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Direct compression and moulding properties of co-extruded isomalt/drug mixtures

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Abstract

Isomalt, a disaccharide alcohol was co-extruded with paracetamol or hydrochlorothiazide (HCT) in order to improve its tabletting properties. After extrusion, isomalt was transformed into an amorphous form, while paracetamol remained crystalline. Hot stage microscopy showed that HCT was amorphous in the isomalt carrier up to a concentration of 1% (w/w). Direct compression of mixtures formulated with co-extruded isomalt/paracetamol powders yielded harder tablets compared with physical mixtures and no powder agglomeration was observed. Direct moulding of isomalt co-extruded with either paracetamol or HCT was feasible, yielding hard tablets. A fast dissolution rate was seen for both the compressed and the moulded tablets ($>80\%$ paracetamol and 60% HCT released within 20 min). The compressed tablets showed a dramatic decrease in tensile strength during storage at 85% RH, while the tensile strength of the moulded tablets remained above 0.80 MPa after 6 months storage at the same conditions. Co-extrusion of isomalt with paracetamol and HCT dramatically improved the tabletting properties of the mixtures (compared with physical mixtures of drug and isomalt). Direct moulding proved to be a suitable technique to produce isomalt based tablets.

Keywords: Isomalt; Co-extrusion; Direct compression; Paracetamol; Hydrochlorothiazide; Direct moulding

1. Introduction

Over the last decade, sugar based excipients received a lot of attention during the development of pharmaceutical formulations mainly because of their safety and pleasant taste. Among these sugar alcohols (polyols) isomalt or Palatinit® (an equimolecular mixture of two stereoisomers: α-D-glucopyranosyl-1,1-D-mannitol, GPM and α-D-glucopyranosyl-1,6-D-sorbitol, GPS) offers several advantageous properties such as taste, mouth feel, low calorie content, acariogenicity, suitability to diabetics, high stability and low hygroscopicity (Strater, 1989; Fritzsching, 1993).

A study on the characterization and direct compression properties of isomalt was reported by Ndindayino et al. (1999) and the investigators showed that a drug load above 30% yielded

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tablets of unacceptable quality. Recently, Ndindayino et al. (2002) reported on the modification of isomalt using melt-extrusion in an attempt to improve its direct compression properties. Although the use of melt-extruded isomalt powder improved the tablet tensile strength, progressive crystallization of the amorphous isomalt affected both the flow properties and compressibility of the powder.

Co-fusion of the drug with an excipient has been reported as a suitable technique to improve the compression properties of a formulation (Kanig, 1964; Sjökvist and Nyström, 1991; Stein et al., 1991; Nagarsenkar and Shenai, 1996) with the added advantages of an increased dissolution rate and improved bioavailability of poorly water-soluble drugs (Nagarsenkar and Shenai, 1996; Leuner and Dressman, 2000). Next to the co-extrusion procedure, moulding can also be used to manufacture tablets whereby a molten mass is collected into tablet-shaped cavities and tablets are recovered upon solidification of the mass. This technique offers several advantages: production of tablets at high drug load; a dust free process; content uniformity of low dosed drugs (dissolved in a molten carrier); minimal influence of the drug's compressibility, particle size and particle shape; ease of scale-up. The only major limitation of this technique is its restriction to heat stable products (Cuff and Raouf, 1999; Serajuddin, 1999; Dobetti, 2000).

The present study was conducted to investigate the direct compression properties of melt co-extruded isomalt/drug powder mixtures and to evaluate direct moulding as an alternative technique to produce isomalt based tablets.

2. Materials and methods

2.1. Materials

Isomalt (melting range, T_m, 145–150 °C) or Palatinit® C (Palatinit-Süßungsmittel, Mannheim, Germany) was used as the carrier material. Paracetamol dense powder (T_m: 169.0–170.5 °C and particle size, $D_{10\%}$, 64.4 μm, $D_{50\%}$, 206.3 μm and $D_{90\%}$, 429.7 μm) (Mallinckrodt, Raleigh, NC) and hydrochlorothiazide (T_m, 273–275 °C, $D_{10\%}$, 51.0 μm, $D_{50\%}$, 153.7 μm and $D_{90\%}$, 337.2 μm) (Ludeco, Brussels, Belgium) were used as model drugs at a concentration of 50 and 10%, respectively. Isomalt tablets were compressed using the following excipients: 5% (w/w) Explotab® (Pennwest Ltd., Patterson, NY), 0.5% (w/w) Aerosil® 200 (< 90 μm) (Ludeco, Brussels, Belgium) and 1% (w/w) magnesium stearate (< 90 μm) (Pharmachemic, Wevelgem, Belgium).

2.2. Co-extrusion of isomalt/paracetamol mixtures

A physical mixture of isomalt and paracetamol (43.5/50.0; w/w) was extruded at different temperatures (120, 140 and 150 °C) using a continuous melt-extruder MP 19 TC 25 (APV Baker, Newcastle-under-Lyme, UK). This lab-scale extruder was equipped with two co-rotating 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 material residence time ranging from 1.0 to 6.5 min. No die was fitted to the exit of the extrusion barrel, hence the material pressure remained below 3 bar during all extrusion runs.

After a storage period of 72 h at ambient conditions ($50 \pm 5\%$ RH and 25 ± 2 °C), each co-extruded mixture was pulverized with pestle and mortar, and the fraction below 500 μm was used for compression experiments.

2.3. Preparation of tablets by direct compression

After pulverization of the isomalt/paracetamol mixtures, the powder was mixed with 5% Explotab® for 10 min. Next, 0.5% (w/w) Aerosil® 200 (< 90 μm) was added 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 final mixtures were compressed into 600 mg tablets using 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.

2.4. Preparation of tablets by a melt-moulding technique

Besides co-extrusion of an isomalt/paracetamol powder blend followed by direct compression as described above, isomalt tablets were also manufactured using a melt-moulding technique. Pure isomalt and the following mixtures were (co-)extruded at 150 °C using the above described procedure: isomalt/paracetamol (50:50), isomalt/paracetamol/Explotab® (45:50:5) and isomalt/hydrochlorothiazide/Explotab® (85:10:5). These molten materials were immediately poured into metal moulds with a thickness and diameter of 4 and 13 mm, respectively. After cooling and solidification of the mixtures at ambient temperature in the moulds, the excess material on the mould surface was removed using a surgical blade. Finally the mould was dismantled and the tablets (± 600 mg) collected.

2.5. Material characterization

2.5.1. Physical properties

Powder X-ray diffraction analysis was performed using a X-ray diffractometer (D 5000, Siemens, Germany) with Cu–K_α 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 the isomalt/drug mixtures co-extruded at 150 °C was evaluated using differential scanning calorimetry (DSC). 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) unit. Considering the effects of the experimental conditions on the MTDSC response, the following parameters were selected: an underlying heating rate of 2 °C/min using dry helium as a purge gas flowing through the MTDSC cell at 40 ml/min and nitrogen 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 between 0 and 200 °C. The fraction of crystalline isomalt in the extruded samples was estimated from the enthalpy of fusion of the isomalt melting peak relative to the fusion enthalpy of a non-extruded sample taking into account the sample water content. The same procedure was used to evaluate the effect of hot stage extrusion on the crystallinity of paracetamol.

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

2.5.2. Drug stability

Following extrusion, the stability of paracetamol was evaluated using the HPLC method described in the USP XXIV. The chromatographic system consisted of a LaChrom® HPLC system (Merck Hitachi, Tokyo, Japan): an isocratic L-7110 pump combined with a L-7400 UV detector set at 243 nm. Chromatographic separation was achieved at room temperature on a 3.9 mm × 30 cm RPC-18 column (Merck, Darmstadt, Germany) using a degassed mixture of methanol and water (1:3) as the mobile phase at a flow rate of 1.5 ml/min. The stability of hydrochlorothiazide after extrusion was also evaluated using the above described chromatographic system (detection at 254 nm) in combination with an Ultrasphere® ODS 4.6 mm × 25 cm RPC-18 column (Beckman Instruments, Fullerton, USA) using a degassed mixture of 0.1 M monobasic sodium phosphate and acetonitrile (pH 3.0 ± 0.1; ratio: 9/1) as a mobile phase flowing at 2 ml/min.

2.5.3. Determination of formation of solid solutions

The solubility of hydrochlorothiazide (HCT) and paracetamol in isomalt was determined by uniformly dispersing these drugs at concentrations ranging between 0.5 and 20% into liquid isomalt (heated to 150 and 190 °C on an electric furnace).

In addition, isomalt was co-extruded with HCT (at a concentration range between 5 and 20%) at 150 and 190 °C using the procedure previously described. After cooling, the resulting solid materials were milled and the powder submitted to X-ray diffraction, hot stage microscopy (Mettler FP 52/FP 5, Mettler-Toledo, Switzerland) and MTDSC. The theoretical glass transition temperature of isomalt/HCT binary mixtures (Tg_{mix}) was determined according to the Gordon–Taylor relationship (Gordon and Taylor, 1952):

$$Tg_{mix} = \frac{(W_1 Tg_1 + K W_2 Tg_2)}{(W_1 + K W_2)}$$

W_1 and W_2 are the weight fractions of isomalt and drug, respectively, while Tg_1 and Tg_2 are the glass transition temperatures in kelvin (Tg of hydrochlorothiazide: 112.5 °C).

K is determined according to Simha-Boyer rule (Simha and Boyer, 1962):

$$K \cong \frac{(\rho_1 Tg_1)}{(\rho_2 Tg_2)}$$

ρ_1 and ρ_2 are the density of amorphous isomalt and drug, respectively.

2.6. Tablet characterization.

The compressed as well as the moulded tablets were characterized by their physical properties. The average tablet weight was determined from 20 individual tablets. In case of the compressed 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 from the tablets was measured according to the method described in the USP XXIV (apparatus 2) at a paddle speed of 50 rpm in 900 ml pH 5.8 phosphate buffer, while the dissolution profile of the moulded tablets containing HCT was evaluated at a paddle speed of 100 rpm in 900 ml 0.1 N HCl (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 blank medium. The paracetamol and HCT concentration of each sample was spectrophotometrically (UV-VIS Spectrometer Lambda 12, Perkin–Elmer, Ueberlingen, Germany) determined at 243 and 272 nm, respectively.

2.7. Physical stability of the co-extruded powders and tablets

An isomalt/paracetamol mixture (48.5/50.0) extruded at 150 °C was used to evaluate the effect of moisture sorption on powder stability and compression properties. The powder samples were stored at ambient temperature (25 ± 2 °C) in a sealed environment at 55 and 75% RH. Their water content, thermal behavior as well as compression properties were examined as a function of storage time using the methods previously described. The tensile strength of compressed and moulded tablets was evaluated during 6 months storage at ambient temperature (25 ± 2 °C) and at a relative humidity of 45 and 85%.

3. Results and discussion

3.1. Characterization of co-extruded isomalt/drug mixtures

3.1.1. Co-extruded isomalt/paracetamol mixtures

It was demonstrated by powder X-ray diffraction and DSC that the isomalt fraction—following melting during extrusion—solidified as an amorphous material, while paracetamol remained a crystalline solid (dispersed in isomalt) as 99.5% of paracetamol's crystallinity was recovered after extrusion (data not shown). Hot stage microscopy showed that paracetamol solubilized at 150 °C into the molten isomalt up to a concentration of

10%, however, no solid solution was formed as drug recrystallization was seen immediately after cooling. The co-extruded mixtures had an improved stability regarding powder agglomeration in comparison to extruded isomalt, which already agglomerated during the milling/sieving process. These observations were confirmed by an increase of the glass transition temperature (Tg) (46.5 ± 1.2 °C) of the isomalt/paracetamol mixture co-extruded at 150 °C compared with the value (39.7 ± 0.8 °C) reported by Ndindayino et al. (2002) for pure isomalt extruded at the same temperature. This is probably due to their different moisture content: 1.9% (w/w) for the isomalt/paracetamol mixture versus 3.1% (w/w) for pure isomalt (Ndindayino et al., 2002).

HPLC analysis did not show any paracetamol degradation during extrusion (99.6 ± 0.5% paracetamol recovered). This was supported by DSC analysis which did not reveal any melting transition at 190 °C corresponding to p-aminophenol, the main thermal degradation product of paracetamol (Faroongsarng et al., 2000).

3.1.2. Co-extruded isomalt/hydrochlorothiazide (HCT) mixtures

As illustrated in Fig. 1, Tg of extruded isomalt/HCT mixtures was not influenced by the drug concentration and remained lower than the theoretical Tg of these binary mixtures calculated using Gordon–Taylor equation. This could be due to phase separation as a molecular dispersion of HCT in isomalt was only formed at drug concentrations below 1% as shown by hot-stage microscopy. During extrusion, HCT could form hydrogen bonds with the carrier (Simonelli et al., 1994), explaining why no drug recrystallization was observed. An increasing Tg of the mixture with increasing extrusion temperature was observed as previously shown by Ndindayino et al. (2002). HPLC analysis confirmed the stability of the drug during extrusion as 101.3 (± 1.4)% HCT was recovered.

3.2. Compression properties of co-extruded isomalt/paracetamol powder

The compression profiles of isomalt/paraceta-

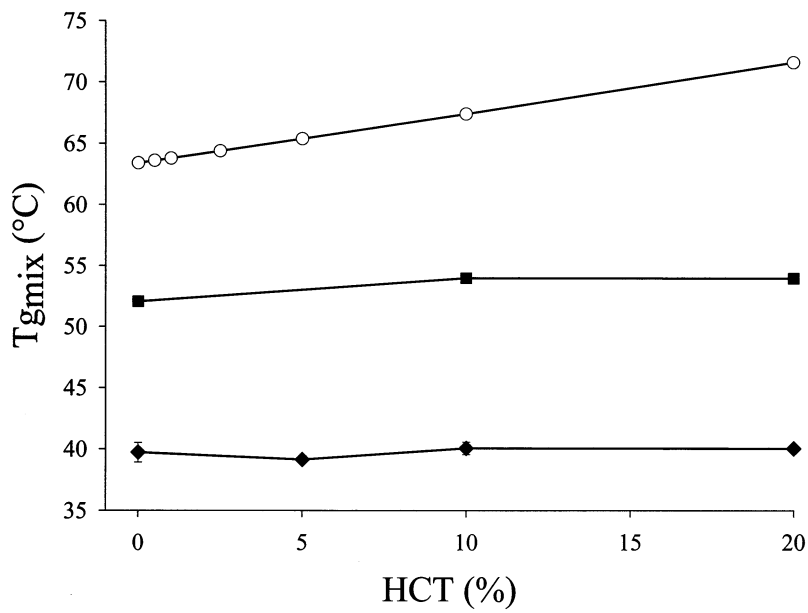

Fig. 1. Glass transition temperature (Tg) ($n = 3$) of isomalt co-extruded with different concentrations of hydrochlorothiazide (HCT) at 150 °C (◆) and 190 °C (■) in comparison to their theoretical Tg (○) calculated using the Gordon–Taylor equation (measurements carried out using MTDSC).

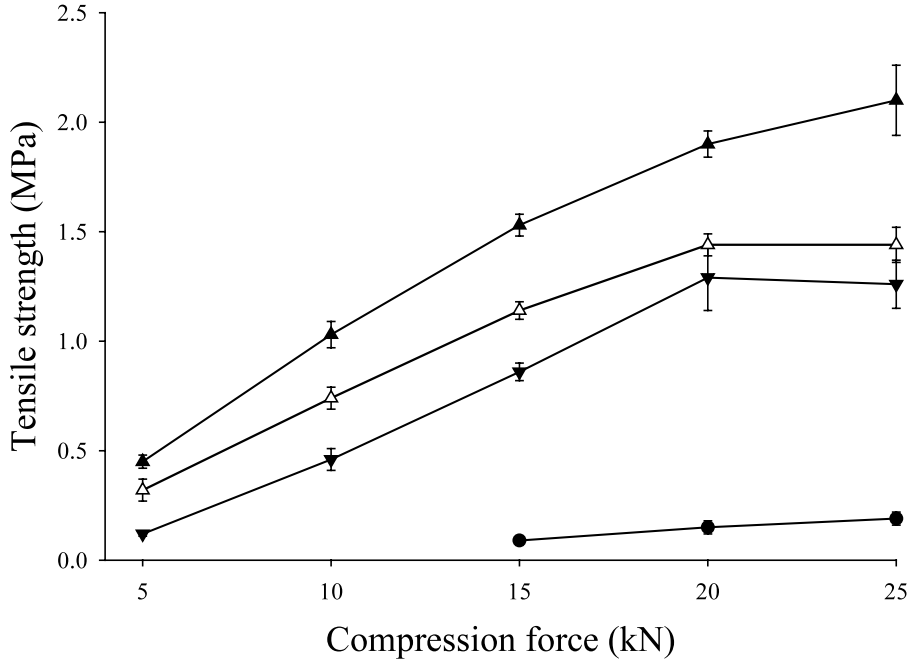

Fig. 2. Compression profile ($n = 10$) of isomalt and paracetamol (43.5/50.0)-mixtures: physical mixture (●), isomalt extruded at 150 °C before preparing a physical mixture with paracetamol (△), mixture co-extruded at 150 °C (▲) and at 120 °C (▼). All formulations contained 5% Explotab®, 0.5% Aerosil® 200 and 1% magnesium stearate.

mol co-extruded at different temperatures are shown in Fig. 2. Although the crystalline nature of paracetamol was not affected by the extrusion process, co-extrusion of paracetamol with isomalt had a beneficial effect on the compression properties. Compared with the tablets formulated using a physical mixture of paracetamol and isomalt, co-extrusion (even at lower extrusion temperatures, 120 °C) induced-at least-a seven fold enhancement of the tablet tensile strength. Furthermore, the tablets manufactured from the powder co-extruded at 150 °C had a slightly higher tensile strength than the tablets formulated with a physical mixture of paracetamol and extruded isomalt (at 150 °C). Due to the co-extrusion process an acceptable tablet tensile strength (≥ 0.80 MPa) was obtained at a compression force of 10 kN for isomalt/paracetamol mixtures co-extruded at 150 °C; yielding values of 1.0 ($\pm$ 0.1) and 2.1 (± 0.2) MPa at compression forces of 10 and 25 kN, respectively.

While plastic deformation of amorphous isomalt improved the tablet tensile strength (Ndindayino et al., 2002), the enhancement of the quality of the tablets formulated with co-extruded isomalt/paracetamol mixtures could be due to the thermo-mechanical treatment of paracetamol during co-extrusion. Modifications of its particle size and/or shape could enhance bond formation between isomalt and paracetamol particles during compression (Serpelloni, 1990; Serpelloni and Croisier, 1995) as-after co-extrusion—the paracetamol consolidation mechanism could change from brittle fracture to plastic deformation as observed for paracetamol solid dispersions prepared by spray drying or kneading (Tasic et al., 1997, 1998). The flow properties of the co-extruded isomalt/paracetamol mixtures were excellent and neither sticking nor agglomeration problems were observed.

The tablet friability and disintegration data are summarized in Table 1. The friability of the tablets formulated with isomalt/paracetamol mixtures co-extruded at 150 °C was lower than the

values reported by Ndindayino et al. (2002) for tablets formulated with a physical mixture of paracetamol and extruded isomalt (friability > 2%). Although, their disintegration time (> 700 s for tablets compressed at > 15 kN) was doubled compared with the data reported by Ndindayino et al. (2002) on extruded isomalt (358 s), all formulations released more than 80% of the drug within 20 min (Fig. 3).

3.3. Direct moulding

Although compression techniques are the most popular methods to produce tablets, direct

Table 1
Friability ($n = 3$) and disintegration time ($n = 6$) of tablets manufactured using direct compression and the moulding technique

Formulations	Friability (%)	Disintegration (%)	Tensile strength (MPa)
Direct compression (following co-extrusion at 150 °C)			
Isomalt/paracetamol (43.5:50)			
10 kN	–	–	1.03 ± 0.06
15 kN	1.2 ± 0.1	701 ± 21	1.53 ± 0.05
20 kN	1.2 ± 0.2	729 ± 20	1.90 ± 0.06
25 kN	1.1 ± 0.1	819 ± 16	2.10 ± 0.16
Direct moulding			
Placebo	–	–	2.92 ± 0.57
Isomalt/paracetamol (50:50)	1.1 ± 0.1	1273 ± 36	1.74 ± 0.39
Isomalt/paracetamol/Explotab® (45:50:5)	0.8 ± 0.1	1108 ± 52	2.00 ± 0.20
Isomalt/HCT/Explotab® (85:10:5)	0.2 ± 0.0	290 ± 4	2.63 ± 0.30

All directly compressed formulations included 5% Explotab®, 0.5% Aerosil® 200 and 1% magnesium stearate. In all cases the extrusion temperature was 150 °C.

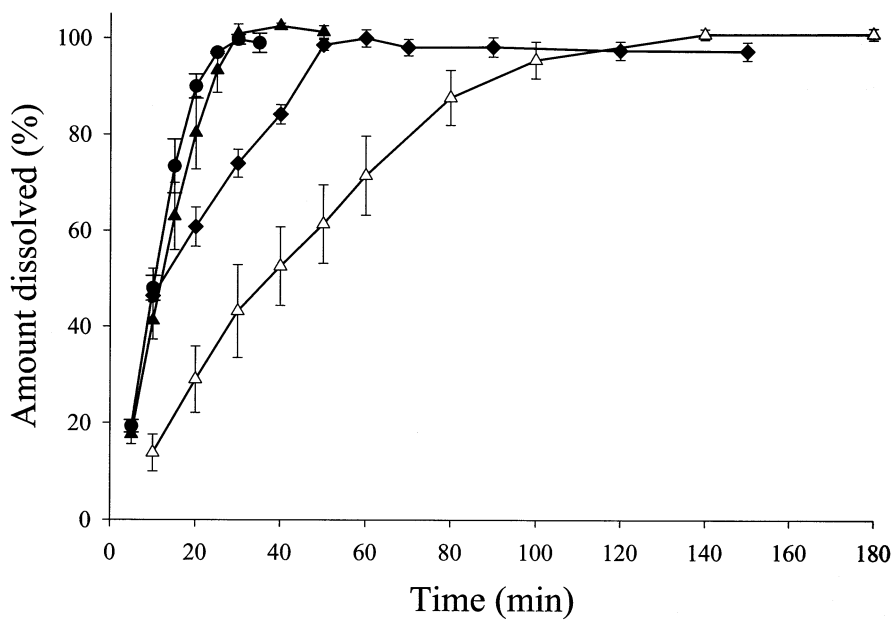

Fig. 3. Dissolution profiles from moulded tablets formulated with isomalt/paracetamol (50/50) (△), isomalt/paracetamol/Explotab® (45/50/5) (▲) and isomalt/HCT/Explotab® (85/10/5) (◆) in comparison to directly compressed (20 kN) tablets formulated with co-extruded isomalt/paracetamol (43.5/50.0) powder (●) containing 5% Explotab®, 0.5% Aerosil® 200 and 1% magnesium stearate.

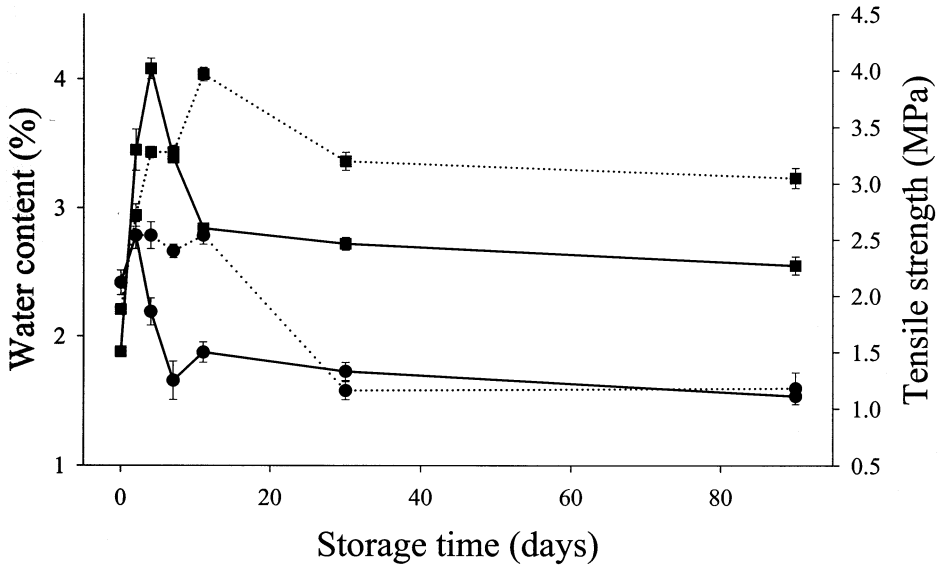

Fig. 4. Influence of water sorption (■) ($n = 3$) on the compressibility (●) ($n = 10$) of isomalt/paracetamol (48.5/50.0) mixtures co-extruded at 150 °C as a function of storage time and relative humidity (RH): 55% (…) and 75% RH (—) (storage temperature: 25 ± 2 °C). All formulations contained 0.5% Aerosil® 200 and 1% magnesium stearate and were compressed at 20 kN.

moulding could be a suitable alternative to manufacture isomalt tablets. Next to the advantages mentioned in the introduction, isomalt tablets were produced by means of the moulding technique without the addition of lubricants and glidants. The molten mixture was viscous liquid (reducing the sedimentation velocity of dispersed material) and solidified inside the cavities within 10 min. The tensile strength of the moulded tablets prepared from the various formulations are presented in Table 1. The moulded placebo tablets had a higher tensile strength compared with the drug containing tablets. The tensile strength of moulded tablets containing paracetamol was not significantly different ($P > 0.05$; independent T-test) from the data obtained for tablets formulated with isomalt/paracetamol mixtures co-extruded at 150 °C and compressed at 20 kN. The HCT containing moulded tablets showed a significantly higher tensile strength ($P < 0.05$; independent T-test) in comparison to all paracetamol-based formulations probably due to the lower drug load.

Although the disintegration time of the moulded tablets was significantly higher (Table 1) ($P < 0.05$; independent T-test), the dissolution rate of paracetamol from the moulded tablets formulated with Explotab® complied with the USP XXIV monograph: more than 80% drug released within 20 min (Fig. 3). As expected from the disintegration data (290 s), the HCT containing moulded tablets also had a fast dissolution rate (> 60% HCT released within 20 min) (Fig. 3). Besides the presence of a disintegration agent and the modification of the particle size of HCT (identified by hot stage microscopy), the fast dissolution should be attributed to the high fraction of the amorphous water soluble carrier as reported in early studies (Simonelli et al., 1994; Tantishaiyakul et al., 1996; Chowdary and Rao, 2000; Dobetti, 2000).

3.4. Stability evaluation

3.4.1. Influence of storage conditions on direct compression properties of co-extruded mixtures

The compressibility and moisture content of isomalt/paracetamol powder mixtures (48.5/50.0) co-extruded at 150 °C, are shown in Fig. 4 as a function of storage time. Under these storage

Table 2
Tensile strength ($n = 10$) as a function of storage time at 85% RH (storage temperature: 25 ± 2 °C)

Storage time (months)	Compressed tablets (MPa)	Moulded tablets	
		Paracetamol (MPa)	Hydrochlorothiazide (MPa)
0	1.92 ± 0.14	2.00 ± 0.20	2.56 ± 0.27
2	0.50 ± 0.09	1.31 ± 0.16	2.16 ± 0.33
6	0.27 ± 0.04	1.05 ± 0.07	1.44 ± 0.11

The moulded tablets were formulated with isomalt/paracetamol/Explotab® (45/50/5) or isomalt/HCT/Explotab® (85/10/5), while the directly compressed tablets were manufactured with co-extruded isomalt and paracetamol (43.5/50.0). The directly compressed tablets contained 5% Explotab®, 0.5% Aerosil® 200 and 1% magnesium stearate and were compressed at 20 kN. In all cases the extrusion temperature was 150 °C.

conditions, similar phenomena related to isomalt recrystallization were observed as previously reported for extruded isomalt powder (Ndindayino et al., 2002). However, the recrystallization rate was significantly delayed for co-extruded mixtures as a melting endothermic peak of isomalt was only observed after 2 months storage at 75 and 55% RH (4.5 and 2.1% crystallinity, respectively) in comparison to extruded isomalt where recrystallization was already observed after 2 days.

Similarly, the evolution of the moisture content correlated well with the compressibility data due to a gradual recrystallization of isomalt. This phenomenon only affected the compressibility of co-extruded isomalt/paracetamol powder as powder agglomeration was not observed.

3.4.2. Tablet stability

The tablet tensile strength of all formulations remained constant during 6 months storage at 45% RH (results not shown). When stored at 85% RH (Table 2), both moulded tablet formulations showed a significant decrease in tensile strength ($P < 0.05$; independent T-test), however, this decrease was much less pronounced than in the case of the compressed tablets formulated with co-extruded isomalt/paracetamol mixtures. The higher reduction in tensile strength recorded for compressed tablets is due to their higher porosity resulting in a higher water absorption rate in comparison to moulded tablets (Bayer, 2000; Petzoldt, 2000).

4. Conclusions

The direct compression properties of isomalt physical mixtures with paracetamol were dramatically improved when the mixtures were co-extruded prior to compression. A slight improvement in tabletting properties was seen after co-extrusion compared with tablets formulated using a physical mixture of drug and extruded isomalt. Although by co-extrusion, the recrystallization of amorphous isomalt during storage at high RH was delayed, the tablet tensile strength dramatically decreased in function of storage time and relative humidity.

The direct moulding of isomalt co-extruded with the drug proved to be a suitable technique to produce tablets with excellent physical characteristics.

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References

Bayer, M., 2000. Injection moulding metal and ceramic powder. Kunststoffe. Plast. Eu. 90, 17–18.

Chowdary, K.P.R., Rao, S.S., 2000. Investigation of dissolution enhancement of itraconazole by solid dispersion in superdisintegrants. Drug Dev. Ind. Pharm. 26, 1207–1211.

Cuff, G., Raouf, F., 1999. A preliminary evaluation of injection moulding as a tabletting technology. Pharm. Tech. Eur. 1, 18–26.

Dobetti, L., 2000. Fast-melting tablets: developments and technologies. Pharm. Tech. Eur. 12, 32–42.

Faroongsarng, D., Kadejinda, W., Sunthornpit, A., 2000. Thermal behaviour of a pharmaceutical solid acetaminophen doped with p-aminophenol. AAPS PharmSci Tech., 1(3) article 23 (http://www.pharmscitech.com).

Fritzsching, B., 1993. Isomalt, a sugar substitute ideal for the manufacture of sugar-free and calorie-reduced confectionery. in: Conference Proceedings-Food Ingredients Europe. Maarssen, The Netherlands, pp. 371–377.

Gordon, M., Taylor, J.S., 1952. Ideal copolymers and the second order transitions of synthetic rubbers I. Non-crystalline copolymers. J. Appl. Chem. 2, 493–5000.

Kanig, J.L., 1964. Properties of fused mannitol in compressed tablets. J. Pharm. Sci. 53, 188–192.

Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.

Nagarsenkar, M.S., Shenai, H., 1996. Influence of hydroxypropyl ß-cyclodextrin on solubility and dissolution profile of ketoprofen in its solid dispersions. Drug Dev. Ind. Pharm. 22, 987–992.

Ndindayino, F., Henrist, D., Kiekens, F., Vervaet, C., Remon, J.P., 1999. Characterization and evaluation of isomalt (Palatinit®) performance in direct compression. Int. J. Pharm. 189, 113–124.

Ndindayino, F., Henrist, D., Kiekens, F., Van den Mooter, G., Vervaet, C., Remon, J.P., 2002. Direct compression properties of melt-extruded isomalt. Int. J. Pharm. 235, 149–157.

Petzoldt, F., 2000. Growth market for powder injection moulding. Kunststoffe. Plast. Eu. 90, 14–16.

Serajuddin, A.T.M., 1999. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems and recent breakthroughs. J. Pharm. Sci. 88, 1058–1066.

Serpelloni, M., 1990. Directly compressible maltitol powder and its preparation procedure. EP No 0 220 103 B1, 28 November.

Serpelloni, M., Croisier, A., 1995. Directly compressible powder composition and its preparation procedure. EP No 0 490 768 B1, 5 April.

Simha, R., Boyer, R.F., 1962. On a general relation involving the glass temperature and coefficients of expansion of polymers. J. Chem. Phys. 37, 1003–1007.

Simonelli, A.P., Meshali, M.M., Abd El-Gawad, A.H., Abdel-Aleem, H.M., Gabr, K.E., 1994. Effects of some polymers on the physicochemical and dissolution properties of hydrochlorothiazide II. Drug Dev. Ind. Pharm. 20, 2741–2752.

Sjökvist, E., Nyström, C., 1991. Physicochemical aspects of drug release. XI. Tabletting properties of drug dispersions using xylitol as a carrier material. Int. J. Pharm. 67, 139–153.

Stein, V.M., Schwabe, L., Frömming, K.H., 1991. Preparation, tabletting and properties of solid dispersions of spironolactone. Pharm. Ind. 53, 186–191.

Strater, P.J., 1989. Palatinit®, the ideal ingredient for confectionery. in: Conference Proceedings-Food Ingredients Europe. Maarssen, The Netherlands, pp. 260–266.

Tantishaiyakul, V., Kaewnopparat, N., Ingkatawornwong, S., 1996. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone K-30. Int. J. Pharm. 143, 59–66.

Tasic, L.J., Pintye-Hódi, K., Szabo-Revesz, P., 1997. Evaluation of the compression behaviour of paracetamol tablets produced by dispersion in ß-cyclodextrin. Part I: scanning electron microscopic study of tablets. J. Incl. Phen. 28, 299–314.

Tasic, L.J., Pintye-Hódi, K., Stupar, M., Kása, P.J.R., Szabo-Revesz, P., 1998. Compression study of paracetamol solid dispersion tablets. Pharmazie 53, 206–207.