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The impact of hot-melt extrusion on the tableting behaviour of polyvinyl alcohol

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Abstract

There is evidence that processing techniques like hot-melt extrusion (HME) could alter the mechanical properties of pharmaceuticals, which may impede further processability (e.g. tableting). The purpose of this study was to evaluate if HME has an impact on the tableting behavior of polyvinyl alcohol (PVA) – formulations. Mixtures of partially hydrolysed PVA grades (with a hydroxylation degree of 75 and 88%) and sorbitol (0, 10 and 40%) were extruded, (cryo-) milled and compressed into compacts of 350 ± 10 mg. Before compression all intermediate products were characterized for their solid-state (T_g , T_m , crystallinity) and material properties (particle size, moisture content, moisture sorption). Because both PVA-grades required higher extrusion temperatures (>180 °C), sorbitol was added to PVA as plasticizing agent to allow extrusion at 140°C . Compaction experiments were performed on both physical mixtures and cryo-milled extrudates of PVA-sorbitol. By measuring tablet tensile strength and porosity in function of compaction pressure, tableting behavior was compared before and after HME by means of the CTC-profiles (compressibility, tabletability, compactibility). A higher amorphous content in the formulation (as a result of HME) negatively influenced the tableting behavior (i.e. lower tablet tensile strength). HME altered the mechanical properties towards more elastically deforming materials, thereby increasing tablet elastic recovery during decompression. The lower tensile strengths resulted from a combined effect of less interparticulate bonding areas (because of higher elastic recovery) and weaker bonding strengths per unit bonding area (between glassy particles).

Keywords: hot-melt extrusion, tableting, elastic recovery, polyvinyl alcohol, oral drug delivery, immediate release.

1. INTRODUCTION

Due to the application of high-throughput screening and medicinal chemistry as drug selection procedures, there has been a significant increase in the number of new chemical entities (NCE) that are poorly water-soluble. Pharmaceutical research, shifted their focus to new formulation strategies, in order to overcome solubility-related problems, for which the formulation of solid dispersions was a viable technique to improve the (oral) bioavailability of poorly water-soluble drug compounds (Janssens and Van den Mooter, 2009; Leuner and Dressman, 2000). Different approaches are reported in order to (molecularly) disperse the active pharmaceutical ingredient (API) in its carrier (Moneghini et al., 2001; Paudel et al., 2013; Sethia and Squillante, 2004), whereby hot-melt extrusion (HME) has the advantage of being a continuous manufacturing process that is generally applicable on industrial scale, without the requirement of further drying steps (Breitenbach, 2002).

Partially hydrolysed polyvinyl alcohols (PVA) were successfully screened as carriers in HME for immediate release applications, whereby PVA-grades with high degree of hydrolysis (70 – 90%) were most promising, as drug release was independent of pH (1-9) and ionic strength (0 – 0.14M) (De Jaeghere et al., 2015). However, PVA-grades with high degree of hydrolysis (> 70%) have a rather high melting point onset (150-170°C), indicating that higher extrusion temperatures are needed in order to extrude these polymers, which impedes the use of thermosensitive API. De Jaeghere et al. evaluated sorbitol as plasticizer for PVA and noticed a sufficient decrease in process temperature, which could extend the application of PVA as carrier in HME (De Jaeghere et al., 2015).

Various downstream processes for HME are available, from injection molding (i.e. finale dosage form) to milling of the extrudates (i.e. intermediate products) for further processability (e.g. tablets) (Treffer et al., 2013). Tablets are still the most popular dosage forms for the pharmaceutical industry and patient since they allow high-precision dosing, ensure patient compliance and provide high manufacturing efficiency. Therefore, previous

research was extended to investigate the processability of PVA and PVA-sorbitol carriers after HME into conventional tablets. The impact of solid dispersion manufacturing techniques such as HME on the tableting behaviour of pharmaceutical polymers whether or not with plasticizer, was only limited investigated (Agrawal et al., 2013; Boersen et al., 2013; Dinunzio et al., 2012; Mohammed et al., 2012) with minimal focus on the mechanical properties of the pure components. These properties are of great importance in solid dosage form development and manufacturing, as they describe the behaviour of a material subjected to an applied stress (Iyer et al., 2013). In this study, PVA and physical mixtures of PVA-sorbitol were processed by HME, characterized, milled to powders of appropriate particle size and eventually processed into tablets. CTC-profiles (compressibility, tabletability, compactibility) of those tablets were drafted and compared with the physical mixtures in order to evaluate the impact of different processing steps on the mechanical properties of these materials. Axial recoveries of the tablets were calculated and linked to the CTC-profiles.

2. MATERIALS AND METHODS

2.1. Materials

Two types of polyvinyl alcohol (PVA) were used, a technical grade PVA₅₀₅ (72-75 % hydrolysed) obtained from Kuraray (Hattersheim am Main, Germany) and a pharmaceutical grade PVA₄₋₈₈ (88% hydrolysed) obtained from Merck (Darmstadt, Germany). Sorbitol (Fagron, Waregem, Belgium) was used as water-soluble plasticizer and celecoxib (CEL) (Sanico, Turnhout, Belgium) was used as model drug.

2.2. Hot-Melt Extrusion (HME)

Physical mixtures of PVA and sorbitol (0, 10, 40 %) were processed with a co-rotating, fully intermeshing twin-screw extruder (Prism Eurolab 16, Thermo Fisher, Germany) operating at a screw-speed of 100 rpm and **a process temperature of 180 °C across the entire barrel**. The extruder was equipped **with a gravimetric feeder (0.300 kg/h)**, two co-rotating twin-screws with 3 mixing zones and a cylindrical die of 3 mm. The extrudates were quench-cooled with liquid nitrogen, (cryo)-milled and sieved through a 300-micron sieve **(De Jaeghere et al., 2015)**.

2.3. Tableting

Tablets (350 ± 10 mg) of physical mixtures and cryo-milled extrudates of PVA-sorbitol were prepared using a rotary tablet press (MODUL™ P, GEA Pharma Systems, Courtoy™, Halle, Belgium) equipped with a round concave (radius: 24mm) Euro B punch of 12 mm diameter at a tableting speed of 5 rpm. The compaction pressure ranged from 100 to 400 MPa after a pre-compression at 17 MPa. Tablets used for thermal analysis were compacted at 305 MPa, after pre-compression at 17 MPa. All tablets were immediately after compression characterized for tablet strength, dimensions and mass.

2.4. Characterization

2.4.1. Thermal analysis

Differential scanning calorimetry (DSC) was performed before and after sample manipulation (HME, cryo-milling, tableting), whereby melting temperature (T_m), glass transition temperature (T_g), crystallization temperature (T_c) and heat of fusion (ΔH_f) was analysed with a Q2000 DSC (TA Instruments, Leatherhead, UK) equipped with a refrigerated cooling system (RCS). The DSC cell was purged with dry nitrogen at a flow rate of 50 ml/min. The samples were evaluated according to DSC conditions (heating rate of 10 °C/min) during 3 cycles (heating, cooling and heating) from -20 to 200 °C. Crystallinity (%) was calculated with reference to the enthalpy of fusion (ΔH_f^*) of a perfect PVA crystal (138.6 J/g) (Mallapragada et al., 1997) with the following formula:

$$X_c = \left(\frac{\Delta H_f}{\Delta H_f^*} \right) \times 100$$

All results were analysed in **triplicate** using the TA instrument Universal Analysis 2000 software. **A one-way analysis of variance (ANOVA) was performed with SPSS Statistics 23 (IBM, New York, United States) to detect significant differences in T_g or T_m during extrusion, cryomilling and tableting of both PVA-grades. Tukey analysis was used to determine differences in T_g and T_m between extrusion, cryomilling and tableting.**

2.4.2. X-ray diffraction

The crystallinity of PVA, sorbitol and CEL was investigated by means of X-ray diffraction. The X-ray diffraction patterns were determined using a D5000 Cu $K\alpha$ diffractor ($\lambda = 0.154$ nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 V in the angular range of $10^\circ < 2\theta < 60^\circ$ using a step scan mode (step width = 0.02°, counting time = 1s/step).

2.4.3. Solid-state 1H -NMR

Solid-state 1H -wide-line NMR measurements were carried out at ambient temperature on a Varian Inova 400 spectrometer in a dedicated wide-line probe equipped with a 5 mm coil using

the solid echo method (Mens et al., 2008). The samples were placed in 5 mm glass tubes, which were closed tightly with Teflon stoppers.

The T_{1H} relaxation decay times (spin-lattice relaxation in the lab frame) were measured by placing an inversion recovery filter in front of the solid echo part ($180^\circ_x - t - 90^\circ_x - t_{se} - 90^\circ_y - t_{se} - \text{acquire}$). The length of the 90° pulse (t_{90}) was set to 1.6 μs and spectra were recorded with a spectral width of 2 MHz (0.5 μs dwell time), allowing an accurate determination of the echo maximum which is formed at $\tau = (3t_{90}/2 + 2t_{se}) = 7 \mu\text{s}$ and this time point is calibrated to time zero. The integrated proton signal intensity was analyzed mono- or bi-exponentially as a function of the variable inversion time t according to:

$$I(t) = I_0^S \left(1 - 2 \exp\left(-t/T_{1HS}\right)\right) + I_0^L \left(1 - 2 \exp\left(-t/T_{1HL}\right)\right) + C^{ste}$$

'S' and 'L' refer to the fractions with short and long decay time, respectively.

All experimental data were analyzed using a non-linear least-squares fit (Levenberg-Marquardt algorithm). A preparation delay of 5 times the longest T_{1H} relaxation decay time was always respected between successive accumulations to obtain quantitative results.

2.4.4. Particle size distribution

Particle size distribution (PSD) of the powders was measured by laser diffraction (Mastersizer-S long bench, Malvern Instruments, Malvern, UK). The measurements were done via dry dispersion method in volumetrical distribution mode using a 300 RF lens combined with a dry powder feeder (Malvern Instruments, Malvern, UK) at a feeding rate of 3.0 G and a jet pressure of 2.0 Bar. Measurements were performed in triplicate.

2.4.5. Dynamic vapour sorption

Dynamic vapour sorption (DVS Advantage, Surface Measurement Systems, Middlesex, UK) was used to assess the overall hygroscopicity of the materials. Approximately 10-20 mg of sample was placed into the instrument microbalance where it was dried under a stream of dry nitrogen at 25°C until equilibrium (i.e. a weight change of less than 0.002 % per minute during at least 15 min). The samples were subsequently exposed to various relative humidities (RH)

at 25°C, increasing from 0 to 80 % in steps of 20 %, from 80 to 90 % and from 90 to 98 % allowing equilibration at each interval.

2.5. Tablet Evaluation

Tablet evaluations were performed onto ten tablets.

2.5.1. Tensile strength, breaking force and dimensions

Tablet breaking force, diameter and thickness were determined using a hardness tester (Type HT10, Sotax, Basel, Switzerland). Tablet diametral tensile strength of the tablets (MPa) was derived using the following equation of Fell and Newton (1968):

$$\text{Tablet Tensile Strength } (\sigma_t) = \frac{2P}{\pi Dt}$$

where P, D and t denote the diametral breaking force (N), tablet diameter (mm) and tablet thickness (mm), respectively. This formula can be used for double-convex cylindrical tablets as was reported by Podczek et al. (Podczek et al., 2013).

2.5.2. Tablet porosity

The porosity of the formed compacts was calculated using the following equation:

$$\text{Tablet Porosity} = 1 - \frac{\rho_{app}}{\rho_{true}}$$

where ρ_{app} and ρ_{true} denote the apparent and true density (g/ml), respectively. Apparent density was calculated by dividing the tablet mass by the volume of the tablet, while the true density of all powders was measured using helium pycnometry (AccuPyc 1330, Micrometrics, Norcross, U.S.A) at an equilibration rate of 0.0050 psig/min with the number of purges set to 10.

2.5.3 Tablet compaction characterization

Compacts were prepared at different compaction pressures (100 to 400 MPa with a pre-compression of 17 MPa), and tableting behaviour (tableability, compressibility and compactibility) was evaluated.

Tableability was analysed by plotting tablet tensile strength to the compaction pressure. *Compressibility* was analysed by assessment of the tablet volume reduction (tablet porosity normalised by compaction pressure). *Compactibility* of pharmaceutical powders is generally described by use of the Ryshkewitch equation:

$$\sigma_t = \sigma_0 e^{-bP}$$

where σ_t and σ_0 denotes the tablet tensile strength (MPa) and limiting tablet tensile strength at zero porosity (MPa), respectively, b is an empirical constant and P denotes the tablet porosity (Ryshkewitch, 1953).

2.5.4. Axial recovery

Axial recovery of the tablets immediately after ejection (IAR) was calculated by use of the Armstrong and Haines-Nutt equation (Armstrong and Haines-Nutt, 1972):

$$IAR (\%) = \left(\frac{T_a - T_{id}}{T_{id}} \right) \times 100$$

where T_a denotes the tablet height immediately after ejection (mm) and T_{id} the tablet height under maximum compression force at main compression (mm). The dimensions of 10 tablets, manufactured at equal conditions, were used to calculate the % IAR of each formulation at 4 compaction pressures.

3. RESULTS AND DISCUSSION

3.1. Characterization

Thermal stability of PVA₅₀₅ and PVA₄₋₈₈ was evaluated by means of thermogravimetric analysis (TGA) (data not shown). This technique showed an onset of thermal polymer degradation at 240°C, which indicated that PVA polymers are stable under the process conditions used in this study (maximum extrusion temperature of 180°C was used) (Alexy et al., 2004; De Jaeghere et al., 2015; Peng and Kong, 2007).

Previous research work already showed the ability of sorbitol to act as low molecular weight plasticizer of PVA. Therefore, melting of PVA-sorbitol mixtures was required to establish molecular interactions between polymer and sorbitol, as no effect of sorbitol was observed during 1st DSC heating cycle. The plasticizing effect of sorbitol was linked to its concentration as more interactions can be established between the OH-groups of both components, thus disrupting the structural regularity of PVA (De Jaeghere et al., 2015). DSC analysis was used to examine the influence of extrusion, cryo-milling and tableting on the physicochemical properties of PVA and sorbitol. T_g of sorbitol was lower in the cryo-milled extrudates due to their higher water content (an increase of 1-1.5% was observed compared to HME samples): after HME and cryo-milling T_g was $-8.1 \pm 0.3^\circ\text{C}$ and $-15.5 \pm 0.1^\circ\text{C}$, respectively, for PVA₅₀₅ and $-3.6 \pm 0.2^\circ\text{C}$ and $-14.5 \pm 1.6^\circ\text{C}$, respectively, for PVA₄₋₈₈. ANOVA showed no significant difference ($p > 0.05$) in T_g of both PVA-grades during extrusion, cryo-milling and tableting, however significant difference ($p < 0.05$) was observed in T_m of both PVA-grades, which was slightly increased during processing (Table 1).

DSC analysis showed endothermic peaks between 60-75°C and after 1 week X-ray diffraction patterns showed some degree of crystallinity in the samples (Fig.1). This phenomena was linked to the crystallization of sorbitol polymorphs during storage (Nezzal et al., 2009; Sztatisz et al., 1977). Due to this (re)-crystallization of sorbitol, the plasticizing effect of sorbitol was reduced and T_m of PVA slightly increased. Furthermore, solid-state ^1H -wideline NMR (Table 2)

was performed, whereby a short relaxation decay time of 6.3s was found for semi-crystalline PVA₄₋₈₈, and a long relaxation decay time of 26.3s for crystalline sorbitol. After extrusion, PVA₄₋₈₈ and sorbitol interacted with each other, as both fractions (I_0^S and I_0^L) were changed compared to the physical mixtures and the relaxation decay times of PVA₄₋₈₈ and sorbitol were decreased. However, phase separation was observed for extrudates containing 40% sorbitol, as evidenced by the presence of 2 relaxation decay times. Therefore, experiments were repeated with extrudates containing less sorbitol (i.e. 10%), whereby only one relaxation decay time of 14.2s was observed, which could mean that sorbitol was homogenized with PVA₄₋₈₈ and more stable inside the extrudates. This result was linked to the DSC results whereas no re-crystallization of sorbitol was observed.

PSD of both PVA-grades and sorbitol were measured by means of laser diffraction (Table 3). Although all powders were sieved to a fraction smaller than 300 micron, d_{90} –values exceeded 300 micron for all samples as there was a tendency for the material to agglomerate during the measurements. Fine powders are more subjected to agglomeration since their small particle size increases surface-mass ratio, which favours the bonding (Parikh, 2010).

DVS was used to calculate moisture sorption and desorption isotherms in order to assess the hygroscopic behavior of the PVA-sorbitol mixtures (physical mixtures and cryo-milled extrudates) (Fig.2). The influence of sorbitol was clearly visible at extreme conditions (21°C/98%RH) as non-extruded PVA (A) had a water content of 30 %, which increased up to 80% by addition of sorbitol (C). This was expected from the sorption isotherms of crystalline sorbitol (data not shown) which revealed water contents >80% at equal conditions. The level of hysteresis was negligible for pure PVA before and after extrusion (A,B) which could be attributed to intermolecular hydrogen bondings between the polymer chains (Assender and Windle, 1998), whereby the hydroxyl groups of PVA are not available for binding with water molecules. Interestingly, when comparing PVA-sorbitol (60:40) before and after extrusion (C,D) there was a remarkable difference in the level of hysteresis. While for the non-extruded formulation hysteresis was clearly present, it became negligible for the extruded formulation.

This was explained by DSC data which showed that interactions between PVA and sorbitol only occurred when sorbitol was melted by HME (De Jaeghere et al., 2015). The resulting extrudates are dense particles (Page and Maurer, 2014). It has been described in literature that for amorphous sugars the packing of molecules affected the water sorption behaviour. In dense glassy particles, adsorption of water occurs mainly on the surfaces (weak interactions) because of the absence of pores penetrable to water (Jouppila, 2006).

This is applicable for the PVA-sorbitol extrudates, since DSC results revealed that amorphous sorbitol clusters are present in the PVA carrier (separate T_g for sorbitol and PVA). The moisture content of all formulations was lower (< 5 %) at laboratory conditions (35-60 % RH).

3.2. Tablet properties

3.2.1. Tableability

Tableability describes the relationship between tensile strength of a tablet and compaction pressure exerted on these tablets (Fig.3) (Joiris et al., 1998). A strong increase of tablet strength was observed at low compaction pressures for most mixtures, however the curves leveled off at higher compaction pressures. This was explained by the phenomenon of elastic recovery, which occurred after removal of the compaction load (i.e. decompression).

As powders are compressed, particles come in closer contact by volume reduction mechanisms (particle rearrangements, fragmentation, plastic/elastic deformation), which reduced tablet porosity. This leads to a steep increase in the bonding area and consequently in tensile strength of the tablets (Duberg and Nyström, 1986). In the low-pressure region, elastic recovery of the tablet after compression was negligible and the tablet strength increased linear with the compaction pressure. At higher compaction pressures, tablet porosity was already reduced considerably so further increase of the compaction pressure led to elastic deformation rather than a further decrease in porosity (Sun and Grant, 2001). Inevitable, such particles store elastic energy, which is linked to a certain elastic recovery at decompression, thereby reducing the bonding area. The associated reduced points of contact between

neighbouring particles in the tablet caused a level off in tensile strength (Sun, 2011). In general, tabletability curves of the extrudates were lower than those of the physical mixtures and the increase in tablet strength was limited (i.e. level off at lower compaction pressures). These results were in line with earlier findings on the tabletability of HME materials (Agrawal et al., 2013; Boersen et al., 2013). While the tensile strength of physical mixtures increased in function of the concentration of crystalline sorbitol (a value of 2.5 MPa was recorded for 40 % sorbitol at a compaction pressure of 300 MPa), the tensile strength of extruded samples was lower at higher amorphous sorbitol content (at 40 % sorbitol content the tablets manufactured at various compaction pressures were even too soft for measuring the diametrical breaking force) (Fig. 3, A). In addition, maximum tabletability (i.e. highest tensile strength) was obtained at lower compaction pressures for extrudates compared to physical mixtures, at about 200 MPa and > 400 MPa, respectively (Fig.3, B). Differences in particle size (Table 2) could explain the lower position of the curves but could not explain the limited increase in tablet strength and the early level off at lower compaction pressures. Agrawal et al. attributed this to the possible weaker interactions between glassy materials resulting in tablets with lower tensile strengths (Agrawal et al., 2013). In this study it was hypothesized that the process of HME altered the mechanical properties of the PVA-sorbitol-carrier and therefore changed its volume reduction mechanism towards a more elastically deforming material. Iyer et al. reported an increase in the elasticity of melt-extruded HPMC-AS and linked this with a likely higher elastic recovery after compression (Iyer et al., 2013). It is possible that the HME-process induced a similar change in the elastic deformation of PVA-sorbitol, leading to higher elastic recoveries with increasing amorphous fraction (Fig.1: the absence of sharp crystalline peaks in the XRD-data of cryo-milled extrudates compared to the physical mixtures). Boersen et al. reported similar findings, where brittle fracture index experiments showed a reduction in the plasticity of HME-powders (Boersen et al., 2013).

Comparison of figures A and B indicated that physical mixtures of non-extruded PVA₄₋₈₈ yielded tablets of higher tensile strengths than physical mixtures of PVA₅₀₅ at equal compaction

pressures (an increase of 80 % in tensile strength was recorded at a compaction pressure of 300 MPa). This was explained by the differences in crystalline content of both polymers, since PVA is a semi-crystalline polymer (Agrawal et al., 2013). The crystalline content of pure PVA₄₋₈₈ (32.1%) was significantly higher compared to pure PVA₅₀₅ (16.6%), which resulted in 'stronger' tablets, and HME reduced the crystallinity of PVA₄₋₈₈ significantly (21.4%) compared to PVA₅₀₅ (14.4%) as the higher extrusion temperatures disrupted inter- and intramolecular hydrogen bonding. Additionally, differences in PSD of the physical mixtures (Table 2) also contributed to this phenomenon.

Tabletability on its own does not provide a fundamental understanding of the tableting behaviour of pharmaceutical powders, since bonding area (reflected by compressibility) and bonding strength per unit bonding area (reflected by compactibility) also determine the tensile strength of tablets. Only by simultaneously analysing particle size, compressibility, compactibility and tabletability, an extensive insight in the tablet properties can be obtained (Sun and Grant, 2001).

3.2.2. Compressibility

Compressibility of a material is its ability to be reduced in volume as a result of an applied pressure (Joiris et al., 1998). The compressibility profiles showed similar trends as tabletability, with physical mixtures having greater compressibility (i.e. yielding lower tablet porosities) compared to the extrudates (Fig. 4). While the lowest tablet porosities were observed for physical mixtures with higher content of crystalline sorbitol, porosities increased in extrudates with more amorphous content (i.e. high sorbitol content). In addition, maximum compressibility (i.e. lowest tablet porosity) was obtained at a lower compaction pressures for extrudates containing (amorphous) sorbitol compared to physical mixtures, at about 250 MPa and >400 MPa, respectively (Fig. 4). The differences between physical mixtures and extrudates were linked to HME. A higher amorphous content in the extrudates induced an early level off in the compressibility profiles, resulting in constant tablet porosity at higher compaction pressures because of the effect of elastic recovery (Fig. 4). These results were in line with tabletability

profiles where an early flattening was observed in tablet tensile strength of the extrudates. Therefore, the assumption of an altered volume reduction mechanism due to hot-melt extrusion was strengthened. If HME altered the mechanical properties of PVA-sorbitol towards a more elastical deforming material, the stored elastic energy increased in function of the applied external force and hence resulted in more elastic recovery of the tablets during decompression (Sun and Grant, 2001). Therefore, the reduced porosity due to elastic deformation was counteracted by the elastic recovery causing a level off in the curve.

By comparing tablet porosities at equal compaction pressures for physical mixtures of PVA₅₀₅ and PVA₄₋₈₈, it was clear that particle size had a strong influence. Lower tablet porosities were detected with PVA₄₋₈₈ –mixtures (tablet porosity was 0.14 and 0.08 for physical mixtures with PVA₄₋₈₈ and PVA₅₀₅, respectively), since these had smaller particle sizes (Table 2). However, the effect of extrusion on the pure polymers was clearly visible. While for PVA₅₀₅ the curves of physical mixtures and extrudates are superimposed (Fig.4,A), this is not the case for PVA₄₋₈₈ since higher tablet porosities were reached for the extrudates of PVA₄₋₈₈ (Fig.4,B). This was explained by the differences in crystalline content of both polymers. Extrusion of pure PVA₄₋₈₈ increased the amorphous fraction of the semi-crystalline polymer, which favoured elastic deformation and hence increased the elastic recovery. This was not the case for pure PVA₅₀₅, since the crystalline content did not change remarkably.

3.2.3. Compactibility

Compactibility describes the relationship between tensile strength and porosity (Fig.5). Tablet tensile strength decreased exponentially with increasing porosities, as described by the Ryshkewitch equation (Ryshkewitch, 1953). Although physical mixtures and extrudates showed large differences in tabletability (i.e. tensile strengths), these differences were less distinct when tablet tensile strength was plotted at zero porosity, especially for PVA₅₀₅.

Since compactibility can be used to quantify bonding strength between particles at zero porosity (Joiris et al., 1998; Maarschalk et al., 1996; Sun, 2011), these results suggested that

the higher tensile strength was more related to the interparticulate bonding area (i.e. compressibility) compared to the bonding strength per unit bonding area (i.e. compactibility). However, compactibility curves of both PVA-types gave evidence of weaker interactions between glassy materials (Agrawal et al., 2013) since compression of physical mixtures with increasing sorbitol content (i.e. higher crystalline fraction) resulted in a higher tensile strength at zero porosities. This effect was clearly reflected in the lower position of the compactibility curve of pure PVA₄₋₈₈ extrudates compared to the physical mixture (Fig.5, B), which was linked to the lower crystalline content of the semi-crystalline polymer after HME. This effect was not significant for PVA₅₀₅ and therefore those curves (PM vs. EX) were almost superimposed at zero porosity (Fig.5,A), indicating that almost no changes in bonding strength occurred. In general, this study revealed that differences in tablet tensile strength for PVA-sorbitol carriers were the result of altered interparticulate bonding areas (elastic recovery and particle size) combined with a change in the bonding strengths for glassy materials (Agrawal et al., 2013) after extrusion.

3.2.4. Axial recovery

Axial recovery of the tablets calculated immediately after tablet ejection (IAR) was selected as the “out-of-die” recovery descriptor. For each formulation, IAR was calculated for tablets of non-extruded physical mixtures and extruded mixtures at 4 compaction pressures. The results are shown in Fig.6 as a ratio of the IAR before and after extrusion in function of the compaction pressure.

All calculated ratios were higher or equal to the value 1 indicating that tablets of extruded powders experienced higher or equal IAR compared to tablets of their physical mixtures (i.e. not subjected to HME). Only for pure PVA₅₀₅, HME had no impact on the IAR-ratio of the tablets (ratio = 1), as no change in crystalline content of pure PVA₅₀₅-polymer was observed after HME. However, IAR-ratios of pure PVA₄₋₈₈ were > 1 since HME affected the amorphous content of the polymer. The addition of sorbitol to the formulations, which changed from crystalline to amorphous state after HME, resulted in higher %IAR ratios of the tablets. These results

398 showed that the higher amorphous content of formulations due to HME was reflected in the
399 IAR of the tablets. Additionally, these results were in line with the CTC-profiles and confirmed
400 the hypothesis that due to HME, materials were transformed towards a more amorphous state,
401 hereby experiencing more elastic deformation during compression.

4. CONCLUSIONS

This study demonstrated that HME could alter the mechanical properties of PVA-sorbitol carriers, thereby negatively affecting the tableting behaviour (i.e. lowering tablet tensile strength) with increasing amorphous content. This resulted from a combined effect of less interparticulate bonding areas (because of higher elastic recoveries) and weaker bonding strengths per unit bonding area (i.e. lower tensile strengths at zero porosity). In general, it can be concluded that it will be necessary to further optimize the formulation (e.g. plasticizer content) in order to improve the tableting behaviour of PVA-sorbitol extrudates.

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506 **Figure 1:** XRD profiles (left) of sorbitol (A), physical mixture PVA-sorbitol (60:40) (B), cryom. extrudate (C) and
507 cryom. extrudate after 1 week (D). DSC profiles (right) of extrudate (EX) and cryom. extrudate after at time point 0
508 and after 1 week.

509 **Figure 2:** DVS sorption (—) and desorption (...) curves of PVA₄₋₈₈ (A) , PVA₄₋₈₈ cryomilled extrudate (B), PVA₄₋₈₈-
510 sorbitol (60:40) physical mixture (C), PVA₄₋₈₈-sorbitol (60:40) cryomilled extrudate (D) and sorbitol (E) at 21 °C.

511 **Figure 3:** Tabletability of physical mixtures (PM) and hot-melt extruded (EX) samples formulated with PVA₅₀₅ (A)
512 or PVA₄₋₈₈ (B),, in combination with 0, 10 or 40% sorbitol (n=10).

513 **Figure 4:** Compressibility of physical mixtures (PM) and hot-melt extruded (EX) samples formulated with PVA₅₀₅
514 (A) and PVA₄₋₈₈ (B), in combination with 0, 10 or 40% sorbitol (n=10).

515 **Figure 5:** Compactibility of physical mixtures (PM) and hot-melt extruded (EX) samples formulated with PVA₅₀₅ (A)
516 or PVA₄₋₈₈ (B), in combination with 0, 10 or 40% sorbitol (n=10).

517 **Figure 6:** IAR-ratio of physical mixtures (PM) and hot-melt extruded samples (EX) at various compaction pressures
518 for formulations containing PVA and sorbitol (n=10).

519

Figure 1: XRD profiles (left) of sorbitol (A), physical mixture PVA-sorbitol (60:40) (B), cryom. extrudate (C) and cryom. extrudate after 1 week (D). DSC profiles (right) of extrudate (EX) and cryom. extrudate after at time point 0 and after 1 week.

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Table 1: Thermal properties of unplasticized and plasticized (containing 40% sorbitol) PVA after extrusion, cryo-milling and tableting using a heating rate of 10°C/min. The significance of the results was determined with ANOVA. Means of T_g (^{a,b}) or T_m (^{c,d}) in the same column with different superscripts are different at the 0.05 level of significance (Tukey) (n = 3).

Table 2: Solid-state ¹H-wideline NMR relaxation decay times (T_{1H}) and fractions (I_o) of PVA₄₋₈₈, sorbitol, physical mixtures and extrudates containing 40% and 10% sorbitol

Table 3: Mean particle size distribution of physical mixtures (PM) and cryo-milled extrudates (EX) of PVA/sorbitol formulations, measured via dry laser diffraction (n=3).

Table 1: Thermal properties of unplasticized and plasticized (containing 40% sorbitol) PVA after extrusion, cryomilling and tableting using a heating rate of 10°C/min. The significance of the results was determined with ANOVA. Means of T_g ^(a,b) or T_m ^(c,d) in the same column with different superscripts are different at the 0.05 level of significance (Tukey) (n = 3).

			505 (72-75%)	4-88 (88%)
<i>UNPLASTICIZED</i> (0% sorbitol)	1 st heating	T_g (°C)	44.9 ±2.1	48.1 ±3.5
		T_m (ons.) (°C)	155.0 ±1.4	164.1 ±1.6
	2 nd heating	T_g (°C)	62.0 ±0.7	67.1 ±1.0
		T_m (ons.) (°C)	131.5 ±6.6	144.7 ±9.6
<i>PLASTICIZED</i> (40% sorbitol)	2 nd heating	EXTRUSION		
		T_g (°C)	34.3 ±3.2 ^a	38.6 ±1.1 ^a
		T_m (ons.) (°C)	117.7 ±2.4 ^c	133.1 ±4.7 ^c
		CRYOMILLING		
		T_g (°C)	30.5 ±2.5 ^a	37.9 ±3.4 ^a
		T_m (ons.) (°C)	121.8 ±5.2 ^c	149.1 ±3.3 ^d
		TABLETING		
		T_g (°C)	31.6 ±1.5 ^a	38.2 ±5.0 ^a
		T_m (ons.) (°C)	131.2 ±3.8 ^d	149.1 ±2.2 ^d

Table 2: Solid-state ¹H-wideline NMR relaxation decay times (T_{1H}) and fractions (I_o) of PVA₄₋₈₈, sorbitol, physical mixtures (PM) and extrudates (EX) containing 40% and 10% sorbitol

SAMPLE	T _{1H} (s)			
	T _{1H} ^S	I _o ^S (%)	T _{1H} ^L	I _o ^L (%)
PVA ₄₋₈₈	6.3	100.0		
Sorbitol			26.3	100.0
PVA ₄₋₈₈ -Sorbitol (60:40) PM	6.0	63.4	25.4	36.6
PVA ₄₋₈₈ -Sorbitol (60:40) EX	3.5	88.0	15.7	12.0
PVA ₄₋₈₈ -Sorbitol (90:10) EX			14.2	100.0

Table 3: Mean particle size distribution of physical mixtures (PM) and cryo-milled extrudates (EX) of PVA/sorbitol formulations, measured via dry laser diffraction (n=3).

		d₁₀ (μm)	d₅₀ (μm)	d₉₀ (μm)
PVA₅₀₅	PM	47.6 ±5.96	204.3 ±4.74	404.1 ±32.98
	EX	68.8 ±0.07	187.6 ±0.69	359.1 ±6.39
PVA₄₋₈₈	PM	22.9 ±0.52	164.4 ±16.71	544.0 ±7.41
	EX	73.4 ±4.43	203.0 ±5.78	367.2 ±4.15