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DIFFERENTIAL SCANNING CALORIMETRY OF AMPICILLIN-DEXTROSE MIXTURE

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ABSTRACT

The possible interaction of anhydrous ampicillin and ampicillin trihydrate with anhydrous dextrose, in the solid state, was investigated by comparing the thermal behavior, using differential scanning calorimetry, of physical mixtures of the respective original components in different molar ratios. Anhydrous dextrose was found to form complexes with anhydrous ampicillin and ampicillin trihydrate. These complexes were found to be dependent on the molar ratios of the mixture components. The stoichiometries of these complexes were determined from the enthalpy change of the DSC transitions of the mixtures and were found to be 1:1, 2:3 and 1:3 molar complexes between ampicillin, anhydrous and trihydrate, and anhydrous dextrose. Complexed ampicillin was found to decompose at markedly lower temperatures than uncomplexed ampicillin.

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INTRODUCTION

A number of reports[1-5] indicated that injections containing dextrose caused the inactivation of ampicillin sodium. Ashwin and Lynn[5] reported that ampicillin sodium was found to be unstable in 5 per cent dextrose solution and inactivation increased with the antibiotic concentration. They concluded that solutions of ampicillin sodium in intravenous fluids containing dextrose should be infused within one hour of preparation. Lynn[6] found that the stability of ampicillin sodium was adversely affected by the addition of glycerol or propylene glycol.

Jacobs et al.[7] reported that solutions containing dextrose at low pH appeared to reduce ampicillin activity and it would be advisable to administer ampicillin dissolved in these solutions during four hours or less.

Moss and Cole[8] found that the degradation of 6-aminopenicillanic acid was accelerated in the presence of dextrose, maltose or lactose. The N-glycosyl, N-maltosyl, and N-lactosyl derivatives of 6-aminopenicillanic acid were found to contain approximately one mole of sugar/mole of 6-aminopenicillanic acid. They concluded that the amino group of 6-aminopenicillanic acid and the reducing group of the sugar were involved in the interaction.

Schneider and de Weck[9] found a reaction between benzylpenicillin and a number of carbohydrates, including reducing sugars, nonreducing sugars, dextran and simple glycols. They speculated that the reaction resulted in the formation of an α-ester of penicilloic acid.

Hem et al.[10] studied the formation of 1:1 molar complexes between sucrose and a number of penicillins including anhydrous ampicillin. They found that the rate of degradation of complexed penicillin was 5-6 times the rate for the uncomplexed penicillin. The results of

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that study indicated that the sucrose-penicillin complex that formed was degraded by the same mechanism, regardless of the penicillin tested. The complexes between penicillin and sucrose appeared to form instantly, no induction period or change in the rate of degradation was observed in any case. They reported that complexation involved the intact penicillin and accelerated the degradation of penicillin but did not appear to change the degradation pathway. Ampicillin was found in that study to have a much lesser degree of complexation. They speculated that the presence of the amino group in the ampicillin side chain, which is unique with ampicillin, may interfere with complex formation due to stearic or charge factors.

Differential scanning calorimetry has previously been used to confirm the formation of complexes using physical mixtures[11]. The present authors[12] previously used differential scanning calorimetry to confirm the formation of aspartame-caffeine complexes. The stoichiometry of the aspartame-caffeine complexes were determined from the enthalpy change of the DSC transitions resulting from the complex formations.

In this study the authors investigate the possible interaction of anhydrous ampicillin and ampicillin trihydrate with anhydrous dextrose in the solid state. This is achieved by comparing the thermal behavior, using DSC, of physical mixtures of the respective original components in different molar ratios.

EXPERIMENTAL

Materials

The following materials were used: anhydrous ampicillin (Wyeth), ampicillin trihydrate (Bristol) and anhydrous dextrose (Baker).

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Preparation of Physical Mixtures

Physical mixtures of anhydrous ampicillin and anhydrous dextrose were prepared by mixing them, using mortar and pestle, in the following molar ratios: 1:0.22, 1:0.50, 1:0.83, 1:1.00, 1:1.29, 1:1.50, 1:1.94, 1:2.91, 1:4.52, 1:7.76 and 1:17.47. Physical mixtures of ampicillin trihydrate and anhydrous dextrose were prepared in the following molar ratios: 1:0.25, 1:0.56, 1:1.00, 1:1.25, 1:1.50, 1:2.00, 1:2.23, 1:3.00, 1:3.36, 1:5.24, 1:8.88 and 1:19.96.

Differential Scanning Calorimetry

Samples (4 mg) were weighed, after being finely powdered, and encapsulated in flat-bottomed aluminum pans with crimped-on lids. The samples were heated in an atmosphere of nitrogen and thermograms were obtained on a Perkin-Elmer DSC-1B Differential Scanning Calorimeter. Thermograms were obtained by heating at a constant heating rate of 10^{o}C per minute, a constant range setting of 8 mcal per second and recorded at a constant chart speed of one inch per minute. The individual substances and the physical mixtures of anhydrous ampicillin and anhydrous dextrose or ampicillin trihydrate and anhydrous dextrose were heated over the temperature range, 3C to 250^{o}C.

The area under the differential scanning calorimetric heating curve was measured using K & E planimeter, and the heat of transition was then calculated as described previously[13]. At least two replicates were made for each DSC thermogram.

RESULTS AND DISCUSSION

DSC thermograms of anhydrous ampicillin exhibit no transition when scanned over the temperature range of 30 to 214^{o}C. At 214^{o}C anhydrous ampicillin decomposed. Therefore, DSC thermograms of physical mixtures of anhydrous ampicillin with anhydrous dextrose

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will reflect the characteristic features of the latter if no interaction occurred.

DSC thermograms of anhydrous dextrose showed a melting endothermic peak with a transition temperature range from 137-163°C and with a maximum peak of transition at 152°C. At about 200°C anhydrous dextrose decomposed.

Figure 1 illustrates the DSC thermograms of anhydrous ampicillin and anhydrous dextrose, separately and in physical mixtures, while Figure 3 illustrates the enthalpy change of the physical mixtures as a function of composition. The data for Figure 3 is shown in Table 1. The DSC thermogram of a 1:0.22 molar ratio of anhydrous ampicillin-anhydrous dextrose physical mixture showed a broadened endothermic peak with an average transition temperature range from 130-159°C and with an average maximum peak of transition at 143°C. This peak corresponds to the melting transition of anhydrous dextrose, with a shift to lower temperatures from that of pure anhydrous dextrose. The decomposition temperature of this mixture was found to be 203°C, i. e., the decomposition of the mixture occurred at a temperature which is lower than that of pure anhydrous ampicillin (214°C) and a slight bit higher than that of pure anhydrous dextrose (200°C).

DSC thermograms of 1:0.5 and 1:0.83 molar ratios of anhydrous ampicillin-anhydrous dextrose physical mixtures showed the same endothermic peak but with the transition temperature range and the maximum peak of transition showing more of a shift to lower temperatures with increasing dextrose concentration. The peak area, and hence enthalpy change, also increased as the concentration of dextrose in the mixture increased (Figures 1 and 3 and Table 1). The decomposition of these mixtures was found to occur at temperatures lower

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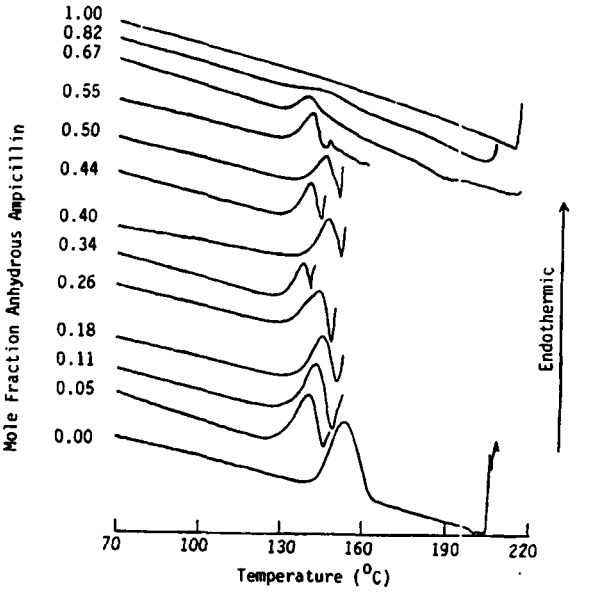

FIGURE 1
DSC thermograms of ampicillin and anhydrous dextrose separately and in physical mixtures.

than those of the pure respective original components and was found to occur, in the case of the 1:0.83 physical mixtures, at 145°C, immediately after the melting endothermic transition.

At a 1:1 molar ratio, the transition temperature range, the maximum peak of transition, the enthalpy change, and the decomposition temperature of the mixture showed higher values than in the case of the 1:0.83 and the 1:1.29 molar ratios of anhydrous ampicillin-anhydrous dextrose physical mixtures. This thermal behavior was again found for the 1:1.5 (2:3) and the 1:3 physical mixtures.

When the enthalpy change of the physical mixtures was plotted against the mole fraction of the components (Figure 3), the enthalpy change was found to pass through three maxima corresponding

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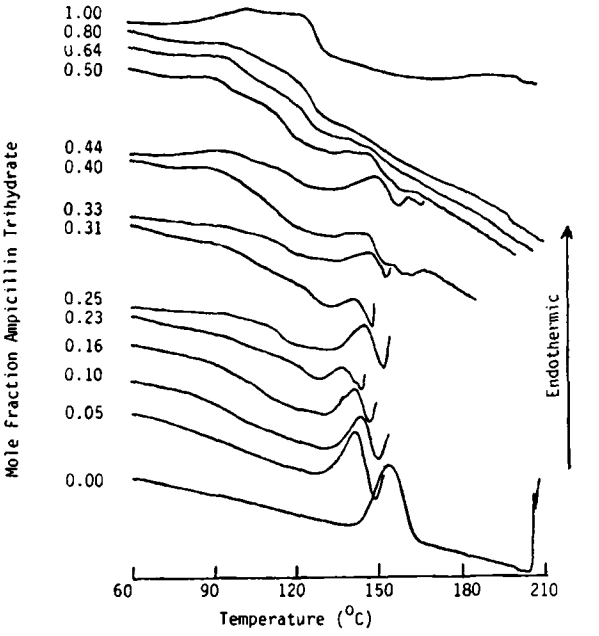

FIGURE 2

DSC thermograms of ampicillin trihydrate and anhydrous dextrose separately and in physical mixtures.

to 1:1, 2:3 and 1:3 molar ratios of anhydrous ampicillin-anhydrous dextrose physical mixtures. Since enthalpy change is an additive property, these three maxima reparsent three optimum complexation ratios, i. e., three complexes according to the method of continous variation for complexation analysis[14]. The 1:1 molar complex is in agreement with other investigations[8-10], while the 2:3 and 1:3 molar complexes of anhydrous ampicillin-anhydrous dextrose appear to be a new finding.

DSC thermograms of ampicillin trihydrate showed a broadened endothermic peak with a transition temperature range from 70-133°C representing the loss of the water of crystallization. After this

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TABLE 1

Enthalpy Change of Ampicillin - Dextrose Mixtures as a Function of Composition

Ampicillin - Dextrose Molar Ratio (mole/mole)	Mole Fraction		Enthalpy Change, Cal/g	Ampicillin Trihydrate-Dextrose Molar Ratio (mole/mole)	Mole Fraction		Enthalpy Change, Cal/g
	Anhydrous Ampicillin	Anhydrous Dextrose			Ampicillin Trihydrate	Anhydrous Dextrose	
1:0.00	1.00	0.00	——	1:0.00	1.00	0.00	——*
1:0.22	0.82	0.18	3.67	1:0.25	0.80	0.20	2.22
1:0.50	0.67	0.33	7.63	1:0.56	0.64	0.36	2.99
1:0.83	0.55	0.45	10.11	1:1.00	0.50	0.50	10.79
1:1.00	0.50	0.50	11.73	1:1.25	0.44	0.56	6.98
1:1.29	0.44	0.56	11.20	1:1.50	0.40	0.60	11.33
1:1.50	0.40	0.60	16.40	1:2.00	0.33	0.67	7.49
1:1.94	0.34	0.66	14.12	1:2.23	0.31	0.69	7.24
1:2.91	0.26	0.74	21.88	1:3.00	0.25	0.75	12.33
1:4.52	0.18	0.82	18.92	1:3.36	0.23	0.77	6.19
1:7.76	0.11	0.89	24.44	1:5.24	0.16	0.84	10.86
1:17.47	0.05	0.95	27.66	1:8.88	0.10	0.90	18.42
0:1.00	0.00	1.00	42.68	1:19.96	0.05	0.95	22.26
				0:1.00	0.00	1.00	42.68

*Ampicillin trihydrate exhibits no transition after the endothermic peak indicative of the water of crystallization loss.

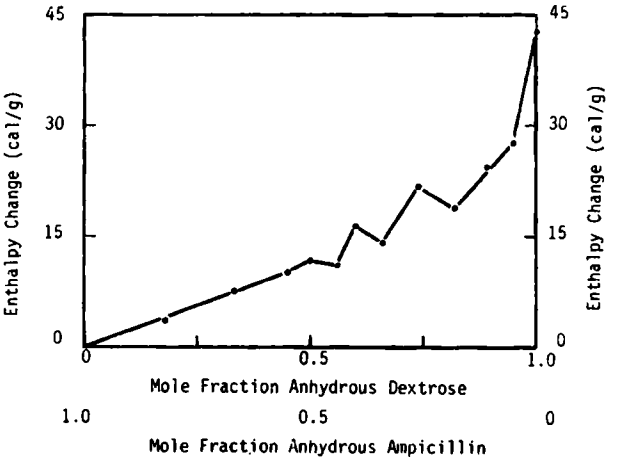

FIGURE 3

Enthalpy change of ampicillin-dextrose physical mixtures as a function of composition.

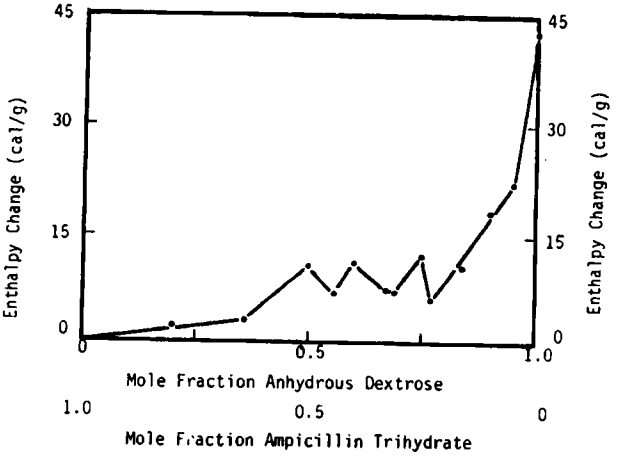

FIGURE 4

Enthalpy change of ampicillin trihydrate-dextrose physical mixtures as a function of composition.

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peak, no transition was traced until 203°C where ampicillin trihydrate decomposed. Therefore, DSC thermograms of physical mixtures of ampicillin trihydrate with anhydrous dextrose will reflect the characteristic features of the thermograms of each component if no interaction occurred.

Figure 2 illustrates the DSC thermograms of ampicillin trihydrate and anhydrous dextrose, separately and in physical mixtures, while Figure 4 illustrates the enthalpy change of the physical mixtures as a function of composition. The data for Figure 4 is presented in Table 1. It is apparent that ampicillin trihydrate-anhydrous dextrose physical mixtures exhibit more or less the same thermal behavior as in the case of the anhydrous ampicillin-anhydrous dextrose physical mixtures. The enthalpy change of the former physical mixtures was found to have lower values than in the case of the latter physical mixtures of the same molar composition. Again three complexes were traced when the enthalpy change of ampicillin trihydrate-anhydrous dextrose physical mixtures was plotted against the mole fraction of the components corresponding to 1:1, 2:3 and 1:3 molar ratios (Figure 4).

It is apparent that the decomposition of physical mixtures of ampicillin, the anhydrous and trihydrate, with anhydrous dextrose occurs at temperatures markedly lower than those of the pure respective original components. Mixtures containing 0.5 mole or more of anhydrous dextrose were found to decompose immediately after their melting transitions. This is in agreement with the conclusion of Hem et al.[10] in that the complexed penicillin degrades 5-6 times as fast as the uncomplexed penicillin and results in an increased overall rate of degradation.

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The enthalpy change of the anhydrous ampicillin and ampicillin trihydrate physical mixtures was found to be 10.7-36.7 or 15.7-75.8 percent less, respectively, than the predicted values calculated from the exact percentage contribution of dextrose to the total enthalpy change of the mixture. This decrease in the enthalpy change also indicates interaction between ampicillin, anhydrous and trihydrate, and anhydrous dextrose, in the solid state, under the experimental conditions.

CORRESPONDENCE

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