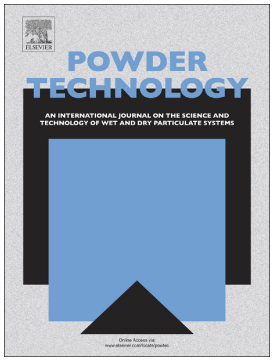

Comparison between twin-screw and high-shear granulation - The effect of filler and active pharmaceutical ingredient on the granule and tablet properties

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PII: S0032-5910(20)30778-6

DOI: https://doi.org/10.1016/j.powtec.2020.08.030

Reference: PTEC 15734

To appear in: *Powder Technology*

Received date: 1 October 2019

Revised date: 25 June 2020

Accepted date: 10 August 2020

Please cite this article as: K.M. Kyttä, S. Lakio, H. Wikström, et al., Comparison between twin-screw and high-shear granulation - The effect of filler and active pharmaceutical ingredient on the granule and tablet properties, *Powder Technology* (2020), https://doi.org/10.1016/j.powtec.2020.08.030

Comparison between twin-screw and high-shear granulation - The effect of filler and active pharmaceutical ingredient on the granule and tablet properties

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ABSTRACT

The aim of the study was to compare continuous twin-screw granulation (TSG) with batch-wise high-shear granulation (HSG). Two different formulations containing either microcrystalline cellulose (MCC) and mannitol or MCC and dibasic calcium phosphate (DCP) as fillers were used. Three different active pharmaceutical ingredients (APIs) (allopurinol, paracetamol and metformin HCl) were used as model substances. To find the suitable liquid-to-solid (L/S) ratio for the granulations, preliminary trials were carried out using a mixer torque rheometry (MTR). Both granule and tablet properties were studied. Granules were characterized with respect to particle size distribution and flowability, while tablets were analysed for tensile strength. Both granulation techniques produced granules with unimodal particle size distribution after milling with the selected L/S ratios. Continuous TSG was less sensitive for liquid amount than HSG when comparing the granule size and tensile strength of tablets. The tabletability of the MCC-DCP formulation was decreased after the wet granulation, whereas the tabletability of MCC-mannitol was increased after

wet granulation. Tablets made of TSG granules had a higher tensile strength than HSG tablets for all formulations. Even the APIs with poor compaction properties produced tablets with sufficient tensile strength. All the model substances behaved in a same way independently of the particle size and solubility of the pure API. These findings confirmed that continuous twin-screw granulation is a good alternative to batch-wise high-shear granulation.

KEYWORDS

Twin-screw granulation, high-shear granulation, mixer torque rheometry, Active Pharmaceutical Ingredient, continuous manufacturing

1. INTRODUCTION

Twin-screw granulation (TSG) is a continuous granulation method that has gained a lot of interest in recent years [1-4]. The advantages of continuous manufacturing over conventional batch manufacturing methods are apparent. These include, for example, smaller footprint, flexibility in product volumes, less product development time, no scale up and better control over quality of the product. However, the differences between high-shear granulation (HSG), the current standard batch method, and TSG are not very well known. Because different formulations have been used in the various studies, there are contradicting results when HSG and TSG have been compared [5-13]. Consequently, it is important to understand the relationship between material properties, processing conditions, and resulting granule attributes. More detailed studies are needed to understand the effect of different formulations and granulation methods [4].

Microcrystalline cellulose (MCC) is one of the most used excipient in the tablet manufacture [14]. MCC has unique compaction properties compared with all the other materials. Microcrystalline cellulose has a porous structure with both crystalline and amorphous regions. The interaction of MCC with water is complicated and several theories have been proposed on how water is bound to

cellulose [15-17]. In the interaction with water MCC particles swell, and during drying the cellulose particles shrink [18,19]. It is believed that increased intraparticle hydrogen bonding during drying causes remarkable increase in density, decrease in porosity and thus loss of plasticity during compaction [20-22]. MCC has been widely used in high-shear granulation [23-25] as well as in twin-screw granulation [7,26,27,28].

There is an increasing interest in using mannitol in tablet formulation [29]. Mannitol is not of animal origin, which makes it free from the concern of contracting bovine diseases as well as lactose intolerance. Mannitol has been increasingly used in tablet formulation using various processes, e.g., direct compression [30,31], roller compaction [32-34] and high-shear wet granulation [35-37]. In twin-screw granulation mannitol has been used both as a hydrophilic model substance [38,39,28] or as a filler in an API containing formulation [40,41,13].

Dibasic calcium phosphate (DCP) is a brittle excipient with a high yield pressure and low strain-rate sensitivity, which makes it attractive excipient in tableting to compliment plastic filler such as MCC. DCP has been used both in high-shear wet granulation [42,43] and in the twin-screw granulation [44-48,13].

Since all excipients have their advantages and disadvantages, a common practice in the pharmaceutical industry is to use two different fillers in the formulations to achieve the desired balance between the material properties. At the moment there is very little literature where mannitol has been used as a binary filler together with MCC [13] or DCP as a binary filler together with MCC [49,50]. This paper addresses the lack of knowledge on this field.

Mixer torque rheometry (MTR) can be used to measure rheology of powders while water is added. The MTR has two intermeshing paddles, and the sample is compressed and expanded between

contra-rotating blades with a changing gap. The behavior of the wet mass within the mixing bowl is continuously recorded via a torque arm fixed to the main body of the mixer and linked to a calibrated dynamometer. The MTR measures two different torque parameters, the amplitude of the oscillations (torque range/amplitude) and the mean torque increase from the baseline (mean torque). The mean torque describes the mean resistance of the mass to mixing and the torque range reflects the rheological heterogeneity of the mass. In the MTR experiments the material exhibits an increase in torque with increasing water content as the consistency of the wet mass rises to a maximum, whereafter it decreases as the material becomes overwetted. Alleva [51], Rowe and Sadeghnejad [52] and Parker et al. [53] have suggested that this behaviour is consistent with the different states of liquid saturation defined by Newitt and Conway-Jones [54]. The maximum torque is reached at the capillary state. Adding more water causes over-wetting of the powder, which decreases the torque. MTR has been used to study the granulation process [55-59], interactions between binders and substrates [60,61], to study the source variation in excipients [52,62,63] and to monitor the wet granule consistency [64,65]. Even though MTR is a low shear mixer, it is able to produce similar data compared with the torque data of a high-shear mixer [66,67].

Granules at maximum torque values (capillary state) are normally too wet for granulation to form tablets but suitable for extrusion [52,58], and consequently MTR peak torque has been previously used as a simple and reliable pre-formulation tool for extrusion-spheronization [58,68,69]. For wet granulation the optimum liquid amount is said to be in the funicular state. To predict the optimum L/S ratio for HSG and TSG both first and second derivative of the MTR curve has been used [19,70-73].

The aim of the study was to compare continuous TSG with batch-wise HSG. Two different prototype formulations containing either MCC and mannitol or MCC and DCP as fillers were used. Three different APIs (allopurinol, paracetamol and metformin HCl) were used as model substances.

Additionally, MTR was used as a pre-formulation tool to estimate a suitable L/S ratio for granulation experiments.

2. MATERIALS AND METHODS

2.1. Materials

Two different prototype formulations were used in the study; MCC-mannitol based and MCC-DCP based (Table 1). MCC is insoluble in water but is able to absorb water into the structure of cellulose. Mannitol is water soluble filler with high intrinsic solubility, whereas DCP is insoluble in water. The formulations contained three different small molecular APIs; allopurinol, paracetamol and metformin hydrochloride (from here on metformin), which were chosen based on different solubilities (Table 2). Purified water was used as granulation liquid and sodium stearyl fumarate (PRUV) was added before tableting to act as a lubricant. Nomenclature of batches is presented in the Figure 1.

2.2. Preliminary trials with a mixer torque rheometer

To find the suitable L/S ratio for the granulations, preliminary trials were carried out using a mixer torque rheometer (MTR, Model MTR, Caleva, Dorset, UK) (Figure 2.). Multiple addition method was used, where the granulation liquid is added in increments and data is logged after every addition. MTR trials were performed using 15 g dry powder in a 125 ml vessel. Fill level was chosen so that the blades were covered with the powder in the beginning of the trial. Water additions (0.05 g/g) were done during 30 s using 20 s logging time after each water addition. A blade speed of 50 rpm was used. Measurements were done in triplicate and the mean torque was calculated.

2.3. Powder blend preparation for granulation

Mannitol was de-lumped before blending using a Quadro Comil U5 (Quadro Engineering, Waterloo, Canada) with a 1397-µm screen and the mill speed was set to 1250 rpm. Metformin and allopurinol were sieved with 1.8-mm screen (Retsch, Germany). Other materials were not de-lumped or sieved since they did not contain lumps. For TSG, the raw materials for each formulation (10 kg) were blended in an 40-L intermediate bulk container (IBC) using an IBC blender (Glatt TAM 160SF blender, GmbH, Binzen, Germany) at 30 rpm for 30 min. Powders for HSG were blended in the granulation bowl prior to granulation.

2.4. Twin-screw granulation

Continuous twin-screw granulation experiments were performed using a ConsiGma™-25 continuous twin-screw granulator (GEA Pharma Systems, Collette, Wommelgem, Belgium). In the ConsiGma™-25, twin-screws are co-rotating with a length-to-diameter ratio of 20:1 and 25 mm diameter screws. The same IBC as in the blending phase was used as container to refill formulation to the feeder. The feeder used was a twin-screw, loss-in-weight K-Tron feeder (KT20, LWF D5 Coperion, Lenzhardweg, Switzerland). Powder feed rate was set to 15 kg/h and screw speed of 500 rpm was used. A liquid addition nozzle of 1.6-mm was used to deliver granulation liquid to the barrel. It was situated so that liquid entered the barrel in front of the first kneading zone (Figure 3). The granulation liquid was pumped using peristaltic pump (Watson Marlow, Falmouth, UK) and temperature of the barrel was set to 25ºC.

All granulations were conducted using standard screw configuration, which refers to the configuration 6k6k, meaning two kneading zones with 6 kneading elements. Staggering angle between kneading discs was 60º and discs were set in a forwarding way (Figure 3). After initiation of the granulation process, granule collecting was started after 45 s. After changing the L/S ratio, there was a 30 s delay before collecting of granules was started so that the process had time to stabilise. L/S ratios can be found in Table 3. Approximately 600 – 900 g of wet granules from every experiment was collected. Process data was collected throughout the granulations.

2.5. High-shear granulation

A small-scale high-shear mixer Diosna Pharma P1/6 (Diosna, Dierks & Söhne Gmbh, Osnabrück, Germany) was used for the high-shear granulations. The granulator bowl size was 4 litres. The impeller speed was 500 rpm and the chopper speed was 1500 rpm. The dry powders (500 g) were dry mixed for 2 min prior to liquid addition. Water was added using a peristaltic pump (505U, Watson Marlow, Falmouth, UK) and the liquid addition time varied between 217 and 632 s based on the L/S ratio used for the experiment. Finally, the granules were wet mixed for 1 min before the bowl was emptied. The L/S ratios for each experiment can be found in Table 3.

2.6. Drying

Drying of all granule batches was done in a fluid bed dryer (non-commercial equipment constructed at AstraZeneca, Mölndal, Sweden). The drying temperature was 60 ºC and the air flow was adjusted for every batch (20 – 60 m^3/h). The drying time varied between 15 and 33 min and the drying endpoint was determined using the outlet air temperature. The temperature was measured by two temperature sensors in the fluid bed chamber. Each batch was dried until the temperature of outlet air was at 27 °C. In addition, loss on drying (LOD) analysis (Mettler Toledo HG63 Halogen, Mettler Toledo GmbH, Switzerland) was used to measure granule moisture content. The temperature used in the LOD measurement was 105ºC and the measurement was finished when weight remained unchanged for 30 s. The target moisture content for the dry granules was 2 − 3% (w/w).

2.7. Milling, final blending and tableting

The dried granules were milled with using a round-holed 1397-µm screen (Quadro Comil U5, Quadro Engineering Inc, Waterloo, Canada). A speed of 1500 rpm was used for all batches. The lubricant, PRUV, was mixed with the dried and milled granules prior to tablet compression. Before

addition, the lubricant was sieved with 800 μm-screen in order to delump the material (Retsch, Haan, Germany). Mixing was carried out using a Turbula tumbling mixer (Turbula T2C, Willy A Bachofen AG Maschinenfabrik, Basel, Switzerland) for 5 min with a speed of 34 rpm. Tablets were compressed using an eccentric Korsch EK0 tabletting machine (Korsch Maschinenfabrik, Berlin, Germany) with 8-mm, round, concave punches at a rate of of 28 tablets/min. Wintab 3 (non-commercial instrument created at AstraZeneca, Mölndal, Sweden) was used to read the upper punch force data. The target tablet core weight was 200 mg. Tablet compression was carried out using three different force levels (5, 10 and 15 kN) to study tabletability and compactibility of the granules. Before collecting tablets, 5 tablets were discarded at all settings.

2.8. Particle size

Particle size distributions for APIs, powder blends and milled granules were measured with laser diffraction (Mastersizer 2000 with Scirocco dry powder dispersion unit, Malvern Instruments, Malvern, UK). Each measurement was done in triplicate. A dispersing air pressure of 0.1 bar and vibration of 20% were used during measurements of granules. For APIs and powder blends, a dispersing air pressure of 1.2 bar and vibration of 35% had to be used, because at lower pressures the particles were not dispersed properly. The particle size distribution was described as d10, d50 and d90 values which are respectively the intercepts for 10%, 50% and 90% of the cumulative mass. Span was calculated according to Eq. 1.

$$span = \frac{d90 - d10}{d50} \qquad \textit{(Eq. 1)}$$

2.9. Mass flow

Mass flow was measured for lubricated granules and powder blends with a granulate flow tester (Erweka GTB, Erweka GmbH, Heusenstamm, Germany). The measuring time was 5 s, stirrer setting 2 and with a 15-mm orifice. Measurements were repeated four times for each batch and average flowability (g/s) and relative standard deviation (RSD) were calculated.

2.10. Ring shear cell

Ring shear cell analysis (Ring shear tester RST-XS, Dietmar Schulze, Wolfenbüttel, Germany) was performed on APIs, lubricated powder blends and granules. Measurements were performed using the Cell XS-Mr with a total volume of 31.37 cm^3 for powder blends and APIs, and with the Cell XS-MV4 (9.65 cm^3) for granules. A method with 4 kPa pre-consolidation stress and normal stresses of 1.0, 1.4, 2.0 and 2.6 kPa to shear to failure was used. Every sample was measured in duplicate and the flow function coefficient (ffc) was automatically calculated by the software. The ffc value is the ratio of consolidation stress and yield strength and larger ffc values indicate better flow [74]. The wall friction angle was determined using the ring shear tester equipped with the XS-WM cell, which has a total volume of 61.28 cm^3. The cell was filled with 10 thin stainless-steel rings and with a stainless-steel wall coupon (0.85 Ra). The highest stress used was equal to 4 kPa, and the wall friction angle was determined at 400 Pa. Duplicate measurements were performed.

2.11. Mercury porosimetry

A mercury intrusion porosimeter (MicroMeritics AutoPore III 9410, MicroMeritics, Norcross, Georgia, USA) was used to measure the porosity of the milled metformin granules. Approximately 0.5 g of the granules was weighed and the pressure was varied from approximately 2 – 60 000 psia. The pressure used detected pores of a size interval between 3.0 nm to 115 µm. The surface tension of mercury was set to 485 mN/m and the contact angle of mercury was set to 130°. The total intruded volume of mercury (cm^3/g) was calculated for intragranular pores (<10 µm pore diameter).

2.12. Compaction properties

A compaction simulator (ESH Phoenix, ESH Testing Ltd., Brierly Hill, West Midlands, UK) with data logging capability was used to characterise the pure APIs. A flat-face 10-mm punch was used. The compaction speeds used were 0.1 mm/s and 300 mm/s. An artificial sawtooth profile was used. All materials were compressed at 35 ± 5 kN.

2.13. Tensile strength

Tablet tensile strength was calculated using Equation 2 [75]. Tablet weight, thickness, diameter and breaking force were measured using Erweka Multicheck (Erweka Multicheck Turbo 3, Erweka GmbH, Heusenstamm, Germany). The results were used to calculate tablet tensile strength. The punch cup depth (H_{cup}) was 0.68 mm for the 8-mm round concave punches used.

$$\text{TS round, curved} = \frac{10\ \text{BF}}{\pi D^2 (2.84\frac{H}{D} - 0.126\frac{H}{(H-2H_{cup})} + 3.15\frac{H-2H_{cup}}{D} + 0.01)} \quad \textit{(Eq. 2),}$$

where BF is breaking force, D tablet diameter, H tablet thickness and H_{cup} punch cup depth.

2.14. Data analysis

The L/S ratio data was scaled for all runs. The amount of water added at the peak torque of the MTR for each API was set to 100%: for metformin (MM) 0.45 g/g, for paracetamol (PM) and allopurinol with MCC-mannitol formulation (AM) 100% was at L/S ratio 0.7 g/g and for allopurinol with MCC-DCP formulation (AD) at 0.75 g/g. % Peak torque value for each L/S ratio are shown in Table 3.

3. RESULTS AND DISCUSSION

3.1. API properties

Allopurinol, paracetamol and metformin were chosen as model substances based on different solubilities in water. The median particle size of the APIs varied from 14 to 439 µm (Table 2 and Figure 4). According to the SEM images (Figure 4) clear differencies can be noticed: allopurinol seems to be small, flaky and cohesive, paracetamol more needle-like and metformin substantially larger in size, but also much more cubical in shape. The flow properties also varied, with allopurinol and paracetamol being cohesive (ffc 2.8 – 2.9) while metformin was easy flowing (ffc 7.9) (Table 2). Allopurinol had the highest WFA (25.7º) and according to AstraZeneca's internal

guideline had moderate adhesion, whereas paracetamol and metformin had low adhesion. Another large difference between the model substances was compaction properties. The tensile strength of paracetamol and metformin was very low (0.2 – 0.3 MPa), whereas allopurinol had excellent compaction properties, with the tensile strength being 5.2 MPa (Table 2).

3.2. Mixer torque rheometry

Average mean torque values, obtained from MTR, were plotted against L/S ratios (Figure 5a). The metformin formulation deviated most from other formulations; the torque started to increase when L/S ratio reached 0.3 g/g and rose rapidly to the maximum value of 0.45 g/g (peak torque). For the MCC-mannitol based allopurinol and paracetamol formulations, the rise in torque can be seen when L/S ratio reaches 0.5 g/g, and the maximum value was reached at 0.70 g/g. One possible explanation why metformin has different mean torque compared to other formulations is differences in solubility. Metformin has notably higher water solubility than other APIs. In addition, the metformin particles have also much larger particle size and hence lower specific surface area compared to other APIs (Table 2).

When comparing the two allopurinol formulations, it was clear that the mean torque of the MCC-mannitol based formulation (AM) started to increase at lower L/S ratio compared with MCC-DCP based formulation (AD) (Figure 5a). Mannitol is a water-soluble filler and dissolves in the added water, thus liquid bridges between particles were formed at lower liquid levels compared with the AD formulation, which only consist of insoluble fillers (MCC and DCP). Based on the MTR curves a L/S ratio screening was done both with TSG and HSG, and appropriate L/S ratios were chosen for the study (Table 3). The purpose was not only to produce optimal granules but to study also the granule and tablet properties when using both under- and over-granulated granules.

3.3. Torque in the twin-screw granulation

The mean torque values of twin-screw granulations are shown in Figure 5B. The TSG torque increased with increasing L/S ratio. The TSG mean torque curves resembled MTR curves by location and magnitude. Similar to the MTR trials, the mean torque curve of AM formulation started to rise with lower L/S ratio compared with AD formulation. The mean torque curve of AM formulation reached the highest torque at 0.6 g/g and started to decrease after that. The peak torque of AM formulation was reached at higher water amount (0.7 g/g) in the MTR experiments. However, the mixing principle is different in these equipment and the shear forces are lower in the MTR compared to the twin-screw granulator. This means that choosing L/S ratio corresponding to the MTR peak torque for the granulation trials would probably produce overwetted granules.

3.4. Particle size distribution

The large differences between the two allopurinol formulations seen both in the MTR curves (Figure 5A) and in the TSG mean torque values (Figure 5B) were also evident in the particle size distributions (Figure 6). For AM formulation the granules with lowest water levels had a shoulder around 100 µm, indicating unranulated fines, which decreased with the increasing water amount and the PSD curves became unimodal (Figure 6A). For AD formulation the PSD of the lowest water amount (ADT35) overlapped with the powder blend PSD (ADPB) and had also another peak around 1000 µm (Figure 6B). The PSD of ADT50 had a broad peak containing both fines and granules. With the highest water amounts PSD became unimodal. High-shear granules had narrower PSD than TSG with all formulations, which was seen also as lower span values (Table 3) and in the cumulative PSD curves where HSG curves were steeper (Figure 6C and 6D). The results agree with the previous studies which showed that the granules produced with HSG were typically more spherical in shape and more uniform in size than twin-screw granules [7-9]. Lee et al. [7] suggested that the differences in granule properties could be explained by the lack of consolidation stage in TSG. In addition, the granulation time is significantly shorter in TSG.

The granule size increased with increasing water levels for all formulations and both granulation techniques (Figure 7). However, at low water levels the TSG granules were larger compared with the HSG granules independently which API was used (Figure 7). Similar results have been reported previously [5,7,13]. Megarry et al. [13] used the same allopurinol MCC-mannitol based formulation as we in this study. They reported that the d50 values of unmilled TSG granules were almost three times larger than d50 values of unmilled HSG granules. This means that the milling process has a larger affect on the particle size distribution of the TSG granules compared with HSG granules. One reason for this could be that in the TSG process the whole powder blend goes through a relatively narrow barrel and is exploited to the same forces in the kneading blocks, whereas in the HSG the relationship between walls and powder is quite different and only part of the powder is colliding with the walls, impeller and chopper. Also water is distributed differently in the TSG and HSG due to the small powder volume in TSG barrel. Shah [7] stated that in the HSG the transport distances to the moving elements and the walls is comparatively larger than in the TSG, causing an accurate distribution of compliments to take more time. The granule size of high-shear granules increased faster than for twin-screw granules, which indicated that HSG was more sensitive to changes in granulation liquid amount than TSG. These results are in agreement with Lee et al. [7] and Rao [11].

3.5. Flowability

The flowability of the powder blends are shown in Table 3. The powder blends of poor flowing APIs (allopurinol and paracetamol) had ffc values 4.1 – 4.7, whereas the better flowing metformin powder blend had ffc 6.3. The mass flow values of powder blends differed more between the ADPB, having the poorest flow (0.6 g/s), and MMPD, having the best flow (15.1 g/s). All granules had mass flow above 10 g/s (Table 3), which is a typical target at AstraZeneca during formulation development. In general, the mass flow values of the granules increased with increasing L/S ratio and the MCC-DCP based (ADT and ADH) granules had better flowability compared with the

MCC-mannitol granules (AMT and AMH). The ffc values of all granules were higher than 10, and consequently were classified as free flowing.

3.6. Tablet tensile strength

The tensile strength of HSG tablets increased with increasing L/S ratio, whereas the tensile strength of TSG tablets was almost constant at the studied L/S ratios (Figure 8). The same phenomena was seen with all APIs when using MCC-mannitol based formulations. This means that when using TSG, high tensile strengths can be achieved already with low water amounts, which could shorten the drying times in the fluid bed. For MCC-DCP based tablets the tensile strength increased slightly with increasing L/S ratio for both HSG and TSG tablets (Figure 8D).

Tabletability graphs for all four formulations are shown in Figure 9. Even the APIs with poor compaction properties produced good tablets with appropriate excipients. Tensile strengths of metformin and paracetamol TSG tablets were similar, around 2.5 MPa at 200 MPa (Figure 9). Allopurinol had the highest tensile strength of the studied model substances (Table 2), which explains the higher tensile strengths of both allopurinol formulations compared with the other formulations.

Tablets made of TSG granules had overall higher tensile strength than tablets made of HSG granules (Figure 9). Similar finding has been reported by Keleb et al. [5], Tan et al. [6], Lee et al. [7], Arndt et al. [10], Miyazaki et al. [12] and Megarry et al. [13]. Lee et al. [3] suggested that the more porous and thus weaker TSG granules are fragmented during tableting. Both Arndt et al. [10] and Miyazaki et al. [12] used granule strength as critical quality attribute. HSG produced denser and stronger granules, whereas TSG granules had comparable results with fluid-bed granulation and showed the higher tensile strength compared with HSG tablets [10]. Miyazaki et al. [12] stated that TSG resulted in superior tablet properties, higher tensile strength and lower ejection force, due to the fact that the TSG granules were bulkier and had a higher d90. In general, twin-screw granules

are also more irregular in shape, which also enhances tablet tensile strength through granule interlocking. Particle size distributions of TSG granules are notably wider, indicating the presence of small particles, which also could have promoted particle bonding during compression.

For tablets to be robust enough for downstream processing, shipping and handling, a general guideline is to target tensile strength ≥ 2 MPa [77,78]. According to AstraZeneca's internal guidelines the region where acceptable tablets can be prepared in routine manufacture on a rotary tablet machine is between 100 to 250 MPa. All TSG tablets (% peak torque varied ~50 – 90%) achieved the target tensile strength at 200 MPa. HSG tablets with MMH and PMH formulations achieved 2 MPa only when using high L/S ratios. For MMH 100% peak torque was required and 93 – 104% for PMH. Formulations containing allopurinol were able to reach 2 MPa also with lower L/S ratios (71% peak torque). For poorly compressible APIs more water was needed to achieve 2 MPa tablet tensile strength. For MCC based formulation the maximum % peak torque was around 50% after which the tablet tensile strength decreased [66]. Consequently, the optimum L/S ratio for granules is probably depended on both filler properties, API properties and the drug load in the formulation.

An interesting difference was noticed between MCC-DCP formulation (Figure 9D) and MCC-mannitol formulations (Figure 9A-C). For MCC-DCP formulation the highest tensile strength was achieved for the powder blend tablets (ADPB) followed by TSG tablets and the lowest tensile strength for HSG tablets (PB > TSG > HSG). For MCC-mannitol based formulations (especially paracetamol and metformin formulations) the powder blends had the lowest tensile strengths and TSG tablets the highest (TSG > HSG > PB).

DCP is practically insoluble and it is also a brittle material that fragmentates during compression [79]. Thus differences in granule properties do not dictate the compactability or tabletability of DCP granules. Djuric and Kleinebudde [45] stated that the tensile strength seems to be more dependent on the creation of new binding surfaces by fragmentation than on granule porosity. Khorseed et al.

[28] explained the unchanged tabletability behavior of DCP granules by the non-deformable and insoluble nature of the powder particle. Granule bonding ability is thus generally determined by other materials in the formulation rather than DCP.

MCC, on the other hand, has a complex interaction with water. Luukkonen et al. [80] stated that the mixing time and the shear forces applied during the granulation process affect the state of water in MCC, and thus the intensity of the water–cellulose interaction. The increased intraparticle hydrogen bonding during drying causes remarkable increase in density, decrease in porosity and thus loss of plasticity during compaction [20]. Consequently, it has been shown that MCC looses tabletability after wet granulation [81,82,23,24].

On the contrary to MCC, the compaction properties of mannitol are improved in wet granulation, as an intraparticular network of pores is formed during the process of granulation and drying [35,36]. Similar results has been published by Khorsheed et al. [28] and Megarry et al. [13]. Khorsheed et al. [28] stated that mannitol, which has been dissolved during granulation, recrystallises to smaller crystals and crystallites, which gives the granules higher surface area than the primary powder leading to better tabletability.

The tensile strength of metformin tablets increased with increasing intragranular porosity of the metformin granules (Figure 10). Higher intragranular porosity has been linked to higher tensile strength in tablets prepared from wet granulated MCC [82,23,83], which could explain the higher tensile strength of TSG tablets in the study.

Fillers (MCC, DCP and mannitol) used in the study have different interactions with water. DCP is insoluble in water and does not seem to be affected by wet granulation. MCC is also insoluble in water, but MCC has a porous structure with both crystalline and amorphous regions, and water is able to form hydrogen bonds with the cellulose. During the interaction with water, MCC particles swell, and during drying the cellulose particles shrink, which will decrease the particle porosity.

Consequently, the tabletability of the MCC-DCP formulation was decreased after the wet granulation. As mentioned earlier, mannitol is water-soluble filler, which forms new pores after recrystallization, and the tabletability is increased after wet granulation. Since we have two fillers in the MCC-mannitol formulation, which tabletability is moving to different directions after wet granulation, the effect is probably dependent on the L/S ratio and shear forces used.

4. CONCLUSIONS

Both granulation techniques produced granules with unimodal particle size distribution after milling with the selected liquid-to-solid (L/S) ratios. High-shear granules had narrower particle size distribution than twin-screw granules with all formulations. The average particle size increased with increasing water levels for all formulations, using both granulation techniques. However, the continuous twin-screw granulation was less sensitive to liquid amount than high-shear granulation when comparing the granule size increase.

API solubility and particle size, together with the filler combination, affected the water absorption capacity and hence the optimal water amount in the wet granulation. Otherwise all the model substances behaved in a same way independently of particle size and solubility of the pure API. Compaction properties of the pure APIs had only minor effect on the tensile strength of the formulated tablets. Even the APIs with poor compaction properties produced tablets with good tensile strength.

Interaction with water differs between different fillers (MCC, DCP and mannitol). DCP is insoluble in water and does not seem to be affected by wet granulation. MCC is also insoluble in water. but MCC has a porous structure and water can interact with cellulose chains in the amorphous regions, which decreases the tabletability of MCC after wet granulation. Consequently, the tabletability of the MCC-DCP formulation was decreased after the wet granulation. On the contrary to MCC, mannitol is a water-soluble filler, which forms new pores after recrystallization, and the tabletability

is increased after wet granulation. Hence the tabletability of MCC-mannitol formulation was increased after wet granulation.

In general, the tablets made of TSG granules had a higher tensile strength than HSG tablets with all formulations. The findings confirmed that continuous twin-screw granulation is a good alternative to batch-wise high-shear granulation.

ACKNOWLEDGEMENTS

Sara Solin is acknowledged for API characterization with ring shear cell and for the SEM images, Ingela Jedvert for compaction simulator experiments, Lina Kronell and Bruno Andersson for help with the ConsiGma™-25.

CRediT author statement

Kaisa M. Kyttä: Investigation, Writing – Original Draft. **Satu Lakio:** Conceptualization, Supervision. **Håkan Wikström:** Conceptualization, Supervision. **Anisa Sulemanji:** Investigation. **Magnus Fransson:** Visualization. **Jarkko Ketolainen:** Supervision. **Pirjo Tajarobi:** Conceptualization, Supervision, Writing Reviewing and Editing.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Authors note: Pictures to be in colour on-line and greyscale in press.

Figure 1. Nomenclature of batches.

Picture width: 1 column.

Figure 2. Mixer torque rheometer.

Picture width: 1 column.

Figure 3. Screw configuration used in TSG.

Picture width: 1.5 column.

Figure 4. SEM images of allopurinol (A. and B.), paracetamol (C. and D.) and metformin HCl (E and F.). Magnification x100 in A., C. and E., x1000 in B. and D. and x300 in F.

Picture width: 1.5 column.

Figure 5. Torques curves for A. Mixer torque rheometer and B. Twin-screw granulation. Average of three replicate measurements are represented with standard deviation.

Picture width: 1.5 column.

Figure 6. Particle size distribution (A. and B.) and cumulative particle size distributions (C. and D.) of allopurinol formulations measured from milled granules A. Allopurinol with MCC and mannitol as fillers and B. Allopurinol with MCC and DCP as fillers.

Picture width: 2 columns.

Figure 7. Mean granule size as a function of L/S ratio for both granulation methods. A. Paracetamol formulation, B. Metformin formulation C. Allopurinol formulation with MCC-mannitol and D. Allopurinol formulation with MCC-DCP. Granule size was measured from milled granules.

Picture width: 2 columns.

Figure 8. Tablet tensile strength at 200 MPa as a function of L/S ratio (% of peak water). A. Paracetamol with MCC-mannitol formulation, B. Metformin with MCC-mannitol formulation C. Allopurinol with MCC-mannitol formulation and D. Allopurinol with MCC-DCP formulation.

Picture width: 2 columns.

Figure 9. Compaction pressure curves for A. Paracetamol tablets (PM), B. Metformin HCl tablets (MM), C. Allopurinol and mannitol tablets (AM), and D. Allopurinol and DCP tablets (AD).

Picture width: 2 columns.

Figure 10. Correlation between intragranular porosity and tensile strength of metformin granules at 200 MPa. CF = Compression force.

Table 1. Formulations.

Material	Trade name	Supplier	MM	PM	AM	AD
Metformin HCl Paracetamol Allopurinol		Sohan Healthcare PVT ltd., India Chemtronica, China Uquifa, Spain	25	25	25	25
Mannitol	Pearlitol 160C	Roquette, Lestrem, France	34	34	34	
Dibasic calcium phosphate dihydrate	Emcompress Premium	JRS Pharma, USA				34
Microcrystalline cellulose	Avicel PH-102	FMC Biopolymer, Ireland	34	34	34	34
Hydroxypropylcellulose	Klucel EXF	Ashland Inc, USA	3	3	3	3
Croscarmellose sodium	Ac-Di-Sol	FMC International,	4	4	4	4

	SD-711	USA				
Sodium stearyl fumarate	PRUV	Moehs, Spain	1.5	1.5	1.5	1.5

Table 2. API properties

API	Solubility in water (mg/ml)	d50 (µm)	ffc	WFA (°)	TS (MPa)
Allopurinol	0.1 - 1 (Very slightly soluble)	14	2.8	25.7	5.2
Paracetamol	10 - 33.3 (Sparingly soluble)	56	2.9	19.8	0.2
Metformin HCl	100 - 1000 (Freely soluble)	439	7.9	12.3	0.3

ffc = flow function coefficient, WFA = wall friction angle, TS = tensile strength of pure API tablet

Table 3. Granulation % peak torque values and granule and powder blend properties. ffc = flow function coefficient

Batch	**% peak torque**	**d10 (µm)**	**d50 (µm)**	**RSD (%)**	**d90 (µm)**	**Span**	**Mass flow (g/s)**	**RSD (%)**	**ffc**
ADPB	-	12	135	0.9	289	2.1	0.6	22.7	4.4
ADT35	47	41	171	6.6	609	3.3	18.0	2.0	23.3
ADT40	53	50	224	14.2	766	3.2	18.6	0.7	22.3
ADT50	71	100	404	3.2	1124	2.5	20.5	1.3	22.6
ADT60	80	220	694	9.4	1378	1.7	28.4	0.1	18.1
ADT64	85	204	648	2.1	1336	1.7	27.4	0.0	25.6
ADH50	71	64	164	3.4	689	3.8	21.1	3.7	25.3
ADH60	80	117	241	1.7	850	3.0	29.1	0.7	66.7
ADH69	92	261	482	3.1	881	1.3	33.6	0.0	86.5
AMPB	-	7	51	4.7	182	3.4	3.6	51.8	4.7

AMT35	50	62	294	18.3	923	2.9	12.0	2.8	14.2
AMT40	57	79	380	6.5	1086	2.7	11.8	3.1	20.3
AMT50	71	77	467	3.1	1192	2.4	13.6	2.2	19.8
AMT60	8691	100	554	2.4	1268	2.1	16.2	1.4	23.9
AMT64		128	597	5.7	1301	2.0	28.0	1.1	18.6
AMH50	71	120	223	1.0	416	1.3	-	-	25.4
AMH60	86	256	500	2.6	964	1.4	24.9	0.1	17.6
AMH69	99	215	636	3.8	1273	1.7	23.5	0.1	19.5
MMPB	-	14	89	2.0	309	3.3	15.1	23.7	6.34
MMT20	44	84	321	11.0	881	2.5	13.7	1.4	50.7
MMT25	56	86	354	10.9	953	2.4	-	-	-
MMT30	67	93	408	12.8	1084	2.4	-	-	-
MMT35	78	106	452	1.6	1170	2.4	-	-	-
MMT40	89	110	488	6.9	1185	2.2	29.5	2.9	34.5
MMH35	78	109	234	1.3	701	2.5	-	-	51.1
MMH40	89	182	382	6.3	732	1.4	-	-	70.5
MMH45	100	265	688	4.2	1342	1.6	-	-	37.6
PMPB	-	7	51	0.4	187	3.5	2.2	20.2	4.14
PMT40	57	52	211	12.6	841	3.6	-	-	-
PMT45	64	53	230	2.8	832	3.4	-	-	-
PMT50	71	63	273	5.3	897	3.1	-	-	-
PMT55	79	71	386	2.0	1075	2.6	-	-	-
PMT60	86	88	449	11.2	1142	2.3	-	-	-
PMT64	91	80	415	14	1073	2.4	-	-	-
PMH57	81	119	246	1.5	499	1.5	-	-	-
PMH65	93	210	409	1.8	738	1.3	-	-	-
PMH73	104	250	656	3.5	1294	1.6	-	-	-

Highlights

- Twin-screw granulation was less sensitive for liquid amount used
- API compaction properties had only minor effect on the tablet tensile strength
- Tablets made of TSG granules had a higher tensile strength than HSG tablets
- Twin-screw granulation is a good alternative to batch-wise high-shear granulation