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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 behaviour 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 (i.e. 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 behaviour 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 behaviour (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).

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. To overcome solubility-related problems pharmaceutical research has shifted its focus to new formulation strategies where solid dispersions are 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 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) of polymeric formulations 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).

In a previous paper we evaluated partially hydrolysed polyvinyl alcohol (PVA) as carriers for immediate release applications processed via HME, whereby PVA-grades with a high degree of hydrolysis (70–90%) were identified as the most promising grades, since drug release from these polymeric solid solutions was independent of pH and ionic strength. However, due to their high melting point onset (150–170 °C) higher extrusion temperatures were required to extrude these polymers, and sorbitol was added as a plasticizer of PVA-based formulations in order to sufficiently decrease the process temperature during HME (De Jaeghere et al., 2015).

Although various downstream processes for HME are available (injection molding, calendaring, milling in combination with tableting), the latter remains an important technique to process hot-melt extruded formulations into their final dosage form (Treffer et al., 2013). Therefore, our previous research on HME of PVA grades was extended to investigate the processability of PVA

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and sorbitol/PVA carriers after HME into tablets via milling and compression. Investigations into the impact of solid dispersion manufacturing techniques such as HME on the tableting behaviour of pharmaceutical polymers has so far been limited (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 during compression (Iyer et al., 2013). In this study, PVA and sorbitol/PVA mixtures were processed by HME, characterized, milled and eventually processed into tablets via compression. 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. The focus of this research paper is essential since altered mechanical properties may impede further processability of the materials during tableting.

2. Materials and methods

2.1. Materials

Two types of polyvinyl alcohol (PVA) were used, a technical grade PVA_{505} (72–75% hydrolysed) obtained from Kuraray (Hattersheim am Main, Germany) and a pharmaceutical grade $PVA_{4\text{-}88}$ (88% hydrolysed) obtained from Merck (Darmstadt, Germany). Sorbitol (Fagron, Waregem, Belgium) was used as water-soluble plasticizer.

2.2. Hot-melt extrusion (HME)

Physical mixtures of PVA and sorbitol (0, 10, 40%) were processed via HME according to the method described by De Jaeghere et al., (2015) using 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 μm sieve.

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: 24 mm) 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 instruments 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 Kα diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 V in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1 s/step).

2.4.3. Solid-state ^1H NMR

Solid-state ^{1}H-wideline 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 ($180°_{x'} - t - 90°_{x'} - t_{se} - 90°_{y'} - t_{se}$ – 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 $\tau = (3t_{90}/2 + 2t_{se}) = 7$ μs 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:

$$I(t) = I_o^S\left(1 - 2\exp\left(-\frac{t}{T_{1H^S}}\right)\right) + I_o^L\left(1 - 2\exp\left(-\frac{t}{T_{1H^L}}\right)\right) + c^{ste}$$

'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.