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DIFFERENTIAL SCANNING CALORIMETRY OF ASPARTAME-MANNITOL MIXTURE

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ABSTRACT

Differential scanning calorimetry was used to study both the qualitative and quantitative thermal properties of mixtures of aspartame with both mannitol and granular mannitol. Aspartame was found to be compatible with both forms of mannitol. No aspartame decomposition was observed in the preparation of a fused aspartame-mannitol mixture prepared at 161-165°C. L-(-)-leucine can be recommended as soluble lubricant for formulations containing aspartame and mannitol.

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INTRODUCTION

Mannitol has been used as a tablet diluent for more than a decade. It is the least hygroscopic of all known carbohydrate tablet diluents[1,2]. Thus, it is a highly desirable additive for water-sensitive drugs[2-4], Mannitol has a sweetness threshold of approximately the same value as glucose[3,5].

Mannitol has been shown to exhibit a pleasant cooling sensation in the mouth, attributed to a negative heat of solution of -28.9 cal/g at 25°C. When used in formulations for tablets intended to be chewed or dissolved in the mouth, it causes no objectionable gritty effect in the mouth, a common problem with previously used chewable tablet bases[3].

The advantages exhibited by mannitol in such tablet formulations have been offset by its inherent shortcomings in that it has poor flow and compression characteristics[6]. Granular mannitol has been developed especially as a directly compressible vehicle for chewable tablets[3,6]. It flows easily and imparts improved fluidity to high levels of materials which normally do not flow. Tests conducted with this material indicate that it cannot be used with concentrations of other materials exceeding 25% by weight[3].

Kanig[6] found that fused mannitol, which is recrystallized and processed by either spray-congealing or screening, possesses exceptionally good tableting characteristics. He showed that the liquid state of mannitol was capable of dissolving or dispersing a number of pharmaceutical adjuvants or physiologically active drugs. Phase diagrams of several of these combinations indicated that solid-

solid solutions were obtained. These solid solutions were found to be directly compressable into tablets, eliminating the necessity for blending procedures and assuring complete uniformity of dosage.

Kanig[6] also utilized fused mannitol to produce eutectic mixtures with other less costly carbohydrates, such as sucrose or lactose. These mixtures were found to possess excellent flow and compression properties when used either as solvents for active principles or when admixed with them as a dry tablet binder.

The original regulation for aspartame approved its use as a sugar substitute in tablet and packet forms[7]. The regulation also permits the use of L-leucine as a lubricant in the manufacture of tablets containing aspartame at a level not to exceed 3.5 percent of the weight of the tablet.

In a previous investigation[8], the compatibility of aspartame with several direct compression excipients was studied. In the present work, the thermal behavior, and hence compatibility, of physical mixtures of aspartame with both mannitol and granular mannitol was investigated along with a fused mixture of ten percent aspartame in mannitol. In addition, differential scanning calorimetry was used to study the compatibility of both aspartame and mannitol with L-(-)-leucine.

EXPERIMENTAL

Materials

The following materials were used: Aspartame (G.D. Searle & Co.), mannitol and granular mannitol (ICI Americas) and L-(-)-leucine (Eastman Kodak).

Fused Mixture

Mannitol was allowed to melt completely in a small beaker dipped in a sand bath placed on an electrically controlled heater. Melted mannitol was allowed to cool gradually and then maintained at 161-165°C. Ten percent aspartame was then added and rapidly mixed. The fused mixture was then quenched by being rapidly removed from the sand bath.

Differential Scanning Calorimetry

Samples (2-10 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 10, 25, 50, 75 and 90 percent physical mixtures of aspartame and mannitol or granular mannitol were heated over the temperature range, 30 to 350°C. All physical mixtures were prepared on a weight/weight percent basis.

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[8]. At least two replicates were made for each DSC thermogram.

RESULTS AND DISCUSSION

Aspartame has been shown, by differential scanning calorimetry, to have two endothermic peaks[8]. The first one, with temperature range of transition 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. The second peak, with temperature range of transition from 234-254°C and with a maximum peak of transition at 240°C, represents the conversion to diketopiperazine (DKP). At 266°C the DKP decomposed, so no melting point can be observed.

DSC thermogram of mannitol showed a melting endothermic peak with a temperature range of transition from 145-170°C and with a maximum peak of transition at 164°C. No decomposition was observed on scanning until 300°C. This is in agreement with previous studies[6] in that mannitol is one of the few carbohydrates that possesses an exceptionally high heat stability.

Figure 1 illustrates the DSC thermograms of aspartame and mannitol, separately and in physical mixtures. The DSC thermogram of a 10 percent aspartame-mannitol physical mixture showed only one peak corresponding to the melting transition of mannitol and the first peak of aspartame, with a shift to lower temperatures from that of either pure compound. No enthalpy change, corresponding to the second peak of aspartame, was observed. The decomposition peak of DKP was also shifted to a lower temperature, 225°C.

A 25 percent aspartame-mannitol physical mixture showed a large endotherm corresponding to the melting of mannitol, followed by two minor peaks corresponding to the first and second peaks of aspartame.

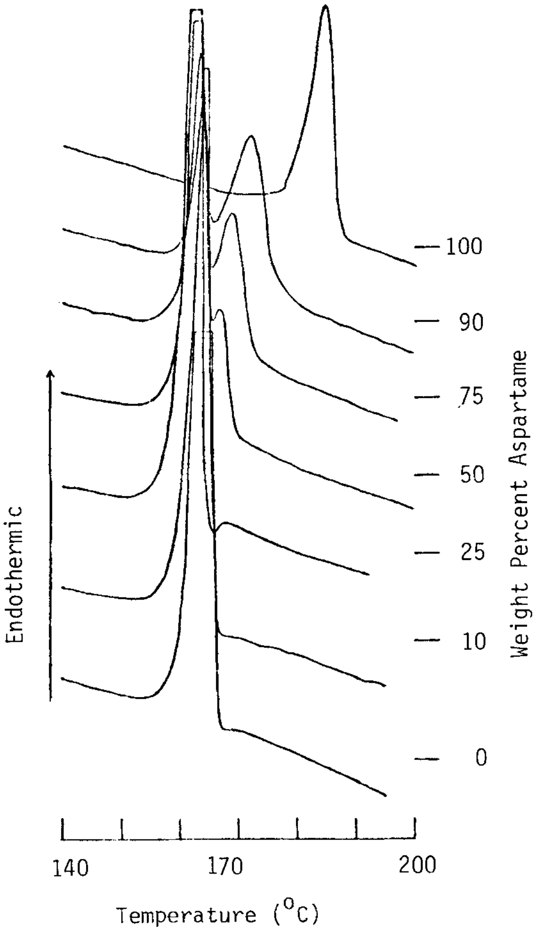

FIGURE 1

DSC thermograms of aspartame and mannitol, separately and in physical mixtures.

All these transitions were found to be shifted to lower temperatures, including DKP decomposition which was found to be at 208°C.

Mixtures containing 50%, 70% and 90% aspartame showed a large double-peaked tranistion corresponding to the melting endotherm of

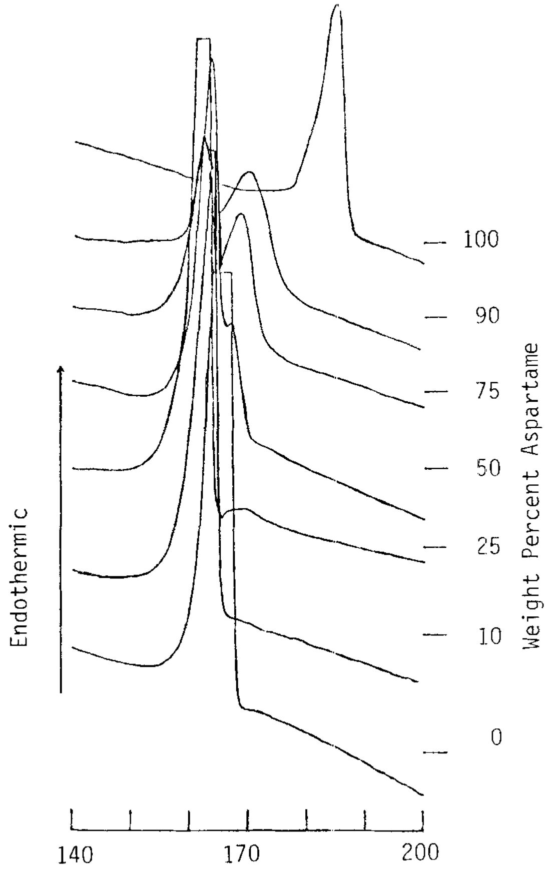

FIGURE 2

DSC thermograms of aspartame and granular mannitol, separately and in physical mixtures.

mannitol superimposed with the first peak of aspartame. As expected, a shift to lower temperatures occurred. A second transition corresponding to the second peak of aspartame was traced along with the decomposition of DKP. Both changes were again found to be shifted to lower temperatures.

The maximum peak of transitions of aspartame and mannitol, separately and in physical mixtures are plotted as a function of composition in Figure 3. It is apparent that the aspartame maximum peak of transition is markedly shifted to lower temperatures as aspartame concentration in the mixture decreases. An effect is evident at a concentration as low as 25 percent where the shift is 21.5°C. For the mannitol maximum peak of transition, there is no more than 1°C shift, an effect which may be attributed to the thermal stability of mannitol.

It was found that DKP decomposes at 225, 208, 230, 232, 232 and 266°C for 10, 25, 50, 75, 90 and 100 percent aspartame concentration. The shift of DKP decomposition to lower temperatures is, therefore, in correlation with the shift of aspartame temperature range of transition and maximum peak of transition.

DSC thermogram of granular mannitol shows a melting endothermic peak, with temperature range of transition at 144-167°C and with a maximum peak of transition at 165°C. The thermal behavior of granular mannitol, alone and in physical mixtures with aspartame, was found to be more or less the same as with mannitol and is illustrated in Figures 2 and 4.

The peak area of the multiple transition, corresponding to the melting endotherm of mannitol or granular mannitol and the first peak of aspartame, was taken as a base for the quantitative measurement of the energy of transition (cal/g) of the physical mixture as a function of composition(Table 1 and Figure 5). The energy of transition (cal/g) of the physical mixtures has been determined as

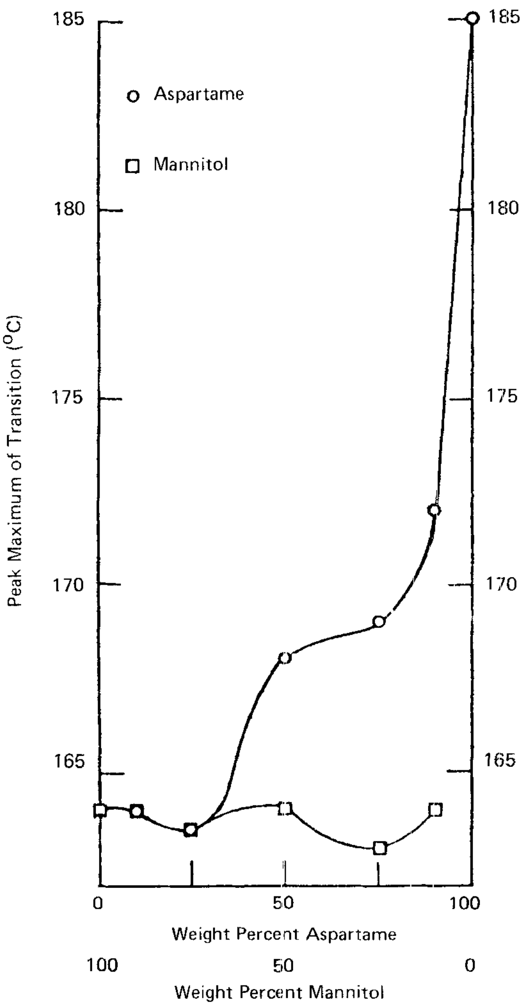

FIGURE 3

Peak maximum of transition of aspartame-mannitol physical mixtures as a function of composition

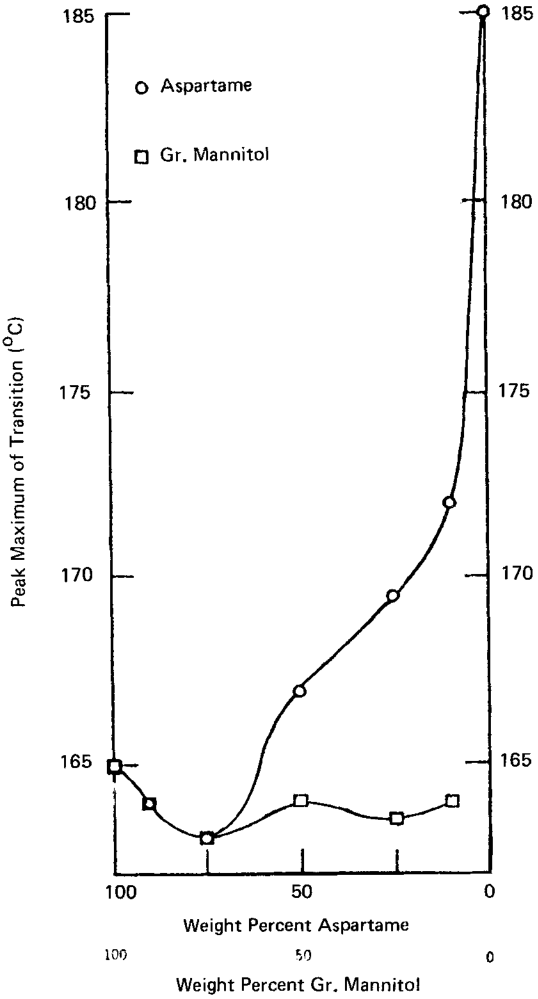

FIGURE 4

Peak maximum of transition of aspartame-granular mannitol physical mixtures as a function of composition.

TABLE I

Energy of transition of aspartame-mannitol and aspartame-granular mannitol physical mixtures as a function of composition.

Weight Percent Concentration		Energy of Transition, cal/g* (Multiple Transition)					
Aspartame	Mannitol or Granular Mannitol	Mannitol			Granular Mannitol		
		Actual	Predicted**	%	Actual	Predicted**	%
10	90	50.01	52.62	95.04	49.85	55.14	90.41
25	75	51.10	47.50	107.58	49.35	49.60	99.50
50	50	38.75	38.97	99.44	39.56	40.37	97.99
75	25	31.92	30.44	104.86	31.53	31.14	101.25
90	10	27.77	25.32	109.68	25.42	25.60	99.30

*Energy of transition of aspartame, mannitol and granular mannitol was found to be 21.91, 56.03 and 58.83 cal/g respectively.

**Predicted values are calculated from the exact percentage contribution of each ingredient to the total energy of transition.

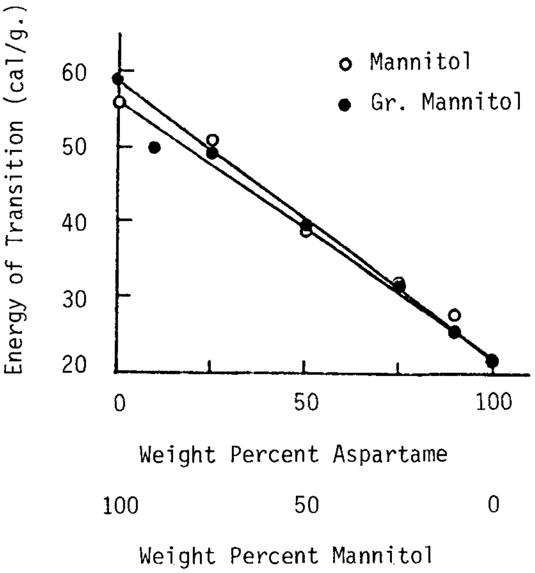

FIGURE 5

Energy of transition of aspartame-mannitol and aspartame-granular mannitol physical mixtures as a function of composition.

a function of composition and compared with predicted values for assessing the compatibility of these mixtures. The agreement between the predictable and the actual values is quite good (Table 1), indicating no incompatibility between aspartame and mannitol or granular mannitol under these conditions.

Mannitol, when fused, becomes a clear, colorless low-viscosity fluid which crystallizes very rapidly when the source of heat is removed[6]. When ten percent aspartame was added to melted mannitol which had been maintained at 161-165°C, rapidly mixed and then quenched by rapid removal of the mixture from the source of heat, a sweet mass crystallized which exhibited no visible signs of decomposition. The actual state of matter which resulted upon congealing of the fused mixture requires additional investigation which is under consideration.

Aspartame decomposition, which was manifested by change in color to dark brown and evolution of a gas, was observed when aspartame was added to melted mannitol at 175-180^{o}C. This decomposition was expected as aspartame begins to loose its methyl ester with consequent loss of sweetness at 167-190^{o}C.

A DSC thermogram of fused mannitol showed the same thermal behavior as that of mannitol. A DSC thermogran of the fused mixture of 10 percent aspartame in mannitol showed one well-shaped peak corresponding to the melting transition of mannitol and the first peak of aspartame, with the transition heat and temperature similar to that of the physical mixture of the same composition. This was followed by a broadened transition at 215-240^{o}C, corresponding to the second peak of aspartame, and a decomposition peak of DKP at 245^{o}C. This means that DKP decomposition is shifted to a lower temperature as compared to pure aspartame (266^{o}C) but occurred at a higher temperature than the physical mixture of the same composition (225^{o}C). This would appear to indicate higher thermal stability in the case of the fused mixture.

The energy of transition (cal/g) of the fused mixture was found to be 97.77% of the predicted value indicating no decomposition due to preparation at high temperatures.

In the previous investigation[8], stearic acid was found to be acceptable as a lubricant in formulations containing aspartame while magnesium stearate was not. In this investigation, the DSC was used to assess the compatibility of L-(-)-leucine as a water soluble

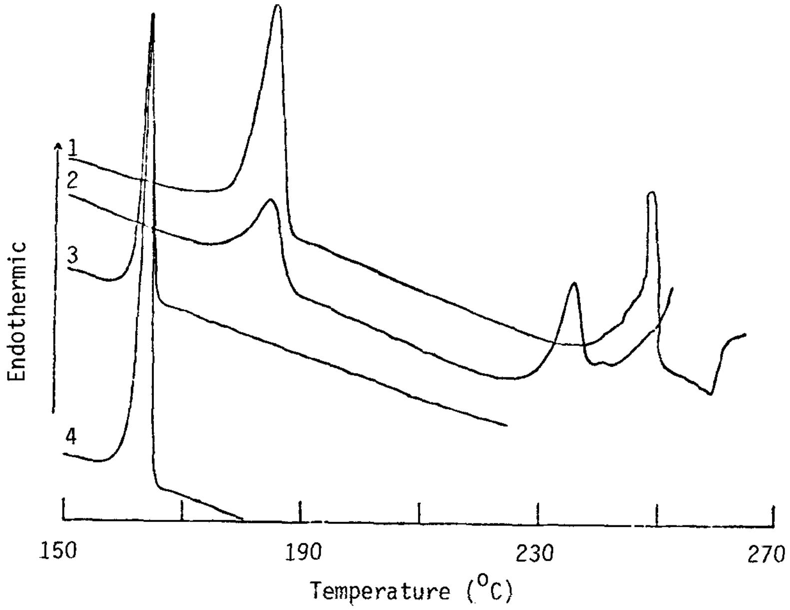

FIGURE 6

DSC thermograms of aspartame, 5 mg (1), 1:1 aspartame - L-(-)-leucine, 5 mg (2), 1:1 mannitol-L-(-)-leucine, 2 mg (3) and mannitol, 2 mg (4).

lubricant[3] with both aspartame and mannitol. Figure 6 illustrates the corresponding thermograms. Due to the variation in sample weights, the energy of transition (cal/g) calculations were normalized to compare the data on an equivalent basis.

L-(-)-leucine exhibits no transition when scanned over the temperature range of 30 to 285°C; after that, a sublimation endotherm begins. Therefore, DSC thermograms of mixtures leucine with aspartame or mannitol will reflect their characteristic features if no incompatibility occurred. This is indeed the case as seen in Figure 6. A shift to lower temperature did occur for the second peak of aspartame and the decomposition of DKP (Trace 2 of Figure

6). The energy of transition of the aspartame-L-(-)-leucine mixture was found to be 92.2% that of aspartame alone, while that of mannitol-L-(-)-leucine was 90.76% that of mannitol, indicating the possible use of L-(-)-leucine as a lubricant in formulations containing aspartame and mannitol.

It is evident, therefore, that a combination of aspartame with granular or fused mannitol in 1:9 ratio can provide a suitable base for chewable tablets as regards the sweetness, the mouthfeel, the absence of unpleasant aftertaste, the low caloric value and all the other properties inherent to mannitol. The low moisture content, the nonhygroscopicity and the direct compression properties of granular or fused mannitol make it ideal for use with aspartame. The compatibility of the mixture ingredients with L-(-)-leucine as a water soluble lubricant is also an advantage.

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