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CEPHALEXIN-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 cephalexin with some of the direct compression excipients. Cephalexin was found to be compatible with Avicel PH 101, Avicel PH 105, Elcema F 150, Elcema G 250, Solka-floc BW 100, Sta-Rx 1500 and Cab-O-Sil, while incompatible with Emdex, Brownex sugar, sorbitol, mannitol, granular mannitol, dicalcium phosphate dihydrate, Di-Tab and Emcompress. Cephalexin appears to interact with Di-Pac after its melting transition. It appears that L-(-)-leucine can be used as lubricant in formulations containing cephalexin while stearic acid and magnesium stearate cannot.

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INTRODUCTION

The authors[1] previously used differential scanning calorimetry (DSC) as a screening technique for assessing the compatibility of aspartame with some of the direct compression excipients. El-Shattawy[2] also used DSC in preformulation stability studies on anhydroud ampicillin. Anhydrous ampicillin was found in that study to be incompatible with magnesium stearate, sorbitol and Di-Pac, and appears to form complexes with mannitol, granular mannitol and Brownex sugar after their melting transitions. The compatibilities of anhydrous ampicillin and ampicillin trihydrate with dextrose[3] and with aspartame[4] were also investigated by the present authors. Anhydrous dextrose and aspartame were found to form complexes with anhydrous ampicillin and ampicillin trihydrate.

Whatever the factors which are considered in the formulation of any of the β-lactame antibiotics, the stability and clinical response of these antibiotics must always be satisfactory. It has been reported that to eliminate penicillin and cephalosporin allergenicity, the final product must be pure and free of contaminants[5]. Obviously, the pharmaceutical formulator must remain aware of the possible degradations of the β-lactame antibiotics and must excercise due care in the design of new dosage forms to ensure that no adjuvant is added that could interact to produce allergenic by-products[6].

Bond et al.[7] discussed some of the problems considered in the formulation of cephalexin. In this study, the authors investigated the compatibility of cephalexin with some of the direct compression excipients. This was achieved by comparing the DSC thermograms of cephalexin and each of the investigated excipients with 1:1 mixtures of cephalexin and excipients. Although it cannot be conclusively

stated that an interaction incompatibility will occur during storage at room temperature, there are often sufficient excipients available in a preformulation program to choose only those unlikely to cause trouble[8].

EXPERIMENTAL

Materials

The following materials were used: cephalexin (Eli Lilly & Co.), Avicel PH 101 and Avicel PH 105 (FMC), Elcema F 150 and Elcema G 250 (Dequssa), Solka-floc BW 100, Emdex and Emcompress (E. Mendell), Sta-Rx 1500 (Staley), Cab-O-Sil (Cabot), Brownex sugar and Di-Pac (Amstar), sorbitol (Pfizer), mannitol and granular mannitol (ICI Americas), dicalcium phosphate dihydrate (Baker), Di-Tab (Stauffer Chemical), L-(-)-leucine (Eastman Kodak), stearic acid (Ruger Chemical) 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-1 B 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 cephalexin and excipients, prepared with mortar and pestle were heated over the temperature range, 30 to 300°C.

The area under the differential scanning calorimetric heating curve was measured using a K & E planimeter and the heat of transi-

tion was then calculated as described previously[1]. At least two replicates were made for each DSC thermogram.

RESULTS AND DISCUSSION

The DSC thermograms of cephalexin (Trace 1 of Figures 1-8) exhibit no transition when scanned over the temperature range of 30 to 178°C. At 178°C cephalexin thermograms showed an exotherm with a transition temperature range from 178-198°C and with a maximum peak of transition at 195°C. At 198°C cephalexin decomposed. Avicel PH 101, Avicel PH 105, Elcema F 150, Elcema G 250, Solka-floc BW 100, Sta-Rx 1500 and Cab-O-Sil exhibit no transition when scanned individually over the temperature range of 30 to 300°C. Therefore, DSC thermograms of mixtures of the excipients with cephalexin 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 175-180°C. At about 175-180°C, exothermic peaks corresponding to cephalexin were observed.

The DSC thermograms of Emdex (Trace 2 of Figure 1) showed two endothermic peaks, the first one with an average transition temperature range from 49-103°C and with an average maximum peak of transition at 78°C, the second one with an average transition temperature range from 129-157°C and with an average maximum peak of transition at 148°C. At about 200°C, Emdex decomposed. The DSC thermogram of the cephalexin-Emdex mixture (Trace 3 of Figure 1) showed the same two endothermic peaks with the transition temperature range and the maximum peak of transition shifted to lower temperatures. The enthalpy change, cal/g, of the first peak was found to be 60.86% of the predicted value calculated from the exact percentage contribu-

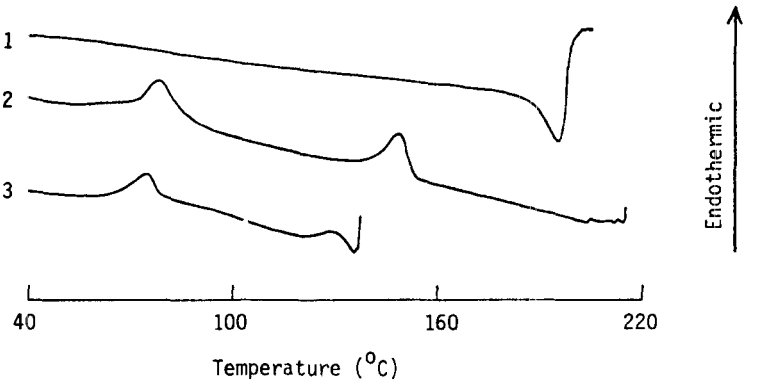

FIGURE 1

DSC thermograms of cephalexin (1), Emdex (2) and 1:1 cephalexin-Emdex mixture (3).

tion of Emdex to the total enthalpy change of the mixture first peak, while that of the second peak was found to be 43.52% of the predicted value indicating the possible incompatibility of Emdex with cephalexin under the experimental conditions. The decomposition of cephalexin-Emdex mixture was found to be at about 138°C, i. e., markedly lower than those of the pure respective original components, again indicated the possible incompatibility.

The DSC thermograms of Brownex sugar (Trace 2 of Figure 2) showed a melting endothermic peak with an average transition temperature range from 168-188°C and with an average maximum peak of transition at 185°C. At about 208°C, Brownex sugar decomposed. The DSC thermogram of cephalexin-Brownex sugar mixture (Trace 3 of Figure 2) showed an endothermic peak corresponding to the melting transition of Brownex sugar. The down curve of this peak continued below the scanning base line to form a sharp exotherm with an average transition temperature range from 178-181°C and with an average maximum peak of transition

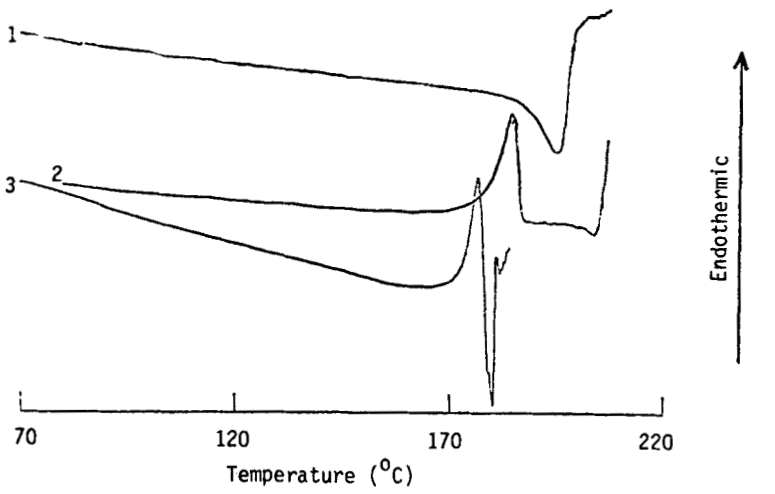

FIGURE 2

DSC thermograms of cephalexin (1), Brownex sugar (2) and 1:1 cephalexin-Brownex sugar mixture (3).

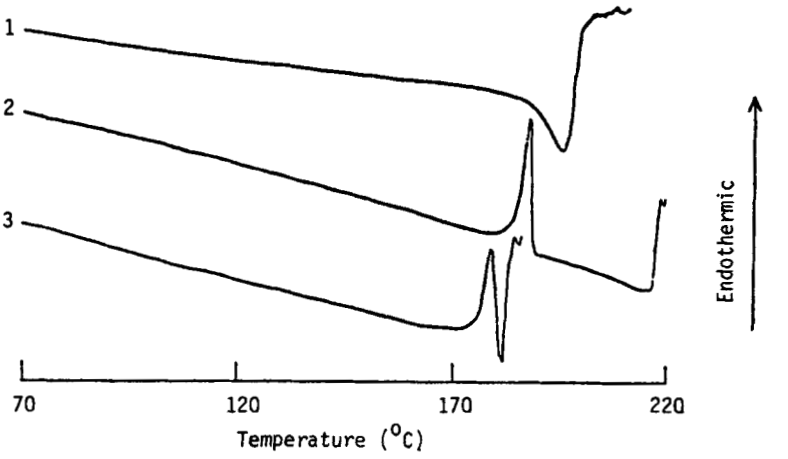

FIGURE 3

DSC thermograms of cephalexin (1), Di-Pac (2) and 1:1 cephalexin-Di-Pac mixture (3).

at 180°C before decomposition occurred at about 181°C. The enthalpy change cal/g of the mixture endotherm was found to be 79.56% of the predicted value indicating the possible incompatibility of Brownex sugar with cephalexin under the experimental conditions.

Trace 3 of Figure 3 is the thermogram of a cephalexin-Di-Pac mixture which shows the same phenomena as in the case of the cephalexin-Brownex sugar mixture but the exotherm that followed the melting endothermic transition of the mixture is small. The enthalpy change of the mixture was found to be quantitatively identical to the predicted value indicating no incompatibility between cephalexin and Di-Pac before the melting transition, i. e., before 163°C. The mixture decomposed at 182°C immediately after the melting transition and at a temperature lower than those of the pure respective original components indicating the possible interaction between cephalexin and Di-Pac after the melting transition.

The DSC thermogram of sorbitol (Trace 2 of Figure 4) 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[1]. The DSC thermogram of the cephalexin-sorbitol mixture (Trace 3 of Figure 4) showed one broadened transition with an average transition temperature range from 51-93°C. The decomposition temperature of the mixture was found to be at 142°C. This change in the thermal behavior of the mixture and its decomposition at markedly lower temperature than those of the pure respective original components indicated the possible incompatibility of sorbitol with cephalexin under the experimental conditions.

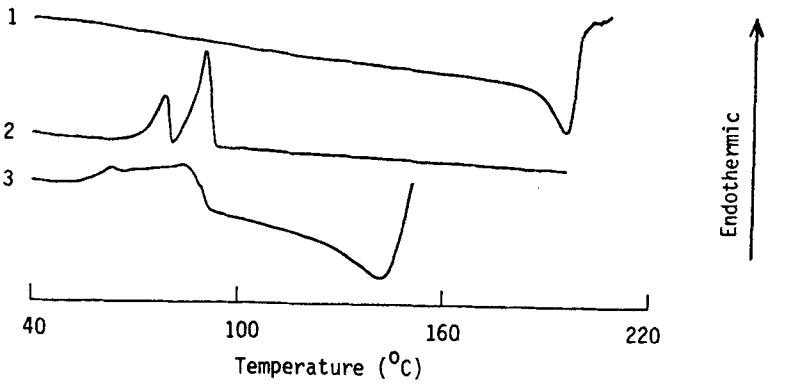

FIGURE 4

DSC thermograms of cephalexin (1), sorbitol (2) and 1:1 cephalexin-sorbitol mixture (3).

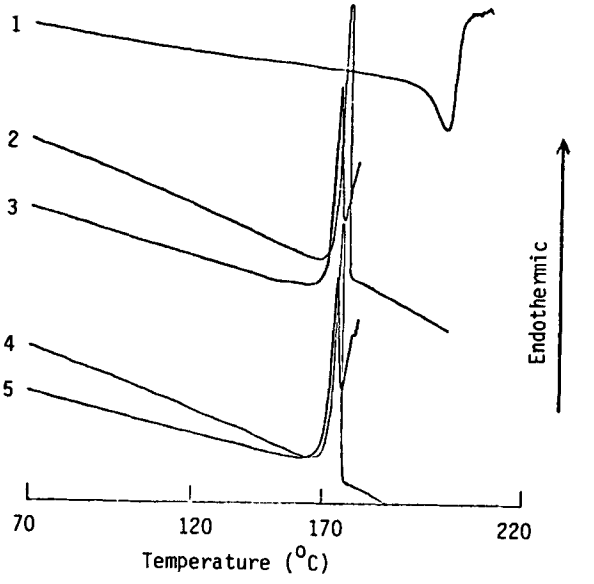

FIGURE 5

DSC thermograms of cephalexin (1), mannitol (2), 1:1 cephalexin-mannitol mixture (3), granular mannitol (4) and 1:1 cephalexin-granular mannitol mixture (5).

The DSC thermogram of mannitol (Trace 2 of Figure 5) 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 cephalexin-mannitol mixture (Trace 3 of Figure 5) showed an endothermic peak corresponding to the melting transition of mannitol. Before the down curve of this peak returned to the program line decomposition occurred at about 165°C indicating the possible incompatibility of mannitol with cephalexin under the experimental conditions.

The thermal behavior of granular mannitol, alone and in physical mixture with cephalexin, was found to be more or less the same as with mannitol and is illustrated in Figure 5 (Traces 4 and 5).

The possible incompatibility of cephalexin with Emdex, Brownex sugar, Di-Pac, sorbitol, mannitol and granular mannitol is in agreement with the literature in that the cephalosporins are readily attacked, smiliar to penicillins, by nucleophilic reagents[5]. This finding is also in agreement with previous work on anhydrous ampicillin[2] and with Schneider and de Weck[9] 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 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 cephalexin-dicalcium phosphate dihydrate mixture which shows the broadened transition corresponding to the loss of dicalcium phosphate dihydrate water of crystallization followed by the melting

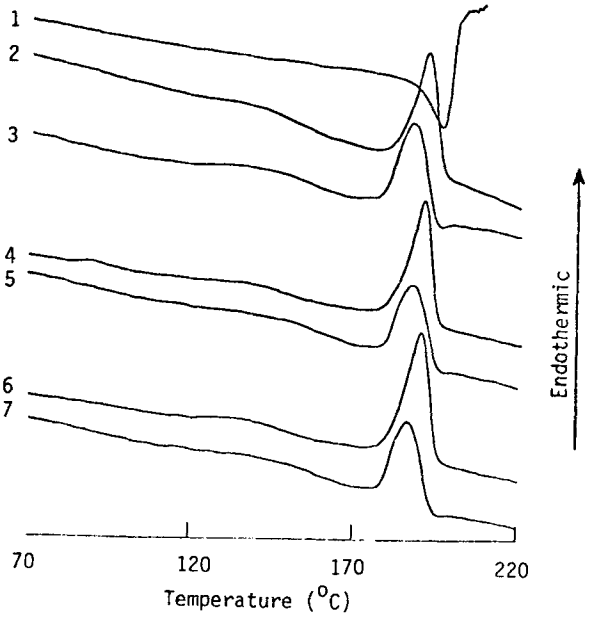

FIGURE 6

DSC thermograms of cephalexin (1), dicalcium phosphate dihydrate (2), 1:1 cephalexin-dicalcium phosphate dihydrate mixture (3), Di-Tab (4), 1:1 cephalexin-Di-Tab mixture (5), Emcompress (6) and 1:1 cephalexin-Emcompress mixture (7).

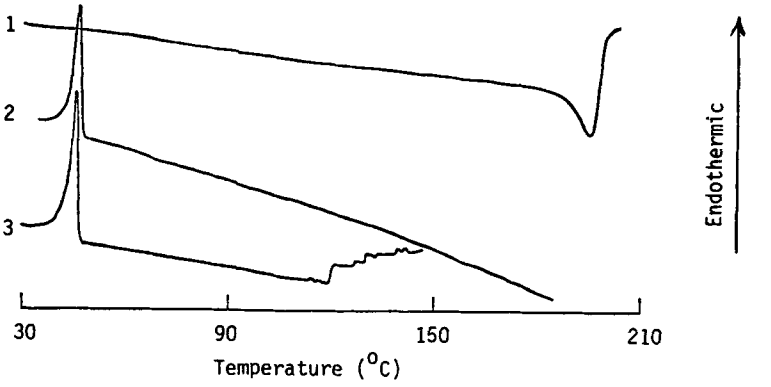

FIGURE 7

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

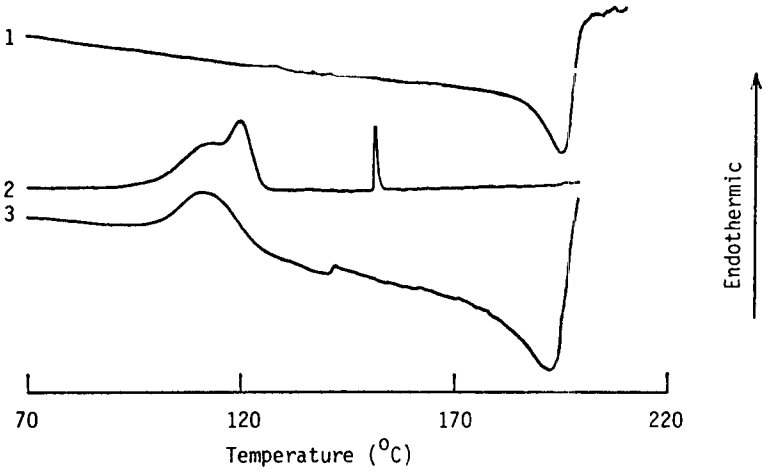

FIGURE 8

DSC thermograms of cephalexin (1), magnesium stearate (2) and 1:1 cephalexin-magnesium stearate mixture (3).

endothermic peak of the latter but with the transition temperature range and the maximum peak of transition slightly shifted to lower temperatures. The thermal behavior of Di-Tab and Emcompress alone and in physical mixtures with cephalexin was found, as expected, to be more or less the same as with dicalcium phosphate dihydrate and is illustrated in Figure 6 (Traces 4-7). The enthalpy change of mixtures of cephalexin with dicalcium phosphate dihydrate, Di-Tab and with Emcompress was found to be 88.54, 83.89 and 75.64%, respectively, of the predicted values indicating the possible incompatibility under these conditions.

L-(-)-leucine exhibits no transition when scanned over the temperature range of 30 to 285°C; after that a sublimation endotherm begins. Therefore, the DSC thermogram of cephalexin-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 175°C. At 175°C the exotherm corresponding to cephalexin was traced.

Trace 3 of Figure 7 is the thermogram of cephalexin-stearic acid mixture which shows the features characteristic of the thermograms of each component until 114°C. At 114°C the mixture decomposed. The enthalpy change of the mixture was found to be quantitatively identical to the predicted value indicating no incompatibility before decomposition, i.e., before 114°C. The unchanged melting point of the stearic acid in the mixture from that observed with pure stearic acid is a further support. However, the decomposition of the mixture at a temperature markedly lower than those of the pure respective original components is a result of a severe test, since stearic acid was present in the mixture in equal weight ratio while the usual concentration of it as a lubricant is only from 1-5%[10]. Decomposition only occurred above 114°C and may not be a problem at room temperature; however, if the reaction does proceed at room temperature, it would probably be observed only after prolonged storage.[8]

Trace 3 of Figure 8 is the thermogram of cephalexin-magnesium stearate mixture. The second endotherm of magnesium stearate has been broadened and shifted to lower temperatures. The enthalpy change of the mixture was found to be 80.66% of the predicted value indicating the possible incompatibility of magnesium stearate with cephalexin under the experimental conditions.

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