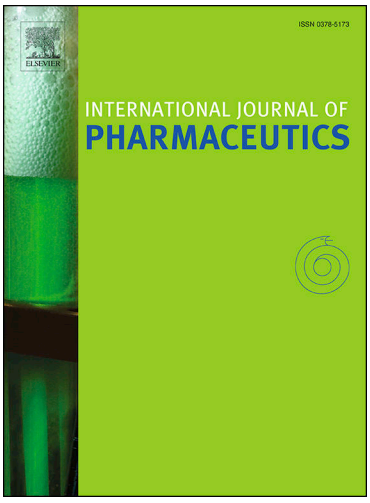
Journal Pre-proofs



Evaluation of binders in twin-screw wet granulation – Optimization of tabletability

Claudia Köster, Peter Kleinebudde

PII: S0378-5173(24)00524-6
DOI: https://doi.org/10.1016/j.ijpharm.2024.124290
Reference: IJP 124290

To appear in: *International Journal of Pharmaceutics*

Received Date: 2 April 2024
Revised Date: 27 May 2024
Accepted Date: 28 May 2024

Please cite this article as: C. Köster, P. Kleinebudde, Evaluation of binders in twin-screw wet granulation – Optimization of tabletability, *International Journal of Pharmaceutics* (2024), doi: https://doi.org/10.1016/j.ijpharm.2024.124290

EVALUATION OF BINDERS IN TWIN-SCREW WET GRANULATION – OPTIMIZATION OF TABLETABILITY

Claudia Köster[a] (claudia.koester@hhu.de)

Peter Kleinebudde[a] (kleinebudde@hhu.de, +49 211 81-14220, corresponding author)

a Institute of Pharmaceutics and Biopharmaceutics, Faculty of Mathematics and Natural Sciences, Heinrich Heine University, Universitätsstr. 1, 40225 Düsseldorf, Germany

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:

Claudia Köster was financed by Nippon Soda, Japan.

ABSTRACT

The influence of hydroxypropyl cellulose type (HPC-SSL SFP, HPC-SSL), concentration (2 %, 3.5 %, 5 %) and filler (lactose, calcium hydrogen phosphate (DCP)/microcrystalline cellulose (MCC)) on twin-screw wet granulation and subsequent tableting was studied. The aim was to identify the formulation of the highest tabletability which still fulfills the requirements of the disintegration. Lactose combined with 5 % binder enabled a higher tabletability and a faster disintegration than DCP/MCC. It was found that tabletability of lactose formulations can be increased by higher binder concentration and higher compression pressure while tabletability of DCP/MCC formulations can be

Abbreviations: L/S, liquid-to-solid ratio; PSD, particle size distribution; LPC, long pitch conveying elements; SPC, short pitch conveying elements; XSPC, extra short pitch conveying elements; KE kneading elements; DCE, distributive conveying elements; MCC, microcrystalline cellulose; DCP, calcium hydrogen phosphate

only increased by higher compression pressure. It was observed that batches containing DCP/MCC failed the disintegration test, if the highest binder concentration and the highest compression pressure were used. To ensure a fast disintegration, the compression pressure or at least the binder concentration had to be low. Changing the disintegrant and its localization improved the DCP/MCC formulation, resulting in faster disintegration than lactose tablets. However, it also resulted in a lower tabletability. In this study best tablets were achieved with 3.5 % or 5 % binder and lactose as filler. These tablets presented the highest tabletability but still disintegrated in less than 500 s.

KEYWORDS

- Binder
- Tablet
- Tablet disintegration
- Tablet tensile strength
- Twin-screw granulation
- Wet granulation

1 INTRODUCTION

The tabletability describes the ability of a material to form a tablet of sufficient mechanical strength after compression (Sun, 2011). An adequate mechanical strength is important to enable further processing as well as transport. The mechanical strength can be measured as tensile strength, where often a tensile strength of at least 2 MPa is targeted (Sun et al., 2009). To increase the mechanical strength of tablets, binders are used to improve the interactions between the particles. Already in an upstream granulation they enhance the product quality (e.g., particle size distribution and granule friability) forming a cohesive network between the different substances in the formulation (Vandevivere et al., 2020). Many binders are described to be useful in the different manufacturing methods. In the case of twin-screw wet granulation a former study showed the increase of tabletability if povidone, copovidone, hydroxypropyl methylcellulose or hydroxypropyl cellulose (HPC) were used in an upstream granulation process (Köster et al., 2021). Several factors are described to be able to influence the tabletability. Beside the properties of the starting material like the plasticity or porosity (Wang et al., 2022), also the properties of the intermediate product can have an impact. The size (Arndt and Kleinebudde, 2018; Skelbæk-Pedersen et al., 2021; Sun and Himmelspach, 2006), shape (Osei-Yeboah et al., 2014a), surface (Osei-Yeboah et al., 2014a), hardness (Skelbæk-Pedersen et al., 2021), porosity (Badawy et al., 2006; Nordström and Alderborn, 2015; Osei-Yeboah et al., 2014a; Tao et al., 2015; van den Ban and Goodwin, 2017) and bulk density (van den Ban and Goodwin, 2017) of the granules were found as influential. Moreover, the granulation method (Nordström and Alderborn, 2015) as well as all process parameters like L/S in wet granulation (Osei-Yeboah et al., 2014a; Tao et al., 2015) or the screw configuration or screw speed (Khorsheed et al., 2019) in twin-screw granulation which cause the listed granule properties can influence the tabletability. During subsequent compression, the tableting speed (Tye et al., 2005) and lubrication (Badawy et al., 2006; Mosig and Kleinebudde, 2014) are known to be of importance.

Nonetheless, fulfilling the dissolution of the active pharmaceutical ingredient is imperative, and disintegration of the tablet may be necessary to facilitate the process. A binder will decelerate the disintegration of the tablet (Joneja et al., 1999). Substances which accelerate the disintegration are disintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate. The mentioned substances are also named as superdisintegrants because already low concentrations between one and four percent are sufficient to ensure a fast disintegration (Fahr and Voigt, 2015). However, the disintegrant type, its localization and concentration have to be chosen carefully dependent on both formulation and process parameters (Köster and Kleinebudde, 2023).

This study aimed to identify a suitable HPC concentration to assure a sufficient tabletability but still allow a disintegration which meets the requirements. The study was performed orientated towards a former study where a suitable disintegrant and its localization were investigated (Köster and Kleinebudde, 2023). Two different fillers were examined. As granulation is a typical manufacturing step before tableting (Khorsheed et al., 2019) but only a few studies investigate the tabletability after wet granulation, this study should help to expand the knowledge about this manufacturing technique. Twin-screw granulation is predestined for continuous production which is a process of great interest caused by less scale-up difficulties, shorter development time and automatic production lines, for instance (Dhenge et al., 2010; Keleb et al., 2004) and results in different granules than other, non-continuous wet granulation techniques like fluid-bed granulation and high-shear granulation (Arndt et al., 2018; Pandey et al., 2018). Thus, this study aims to expand the understanding of twin-screw granulation.

2 Material and methods

2.1 Material

Table 1: Applied material

Product name	**Substance**	**Supplier**	**Abbreviation/ Name in study**	**Function**
Avicel PH-101	Microcrystalline Cellulose	Dupont, Wilmington, USA	MCC DM	Filler
DI-CAFOS A 60	Calcium hydrogen phosphate anhydrate	Chemische Fabrik Budenheim, Budenheim, Germany	DCP	
Granulac® 200	Alpha-lactose monohydrate	Meggle, Wasserburg am Inn, Germany	Lactose (L)	Filler
HPC-SSL SFP	Hyprolose	Nippon Soda, Tokyo, Japan	SSL SFP	Binder
HPC-SSL	Hyprolose	Nippon Soda, Tokyo, Japan	SSL	Binder
Kollidon® CL-SF	Crospovidone	BASF, Ludwigshafen, Germany	xPVP	Disintegrant
Primellose®	Croscarmellose sodium	DFE Pharma, Goch, Germany	xCMC	Disintegrant

Parteck LUB MST	Magnesium stearate	Merck, Darmstadt, Germany	MgSt	Lubricant

Table 1 shows the materials which were used in this study.

2.2 Methods

Table 2: Composition of tablets and upstream produced granules.

	Material	**Concentration in the tablet [%]**			
Intragranular	DCP/MCC (75:25) or lactose	93	91.5	90	90
	SSL SFP or SSL	2	3.5	5	5 SSL SFP
	xCMC	0	0	0	4
Extragranular	MgSt	1	1	1	1
	xPVP	4	4	4	0
Batch name		2 SSL DM 30	3.5 SSL DM 30	5 SSL DM 30	5 SSLSFP DM 30-xCMC
		2 SSL L 9	3.5 SSL L 7.5	5 SSL L 7	
		2 SSLSFP DM 30	3.5 SSLSFP DM 30	5 SSLSFP DM 30	
		2 SSLSFP L 9	3.5 SSLSFP L 7.5	5 SSLSFP L 7	

The batch names are formed by characteristics of the batch: [binder amount in the tablet] [binder abbreviation] [filler abbreviation] [liquid-to-solid ratio] (Table 2). Initially, experiments were made with each filler-binder combination at three binder concentrations. The center point (3.5 % as the median binder concentration) was tripled for each filler-binder combination, resulting in a total of 20 experiments. An additional experiment was implemented to optimize the DCP/MCC formulation (Table 2, last column).

2.2.1 Characterization of base material

The particle size distribution (PSD) of the substances was analyzed by laser diffraction (Mastersizer 3000, Malvern Panalytical, Malvern, Great Britain).

2.2.2 Preparation of granules and tablets

Table 2 presents the composition of the granules and tablets. The manufacturing process included several steps. Initially, all intragranular ingredients were blended for 20 min at 30 rpm (LM 40, L.B. Bohle Maschinen und Verfahren, Ennigerloh, Germany). Continuous twin-screw wet granulation was performed with QbCon® 1 (L.B. Bohle Maschinen und Verfahren, Ennigerloh, Germany). The screw of 16 mm diameter and 20.25 D length comprised long pitch conveying elements (LPC), short pitch conveying elements (SPC), extra short pitch conveying elements (XSPC), kneading elements (KE) and distributive conveying elements (DCE): 4D LPC ≫ 3.75D SPC ≫ 1.2D KE (6 KE 60°) ≫ 5D SPC ≫ 1.2D KE (6 KE 60°) ≫ 3D XSPC ≫ 2D DCE. The powder was fed on the LPC (1 kg/h). Water as granulation liquid was fed on the SPC before the first kneading block. The liquid-to-solid ratio (L/S) was maintained if possible but needed to be adopted sometimes to reduce fines and coarse granules. It was maintained if DCP/MCC was used as filler. In the case of lactose, the L/S had to be adopted dependent on the binder amount (Table 2 batch names). The barrel temperature was set at 25 °C (Chill Compact C.2.L, Single Temperiertechnik, Hochdorf, Germany) and the screw speed was set at 125 rpm. The granules left the granulation unit and fell into the drying unit. The granules were dried by a warm air flow (15-18 Nm^3/h, 80-85 °C) which passed the grid bottom-up, while they were moved through the dryer by the air flow and vibration (6 m/s^2). To dry the granules which were produced by different L/S, different temperatures and air flows had to be used to reach a residual moisture below 3 %. At the end of the grid, the granules fell onto the rotary valve and were transported out of the dryer. The moisture of the product was analyzed (Sartorius Moisture Analyzer MA100, Sartorius, Göttingen, Germany) to ensure the target residual moisture below 3 %. A sample of 500 g granules was collected from each batch 25 min after start of granulation. Former experiments showed that after 25 min the process is stable and stable granules characteristics are received.

The next step ensured the absence of coarse granules. The granules were sieved with Bohle turbo sieve (BTS 100, L.B. Bohle Maschinen und Verfahren, Ennigerloh, Germany) equipped with a 1.5 mm rasp sieve. The impeller speed was set at 600 rpm.

xPVP as extragranular disintegrant was added and blended with the sieved granules for 12 min (T2F, Willy A. Bachofen, Muttenz, Switzerland). MgSt was used as internal lubricant and blended for 2 min with the granules. Directly after blending with the lubricant, tableting was performed using 8 mm flat-faced Euro-B punches at STYL'One Evo (Medelpharm, Beynost, France). Each granule batch was compressed at three compression pressures (180, 240, 300 MPa) to produce 50 tablets of 200 mg.

To improve the disintegration of DCP/MCC tablets, one batch with 5 % SSL SFP and 4 % xCMC intragranular was manufactured.

2.2.3 Characterization of granules

To achieve representative sub-samples, samples were divided (Sample divider PT and PT 100, both Retsch, Haan, Germany). The PSD of the granules was analyzed after both drying and sieving. Dynamic image analysis was used (CAMSIZER XT, Retsch, Haan, Germany). Three sub-samples per batch were examined and at least 1,000,000 particles of each batch were analyzed. The Feret diameter was applied and quantiles of the volume distribution (x10%, x25%, x50%, x75%, x90%) were used to assess the granules. Two target values regarding the PSD distribution were set: x50% should be larger than 200 µm and x90% should be smaller than 1500 µm. Additionally, the span as parameter for broadness of the PSD was calculated applying equation (1).

$$Span = \frac{x90\%\ [\mu m] - x10\%\ [\mu m]}{x50\%\ [\mu m]} \quad (1)$$

The sieved granules were additionally analyzed for flowability and friability. To characterize the flowability, the flow through an orifice was measured. Approximately 250 g of sample were filled in and the time to pass through the 1.5 cm orifice was measured (Ph.Eur. 2.9.16 (Europäische Arzneibuchkommission, 2023)). The mass of the sample was related to this time. Furthermore, the granule friability was examined according to Djuric and Kleinebudde (Djuric and Kleinebudde, 2008).

2.2.4 Characterization of tablets

The tensile strength as well as the disintegration of the tablets were investigated. The Smart Test 50 (Pharmatron Dr. Schleuniger, Thun, Switzerland) was used to measure the diameter (*D*), the thickness (*T*) and the crushing force (*CF*). The tensile strength was calculated applying equation (2) (Fell and Newton, 1970). A tensile strength of at least 1.7-2 MPa implies sufficient mechanical strength to resist subsequent processing and transport (Pitt and Heasley, 2013; Sun et al., 2009). Therefore, a tensile strength of at least 2 MPa was targeted in this study.

$$Tensile\ strength[MPa] = \frac{2 \times CF[N]}{\pi \times T[mm] \times D[mm]} \quad (2)$$

The tablet disintegration was investigated according to Ph.Eur. 2.9.1 (Europäische Arzneibuchkommission, 2023) using Erweka ZT32 (Erweka, Langen, Germany). Contrary to the Ph.Eur., the test was performed until the tablets were disintegrated but stopped latest after 25 min. Independent if the six tablets disintegrated or not, the test was not repeated with further 12 tablets.

The tablet dimensions and weight (Smart Test 50, Pharmatron Dr. Schleuniger, Thun, Switzerland) as well as the particle density of the primary powders (AccuPyc 1330, micromeritics, Norcross, USA) were measured. To calculate the particle density of the powder blend, the harmonic mean was used. The solid fraction can be calculated using equation (3).

$$Solid\ fraction = \frac{tablet\ density}{particle\ density} \quad (3)$$

3 RESULTS AND DISCUSSION

3.1 Characterization of base material

The particle size distributions of SSL SFP and SSL are shown in Figure 1. SSL SFP exhibited smaller particles than SSL. A smaller particle size results in a larger specific surface which enables a larger contact area with the granulation liquid and therefore might improve the granulation by a faster dissolution of the binder. Twin-screw granulation is characterized by short residence times, typically in the range of seconds (El Hagrasy et al., 2013; Kumar et al., 2014; Kumar et al., 2016; Vercruysse et al., 2014). This property requires binders with a high dissolution rate to form granules and consequently smaller particles can be advantageous.

3.2 Characterization of granules

If lactose was the filler, it was not possible to maintain the L/S. The L/S had to be adopted for different binder concentrations to achieve granules and not only powder or lumps. A water-soluble filler requires a low L/S for granulation, but has a higher sensitivity with respect to the L/S. Caused by the adjustment of the L/S, PSD of the SSL SFP granules seemed to be comparable (Figure 2). However, in the case of SSL, 5 % binder resulted in larger particles. The repetition of the center point resulted in comparable PSD. Comparing the binders, no pronounced effect of the particle size of the binder was observed. Only in the case of 5 % binder, slightly larger granules were produced using SSL. Becker et al. assumed a negative effect of smaller binder particle size resulting in a smaller granule size (Becker et al., 1997). This effect of the binder particle size could not be confirmed in the current study. However, the span for the center point was larger in the case of SSL (2.9, 2.9, 2.9) compared to SSL SFP (2.1, 1.9, 2.3).

Milling reduced the particle size but did not influence differences between the batches. The thresholds for x90% and x50% were not exceeded. Besides, the span was increased after milling.

In the case of DCP/MCC, it was possible to get granules without adaption of the L/S. A much higher L/S is required for granulation due to the lower solubility and higher water absorption capacity of MCC. The PSD is presented in Figure 3. Depending on the binder concentration, the PSD varied. However, a clear trend of increasing quantiles at increasing binder concentration was not observed. The quantiles x10%, x25% and x50% were increasing while x75% and x90% were largest in the case of 3.5 % binder. Comparable to lactose granules, the center point granules showed similar PSD and no clear influence of the binder particle size was observed. The absence of a correlation between binder concentration and particle size was consistent with some literature. However, the literature is inhomogeneous regarding the influence of the binder concentration on the granule size. A high correlation between granule size and binder level was described by D'Alonzo et al. who performed granulation in a high intensity mixer (D'Alonzo et al., 1990). A higher concentration of the binder resulted in larger granules (D'Alonzo et al., 1990). The results of Becker et al. were not clear (Becker et al., 1997). Only in some cases, the increase of the concentration of different binders (2 %, 6 %, 10 %) resulted in an increase of the mean particle size (Becker et al., 1997). Often the increase of the mean particle size was only observed from 2 % to 6 % and then did not increase or even decreased for 10 % binder (Becker et al., 1997). They assumed that the binding mechanism alters above a certain value (Becker et al., 1997). Li et al. found a decrease of fines visible as increase of x10 % as well as a narrowing of the PSD at increasing binder concentration for HPC and two polyvinyl pyrrolidone types (Li et al., 2011). However, for the binder hydroxypropyl methylcellulose this trend was not observed (Li et al., 2011). In another study, 4 % HPC in the granulation liquid increased the granules compared to 2 % HPC in the granulation liquid (Yu et al., 2014) but the trend was not significant. Consequently, the concentration of the binder seems to be important but not the only relevant factor for the granule size.

The span decreased at higher binder concentration. In the case of both binders it was reduced from about 6.1 (2 % binder) to about 3.0 (3.5 % binder) to 2.4 (5 % SSL SFP) and 2.0 (5 % SSL). Thus, an increase of the binder concentration narrowed the PSD which may improve the flowability.

Comparable to lactose, milling reduced the particle size but did not influence the differences between the batches. The x50% of granules with 2 % binder was below the threshold of 200 µm. The span increased by sieving.

The L/S is described as highly influential factor in twin-screw granulation (Dhenge et al., 2010; El Hagrasy et al., 2013; Keleb et al., 2004; Portier et al., 2020; Ryckaert et al., 2021; Verstraeten et al., 2017). Therefore, it is difficult to compare fillers which needed to be granulated at different L/S. However, the particle size of the granules was the basis for the selection of the applied L/S. Working with the same L/S for both formulations would not lead to granules for both formulations. Thus, a comparison despite a large difference in L/S is done. The influence of the filler was visible in the pronounced difference of the L/S. For the granules with a high amount of insoluble DCP and water-absorbing MCC, the granulation needed a higher L/S to form granules of the same particle size as the lactose formulation. The properties of the fillers are described to be important for the granule nucleation mechanism (Kashani Rahimi et al., 2020). Moreover, for an effective wet granulation process, the compatibility of binder and filler should be given (Bika et al., 2005). Otherwise, the strength of the intragranular solid bridges formed by binding polymer and filler (if soluble in the granulation liquid) are weaker than in absence of the binder (Bika et al., 2005).

The flow rate was measured for the milled granules and was neither influenced by the binder concentration nor the binder type (Figure 4). The flow rate of 2 % and 5 % binder was in the variation of the center point replicates. Only the filler was important for the flow rate. In the case of lactose granules, a flow rate of about 25 g/s was measured, while in the case of DCP/MCC granules the flow rate was a about 35 g/s. This difference might be caused by the higher density of DCP. The particle size of the granules did not seem to be crucial for the flow rate. For both lactose and DCP/MCC granules, x10% was between 52 µm and 73 µm and x50% was between 213 µm and 365 µm (lactose) and 116 µm and 375 µm (DCP/MCC), respectively. Consequently, the decrease of span did not increase the flowability. Although the particle sizes and span differed, the flow rates were comparable for the same filler.

A good granule flowability is important for the die filling during the tableting process. An improvement of the flowability after granulation can be achieved by surface smoothing, particle shape rounding, densification or size enlargement (Osei-Yeboah et al., 2014a). In the current study the size was measured but an influence of the size on the flow was not observed as described in the literature.

The granule friability after milling is presented in Figure 5. In the case of lactose, an influence of the binder concentration was not visible because of the high variation in the triple determination (SSL) and comparable friability results at the different binder concentrations (SSL SFP). The friability of 2 % and 5 % binder was in the variation of the center point replicates. The granule friability at the same binder concentration was always lower for SSL SFP than for SSL. This result might be explained by the smaller particle size of SSL SFP which could lead to a better binder distribution in the granule increasing the granule strength.

For DCP/MCC granules, the friability decreased at increasing binder concentration. This was observed for both SSL SFP and SSL granules. The values for 2 % and 5 % binder were higher and lower, respectively, than those measured at the center point due to lower variability. A difference between the binders was only pronounced at 2 % binder concentration. Less binder results in fewer intragranular bonds, making the granules weaker and more friable. The greater mass loss may result from either the abrasion of particles from the granule surface or the fracturing of granules into agglomerates that are smaller than the sieve.

In the case of friability, no general influence of the filler was observed. Vandevivere et al. (Vandevivere et al., 2021) found that dependent on the character of the formulation (highly soluble or

poorly soluble) different binder attributes are important for the granule quality. In this work, the binders seemed to be equally suitable for the fillers although the fillers differ in their solubility.

Considering the PSD of SSL SFP granules, larger x10%, x25% or x50% seemed to reduce the friability. Smaller agglomerates exhibit a larger surface and therefore a larger contact area to the air stream which could increase the abrasion. However, this trend was not observed for SSL granules. In addition, small granules themselves can fall through the sieve after some abrasion, thus contributing to mass loss and increasing the calculated value for friability.

In addition to the method used in the current study, the literature also describes other processes to test the granule friability or in general the mechanical strength of granules (Becker et al., 1997; Li et al., 2011). Becker et al. used an oscillating friability testing machine (Becker et al., 1997) and found for each increase of the binder concentration an increase in the strength of the granules in four out of ten formulations (Becker et al., 1997). In some cases, the change from placebo to paracetamol formulations resulted in a different effect of the binder concentration on the granule strength (Becker et al., 1997). Li et al. observed an increase of granule strength at higher binder concentration (Li et al., 2011). Their method included mixing with a turbula blender using glass balls (Li et al., 2011). For some formulations, increasing of the binder concentration seemed to be a useful step to reduce the granule friability, but in the literature and also in the current study, it can be seen that a decrease in the friability cannot generally be achieved by increasing the amount of binder. Another option to reduce friability might be the L/S. Vandevivere et al. found lower friability at higher L/S (Vandevivere et al., 2020). However, caused by the different test methods, a comparison of the results is difficult.

3.3 Characterization of tabletability

The coefficient of variation of the mass of the tablet was below 1.4 %. This statement indicates that an essential quality standard has been fulfilled, allowing for the characterization of further tablet properties.

All tablets fulfilled the requirement of at least 2 MPa tensile strength. The tabletability plots show an increase of the tensile strength at increasing compression pressure (Figure 6). Caused by the increasing pressure, more deformation and fragmentation of the granules arose and consequently more contact areas are created which increase the tablet strength (Nguyen et al., 2015). If the compression pressure is high enough, a plateau can be observed (Sun and Himmelspach, 2006). The plateau was not achieved in the current study. Tablets containing lactose as filler showed a strong influence of the binder concentration on the tensile strength. The values for 2 % and 5 % binder were lower and higher, respectively, than those measured at the center point. Both an increase in the concentration of the binder and an increase of the compression pressure increased the tensile strength. The availability of more binder allows the formation of more binder bridges between the particles and therefore results in a higher mechanical stability of the tablets. The binder type did not clearly influence the tensile strength. In the case of DCP/MCC, the tensile strength was neither influenced by the binder concentration nor the binder type. The tensile strength of 2 % and 5 % binder was in the variation of the center point replicates. In a comparison of different binders using a lactose MCC blend as filler, Becker et al found an increase of the crushing strength at increasing binder concentration for most binders (Becker et al., 1997). So, the results were comparable to the lactose tablets in the current study but not to the DCP/MCC tablets. A general increase of the mechanical strength of the tablet at increasing binder concentration as described by Hiremath (Hiremath et al., 2019) was neither found in the current study nor in the studied literature.

Comparing the different fillers, DCP/MCC led to comparable or lower tensile strength than 3.5 % binder in the case of lactose but higher than lactose tablets with 2 % binder. The results for the tabletability are not only influenced by the excipients but also by the manufacturing technique. For MCC it is described that after wet granulation the ability to form hard tablets is forfeited (Etzler et al., 2011; Khorsheed et al., 2019). Diverging results from studies estimating direct compression can

be explained by this effect. Khorsheed et al. found that the deformation behavior correlates with the tabletability after granulation (Khorsheed et al., 2019). Plastically deformable materials like MCC show a lower tabletability after granulation while brittle materials like DCP retain the tabletability (Khorsheed et al., 2019). The reduction in tabletability is explained by a densification during granulation which reduces the tensile strength of the later produced tablet because less densification can follow (Khorsheed et al., 2019). DCP is brittle and insoluble in the used granulation liquid and therefore no change in particles occurred (Khorsheed et al., 2019). Lactose also belongs to brittle materials (Paul and Sun, 2017) and would maintain the tabletability according to their assumption. The difference in the tensile strength dependent on the filler might be caused by the former mentioned effect of the granulation process on the fillers. Shi et al. also observed reduced tabletability of MCC after granulation and with increasing L/S (Shi et al., 2011). They explain this effect of the granulation by reduction of bonding surface area caused by surface smoothing, granule densification and granule rounding (Shi et al., 2011). MCC is insoluble in water and has porous structure with crystalline and amorphous regions (Kyttä et al., 2020). Water can interact with cellulose forming hydrogen bonds (Kyttä et al., 2020). The interaction results in swelling of the MCC particles during wetting and shrinking during drying (Kyttä et al., 2020). The latter decreases the porosity of the particles (Kyttä et al., 2020). However, in the current study not only MCC but a mixture with DCP (25:75) was used. Osei-Yeboah et al. examined tabletability of granules made by high-shear wet granulation containing a mixture of MCC and DCP (100:0; 60:40; 40:60; 20:80) and povidone as binder (Osei-Yeboah et al., 2014b). The tabletability of MCC and also DCP/MCC was reduced at increasing L/S but in the case of DCP/MCC, the tabletability rose after a minimum. Therefore, the tabletability of DCP/MCC was higher than the tabletability of MCC at high L/S. DCP was able to reduce the loss of tabletability of MCC after wet granulation where an increase in DCP concentration led to an increase in the tabletability. They explain the L/S dependent improvement of the tabletability by the size enlarging effect of a higher L/S (Osei-Yeboah et al., 2014b). Larger granules undergo more extensive fragmentation during compaction which leads to new, unlubricated surfaces. Between these surfaces bonds are created and stronger tablets emerge. The ability of DCP to reduce the effect of granulation is explained by the brittle nature of the excipient which allow fracture of the granules during tableting (Osei-Yeboah et al., 2014b). The lower tabletability of DCP/MCC compared to lactose with 5 % binder in the current study might be caused by the L/S. The use of a lower L/S for MCC/DCP would possibly result in a higher tabletability. However, the used L/S was necessary to avoid too high proportion of fines.

The characteristics of the granules directly influence the character of the resulting tablet (Macho et al., 2023). In the current study, neither the granule size nor the granule friability were decisive for the tensile strength. Batches of comparable granule friability led to different tensile strength of lactose tablets and batches of different granule size led to the same tensile strength in the case of DCP/MCC, for example. The granule size seemed to have no important influence on the tabletability in this study. Similar to this, Nguyen et al. found only little effect of the granule size on the tablet properties (Nguyen et al., 2015). Contrary, Macho et al. described a positive effect of wider PSD. The space between large particles can be filled with small particles which reduces the energy which is needed during tableting and results in stronger tablets (Macho et al., 2023). Patel et al. highlighted the effect of the granule size on the tabletability and the effect of the granules density if the granule size is comparable (Patel et al., 2011). A higher granule density reduces the tabletability because stronger granules undergo less fragmentation during tableting (Patel et al., 2011). The influence of the granule size on the tabletability is not clear yet. Khorsheed et al. found an influence dependent on the filler type, sometimes even the different trade products of one substance performed different (Khorsheed et al., 2019). This may be due to differences in molecular weight, particle morphology or particle size. Shi et al. found for MCC a decrease of tensile strength at increasing median particle size (Shi et al., 2010). Osei-Yeboah et al. did not find a correlation between granule size and tensile strength. A correlation was rather observed between the specific surface area of the granules and the tensile strength as well as the porosity of the granules and the tensile strength (Osei-Yeboah et al., 2014a). However, they also assumed, that the dominate factor can change with increasing compression pressure. At lower compression pressure the bonding area might be the dominant factor while at higher compression pressure the bonding area differences between different starting materials are reduced and the dominant factor might change to the bonding strength (Osei-Yeboah et al., 2014a).

The granule size can be important for the tabletability because of lubricant effects. In the case of larger particles, less surface is available and a higher amount of surface is therefore covered by the lubricant. The bonding area and bonding strength is reduced and thus the tabletability decreased (Osei-Yeboah et al., 2014a). Sun and Himmelspach explained the granule size dependent tabletability by the availability of surfaces for bonding (Sun and Himmelspach, 2006). Without extensive break, larger particles exhibit less surfaces (Sun and Himmelspach, 2006). Korsheed et al. described for the same material (in this case MCC), the granule density or strength to be very important for the tabletability whereas different materials despite same granule density can show different tabletability (Khorsheed et al., 2019).

Beside the tensile strength, another difference between lactose and DCP/MCC tablets was measured. The solid fraction of lactose tablets (0.88-0.95) was higher than the solid fraction of DCP/MCC tablets (0.78-0.86). A lower compressibility of DCP/MCC tablets might be related to the lower tensile strength. The densification of the material during tableting occurs trough particle rearrangement, particle fracture and particle deformation (Etzler et al., 2011). The extent of the mechanisms is dependent on the compression pressure and the mechanical properties (Etzler et al., 2011). Tablets with lower solid fraction have a higher porosity. Thus, less particles interact with each other to increase the mechanical stability. However, despite a higher compressibility, the tabletability of the lactose batches with 2 % binder is lower than the tabletability of all DCP/MCC batches. There might be more interparticular interactions in the case of the lactose tablets, but the interparticular interactions inside the DCP/MCC tablets seemed to be stronger. In the case of 2 %, a higher bonding strength in the DCP/MCC tablets seemed to be more important for the tensile strength than the greater number of interparticular interactions in the lactose tablets. According to Etzler et al., the quality of the interaction depends on the specific surface chemical properties of the materials (Etzler et al., 2011).

In direct compression of binary mixtures the tensile strength is mainly dependent on the solid fraction (Wu et al., 2005). A proportional relation between the solid fraction and the logarithm of the tensile strength was found by Wu et al. (Wu et al., 2005). Markl et al. also emphasize the importance of the tablet porosity and bonding structure/mechanisms, whereas the properties of the granules like the granule density are not influencing the hardness of the tablet significantly (Markl et al., 2017). However, the described relation between solid fraction and tablet tensile strength found by Wu et al. and Markl et al. could not be confirmed by the current study.

3.4 Characterization of tablet disintegration

In the case of lactose as filler, tablets eroded within 455 s and thus passed the disintegration test according to Ph. Eur 2.9.1. (Europäische Arzneibuchkommission, 2023) (Figure 7). An increase in compression pressure as well as an increase in the concentration of the binder decelerated the disintegration. The disintegration for 2 % and 5 % binder was faster and slower, respectively, than that measured at the center point. At increasing binder concentration, the effect of compression pressure rose. Tablets manufactured with SSL SFP disintegrated slightly slower than those manufactured with SSL. Almost, a correlation of disintegration and tensile strength was observed. A higher compression pressure results in less tablet porosity because more particle interactions are created which in turn increase the tensile strength. More interactions and less pores impede the disintegration because the water penetration into the tablet is hampered. However, this relationship is not generally applicable. The disintegration was not related to the tensile strength in a dry granulation and tableting study of Arndt and Kleinebudde (Arndt and Kleinebudde, 2018). The order of tensile strength was not the same as for the disintegration (Arndt and Kleinebudde, 2018). One explanation for the diverging results of their study to the current study can be the different granulation technique but also other factors like the formulation excipients seemed to be influential.

In the case of DCP/MCC as filler, passing the disintegration test depended on the amount of binder and the compression pressure. All tablets showed an erosion. Tablets with 5 % binder and compression pressure of 240 or 300 MPa did not pass the disintegration test. At a compression

pressure of 300 MPa no tablet disintegrated within 25 min. Similar to lactose tablets, higher compression pressure or increasing concentration of the binder slowed the disintegration. The effect of the compression pressure was more pronounced at higher binder concentration. The disintegration-slowing effect of higher binder concentration can be explained by viscosity effects. Depending on the concentration, the molecular weight and the degree of substitution, HPC produces viscous aqueous solutions or gels. The viscosity increases at higher concentrations. During disintegration, viscous areas can be formed by HPC which hamper the penetration of water into the tablet and therefore decelerate the disintegration.

An effect of the filler was observed. The influence of the compression pressure was more pronounced for DCP/MCC tablets than for those with lactose. This resulted in comparable or faster disintegration of MCC/DCP tablets for 180 MPa, rather slower disintegration for 240 MPa and markedly slower disintegration for 300 MPa. The slower disintegration might be explained by the low solubility of DCP and MCC in water compared to lactose. However, at low compression pressure a higher porosity might allow the fast disintegration of DCP/MCC tablets.

In the literature, both similar and opposite effects to those in the study were found. Comparable to the current study, Becker at al. found rather an increase of the disintegration time when the binder concentration was increased. However, in some cases the disintegration was slowest for the medium binder concentration. They manufactured tablets with lactose/MCC as filler (Becker et al., 1997).

In contrast to the current study, where the solid fraction was not the most important influencing factor, van den Ban and Goodwin described the disintegration to be only dependent on the tablet solid fraction (van den Ban and Goodwin, 2017). The importance of the solid fraction and thus the porosity was also described by Markl et al. In their study the disintegration is particularly influenced by the pore structure and density (Markl et al., 2017). In another study, the importance of the solid fraction on the disintegration was dependent on the compression pressure. At low compression pressure, disintegration was mainly associated with the solid fraction (Arndt and Kleinebudde, 2018). A low solid fraction allows water penetration through the high number of pores. At higher tableting pressure, gelation has an increasing influence (Arndt and Kleinebudde, 2018).

Tablet disintegration can follow the mechanism of disintegration of the tablet into smaller units or an erosion of the surface resulting in a progressive shrinkage of the tablet. The latter was described by van den Ban and Goodwin (van den Ban and Goodwin, 2017) and Arndt and Kleinebudde (Arndt and Kleinebudde, 2018), for instance. Arndt and Kleinebudde also described an erosion for their DCP tablets which were manufactured out of roll compacted granules. The effect was observed for several binders except to fast disintegration leading MCC and coarse xPVP (Arndt and Kleinebudde, 2018). The fast disintegration of MCC tablets (within approximately ten seconds) (Arndt and Kleinebudde, 2018) contradicted the findings of the current study, where tablets which also mainly contained MCC and DCP disintegrated quickly (within 30 s) or very slowly (taking more than 25 min) depending on the concentration of the binder and the compression pressure.

3.5 Improving disintegration

Extragranular xPVP seemed to be an inappropriate disintegrant for the DCP/MCC formulation. Tablets with 3.5 % binder disintegrated more slowly than those with lactose and the disintegration of 5 % binder at 240 and 300 MPa failed. In the former study, xCMC as intragranular disintegrant presented promising properties (Köster and Kleinebudde, 2023). Intragranular localization of the disintegrant improve the water penetration into the former granules in the tablet. Therefore, the whole manufacturing process was performed with SSL SFP as binder in a concentration of 5 %, DCP/MCC as filler and xCMC as intragranular disintegrant (5 SSLSFP DM “L/S”-xCMC).

At the same process conditions, granules containing intragranular xCMC exhibited a broader PSD with a higher amount of fines and oversized particles than without intragranular disintegrant like in the

former experiments (Figure 3: 5 SSLSFP DM 30 compared to Figure 8: 5 SSLSFP DM 30-xCMC). An increase of the L/S narrowed the PSD to more comparable values. A PSD-widening effect of a disintegrant during granulation was already observed (Köster and Kleinebudde, 2023). It was explained by water absorption of the disintegrant which reduces the available water to dissolve the binder and form granules (Köster and Kleinebudde, 2023). Underwetting during granulation often results in broad PSD with fines and oversized granules.

For better comparability, granules produced at L/S 30% were selected for further processing.

The mass flow rate averaged 30.7 g/s (n=3) and thus the flowability was worse compared to DCP/MCC granules with extragranular xPVP. This outcome might be caused by the broader PSD.

The friability of granules containing xCMC was 6.0 % (standard deviation 0.7 %, n=3) and consequently higher than the friability of the formulation without xCMC manufactured at the same conditions. The dissimilarity could be attributed to the divergence in the PSD. The smaller particles of the batch including xCMC offer a larger contact area with the stream. This might explain the higher friability. Another possibility would be a reduction of the intragranular interactions due to xCMC.

Beside the granule friability, the tabletability also showed a lower mechanical stability of the formulation containing intragranular xCMC (Table 3). The target tensile strength was not achieved at the lowest compression pressure but was attainable with a compression pressure of 240 MPa. A previous study observed the opposite effect of the disintegrant localization on the tensile strength. When SSL SFP was used, xCMC intragranular resulted in higher tensile strength than xPVP extragranular (Köster and Kleinebudde, 2023). However, comparable tensile strengths for both disintegrant localizations were observed in experiments with other HPC types (HPC-SL and HPC-SL FP, Nippon Soda, Tokyo, Japan) (Köster and Kleinebudde, 2023).

Table 3: Tensile strength (n=10) and disintegration (n=6) of 5 SSL SFP DM 30-xCMC dependent on the compression pressure. The means and standard deviations are shown.

Compression pressure [MPa]	**180**	**240**	**300**
Tensile strength [MPa]	1.63 ± 0.11	2.22 ± 0.10	2.69 ± 0.17
Disintegration [s]	126 ± 10	271 ± 15	380 ± 11

The disintegration was accelerated compared to extragranular xPVP (Figure 7, Table 3). and was faster than the disintegration of lactose tablets with 5 % binder and extragranular xPVP. Instead of disintegrating, the tablet eroded, likely due to the disintegrant's intragranular localization. The disintegrant is distributed inside the granules and therefore can reduce the intragranular bonds. This might enable a faster disintegration which fulfilled the requirements of the Ph.Eur. disintegration test.

4 CONCLUSION

The purpose of this study was to evaluate the HPC concentration and particle size in twin-screw wet granulation to optimize the tabletability of different formulations. SSL SFP as well as SSL in a concentration between 2 % and 5 % promoted a good tabletability for a lactose as well as a DCP/MCC formulation. The effect of the binder concentration on the tabletability was thereby dependent on the filler. In the case of lactose, increasing the binder concentration or the compression pressure enhanced the tabletability, whereas the concentration was negligible in the case of DCP/MCC. In contrast to DCP/MCC, lactose tablets always disintegrated within the pharmacopoeial limits while DCP/MCC

tablets failed for 5 % binder and high compression pressure. Changing the disintegrant from xPVP extragranular to xCMC intragranular for DCP/MCC improved the disintegration but reduced the tabletability. The influence of the binder particle size seemed to be negligible at the applied process conditions and performed tests. Moreover, it was shown that changes in the formulation can strongly influence the properties of the product and require an adaption of the process, e.g. another L/S.

Many studies perform granulation or tableting and do not investigate the combined process, although tableting after granulation is a common industrial process. Thus, the knowledge of the influence of different formulations in twin-screw granulation and subsequent tableting has been successfully extended. However, more research on other materials, the influence of active pharmaceutical ingredients and a fully continuous process is needed to complete the understanding of this promising process for the shift to continuous manufacturing.

5 Funding

This research was funded by Nippon Soda. Kollidon CL-SF was provided by BASF Pharma, Primellose by DFE Pharma, Granulac 200 by Meggle and DI-CAFOS A 60 by Budenheim.

6 Declaration of Competing Interest

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 funders had no role in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

7 Acknowledgments

The authors thank Edmont Stoyanov (Nisso Chemicals Europe) for intensive discussion.

8 References

Arndt, O.-R., Baggio, R., Adam, A.K., Harting, J., Franceschinis, E., Kleinebudde, P., 2018. Impact of Different Dry and Wet Granulation Techniques on Granule and Tablet Properties: A Comparative Study. J Pharm Sci 107 (12), 3143–3152. https://doi.org/10.1016/j.xphs.2018.09.006.

Arndt, O.-R., Kleinebudde, P., 2018. Influence of binder properties on dry granules and tablets. Powder Technol 337, 68–77. https://doi.org/10.1016/j.powtec.2017.04.054.

Badawy, S.I.F., Gray, D.B., Hussain, M.A., 2006. A study on the effect of wet granulation on microcrystalline cellulose particle structure and performance. Pharm Res 23 (3), 634–640. https://doi.org/10.1007/s11095-005-9555-z.

Becker, D., Rigassi, T., Bauer-Brandl, A., 1997. Effectiveness of Binders in Wet Granulation: A Comparison Using Model Formulations of Different Tabletability. Drug Dev Ind Pharm 23 (8), 791–808. https://doi.org/10.3109/03639049709150550.

Bika, D., Tardos, G.I., Panmai, S., Farber, L., Michaels, J., 2005. Strength and morphology of solid bridges in dry granules of pharmaceutical powders. Powder Technol 150 (2), 104–116. https://doi.org/10.1016/j.powtec.2004.11.024.

D'Alonzo, G.D., O'Connor, R.E., Schwartz Joseph B., Schwartz, J.B., 1990. Effect of Binder Concentration and Method of Addition on Granule Growth in a High Intensity Mixer. Drug Dev Ind Pharm 16 (12), 1931–1944. https://doi.org/10.3109/03639049009028348.

Dhenge, R.M., Fyles, R.S., Cartwright, J.J., Doughty, D.G., Hounslow, M.J., Salman, A.D., 2010. Twin screw wet granulation: Granule properties. Chem Eng J 164 (2-3), 322–329. https://doi.org/10.1016/j.cej.2010.05.023.

Djuric, D., Kleinebudde, P., 2008. Impact of screw elements on continuous granulation with a twin-screw extruder. J Pharm Sci 97 (11), 4934–4942. https://doi.org/10.1002/jps.21339.

Etzler, F.M., Bramante, T., Deanne, R., Sienkiewicz, S., Chen, F.J., 2011. Tablet Tensile Strength: An Adhesion Science Perspective. J Adhes Sci Technol 25 (4-5), 501–519. https://doi.org/10.1163/016942410X525687.

Europäische Arzneibuchkommission, 2023. Europäisches Arzneibuch: Amtliche deutsche Ausgabe (Ph. Eur. 11.0), 11th ed. Deutscher Apotheker Verlag, Stuttgart, 6490 pp.

Fahr, A., Voigt, R., 2015. Voigt Pharmazeutische Technologie: Für Studium und Beruf, 12., completely revised ed. Deutscher Apotheker-Verlag, Stuttgart, 687 pp.

Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by the diametral-compression test. J Pharm Sci 59 (5), 688–691. https://doi.org/10.1002/jps.2600590523.

Hiremath, P., Nuguru, K., Agrahari, V., 2019. Material Attributes and Their Impact on Wet Granulation Process Performance, in: , Handbook of Pharmaceutical Wet Granulation. Elsevier, pp. 263–315.

Joneja, S.K., Harcum, W.W., Skinner, G.W., Barnum, P.E., Guo, J.H., 1999. Investigating the fundamental effects of binders on pharmaceutical tablet performance. Drug Dev Ind Pharm 25 (10), 1129–1135. https://doi.org/10.1081/ddc-100102279.

Keleb, E.I., Vermeire, A., Vervaet, C., Remon, J.P., 2004. Twin screw granulation as a simple and efficient tool for continuous wet granulation. Int J Pharm 273 (1-2), 183–194. https://doi.org/10.1016/j.ijpharm.2004.01.001.

Khorsheed, B., Gabbott, I., Reynolds, G.K., Taylor, S.C., Roberts, R.J., Salman, A.D., 2019. Twin-screw granulation: Understanding the mechanical properties from powder to tablets. Powder Technol 341, 104–115. https://doi.org/10.1016/j.powtec.2018.05.013.

Köster, C., Kleinebudde, P., 2023. Evaluation of binders in twin-screw wet granulation - Optimal combination of binder and disintegrant. Eur J Pharm Biopharm 186, 55–64. https://doi.org/10.1016/j.ejpb.2023.03.003.

Köster, C., Pohl, S., Kleinebudde, P., 2021. Evaluation of Binders in Twin-Screw Wet Granulation. Pharmaceutics 13 (2). https://doi.org/10.3390/pharmaceutics13020241.

Kyttä, K.M., Lakio, S., Wikström, H., Sulemanji, A., Fransson, M., Ketolainen, J., Tajarobi, P., 2020. Comparison between twin-screw and high-shear granulation - The effect of filler and active pharmaceutical ingredient on the granule and tablet properties. Powder Technol 376, 187–198. https://doi.org/10.1016/j.powtec.2020.08.030.

Li, J., Tao, L., Dali, M., Buckley, D., Gao, J., Hubert, M., 2011. The effect of the physical states of binders on high-shear wet granulation and granule properties: a mechanistic approach toward understanding high-shear wet granulation process. Part II. Granulation and granule properties. J Pharm Sci 100 (1), 294–310. https://doi.org/10.1002/jps.22261.

Macho, O., Gabrišová, Ľ., Guštafík, A., Jezso, K., Juriga, M., Kabát, J., Blaško, J., 2023. The Influence of Wet Granulation Parameters on the Compaction Behavior and Tablet Strength of a Hydralazine Powder Mixture. Pharmaceutics 15 (8). https://doi.org/10.3390/pharmaceutics15082148.

Markl, D., Sauerwein, J., Goodwin, D.J., van den Ban, S., Zeitler, J.A., 2017. Non-destructive Determination of Disintegration Time and Dissolution in Immediate Release Tablets by Terahertz Transmission Measurements. Pharm Res 34 (5), 1012–1022. https://doi.org/10.1007/s11095-017-2108-4.

Mosig, J., Kleinebudde, P., 2014. Evaluation of lubrication methods: How to generate a comparable lubrication for dry granules and powder material for tableting processes. Powder Technol 266, 156–166. https://doi.org/10.1016/j.powtec.2014.06.022.

Nguyen, T.H., Morton, D.A., Hapgood, K.P., 2015. Predicting Tablet Strength from the Wet Granulation Conditions via the Unified Compaction Curve. Procedia Eng 102, 517–526. https://doi.org/10.1016/j.proeng.2015.01.203.

Nordström, J., Alderborn, G., 2015. The granule porosity controls the loss of compactibility for both dry- and wet-processed cellulose granules but at different rate. J Pharm Sci 104 (6), 2029–2039. https://doi.org/10.1002/jps.24439.

Osei-Yeboah, F., Feng, Y., Sun, C.C., 2014a. Evolution of structure and properties of granules containing microcrystalline cellulose and polyvinylpyrrolidone during high-shear wet granulation. J Pharm Sci 103 (1), 207–215. https://doi.org/10.1002/jps.23776.

Osei-Yeboah, F., Zhang, M., Feng, Y., Sun, C.C., 2014b. A formulation strategy for solving the overgranulation problem in high shear wet granulation. J Pharm Sci 103 (8), 2434–2440. https://doi.org/10.1002/jps.24066.

Pandey, P., Levins, C., Pafiakis, S., Zacour, B., Bindra, D.S., Trinh, J., Buckley, D., Gour, S., Sharif, S., Stamato, H., 2018. Enhancing tablet disintegration characteristics of a highly water-soluble high-drug-loading formulation by granulation process. Pharm Dev Technol 23 (6), 587–595. https://doi.org/10.1080/10837450.2016.1264416.

Patel, S., Dahiya, S., Sun, C.C., Bansal, A.K., 2011. Understanding size enlargement and hardening of granules on tabletability of unlubricated granules prepared by dry granulation. J Pharm Sci 100 (2), 758–766. https://doi.org/10.1002/jps.22315.

Paul, S., Sun, C.C., 2017. Lubrication with magnesium stearate increases tablet brittleness. Powder Technol 309, 126–132. https://doi.org/10.1016/j.powtec.2016.12.012.

Pitt, K.G., Heasley, M.G., 2013. Determination of the tensile strength of elongated tablets. Powder Technol 238, 169–175. https://doi.org/10.1016/j.powtec.2011.12.060.

Shi, L., Feng, Y., Sun, C.C., 2010. Roles of granule size in over-granulation during high shear wet granulation. J Pharm Sci 99 (8), 3322–3325. https://doi.org/10.1002/jps.22118.

Shi, L., Feng, Y., Sun, C.C., 2011. Origin of profound changes in powder properties during wetting and nucleation stages of high-shear wet granulation of microcrystalline cellulose. Powder Technol 208 (3), 663–668. https://doi.org/10.1016/j.powtec.2011.01.006.

Skelbæk-Pedersen, A.L., Vilhelmsen, T.K., Rantanen, J., Kleinebudde, P., 2021. The relevance of granule fragmentation on reduced tabletability of granules from ductile or brittle materials produced by roll compaction/dry granulation. Int J Pharm 592, 120035. https://doi.org/10.1016/j.ijpharm.2020.120035.

Sun, C.C., 2011. Decoding Powder Tabletability: Roles of Particle Adhesion and Plasticity. J Adhes Sci Technol 25 (4-5), 483–499. https://doi.org/10.1163/016942410X525678.

Sun, C.C., Himmelspach, M.W., 2006. Reduced tabletability of roller compacted granules as a result of granule size enlargement. J Pharm Sci 95 (1), 200–206. https://doi.org/10.1002/jps.20531.

Sun, C.C., Hou, H., Gao, P., Ma, C., Medina, C., Alvarez, F.J., 2009. Development of a high drug load tablet formulation based on assessment of powder manufacturability: moving towards quality by design. J Pharm Sci 98 (1), 239–247. https://doi.org/10.1002/jps.21422.

Tao, J., Pandey, P., Bindra, D.S., Gao, J.Z., Narang, A.S., 2015. Evaluating scale-up rules of a high-shear wet granulation process. J Pharm Sci 104 (7), 2323–2333. https://doi.org/10.1002/jps.24504.

Tye, C.K., Sun, C.C., Amidon, G.E., 2005. Evaluation of the effects of tableting speed on the relationships between compaction pressure, tablet tensile strength, and tablet solid fraction. J Pharm Sci 94 (3), 465–472. https://doi.org/10.1002/jps.20262.

van den Ban, S., Goodwin, D.J., 2017. The Impact of Granule Density on Tabletting and Pharmaceutical Product Performance. Pharm Res 34 (5), 1002–1011. https://doi.org/10.1007/s11095-017-2115-5.

Vandevivere, L., Denduyver, P., Portier, C., Häusler, O., Beer, T. de, Vervaet, C., Vanhoorne, V., 2020. Influence of binder attributes on binder effectiveness in a continuous twin screw wet granulation process via wet and dry binder addition. Int J Pharm 585, 119466. https://doi.org/10.1016/j.ijpharm.2020.119466.

Vandevivere, L., Vangampelaere, M., Portier, C., Backere, C. de, Häusler, O., Beer, T. de, Vervaet, C., Vanhoorne, V., 2021. Identifying Critical Binder Attributes to Facilitate Binder Selection for Efficient Formulation Development in a Continuous Twin Screw Wet Granulation Process. Pharmaceutics 13 (2). https://doi.org/10.3390/pharmaceutics13020210.

Wang, Y., Cao, J., Zhao, X., Liang, Z., Qiao, Y., Luo, G., Xu, B., 2022. Using a Material Library to Understand the Change of Tabletability by High Shear Wet Granulation. Pharmaceutics 14 (12). https://doi.org/10.3390/pharmaceutics14122631.

Wu, C.-Y., Best, S.M., Bentham, A.C., Hancock, B.C., Bonfield, W., 2005. A simple predictive model for the tensile strength of binary tablets. Eur J Pharm Sci 25 (2-3), 331–336. https://doi.org/10.1016/j.ejps.2005.03.004.

Yu, S., Reynolds, G.K., Huang, Z., Matas, M. de, Salman, A.D., 2014. Granulation of increasingly hydrophobic formulations using a twin screw granulator. Int J Pharm 475 (1-2), 82–96. https://doi.org/10.1016/j.ijpharm.2014.08.015.

FIGURE CAPTIONS

Figure 1: Density distribution of SSL SFP (black) and SSL (grey).

Figure 2: PSD presented as quantiles (x10%, x25%, x50%, x75%, x90%) of lactose granules manufactured with SSL SFP (left) or SSL (right) after drying (filled symbols) and after milling (empty symbols). Mean values and standard deviations are shown (n=3).

Figure 3: PSD presented as quantiles (x10%, x25%, x50%, x75%, x90%) of DCP/MCC granules manufactured with SSL SFP (left) or SSL (right) after drying (filled) and after milling (empty symbols). Mean values and standard deviations are shown (n=3).

Figure 4: Flow properties of milled granules containing SSL SFP (○) or SSL (◇) measured as flow through an orifice. Mean values and standard deviations are shown (n=3).

Figure 5: Granule friability of milled granules manufactured with lactose (left) or DCP/MCC (right) and SSL SFP (○) or SSL (◇). Mean values and standard deviations are shown (n=3).

Figure 6: Tabletability of lactose (left) and DCP/MCC (right) formulations with different concentrations of SSL SFP (●) and SSL (◆). The binder concentration is illustrated green (2 %), blue (3.5 %) and yellow (5 %). The means and the standard deviations are shown (n=10). The pink line marks the threshold.

Figure 7: Tablet disintegration of lactose (left) and DCP/MCC (right) formulations with different concentrations of SSL SFP (●) and SSL (◆). The binder concentration is illustrated green (2 %), blue (3.5 %) and yellow (5 %) and the compression pressure is increasing from left to right (180 MPa, 240 MPa, 300 MPa). The single values are shown (n=6). The pink line marks the threshold.

Figure 8: PSD presented as quantiles (x10%, x25%, x50%, x75%, x90%) of DCP/MCC granules manufactured with 5 % SSL SFP and xCMC at different L/S after drying (filled) and after milling (empty symbols, only for L/S 30 %). The means and the standard deviations are shown (n=3).