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STUDY OF THERMAL BEHAVIOUR OF SUGAR ALCOHOLS

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Abstract

Mannitol and sorbitol are widely used in the pharmaceutical and food industry. There are some technological procedures such as spray-drying, freeze-drying, tablet compression, during which there is a possibility of heat effect. The purpose of this work was to study the thermal properties of sorbitol, mannitol and their mixtures. Furthermore, these materials and their tablet pressing were studied after melting and solidification. The results of the study prove that the use of sorbitol or mannitol alone is disadvantageous in melt technology. The use of mannitol is limited because of its high melting point (165ºC) and the polymorph transition after melting. Sorbitol (melting point: 96.8ºC) vitrifies from melt, therefore it is hard to handle during further processing. The melting point of the eutectic mixture (1.8% mannitol and 98.2% sorbitol) was 93.6ºC. This mixture was unsuited for pressing because of its glassy property. Our results showed that the most favourable composition was the mixture of 30% mannitol and 70% sorbitol (melting point: 131.8ºC) for tablet formulation. This mixture can be recommended for the formulation of such lozenge and hard candy tablets, where the active ingredient decomposes at higher temperature (>131.8ºC).

Keywords: crushing strength, glass transition, mannitol, sorbitol, X-ray powder diffraction

Introduction

Sugar alcohols such as mannitol and sorbitol are widely used in the pharmaceutical and food industry. They have the sweetness of sugars but they have lower caloric value, they are not cariogenic and they are suitable for diabetics.

Mannitol has a strong tendency to crystallize, nonetheless exist in fully or partially amorphous state in certain formulations [1]. Because of low chemical reactivity and low hygroscopicity, it is used in tablet formulation as filling and binding material in a direct compression of suckable-, chewable- and effervescent tablets. In the food industry they are used for the production of sweets and chewing gums. The modern use of spray-dried mannitol is the stabilization of proteins in aerosol [2]. It is also frequently used as auxiliary material in spray- and freeze drying [3].

Sorbitol is the stereoisomer of mannitol, it is easily compressible but its disadvantage is high hygroscopicity.

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Both materials can be used for the preparation of solid dispersions, in order to increase the dissolution rate of poorly water soluble drugs and to amorphization of materials with propensity for polymorphism. In preparation of solid dispersion systems the drugs can be mixed in melted excipients and after solidification this is suitable for further processing [4]. Sorbitol and mannitol are suitable for this purpose, because they are very stable to heat and melt without decomposition.

During spray-drying and preparation of solid dispersion heating of the materials takes place. There are other procedures such as tablet compression, during which there is a possibility of heat effect.

Therefore it is very important to know the thermal behaviour of these materials, so the changes in the base materials can be predicted during various technological processes [5–7].

The purpose of this work was to study the thermal properties of pure sorbitol, mannitol and their mixtures. Furthermore these materials and their processing were studied after melting and solidification with the purpose of tablet formulation.

Experimental section

Materials

β-*D*-mannitol (Ph.Eur.3) and *D*-sorbitol (Ph.Eur.3) were used for the study. The particle size of both materials was in the range of 0.16–0.32 mm. At first, physical mixtures were prepared to achieve 0, 10, 30, 50, 70, 90 and 100% sorbitol content by mass. The components were weighed and then mixed in a Turbula mixer (Turbula WAB, System Schatz, Switzerland) for 10 min. The prepared mixtures were divided into two parts. The first portion was processed hereafter as a 'physical mixture', the second portion was melted and then the solidified melt was used for further studies. During melting, the mixtures were heated in a furnace up to 170ºC and then cooled at room temperature. The solidified by cooling materials were pulverized and sieved (0.16–0.32 mm). During the preparation and storage of the mixtures <55% relative humidity was ensured because of the strong plasticizing effect of water.

Korsch EKO eccentric tablet machine (Emil Korsch Mashinenfabrik, Berlin, Germany) was applied for tablet forming. The compression tools were single, flat punches 10 mm in diameter, furnished with strain gauges. The rate of compression was 30 tablets/min with a pressure forces 2, 4 and 6 kN, at room temperature of 24ºC and relative humidity of 45%. The mass of tablets was 0.20 g.

Methods

X-ray powder diffraction (XRPD)

X-ray powder diffraction profiles were taken with an X-ray diffractometer (Philips PW 1050/70 PW 1710). The measurement conditions were as follows: radiation source: CuK_{α}, scan speed (2θ): 0.035, step size (2θ): 0.035, time per step: 1.0 s.

Differential scanning calorimetry (DSC)

DSC studies were performed using a DSC 821^e (Mettler-Toledo GmbH, Switzerland). The instrument was calibrated using indium. The samples of 15–20 mg were heated in a hermetically sealed aluminium pan. At first the samples were heated from 25 to 200ºC at heating rate of 3.5 K min^{-1}. Then the samples were cooled in liquid nitrogen, subsequently the mixtures were reheated from –20 to 200ºC at the rate of 3.5 K min^{-1}.

Study of tablets

The tablets were stored in sealed glass containers at room temperature of 20±2ºC and 50±5% relative humidity. The crushing strength was investigated with Heberlein apparatus (Flisa, Le Locle, Switzerland). The crushing strength was determined one day (24 h) after formulation because of the texture change (elastic recovery).

Results

Thermal behaviour of pure sorbitol and mannitol

On the first DSC scan pure sorbitol melted at 96.8ºC, and by cooling it cannot be recrystallized from its melt. If vitrified systematically, this leads to an amorphous state, which can be proved by X-ray powder diffraction (Fig. 1). On the second DSC scan at –2.3ºC glass transition (T_g) was observed (Table 1).

The starting mannitol was β-*D*-mannitol, observed by XRPD, which melted at 165ºC on the first heating. The melt crystallized during cooling as α-*D*-mannitol,

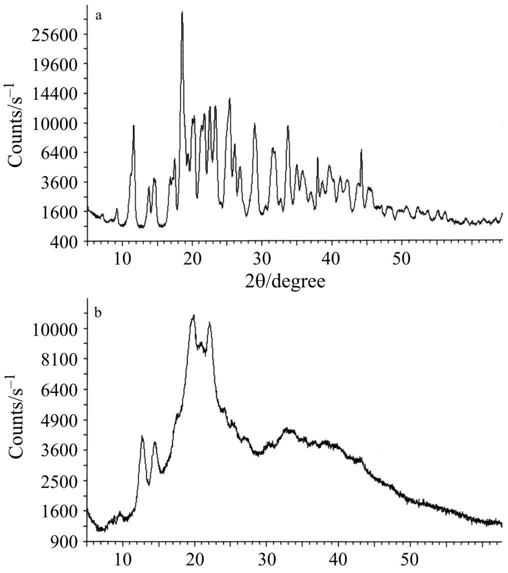

Fig. 1 X-ray powder diffractograms of a – pure sorbitol and b – sorbitol cooled after melting

Table 1 Characteristic thermal parameters of sorbitol and mannitol

	T_m/°C	ΔH_m/J g^{-1}	T_g/°C
D-sorbitol	96.8	217	–2.3
β-*D*-mannitol	165	338	–

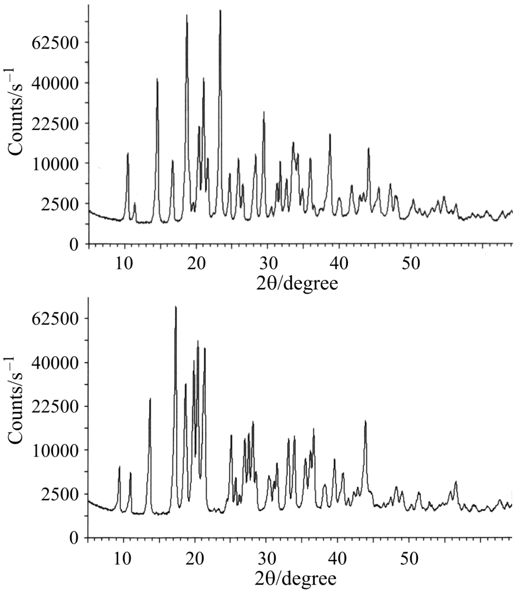

Fig. 2 X-ray powder diffractograms of a – pure mannitol and b – mannitol cooled after melting

therefore polymorph transition took place (Fig. 2). In case of mannitol no glass transition was observed on the second DSC scan (Table 1). It can be stated that neither pure mannitol nor pure sorbitol is suitable for hot melt technology. Because of mannitol's high melting temperature, it cannot be used in case of such materials, which decompose at this temperature. Sorbitol's vitrified state after melting is difficult to handle during further processing. Our additional aim was to eliminate these problems with mixing the two sugar alcohols.

Thermal behavior of the different sorbitol and mannitol mixtures

During the examination of the mixtures, decrease in mannitol's melting temperature was observed, when sorbitol's ratio was increased in the mixture, because mannitol dissolves in sorbitol melt. On the other hand, the melting point of sorbitol was only slightly affected by the presence of mannitol with a higher melting point (Fig. 3). The eutectic temperature was detected at 93.6ºC. In case of the 50% mannitol and 50% sorbitol mixture, the melting of sorbitol and mannitol was observed in the form of

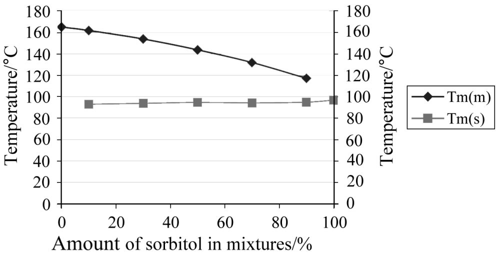

Fig. 3 The melting temperature (T_m) of sorbitol (s) and mannitol (m) in relation to mole fraction of sorbitol in the mixtures

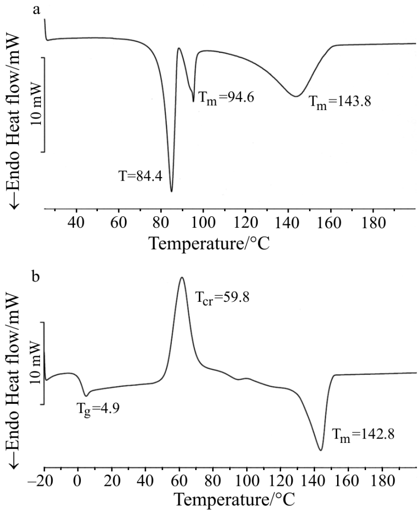

Fig. 4 DSC curve of the mixture with 50% mannitol+50% sorbitol (a – first scan and b – second scan)

two endothermic peaks (94.6 and 143.8ºC). The endothermic peak at 84.4ºC was not characterized. During the second DSC scan glass transition was detected at 4.9ºC, this was followed by crystallization exotherm of mannitol 59.8ºC and melting endo-

Table 2 Thermal parameters of sorbitol and mannitol mixtures during the second heating

Sorbitol content/%	T_g/°C	T_{cr}/°C	T_m/°C
0	–	–	165.0
10	–	58.0	161.5
30	–	52.2	154.0
50	4.9	59.8	142.8
70	1.96	81.2	131.8
90	5.5	–	–
100	–2.3	–	–

therm of mannitol at 142.8ºC (Fig. 4). When the ratio of sorbitol was lower than 30% no glass transition was detected on the second DSC scan. When sorbitol content was above 90% only glass transition was detected (Table 2).

It can be stated, that the vitrification of sorbitol cannot be avoided with the addition of mannitol. However much mannitol is mixed with sorbitol, crystallization of sorbitol cannot be achieved. When the high melting point of mannitol is the problem during processing, with the addition of sorbitol this can be improved. The melting point of mannitol decreases when mixed with sorbitol as seen in Fig. 3. Additional issue, are these mixtures technologically suitable for further processing.

Results of tablet study

In case of tablets prepared from physical mixtures the crushing strength increased with the increase of sorbitol ratio, at all three pressure forces (Table 3).

The melted and solidified mixtures were pressed with the same method as the simple physical mixtures. In the case of melted mannitol, tablets cannot be pressed with pressure forces 2 and 4 kN because the tablets broke easily and disintegrated. With the other mixtures all three pressure forces could be used. The crushing strength of the tablets prepared from melted mixtures increased with the increase of pressure forces and also with the increase of sorbitol ratio. The tablets formulated from the solidified melt of pure sorbitol were the strongest.

The comparison of physical mixtures and melted/solidified samples with the same component ratio shows that, when sorbitol content was lower than 50%, tablets of physical mixtures were stronger, and when sorbitol content was above or equal to 50%, the tablets of melted mixtures had higher crushing strength values (Table 3).

Table 3 Crushing strength of tablets (*N*) at different pressure forces

Sorbitol/%	2 kN		4 kN		6 kN	
	Physical mixture	Melted mixture	Physical mixture	Melted mixture	Physical mixture	Melted mixture
0	31.6	–	38	–	51.2	22.4
10	39.6	18	43.6	26	52.8	40
30	47.2	26	60	55.3	74.8	66
50	50.6	62	62	90.7	75.2	114.6
70	76.8	163.3	109.6	176	114.4	177.3
90	122	192.6	162.4	195.3	171.6	197.3
100	126	198.7	166	>200	179.6	>200

Conclusions

The results of the study prove that the use of sorbitol or mannitol alone is disadvantageous in melt technology. Although neither material decomposes at melting temperature, they are not suitable for preparation of solid dispersion. The use of mannitol is limited because of its high melting point and the polymorph transition after melting. Sorbitol vitrifies from melt, therefore it is hard to handle during further processing.

We tried to eliminate these disadvantages by mixing the two components. It can be concluded from our research, that the vitrification of sorbitol cannot be avoided with the addition of mannitol, and sorbitol crystallization cannot be achieved. The high melting point of mannitol can be decreased with the addition of sorbitol. Therefore the melting temperature of pure mannitol (165ºC) can even be lowered to 115ºC. In this case however the mix shows vitrification, characteristic of pure sorbitol.

When thermoanalytical data are compared to the study of crushing strength, it can be inferred that the most favourable composition was the mixture of 30% mannitol and 70% sorbitol. This sample's melting point was 131.8ºC. After melting and solidification this mixture was the easiest to handle during tablet pressing (friction, adhesion) and high crushing strength tablets were pressed even at 2 kN pressure force. This mixture can be recommended for the formulation of such lozenge and hard candy tablets, where the active ingredient decomposes at high temperature (>131.8ºC).

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