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ASPARTAME-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 Aspartame with some of the currently available direct compression excipients. Aspartame was found to be compatible with Avicel PH 101, Avicel PH 105, Elcema F 150, Elcema G 250, Sta-Rx 1500, Cab-O-Sil, Sorbitol, Di-Pac and Brownex Sugar, while incompatible with dicalcium phosphate dihydrate. It appears that stearic acid can be used as a lubricant in formulations containing Aspartame while magnesium stearate cannot.

INTRODUCTION

Aspartame, a new intense sweetener, is N-L-aspartyl-L-phenylalanine-1-methyl ester. It was found to have a potency of 100-200 times sucrose and to be devoid of unpleasant aftertaste[1-6]. Unlike any other sweetener, aspartame is a protein and is metabolized by the body in its normal pathways. It is not an artificial sweetener under U.S. law. The original regulation for Aspartame approved its use as a sugar substitute in tablet and packet forms[6].

The presence of both the free, unsubstituted amino and one carboxyl group of aspartic acid as well as the distance between them and the absolute configuration of the asymmetric carbon are completely critical for sweetness; the requirement of absolute L configuration also holds for phenylalanine[3]. The methyl ester is the most potent ester[5].

Aspartame contains an ester linkage that, under certain moisture, temperature and pH conditions, may hydrolyze to the dipeptide, aspartylphenlalanine, which can then cyclize to the corresponding diketopiperazine (DKP). Prolonged cooking temperatures can cause significant breakdown of aspartame to diketopiperazine, with a consequent loss of sweetness[6]. Aspartame did not degrade with storage for 12 weeks at 50^{0}C and 50% relative humidity[1]. It, however, discolors in the presence of ascorbic and tartaric acids[1].

Lee and Hersey[7] reported the utility of differential thermal analysis in preformulation stability screening of oxytetracycline tablet formulations. Simon[8], Jacobson and Reier[9] and Geneidi et al.[10-12] have utilized this technique as a tool for the rapid evaluation of

interactions of drugs with excipients in preformulation stability studies.

Kono et al.[13] utilized differential scanning calorimetry in a study of compatibility problems involving phenobarbital. They performed the analysis by running DSC curves on the individual components in the mixture and finally on the mixture itself. In this manner they were able to detect any possible interactions and potential compatibility problems.

Whenever a material undergoes a change in physical state, such as melting or transition from one crystalline form to another, or whenever it reacts chemically, heat is either absorbed or liberated. Many such processes can be initiated simply by raising the temperature of the material. Modern differential scanning calorimeters are designed to determine the enthalpies of these processes by measuring the differential heat flow required to maintain a sample of the material and an inert reference at the same temperature. This temperature is usually programmed to scan a temperature range by increasing linearly at a predetermined rate. DSC yields data which are inherently more quantitative and more amenable to theoretical interpretation than the technique of DTA[14].

By comparing the DSC thermogram of aspartame and each of a number of excipients currently used in direct compression with mixtures of aspartame and excipient, it is possible to ascertain if an excipient is likely to be suitable in a formulation containing aspartame. While this is not conclusive, because of the elevated temperatures used[7], 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: Aspartame (G.D. Searle & Co.), Avicel PH 101 and Avicel PH 105 (FMC), Elcema F 150 and Elcema G 250 (Dequssa), Sta-Rx 1500 (Staley), Cab-O-Sil (Cabot), Sorbitol (Pfizer), Di-Pac and Brownex sugar (Amstar), dicalcium phosphate dihydrate (Baker), stearic acid (Ruger Chemical) and magnesium stearate (Mallinckrodt).

Differential Scanning Calorimetry

Samples (2-10 mg) were weighed, after being finely powdered, and encapsulated in flat-bottomed aluminum pans with crimped-on lids; these 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 1:1 physical mixtures of aspartame and excipients, prepared with mortar and pestle, were heated over the temperature range, 30 to 350^{o}C.

The measurement of the area under the curve provided the direct base for the calculation of the energy needed for the transition. This measurement was taken by a planimeter (K & E). In order to convert this area reading to calories, a rectangular area on the

chart which is one half of the chart in width and in length equal to one minute of run was measured by the planimeter. The heat of transition was then calculated by the following general equation[15]:

$$\text{Transition energy of sample (calories)} = \frac{\text{area of the sample transition peak} \times \text{RANGE setting} \times 60}{\text{area of the rectangle} \times 1000 \times 2}$$

At least two replicates were made for each DSC thermogram.

RESULTS AND DISCUSSION

Trace 1 of Figure 1 is that of aspartame. The first endothermic peak, with temperature range of transition at 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. The second endothermic peak, with temperature range of transition at 234-254°C and with a maximum peak of transition at 249°C, represents the converstion to the DKP. At 266°C the DKP decomposed. The enthalpy change (cal/g) of the first transition of aspartame was taken as a base for assessing its stability in this work. This is because a DSC peak area is a true electrical energy measurement, the magnitude of which does not depend on any of the thermal constants of the sample or apparatus[16].

Traces 2-7 of Figure 1 are the thermograms of 1:1 physical mixtures of aspartame with Avicel PH 101, Avicel PH 105, Elcema F 150, Elcema G 250, Sta-Rx 1500 and Cab-O-Sil respectively. These excipients exhibit no transition when scanned individually over the temperature range of 30 to 350°C. Therefore, DSC thermograms of mixtures of the excipients with aspartame will reflect the characteristic features of aspartame if no incompatibility occurred. This

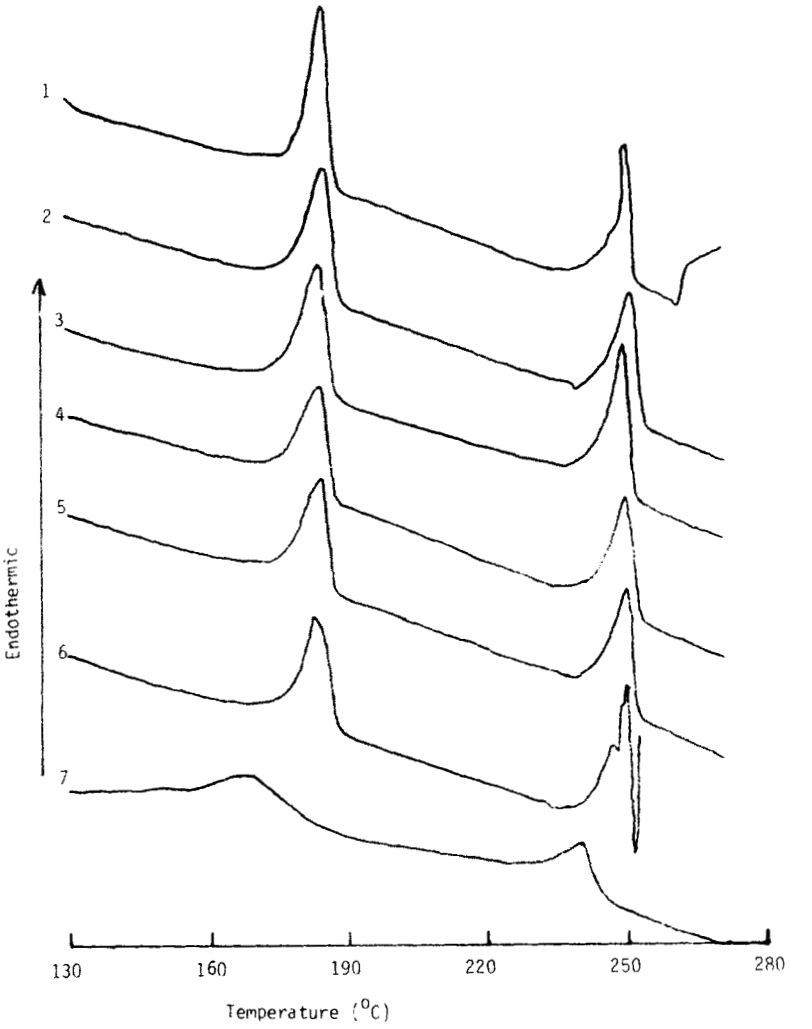

FIGURE 1

DSC thermograms of Aspartame (1) and mixtures thereof with Avicel PH 101 (2), Avicel PH 105 (3), Elcema F 150 (4), Elcema G 250 (5), Sta-Rx 1500 (6) and Cab-O-Sil (7).

is indeed the case as seen in Figure 1 and Table 1. Some change in peak shape and height-to-width ratio was expected because of possible differences in the mixture sample geometry[17, 18].

TABLE 1: DSC thermogram characteristics of 5 mg sample of aspartame and 10 mg 1:1 mixtures thereof with different excipients.

Thermogram of	First Transition				Second Transition	
	Temp. Range of Transition, °C	Peak Maximum of transition, °C	Peak Area Cal.	Enthalpy Change Cal/g	Temp. Range of Transition, °C	Peak Maximum of transition, °C
Aspartame	167-190	185	0.1095	21.91	234-254	249
Aspartame - Avicel PH 101	165-190	185	0.1049	20.97	234-254	250
Aspartame - Avicel PH 105	165-190	184	0.1086	21.72	234-253	249
Aspartame - Elcema F 150	160-189	184	0.1062	21.23	234-253	249
Aspartame - Elcema G 250	160-189	184	0.1041	20.81	234-252	249
Aspartame - Sta-Rx 1500	160-192	183	0.1112	22.23	232-250	249
Aspartame - Cab-O-Sil	135-188	167	0.1107	22.14	210-256	239

Trace 7 of Figure 1 is the thermogram of the aspartame-Cab-O-Sil mixture. The transition temperature range is much broader than that of the other mixtures and the two peaks are shifted to lower temperatures; however, the enthalpy change of the mixture is quantitatively identical to that of aspartame alone, as seen in Table 1, indicating no incompatibility under these conditions. One interesting finding is that with all mixtures, except that containing Sta-Rx 1500, there was no decomposition traced at 266°C. While this delay in DKP decomposition may be attributed to the presence of these excipients, the more or less rapid decomposition with Sta-Rx 1500 at 250°C may be due to the moisture content of starch.

The thermogram of the aspartame-sorbitol mixture shown in Trace 3 of Figure 2 combined the features characteristic of the thermograms of each component. The temperatures of transition of the two peaks characteristic to aspartame were shifted to lower temperatures as was the temperature of decomposition of DKP. The width of the peaks broadened and the peak's shape became irregular in comparison to those of aspartame alone. This change in peak's shape did not alter the energy of transition of the mixture which was found to be 22.04 cal/g, i.e., quantitatively identical to that of aspartame alone indicating no incompatibility under these conditions.

Trace 2 of Figure 3 is the thermogram of Di-Pac, which shows one well-shaped peak close to that of aspartame. Trace 3 of Figure 3 is the thermogram of aspartame-Di-Pac mixture. Four transitions were observed corresponding to the first peak of aspartame, the Di-Pac peak, the Di-Pac decomposition and the second peak of aspar-

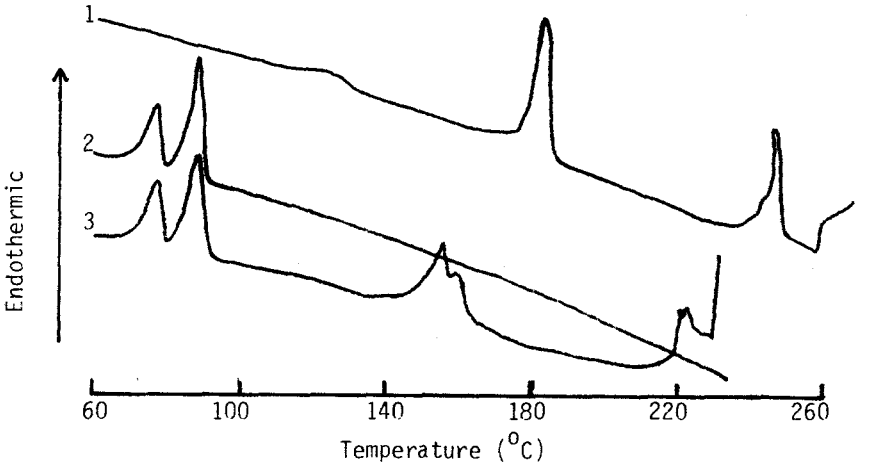

FIGURE 2

DSC thermograms of Aspartame (1), Sorbitol (2) and 1:1 Aspartame-Sorbitol mixture (3).

ame respectively, but with a shift to lower temperatures. The enthalpy changes, corresponding to the first peak of aspartame and the Di-Pak peak, was found to have a value of 22.53 cal/g which is close to the mean of the enthalpy changes of aspartame and Di-Pac (22.28 cal/g). This means that there was no change in the energy of transition of the two components as a result of mixing them together. indicating no incompatibility under these conditions.

Trace 3 of Figure 4 is the thermogram of an aspartame-Brownex sugar mixture, which shows the same phenomena as in the case of aspartame-Di-Pac mixture, but with an additional transition corresponding to the DKP decomposition with a shift to lower temperature. The enthalpy change, corresponding to the first peak of aspartame and the Brownex sugar peak, was found to have a value of 20.57 cal/g.

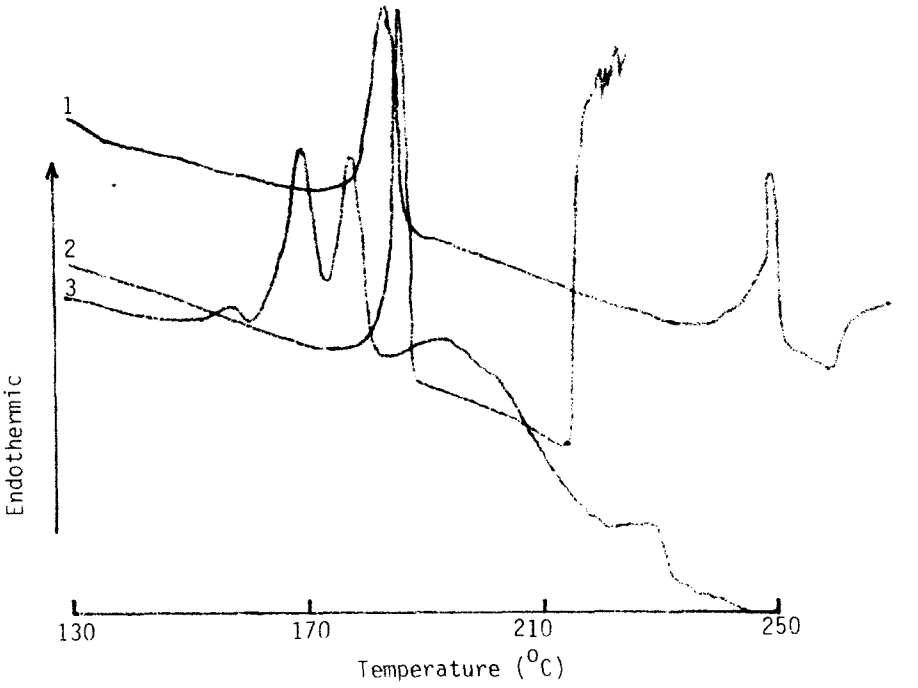

FIGURE 3

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

This value is about 93.3% the mean of the enthalpy changes of aspartame and Brownex sugar, indicating no incompatibility under these conditions.

Trace 2 of Figure 5 is the thermogram of a 5 mg sample of dicalcium phosphate dihydrate, which shows one well-shaped peak close to that of aspartame. Trace 3 of Figure 5 is the thermogram of a 4 mg sample of a 1:1 aspartame-dicalcium phosphate dihydrate mixture. Two transitions were observed, the first one representing the sum of the enthalpy change of the aspartame first peak and that

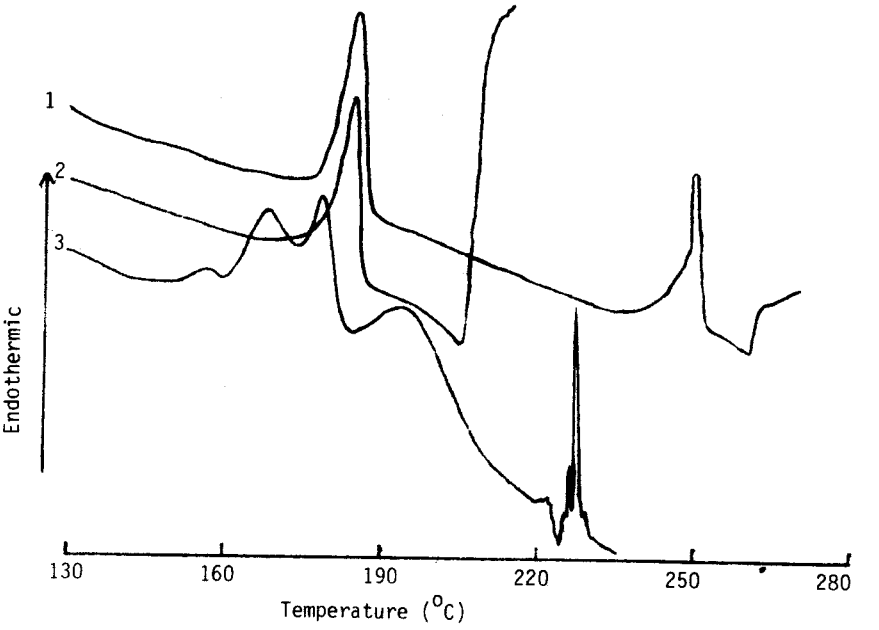

FIGURE 4

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

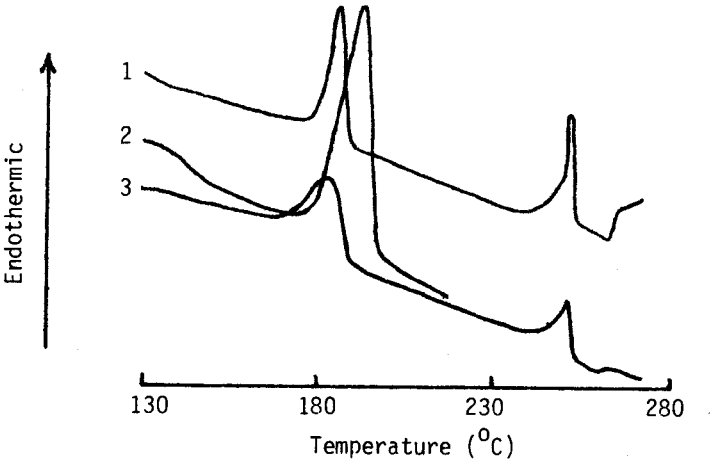

FIGURE 5

DSC thermograms of Aspartame (1), Dicalcium phosphate dihydrate (2) and 1:1 Aspartame-Dicalcium phosphate dihydrate mixture (3).

of dicalcium phosphate dihydrate, while the second one representing the second peak of aspartame. The first enthalpy change was found to have a value of 43.81 cal/g. This value is about 83.9% the mean of the enthalpy changes of aspartame and dicalcium phosphate dihydrate. This decrease in the enthalpy change of the mixture may be attributed to the partial loss of the methyl ester of aspartame, and hence, the partial conversion to the dipeptide before the transition temperature. It may, therefore, be indicative of an incompatibility at higher temperatures.

Trace 3 of Figure 6 is the thermogram of an aspartame-magnesium stearate mixture. The endotherms characteristic to aspartame and the second endotherm of magnesium stearate have been obliterated and a rapid decomposition at 128°C occurred. This indicates the possible incompatibility of magnesium stearate with aspartame.

Trace 3 of Figure 7 is the thermogram of aspartame-stearic acid mixture which combined the features characteristic of the thermograms of each component, but with a shift to lower temperatures as regards the two peaks of aspartame and the decomposition of DKP. A new transition with an irregular peak shape following the melting endotherm of stearic acid was observed which may be due to salt formation or the dissolution of aspartame in the stearic acid melt. In spite of the change in the peak shape characteristic for the first transition of aspartame, the energy of transition was found to be 21.27 cal/g, almost quantitatively identical to that of aspartame alone indicating the possible use of stearic acid as a lubricant in formulations containing aspartame.

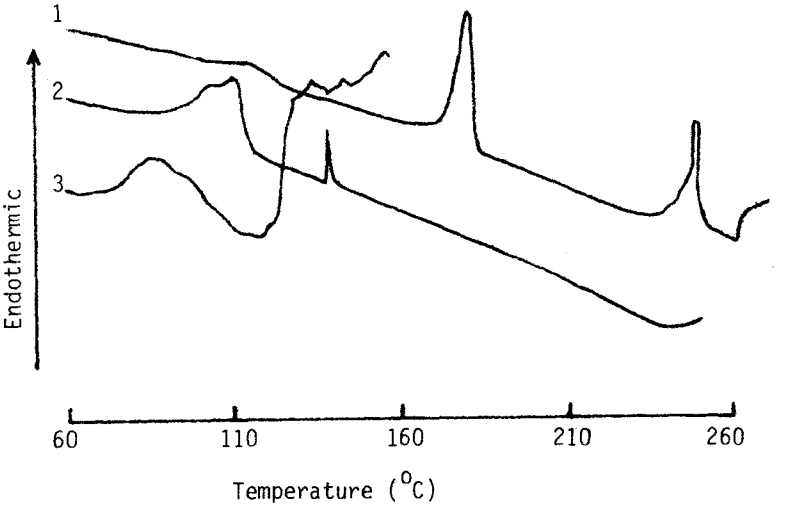

FIGURE 6

DSC thermograms of Aspartame (1), Magnesium stearate (2) and 1:1 Aspartame-Magnesium stearate (3).

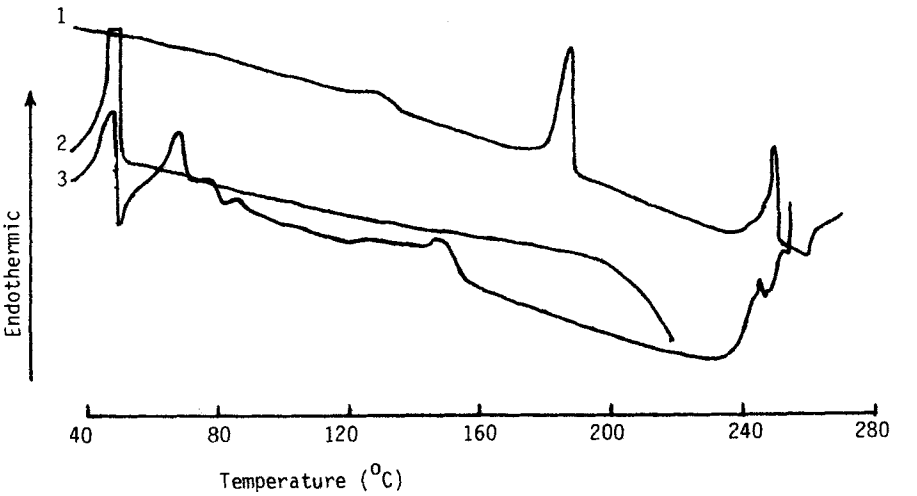

FIGURE 7

DSC thermograms of Aspartame (1), Stearic acid (2) and 1:1 Aspartame-Stearic acid mixture (3).

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