Reduction of tablet weight variability by optimizing paddle speed in the forced feeder of a high speed rotary tablet press

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Abstract

Context: Tableting is a complex process due to the large number of process parameters that can be varied. Knowledge and understanding of the influence of these parameters on the final product quality is of great importance for the industry, allowing economic efficiency and parametric release.

Objective: The aim of this study was to investigate the influence of paddle speeds and fill depth at different tableting speeds on the weight and weight variability of tablets.

Materials and methods: Two excipients possessing different flow behavior, microcrystalline cellulose (MCC) and dibasic calcium phosphate dihydrate (DCP), were selected as model powders. Tablets were manufactured via a high speed rotary tablet press using design of experiments (DoE). During each experiment also the volume of powder in the forced feeder was measured.

Results and discussion: Analysis of the DoE revealed that paddle speeds are of minor importance for tablet weight but significantly affect volume of powder inside the feeder in case of powders with excellent flowability (DCP). The opposite effect of paddle speed was observed for fairly flowing powders (MCC). Tableting speed played a role in weight and weight variability, whereas changing fill depth exclusively influenced tablet weight.

Conclusion: The DoE approach allowed predicting the optimum combination of process parameters leading to minimum tablet weight variability. Monte Carlo simulations allowed assessing the probability to exceed the acceptable response limits if factor settings were varied around their optimum. This multi-dimensional combination and interaction of input variables leading to response criteria with acceptable probability reflected the design space.

1. Introduction

Solid dosage forms, and primarily tablets, are the most widely used systems for oral drug delivery, mainly due to their ease of manufacturing, accurate dosing and high patient compliance.[1-5] Today, tablets still account for more than 80 % of all pharmaceutical preparations.[6]

The tableting process on a high speed rotary tableting press can generally be divided into three distinct stages: die filling, compaction and ejection.[7-9] This study focuses on the first stage of the tableting cycle, the die filling, which is a crucial control variable. The amount of powder in the die determines the weight of the tablet, hence the drug content.[10] The reproducibility of the process is also very important, as weight variations contribute to variations in drug content and other critical quality attributes, including tensile strength, porosity and drug release.[11, 12]

Accurate die filling is a complicated process comprising different mechanisms, which act simultaneously and contribute to the complexity of this step in the compression cycle.[3, 7, 8, 13] These mechanisms include gravity feed (powder falls into the die), forced feed (rotating wheels in the feeding shoe transfer powder into the die, but induce shear stress in the powder bed), suction fill (at the overfilling station the lower punch is rapidly lowered, creating a partial vacuum which pulls the powder into the die cavity), weight control (after the die is overfilled, the lower punch moves upwards to eject some of the powder), centrifugal forces (caused by the rotational movement of the turret), vibrations of the press and overhead pressure (pressure on the powder in the feeder and die caused by the weight of the powder in the hopper and tubing).[3, 7, 8, 13]

Irrespective of the tooling and the machine settings, powder flow is another important factor influencing the die filling process. The flow behavior of a powder is determined by powder

characteristics and operating conditions. Also environmental conditions, the pre-conditioning of the powder and applied loads should be taken into account.[1, 3, 8, 11, 13-16]

For a number of researchers the die filling process has also been of particular interest. In early experiments, Ridgway et al. constructed an automatic weight-control device. Their findings contributed to the development of the closed-loop weight-control systems used in rotary tableting machines today.[17] Wu et al. used transparent stationary dies and moving feeding shoes of simple and complex geometries to study the powder flow of different metallurgical powder components in air and vacuum.[18] His experiments showed that powder characteristics, shoe speed, die geometry and airflow play an important role in the die filling process. Sinka et al. applied the same system in an attempt to characterize the flow behavior of pharmaceutical powders in dies and made similar observations as Wu et al..[13, 18] Mendez et al. used a fixed feed frame and a moving die disc system to examine the effect of blend composition, shoe properties and die parameters on flow properties, uniformity of die filling and applied shear of pharmaceutical blends.[10] This study showed that the amount of powder entering the dies depended on blend flow properties, the speed of the paddles in the feed frame and die disc speed. Furthermore they concluded that blend properties changed after passing the feeder and the flowability of lubricated blends improved significantly as the feed frame speed was increased. Also research in the field of computer modeling focused on the flow behavior of powder systems in dies.[9, 19]

While this former research contributed to the understanding of die filling on high speed rotary presses, the majority of these experiments were conducted on simplified systems. Although attempts were made to simulate a real-life setting, often important parameters were not taken into account or intentionally disregarded. Wu et al., for instance, ignored the effects of airflow, air pressure and cohesive forces in his DEM simulations, whilst other researchers draw their conclusions about die filling on a high speed rotary tablet press from passive die filling experiments (moving fill shoe and steady die).[9, 13, 18] Hence no set-up covered the

complete range of factors involved in this complex process. Furthermore, the existing conventional techniques for measuring flowability do not directly provide relevant and applicable information for the selection of press parameters during die filling on a rotary tablet press.[20] Therefore, the experiments in this study were performed on an industrial tableting machine whereby all possible mechanisms affecting die filling are involved, without simplifications.

Although a complex process, the die filling process for a given tablet press is mainly controlled by four parameter settings: turret speed (tableting speed), speed of the first paddle wheel (paddle speed 1), speed of the second paddle wheel (paddle speed 2) and fill depth. The aim of this current research was to investigate the influence of these important control variables on the weight and weight variability of tablets manufactured using an industrial high-speed rotary tablet press. The volume of powder in the feeder was monitored to assess the powder densification in the feeding shoe. Moreover, these results were correlated with specific powder characteristics, utilizing two commonly used powders with different flow behavior: microcrystalline cellulose and dibasic calcium phosphate dehydrate.[5, 21-24] A design of experiments (DoE) was used to study the effect of the four selected process variables at the die filling station of a rotary tablet press.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel® PH-102, FMC Biopolymer, Cork, Ireland) and dibasic calcium phosphate dehydrate (Emcompress®, JRS Pharma, Budenheim, Germany) were selected as model powders. A lubricant, sodium stearyl fumarate (Lubrisanaq®, Pharmatrans Sanaq, Basel, Switzerland) was added (0.5 % to microcrystalline cellulose and

1% to dibasic calcium phosphate dihydrate). These powder mixtures are further referred to as MCC and DCP, respectively.

2.2. Preparation of powder mixtures

Both mixtures (MCC_{start}; DCP_{start}) were prepared by low shear mixing (15 minutes, 25 rpm) in a 20 L stainless steel drum with a filling degree of 60 %, using a tumbling mixer (Inversina, Bioengineering, Wald, Switzerland).

Since powder flow is an important factor influencing the die filling process and can be affected by operating conditions and applied loads, it was investigated whether the shear forces in the forced feeder had an influence on the powder properties.[16] To mimic this process, the forced feeder was filled with powder and both paddles were run at maximum (140 rpm) speed for 2 minutes, while the die table was kept stationary (MCC_{shear}; DCP_{shear}). For each powder, the experiments were performed in triplicate.

2.3. Preparation of tablets

Tablets were prepared using a MODUL^{TM} P tablet press (GEA Process Engineering - Courtoy^{TM}, Halle, Belgium) equipped with an overfill cam of 16 mm and a feed frame as shown in Figure 1. As the die table (turret) rotates, powder is fed from the forced feeder into the dies at the overfilling station. After weight adjustment at the filling station, the punches (n=10, ∅ 12 mm, concave radius 24 mm) pass through the pre- and main compression station and the ejection cam mechanism.

The die fill system of this tableting machine includes a gravity hopper connected to a feed frame. The feed frame consists of a top plate, two coplanar paddle wheels and a base plate. A connection tube from the hopper delivers powder into the feed frame via an opening in the

top plate. The first wheel, the feeding wheel (Figure 1a) is composed of eight curved paddles and is located above the overfilling station. It transports powder from the powder feeding tube towards the overfilling region. The second wheel, the metering wheel (Figure 1b), has twelve curved paddles and is located at the filling station. This wheel recovers the excess of powder ejected from the dies after weight adjustment and returns this powder to the feeding wheel. Both wheels are motor driven and rotate in opposite directions. Their speed can be adjusted independently from one another and from the turret speed.

In order to avoid confounding factors, each experiment was run on an empty and cleaned tablet press. The machine was filled (MCC_{start}; DCP_{start}) and run for 1 minute. Then tablets were sampled during 30 seconds. Room temperature (21 ± 2 °C) and relative humidity (30 ± 2 %) were controlled.

2.4. Powder characterization

2.4.1. Particle size analysis

Particle size analysis was done by sieve analysis, using a sieve shaker (Retsch VE 1000, Haan, Germany). 100 g of powder mixture was placed on the upper sieve of the installed set (50, 90, 125, 180, 250, 300, 500 and 710 µm) and shaken at an amplitude of 2 mm for 5 minutes. The amount of powder retained on each sieve was determined. All batches were measured in triplicate.

2.4.2. Density

The density of the powders was measured using a helium pycnometer (Accupyc 1330 pycnometer, Micrometrics Instruments, Norcross Georgia, USA). Each sample was

measured in triplicate, with ten purges and ten runs per measurement. Prior to the measurements, the apparatus was calibrated. All tests were performed at 22 ± 2 °C.

2.4.3. Flow properties

In the flow-through-an-orifice method, the time required for the powder (an amount equivalent to 150 ml) to flow through a stainless steel funnel with a 10 mm orifice was measured using a powder flow tester (Pharma Test PTG-S2, Hainburg, Germany). Each sample was measured in triplicate. The results were expressed as the amount of powder (in g) per second that flowed through the orifice.

The bulk and tapped density of the powder mixture (25 g and 60 g for MCC and DCP, respectively) was determined in a 100 ml graduated cylinder, mounted on a tapping machine (J. Engelsmann, Ludwigshafen am Rhein, Germany). The initial volume (V_0) as well as the volume after 1250 taps (V_{1250}) was recorded. Each sample was measured in triplicate. Bulk and tapped densities were calculated as the amount of powder (g)/V_0 and the amount of powder (g)/V_{1250}, respectively. These values were used to calculate the compressibility index (CI) (Equation (1)):

$$CI = \{(\rho_{1250} - \rho_0) / \rho_{1250} * 100\} \qquad (1)$$

2.5. Tablet evaluation

Immediately after production of the tablets, the tablet weight (n=50) was determined. The variation coefficient (VC) (%) as an indication of weight variability was calculated.

2.6. Volume of powder in the feeder

After each experiment, the powder remaining in the hopper and tubing above the feed shoe was removed. The powder left in the forced feeder was collected and poured into a 1000 ml graduated cylinder to determine the bulk volume.

2.7. Design of experiments

A D-optimal design with 26 experiments, including 3 repeated center points, was used to study the influence of four process variables (factors) - fill depth (mm), tableting speed (tpm (tablets per minute)), paddle speed 1 (rpm) and paddle speed 2 (rpm) - on the responses weight (mg), weight variability (%) and volume of powder in the forced feeder (ml). Table 1 shows the experimental space within which the selected DoE parameters were varied. The factor ranges were selected based on preliminary experiments and by taking into account the operational ranges of the tablet press.

As the feeding wheel delivers the powder to the dies and the metering wheel recuperates the powder at the filling station, it is important that the rotation speed of the feeding wheel is lower than the speed of the metering wheel to avoid overfilling and compaction in the forced feeder. Hence, a constraint was introduced in the design: paddle speed 1 must be lower than or equal to paddle speed 2. Due to this constraint, the experimental space became irregular and a D-optimal design was selected.[25] An overview of the DoE is given in Table 2.

The results of the DoE experiments were analyzed using the MODDE 9.1 software (Umetrics, Umeå, Sweden). After evaluating the effects, DoE models were calculated for each response herewith deleting the non-significant coefficients. Furthermore, after defining the desired responses (weight 450 mg and 1000 mg for MCC and DCP respectively; weight variability lower than 1.5 % as acceptable limit; volume of powder in the feeder not exceeding the maximal volume of the feeder to avoid packing) (Table 3), the optimum combination of factors yielding tablets with these desired responses was determined from

the DoE models. Subsequently the probability to exceed the acceptable response limits was assessed via Monte Carlo simulations by varying the factor settings around these determined optima.

3. Results and discussion

3.1. Evaluation of the powder characteristics

For DCP, no difference in powder properties could be observed between the starting material (DCP_{start}) and the powder subjected to shear (DCP_{shear}), as summarized in Table 4. The particle size (distribution) of MCC on the other hand, was clearly affected by the applied shear, with significantly smaller particles being formed due to shearing forces. This effect can be explained by the structure of MCC particles, which are a mixture of primary particles and agglomerates of needle-like micro crystals.[5, 6, 24, 26] The agglomerates are broken down by the shear inside the forced feeder, resulting in a higher amount of primary particles. Nevertheless, the flow properties were not significantly affected by this change in particle size distribution. Consequently, the flow of the starting material (MCC_{start}; DCP_{start}) and the powders subjected to shear (MCC_{shear}; DCP_{shear}) could be considered equal.

MCC and DCP could be distinguished on the basis of their flow properties, as shown in Table 4. The values of flowability show that the DCP powder flows almost seven times faster through an orifice than MCC. Likewise, based on the CI values, the MCC mixture was identified as a fairly flowing powder, while the DCP mixture had excellent flow properties (Carr).[27]

3.2. Experimental design analysis

3.2.1. Weight

In order to analyze the influence of the critical parameters on the tablet weight an effect plot (Figure 2) for this response was constructed. An effect plot displays the change in the response when a factor varies from its low level to its high level, with all other factors kept constant at their average.[25] As expected, for both powders a higher fill depth significantly (confidence interval does not include zero) increased the tablet weight, as the volume of the die increased. Obviously the absolute increase of tablet weight is higher for DCP compared to MCC tablets (430 mg versus 145 mg), owing to its higher density. However, as the increase in percentage of tablet weight at higher fill depth is 43.0 and 32.2 % for DCP and MCC mixtures, respectively, this difference in weight is not only caused by the true density of both powders. A better packing of DCP particles in comparison to MCC particles also contributed to the weight gain at higher filling depth. This observation can be linked to the low CI of DCP (Table 4) which indicates that the powder consolidation upon tapping is limited as the unsettled particles are already quite tightly packed and interparticular voids are small (i.e. high bulk density).

A negative effect was observed for the tableting speed. An increase of this parameter from the lowest (250 tpm) to the highest (1000 tpm) value significantly decreased the tablet weight. At higher tableting speeds, the die is exposed to the powder bed for a shorter period of time, allowing a shorter filling time. These results were also obtained by other researchers.[10, 20] Although the absolute reduction in tablet weight is larger for DCP (90 mg versus 60 mg), the reduction in terms of percentage for the MCC powder was slightly larger (13.3 % versus 9 %), due to the better flowability of the DCP mixture (i.e. faster die filling), which was also observed by Mendez et al..[10] Another contributing factor can be the higher centrifugal forces generated at higher tableting speed. As the powder bed in the die is freely exposed at the surface of the turret after the filling station (the upper punch seals the die opening only at the (pre-) compression station), powder can be ejected from the die during this short exposure.

For the MCC mixture, paddle speed 1 had a significant positive effect on the tablet weight, in contrast to the DCP mixture where the effect of paddle speed 1 is insignificant. This is related to the flowability of both powders. Paddle 1 assists the powder into the dies, while paddle 2 removes the excess of material at the filling station. Due to the good flowability of the DCP mixture, paddle 1 did not affect the flow of this powder into the die opening. In contrast, varying the paddle speed 1 changed the die filling of MCC, indicating that this powder is more subjected to force feeding than gravity feeding, mainly because of its poor flowability. The interaction effect between the tableting speed and paddle speed 1, as depicted in Figure 3, supported this theory. At a high tableting speed, an increase in paddle speed 1 only resulted in a minor increase in tablet weight, whereas at low tableting speeds the effect of paddle speed 1 was significant. Due to the poor flowability of MCC, the highest impact of force feeding is observed at low tableting speeds. At high speeds, the turret moves too fast, and even a high paddle speed 1 is unable to force as much powder into the die as at low tableting speeds. These results suggest that the flowability of powders is the rate limiting step in die filling.[10] From this it could be expected that, besides paddle speed, also paddle design (e.g. shape and amount of fingers) can play a major role in the flow behavior of powders in the feed shoe.

3.2.2. Weight variability

The influence of the critical parameters on the tablet weight variability is graphically presented in Figure 4. As also observed by Mehrotra et al. and Yaginuma et al., a higher tableting speed caused a significant increase in tablet weight variability for both powder mixtures.[19] This result could be linked with the lower tablet weight at higher tableting speeds. A decrease in the weight suggests a lower fill density of the powders or an incomplete filling of the dies at higher tableting speed, an observation already reported in literature.[10, 20] This effect combined with more material loss after filling due to higher centrifugal forces increased

weight variability. Although no significant difference was observed between the absolute increase in weight variability, it should be mentioned that the overall weight variability for MCC tablets is higher than for DCP tablets (Table 2), which is linked to their powder flow properties.

3.2.3. Volume of powder in the feeder

For the DCP mixture, as shown in Figure 5, paddle 1 and paddle 2 had a significant positive and negative effect, respectively, on the volume of powder in the forced feeder. A higher paddle speed 1 increased the transfer rate of powder towards the dies. However, as the production rate remained constant and the speed of paddle 1 had no influence on tablet weight (Figure 2), the consumption rate of the powder is not affected. As a result more powder must be recirculated back to the powder infeed (Figure 1c), and the powder volume in the recirculation area (Figure 1d) of paddle wheel 1 will increase, hence the total volume of powder in the feeder. An increase in the speed of paddle wheel 2 on the other hand resulted in a higher rate at which expelled powder at the dosing station is removed. However, since the production speed remains constant, the rate at which powder is expelled from the dies during dosing does not change. This resulted in more powder transferred towards paddle wheel 1 where the powder is reused to fill the passing dies and consequently in a reduced volume of powder in the feeder.

Also the tableting speed has a small negative effect on the volume of DCP powder inside the forced feeder. At higher tableting speed more dies pass the filling station, and - although the tablet weight is lower at these settings in comparison to lower tableting speeds - the overall material clearing from the feeder per unit of time is higher, resulting in less powder left in the feeder. This hypothesis can be supported mathematically by Equation (2):

$$x = (W * v_t) / 60 \qquad (2)$$

where x is the net material clearing from the feeder (g/s), W the mean tablet weight (g) and v_t the tableting speed (tpm). With the Modde software it could be determined that, keeping all other parameters constant at their mean value, the weight for the DCP tablets is 1207 and 1116 mg at 250 and 1000 tpm respectively, which is in agreement with the results shown in Figure 2 where a weight decrease of about 90 mg was observed if the tableting speed increases from 250 to 1000 tpm. Applying Equation (2), the net material clearing from the feeder is 5.03 g/s at 250 tpm and 18.61 g/s at 1000 tpm.

For the MCC mixture, none of the factors had a significant effect (data not shown) on the volume of powder present in the feeder. Although differences in the absolute values can be observed (Table 2), these could not be linked to changes in factor settings, hence it was not possible to model this effect. This observation might be explained by the high CI of MCC. Powder is not only set into motion by the movement of the paddles, but also densified. For specific runs, mainly at high paddle speeds, some packing of powder in the feed shoe could be observed.

3.3. Process optimization

Using the Modde optimizer, it was possible to calculate the combination of factors (fill depth, tableting speed, paddle speed 1 and paddle speed 2) yielding tablets which meet all the specifications (weight, weight variability and volume of powder in the feeder) as defined in Table 3. The sweet spot plots (Figure 6) show the regions for all combinations of examined variables where these targets are reached. Due to the lower flowability of the MCC mixture and the different effects of process variables, the sweet spot area is smaller for the MCC formulation compared to the DCP mixture.

The optimal response criteria (Table 3) can be met when several combinations of fill depth, tableting speed and paddle speeds are applied. Since the risk of not meeting the target specifications is higher when a combination of variables close to the border of the sweet spot is selected, one is advised to work at the center of the sweet spot. However, since the highest possible tableting speed is preferred from a production point of view, the following optimum combination of factors were selected by the Modde optimizer: (i) for MCC: fill depth = 10.36 mm; tableting speed = 900 tpm; paddle speed 1 = 114 rpm and paddle speed 2 = 140 rpm; and (ii) for DCP: fill depth = 9.35 mm; tableting speed = 1000 tpm; paddle speed 1 = 20 rpm and paddle speed 2 = 140 rpm.

Limitations with a sweet spot plot presentation are the number of dimensions and the lack of probability estimate in the predicted surface.[25] Performing Monte Carlo simulations on the established optimum factor settings for the MCC formulation showed there is a probability of 0.009 % for tablet weight, 33.14 % for weight variability and 0.043 % for volume of powder in the feeder to exceed the specification limit values when the optimum process settings are used (Figure 7a). Performing Monte Carlo simulations for the DCP formulation showed there is a probability of 1.43 % for the tablet weight, 18.73 % for the weight variability and 0.000 % for the volume of powder in the feeder to exceed the specification limit values when the optimum process settings for this powder are used (Figure 7b). Although the probability for exceeding the weight variability specification limit seems rather large (33.14 % and 18.73 % for MCC and DCP respectively), it should be mentioned that the chosen limit of weight variability is quite narrow (1.5 %). If a variation coefficient of 2 % is selected, the probability of exceeding this specification limit is close to zero.

Due to the different mechanisms that influence the die filling on a rotary tablet press and their relation to each other, it is difficult to study the contribution of all these factors separately. Even compaction simulators cannot cover all events influencing this process (e.g. centrifugal forces). As shown in this research, the best practical approach is to conduct

a series of experiments in an ordered way on an industrial tablet press, whereby all possible mechanisms involved are covered, without simplifications. Even if the contribution of a certain effect cannot be completely distinguished (e.g. effect of tableting speed due to inadequate filling or centrifugal forces), it can be accounted for. DoE is a powerful tool to identify in a quick and simple way the critical process parameters in a die filling process. It is also an essential instrument to set up a prediction model which includes powder characteristics and process parameters. Although these experiments can be repeated easily and fast, it should be mentioned that the obtained results cannot be extrapolated to other machines nor to the same machine with other tooling or another formulation.

4. Conclusions

Using DoE, this study indicated that the paddle speeds in the forced feeder are of minor importance for tablet weight (variability) in case of powders with excellent flowability (DCP), whereas the paddle speeds affected tablet weight of fairly flowing powders (MCC). The opposite phenomenon could be seen on the volume of powder in the feeder. Tableting speed played a role in the tablet weight and weight variability, whereas changing fill depth exclusively influenced the tablet weight for both powders. The DoE approach also allowed predicting the optimum combination of studied process parameters yielding the minimum tablet weight variability. Using Monte Carlo simulations the robustness of the process was assessed. This multi-dimensional combination and interaction of input variables (factor ranges) reflected the design space which results in acceptable response criteria with a reasonable probability.

Declaration of interest

The authors report no declarations of interest.

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Table 1: Overview of the upper and lower levels of the process variables.

Process variable	Lower level	Upper level
Fill depth (mm)	8	12
Tableting speed (tpm)	250	1000
Paddle speed 1 (rpm)	20	140
Paddle speed 2 (rpm)	20	140

Table 2: Overview of the performed experimental design.

Run	Factors				Responses					
	Fill depth (mm)	Tableting speed (tpm)	Paddle speed 1 (rpm)	Paddle speed 2 (rpm)	Weight (mg)		Weight variability (%)		Volume of powder in the feeder (ml)	
					MCC	DCP	MCC	DCP	MCC	DCP
1	8	250	140	140	428.1	981.9	0.63	0.58	570	495
2	12	250	140	140	613.0	1436.4	0.35	0.40	550	545
3	8	250	20	60	367.1	977.5	0.80	0.51	500	430
4	12	250	20	100	528.7	1408.0	1.12	0.27	410	335
5	12	250	20	140	517.6	1401.4	1.35	0.34	330	325
6	12	250	60	60	551.0	1430.0	0.47	0.37	522	505
7	10	625	60	100	442.6	1173.8	1.29	0.46	445	410
8	10	625	80	140	442.5	1182.3	1.35	0.52	430	390
9	9.33	250	20	140	412.6	1131.4	1.02	0.5	350	325
10	12	1000	140	140	502.9	1339.4	1.79	1.07	430	465
11	10	625	60	100	435.1	1194.3	1.45	0.45	430	410
12	8	1000	100	140	354.0	907.6	1.47	1.71	420	415
13	10	625	60	100	432.8	1193.9	1.44	0.56	435	415
14	10	625	20	80	432.2	1184.7	1.06	0.47	385	350
15	8	500	20	20	376.0	978.4	0.32	0.36	460	485
16	9.33	1000	140	140	418.4	1046.1	1.65	1.49	460	460
17	12	1000	20	140	458.4	1224.8	1.60	1.18	265	255
18	8	250	60	140	380.0	985.0	0.90	0.62	415	415
19	12	1000	20	20	470.5	1309.1	1.93	1.55	420	420
20	8	250	100	100	405.6	985.2	0.67	0.40	540	510
21	8	1000	20	140	335.0	889.6	1.58	1.28	300	275
22	8	1000	20	20	367.0	911.0	2.06	1.74	480	490
23	10.66	250	20	20	480.7	1280.1	0.45	0.39	525	490
24	8	750	140	140	389.0	951.5	1.31	0.80	540	510
25	8	1000	60	60	353.4	906.6	2.17	1.55	500	490
26	8	500	20	140	352.3	963.4	0.84	0.67	540	310

Table 3: Overview of the optimal responses and their limits.

Response		Lower limit	Optimal response	Upper limit
Weight (mg)	MCC	441	450	459
	DCP	980	1000	1020
Weight variability (%)		N/A	N/A	1.5
Volume of powder in the feeder (ml)		N/A	N/A	500

Table 4: Flow properties, true density and particle size distribution of the powder mixtures. Start: properties of the starting material; Shear: properties of the material subjected to shear forces by filling the forced feeder with powder and running both paddles for 2 minutes at maximum speed (140 rpm).

	MCC		DCP	
	Start	Shear	Start	Shear
Flowability (g/s)	2.17 ± 0.06	2.44 ± 0.13	14.64 ± 0.33	14.72 ± 0.14
Bulk density (g/cm^3)	0.34 ± 0.00	0.35 ± 0.00	0.97 ± 0.00	0.94 ± 0.01
Tapped density (g/cm^3)	0.41 ± 0.00	0.41 ± 0.00	1.04 ± 0.00	1.04 ± 0.01
Compressibility index (CI) (%)	18.09 ± 0.31	15.35 ± 0.59	7.41 ± 0.56	8.92 ± 1.13
True density (g/cm^3)	1.55 ± 0.00	1.55 ± 0.00	2.31 ± 0.00	2.31 ± 0.00
Particle size distribution				
d10 (µm)	106.6 ± 1.4	29.2 ± 0.8	103.1 ± 1.5	102.8 ± 0.9
d50 (µm)	167.2 ± 1.1	109.5 ± 0.5	160.2 ± 0.2	160.6 ± 0.7
d90 (µm)	240.8 ± 1.5	212.8 ± 1.8	257.9 ± 1.1	258.5 ± 1.3

Figures

Figure 1: Schematic overview of the feed frame with two paddles: (a) feeding paddle; (b) metering paddle; (c) infeed; (d) recirculation area of the feeding paddle. Arrows depict schematically the movement of the powder through the feed frame.

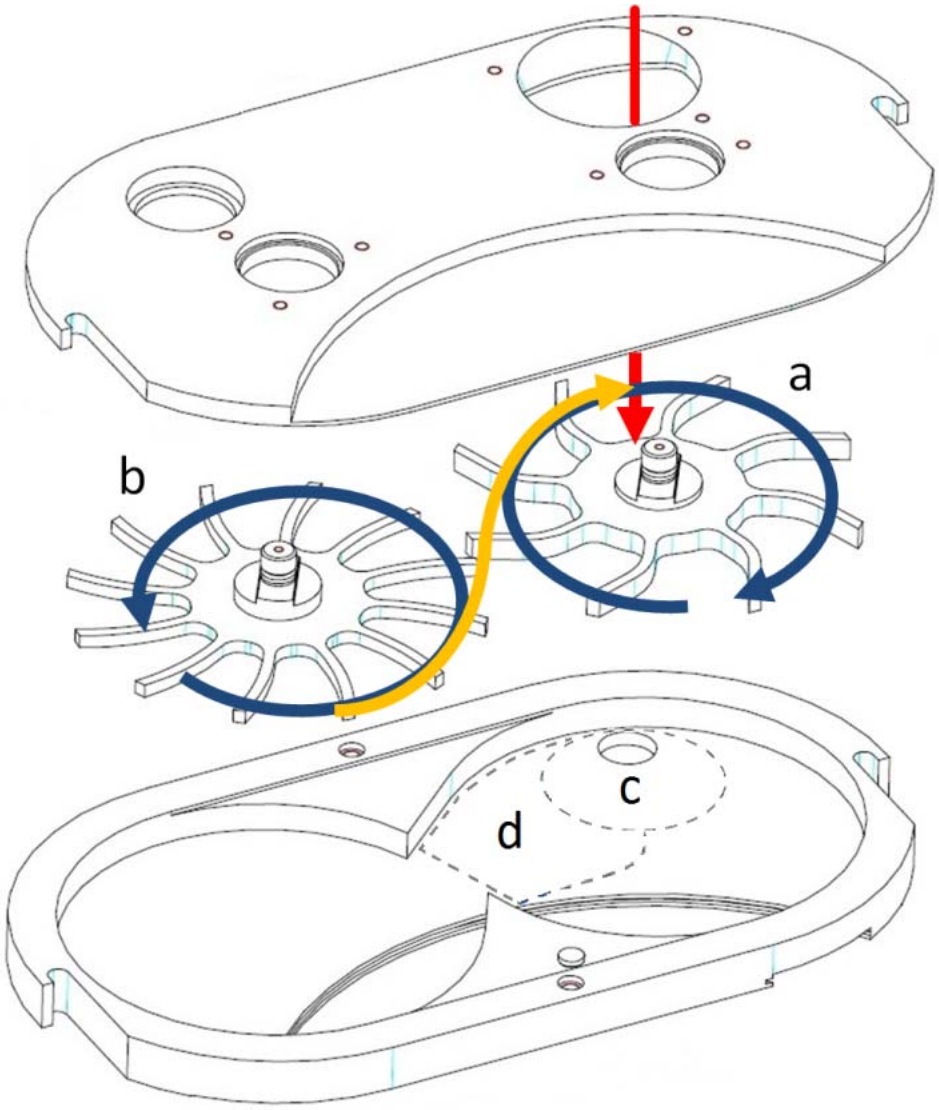

Figure 2: Effect plot of tablet weight. (a) MCC, (b) DCP.

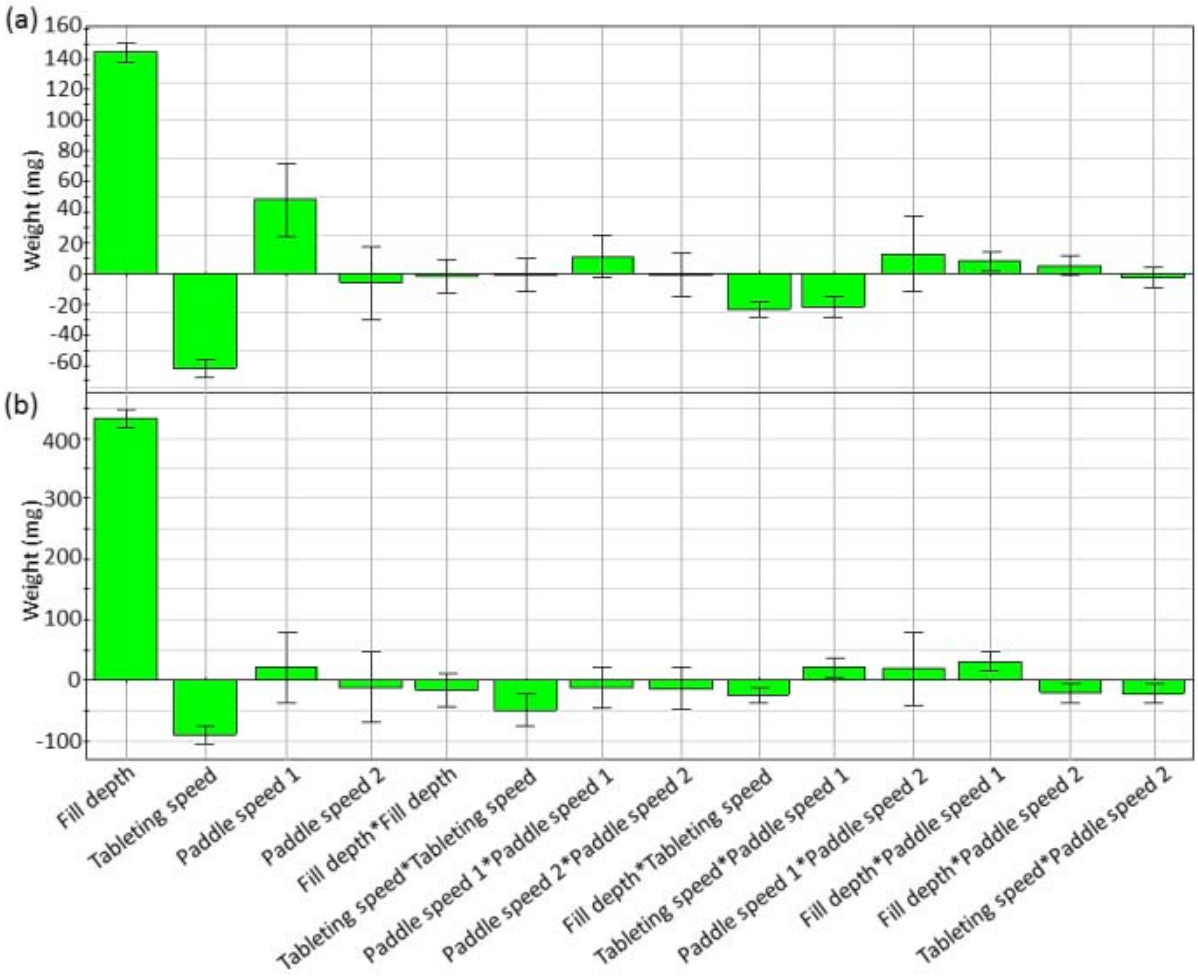

Figure 3: Interaction plot of tableting speed and paddle speed 1 for the weight of MCC tablets. Pad (high): paddle speed 1 = 140 rpm; Pad (low): paddle speed 1 = 20 rpm.

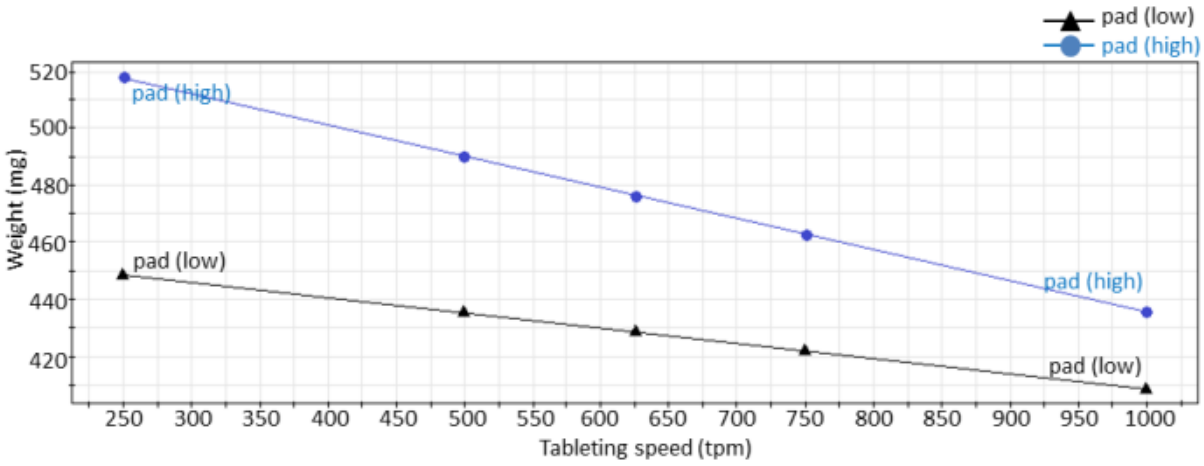

Figure 4: Effect plot of tablet weight variability. (a) MCC, (b) DCP.

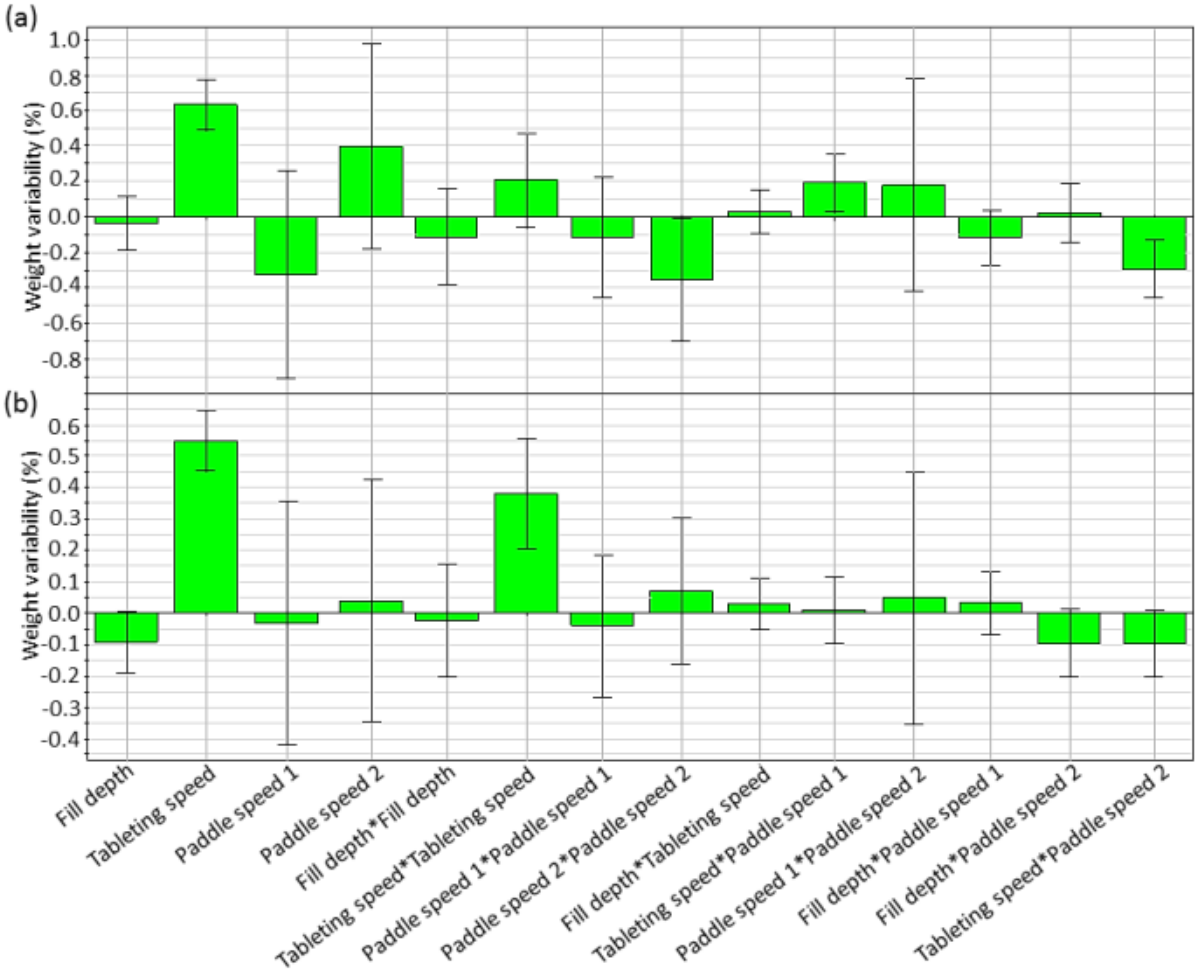

Figure 5: Effect plot of volume of powder in the feeder for the DCP powder.

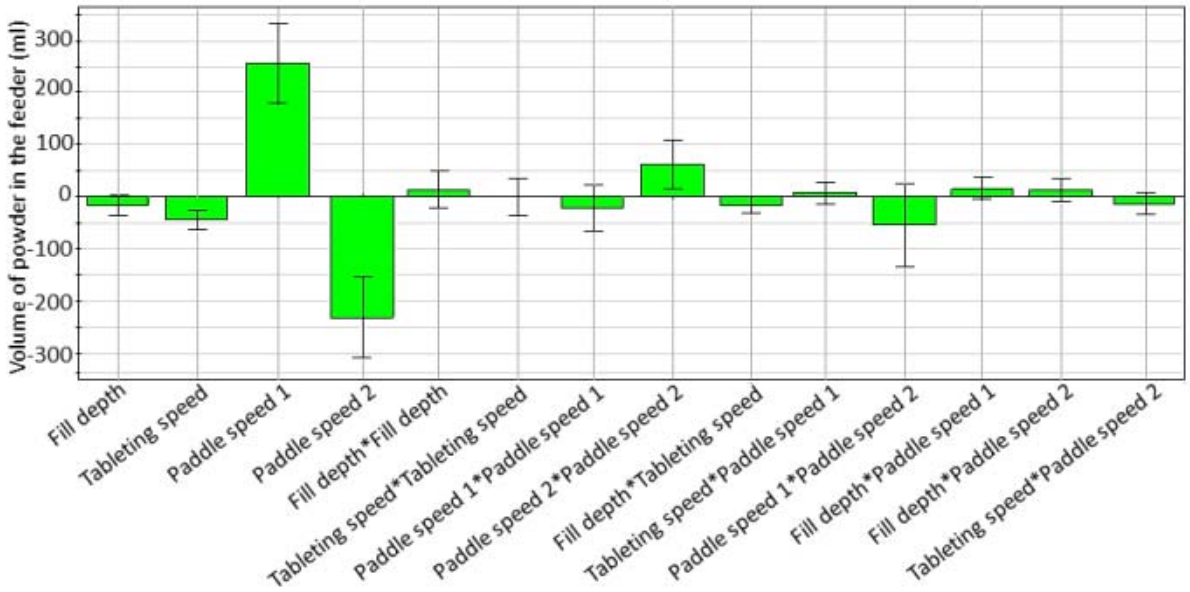

Figure 6: Sweet spot plots for (a) MCC and (b) DCP, showing the combination of process parameters which yield tablets with the required responses.

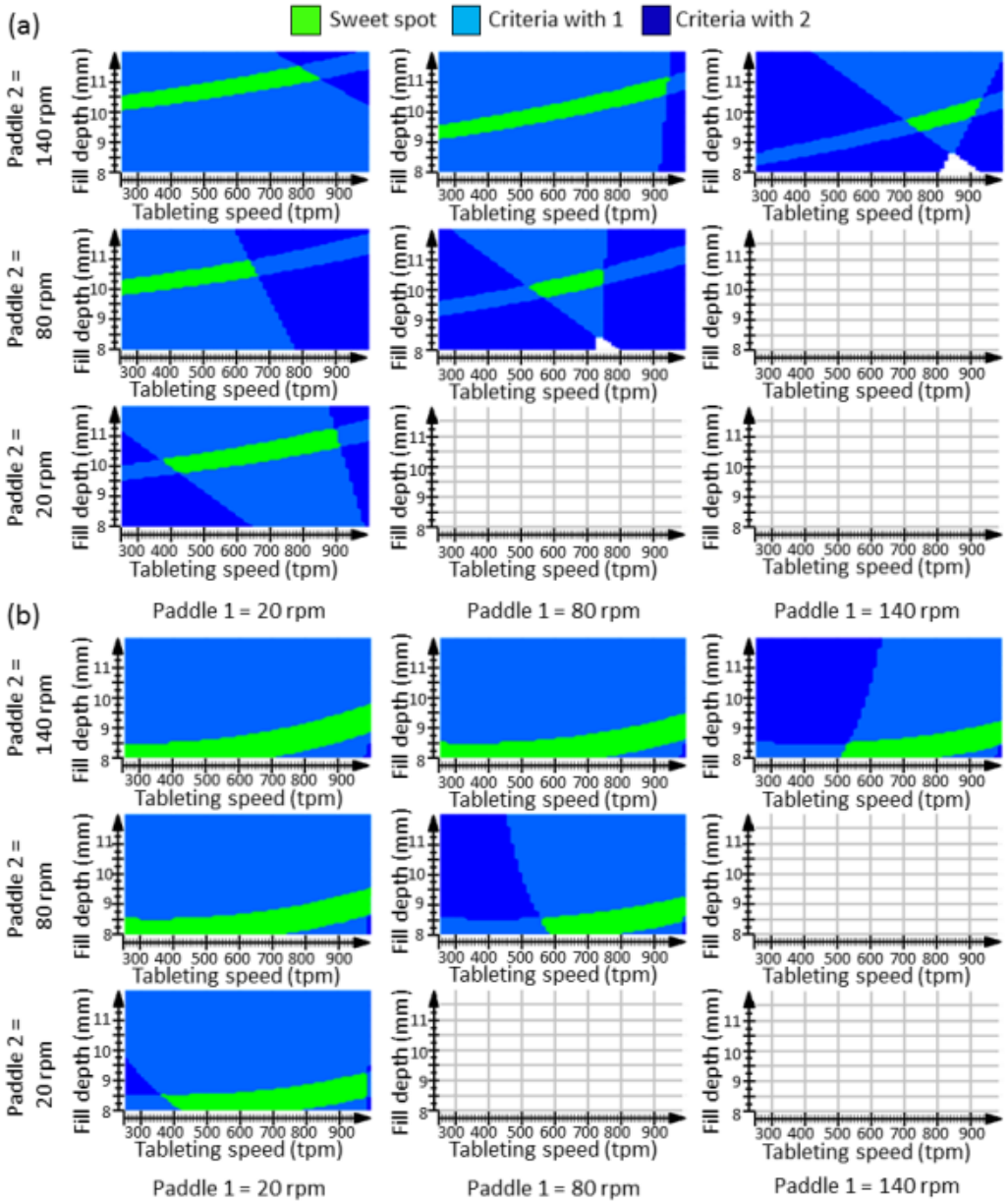

Figure 7: Monte Carlo simulations for (a) MCC and (b) DCP.