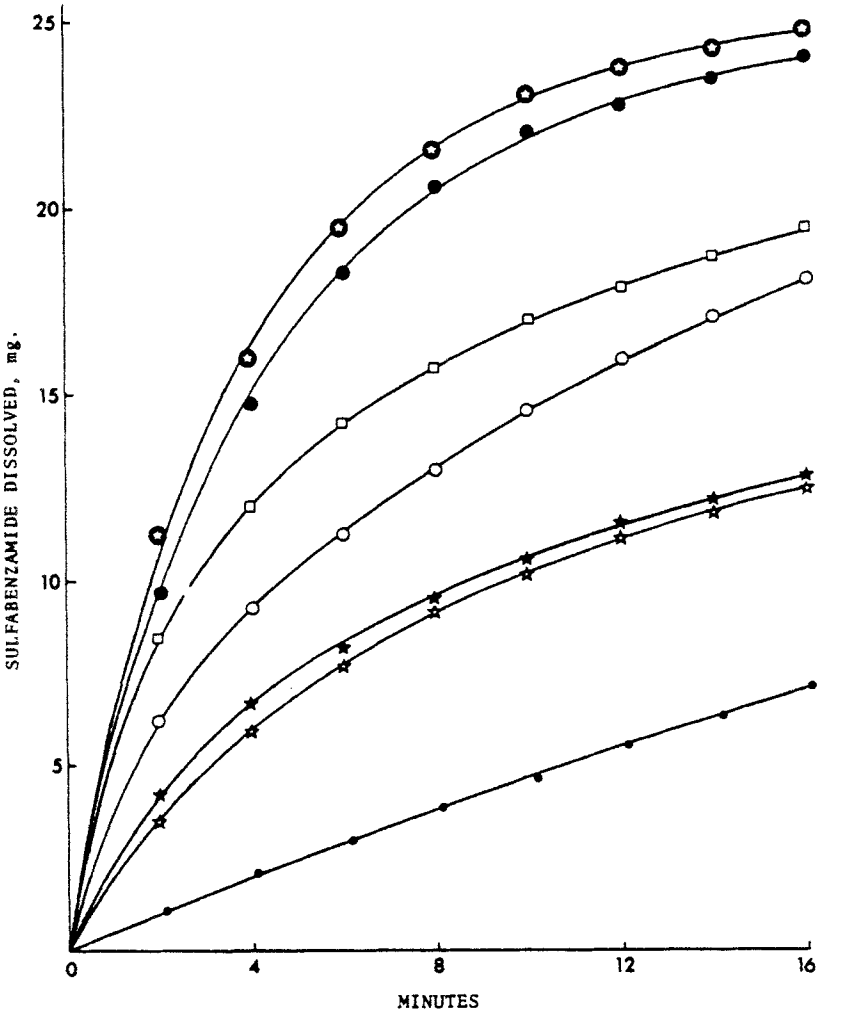

FIGURE 4.

Dissolution profiles of sulfabenzamide and sulfabenzamide - PEG 6000 solid dispersions at 25°. • pure sulfabenzamide. ☆1:1 melt. ★1:1 co-ppt. ○1:3 melt. □1:3 co-ppt. ● 1:6 melt. ✪1:6 co-ppt.

solvent dispersion method, resulting in a slower dissolution rate. To explain the reason for the reverse situation occurring with the sulfabenzamide - PEG 6000 system, a large amount of the drug may have precipitated on the surface of the glycol. The surface deposited drug may pass more freely into the dissolution medium than drug embedded in the matrix of the glycol as might result from the melt method. Two possible mechanisms controlling drug release from the melt include the diffusion of drug from undissolved glycol and the dissolution rate of PEG 6000 itself. The latter was much slower than urea and dextrose under the experimental conditions. This phenomenon of coprecipitates producing a faster dissolution rate of dispersed drug than melt preparations has also been shown true in these laboratories for indomethacin at 37° (16). A comparison of PEG 6000 dispersions with several poorly soluble drugs, prepared by the two techniques is currently being studied.

Solid Dispersions of Citric Acid and Succinic Acid - Sulfabenzamide was stable at the melting temperatures of these acids; however drug degradation occurrs with both these carriers when drug and carrier were heated to form the melt samples. Also the succinic acid alone, exhibited stability problems near its melting point. Chiou and Riegelman (7) showed citric acid to be an excellent carrier for griseofulvin. The influence of citric acid and succinic acid coprecipitates on the dissolution rate of sulfabenzamide is shown in Fig. 5 and Fig. 6 respectively. A comparison of the data for citric acid coprecipitates in

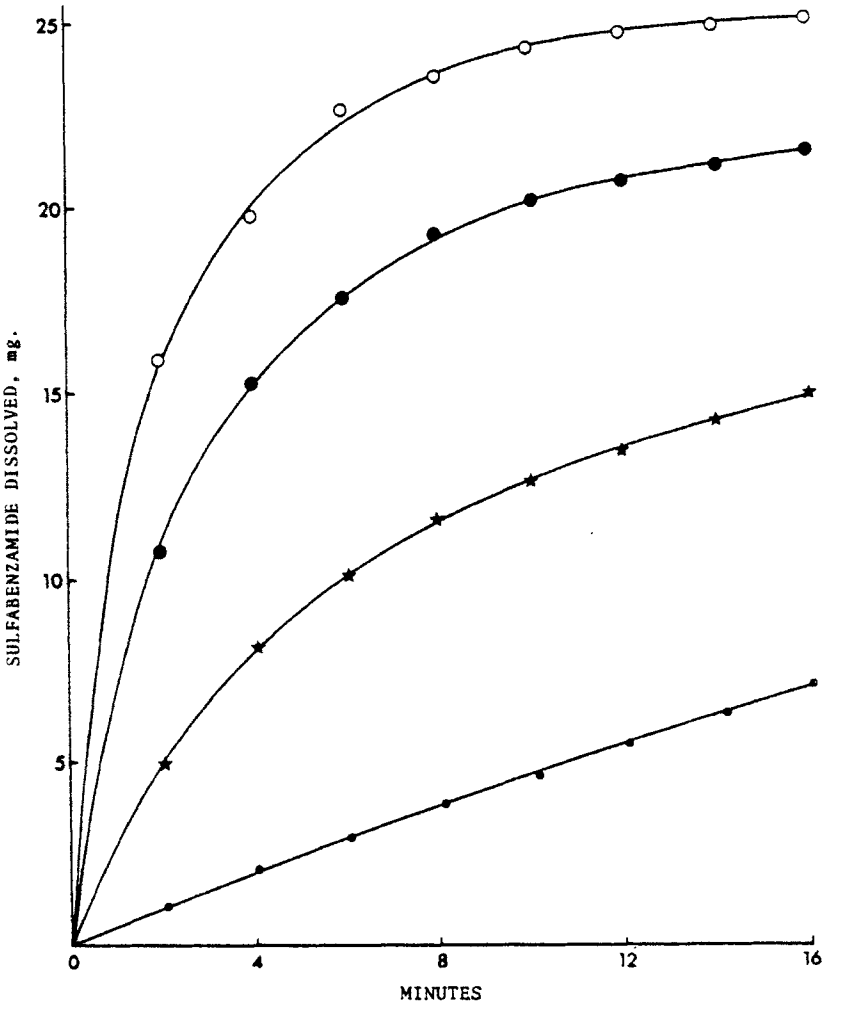

FIGURE 5.

Dissolution profiles of sulfabenzamide and sulfabenzamide - citric acid solid dispersions at 25°. • pure sulfabenzamide. ★1:1 co-ppt. ● 1:3 co-ppt. ○ 1:6 co-ppt.

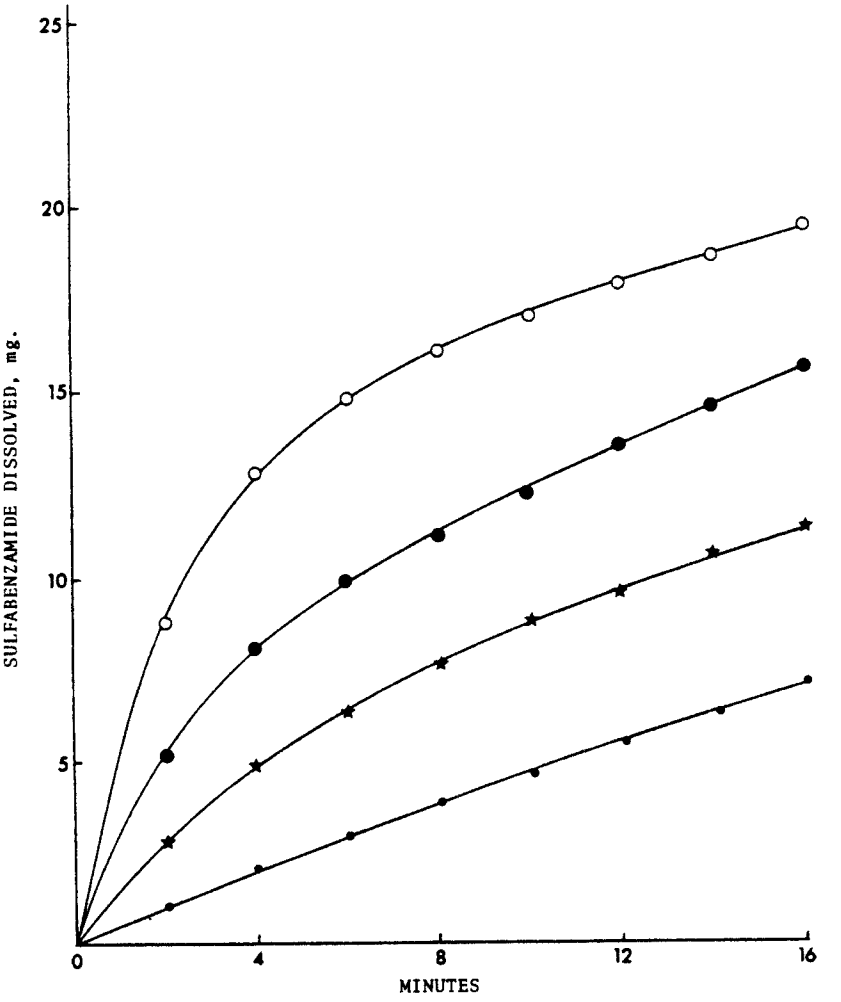

FIGURE 6.

Dissolution profiles of sulfabenzamide and sulfabenzamide - succinic acid solid dispersions at 25°. •pure sulfabenzamide. ★1:1 co-ppt. ●1:3 co-ppt. ○1:10 co-ppt.

Fig. 5 and PEG 6000 in Fig. 4 showed the citric acid to be superior at the three concentration levels studied. The family of curves in Fig. 7 compares the release rates from coprecipitates of the six carriers studied. The dissolution data from melts of dextrose, urea, PEG 6000 and mannitol are displayed in Fig. 8. From Fig. 7 and Fig. 8, solid dispersions prepared by the solvent and melt methods containing dextrose produced the fastest dissolution rate of sulfabenzamide and drug release from this agent would be expected to render optimal conditions for absorption of sulfabenzamide. Succinic acid produced the least influence on increasing the dissolution rate of the drug. A comparison of the times for 25, 50 and 75% of sulfabenzamide to pass into solution from the solid dispersions studied is listed in Table I.

SUMMARY AND CONCLUSION

A comparison of several methods used to prepare solid dispersions on the dissolution rate of sulfabenzamide showed that melts of dextrose and urea were superior to coprecipitates prepared by the solvent method. The reverse was true for PEG 6000 and mannitol where coprecipitates of the sulfonamide produced faster release rates than melt dispersions.

Of the carriers studied, dextrose exhibited the maximal increase in dissolution rates of sulfabenzamide from both coprecipitate and melt dispersion. However, difficulties encountered in the preparations of these dispersions due to

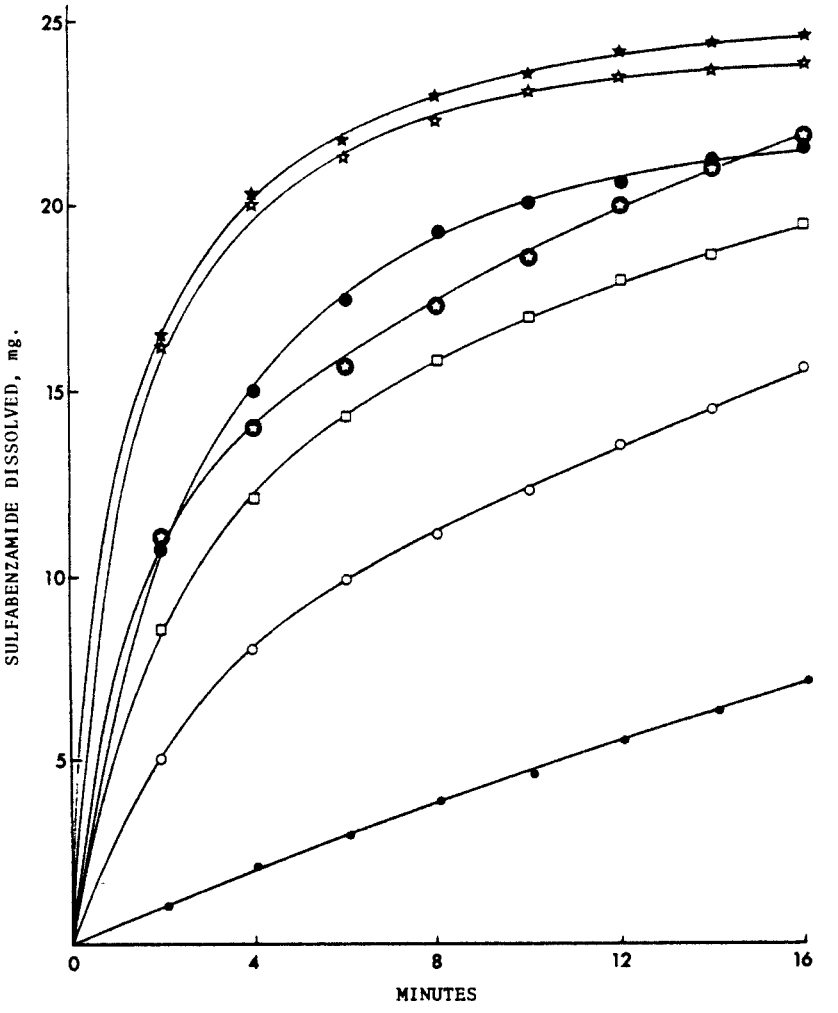

FIGURE 7.

Dissolution profiles of sulfabenzamide and sulfabenzamide - carrier coprecipitates (1:3) at 25°. ● pure sulfabenzamide. ○ succinic acid. □ PEG 6000. ✪ citric acid. ● mannitol. ☆ urea. ★ dextrose.

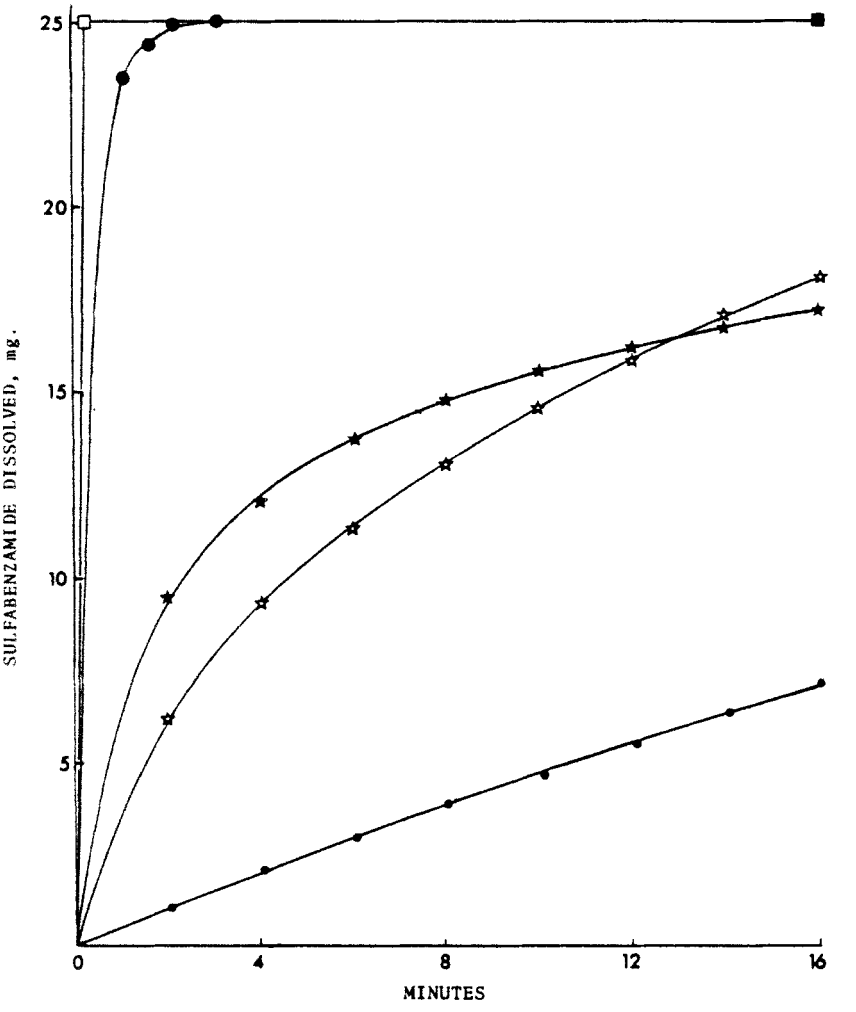

FIGURE 8

Dissolution profiles of sulfabenzamide and sulfabenzamide - carrier melts (1:3) at 25°. • pure sulfabenzamide. ★mannitol. ☆PEG 6000 ● urea. □ dextrose.

Table I - Time (min) for 25, 50 and 75 Percent of Drug from Solid Dispersions to Pass into Solution

Carrier	Ratio of Drug:Carrier Coprecipitate	Melt	t_{25}	t_{50}	t_{75}
Dextrose	1:0.5		2.05	9.50	>16.00
	1:1		1.00	2.24	5.95
	1:3		0.60	1.30	2.95
		1:3	0.06	0.10	0.14
Mannitol	1:1		2.25	11.00	>16.00
	1:3		0.83	2.83	10.30
		1:1	4.35	>16.00	>16.00
		1:3	1.10	4.30	>16.00
Urea	1:05		3.20	9.65	>16.00
	1:1		1.38	2.70	9.25
	1:3		0.70	1.25	3.10
		1:3	0.18	0.28	0.45
PEG 6000	1:1		3.60	15.40	>16.00
	1:3		1.32	4.40	14.40
	1.6		0.98	2.45	5.55
		1:1	4.35	>16.00	>16.00
		1:3	2.05	7.50	>16.00
		1:6	1.20	3.00	6.40
Citric Acid	1:1		2.70	9.90	>16.00
	1:3		1.20	1.58	7.40
	1:6		0.62	1.30	3.55
Succinic Acid	1:1		6.00	>16.00	>16.00
	1:3		2.70	10.40	>16.00
	1:10		1.35	3.90	14.50
Control[a]			14.15	>16.00	>16.00

[a]Pure drug, in absence of carrier

the poor solubility of dextrose in common organic solvents and the problems experienced in preparing a free flowing powder from the melt dispersion suggest limited practical application of this sugar without further formulation design modifications.

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