Downstream processing from melt granulation towards tablets: In-depth analysis of a continuous twin-screw melt granulation process using polymeric binders.

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Abstract

The concept of twin-screw melt granulation (TSMG) has steadily (re)-gained interest in pharmaceutical formulation development as an intermediate step during tablet manufacturing. However, to be considered as a viable processing option for solid oral dosage forms there is a need to understand all critical sources of variability which could affect this granulation technique. The purpose of this study was to provide an in-depth analysis of the continuous TSMG process in order to expose the critical process parameters (CPP) and elucidate the impact of process and formulation parameters on the critical quality attributes (CQA) of granules and tablets during continuous TSMG. A first part of the study dealt with the screening of various amorphous polymers as binder for producing high-dosed melt granules of two model drug (i.e. acetaminophen and hydrochlorothiazide). The second part of this study described a quality-by-design (QbD) approach for melt granulation of hydrochlorothiazide in order to thoroughly evaluate TSMG, milling and tableting stage of the continuous TSMG line. Using amorphous polymeric binders resulted in melt granules with high milling efficiency due to their brittle behaviour without producing excessive amounts of fines, providing high granule yields with low friability. Therefore, it makes them extremely suitable for further downstream processing. One of the most important CPP during TSMG with polymeric binders was the granulation-torque, which - in case of polymers with high T_g - increased during longer granulation runs to critical levels endangering the continuous process flow. However, by optimizing both screw speed and throughput or changing to polymeric binders with lower T_g it was possible to significantly reduce this risk. This research paper highlighted that TSMG must be considered as a viable option during formulation development of solid oral dosage forms based on the robustness of the CQA of both melt granules and tablets.

Keywords: continuous manufacturing, twin-screw melt granulation, polymeric binders, tableting, quality by design, multivariate data analysis.

1. INTRODUCTION

Downstream processing of a drug compound into tablets is often the preferred choice during formulation development as it combines a high economic efficiency with good patient compliance. This is clearly reflected in the number of oral solid dosage forms reaching the market, for which over 70% are tablets (Patel et al., 2006). Direct compression (DC) of a formulation is intuitively the preferred tablet manufacturing route based on its simplicity and cost efficiency, however the powder mixture requires specific properties (e.g. high flowability, low segregation tendency and high compactibility) which are often lacking (Patel et al., 2006). The addition of directly compressible excipients may overcome some of these problems and yield satisfactory tablets for such materials. However, these products are often relatively expensive. Moreover, in case of high-dose formulated DC-mixtures (e.g. acetaminophen) this may lead to very large tablets, hampering the patient compliance (Gohel et al., 2005). Regarding low-dose formulations, DC is challenging since poorly flowing and cohesive drugs need to be uniformly dispersed in a powder blend to guarantee an acceptable tablet content uniformity (Bi et al., 2011). Considering the possible drawbacks of DC, pharmaceutical companies often implement granulation as a pre-treatment step in the tablet manufacturing route in order to reduce the risk of final product failure.

Granulation is a well-established pharmaceutical processing technique to agglomerate primary drug and excipient particles into larger secondary particles (granules) which meet the required properties (e.g. flowability, compactibility and content uniformity) for processing into a final dosage form (Dhenge et al., 2013; Liu et al., 2017; Van Melkebeke et al., 2008; Vercruysse et al., 2015). A variety of both wet- and dry granulation techniques are used in the pharmaceutical field and have been reviewed where twin-screw wet granulation is most prominently investigated during the last decade especially in the context of continuous granulation (Fonteyne et al., 2011; Vervaet and Remon, 2009). However, some pharmaceuticals experience stability and degradation issues by wet processing and proper control of the drying-

step is critical during continuous twin-screw wet granulation (TSWG) to avoid flow and compression issues (Lakshman et al., 2011).

Twin-screw melt granulation (TSMG) can counter some of the wet-granulation drawbacks since the agglomeration is initiated by a softened or molten binder instead of a granulation liquid, making TSMG extremely suitable for moisture-sensitive drugs (Kowalski et al., 2009). Lakshman et al. evaluated various granulation techniques for the development of a robust manufacturing process for high-dose metformin HCL whereby TSMG was the most suitable technique. Enhanced tableting properties of the poorly compactible high-dosed drug were noticed whereas highly reproducible low moisture levels of the granules ensured end product stability and quality (Lakshman et al., 2011). Moreover, the technology enabled to reduce both process time and energy consumption since no additional drying-step is needed after granulation compared to TSWG (Monteyne et al., 2016a). This makes TSMG extremely interesting in the context of continuous manufacturing and therefore the technique steadily regained interest of research groups and industry (Batra et al., 2017; Kidokoro et al., 2002; Monteyne et al., 2016b; Mu and Thompson, 2012). Continuous processing is currently a main focus in pharmaceutical manufacturing to accelerate the transition towards more robust and efficient processes, reducing development and manufacturing costs and eventually increase the quality of the end product (Plumb, 2005; Schaber et al., 2011).

The aim of this research paper was to establish a continuous TSMG concept using a twin-screw extruder and evaluate various critical stages in such continuous line using amorphous polymeric binders. Previous research successfully used amorphous polymers as carriers in solid dispersions prepared by continuous hot-melt extrusion for downstream processing towards tablets (Grymonpré et al., 2017a, 2017b). The high milling efficiency and excellent tableting properties of these polymers suggested their use as polymeric binder during TSMG. In a first part of the study, five amorphous polymers were screened with two model drugs for their potential as polymeric binder. Afterwards, a quality-by-design (QbD) approach was implemented to thoroughly understand the critical process parameters (CPP) during TSMG and to elucidate the impact of process and formulation parameters on the critical quality

attributes (CQA) of granules and tablets during continuous manufacturing of high drug-loaded melt granules.

2. MATERIALS

Three amorphous polymers were selected from a previously established polymer database for hot-melt extrusion/tableting (Grymonpré et al., 2017b). Kollidon® VA64 (VA64) and Soluplus® (SOL) were kindly donated by BASF (Ludwigshafen, Germany), while Eudragit® EPO (EPO) was provided by Evonik (Darmstadt, Germany). Two HPMC-grades developed for hot-melt extrusion (HME) (Affinisol™) with varying molecular weight were donated by DOW (Bomlitz, Germany): 15 LV and 4M having a low and high molecular weight, respectively. Acetaminophen (APAP, Mallinckrodt, St. Louis, USA) and hydrochlorothiazide (HCT, UTAG, Amsterdam, The Netherlands) were used as model drugs for melt granulation based on their different melting point (171 and 272 °C for APAP and HCT, respectively) which might reflect in their behaviour during melt granulation. All raw materials and their characteristics are listed in Table 1.

3. METHODS

3.1. Continuous twin-screw melt granulation

This research paper intended to introduce a concept for implementation of TSMG into a continuous tablet manufacturing line by combining mixing, TSMG, milling and compression. Fig. 1 gives a schematic overview of the process-flow and the possible integration of the various stages in a continuous manufacturing line. The feeding and continuous mixing stage has been thoroughly investigated and evaluated at our department by Van Snick et al. for a continuous direct compression line (Van Snick et al., 2017a, 2017b). Therefore, this research paper mainly focused on the later stages of the continuous concept with TSMG being the first unit following the feeding/mixing stage.

3.1.1. Blending and gravimetric feeding

Before blending the active pharmaceutical ingredient (API) and polymer, the neat API was milled (Quadro® U5, Waterloo, Canada) using a round arm impeller at 900 rpm with a 1395-micron screen to break up possible powder lumps. Afterwards, blends were prepared for both model drugs with all amorphous polymers using a tumbling mixer (W.A. Bachofen, Basel, Switzerland) for 10 min at 15 rpm. These blends were gravimetrically fed to the granulation unit using a DD Flexwall® gravimetric feeder (Brabender Technology, Germany).

3.1.2. Twin-screw melt granulation

A co-rotating intermeshing twin-screw extruder (Prism Eurolab 16, ThermoFischer Scientific, Karlsruhe, Germany) was used as granulator with a barrel length of 25 L/D, where L is the axial screw length and D the inner bore diameter corresponding to one of the screws. The screw configuration was identical for all experiments, with 2 mixing zones in the third and fifth segment, each consisting of 6 kneading discs at 60° stagger angle in reversed direction and a screw-mixing element at the end of each screw intended for break-up of potentially large melt-granule lumps. The granulation barrel is divided into 6 segments ($T_{1\text{-}6}$) which can be heated/cooled separately. The temperature at the end of the barrel (T_6) was lowered to 40 °C during all runs in order to cool the granules below the glass transition temperature (T_g) of the polymers, enabling break up of very large agglomerates by the screw-mixing elements and avoiding sticking of the granules when leaving the barrel. All other segments in the granulator ($T_{1\text{-}5}$) were kept constant at the same temperature, except for mixtures with EPO for which the temperature of the feeding segment (T_1) was lowered to 80 °C to prevent feeding obstruction. The granulator was equipped with a data logging system to monitor the screw torque and barrel temperature during granulation. Sample collection for evaluation of granule properties before milling was done at stable granulation conditions, based on the process torque values.

3.1.3. Milling

After granulation the granules were manually transferred to a Quadro® Comil® (U10, Quadro®, Ontario, Canada). Milling was performed with a square impeller at 300 rpm, forcing the granules through a 1000 μm grater screen.

3.1.4. Tableting

All milled formulations and their physical mixtures (PM) were compressed to tablets on a rotary tablet press (MODUL™ P, GEA Pharma Systems, Halle, Belgium) equipped with cylindrical flat-faced Euro B punches of 10 mm diameter and an overfill cam of 16 mm. Tablets (250 ± 5 mg) were compressed on 7 different main compaction pressures: 65, 130, 190, 255, 320, 380 and 510 MPa without the use of a pre-compression step at a turret speed of 5 rpm. All tablets were analysed for 'out-of-die' properties (tablet strength, dimensions and mass) immediately after ejection. Punch deformation at each compaction pressure was calculated and corrected for during this study. In-die measurements of the compaction properties was performed by linear variable displacement transducers (LVDT) incorporated inside the turret and clamped onto one pair of punches, enabling the monitoring of punch stroke movements during a compression cycle (GEA Pharma Systems, Halle, Belgium). Calibration was performed prior to processing each formulation, by interpolating the output voltage of the sensor to physical values during static measurements. A wireless transmission system continuously transmitted the data from these sensors to a data acquisition and analysis system (CDAAS™, GEA Pharma Systems, Halle, Belgium).

3.2. Polymer screening

Physical mixtures with an API-to-polymer ratio of 85/15 (w/w %) were prepared for screening of the various amorphous polymers as binders in TSMG at fixed material throughput (0.350 kg/h) and screw speed (150 rpm). The granulation temperatures needed for each formulation are listed in Table 2. These values represent the minimal granulation temperature needed for each formulation at a certain screw speed and throughput to ensure granulation.

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198 ### 3.3. QbD approach for HCT

199 Design of experiments (DOE) was applied to evaluate the critical process parameters during
200 continuous TSMG and tableting. A 31-experiment D-optimal design was developed to evaluate
201 the influence of process parameters: T_1 (80°C), $T_{2\text{-}5}$ (160-200 °C), T_6 (40 °C), screw speed
202 (100-200 rpm), throughput (0.200-0.500 kg/h) together with formulation parameters: polymer
203 type (SOL, EPO, VA64) and binder concentration (15-25 %) on the CQA of granules and
204 tablets containing HCT. Six centerpoints (two for each polymer type) were included to evaluate
205 the model reproducibility. In between each experimental run, the granulation unit (i.e.
206 gravimetric feeder, barrel, screws and co-mill) were cleaned. The results were analysed using
207 MODDE 10.1 software (Umetrics, Umeå, Sweden). Multiple linear regression (MLR) was used
208 for calculation of the regression models for each response, whereas all factors were scaled
209 and centered making the regression coefficients comparable for the different factors. 95%
210 confidence intervals were calculated for all regression coefficients in order to evaluate if factors
211 or factor interactions were significant (i.e. 95% confidence interval of the corresponding
212 regression coefficient not including zero).
213

214 ### 3.4. Evaluation of the TSMG process

215 During the granulation process, the torque on the screws was monitored and based on
216 these values, granule sampling was started after initial torque stabilization. A reading of 100
217 % corresponded to the maximum allowable torque of 12 Nm. Prior to each run, the friction
218 torque was determined by running the extruder with screws attached and the barrel empty at
219 the specific conditions. This friction torque was subtracted from the total recorded torque to
220 obtain the net torque (Godavarti and Karwe, 1997). The time necessary for each run to reach
221 torque stabilization was recorded and an evaluation of the variation in torque over the running
222 time was performed after reaching torque stabilization for each experiment:

$$\Delta \mathrm{T/t}\ (\%/\mathrm{min}) = \frac{T_{end} - T_S}{t} \quad (1)$$

where T_{end} and T_S represent the net torque at the end of the granulation experiment and the initial stable torque value of the experiment, respectively, over the total granulation time starting from initial torque stabilization (t).

3.5. Raw material and granule characterization

3.5.1. Solid state characterization

Thermogravimetric analysis (TGA 2950, TA instruments, Leatherhead, UK) was conducted on all polymers and drugs to investigate their thermal stability. Samples (± 15 mg) were heated up to 600 °C after equilibration at 25 °C using a heating rate of 10 °C/min.

Differential scanning calorimetry (DSC, Q2000, TA Instruments, Leatherhead, UK) was used for raw material screening and comparing PM before and after granulation based on the T_g, T_m and melting enthalpy. The DSC-device is equipped with a refrigerated cooling system and the cell was purged with dry nitrogen at a flow rate of 50 ml/min. A heating rate of 10 °C/min was used during 3 cycles (heat, cool, heat) from 0 °C to 200 °C for APAP-formulations and 0 °C to 290 °C for HCT-formulations of around 10 mg weighed in T-zero pans. Crystallinity X_c (%) of APAP in the granules was calculated based on the enthalpy of fusion of APAP in the corresponding physical mixture (PM) using following equation:

$$X_c\ (\%) = \left(\frac{\Delta H_f}{\Delta H_f^*}\right) x\ 100 \quad (2)$$

with ΔH_f and ΔH_f^* representing the enthalpy of fusion (J/g) for APAP in granules and PM, respectively.

X-ray Diffraction (XRD) was performed on both PM and melt granules (MG). A D5000 CU Kα diffractor (λ= 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 V in the angular

range of 10° < 2θ < 20° was used in a step scan mode (step width = 0.02°, counting time = 1 s/step).

3.5.2. Moisture content

Loss on drying (LOD) was performed (n=3) on the raw materials, physical mixtures and granules before tabletting to determine residual moisture content using a Mettler LP16 moisture analyser, including an infrared dryer and a Mettler PM460 balance (Mettler-Toledo, Zaventem, Belgium). Approximately 1 g of sample was dried at 105 °C until the rate of change was less than 0.1 w/w % over 30 s.

3.5.3. True density

Helium pycnometry (AccuPyc 1330, Micromeritics, Norcross, USA) was performed on raw materials, PM, milled and unmilled granules in order to determine the true densities ***(g/ml)***. The number of purges was set to 10 with an equilibration rate of 0.00050 psig/min. Calibration was performed between the formulations.

3.5.4. Particle size and shape analysis

For the raw materials, particle size distribution (PSD) was determined (n=3) by laser diffraction (Mastersizer-S long bench, Malvern Instruments, Malvern, UK) via dry dispersion method in volumetrical distribution mode using a 300 RF lens combined with a dry powder feeder at feeding rate of 3.0 G and jet pressure of 4.0 bar (Malvern Instruments, Malvern, UK). Analysis of the granule size before and after milling was done via dynamic image analysis using the QICPIC™ system (Sympatec, Clausthal-Zellerfeld, Germany) equipped with a vibrating feeder system (VIBRI/L™) for gravimetrical addition of the granules. Approximately 20 g of sample was analysed to determine the median granule size (d_{50}) as the equivalent projected circle diameter, median aspect ratio (AR) and median sphericity (S) by using Windox 5 Software (Sympathec, Clausthal-Zellerfeld, Germany). All calculations were volume based. The aspect ratio is defined as the ratio of the maximal Feret diameter to the diameter orthogonal to it, and sphericity is the ratio of the perimeter of the equivalent circle to the real perimeter. Perfectly regular and spherical particles have AR and S values of 1. The amount of fines and oversized

granules were defined as the fractions <150 µm and >1000 µm, respectively, whereas the yield of the process was defined as the percentage of granules between 150 µm and 1000 µm. The milling efficiency (%) of the co-mill for all formulations was determined by calculating the difference between % oversized granules before and after milling normalized by the initial % oversized granules.

3.5.5. Granule friability

Granule friability was determined in duplicate using a friabilator (PTF E Pharma Test, Hainburg, Germany). 10 g of granules (I_{wt}) together with 200 glass beads (d=4mm***)*** were rotated in an abrasion wheel for 10 min at a speed of 25 rpm, subjecting them to falling shocks.

Prior to the analysis, the fraction < 250 µm was removed by sieving to assure similar starting conditions. Afterwards, the glass beads were removed and the weight retained on a 250 mm sieve (F_{wt}) was determined. The friability was calculated using equation (3)

$$Friability\ (\%) = \frac{(I_{wt} - F_{wt})}{I_{wt}}\ x\ 100 \qquad (3)$$

3.5.6. Rheology

Rheological analyses were performed on polymeric binders using a Thermo Scientific HAAKE MARS III (Modular Advanced Rheometer System, Thermo Fisher Scientific, Karlsruhe, Germany) with a parallel plate (d=20 mm) as geometrical set-up in order to evaluate the viscoelastic behaviour of the binders at various angular frequencies. At first, an amplitude sweep was performed on the samples to determine the linear viscoelastic region. Oscillation frequency sweeps were performed at 160 °C by increasing the angular frequency from 0.1 to 100 ° Hz using an applied strain of 1 %.

3.6. Tablet evaluation

3.6.1 Out-of-die tablet properties

Tablet diametral tensile strength was calculated using the equation described by Fell and Newton (1968):

$$Tablet\ Tensile\ Strength\ (\sigma_t) = \frac{2P}{\pi Dt} \quad (4)$$

where *P*, *D* and *t* denotes tablet diametral breaking force (N), tablet diameter (mm) and tablet thickness (mm), respectively, which are determined using a combitester (Multitest 50, Dr. Schleuniger, Sotax, Basel, Switzerland).

In order to determine the porosity of the compacts following equation is used:

$$Tablet\ Porosity = 1 - \frac{\rho_{app}}{\rho_{true}} \quad (5)$$

where ρ_{app} and ρ_{true} denote the apparent and true density (g/ml), respectively. The latter was measured using helium pycnometry while the apparent density was calculated by dividing the tablet mass by the volume of the tablet.

Compactibility of the formulations was assessed by plotting tablet tensile strength in function of tablet porosity, a relationship that was described by Ryshkewitch:

$$\sigma_t = \sigma_0\, e^{-bP} \quad (6)$$

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).

3.6.2. In-die tablet properties

Energy plots (i.e. force-displacement curves) were recorded during the compression cycles which enabled the calculation of the energy consumption or dissipation at each phase from the area under the curve (Michaut et al., 2010):

$$E = \int F\, dh \quad (7)$$

where *F* denotes the compression force (kN) and *h* the punch separation (mm). All energies are normalised by taking the compact mass into account to allow comparison between the different formulations. Resulting energies are used for calculating two specific compaction properties:

- A plasticity factor (PF) which represents the energy of compaction used for plastic deformation and fragmentation:

$$PF\ (\%) = \frac{net\ energy}{total\ energy}\ x\ 100 \quad (8)$$

- In-die elastic recovery (IER) which represents the elasticity of a material:

$$IER\ (\%) = \frac{T_d - T_c}{T_c}\ x\ 100 \quad (9)$$

where T_d and T_c represents the punch separation after decompression and the minimal punch separation during compression, respectively.

All calculations for in-line measuring the compaction properties were done using the CDAAS software (GEA Pharma Systems, Halle, Belgium) on at least 3 compacts for each formulation.

Using the in-die data of the CDAAS system, Heckel analysis was performed on all formulations. The theory of Shapiro-Konopicky-Heckel is based on following equation (Heckel, 1961):

$$ln\ \frac{1}{E} = KP + A \quad (10)$$

where *E* is the porosity of the powder bed at a compaction pressure *P*, *K* is the slope of the linear part of the plot (with the best R^2 fit) and *A* is the Y intercept with the linear part of the plot. The mean Heckel yield pressures (P_y) are given by the reciprocal values *K*, while the intercept of both the linear part of the plot (A) and the non-linear part (I) are used to calculate D_a, D_I.

$$D_{a\,(I)} = 1\text{-}\, e^{-A\,(I)} \quad (11)$$

The difference between D_a and D_I denotes D_b, a fragmentation factor, which describes the reduction in volume due to rearrangement of the particles since A is said to reflect low pressure densification by interparticulate motion (Tarlier et al., 2015).

$$D_b = D_a - D_I \quad (12)$$

3.7. Multivariate data analysis

Principal component analysis (PCA) was executed on the relevant compaction data in order to classify the DOE-experimental runs according to their compaction behaviour using the multivariate data analysing software SIMCA 13.0.3 (Umetrics, Umeå, Sweden). The dataset consisted of 31-rows (i.e. the DOE-experiments) for 5 variables (i.e. PF, PF-slope, IER, D_b and P_y). PCA is a multivariate projection method which extracts and displays the variation in the data set (Pieters et al., 2013). The data was pre-processed by unit variate scaling and centered in order to balance the weight of each variable.

4. RESULTS AND DISCUSSION

4.1. Polymer screening for TSMG

4.1.1. TSMG-process

Preliminary experiments were performed in order to determine the minimal polymer concentration required to prepare granules. Overall, a binder concentration of 15 % resulted in good granules for all polymer types in combination with APAP and HCT, which was therefore selected as binder concentration during the polymer screening (Table 2).

TGA indicated that all formulations were thermally stable during the TSMG experiments, as the degradation temperatures of the components are higher than the used processing temperatures (Table 1). The processing temperatures at which granulation occurred depended on the polymeric binder: both Affinisol™-grades needed substantially higher temperatures compared to the other amorphous polymers (Table 2). This was linked to the high complex viscosities of these polymers in low shear regions (Gupta et al., 2016). Although good granules were produced at those elevated temperatures, the application of Affinisol™-grades as polymeric binder in TSMG is expected to be limited to a few active pharmaceutical ingredients which are thermally stable at temperatures over 200 °C.

During this study, it was important to verify if the granulation process induced polymorphisms or changes in the physical state of the drug, especially for APAP-formulations since some processing temperatures exceeded T_m of the component and it has been reported that extrusion of APAP with amorphous polymers (SOL and VA64) at elevated temperatures induced polymeric transformation of APAP from the most stable monoclinic Form I to a orthorhombic Form II with minor stability (Maniruzzaman et al., 2014). Changes in the crystalline structure of a molecule can lead to significant changes in the mechanical properties of the molecule and could therefore confound the tableting results if not considered (Grymonpré et al., 2016). The orthorhombic form of APAP exhibits more fragmentation and plastic deformation under compression leading to far better tabletability compared to the

401 monoclinic form, caused by sliding planes present in the orthorhombic form (Joiris et al., 1998).
402 Both XRD and DSC results confirmed the monoclinic form in the starting material, with distinct
403 crystalline peaks in the diffractogram at 2θ values of 12.12°, 13.88°, 15.52°, 18.20°, 20.42°,
404 23.55°, 24.36° and 26.58° and a sharp melting endotherm at 170.6 °C in the thermograms.
405 The transition from polymorphic Form I to II described by Maniruzzaman et al. during extrusion
406 was characterized by a shift of the peak at 24.36° 2θ to a higher intensity peak at 24.03° 2θ
407 (Maniruzzaman et al., 2014) which was not noticed comparing the APAP physical mixtures
408 before and after TSMG. Moreover, the thermograms of both formulations showed similar sharp
409 melting point (± 171 °C) highlighting the resistance of the formulation to polymorphic transition
410 (Form I to II) ruling out possible confounding of the tableting results. Due to the design of the
411 equipment used for continuous melt granulation, material residence time is reduced
412 significantly (i.e. several seconds) compared to traditional batch processing (Monteyne et al.,
413 2016a). Therefore, it was assumed that even at processing temperatures exceeding T_m it is
414 unlikely that complete melting of APAP occurred especially since the drug load of the melt-
415 granules was high. However, the process conditions during TSMG affected the crystallinity of
416 APAP after processing (Table 2). 96.0-98.9 % of APAP was in the crystalline state processed
417 at temperatures below T_m, while only 87.2%-88.5% crystalline APAP was detected in
418 combination with the Affinisol™ binders as these were processed at temperatures exceeding
419 T_m of the drug. This lower fraction of crystalline APAP in the Affinisol™ formulations was
420 probably not only induced by melting of APAP, but amplified by the higher miscibility of APAP
421 in these binders, linked to the lower differences in solubility parameters (Δδ) between API-
422 polymer (Table 2). Greenhalgh et al. investigated trends in solubility parameters of various
423 API-carrier systems and postulated that compounds with a $\Delta\delta<7.0$ $MPa^{0.5}$ were likely to be
424 miscible, but likely to be immiscible when $\Delta\delta>10$ $MPa^{0.5}$(Greenhalgh et al., 1999). Three-
425 dimensional Hansen's solubility parameters calculated by the group contribution methods
426 (Fedors, 1974; Van Krevelen and Hoftyzer, 1976) were obtained from literature and used to
427 estimate the miscibility of API-polymer (Table 1). Regarding the HCT-formulations, no
428 polymorphic transition or change in physical state during TSMG was expected since the

429 granulation temperatures were far below T_m of HCT and the high Δδ values between HCT and
430 the polymeric binders (>10 $MPa^{0.5}$) were observed.
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432 ***4.1.2. Granule properties***
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434 From a continuous manufacturing perspective, ideal granule properties include low moisture
435 content (<1 %), high granule sphericity, small fraction of fines (<10 %) after milling and a high
436 granule yield in the desired size-fraction for tabletting (Meena et al., 2017). In the proposed
437 manufacturing line (Fig.1), the target PSD of granules was in the 150-1000 µm range to enable
438 an efficient powder transfer towards the rotary tablet press and to avoid segregation when
439 adding extragranular components before tableting. In this respect, the formulations were
440 evaluated on binder efficiency (reflected in the % fines of the unmilled granules) and their
441 milling efficiency since the oversized granule fraction needed to be sufficiently reduced by
442 milling (<1000 µm) without creating an excess of fines.
443 For all formulations, granule moisture content was < 1 % and the granule sphericity was
444 between 0.81-0.85, indicating regularly shaped granules with good flow properties, ideal
445 conditions for further downstream processing in the continuous manufacturing line (Meena et
446 al., 2017). Table 3 provides an overview of the granule properties for both unmilled and milled
447 fractions. The fines fraction of the unmilled samples indicated that granules of most
448 formulations had a high initial strength (i.e. <1% fines), except for HCT combined with Affinisol™
449 (H-4M, H-15LV). This might be due to a difference in granulation mechanism, as the
450 opportunity for interaction between HCT and the Affinisol™-grades was higher compared to the
451 other polymeric binders, based on the Δδ values (Table 2). The correlation between API/binder
452 miscibility and granulation mechanism (i.e. binder distribution) is described by Monteyne et al.,
453 which could be related to the different initial granule strengths observed in the present study
454 (Monteyne et al., 2016a).
455 In this study, process settings and screw configurations were deliberately not adapted to
456 generate a low initial oversize fraction which resulted in a high fraction of oversized (unmilled)

457 granules (Table 3). This approach enabled an evaluation of the co-mill unit on its ability to
458 eliminate potential deviations in granule PSD after the TSMG process. A good control of the
459 PSD is crucial for both downstreaming or end-product quality and therefore an efficient milling-
460 unit is indispensable in the proposed manufacturing line. To guarantee a high yield of the
461 process, deviations in the granule PSD at the granulation unit during continuous processing
462 can be bypassed with the co-mill unit if the formulation has a high milling efficiency.
463 This was the case when using amorphous polymers as binder in TSMG for both model drugs
464 with milling efficiencies of minimal 92.2 % (Table 3). Previous research stated the excellent
465 milling properties of these amorphous polymers when used as carriers for solid dispersions
466 based on their brittle behaviour (Grymonpré et al., 2017b). The highest efficiencies were
467 reached when using EPO and the Affinisol™-grades as binder, however milling of these
468 granules resulted in more fines compared to granules formulated with SOL and VA64 as
469 binder, indicating slightly lower resistance towards the impeller impact during milling. The
470 importance of the milling process after granulation is clearly reflected in Fig. 2, where the yield
471 of granules for further downstreaming is plotted in function of the formulation. Milling increased
472 the yield to at least 89.6 % for all formulations by breaking up the oversized granules.
473 When focussing on the desired granule properties, all screened amorphous polymers showed
474 good potential as TSMG-binder when processing APAP and HCT. In this context, SOL and
475 VA64 could be recommended as polymeric binders since they combine a high milling efficiency
476 with a higher resistance to fine formation.
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4.1.3. Tablet properties

The tableting behaviour of the granules was evaluated in comparison to the physical mixtures of the various formulations by plotting the tabletability (Fig. 3). The latter describes the ability of a material to form compacts with a certain tensile strength (TS) in function of the compaction pressure exerted on the powder bed. For melt granules of both APAP and HCT formulations, significantly higher tabletabilities were noticed in comparison with their physical mixtures.

Improvement of the tableting behaviour of a drug by co-processing with excipients has been reported previously in literature. Shi et al. reported a co-processing method for improving the tabletability of acetaminophen by crystal coating with hydroxypropyl cellulose (HPC) (Shi and Sun, 2011). Lakshman et al. formulated melt granules of metformin hydrochloride with increased compactibility using HPC as binder (Lakshman et al., 2011), while recent work by Batra et al. confirmed the potential of polymeric binders in melt-granulation to improve the compactibility of drugs (Batra et al., 2017). In general, the underlying mechanism for improvement of the tabletability is the same for all cited examples. The poorly compactible drug crystals are coated with a layer of polymer, which displayed more plastic and/or brittle behaviour, creating more interparticulate contacts (i.e. higher bonding area) and forming stronger bondings under compaction. For the present study, it is postulated that the polymeric binder behaved as a separate phase which distributed over the drug particles when softened during TSMG, as was reported by Lakshman et al. and confirmed by Monteyne et al. for immiscible drug-binder blends (Lakshman et al., 2011; Monteyne et al., 2016a).

Only minor differences were noticed in tablet TS between melt-granules of both drug formulations while the EPO-formulations had higher bonding strengths at zero porosity when analysing the compactibility plots (Fig. 4). This could be explained by the tendency of EPO to experience a more extensive elastic recovery during decompression, possibly disrupting some previously formed interparticulate bondings. When comparing the bonding strengths at zero porosity (Fig. 4) for HCT-melt granules, it showed slightly higher tablet tensile strengths at zero

porosity compared to APAP-melt granules for all screened polymeric binders. This was assigned to the better initial tabletability of neat HCT compared to APAP (Fig. 3).

4.2. QbD approach for HCT

HCT was selected as model drug for the QbD melt-granulation approach based on experimental knowledge obtained during the polymer screening. HCT-formulations exhibited better feeding performances enabling good throughput variations as the true density of HCT is significantly higher compared to APAP (Table 1).

Both Affinisol™-grades were excluded in this part of the study, as excessive temperatures were needed to initiate granulation with all model drugs (Table 2) and therefore have less potential as polymeric binder in TSMG from our opinion. An overview of all individual experiments of the DOE is provided in Table 4.

4.2.1. Evaluation of the TSMG-process

When granulation trials were started, the process torque showed large fluctuations up to a point where the torque readings were stable. This phenomenon was attributed to layering of the barrel wall and screws (Vercruysse et al., 2012). For the majority of the DOE-runs, the time needed for stabilizing the torque was < 10 min with a remarkable reduction at higher material throughput.

The average torque values after initial torque stabilization were influenced by both formulation and process factors of the DOE. Using VA64 as polymeric binder resulted in significantly higher basal torque values (i.e. the stabilized torque value at the start of the sampling period), whereas for EPO-formulations the response was remarkably lower. This was correlated with the T_g of the binders (Table 1) as the melt viscosity of VA64-formulations during processing was higher compared to EPO-formulations at similar granulation conditions, especially when incorporating a higher binder concentration (Grymonpré et al., 2017b).

Softening of the polymer is required to lower the melt viscosity of a formulation as reflected by the influence of barrel temperature and screw speed on the basal torque values: while a direct impact of temperature was observed, a higher screw speed reduced the melt viscosity via shear thinning of the binder (Bochmann et al., 2017; Deshmukh et al., 2016; Villmow et al., 2010). The effect of shear rate on the binders was studied by measuring the complex viscosity (η^*) as function of angular frequency (Fig. 5) at a temperature of 160 °C. During granulation, materials undergo high shear due to the rotating screws. A reduction of the complex viscosity at higher angular frequency is indicative for shear thinning (Gupta et al., 2016), which occurred for all binders (Fig. 5). When comparing the polymeric binders, a strong difference in complex viscosity was observed, VA64 having the highest viscosity and EPO a rather low viscosity. Based on Fig. 5 it is evident that VA 64 and SOL were more prone to shear thinning compared to EPO as the onset of the reduction in complex viscosity already occurred at lower angular frequencies. However, the impact of shear thinning was expected to be more substantial for EPO-formulations (despite the lower onset of shear thinning) since the complex viscosity values were below 1000 Pa.S and hence the binder behaved fluid-like during melt granulation at high shear conditions (Gupta et al., 2015).

At higher throughputs, more energy input is required in order to reduce the melt viscosity of the formulations at similar granulation conditions, resulting in higher basal torque levels. In a continuous manufacturing line, it is crucial that all processing steps are run in a robust and efficient way. When focussing on the granulation stage, barrel obstruction due to torque overload must therefore be avoided. As can be seen in Fig. 6 for the centerpoint runs (i.e. at similar granulation settings) with the three polymeric binders, the torque increased from the basal torque value to higher levels in function of sampling time.

As the VA64-formulation showed a much higher basal torque value, this tendency resulted in obstruction of the granulation unit due to torque overload. However, Fig. 6 represents only the torque profile at specific granulation conditions. By including the torque variation over time as response in the DOE, in-depth knowledge was gained on the impact of formulation and process factors on this response and how to reduce the risk of granulation obstruction for challenging

565 formulations. Fig. 7 shows the coefficient plot of the latter response, displaying the regression
566 coefficients of each factor and factor interaction. The regression coefficient of a specific factor
567 represents the quantitative change in response value when this factor is increased from its
568 average to its high level, keeping all other factors at their average value.
569 VA 64-formulations showed a significantly higher torque increase in function of granulation
570 time which was in line with the tendency observed in Fig. 6. Although the risk of obstruction
571 during melt granulation was higher using VA64-containig formulations, the observed
572 interactions between polymer type and granulation settings allowed to adjust granulation
573 settings during TSMG in order to reduce this risk.
574 Important interactions with the polymer type were noticed for screw speed and throughput,
575 from analysing the interaction plots in Fig. 8. Precaution should be taken when increasing the
576 screw speed for EPO-formulations, as the resulting shear thinning effect could result in a more
577 extensive binder distribution inside the barrel and hence increasing torque levels over longer
578 time (Fig. 5). The challenging VA 64 formulations (i.e. polymeric binder with high T_g) showed
579 a significant decrease in torque over time when processed at high screw speed and low
580 throughput. At those granulation settings, the use of VA 64 as polymeric binder will result in
581 successful granulation without barrel obstruction during a continuous granulation process.
582 Regarding continuous processing, SOL would be the most deliberate option as binder for
583 TSMG since this polymer is less prone for torque increase during longer granulation trials,
584 independent of the process settings (Fig. 8). A more extensive self-wiping effect of the screws
585 was noticed when using SOL-formulations, explaining the torque decrease over time. Fig. 7
586 revealed an interaction between binder concentration and barrel temperature. It is
587 recommended when processing formulations with higher percentage of binder and comparable
588 thermal properties, to increase the granulation temperatures in order to minimize the risk for
589 barrel obstruction.
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4.2.2. Evaluation of melt granule quality

During the polymer screening, it was noticed that a high amount of oversized granules (>1000 µm) were produced with all polymeric binders and the importance of an efficient milling step was highlighted in order to generate a high granule yield (150-1000 µm) for downstreaming into tablets. The percentage of initial oversized granules was high for all polymeric binders (62-98 %). No statistical significant correlations between % oversized unmilled granules and formulation or process factors were detected, except for an interaction between polymer type and screw speed (Fig. 9). The % of oversized granules for VA64-formulations was significantly decreased by granulation at higher screw speed. This was explained by the more brittle behaviour of VA64-formulations at the end of the granulation barrel (i.e. T_6=40°C) as the temperature difference with the T_g of VA64 is high (ΔT=68°C) compared to SOL (ΔT=24°C) and especially EPO (ΔT=13°C).

The percentage of fines leaving the granulation barrel was low (<1.7%) for all runs, indicating a high robustness of the TSMG-process for this response within the DOE- granulation settings. For all formulations, highly efficient break-up of the oversized granule fraction occurred as evidenced by the milling efficiency (Fig. 10, A). A slight reduction in this response was noticed with increasing percentages of binder, however the milling efficiency of all runs remained high (> 87 %). The fines induced by milling was not excessive (Fig. 10, B), with the highest amount of fines reached in the design still being an acceptable 5.98%. Overall, the co-milling unit in this line performed with a high efficiency for melt-granules of amorphous polymeric binders resulting in high yield values (>85.6 %) independent of the TSMG process-settings (Fig. 10, C). Granule friability of the melt-granules was very low (< 9 %) with all polymeric binders, independent of the binder concentration or TSMG process settings (Fig. 10, D). These low friability values indicated a high granule strength, which make these melt granules extremely suitable for downstream processing. Melt-granules with SOL as polymeric binder showed the lowest friability (< 4%).

4.2.3. Evaluation of the tableting behaviour

The beneficial effects of formulating HCT as melt granules with polymeric binders on the tabletability was described earlier in the section polymer screening. A more in-depth evaluation of the tableting behaviour for all experimental runs was done by in-line monitoring of the compaction properties at the tableting stage (Table 5). PCA was a useful tool to summarize the behaviour under compaction of the melt granules in a comprehensive way, as represented in the bi-plot at Fig. 11. The two principal components (PC) in the current model accounted for 88.6 % of the total variance in the dataset with PC_1 and PC_2 comprising 78.0 % and 10.6 %, respectively. The loadings indicated that PC_1 (x-direction) differentiated mainly between the deformation mechanisms under compression. The plastic deformation potential (i.e. PF and P_y) was anti-correlated with the elastic recovery (i.e. IER) and the PF slope. PC_2 (y-direction) captured the fragmentary behaviour of the materials (i.e. D_b) while being correlated with PF and P_y of PC_1.

Formulations which underwent more extensive plastic deformation during compression are located left of the origin in PC_1- direction (high PF and P_Y), which was the case for melt granules with SOL (red circles) and VA64 (orange boxes) as polymeric binders. A clear cluster was seen for the experimental runs with EPO (blue triangles) as polymeric binder, located right of the origin in PC_1-direction, indicative of higher in-die elastic recovery after compression (high IER and low P_y) especially for runs 8-11 which represent EPO-concentrations of 25 % (Patel et al., 2007). Moreover, the formulations which deform more plastically (i.e. SOL and VA64) have a higher tendency of initial fragmentation under compression (high D_b) in contrast to EPO-formulations. These results were in line with earlier research on compression with amorphous polymers, highlighting the higher elastic deformability and low fragmentary behaviour of EPO (Grymonpré et al., 2017b). For VA64 and EPO-formulations, it was noticed that the contribution of PC_2 was relatively small and no distinction could be made in function of process settings and binder concentration. However, this was not the case for SOL-formulations as reflected more specifically by experiment 12 and 19. Run 19 of the DOE differed from run 12 in polymer

concentration and screw speed (Table 4), with higher % of SOL-binder and screw speed leading to more fragmentary behaviour of the melt-granules (i.e. D_b). This was explained by the 'brittle' behaviour of the polymer itself while higher screw speed during TSMG can lead to a more extensive polymer distribution on the melt-granules.

When plotting PF in function of the compaction pressures for the formulations, a linear relation was found ($R^2 > 0.99$). Therefore, the slope of these curves could be used as response to evaluate the plastic deformation of the formulations at all exerted compaction pressures. Higher slopes are indicative for less plastic deformation under compaction. Significantly higher PF-slopes were noticed for EPO-formulations. Melt granules of VA64-fromulations had significantly lower slopes, highlighting their plastic deformation under compression. These results explain the positioning of the scores on the bi-plot (Fig. 11) in the direction of PC_1.

5. CONCLUSIONS

Amorphous polymers have a high potential as polymeric binders for TSMG, resulting in melt-granules with extremely low friability whereas the good milling efficiency of these formulations provide a high granule yield for downstream processing towards tablets with improved tabletability. One of the most critical stages during continuous TSMG with polymeric binders was the granulation unit since some experimental runs (with VA64 as polymeric binder) exhibited a significant torque increase over granulation time eventually resulting in a barrel obstruction, which was linked to the high T_g of the polymer. However, by fine-tuning the granulation settings (i.e. screw speed and throughput), this risk was significantly reduced whereas the use of polymers with lower T_g (i.e. SOL and EPO) guaranteed a more stable granulation process over time. In similar context, when using higher concentrations of polymeric binders, it is recommended to increase the granulation temperature in order to minimize the risk for barrel obstruction. The tableting behaviour under compression is dependent on the type of polymeric binder, with EPO-formulations exhibiting less fragmentation and more elastic deformation under compression compared to SOL and VA64-formulations. Overall, this research emphasized that the twin-screw melt granulation process was very robust regarding the CQA of both high-drug loaded melt granules and their tablets, which are important features in the concept of continuous manufacturing. Therefore, TSMG can be considered as a viable processing technique during formulation development of pharmaceutical oral solid dosage forms.

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