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International Journal of Pharmaceutics 235 (2002) 149–157

international journal of pharmaceutics

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Direct compression properties of melt-extruded isomalt

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Received 4 June 2001; received in revised form 5 December 2001; accepted 11 December 2001

Abstract

Isomalt, a sugar alcohol, was melt-extruded prior to compression in order to improve its tabletting properties. After fusion, crystalline isomalt was transformed into an amorphous form as shown by X-ray diffraction and differential scanning calorimetry (DSC). The tabletting properties of amorphous isomalt were dramatically improved. Mixtures formulated with paracetamol (50%) and extruded isomalt yielded hard tablets. However, extruded isomalt powder showed agglomeration problems due to recrystallization of the amorphous phase into a stable crystalline form in the presence of atmospheric moisture. The evolution of the moisture content correlated well with the compressibility data. The tablets made of extruded isomalt powder had a lower friability in comparison to the tablets formulated with non-extruded isomalt powder. Their disintegration was fast and a rapid dissolution rate was recorded. Extruded isomalt displayed excellent tabletting properties; however, further experiments should be conducted to delay or even prevent recrystallization of amorphous isomalt.

Keywords: Isomalt; Melt-extrusion; Direct compression; Paracetamol, recrystallization

1. Introduction

Isomalt (Palatinit®), a sugar alcohol, is an equimolecular mixture of two stereoisomers: α-D-glucopyranosyl-1,1-D-mannitol (GPM) and α-D-glucopyranosyl-1,6-D-sorbitol (GPS). Due to its properties such as taste, mouth feel, low calorie content, acariogenicity, suitability to diabetics and low hygroscopicity, it offers several advantages over most polyols when formulated in pharmaceutical dosage forms, particularly when used as a tablet excipient (Sträter, 1989; Fritzsching, 1993). Recently, the compression characteristics of isomalt were investigated by Ndindayino et al. (1999). Although isomalt containing tablets could be manufactured by direct compression, the drug concentration of these tablets was limited to 30% as higher drug loads yielded tablets of unacceptable quality. However, literature reports indicated that the compression properties of polyols were

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0378-5173/02/$ - see front matter
PII: S0378-5173(01)00993-0

successfully enhanced when these products were melted prior to compression. As early as 1964, Kanig (1964) reported on the improved tabletting properties of mannitol after fusion. More recently, Serpelloni (1990) prepared a direct compressible maltitol powder using melt-extrusion, while Sjökvist and Nyström (1991) demonstrated that the tabletting properties of xylitol and xylitol/griseofulvin mixtures were improved after fusion. Further studies on the melt-extrusion of xylitol were conducted by Serpelloni and Croisier (1995) who produced a highly compressible powder by co-extrusion of xylitol with other polyols such as sorbitol.

As the melting range of isomalt is between 145 and 150 °C and no decomposition is detected when the product is melted (Cammenga and Zielasko, 1996b), this material can be thermally treated using the hot stage extrusion technique (melt-extrusion). Furthermore, neither browning reactions nor caramel tasting were observed after melting of isomalt (Sträter, 1989; Fritzsching, 1993).

In the present study, the suitability of extruded isomalt as a vehicle in direct compression was evaluated.

2. Materials and methods

2.1. Materials

Palatinit®C (melting range: 145–150 °C) (Palatinit–Süßungsmittel GmbH, Mannheim, Germany) was used to evaluate the compression properties of melt-extruded isomalt compared with non-extruded powder. Isomalt containing tablets were prepared using the following excipients: 5% (w/w) Explotab® (Pennwest Ltd, Patterson, NY) as a disintegrant, 0.5% (w/w) Aerosil® 200 (< 90 μm) (Ludeco S.A, Brussels, Belgium) as a glidant and 1% (w/w) magnesium stearate (< 90 μm) (Pharmachemic, Wevelgem, Belgium) as a lubricant. Paracetamol dense powder (Mallinckrodt Chemical Ltd, Raleigh, NC) was used as a model drug at a concentration of 50% (w/w).

2.2. Methods

2.2.1. Melt-extrusion

Isomalt was extruded using a continuous melt-extruder, MP 19 TC 25 (APV Baker, Newcastle-under-Lyme, UK). This lab-scale extruder was equipped with two corotating screws and a twin screw powder feeder. The powder feed rate was set at 1.5 kg/h, while the screw speed was 40 rpm. These settings resulted in a residence time ranging from 1.0 to 6.5 min. As no die was fixed to the exit of the extrusion barrel, the material pressure remained below 3 bar during all extrusion runs. Pure isomalt was extruded at different temperatures: 130, 140, 150 and 190 °C. After a storage period of 72 h at ambient conditions ($50 \pm 5\%$ relative humidity (RH) and 25 ± 2 °C), the extruded material was pulverized with pestle and mortar, and the fraction below 500 μm was used during the compression experiments.

2.2.2. Characterization of melt-extruded material

X-ray diffraction analysis was performed using an X-ray diffractometer (D 5000, Siemens, Germany) with Cu–Kα radiations ($\lambda = 1.5406$ Å). The diffraction patterns were collected with a voltage of 40 kV and a current of 50 mA at a scanning rate of 1°/min for 2θ in the angular range of $2° < 2\theta < 90°$.

The thermal behavior of isomalt powder was evaluated using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

Standard DSC experiments were performed using a TA Instruments DSC 2920 calorimeter (New Castle, DE, USA) with liquid nitrogen as a cooling gas. A heating rate of 10 °C/min was used with nitrogen as purge gas flowing through the DSC cell at 25 ml/min. Modulated temperature DSC experiments were conducted using a TA Instruments MTDSC 2920 calorimeter (Leatherhead, UK) equipped with a refrigerated cooling system (RCS). Considering the effects of the experimental conditions on the MTDSC response (Guinot and Leveiller, 1999), the following parameters were selected: an underlying heating rate of 2 °C/min using helium as a purge gas flowing through the MTDSC cell at 40 ml/min and through the RCS unit at 150 ml/min, a

cooling rate of 20 °C/min, a modulation amplitude of 0.212 °C and a modulation period of 40 s. For both DSC techniques, the samples (2–5 mg) were carefully weighed into 40 μl aluminium pans, hermetically sealed and scanned using the following temperature range profile: a heating cycle from −30 to 200 °C, followed (in some cases) by a cooling phase to 0 °C and a second heating cycle to 200 °C. The fraction of crystalline isomalt in the extruded samples was estimated from the heat absorbed (ΔHf) during isomalt melting relative to the fusion enthalpy of a non-extruded sample (Van den Mooter et al., 2001).

TGA was performed using a Setaram TG-DTA 92 analyzer (St-Claud, France). Samples of approximately 30 mg were heated in a platinum crucible at 2 °C/min from 20 to 180 °C using an oxygen–helium (30:70) atmosphere.

The moisture content of the powder samples was measured using a Karl Fischer titrator, DL 35 (Mettler–Toledo, Beersel, Belgium).

2.2.3. Compression and tablet characterization

Placebo tablets as well as paracetamol containing tablets were produced. The placebo formulations were based on non-extruded isomalt (used as received) or on isomalt powder extruded at different temperatures (130, 140, 150 and 190 °C). In addition, a second series of tablets was prepared with mixtures containing 50% paracetamol and formulated with either non-extruded isomalt or isomalt extruded at 150 °C. 5% Explotab® was added to the drug/polyol mixtures and these ternary blends were homogenized for 10 min. 0.5% (w/w) Aerosil® 200 (<90 μm) was added to all formulations and mixed for 5 min. Finally, 1% magnesium stearate (<90 μm) was added and blended for an additional 5 min. All mixing operations were performed in a T2A Turbula mixer (W.A. Bachofen Maschinenfabrik, Basel, Switzerland).

The formulations were compressed on a single-punch tabletting machine (Korsch Type EKO, Frankfurt, Germany), fitted with 13 mm circular flat punches and equipped with a piezoelectric cell for compression force measurements. The average tablet weight was determined from 20 individually weighed tablets. A tensile strength versus compaction force profile of each formulation was generated over a pressure range from 5 to 25 kN. The tablet tensile strength ($n = 10$) was calculated from its diametral crushing force measured using a hardness tester, Type PTB (Pharma Test, Hainburg, Germany). Tablet friability ($n = 3$) was calculated as the percentage weight loss of 20 tablets after 100 rotations in a friabilator, Type PTF (Pharma Test, Hainburg, Germany). The disintegration time ($n = 6$) was measured according to Eur. Ph. III (Pharma Test disintegrator, Type PTZ, Hainburg, Germany) in 0.1 N HCl at 37 ± 0.5 °C using disks.

The dissolution profile of paracetamol tablets was measured according to USP XXIII method apparatus 2 at a paddle speed of 50 rpm in 900 ml phosphate buffer pH 5.8 (37 ± 0.5 °C), using an automated dissolution tester VK 7000 (Vankel, Edison, NJ, USA). Samples were withdrawn at regular intervals through a filter and replaced with pure medium. The drug concentration of each sample was spectrophotometrically determined at 243 nm (UV–Vis Spectrometer Lambda 12, Perkin–Elmer, Ueberlingen, Germany).

2.2.4. Physical stability of extruded isomalt powder

To investigate the moisture sorption and its effect on powder stability and compression properties, samples of extruded isomalt powder were stored in sealed chambers at different RHs (<10; 31; 55; 75%) over saturated salt solutions at a temperature of 25 ± 2 °C. Silica was used to obtain a RH of <10%. Their water content and thermal behavior as well as the compression properties were examined as a function of storage time using the methods previously described. The placebo formulations without disintegration agent were used to evaluate the compression stability of the samples. Recrystallization of extruded isomalt powder was monitored using a hot stage microscopy with a Mettler FP52/FP5 hot stage (Mettler-Toledo AG, Switzerland).

2.2.5. Post-compaction stability of tablets

Placebo tablets formulated with extruded isomalt and compressed at 20 kN immediately after milling and sieving were stored at <10 and 31%

RH (25 ± 2 °C) to evaluate the tensile strength of these tablets at regular time intervals.

3. Results and discussion

3.1. Characterization of melt-extruded isomalt

The crystalline nature of isomalt was previously reported by Perkkalainen and Halttunen (1997), Ndindayino et al. (1999). X-ray diffraction and DSC analysis showed that when isomalt was extruded below 140 °C, a partially amorphous product was obtained (±70% crystallinity at 130 °C) while extrusion above this temperature resulted in a completely amorphous material. The glass transition temperature (T_g) of isomalt measured using standard DSC was 60.8 ± 1.0 °C and the onset melting point (T_m) 150.4 ± 0.8 °C. These values were confirmed using MTDSC: T_g was 63.4 ± 0.1 °C and T_m 148.1 ± 0.1 °C. The T_g value was in good agreement with the data reported by Cammenga et al. (1996), Cammenga and Zielasko (1996a). However, the melting point was about 10 °C above the value given by these authors (141 °C), but correlated well with the results reported by Fritzsching (1993), Sträter, (1989) (145–150 °C). As shown in Table 1, the extrusion temperature significantly affected the moisture content and consequently the T_g of extruded isomalt. Compared with the non-extruded product, isomalt extruded at temperatures around its melting point (140 and 150 °C), showed a slightly higher moisture content immediately after processing. However, the moisture content decreased to 1.5% when isomalt was extruded at a higher temperature (190 °C). Simultaneously, this resulted in an increase of T_g and thus a relative improvement of the powder physical stability with respect to recrystallization and particle agglomeration (Fritzsching, 1993; Hancock and Zografi, 1994; Saleki-Gerhardt and Zografi, 1994; Royall et al., 1999). Extrusion at elevated temperatures did not induce chemical decomposition of isomalt as no thermal degradation was detected on DSC thermograms up to 200 °C.

Table 1
Influence of extrusion temperature on water content and glass transition temperature (T_g) of isomalt

Extrusion temperature (°C)	Water content (%)	T_g (°C)
Non-extruded	2.6 ± 0.1	63.4 ± 0.1*
140	3.3 ± 0.1	42.4 ± 0.2
150	3.1 ± 0.2	39.7 ± 0.8
190	1.5 ± 0.0	52.1 ± 0.2

* Determined during a second heating cycle.
T_g was determined by MTDSC analysis. All analysis were performed immediately after extrusion of isomalt and were run in triplicate.

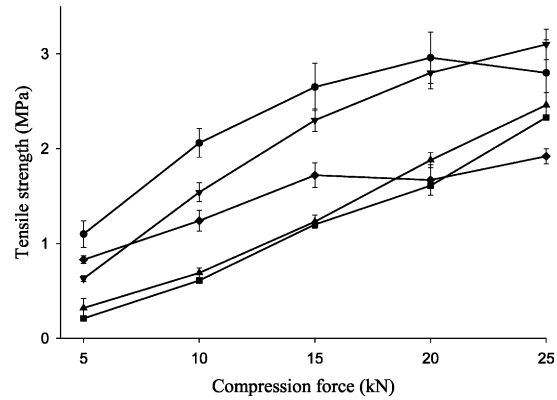

Fig. 1. Compression profiles ($n = 10$) of placebo formulations based on isomalt powder extruded at 130 (▲); 140 (▼); 150 (●) and 190 °C (◆) compared with non-extruded isomalt mixtures (■). All formulations included 0.5% Aerosil® 200 and 1% magnesium stearate. The compression data of tablets formulated with non-extruded isomalt was obtained from Ndindayino et al. (1999).

3.2. Tabletting properties

The influence of the extrusion temperature on the compressibility of isomalt powder is illustrated in Fig. 1. The tensile strength of the tablets formulated with extruded isomalt increased with increasing extrusion temperature between 130 and 150 °C. At 130 °C, the tensile strength was very similar to the one of tablets made of non-extruded isomalt, due to the presence of mainly crystalline material when isomalt was processed at a temperature below its melting point (Sebhatu et al., 1994).

However, compared with the tablets containing non-extruded isomalt, the tensile strength of placebo tablets was nearly doubled when the tablets were formulated with isomalt powder extruded at 150 °C ($P < 0.001$; independent t-test). At a compression force of 20 kN the tensile strength was about 3 MPa for the tablets made of extruded isomalt, while it was only 1.61 MPa for the tablets based on non-extruded material (Ndindayino et al., 1999). It is suggested that the increased compressibility after melt-extrusion of isomalt at 150 °C is due to its amorphous character offering an increased possibility to the material to deform plastically. This observation was supported by recent findings (Sebhatu et al., 1994; Larhrib and Wells, 1997; Maggi et al., 1998; Tolstoguzov, 2000) claiming that the amorphous phase absorbed water acting as a plasticizer and thereby increasing the plastic deformation during compaction. These authors attributed the increased tablet tensile strength either to the enhanced fusion of particles or to an increased plastic flow, resulting in denser packing of particles and an increase of the available surface area for binding formation within the tablet.

Isomalt processed at 190 °C yielded a lower compressibility compared with the material extruded at 140 and 150 °C. This is probably due to the low moisture content after extrusion at this higher temperature. However, at compression forces below 20 kN the compressibility was somewhat improved compared with non-extruded material. Similar results were reported by Sebhatu et al. (1994) in their work about the effect of moisture sorption on the tabletting characteristics of spray dried lactose. These authors described that, even at very low moisture contents, an amorphous glassy material could change into a rubbery state during compression due to an increased local temperature (and/or pressure). The amorphous bridges formed revert back to the glassy state on the release of the pressure and the subsequent decrease of temperature. Moreover, even a relatively small amount of adsorbed water can be an efficient plasticizer (Tolstoguzov, 2000).

The compression profiles of isomalt formulations containing 50% (w/w) paracetamol are shown in Fig. 2. The tensile strength of tablets formulated with extruded isomalt powder significantly decreased when 50% paracetamol was included in the formulation. However, these tablets still had an acceptable tensile strength (> 0.80 MPa) when produced at a compression force above 10 kN. In comparison with tablets made with non-extruded isomalt powder, a seven fold increase of the tensile strength was seen for paracetamol tablets formulated with extruded isomalt ($P < 0.001$; independent t-test). As expected, the tensile strength of the tablets processed with extruded isomalt depended on the compression force: a higher compression force yielded harder tablets.

Extruded isomalt proved to have excellent compression properties, but agglomeration phenomena affected its flow properties resulting in a relatively high weight variation (R.S.D. $> 0.5\%$). As shown in Table 2, paracetamol tablets formulated with extruded isomalt had a lower friability than those prepared with non-extruded isomalt. These tablets also yielded a fast disintegration and a rapid dissolution ($> 80\%$ paracetamol dissolved within 20 min).

3.3. Effect of storage conditions on the stability of melt-extruded isomalt

As reported by Fritzsching (1993), powder agglomeration after extrusion at 190 °C was de-

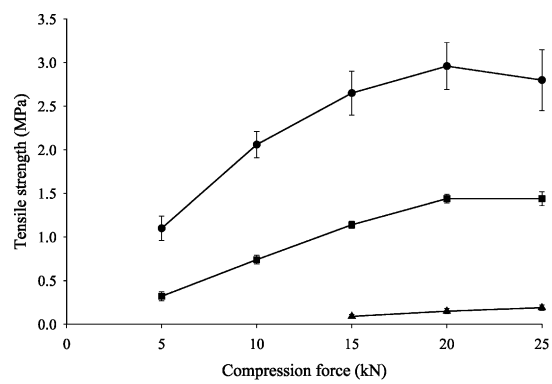

Fig. 2. Compression profiles of formulations containing: isomalt extruded at 150 °C and 50% paracetamol (■); isomalt extruded at 150 °C (placebo) (●); non-extruded isomalt and 50% paracetamol (▲). All formulations contained 0.5% Aerosil® 200 and 1% magnesium stearate. 5% Explotab® was added to the drug-containing formulations, $n = 10$.

Table 2
Average tablet friability and disintegration time (mean ± S.D.) of tablets formulated with isomalt (extruded at 150 °C) and paracetamol (50%)

Compression force (kN)	Extruded isomalt		Non-extruded isomalt	
	Friability (%)	Disintegration time (s)	Friability (%)	Disintegration time (s)
15	3.4 ± 0.1	358 ± 14	–	–
20	2.5 ± 0.1	383 ± 7	11.0 ± 1.0	103 ± 13
25	2.3 ± 0.2	433 ± 10	4.5 ± 0.3	200 ± 10

The formulation included 5% Explotab®, 0.5% Aerosil® 200 and 1% magnesium stearate.

layed in comparison with material extruded at 140 and 150 °C which already agglomerated during milling and sieving. These agglomeration phenomena were not observed for powder extruded at a temperature of 130 °C because of its mainly crystalline nature.

The water sorption of amorphous isomalt (extruded at 190 °C) as a function of storage time at room temperature and different RHs is illustrated in Fig. 3. During the initial 2 days of sample storage at 55 and 75% RH (Fig. 3), isomalt extruded at 190 °C rapidly absorbed atmospheric moisture (up to a maximum of about 3.5%), followed by a gradual loss of water due to a progressive transformation of amorphous isomalt into a partial crystalline material as shown in Table 3. During this transformation, GPS recrystallized with the release of water in the form of vapor, while GPM recrystallized with two molecules of water (Cammenga and Zielasko, 1996b). Due to water absorption, the particle surface was transformed into a highly viscous solution, became sticky and fused together as observed in earlier studies (Palmer et al., 1956; Elamin et al., 1994). As a result, the powder formed an agglomerated cake after 2 days of storage due to the formation of strong interparticulate bonds caused by recrystallization. Due to the plasticizing effect of the absorbed water, the T_g of the amorphous phase decreased as shown in Table 3.

The melting point of recrystallized extruded isomalt was lower (Table 3) compared with non-extruded material probably due to factors such as the presence of an amorphous fraction acting as an impurity; differences in physical properties of the crystals such as crystal size and shape (Palmer et al., 1956) and the presence of water (Slade and Levine, 1995; Tolstoguzov, 2000). After 17 days of storage (at 55% and 75% RH) the formed powder compact was deagglomerated with mortar and pestle; the resulting powder fraction (< 500 μm) did not reagglomerate during a storage period of up to 6 months at 55 and 75% RH due to its crystalline nature. However, this material was poorly compressible as could be expected because of its mainly crystalline nature.

When stored at 31% RH (Fig. 3) similar phenomena as observed at high relative humidity were occurring, but at a slower rate (drop in water content after about 2 months).

The progressive crystallization as a function of storage time was confirmed using hot stage mi-

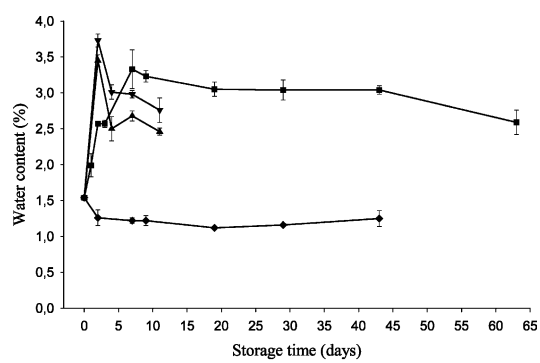

Fig. 3. Water sorption of isomalt extruded at 190 °C in function of storage time at room temperature (25 ± 2 °C) and different RHs: < 10 (◆); 31 (■); 55 (▼) and 75% RH (▲), $n = 3$.

Table 3
Recrystallization of isomalt (extruded at 190 °C) as a function of the storage time at 55 and 75% relative humidity

RH	Time (days)	Water (%)	T_g (°C)	T_m (°C)	ΔHf (j/g)	Crystallinity (%)
Extruded isomalt at 190 °C						
55%	0	1.50 ± 0.01	53.5	–	–	0.0
	2	3.73 ± 0.09	51.8	129.3	0.46	0.3
	7	2.98 ± 0.05	22.7	123.1	4.77	3.5
	11	2.76 ± 0.17	16.9	117.0	9.93	7.2
75%	0	1.50 ± 0.01	53.5	–	–	–
	2	3.45 ± 0.08	52.8	121.0	5.58	4.1
	7	2.58 ± 0.07	18.7	111.4	17.15	12.5
	11	2.46 ± 0.04	6.4	108.3	17.40	12.7
Non-extruded isomalt						
Ambient	0	2.61 ± 0.09	63.4 ± 0.1	150.4 ± 0.8	137.3 ± 0.9	100.0

Thermo-analysis was performed by standard DSC-analysis. ΔHf: enthalpy of fusion; T_m, melting temperature.

croscopy after 19 and 29 days of storage. Moreover, recrystallization was confirmed by TGA as water evaporation still occurred above 100 °C due to the presence of crystallization water and complete evaporation was only obtained at 180 °C.

The moisture content of extruded isomalt correlated well with its compressibility during storage at 31% RH (Fig. 4) and at $< 10\%$ RH (results not shown). Samples stored at $< 10\%$ RH, after a decrease in moisture content from ± 1.5 to $\pm 1\%$ during the first day, showed a fairly constant water content during the remaining storage time. Consequently, T_g was constant and no recrystallization or agglomeration phenomena were observed, yielding a constant tablet quality.

3.4. Effects of moisture sorption on the post-compaction tablet strength

The influence of storage conditions on the tensile strength of placebo tablets formulated with extruded isomalt is shown in Fig. 5. During storage at 31% RH, an increasing tensile strength was seen between day 3 and 9, due to the sorption of moisture and recrystallization of amorphous isomalt. After 25 days of storage the tendency of a decreasing tensile strength could be attributed to a continuous moisture sorption occurring at a slower rate, breaking or softening hydrogen bonds in the amorphous phase or in crystalline bridges previously formed between particles (Sebhatu et al., 1994). Storage of the tablets at $< 10\%$ RH resulted in a constant tensile strength up to 9 days due to the absence of water sorption. Next, a slight increase in tablet tensile strength with storage time was observed probably because of the drying of the amorphous bridges on water desorption (Sebhatu et al., 1994).

4. Conclusions

The direct compression properties of isomalt dramatically improved when the material was melt-extruded prior to compression due to the

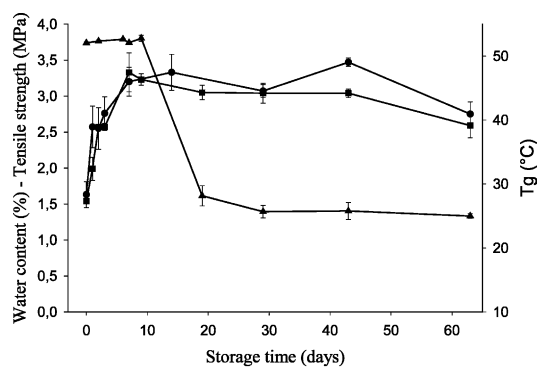

Fig. 4. Influence of water sorption (■) on the glass transition temperature (T_g) (▲) and the compressibility (●) of isomalt extruded at 190 °C as a function of storage time at 31% RH (a) RH (25 ± 2 °C), $n = 3$.

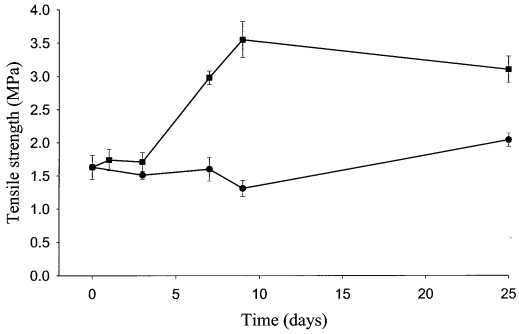

Fig. 5. Tablet strength as a function of storage time at <10 (●) and 31% (■) RH (25 ± 2 °C).

formation of an amorphous material. A seven fold increase in tablet tensile strength was seen when the melt-extruded isomalt was used to make tablets containing 50% paracetamol. These tablets had a low friability, a fast disintegration and a rapid dissolution. However, recrystallization of amorphous isomalt during storage at higher RH affected both the flow properties and compressibility of the powder. Therefore, further research will concentrate on delaying or even preventing recrystallization of extruded isomalt.

Acknowledgements

F. Ndindayino is supported by the Belgium Catholic Foundation for African Student Grants (FONCABA). D. Henrist is a research assistant of the Fund for Scientific Research, Flanders, Belgium (F.W.O) and G. Van den Mooter acknowledges the financial support provided by the Fund for Scientific Research, Flanders, Belgium (F.W.O).

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