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# DIFFERENTIAL SCANNING CALORIMETRY OF CEPHALEXIN-DEXTROSE AND CEPHALEXIN-ASPARTAME MIXTURES

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## ABSTRACT

The possible interaction of cephalexin with anhydrous dextrose and with aspartame, in the solid state, was investigaged by comparing the thermal behavior of physical mixtures of the respective original components in different molar ratios, using differential scanning calorimetry. Both anhydrous dextrose and aspartame were found to form complexes with cephalexin. The stoichiometries of these complexes were found to be 1:1 molar complexes between cephalexin and anhydrous dextrose and 4:1 and 1:1 molar complexes between cephalexin and aspartame. Complexed cephalexin was found to decompose at markedly lower temperatures than uncomplexed cephalexin.

## INTRODUCTION

Whatever the factors which are considered in the formulation of any of the B-lactam antibiotics, the stability and clinical response

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of these antibiotics must always be satisfactory. Besides the proteinaceous contaminants which may be largely responsible for the induction of hypersensitivity and anaphylactic reactions in patients treated with the B-lactam antibiotics[1-6], these antibiotics contain polymers that are formed in solution by internal reactions between the intact and degraded molecules[7,8]. The polymerization normally takes place as a chain reaction, initiated by the degradation product and influenced by pH, temperature, oxygenation and other factors[9]. Thus, to eliminate penicillin and cephalosporin allerginicity, the final product must be pure and free of contaminants. Obviously, the pharmaceutical formulator must remain aware of the possible degradations of the B-lactam 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[10].

The authors previously used differential scanning calorimetry (DSC) for assessing the compatibilities of anhydrous ampicillin and ampicillin trihydrate with dextrose[11] and with aspartame[12]. Anhydrous dextrose and aspartame were found to form complexes with anhydrous ampicillin and ampicillin trihydrate. The authors[13] also used DSC in preformulation stability studies on cephalexin. Cephalexin was found in that study to be incompatible with Emdex, Brownex sugar, sorbital, mannitol, granular mannitol, dicalcium phosphate dihydrate, Di-Tab, Emcompress, stearic acid, and magnesium stearate and appears to interact with Di-Pac after its melting transition.

In this study the authors investigate the possible interaction of cephalexin with anhydrous dextrose and with aspartame in the solid state. This was 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: cephalexin (Eli Lilly & Co.), anhydrous dextrose (Baker) and aspartame (G.D. Searle & Co.).

### Preparation of Physical Mixtures

Physical mixtures of cephalexin and anhydrous dextrose were prepared by mixing them, using a mortar and pestle, in the following molar ratios: 1:0.17, 1:0.25, 1:0.33, 1:0.50, 1:1.00, 1:1.25, 1:1.50, 1:1.75, 1:2.00, 1:2.50, 1:3.00, 1:4.00, 1:6.00, 1:9.00 and 1:12.00 Physical mixtures of cephalexin and aspartame were prepared in the following molar ratios: 1:0.17, 1:0.25, 1:0.33, 1:0.50, 1:1.00, 1:1.25, 1:1.50, 1:2.00, 1:3.00, 1:4.00, 1:6.00 and 1:9.00.

### 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 cephalexin and anhydrous dextrose were heated over the temperature range of 30 to $230^{o}$C, while in the case of cephalexin and aspartame, they were heated over the temperature range of 30 to $280^{o}$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[14]. At least two replicates were made for each DSC thermogram.

## RESULTS AND DISCUSSION

DSC thermograms of cephalexin 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.

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. Therefore, DSC thermograms of physical mixtures of cephalexin with anhydrous dextrose will reflect the characteristic features of the thermograms of each component if no interaction occurred.

Figure 1 illustrates the DSC thermograms of cephalexin and anhydrous dextrose, separately and in physical mixtures, while Figure 2 illustrates the enthalpy change of the physical mixtures as a function of composition. The data in Figure 2 is shown in Table 1. The DSC thermogram of a 1:0.17 molar ratio of cephalexin-anhydrous dextrose physical mixture showed two transitions. The first one is a broadened exothermic peak with an average transition temperature range from 130-161°C and with an average maximum peak of transition at 147°C. This peak corresponds to the melting transition of anhydrous dextrose, with a shift to lower temperatures from that of pure anhydrous dextrose. The second transition with transition temperature range from 175-200°C and with maximum peak of transition at 196°C, corresponds to the exothermic peak of cephalexin, with a change in the peak's height-to-width ratio. The mixture decomposed immediately after the exothermic peak.

DSC thermograms of 1:0.25 and 1:0.33 molar ratios of cephalexin-anhydrous dextrose physical mixtures showed the same transitions as

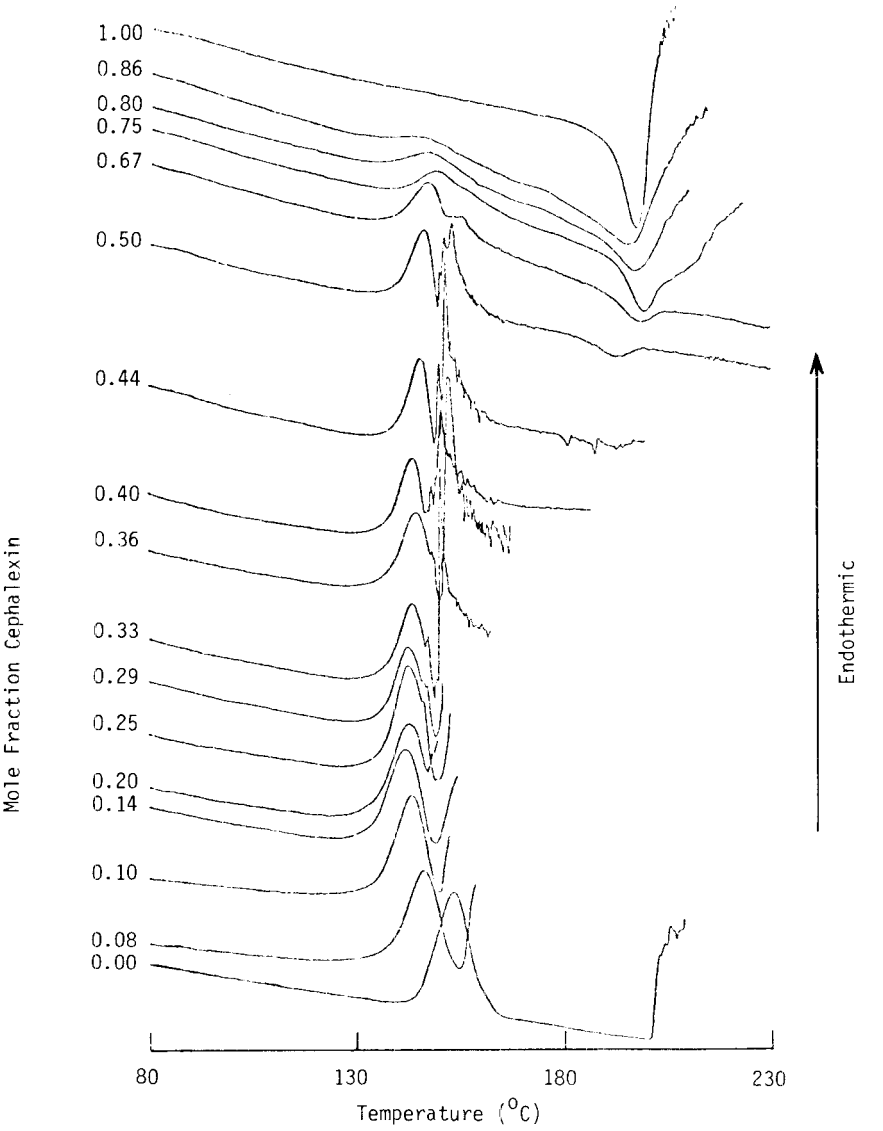


FIGURE 1

DSC thermograms of cephalexin and anhydrous dextrose separately and in physical mixtures.

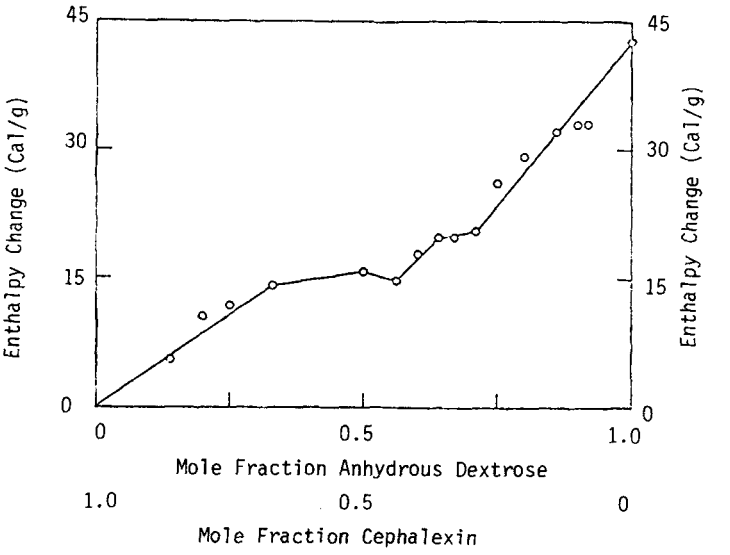


FIGURE 2

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

in the case of the 1:0.17 mixture but with the transition temperature range and the maximum peak of transition of the endotherm and the exotherm as well as the decomposition temperature of the mixtures shifted to higher temperatures with increasing dextrose concentration.

At a 1:0.5 molar ratio, a multiple endothermic transition with an average transition temperature range from 130-168°C and with an average maximum peak of transition at 148°C was traced. The exothermic transition corresponding to cephalexin showing more of a shift to higher temperatures.

At a 1:1 molar ratio, a decomposition was traced at 150°C following immediately the melting endothermic peak of dextrose. This may be attributed to a decomposition of cephalexin-dextrose complex formed during the melting transition of dextrose. The DSC thermograms of

TABLE 1

Enthalpy Change of Cephalexin-Anhydrous Dextrose and Cephalexin-Aspartame Mixtures as a Function of Composition

| Cephalexin-Anhydrous Dextrose Molar Ratio (mole/mole) | Mole Fraction | | Enthalpy Change Cal/g | Cephalexin-Aspartame Molar Ratio (mole/mole) | Mole Fraction | | Enthalpy Change Cal/g |
|---|---|---|---|---|---|---|---|
| | Cephalexin | Anhydrous Dextrose | | | Cephalexin | Aspartame | |
| 1 : 0.00 | 1.00 | 0.00 | ——* | 1 : 0.00 | 1.00 | 0.00 | ——* |
| 1 : 0.17 | 0.86 | 0.14 | 5.48 | 1 : 0.17 | 0.86 | 0.14 | 1.67 |
| 1 : 0.25 | 0.80 | 0.20 | 10.52 | 1 : 0.25 | 0.80 | 0.20 | 2.30 |
| 1 : 0.33 | 0.75 | 0.25 | 11.87 | 1 : 0.33 | 0.75 | 0.25 | 2.20 |
| 1 : 0.50 | 0.67 | 0.33 | 14.11 | 1 : 0.50 | 0.67 | 0.33 | 2.81 |
| 1 : 1.00 | 0.50 | 0.50 | 15.76 | 1 : 1.00 | 0.50 | 0.50 | 4.66 |
| 1 : 1.25 | 0.44 | 0.56 | 14.76 | 1 : 1.25 | 0.44 | 0.56 | 4.12 |
| 1 : 1.50 | 0.40 | 0.60 | 17.92 | 1 : 1.50 | 0.40 | 0.60 | 7.25 |
| 1 : 1.75 | 0.36 | 0.64 | 19.76 | 1 : 2.00 | 0.33 | 0.67 | 10.84 |
| 1 : 2.00 | 0.33 | 0.67 | 19.80 | 1 : 3.00 | 0.25 | 0.75 | 14.58 |
| 1 : 2.50 | 0.29 | 0.71 | 20.51 | 1 : 4.00 | 0.20 | 0.80 | 16.26 |
| 1 : 3.00 | 0.25 | 0.75 | 26.16 | 1 : 6.00 | 0.14 | 0.86 | 18.05 |
| 1 : 4.00 | 0.20 | 0.80 | 29.25 | 1 : 9.00 | 0.10 | 0.90 | 19.66 |
| 1 : 6.00 | 0.14 | 0.86 | 32.13 | 0 : 1.00 | 0.00 | 1.00 | 21.91 |
| 1 : 9.00 | 0.10 | 0.90 | 33.06 | | | | |
| 1 :12.00 | 0.08 | 0.92 | 33.20 | | | | |
| 0 : 1.00 | 0.00 | 1.00 | 42.68 | | | | |

*Cephalexin exhibits no transition before the exothermic peak preceding its decomposition.

all the other investigated mixtures showed the same thermal behavior as in the case of the 1:1 mixture. The interaction of cephalexin with anhydrous dextrose is in agreement with the literature in that the cephalosporins are readily attacked, similar to penicillins, by nucleophilic reagents[15]. The immediate decomposition of the cephalexin-dextrose mixtures after the melting transition and at a temperature markedly lower than those of the pure respective original components indicates that complexed cephalexin decomposes at markedly lower temperatures than uncomplexed cephalexin. This finding is in agreement with the previous conclusion[11,12] with ampicillin and also in agreement with the conclusion of Hem et al.[16] that the complexed penicillin degrades 5-6 times as fast as the uncomplexed penicillin and results in an increased overall rate of degradation.

When the enthalpy change of the physical mixtures was plotted against the mole fraction of the components (Figure 2), the enthalpy change was found to pass through a maximum corresponding to 1:1 molar ratio of cephalexin-anhydrous dextrose physical mixture. Since enthalpy change is an additive property, this maximum represents an optimum complexation ratio according to the method of continuous variation for complexation analysis[17].

In a previous investigation[14], aspartame has been shown by DSC to have two endothermic peaks. The first one, with a transition temperature range from 167-190°C and with a maximum peak of transition at 185°C, represents the loss of the methyl ester and conversion to the dipeptide, aspartylphenylalanine. The second peak, with a transition temperature range from 234-254°C and with a maximum peak of transition at 249°C, represents the conversion to diketopiperazine (DKP). At 266°C the DKP decomposed. Therefore, DSC thermograms of

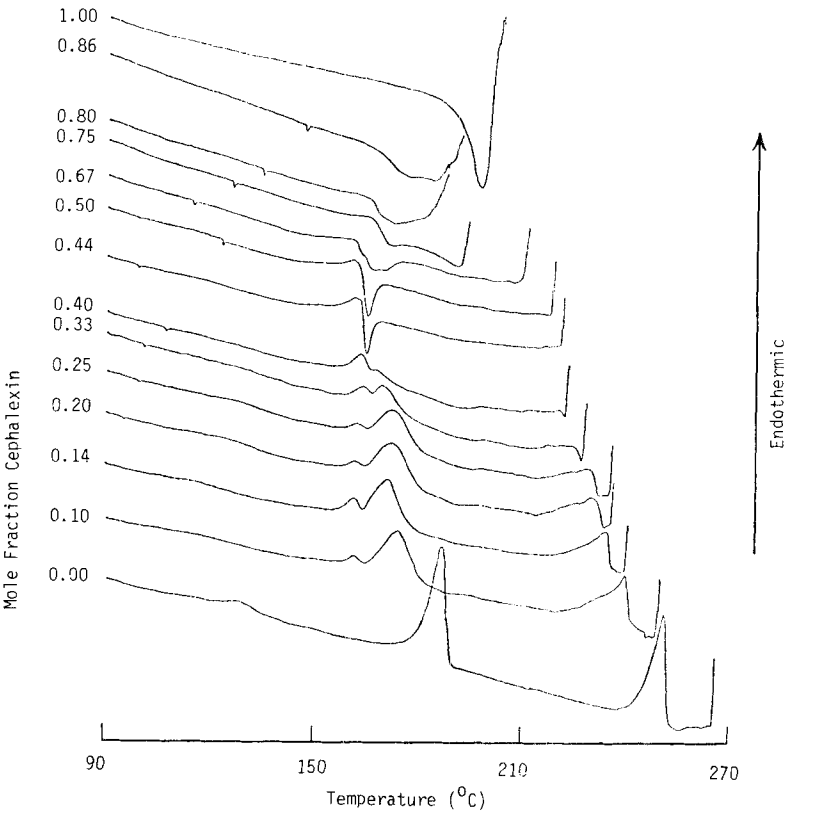


FIGURE 3

DSC thermograms of cephalexin and aspartame separately and in physical mixtures.

physical mixtures of cephalexin with aspartame will reflect the characteristic features of the thermograms of each component if no interaction occurred.

Figure 3 illustrates the DSC thermograms of cephalexin and aspartame, 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 shown in Table 1. The DSC thermogram of 1:0.17 molar ratio of cephalexin-aspartame physical

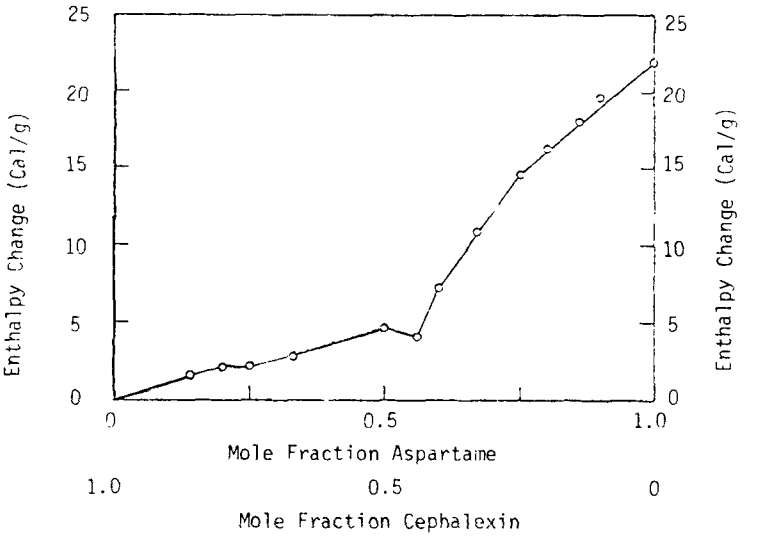


FIGURE 4

Enthalpy change of cephalexin-aspartame physical mixtures as a function of composition.

mixture showed a small exotherm with a maximum peak of transition at 147°C followed by a broadened endotherm with a transition temperature range from 149-169°C and with a maximum peak of transition at 164°C. This endotherm corresponds to the first peak of aspartame with a shift to lower temperatures from that of pure aspartame. The decomposition of this mixture was found to be 172°C, i. e., the mixture decomposed at a temperature which is markedly lower than those of the pure respective original components. The enthalpy change of this mixture was found to be 35% less than the predicted value calculated from the exact percentage contribution of aspartame to the total enthalpy change of the mixture. This decrease in the enthalpy change indicates interaction between cephalexin and aspartame in the solid state under the experimental conditions.

A 1:0.25 molar ratio of cephalexin-aspartame physical mixture showed the same peaks as in the case of the previously mentioned mixture but with the transition temperature range and the maximum peak of transition shifted to lower temperatures. At this molar ratio, the decomposition temperature of 168°C was the minimum observed for all the physical mixtures investigated and the decomposition was found to occur immediately after the endothermic transition. The immediate decomposition of the mixture after the transition and at a temperature markedly lower than those of the pure respective original components is in agreement with previous conclusion in this study that complexed cephalexin decomposes at markedly lower temperatures than uncomplexed cephalexin.

DSC thermograms of 1:0.33, 1:0.50, 1:1 and 1:1.25 molar ratios of cephalexin-aspartame physical mixtures showed the same peaks as in the case of the 1:0.17 and 1:0.25 mixtures but the down curve of the endothermic peak continued below the scanning base line to form an exotherm. Since the first peak of aspartame represents the loss of the methyl ester, this exothermic peak may be attributed to a complex rearrangement involving the resulting free carboxyl group. The area of this exotherm increases to a maximum reflecting a new complex stoichiometry at 1:1 molar ratio of cephalexin to aspartame. A small endothermic peak, representing uncomplexed aspartame, appears immediately after the up curve of this exotherm. The decomposition temperatures of these mixtures were found to be 192, 203, 212 and 220°C, i. e., the decomposition temperatures increasedas the concentration of aspartame in the mixture increased reflecting the relative thermal stability of the rearranged complexes. One interesting finding is that the thermal behavior of these cephalexin-aspar-

tame mixtures is more or less the same as in the case of anhydrous ampicillin-aspartame mixtures but with different molar ratios[12].

When the enthalpy change of the physical mixtures was plotted against the mole fraction of the components (Figure 4), the enthalpy change was found to pass through two maxima corresponding to 1:0.25 (4:1) and 1:1 molar ratios of cephalexin-aspartame physical mixtures; these maxima represent two optimum complexation ratios[17].

DSC thermograms of 1:1.5, 1:2, 1:3, 1:4, 1:6 and 1:9 molar ratios of cephalexin-aspartame physical mixtures showed a double peaked transition. The area of the first peak, representing complexed aspartame, decreased as the concentration of aspartame in the mixtures increased, reflecting the decreasing amount of cephalexin present. As would be expected, the area of the second peak, representing uncomplexed aspartame, and the final peak of aspartame, representing DKP formation, increased as the concentration of aspartame in the mixture increased. The decomposition temperatures of these mixtures were also shifted to higher temperatures as aspartame concentration in the mixture increased.

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