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

3
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35 **Abstract**

36
37 The concept of twin-screw melt granulation (TSMG) has steadily (re)-gained interest in
38 pharmaceutical formulation development as an intermediate step during tablet manufacturing.
39 However, to be considered as a viable processing option for solid oral dosage forms there is a
40 need to understand all critical sources of variability which could affect this granulation
41 technique. The purpose of this study was to provide an in-depth analysis of the continuous
42 TSMG process in order to expose the critical process parameters (CPP) and elucidate the
43 impact of process and formulation parameters on the critical quality attributes (CQA) of
44 granules and tablets during continuous TSMG. A first part of the study dealt with the screening
45 of various amorphous polymers as binder for producing high-dosed melt granules of two model
46 drug (i.e. acetaminophen and hydrochlorothiazide). The second part of this study described a
47 quality-by-design (QbD) approach for melt granulation of hydrochlorothiazide in order to
48 thoroughly evaluate TSMG, milling and tableting stage of the continuous TSMG line. Using
49 amorphous polymeric binders resulted in melt granules with high milling efficiency due to their
50 brittle behaviour without producing excessive amounts of fines, providing high granule yields
51 with low friability. Therefore, it makes them extremely suitable for further downstream
52 processing. One of the most important CPP during TSMG with polymeric binders was the
53 granulation-torque, which - in case of polymers with high T_g - increased during longer
54 granulation runs to critical levels endangering the continuous process flow. However, by
55 optimizing both screw speed and throughput or changing to polymeric binders with lower T_g it
56 was possible to significantly reduce this risk. This research paper highlighted that TSMG must
57 be considered as a viable option during formulation development of solid oral dosage forms
58 based on the robustness of the CQA of both melt granules and tablets.

59

60

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

63 1. INTRODUCTION

64

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

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

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

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

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

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

120 **2. MATERIALS**

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

132 **3. METHODS**

133 **3.1. Continuous twin-screw melt granulation**

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

142 **3.1.1. Blending and gravimetric feeding**

143
144 Before blending the active pharmaceutical ingredient (API) and polymer, the neat API was
145 milled (Quadro® U5, Waterloo, Canada) using a round arm impeller at 900 rpm with a 1395-
146 micron screen to break up possible powder lumps. Afterwards, blends were prepared for both
147 model drugs with all amorphous polymers using a tumbling mixer (W.A. Bachofen, Basel,
148 Switzerland) for 10 min at 15 rpm. These blends were gravimetrically fed to the granulation
149 unit using a DD Flexwall® gravimetric feeder (Brabender Technology, Germany).

150 **3.1.2. Twin-screw melt granulation**

151
152 A co-rotating intermeshing twin-screw extruder (Prism Eurolab 16, ThermoFischer Scientific,
153 Karlsruhe, Germany) was used as granulator with a barrel length of 25 L/D, where L is the
154 axial screw length and D the inner bore diameter corresponding to one of the screws. The
155 screw configuration was identical for all experiments, with 2 mixing zones in the third and fifth
156 segment, each consisting of 6 kneading discs at 60° stagger angle in reversed direction and a
157 screw-mixing element at the end of each screw intended for break-up of potentially large melt-
158 granule lumps. The granulation barrel is divided into 6 segments (T_{1-6}) which can be
159 heated/cooled separately. The temperature at the end of the barrel (T_6) was lowered to 40 °C
160 during all runs in order to cool the granules below the glass transition temperature (T_g) of the
161 polymers, enabling break up of very large agglomerates by the screw-mixing elements and
162 avoiding sticking of the granules when leaving the barrel. All other segments in the granulator
163 (T_{1-5}) were kept constant at the same temperature, except for mixtures with EPO for which the
164 temperature of the feeding segment (T_1) was lowered to 80 °C to prevent feeding obstruction.
165 The granulator was equipped with a data logging system to monitor the screw torque and barrel
166 temperature during granulation. Sample collection for evaluation of granule properties before
167 milling was done at stable granulation conditions, based on the process torque values.

168 **3.1.3. Milling**

169

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

173 **3.1.4. Tableting**

174
175 All milled formulations and their physical mixtures (PM) were compressed to tablets on a rotary
176 tablet press (MODUL™ P, GEA Pharma Systems, Halle, Belgium) equipped with cylindrical
177 flat-faced Euro B punches of 10 mm diameter and an overfill cam of 16 mm. Tablets (250 ± 5
178 mg) were compressed on 7 different main compaction pressures: 65, 130, 190, 255, 320, 380
179 and 510 MPa without the use of a pre-compression step at a turret speed of 5 rpm. All tablets
180 were analysed for 'out-of-die' properties (tablet strength, dimensions and mass) immediately
181 after ejection. Punch deformation at each compaction pressure was calculated and corrected
182 for during this study. In-die measurements of the compaction properties was performed by
183 linear variable displacement transducers (LVDT) incorporated inside the turret and clamped
184 onto one pair of punches, enabling the monitoring of punch stroke movements during a
185 compression cycle (GEA Pharma Systems, Halle, Belgium). Calibration was performed prior
186 to processing each formulation, by interpolating the output voltage of the sensor to physical
187 values during static measurements. A wireless transmission system continuously transmitted
188 the data from these sensors to a data acquisition and analysis system (CDAAS™, GEA Pharma
189 Systems, Halle, Belgium).

190

191 **3.2. Polymer screening**

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

197

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_{2-5} (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:

223
$$\Delta T/t (\%/min) = \frac{T_{end}-T_s}{t} \quad (1)$$

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

227

228 **3.5. Raw material and granule characterization**

229 **3.5.1. Solid state characterization**

230
231 Thermogravimetric analysis (TGA 2950, TA instruments, Leatherhead, UK) was conducted on
232 all polymers and drugs to investigate their thermal stability. Samples (± 15 mg) were heated
233 up to 600 °C after equilibration at 25 °C using a heating rate of 10 °C/min.

234 Differential scanning calorimetry (DSC, Q2000, TA Instruments, Leatherhead, UK) was used
235 for raw material screening and comparing PM before and after granulation based on the T_g ,
236 T_m and melting enthalpy. The DSC-device is equipped with a refrigerated cooling system and
237 the cell was purged with dry nitrogen at a flow rate of 50 ml/min. A heating rate of 10 °C/min
238 was used during 3 cycles (heat, cool, heat) from 0 °C to 200 °C for APAP-formulations and 0
239 °C to 290 °C for HCT-formulations of around 10 mg weighed in T-zero pans. Crystallinity X_c
240 (%) of APAP in the granules was calculated based on the enthalpy of fusion of APAP in the
241 corresponding physical mixture (PM) using following equation:

242

243
$$X_c (\%) = \left(\frac{\Delta H_f}{\Delta H_f^*} \right) \times 100 \quad (2)$$

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

246

247

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

250 range of $10^\circ < 2\theta < 20^\circ$ was used in a step scan mode (step width = 0.02° , counting time = 1
251 s/step).

252 **3.5.2. Moisture content**

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

258 **3.5.3. True density**

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

263 **3.5.4. Particle size and shape analysis**

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

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

282 **3.5.5. Granule friability**

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

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

$$289 \quad \text{Friability (\%)} = \frac{(I_{wt} - F_{wt})}{I_{wt}} \times 100 \quad (3)$$

290 **3.5.6. Rheology**

291 Rheological analyses were performed on polymeric binders using a Thermo Scientific HAAKE
292 MARS III (Modular Advanced Rheometer System, Thermo Fisher Scientific, Karlsruhe,
293 Germany) with a parallel plate ($d=20\text{ mm}$) as geometrical set-up in order to evaluate the
294 viscoelastic behaviour of the binders at various angular frequencies. At first, an amplitude
295 sweep was performed on the samples to determine the linear viscoelastic region. Oscillation
296 frequency sweeps were performed at 160 °C by increasing the angular frequency from 0.1 to
297 100 ° Hz using an applied strain of 1 %.

298
299

300

301 **3.6. Tablet evaluation**

302 **3.6.1 Out-of-die tablet properties**

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

305
$$\text{Tablet Tensile Strength } (\sigma_t) = \frac{2P}{\pi Dt} \quad (4)$$

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

309

310

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

312
$$\text{Tablet Porosity} = 1 - \frac{\rho_{app}}{\rho_{true}} \quad (5)$$

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

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

318

319
$$\sigma_t = \sigma_0 e^{-bP} \quad (6)$$

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

323 **3.6.2. In-die tablet properties**

324

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

328
$$E = \int F dh \quad (7)$$

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

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

335
$$PF (\%) = \frac{\text{net energy}}{\text{total energy}} \times 100 \quad (8)$$

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

337
$$IER (\%) = \frac{T_d - T_c}{T_c} \times 100 \quad (9)$$

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

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

342 Using the in-die data of the CDAAS system, Heckel analysis was performed on all
 343 formulations. The theory of Shapiro-Konopicky-Heckel is based on following equation (Heckel,
 344 1961):

345
$$\ln \frac{1}{E} = KP + A \quad (10)$$

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

351
$$D_{a(l)} = 1 - e^{-A(l)} \quad (11)$$

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

$$355 \quad D_b = D_a - D_l \quad (12)$$

356 **3.7. Multivariate data analysis**

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

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374 4. RESULTS AND DISCUSSION

375 4.1. Polymer screening for TSMG

376 4.1.1. TSMG-process

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

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

390 During this study, it was important to verify if the granulation process induced polymorphisms
391 or changes in the physical state of the drug, especially for APAP-formulations since some
392 processing temperatures exceeded T_m of the component and it has been reported that
393 extrusion of APAP with amorphous polymers (SOL and VA64) at elevated temperatures
394 induced polymeric transformation of APAP from the most stable monoclinic Form I to a
395 orthorhombic Form II with minor stability (Maniruzzaman et al., 2014). Changes in the
396 crystalline structure of a molecule can lead to significant changes in the mechanical properties
397 of the molecule and could therefore confound the tableting results if not considered
398 (Grymonpré et al., 2016). The orthorhombic form of APAP exhibits more fragmentation and
399 plastic deformation under compression leading to far better tableability compared to the
400

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 $24.36^\circ 2\theta$ to a higher intensity peak at $24.03^\circ 2\theta$
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 ($\pm 171^\circ\text{C}$) 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 ($\Delta\delta$) 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 $\Delta\delta < 7.0 \text{ MPa}^{0.5}$ were likely to be
424 miscible, but likely to be immiscible when $\Delta\delta > 10 \text{ MPa}^{0.5}$ (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 $\Delta\delta$ values between HCT and
430 the polymeric binders ($>10 \text{ MPa}^{0.5}$) were observed.

431

432 **4.1.2. Granule properties**

433

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 tableting (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 ($<1000 \mu\text{m}$) 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 $\Delta\delta$ 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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484 **4.1.3. Tablet properties**

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

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

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

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

513

514 **4.2. QbD approach for HCT**

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

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

523 **4.2.1. Evaluation of the TSMG-process**

524
525 When granulation trials were started, the process torque showed large fluctuations up to a
526 point where the torque readings were stable. This phenomenon was attributed to layering of
527 the barrel wall and screws (Vercruyssen et al., 2012). For the majority of the DOE-runs, the time
528 needed for stabilizing the torque was < 10 min with a remarkable reduction at higher material
529 throughput.

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

537 Softening of the polymer is required to lower the melt viscosity of a formulation as reflected by
538 the influence of barrel temperature and screw speed on the basal torque values: while a direct
539 impact of temperature was observed, a higher screw speed reduced the melt viscosity via
540 shear thinning of the binder (Bochmann et al., 2017; Deshmukh et al., 2016; Villmow et al.,
541 2010). The effect of shear rate on the binders was studied by measuring the complex viscosity
542 (η^*) as function of angular frequency (Fig. 5) at a temperature of 160 °C. During granulation,
543 materials undergo high shear due to the rotating screws. A reduction of the complex viscosity
544 at higher angular frequency is indicative for shear thinning (Gupta et al., 2016), which occurred
545 for all binders (Fig. 5). When comparing the polymeric binders, a strong difference in complex
546 viscosity was observed, VA64 having the highest viscosity and EPO a rather low viscosity.
547 Based on Fig. 5 it is evident that VA 64 and SOL were more prone to shear thinning compared
548 to EPO as the onset of the reduction in complex viscosity already occurred at lower angular
549 frequencies. However, the impact of shear thinning was expected to be more substantial for
550 EPO-formulations (despite the lower onset of shear thinning) since the complex viscosity
551 values were below 1000 Pa.S and hence the binder behaved fluid-like during melt granulation
552 at high shear conditions (Gupta et al., 2015).

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

560 As the VA64-formulation showed a much higher basal torque value, this tendency resulted in
561 obstruction of the granulation unit due to torque overload. However, Fig. 6 represents only the
562 torque profile at specific granulation conditions. By including the torque variation over time as
563 response in the DOE, in-depth knowledge was gained on the impact of formulation and process
564 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-containing 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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592 **4.2.2. Evaluation of melt granule quality**

593
594 During the polymer screening, it was noticed that a high amount of oversized granules (>1000
595 μm) were produced with all polymeric binders and the importance of an efficient milling step
596 was highlighted in order to generate a high granule yield (150-1000 μm) for downstreaming
597 into tablets. The percentage of initial oversized granules was high for all polymeric binders (62-
598 98 %). No statistical significant correlations between % oversized unmilled granules and
599 formulation or process factors were detected, except for an interaction between polymer type
600 and screw speed (Fig. 9). The % of oversized granules for VA64-formulations was significantly
601 decreased by granulation at higher screw speed. This was explained by the more brittle
602 behaviour of VA64-formulations at the end of the granulation barrel (i.e. $T_6=40^\circ\text{C}$) as the
603 temperature difference with the T_g of VA64 is high ($\Delta T=68^\circ\text{C}$) compared to SOL ($\Delta T=24^\circ\text{C}$)
604 and especially EPO ($\Delta T=13^\circ\text{C}$).

605
606 The percentage of fines leaving the granulation barrel was low (<1.7%) for all runs, indicating
607 a high robustness of the TSMG-process for this response within the DOE- granulation settings.
608 For all formulations, highly efficient break-up of the oversized granule fraction occurred as
609 evidenced by the milling efficiency (Fig. 10, A). A slight reduction in this response was noticed
610 with increasing percentages of binder, however the milling efficiency of all runs remained high
611 (> 87 %). The fines induced by milling was not excessive (Fig. 10, B), with the highest amount
612 of fines reached in the design still being an acceptable 5.98%. Overall, the co-milling unit in
613 this line performed with a high efficiency for melt-granules of amorphous polymeric binders
614 resulting in high yield values (>85.6 %) independent of the TSMG process-settings (Fig. 10,
615 C). Granule friability of the melt-granules was very low (< 9 %) with all polymeric binders,
616 independent of the binder concentration or TSMG process settings (Fig. 10, D). These low
617 friability values indicated a high granule strength, which make these melt granules extremely
618 suitable for downstream processing. Melt-granules with SOL as polymeric binder showed the
619 lowest friability (< 4%).

620 **4.2.3. Evaluation of the tableting behaviour**

621

622 The beneficial effects of formulating HCT as melt granules with polymeric binders on the
623 tableability was described earlier in the section polymer screening. A more in-depth evaluation
624 of the tableting behaviour for all experimental runs was done by in-line monitoring of the
625 compaction properties at the tableting stage (Table 5). PCA was a useful tool to summarize
626 the behaviour under compaction of the melt granules in a comprehensive way, as represented
627 in the bi-plot at Fig. 11. The two principal components (PC) in the current model accounted for
628 88.6 % of the total variance in the dataset with PC₁ and PC₂ comprising 78.0 % and 10.6 %,
629 respectively. The loadings indicated that PC₁ (x-direction) differentiated mainly between the
630 deformation mechanisms under compression. The plastic deformation potential (i.e. PF and
631 P_y) was anti-correlated with the elastic recovery (i.e. IER) and the PF slope. PC₂ (y-direction)
632 captured the fragmentary behaviour of the materials (i.e. D_b) while being correlated with PF
633 and P_y of PC₁.

634 Formulations which underwent more extensive plastic deformation during compression are
635 located left of the origin in PC₁-direction (high PF and P_y), which was the case for melt granules
636 with SOL (red circles) and VA64 (orange boxes) as polymeric binders. A clear cluster was seen
637 for the experimental runs with EPO (blue triangles) as polymeric binder, located right of the
638 origin in PC₁-direction, indicative of higher in-die elastic recovery after compression (high IER
639 and low P_y) especially for runs 8-11 which represent EPO-concentrations of 25 % (Patel et al.,
640 2007). Moreover, the formulations which deform more plastically (i.e. SOL and VA64) have a
641 higher tendency of initial fragmentation under compression (high D_b) in contrast to EPO-
642 formulations. These results were in line with earlier research on compression with amorphous
643 polymers, highlighting the higher elastic deformability and low fragmentary behaviour of EPO
644 (Grymonpré et al., 2017b). For VA64 and EPO-formulations, it was noticed that the contribution
645 of PC₂ was relatively small and no distinction could be made in function of process settings
646 and binder concentration. However, this was not the case for SOL-formulations as reflected
647 more specifically by experiment 12 and 19. Run 19 of the DOE differed from run 12 in polymer

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

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

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676 **5. CONCLUSIONS**

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

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730 **6. LITERATURE**

- 731 Batra, A., Desai, D., Serajuddin, A.T.M., 2017. Investigating the Use of Polymeric Binders in
 732 Twin Screw Melt Granulation Process for Improving Compactibility of Drugs. *J. Pharm.*
 733 *Sci.* 106, 140–150. doi:10.1016/j.xphs.2016.07.014
- 734 Bi, M., Sun, C.C., Alvarez, F., Alvarez-nunez, F., 2011. The Manufacture of Low-Dose Oral
 735 Solid Dosage Form to Support Early Clinical Studies Using an Automated Micro-Filing
 736 System. *AAPS PharmSciTech* 12, 88–95. doi:10.1208/s12249-010-9549-y
- 737 Bochmann, E.S., Üstüner, E.E., Gryczke, A., Wagner, K.G., 2017. Predicting melt rheology
 738 for hot-melt extrusion by means of a simple T_g-measurement. *Eur. J. Pharm.*
 739 *Biopharm.* 119, 47–55. doi:10.1016/j.ejpb.2017.05.010
- 740 Deshmukh, S.S., Gabbott, I., Booth, J., Kelly, A.L., 2016. Prediction of Melt Rheology of
 741 Amorphous Polymers for Hot Melt Extrusion, in: *AAPS Abstract*. p. 2.
- 742 Dhenge, R.M., Washino, K., Cartwright, J.J., Hounslow, M.J., Salman, A.D., 2013. Twin
 743 screw granulation using conveying screws : Effects of viscosity of granulation liquids and
 744 flow of powders. *Powder Technol.* 238, 77–90. doi:10.1016/j.powtec.2012.05.045
- 745 Fedors, R.F., 1974. A Method for Estimating Both the Solubility Parameters and Molar
 746 Volumes of liquids. *Polym. Eng. Sci.* 14, 147–154.
- 747 Fonteyne, M., Vercruyse, J., Díaz, D.C., Gildemyn, D., Vervaet, C., Remon, J.P., De Beer,
 748 T., 2011. Real-time assessment of critical quality attributes of a continuous granulation
 749 process. *Pharm. Dev. Technol.* 13, 1–13. doi:10.3109/10837450.2011.627869
- 750 Godavarti, S., Karwe, M. V, 1997. Determination of Specific Mechanical Energy Distribution
 751 on a Twin-Screw Extruder. *J. Agric. Engng Res* 67, 277–287.
- 752 Gohel, M.C., Jogani, P.D., Marg, B.S.D., 2005. A review of co-processed directly
 753 compressible excipients. *J. Pharm. Sci.* 8, 76–93.
- 754 Greenhalgh, D.J., Williams, A.C., Timmins, P., York, P., 1999. Solubility Parameters as
 755 Predictors of Miscibility in Solid Dispersions. *J. Pharm. Sci.* 88, 1182–1189.
- 756 Grymonpré, W., Bostijn, N., Van Herck, S., Verstraete, G., Vanhoorne, V., Nuhn, L.,
 757 Rombouts, P., Remon, J., Vervaet, C., 2017a. Downstream processing from hot-melt
 758 extrusion towards tablets: a quality by design approach. *Int. J. Pharm.* 531, 235–245.
 759 doi:http://dx.doi.org/10.1016/j.ijpharm.2017.08.077
- 760 Grymonpré, W., De Jaeghere, W., Peeters, E., Adriaensens, P., Remon, J.P., Vervaet, C.,
 761 2016. The impact of hot-melt extrusion on the tableting behaviour of polyvinyl alcohol.
 762 *Int. J. Pharm.* 498, 254–262. doi:10.1016/j.ijpharm.2015.12.020
- 763 Grymonpré, W., Verstraete, G., Bockstal, P.J. Van, Renterghem, J. Van, Rombouts, P.,
 764 2017b. In-line monitoring of compaction properties on a rotary tablet press during tablet
 765 manufacturing of hot-melt extruded amorphous solid dispersions. *Int. J. Pharm.* 517,
 766 348–358. doi:10.1016/j.ijpharm.2016.12.033
- 767 Gupta, S.S., Parikh, T., Meena, A.K., Mahajan, N., Vitez, I., Serajuddin, A.T.M., 2015. Effect
 768 of carbamazepine on viscoelastic properties and hot melt extrudability of Soluplus. *Int.*
 769 *J. Pharm.* 478, 232–239. doi:10.1016/j.ijpharm.2014.11.025
- 770 Gupta, S.S., Solanki, N., Serajuddin, A.T.M., 2016. Investigation of Thermal and Viscoelastic
 771 Properties of Polymers Relevant to Hot Melt Extrusion, IV: Affinisol™ HPMC HME
 772 Polymers. *AAPS PharmSciTech* 17, 148–157. doi:10.1208/s12249-015-0426-6
- 773 Heckel, R.W., 1961. An analysis of powder compaction phenomena. *Trans. Met. Soc. AIME*
 774 1001–1008.
- 775 Joiris, E., Martino, P. Di, Berneron, C., Guyot-Hermann, A.-M., Guyot, J.-C., Joiris, J.-C.,
 776 1998. Compression Behavior of Orthorhombic Paracetamol. *Pharm. Res.* 15, 1122–
 777 1130. doi:10.1023/A:1011954800246
- 778 Kidokoro, M., Haramiishi, Y., Sagasaki, S., Shimizu, T., 2002. Application of fluidized hot-
 779 melt granulation (FHMG) for the preparation of granules for tableting: properties of
 780 granules and tablets prepared by FHMG. *Drug Deliv. Transl.Res.* 28, 67–76.
- 781 Kowalski, J., Kalb, O., Joshi, Y.M., Serajuddin, A.T.M., 2009. Application of melt granulation
 782 technology to enhance stability of a moisture sensitive immediate-release drug product
 783 381, 56–61. doi:10.1016/j.ijpharm.2009.05.043

784 Lakshman, J.P., Kowalski, J., Vasanthavada, M., Tong, W.-Q., Joshi, Y.M., 2011. Application
785 of Melt Granulation Technology to Enhance Tableting Properties of Poorly Compactible
786 High-Dose Drugs. *J. Pharm. Sci.* 100, 1553–1565. doi:10.1002/jps

787 Liu, H., Galbraith, S.C., Ricart, B., Stanton, C., Smith-goettler, B., Verdi, L., Connor, T.O.,
788 Lee, S., Yoon, S., 2017. Optimization of critical quality attributes in continuous twin-
789 screw wet granulation via design space validated with pilot scale experimental data. *Int.*
790 *J. Pharm.* 525, 249–263. doi:10.1016/j.ijpharm.2017.04.055

791 Maniruzzaman, M., Islam, M.T., Moradiya, H.G., Halsey, S.A., Slipper, I.A.N.J., Chowdhry,
792 B.Z., Snowden, M.J., Douroumis, D., 2014. Prediction of Polymorphic Transformations
793 of Paracetamol in Solid Dispersions. *J. Pharm. Sci.* 103, 1819–1828.
794 doi:10.1002/jps.23992

795 Meena, A.K., Desai, D., Serajuddin, A.T.M., 2017. Development and Optimization of a Wet
796 Granulation Process at Elevated Temperature for a Poorly Compactible Drug Using
797 Twin Screw Extruder for Continuous Manufacturing. *J. Pharm. Sci.* 106, 589–600.
798 doi:10.1016/j.xphs.2016.10.020

799 Michaut, F., Busignies, V., Fouquereau, C., Huet De Barochez, B., Leclerc, B., Tchoreloff, P.,
800 2010. Evaluation of a Rotary Tablet Press Simulator as a Tool for the Characterization
801 of Compaction Properties of Pharmaceutical Products. *J. Pharm. Sci.* 99, 2874–2885.
802 doi:10.1002/jps.22032

803 Monteyne, T., Heeze, L., Thérèse, S., Mortier, F.C., Oldörp, K., Nopens, I., Remon, J.,
804 Vervaet, C., Beer, T. De, 2016a. The use of rheology to elucidate the granulation
805 mechanisms of a miscible and immiscible system during continuous twin-screw melt
806 granulation. *Int. J. Pharm.* 510, 271–284. doi:10.1016/j.ijpharm.2016.06.055

807 Monteyne, T., Vancoillie, J., Remon, J., Vervaet, C., Beer, T. De, 2016b. Continuous melt
808 granulation: Influence of process and formulation parameters upon granule and tablet
809 properties. *Eur. J. Pharm. Biopharm.* 107, 249–262. doi:10.1016/j.ejpb.2016.07.021

810 Mu, B., Thompson, M.R., 2012. Examining the mechanics of granulation with a hot melt
811 binder in a twin-screw extruder. *Chem. Eng. Sci.* 81, 46–56.

812 Patel, S., Kaushal, A.M., Bansal, A.K., 2006. Compression Physics in the Formulation
813 Development of Tablets. *Crit. Rev. Ther. Drug Carr. Syst.* 23, 1–65.

814 Patel, S., Kaushal, A.M., Bansal, A.K., 2007. Effect of Particle Size and Compression Force
815 on Compaction Behavior and Derived Mathematical Parameters of Compressibility.
816 *Pharm. Res.* 24, 111–124. doi:10.1007/s11095-006-9129-8

817 Pieters, S., Vander Heyden, Y., Roger, J.-M., DHondt, M., Hansen, L., Palagos, B., De
818 Spiegeleer, B., Remon, J.-P., Vervaet, C., De Beer, T., 2013. Raman spectroscopy and
819 multivariate analysis for the rapid discrimination between native-like and non-native
820 states in freeze-dried protein formulations. *Eur. J. Pharm. Biopharm.* 85, 263–271.
821 doi:10.1016/j.ejpb.2013.03.035

822 Plumb, K., 2005. Continuous Processing in the pharmaceutical industry: Changing the mind
823 set. *Chem. Eng. Res. Desing* 83, 730–738. doi:10.1205/cherd.04359

824 Ryshkewitch, E., 1953. Compression Strength of Porous Sintered Alumina and Zirconia. *J.*
825 *Am. Ceram. Soc.* 36, 65–68. doi:10.1111/j.1151-2916.1953.tb12837.x

826 Schaber, S.D., Gerogiorgis, D.I., Ramachandran, R., Evans, J.M.B., Barton, P.I., Trout, B.L.,
827 2011. Economic analysis of integrated continuous and batch pharmaceutical
828 manufacturing : A case study. *Ind. Eng. Chem. Res.* 50, 10083–10092.

829 Shi, L., Sun, C.C., 2011. Overcoming Poor Tabletability of Pharmaceutical Crystals by
830 Surface Modification. *Pharm. Res.* 28, 3248–3255. doi:10.1007/s11095-011-0518-2

831 Tarlier, N., Soulairol, I., Bataille, B., Baylac, G., Ravel, P., Nofrerias, I., Lefèvre, P., Sharkawi,
832 T., 2015. Compaction behavior and deformation mechanism of directly compressible
833 textured mannitol in a rotary tablet press simulator. *Int. J. Pharm.* 495, 410–419.
834 doi:10.1016/j.ijpharm.2015.09.007

835 Van Krevelen, D.W., Hoftyzer, P.J., 1976. Properties of polymers: their estimation and
836 correlation with chemical structures. Elsevier, Amsterdam.

837 Van Melkebeke, B., Vervaet, C., Remon, J.P., 2008. Validation of a continuous granulation
838 process using a twin-screw extruder. *Int. J. Pharm.* 356, 224–230.

839 doi:10.1016/j.ijpharm.2008.01.012
840 Van Snick, B., Holman, J., Cunningham, C., Kumar, A., Vercruyse, J., De Beer, T., Remon,
841 J.P., Vervaet, C., 2017a. Continuous direct compression as manufacturing platform for
842 sustained release tablets. *Int. J. Pharm.* 519, 390–407.
843 doi:10.1016/j.ijpharm.2017.01.010
844 Van Snick, B., Holman, J., Vanhoorne, V., Kumar, A., De Beer, T., Remon, J.P., Vervaet, C.,
845 2017b. Development of a continuous direct compression platform for low-dose drug
846 products. *Int. J. Pharm.* 529, 329–346. doi:10.1016/j.ijpharm.2017.07.003
847 Vercruyse, J., Díaz, D.C., Peeters, E., Fonteyne, M., Delaet, U., Assche, I. Van, Beer, T.
848 De, Remon, J.P., Vervaet, C., 2012. Continuous twin screw granulation : Influence of
849 process variables on granule and tablet quality. *Eur. J. Pharm. Biopharm.* 82, 205–211.
850 doi:10.1016/j.ejpb.2012.05.010
851 Vercruyse, J., Peeters, E., Fonteyne, M., Cappuyns, P., Delaet, U., Van Assche, I., De
852 Beer, T., Remon, J.P., Vervaet, C., 2015. Use of a continuous twin screw granulation
853 and drying system during formulation development and process optimization. *Eur. J.*
854 *Pharm. Biopharm.* 89, 239–247. doi:10.1016/j.ejpb.2014.12.017
855 Vervaet, C., Remon, J.P., 2009. Continuous Granulation, in: Parikh, D.M. (Ed.), *Handbook of*
856 *Pharmaceutical Granulation Technology*. Informa Healthcare, New York (USA), pp.
857 308–322.
858 Villmow, T., Kretzschmar, B., Pötschke, P., 2010. Influence of screw configuration ,
859 residence time , and specific mechanical energy in twin-screw extrusion of
860 polycaprolactone / multi-walled carbon nanotube composites. *Compos. Sci. Technol.*
861 70, 2045–2055. doi:10.1016/j.compscitech.2010.07.021
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