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AMPICILLIN-DIRECT COMPRESSION EXCIPIENTS: PREFORMULATION STABILITY SCREENING USING DIFFERENTIAL SCANNING CALORIMETRY

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ABSTRACT

Differential scanning calorimetry was used as a screening technique for assessing the compatibility of anhydrous ampicillin with some of the direct compression excipients. Anhydrous ampicillin was found to be compatible with Avicel PH 101, Avicel PH 105, Elcema F 150, Elcema G 250, Sta-Rx 1500 and Cab-O-Sil, while incompatible with sorbitol, Di-Pac and dicalcium phosphate dihydrate. Anhydrous ampicillin appears to form complexes with mannitol, granular mannitol and Brownex sugar after their melting transitions. It appears that stearic acid and L-(-)-leucine can be used as lubricants in formulations containing anhydrous ampicillin while magnesium stearate cannot.

INTRODUCTION

Simon[1], Jacobson and Reier[2], Lee and Hersey[3] and Geneidi et al.[4-6] have utilized differential thermal analysis (DTA) as a tool for the rapid evaluation of interactions of drugs with excipients in preformulation stability studies. Guillory et al.[7] evaluated the utility of thermal methods, including DTA, for the detection of possible interactions

occurring between solid components of pharmaceuticals. Geneidi et al.[6] concluded that DTA at the preformulation stage offers a possible help in the solution of the problem of drug-drug and drug-additives interactions.

Although differential scanning calorimetry (DSC) yields data which are inherently more quantitative and more amenable to theoretical interpretation than the technique of DTA, it does not seem to have been used as widely at the latter[8]. Kono et al.[9] utilized DSC in a study of comaptibility problems involving phenobarbital. El-Shattawy et al.[10] previsouly used DSC as a screening technique for assessing the compatibility of aspartame with some of the direct compression excipients. In this investigation, the author used DSC in preformulation stability studies on anhydrous ampicillin.

Ampicillin and its sodium salt were reported to be incompatible with several pharmaceuticals[11-13]. A number of reports[14-17] indicated that injections containing dextrose, sodium chloride, or dextrose and sodium chloride, laevulose and sodium lactate caused the inactivation of ampicillin sodium. Lynn[18] found that the stability of ampicillin sodium was adversely affected by the addition of glycerol or propylene glycol.

Hem et al.[19] studied the formation of 1:1 molar complexes between sucrose and a number of penicillins including anhydrous ampicillin. Ampicillin was found in that study to have a much lesses degree of complexation. El-Shattawy et al[20] utilized DSC to confirm the formation of 1:1, 2:3 and 1:3 molar complexes between ampicillin, anhydrous and trihydrate, and anhydrous dextrose.

In this study the author investigated the compatibility of anhydrous ampicillin with some of the direct compression excipients.

This is achieved by comparing the DSC thermogram of ampicillin and each of the investigated excipients with 1:1 mixtures of ampicillin and excipient. Although it cannot be conclusively stated that an interaction incompatibility will occur during storage at room temperature[3], DSC can distinguish between those excipients unlikely to cause a problem and those that may cause trouble and thereby a more rational approach to early formulation designs can be established.

EXPERIMENTAL

Materials

THe following materials were used: anhydrous ampicillin (Wyeth), Avicel PH 101 and Avicel PH 105 (FMC), Elcema F 150 and Elcema G 250 (Dequssa), Sta-Rx 1500 (Staley), Cab-O-Sil (Cabot), mannitol and granular mannitol (ICI Americas), sorbitol (Pfizer), Brownex sugar and Di-Pac (Amstar), dicalcium phosphate dihydrate (Baker), stearic acid (Ruger Chemical), L-(-)-leucine (Eastman Kodak) and magnesium stearate (Mallinckrodt).

Differential Scanning Calorimetry

Samples (2-8 mg) were weighed, after being finely powdered, and encapsulated in flat-bottomed aluminum pans with crimped-on lids. Volatile sample pans with tightly sealed lids were used for those samples containing L-(-)-leucine. 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°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 1:1 physical mixtures of ampicillin and excipients, prepared with mortar and pestle, were heated over the temperature range, 30 to 250°C.

The area under the differential scanning calorimetric heating curve was measured using a K & E planimeter, and the heat of transition was then calculated as described previously[10]. At least two replicates were made for each DSC thermogram.

RESULTS AND DISCUSSION

In a previous investigation[20], anhydrous ampicillin has been shown by DSC to exhibit no transition when scanned over the temperature range of 30 to 214°C. At 214°C anhydrous ampicillin decomposed. Avicel PH 101, Avicel PH 105, Elcema F 150, Elcema G 250, Sta-Rx 1500 and Cab-O-Sil exhibit no transition when scanned individually over the temperature range of 30 to 350°C[10]. Therefore, DSC thermograms of mixtures of the excipients with anhydrous ampicillin will reflect the characteristic features of the thermograms of each component if no interaction occurred. This is indeed the case as the resulting DSC thermograms showed no transition over the temperature range of 30 to about 200°C At about 200°C, decomposition peaks corresponding to anhydrous ampicillin decomposition, with a slight shift to lower temperatures, were observed.

The DSC thermogram of mannitol (Trace 2 of Figure 1) showed a melting endothermic peak with an average transition temperature range from 155-169°C and with an average maximum peak of transition at 166°C. No decomposition was observed on scanning until 300°C. The DSC thermogram of anhydrous ampicillin-mannitol mixture (Trace 3 of Figure 1) showed an endothermic peak corresponding to the melting transition of mannitol. The down curve of this peak continued below the scanning base line to form a small exotherm, with an average transition temperature range from 169-172°C and with an average maximum peak of transition at 170°C, before decomposition occurred at 172°C. This small exothermic peak may be attributed to the formation of an anhydrous

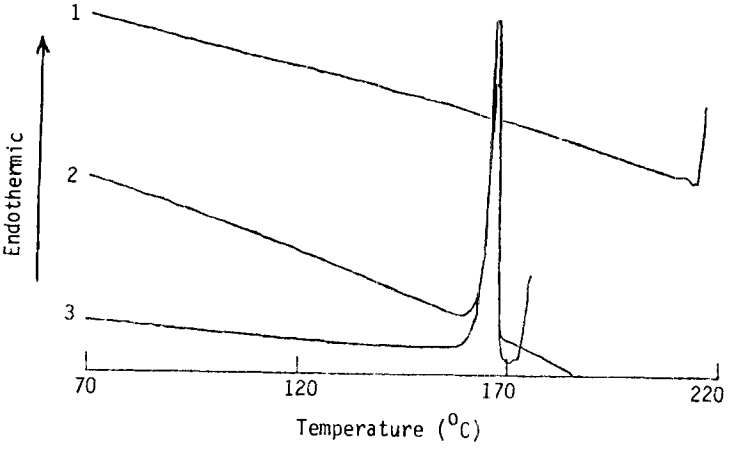

FIGURE 1

DSC thermogram of ampicillin (1), mannitol (2) and 1:1 ampicillin mannitol mixture.

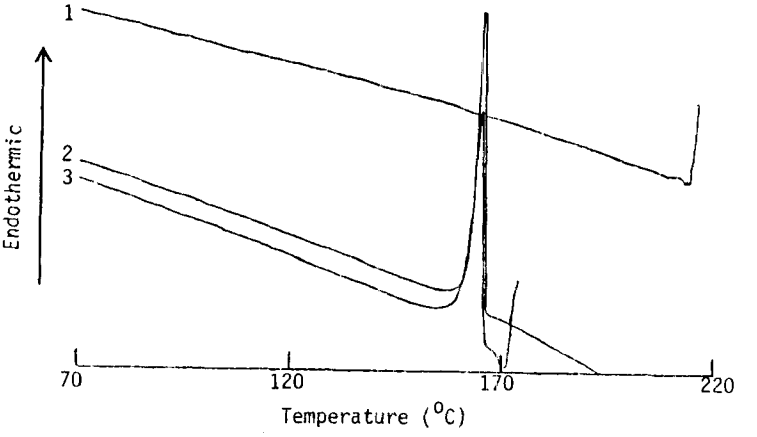

FIGURE 2

DSC thermogram of ampicillin (1), granular mannitol (2) and 1:1 ampicillin-granular mannitol mixture (3).

ampicillin-mannitol complex. The immediate decomposition of the anhydrous ampicillin-mannitol mixture after the melting transition and at temperatures markedly lower than those of the pure respective original components is in agreement with previous conclusions[20] in that complexed ampicillin decomposed at markedly lower temperatures than uncomplexed ampicillin. This finding is also in agreement with the conclusion of Hem et al.[19] in that the complexed penicillin degrades 5-6 times as fast as the uncomplexed penicillin and results in an increased overall rate of degradation. The enthalpy change of the mixture was found to be 28.02 cal/g, i. e., quantitatively identical to the predicted value calculated from the exact percentage contribution of mannitol to the total enthalpy change of the mixture indicating no incompatibility between anhydrous ampicillin and mannitol before the melting transition, i. e., before 155°C.

The thermal behavior of granular mannitol, alone and in physical mixture with anhydrous ampicillin, was found to be more or less the same as with mannitol and is illustrated in Figure 2.

The DSC thermogram of sorbitol (Trace 2 of Figure 3) showed a double peaked transition, the first one with a transition temperature range from 65-80°C and with a maximum peak of transition at 78°C, the second one with a transition temperature range from 80-94°C and with a maximum peak of transition at 90°C. No decomposition was observed on scanning until 240°C[10]. The DSC thermogram of the anhydrous ampicillin-sorbitol mixture (Trace 3 of Figure 3) showed the same double peaked transition with the same transition temperature range and maximum peak of transition. The enthalpy change, cal/g of the first peak was found to be 71.8% the predicted value calculated for the mixture first peak. It has been reported that sorbitol is hygroscopic and

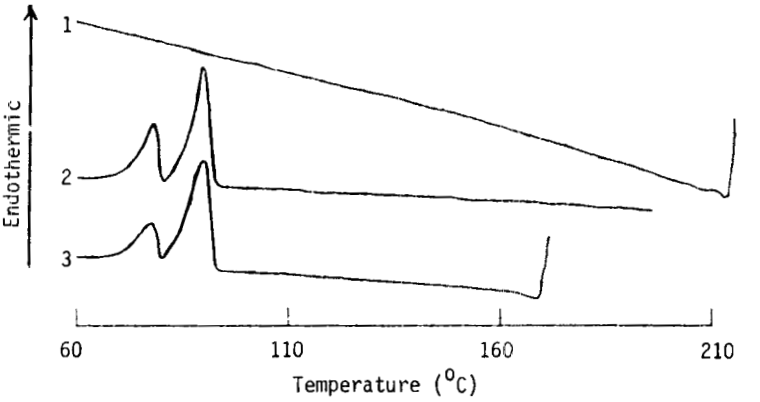

FIGURE 3

DSC thermograms of ampicillin (1), sorbitol (2) and 1:1 ampicillin-sorbitol mixture.

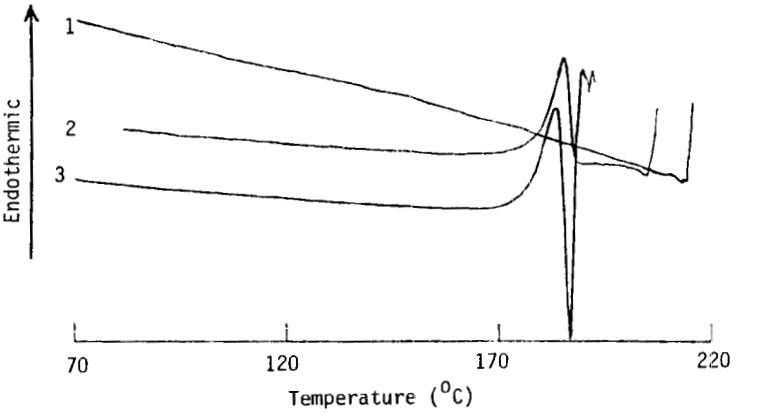

FIGURE 4

DSC thermogram of ampicillin (1), Brownex sugar (2) and 1:1 ampicillin-Brownex sugar mixture.

that its moisture content could make it deleterious to most active ingredients with which it might be tableted[21,22]. As the first sorbitol endotherm occurs from 65°to 80°, it is possible that the incompatibility of sorbitol with anhydrous ampicillin may be due, in part,

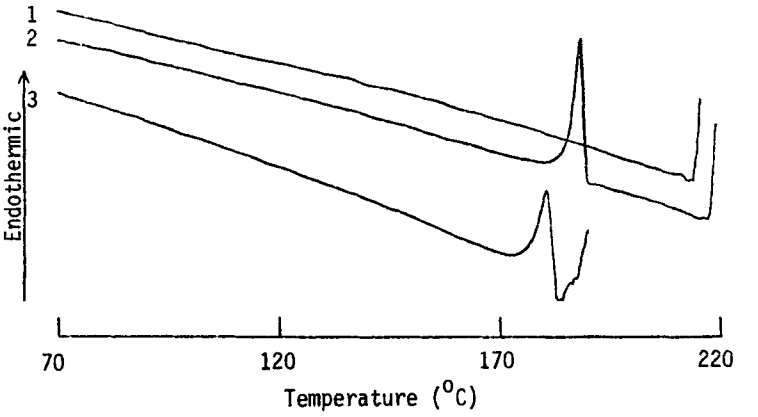

FIGURE 5
DSC thermogram of ampicillin (1), Di-Pac (2) and 1:1 ampicillin-Di-Pac mixture.

to moisture present in sorbitol. The decomposition of anhydrous ampicillin-sorbitol mixture was found to be at about 170°C, i. e., markedly lower than those of the pure respective orginal components.

Trace 3 of Figure 4 is the thermogram of an anhydrous ampicillin-Brownex sugar mixture which shows the same phenomena as in the case of the anhydrous ampicillin-mannitol mixture, but the exotherm that followed the melting endothermic transition of the mixture is sharp and more distinct. The mixture decomposed at 188°C immediately after the melting transition and at a temperature lower than those of the pure repsective original components. The enthalpy change of the mixture was found to be quantitatively identical to the predicted value indicating no incompatibility between anhydrous ampicillin and Brownex sugar before the melting transition, i. e., before 165°C.

Trace 3 of Figure 5 is the thermogram of an anhydrous ampicillin-Di-Pac mixture, which shows the melting endothermic peak corresponding to Di-Pac with the transition temperature range and maximum peak

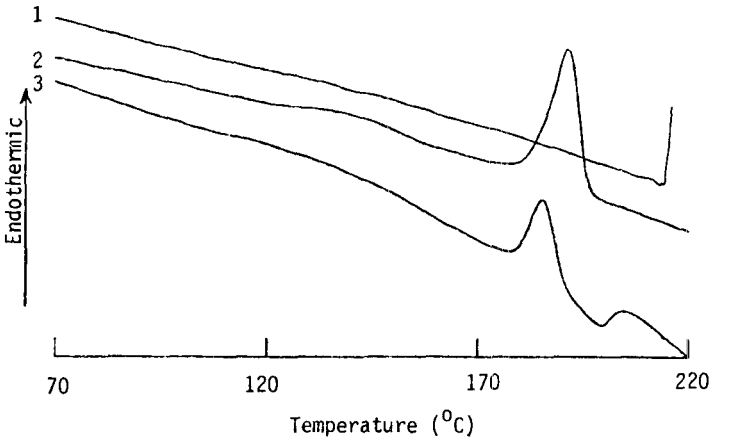

FIGURE 6

DSC thermogram of ampicillin (1), dicalcium phosphate dihydrate (2) and 1:1 ampicillin-dicalcijm phosphate dihydrate mixture.

of transition shifted to lower temperatures. As in the case of the anhydrous ampicillin-mannitol mixture, the melting endothermic peak was followed by a small exotherm before decomposition occurred at 186°C, i. e., immediately after the melting transition and at a temperature markedly lower than those of the pure respective original components. The enthalpy change of the mixture was found to be 86.1% of the predicted value indicating the possible incompatibility between anhydrous ampicillin and Di-Pac under these conditions. Di-Pac is prepared by the co-crystallization of sucrose with small amounts of modified dextrins[21]. Therefore, its interaction with anhydrous ampicillin is in agreement with Schneider and de Weck[23] who found a reaction between benzylpenicillin and a number of carbohydrates, including reducing sugars, nonreducing sugars, dextran and simple glycols.

The DSC thermogram of dicalcium phosphate dihydrate (Trace 2 of Figure 6) showed a broadened transition corresponding to the loss of water

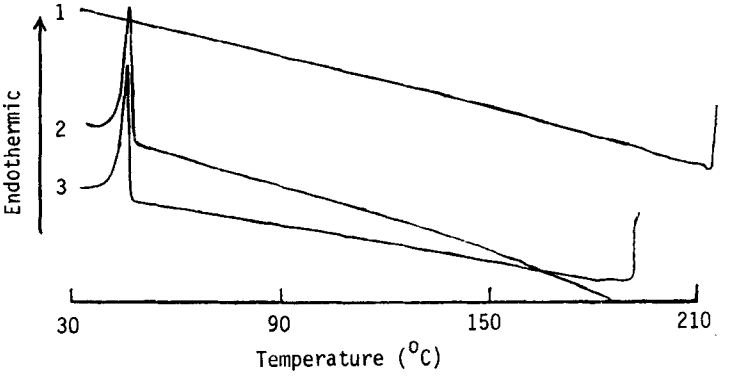

FIGURE 7

DSC thermograms of ampicillin (1), stearic acid (2) and 1:1 ampicillin-stearic acid mixture (3).

of crystallization followed by a melting endothermic peak with a transition temperature range from 172-202°C and with a maximum peak of transition at 191°C. Trace 3 of Figure 6 is the thermogram of anhydrous ampicillin-dicalcium phosphate dihydrate mixture, which shows the broadened transition corresponding to the loss of dicalcium phosphate dihydrate water of crystallization followed by the melting endothermic peak of the latter but with the transition temperature range and the maximum peak of transition shifted to lower temperatures. A decomposition peak was traced at 198°C corresponding to anhydrous ampicillin decomposition with a slight shift to lower temperature. The enthalpy change of the mixture was found to be 48.8% the predicted value indicating the possible incompatibility under these conditions.

Trace 3 of Figure 7 is the thermogram of anhydrous ampicillin-stearic acid mixture which combined the features characteristic of the thermograms of each component, but with anhydrous ampicillin decomposition slightly shifted to lower temperature at 191°C. The

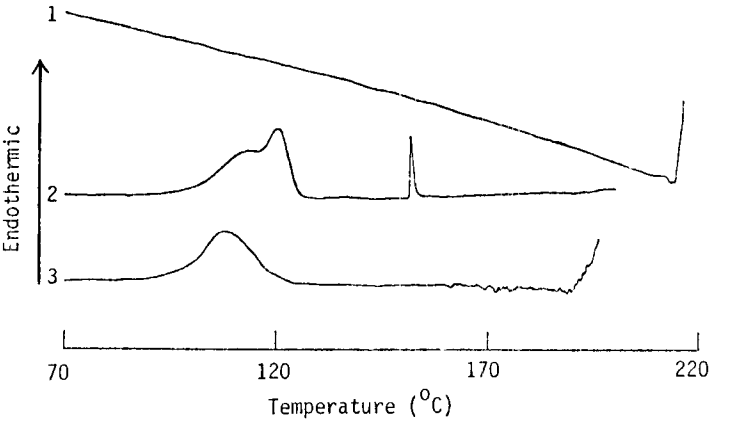

FIGURE 8

DSC thermogram of ampicillin (1), magnesium stearate (2) and 1:1 ampicillin-magnesium stearate mixture (3).

enthalpy change of the mixture was found to be quantitatively identical to the predicted value indicating no incompatibility under these conditions. This finding is in agreement with Jacobson and Reier[2] who concluded that the DTA thermal pattern for the ampicillin trihydrate-stearic acid mixture showed no significant alterations and that mixture was presumed to be stable.

L-(-)-leucine exhibits no transition when scanned over the temperature range of 30 to 285°C; after that a sublimation endotherm begins. Therefore, DSC thermogram of anhydrous ampicillin-leucine mixture will reflect the characteristic features of the thermograms of each component if no interaction occurred. This is indeed the case as the DSC thermogram of the mixture showed no transition over the temperature range of 30 to 206°C. At 206°C decomposition peak corresponding to anhydrous ampicillin decomposition, with a slight shift to lower temperature, was observed.

Trace 3 of Figure 8 is the thermogram of an anhydrous ampicillin-magnesium stearate mixture. The second endotherm of magnesium stearate has been obliterated and a rapid decomposition at 160°C occurred. The enthalpy change of the mixture was found to be 68.8% the predicted value indicating also the possible incompatibility of magnesium stearate with anhydrous ampicillin.

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