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ASPARTAME-MANNITOL RESOLIDIFIED FUSED MIXTURE: CHARACTERIZATION STUDIES BY DIFFERENTIAL SCANNING CALORIMETRY, THERMOMICROSCOPY, PHOTOMICROGRAPHY AND X-RAY DIFFRACTOMETRY

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ABSTRACT

Differential scanning calorimetry, thermomicroscopy, photomicrography and X-ray diffractometry were used to characterize the physical nature of the resolidified ten percent aspartame-mannitol fused mixture. It is concluded that the binary system is a eutectic mixture with some solid-solid solubility. The increased hardness of the

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eutectic is regarded as an advantage for the mixture as a base for chewable tablets.

INTRODUCTION

Aspartame, a new intense sweetener, contains an ester linkage that, under certain moisture, temperature and pH conditions, may hydrolyze to the dipeptide, aspartylphenylalanine, which can then cyclize to the corresponding diketopiperazine (DKP)[1]. Aspartame does break down spontaneously to DKP. Diketopiperazine is routinely present in the sweetener at levels up to about 1 percent of the aspartame. If present in large amounts,DKP can make aspartame lose its sweetness[2]. However, under the uses approved by FDA, DKP normally comprises less than 2 percent of the final aspartame product which does not detract from the product's sweet tastes. Prolonged cooking temperatures can cause significant breakdown of aspartame to DKP, with a consequent loss of sweetness[3]. FDA advises that any future requests for uses of aspartame which involve a prospect at significant breakdown to higher levels of DKP will be required, prior to approval,to demonstrate affirmatively that the anticipated higher levels are safe[3].

In recent years, mannitol has been shown to exhibit a uniquely cooling and pleasant mouthfeel when used in formulations for tablets intended to be chewed or dissolved in the mouth[4-7]. Several types of medicaments, including antacids, analgesics, multivitamins, and anti-

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histamines are being marketed in the form of chewable tablets prepared in a mannitol base[4,7-10]. The low moisture content and nonhygroscopicity of mannitol make it ideal for use with moisture-sensitive medicaments[5,7,10].

Krahnke and Becker[11] substantiated the inertness of mannitol toward sensitive therapeutic entities. Ward et al.[12] conducted accelerated stability studies with seven representative compounds and demonstrated the inertness of mannitol in various mechanisms associated with drug-excipient compatibility. Mannitol and granular mannitol were found, by the present authors, to be compatible with erythromycin[13], while incompatible with cephalexin[14]. Anhydrous ampicillin[15] appears to form complexes with mannitol and granular mannitol after their melting transitions.

Kanig[4] reported that the unusual heat stability of mannitol has led to the development of several new applications which possess a high degree of potential. Foremost among these is the discovery that fused mannitol, which is recrystallized and processed by either spray-congealing or screening, possesses exceptionally good tableting characteristics. He found 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.

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Kanig[4] 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.

In a previous study[16], the thermal behavior, using differential scanning calorimetry, of physical mixtures of aspartame with both mannitol and granular mannitol was investigated along with a fused mixture of ten percent aspartame in mannitol. Aspartame was found in that study to be compatible with both forms of mannitol. It was found, also, that when ten percent aspartame was added to melted mannitol which had been maintained at 161-165°C, rapidly mixed and then quenched, a sweet mass crystallized which exhibited no visible signs of decomposition. This was not the case when aspartame was added to melted mannitol at 175-180°C, where aspartame decomposition occurred.

In this study, the authors explored more thoroughly the actual state of matter which resulted upon congealing of the fused mixture containing ten percent aspartame in mannitol. This was achieved by comparing the thermal behavior, using differential scanning calorimetry and hot-stage microscopy, the photomicrograph and the X-ray diffraction spectrogram of each of aspartame and mannitol with those of 1:9 physical and fused mixtures of aspartame and mannitol.

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EXPERIMENTAL

Materials

The following materials were used: Aspartame (G.D. Searle & Co.) and mannitol (ICI Americas).

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

The procedure and instrumentation were identical to those reported previously[1,13-16].

Hot-Stage Microscopy

About 1 mg of sample was placed between a microscope slide and a cover slide and heated at 1-10°C per minute under a Mettler FP2 Hot-Stage Microscope (Mettler Instruments, Zurich, Switzerland). The onset of melting was characterized by the first appearance of liquid, and the completion of melting was considered as the final disappearance of solid. These two temperatures were used to defind the melting ranges from hot-stage microscopy[17].

Photomicrography

The samples were observed under a Nikon Labophot with Phase Contrast Microscope (Nippox Kogaku U.S.A. Inc., Garden City, NY 11530, U.S.A.) and the images were photographed with a Nikon FX Camera.

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X-Ray Diffractometry

X-ray diffractometry was carried out using a General Electric XRD-5 Diffractometer by Ni-filtered Cu-Kα radiation.

RESULTS AND DISCUSSION

Mannitol has been found to melt at 165°C and crystallize at 160°C, when it was allowed to melt and crystallize in a small beaker dipped in a sand bath placed on an electrically controlled heater. This is in agreement with previous studies[4] in that mannitol, when fused, becomes a clear,colorless low-viscosity fluid which crystallizes very rapidly when the source of heat is removed. On the other hand, mannitol, has been shown, by differential scanning calorimetry[16], to have a melting endothermic peak with a temperature range of transition from 145-170°C and with a maximum peak of transition at 164°C. When DSC cooling mode was addopted, after the DSC trace was returned to the programme line, and at the same scanning rate of 10°C per minute, melted mannitol, showed a crystallization exothermic peak with a temperature range of transition from 93-98°C and with a maximum peak of transition at 96°C.

The thermal behavior of fused mannitol, under hot-stage microscopy, was found to be more or less dependent on the rate of cooling of the melt. Figure 1 shows the photomicrograph of mannitol as received. Figure 2 shows the photomicrograph of mannitol after being melted in hot-stage microscope and then cooled rapidly, while

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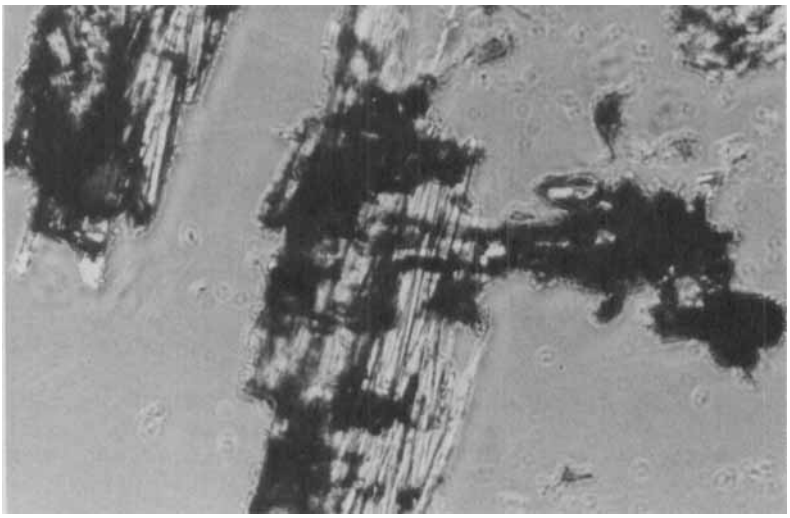

FIGURE 1

Photomicrograph of mannitol as received (X 200).

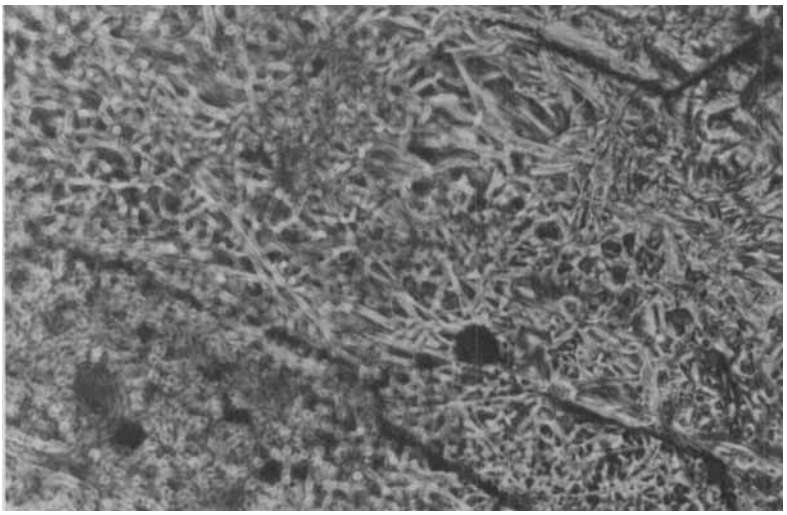

FIGURE 2

Photomicrograph of mannitol after being melted in hot-stage microscope and then cooled rapidly (X 200).

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Figure 3 shows the photomicrograph of mannitol after being melted in hot-stage microscope and then cooled gradually, i.e., mannitol crystallized after supercooling.

It is obvious, therefore, that fused mannitol, when cooled, may either freeze into a crystalline solid, if cooled rapidly, or it may continue as a supercooled liquid, if cooled gradually. The supercooling behavior of fused mannitol may be presumably due to its strong hydrogen bonding, being a polyhydroxyl compound, which may prevent its crystallization[18].

It was found, in a previous study[16], that 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 and characterized by increased hardness. Figures 4-6 show the photomicrographs of aspartame, ten percent aspartame-mannitol physical mixture and of ten percent aspartame-mannitol resolidified fused mixture, respectively. When aspartame was added to melted mannitol at 175-180°C, aspartame decomposition, which was manifested by change in color to dark brown and evolution of a gas, was observed[16]. Figure 7 shows the photomicrograph of that decomposed fused mixture.

Photomicrograph of aspartame-mannitol resolidified fused mixture (Figure 6) shows that aspartame was found as crystals in a crystalline mannitol matrix. This obviate that aspartame-mannitol solid dispersion may be a

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FIGURE 3

Photomicrograph of mannitol after being melted in hot-stage microscope and then cooled gradually (X 400).

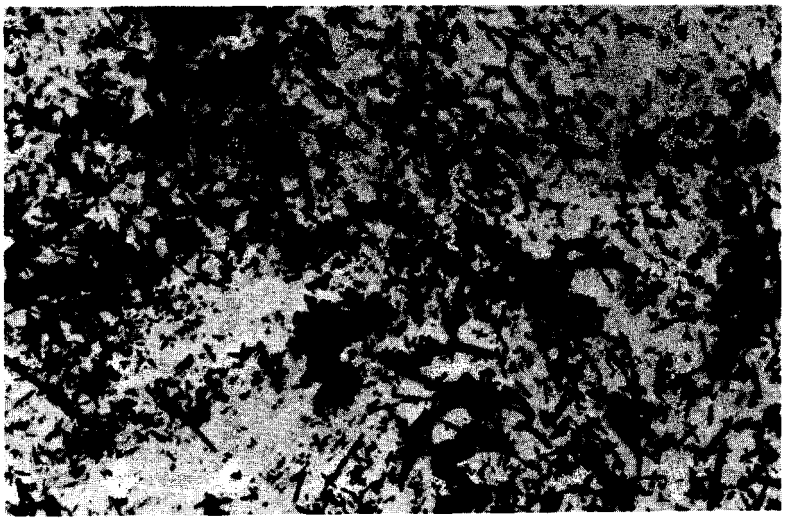

FIGURE 4

Photomicrograph of aspartame (X 200).

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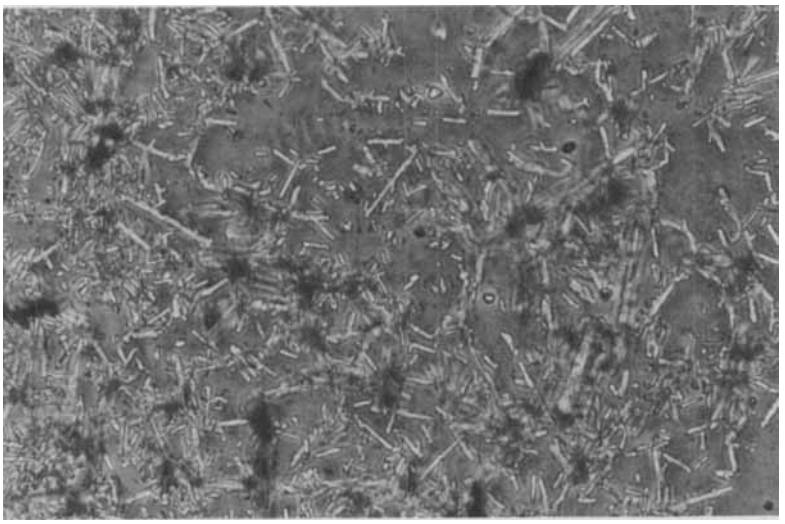

FIGURE 5

Photomicrograph of 10% aspartame-mannitol physical mixture (X 200).

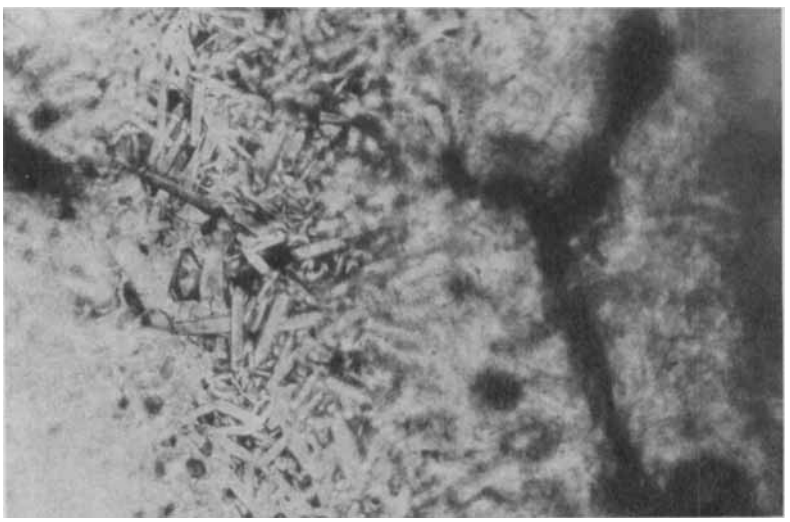

FIGURE 6

Photomicrograph of 10% aspartame-mannitol resolidified fused mixture (X 200).

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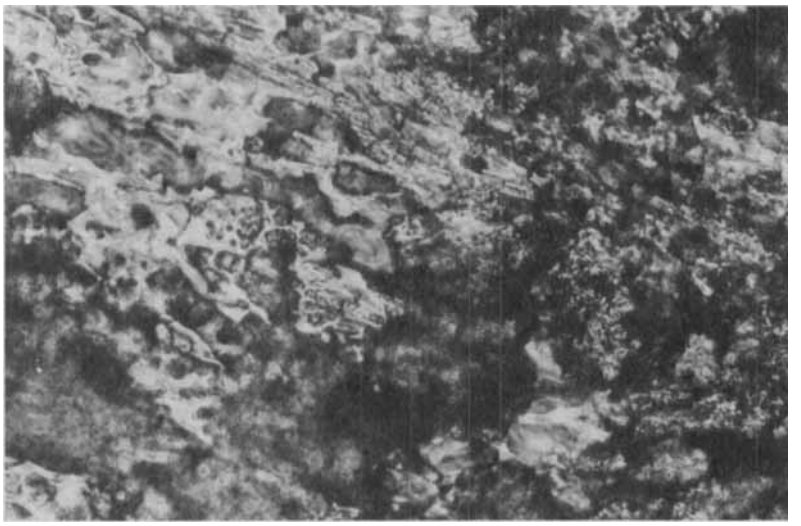

FIGURE 7

Photomicrograph of 10% asppartame-mannitol resolidified decomposed fused mixture (X 400).

eutectic mixture rather than a solid solution or glass solution, or an amorphous precipitation in a crystalline carrier, or a compound or complex formations.

Figures 8 and 9 are phase diagrams established by plotting the maximum peak of transitions of aspartame and mannitol (powder and granular), separately and in physical mixtures as a function of composition. The minimum observed at 25 percent aspartame concentration, in both figures, again indicates the possibility of forming a eutectic mixture.

Figure 10 is the X-ray diffraction spectra of aspartame (Trace 1), mannitol (Trace 2), ten percent aspartame-mannitol physical mixture (Trace 3) and of ten percent aspartame-mannitol resolidified fused mixture (Trace 4).

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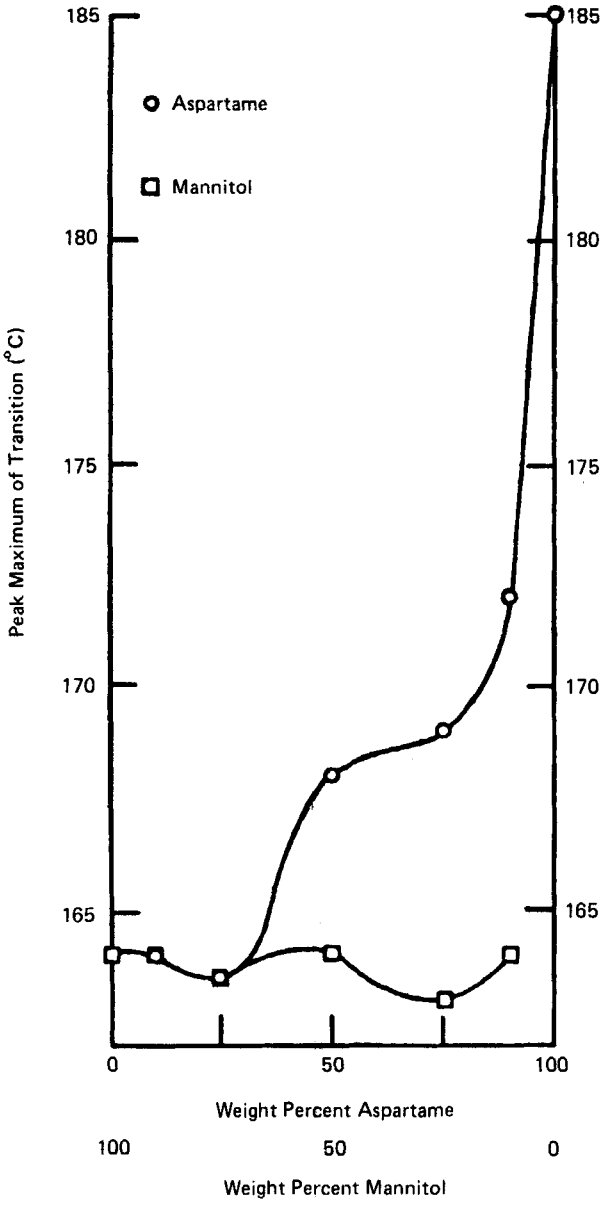

FIGURE 8

Peak maximum of transition of aspartame-mannitol physical mixtures as a function of composition (from Reference 16 of the present authors).

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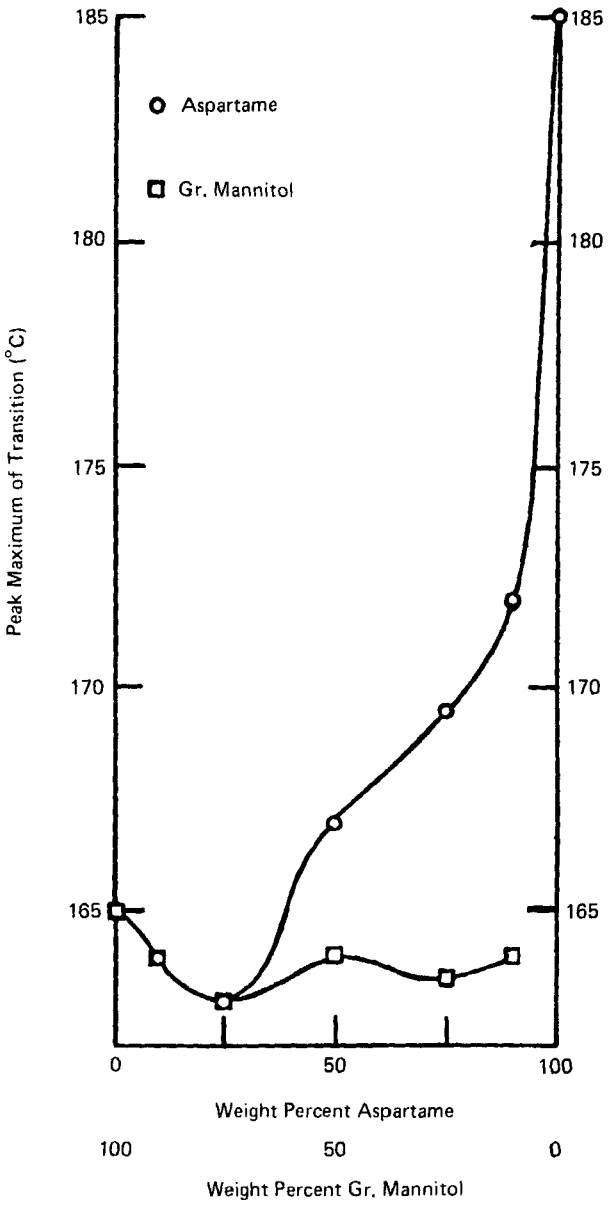

FIGURE 9

Peak maximum of transition of aspartame-granular mannitol physical mixtures as a function of composition (from Reference 16 of the present authors).

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As shown in Trace 3 of Figure 10, the diffraction spectrum of the ten percent aspartame-mannitol physical mixture contains none of the diffraction peaks of aspartame but only those of mannitol. The complete absence of any aspartame diffraction peaks may be due to the presence of aspartame, as a result of grinding during physical mixture preparation, in extremely fine crystallites[19-21]. On the contrary, the peaks due to aspartame crystals in the resolidified fused mixture, can be readily identified, as shown by checkmarks in the spectrum (Trace 4 of Figure 10). The presence of these identical aspartame diffraction peaks in terms of diffraction angles, with a decreasing intensity, in the spectrum of the resolidified fused mixture together with those of mannitol unmistakably show that the system is a eutectic mixture. Theoretically, if the aspartame dissolved completely as a minor component in the mannitol at the solid state, i.e., solid solution formation, one should not be able to find these typical aspartame diffraction peaks. However, there existed certain degrees of solid-solid solubilities as indicated by the little change of the crystalline lattice parameters of both aspartame and mannitol in the resolidified fused mixture[20,22,23].

It has been reported that the rapidly crystallized (quenched) eutectics are characterized by increased hardness due to the high degree of strain resulting from the action of mechanical forces[24]. This is the case for aspartame-mannitol resolidified fused mixture. It is

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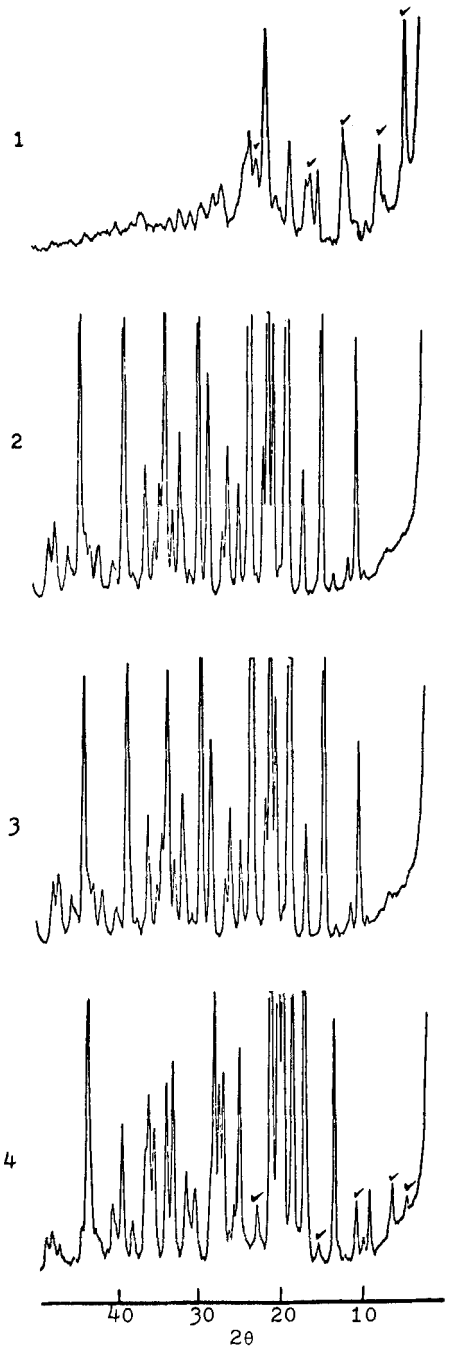

FIGURE 10

X-ray diffraction spectra of aspartame (1), mannitol (2), 10% aspartame-mannitol physical mixture (3), and 10% aspartame-mannitol resolidified fused mixture (4).

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believed that the hardening effect of the eutectic may play a role in retarding dissolution[25]. This can be regarded as an advantage for aspartame-mannitol resolidified fused mixture as a base for chewable tablets beside the aforementioned properties of this binary mixture[16].

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