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THERMAL ANALYSIS OF SULPHAMETHOXAZOLE - SUGAR PHYSICAL MIXES

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ABSTRACT

Differential scanning calorimetry and hot stage microscopy have been used to study the interactions between sulphamethoxazole and the sugars maltose, glucose, sucrose and mannitol. Only the sulphamethoxazole-mannitol system appeared to be stable and presented a eutectic containing 90.3% sulphamethoxazole. Heats of fusion for sulphamethoxazole, mannitol and their eutectic were 33.4, 73.6 and 39.9 cal g^{-1} respectively.

INTRODUCTION

Since the concept of solid dispersions was introduced [1] many water soluble carriers have been investigated for their potential to increase the dissolution rate of drugs whose aqueous solubility is limited. These carriers have included citric acid [2], bile acids and related compounds [3], urea [4], surfactants [5] and polymers such as polyethylene glycol [2,6] or polyvinyl-pyrrolidone [7]. Sugars have also been examined since they possess the advantages of low toxicity, high aqueous solubility and physiological acceptance bu'. many are unstable at or around their melting points.

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Mannitol is stable above its melting point of 167°C to a temperature of in excess of 250°C and has good flow and compaction properties [8]. For instance, paracetamol, a drug known to be poorly compressible, was compacted into tablets following dispersion with mannitol [9]. In the fused state, mannitol is immiscible with corticosteroids [10], tolbutamide [11] and many sulphonamides [8,12]. Other drugs that have been dispersed with mannitol include spironolactone [13], diazepam [13], trimethoprim [14], hydrocortisone [15], prednisone [15] and glibenclamide [16].

Ghanem and his co-workers have compared the ability of several sugars (sucrose, mannitol, sorbitol, glucose, galactose, maltose and fructose) to increase the dissolution rates of trimethoprim [14] and sulphamethoxazole [17]. However, galactose, sorbitol, lactose, fructose and maltose decompose at or about their melting points [18]. This paper examines the stability of sulphamethoxazole with the sugars maltose, glucose, mannitol and sucrose using hot stage microscopy (H.S.M.) and differential scanning calorimetry (D.S.C.). Construction of the phase diagram of a drug and its prospective carrier from thermal analysis data is generally regarded as an important preliminary exercise in evaluating solid dispersions [6,19] and D.S.C. is a valuable technique in identifying instabilities between drugs and other pharmaceutical excipients [20,21].

MATERIALS AND METHODS

Materials

The sugars maltose, glucose, mannitol and sucrose were all analar reagents (British Drug Houses, U.K.) and together with sulphamethoxazole B.P. were used without further purification. Physical mixes were prepared by trituration using a glass mortar and pestle. Sulphamethoxazole:sugar ratios containing 0, 25, 50, 75 and 100% drug were prepared for maltose, glucose or sucrose. Mixes of sulphamethoxazole-mannitol, but at 5% intervals, were similarly prepared.

Differential Scanning Calorimetry

A Perkin-Elmer Model DSC-1B differential scanning calorimeter was used. Aluminium sample pans and pan lids were used for all samples, the lids being crimped into position. Samples, 5-7 mg accurately weighed, were analysed at 4^{o} min^{-1} using nitrogen as purge gas at a flow rate of 20 ml min^{-1}. Temperatures of transitions or interactions were determined after calibration with an indium standard. The heats of fusion for eutectic and excess components of the sulphamethoxazole-mannitol mixes were determined following calibration with indium (heat of fusion: 6.80 cal g^{-1}) using integration of the areas under the curves for the melting endotherms by an Autolab Minigrator (Spectra-Physics).

Hot Stage Microscopy

Samples, 5-10 mg, of the mixes were placed on a microscope slide and covered with a coverslip. A Reichert-Koffler hot stage microscope was used and the samples were heated, uninterruptedly from room temperature at a heating rate of 5-10^{o}C. min^{-1}. For the sulphamethoxazole-mannitol mix, the solidus temperatures were taken as the first signs of melting and the liquidus temperatures as those immediately before the final traces of crystal melted within the field of vision.

RESULTS AND DISCUSSION

The D.S.C. traces of sucrose, maltose, glucose and mannitol are given in figures 1-4 respectively and a summary of their melting points derived from D.S.C. and H.S.M., together with various literature values are given in table 1. The differences between H.S.M. and D.S.C. data are due to the different sensitivities of the methods [6].

Sucrose (figure 1) displayed a broad melting range and although slight discolouration of the molten sugar was observed under H.S.M. between 189-194^{o}C, no further deepening of this amber colour occurred by 200^{o}C. Irregularities in the D.S.C. trace above 200^{o}C probably indicated further decomposition.

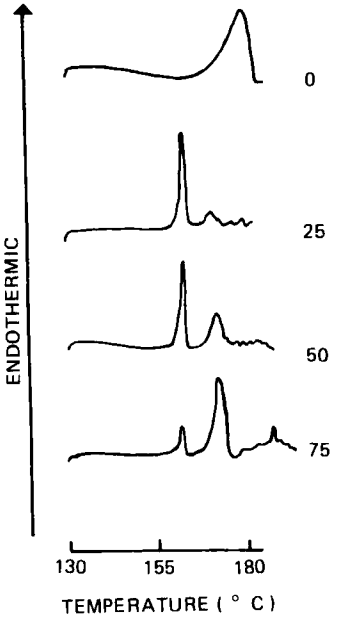

FIGURE 1

D.S.C. curves of sucrose and sulphamethoxazole-sucrose physical mixes. Percentages refer to % sulphamethoxazole content.

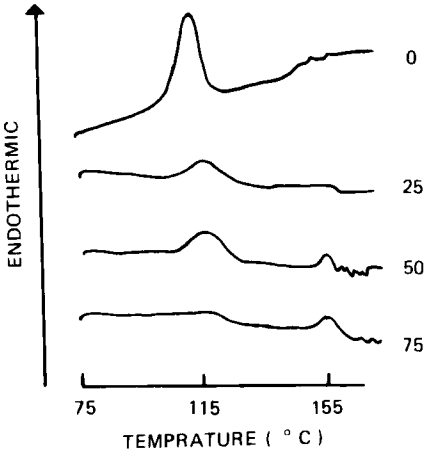

FIGURE 2

D.S.C. curves of maltose and sulphamethoxazole-maltose physical mixes. Percentages refer to % sulphamethoxazole content.

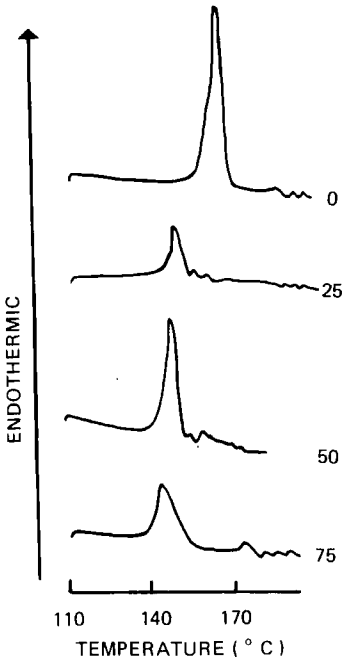

FIGURE 3

D.S.C. curves of glucose and sulphamethoxazole-glucose physical mixes. Percentages refer to % sulphamethoxazole content.

Maltose, under H.S.M., displayed clearing of crystal structure between 106-120°C and complete fusion by 126°C. The D.S.C. curve gave a broad melting range of 104-117°C but no fusion endotherm at around 126°C (figure 2). Although no charring occurred at up to 160°C (H.S.M.), apparent gas formation occurred within the melt at elevated temperatures and together with the appearance of small endotherms above 155°C, it was construed that maltose was unstable above circa 140°C.

Glucose behaved similarly to maltose under thermal analysis.

Melting ranges were derived (table 1) and, above 180°C, gas formation and an intense yellow discolouration became apparent. The broad endotherm (figure 3) was followed by violent fluctuations

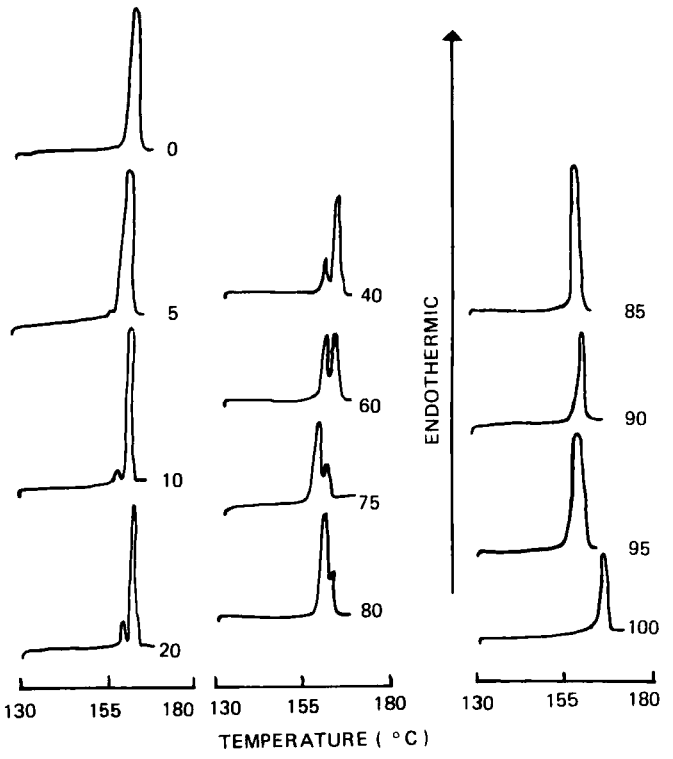

FIGURE 4

D.S.C. curves of mannitol, sulphamethoxazole and their physical mixes. Percentages refer to % sulphamethoxazole content.

TABLE 1

Melting ranges (^{o}C) of the sugars used in this study.

	DETERMINATIONS BY		LITERATURE SOURCES	
SUGAR	H.S.M.	D.S.C.	BRITISH PHARMACOPOEIA [22]	MERCK [23]
SUCROSE	182-189	164-185	-	160-186*
MALTOSE	110-126	104-117	-	102-103
GLUCOSE	151-166	141-169	-	146
MANNITOL	163-167	162-168	166-169	166-168

*Decomposition temperature

in the base line. The melting points of carbohydrates are not usually sharp and are best expressed as decomposition temperatures [18]. The variations in the derived values expressed in table 1 re-emphasise the problems of determining melting ranges for sugars.

Mannitol, however, gave a sharp uncomplicated melting endotherm and no apparent decomposition up to at least 200°C (figure 4). Sulphamethoxazole gave a single sharp endotherm corresponding to a melting range of 166-169°C.

The D.S.C. curves of the sulphamethoxazole-sugar mixes are shown in figures 1-4. Sulphamethoxazole-sucrose (figure 1) displayed melting behaviour typical of a simple eutectic mixture. Initial melting of the eutectic component occurred at about 160°C, peaking at 166°C which is some 3° lower than the melting point of sulphamethoxazole. The melting endotherms of the excess component at 174-184°C were followed by wide fluctuations of the D.S.C. baseline indicative of severe decomposition. Hot stage microscopy indicated that the two components were only slowly miscible and that intense yellowing of the melt occurred above 180°C. This charring was more evident with sucrose than with the other sugars.

Sulphamethoxazole mixes with maltose or glucose showed similarities. Although maltose possessed a lower melting range than glucose, each system displayed melting of a eutectic component peaking at about 114°C for maltose mixes and 130°C for glucose mixes (figures 2 and 3 respectively). However the size of a second endotherm, equivalent to the component in excess of the eutectic mass, was considerably lower than expected for maltose and absent for glucose. This reduction in or loss of a second endotherm in the D.S.C. of binary mixtures is indicative of incompatability [20,21] which is further reinforced by the fluctuations in baseline of the D.S.C. traces (figures 2 and 3). However, gas formation, apparent under H.S.M. occurred for the maltose mixes at above 150° and the glucose dispersions at above

160°C. Ghanem et al [17] investigated the dissolution of sulphamethoxazole-sugar dispersions prepared by the melt method. Following thin layer chromatography of these dispersions, only one spot, equivalent to sulphamethoxazole, was detected for the dispersions containing the non-reducing sugars sucrose and mannitol [17]. The glucose and maltose dispersions showed two spots, one corresponding to sulphamethoxazole and another remaining at the origin. However their technique of spot-detection using fluorescent silica ge G plates would not locate the sugar moieties. It was postulated [17] that, where two spots were located, one fraction of the drug occurred as freemolecules whereas another fraction complexed with the reducing sugars. In the light of the D.S.C. and H.S.M. evidence presented here, it would seem more plausible that a degradation reaction occurred between both maltose and glucose with sulphamethoxazole and that the second spot, previously located [17], was due to a degradate of sulphamethoxazole. On the other hand, the charring of the sucrose dispersions probably indicated degradation of the sugar alone, but not of sulphamethoxazole.

The sulphamethoxazole-mannitol mixes displayed no obvious incompatibilities. The mixes were readily miscible under H.S.M. and no gas evolution was detected. The D.S.C. data (figure 4) presented a typical eutectic reaction. However because of the similarities in the melting points of mannitol and sulphamethoxazole (melting ranges by D.S.C. of 162-168°C and 166-169°C respectively) and their closeness to the eutectic temperature (158°C by D.S.C.), the phase diagram (especially its eutectic position) was difficult to quantify from temperature measurements by D.S.C., since the reproducibility of the endotherm peaks (about ± 1.5°C) represented 30% of the difference between the melting points of the pure components and the eutectic temperature. Additionally the D.S.C. traces of mixes containing in excess of 80% sulphamethoxazole displayed only one fused melting endotherm. The phase diagram, constructed from H.S.M. data (figure 5), displayed a eutectic at about 85% sulphamethoxazole : 15% mannitol,

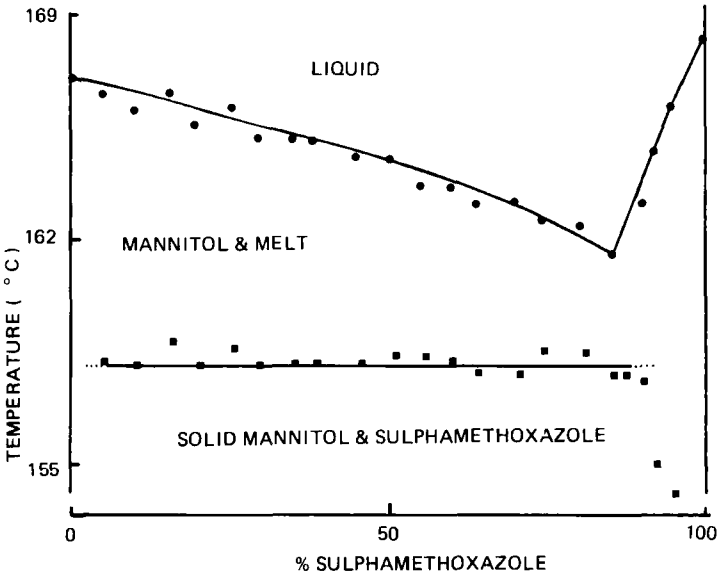

FIGURE 5

Phase diagram of the sulphamethoxazole-mannitol system constructed from H.S.M. data from physical mixes.

Key ●: liquidus temperatures
■: solidus temperatures

but again its exact position was somewhat uncertain. The endotherm areas (figure 4) were used to calculate the heats of fusion of mannitol, sulphamethoxazole and, in their mixes, of the eutectic components and the material present in excess of the eutectic. The heats of fusion from mannitol and sulphamethoxazole were determined as 73.6 and 33.4 cal.g^{-1} respectively. Figure 6 was constructed from the heats of fusion of mixes containing up to 80% sulphamethoxazole. Straight-line relationships existed between the heats of fusion for both the eutectic component and the excess mannitol when presented as a function of composition. The equation describing the relationship for the excess mannitol curve is:-

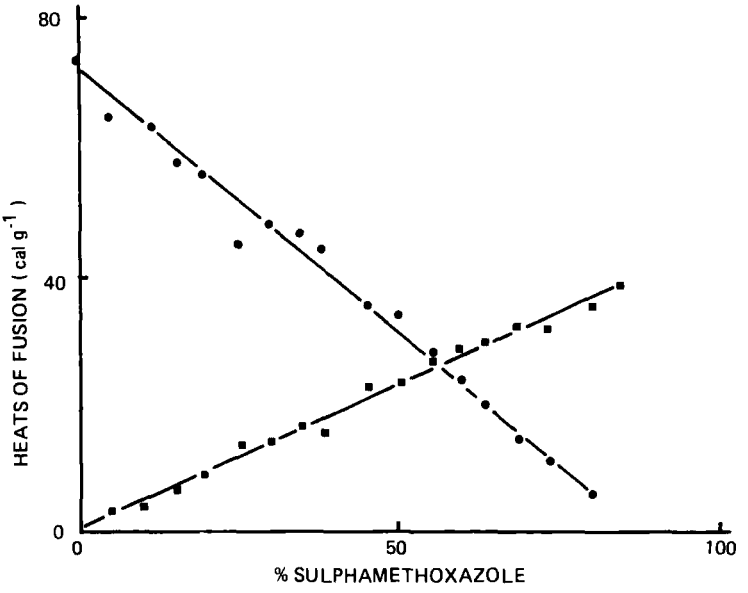

FIGURE 6

Heats of fusion of the eutectic components and excess mannitol components of sulphamethoxazole-mannitol physical mixes derived from D.S.C. data plotted as a fraction of sulphamethoxazole content.

Key ■ : eutectic component
● : excess mannitol component

Each point is the mean of two determinations.

$$\Delta H._{(X.S.\ MAN)} = 70.53 - 0.781\ \%_s \qquad \text{equation 1}$$

where $\Delta H._{(X.S.\ MAN)}$ = heat of fusion due to the excess mannitol component

and $\%_s$ = percentage of sulphamethoxazole.

Substitution of a zero value in equation 1 for the heat of fusion due to excess mannitol, a situation that will occur at the eutectic, gives a eutectic composition of 90.3% sulphamethoxazole:

9.7% mannitol. The regression coefficient r for the 34 pairs of data defined by equation 1 was 0.9904 which is significant at $p < 0.001$.

The regression equation derived for the curve corresponding to the eutectic component in figure 6 is:-

$$\Delta H_{(EUT)} = 1.22 + 0.428\ \%_s \qquad \text{equation 2}$$

where $\Delta H_{(EUT)}$ = Heat of fusion due to the eutectic component.

The value of r was 0.991 (34 points) with $p < 0.001$. Substituting the derived $\%_s$ of 90.3 in equation 2 gives a heat of fusion of the pure eutectic of 39.9 cal g^{-1}. Thus the use of D.S.C. scans of physical mixes to determine the eutectic composition can be supplemented by the energies of transition which they describe, and in this case permitted the accurate identification of the eutectic composition of the sulphamethoxazole -mannitol system where the melting points of two components and the eutectic were not dissimilar. However, because of the fused endotherms to the drug rich side of the eutectic, similar data treatment was not undertaken.

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REFERENCES

[1] K. Sekiguchi and N. Obi, Chem. Pharm. Bull., 9, 866 (1961).

[2] W.L. Chiou and S. Riegelman, J. Pharm. Sci., 58, 1505 (1969).

[3] R.G. Stoll, T.R. Bates, K.A. Neiforth and J. Swarbrick, J.Pharm. Sci., 58, 1457 (1969).

[4] A.H. Goldberg, M. Gibaldi and J.L. Kanig, J. Pharm. Sci., 54, 1145 (1965).

[5] R.K. Reddy, S.A. Khalil and M.W. Gouda, J. Pharm. Sci., 65, 1753 (1976).

[6] J.L. Ford and M.H. Rubinstein, Pharm. Acta Helv., 53, 327 (1978).

[7] A.P. Simonelli, S.C. Mehta and W.I. Higuchi, J. Pharm. Sci., 58, 538 (1969).

[8] J.L. Kanig, J. Pharm. Sci., 53, 188 (1964).

[9] H.M. El-Banna, A.G. Eshra and Y. Hammouda, Pharmazie, 32, 511 (1977).

[10] L.V. Allen, Ph.D. Thesis, University of Texas at Austin (1972).

[11] H.M. El-Banna, N.A. Daabis, L.M. Mortada and S. Abd-Elfattah, Pharmazie, 30, 788 (1975).

[12] J.W. McGinity, D.D. Maness and G.J. Yakatan, Drug Dev. Comm. 1, 369 (1974).

[13] A.S. Geneidi and H. Hamacher, Pharm. Ind., 42, 401 (1980).

[14] M. Meshali, A. Ghanem and Y. Ibraheem, Pharm. Acta Helv., 58, 62 (1983).

[15] L.V. Allen, R.S. Levinson and D.D. Martono, J. Pharm. Sci., 67, 979 (1978).

[16] A.S. Geneidi, M.S. Adel and E. Shehata, Can. J. Pharm. Sci., 15, 78 (1980).

[17] A. Ghanem, M. Meshali and Y. Ibraheem, J. Pharm. Pharmac., 32, 675 (1980).

[18] Vogel's Textbook of Practical Organic Chemistry, Pub: Longman, New York (1978).

[19] W.L. Chiou and S. Riegelman, J. Pharm. Sci., 60, 1281 (1971).

[20] J.L. Ford and M.H. Rubinstein, Drug Devel. Ind. Pharm., 7, 675 (1981).

[21] J.E. Fairbrother, Pharm. J., 290, 730 (1983).

[22] British Pharmacopoeia 1980. H.M.S.O., London.

[23] The Merck Index, 10th Edition; Pub. Merck and Co. Inc., Rahway, New Jersey, N.Y., (1983).